

A Guide To
**BIOTECHNOLOGY
FINANCE**

First Edition

A Collaborative Effort

MINNESOTA DEPARTMENT
OF EMPLOYMENT AND
ECONOMIC DEVELOPMENT

LINDQUIST & VENNUM^{LLP}

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A Guide To BIOTECHNOLOGY FINANCE

First Edition

August 2005

**A Collaborative Effort
Minnesota Department of Employment and Economic Development
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FOREWORD

Biotechnology is on the forefront of a technological explosion. Indeed, this has already been dubbed the “Century of Biology.” In little more than a dozen years, the biotechnology industry has grown from a handful of companies to a \$40 billion worldwide industry that increasingly has an impact on a broad spectrum of fields including, health care, agriculture and energy production. Waves of new products, including those that help save lives, grow disease resistant foods and produce environmentally friendly fuels, are coming to market.

The expansion of the industry is being driven by three global demographic trends: a growing population, longer life expectancies and an increasing percentage of elderly people in the total population. Developing and manufacturing biotechnology medicines and products, however, is a complex and costly process. Research and development, for example, now cost biotech companies up to \$100,000 per employee annually.

To capitalize on the extraordinary opportunities presented by the industry, biotechnology companies must be on the cutting edge of modern financing. Success increasingly depends on knowledge of the specific issues that affect the industry and creative strategies that develop from that understanding. Whether in early stages of growth or more mature phases of development, companies are eager to attract grants, investment and corporate partners.

This Guide is a most welcome addition to the biotechnology entrepreneur’s toolkit. It provides the fundamentals of financing for this evolving field in a concise manner without glossing over the details that provide the reader with a greater understanding of the complexity of the issues. In that sense, it is truly a guide, and not merely an introduction, to this exciting new field.

Don Gerhardt, CEO, Medical Alley / MNBIO

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I. INTRODUCTION

A. The Purpose of This Guide

This Guide provides a practical business and legal roadmap for understanding the financing options available to biotechnology companies and the circumstances in which these options are available. Biotechnology finance options are shaped not only by factors that affect all businesses, but also by a set of variables that apply specifically to this industry. In the overview that follows, we discuss these variables and the manner in which they may affect the financing decisions of the biotechnology company. Later in the Guide, we provide a more detailed discussion of each of these specific factors. Depending on the circumstances a company faces, some of these factors may be more important than others in charting a successful financing strategy.

The heart of the book, of course, is the section on the financing options available to biotechnology companies and the related discussion of the requirements or restrictions that apply to the use of each of those alternatives. Because many options are based on the structure of the company and the company's stage of development, we provide a detailed explanation of the choice of business entities available to biotechnology companies in the chapter immediately preceding the finance section. We also provide a discussion of the various stages of the company's life cycle. An understanding of a company's stage of development is critical to determining the most appropriate sources and methods of financing.

B. What is "Biotechnology?"

Throughout this Guide, "biotechnology" is used to describe the science of developing and manufacturing new products derived from living organisms or parts of living organisms (e.g., cells, genes or proteins). Evolving technologies in healthcare, however, are causing a convergence of the pharmaceutical, medical device and biotechnology fields. The resulting new product platforms (i.e., products resulting from combining cellular byproducts with devices) are contemplated here as a segment within biotechnology.

In the glossary at the end of the Guide, we have labored to provide very specific definitions for the various scientific, industrial, governmental, financial, legal and other terms used in the field.

C. Legal Advice

Although we have worked hard to summarize the most important issues affecting biotechnology finance today, this Guide is only intended to be a general summary and does not constitute legal advice. Appropriate legal advice can only be rendered upon a specific set of facts. Lindquist & Vennum PLLP and the Minnesota Small Business Assistance Office cannot and do not assume responsibility for decisions based upon the information provided in this Guide. *You should consult with legal counsel for specific advice regarding your situation before acting on any matter.* As this Guide suggests, there are many issues to consider in biotechnology finance.

To ensure compliance with requirements imposed by the U.S. Treasury, we inform you that any U.S. federal tax advice contained in this Guide is not intended or written to be used, and cannot be used, for the purpose of avoiding penalties under the Internal Revenue Code of 1986, as amended (“Code”), or promoting, marketing or recommending to another party any transaction or matter that is contained in this Guide.

II. OVERVIEW OF BIOTECHNOLOGY FINANCE

A. The Nature of Finance

Finance is the science of money management.¹ As a practical matter, biotechnology companies are primarily concerned with that aspect of financing that involves the allocation of resources. Financing is required to fund operations, develop products and successfully enter the market.

Like corporate finance in general, biotechnology finance is fundamentally driven by the relationship between risk and return. Risk is defined as the degree of uncertainty of return on an asset while return is defined as the change in the value of a portfolio of assets over an evaluation period, including any distributions made from the portfolio during that period.² The basic rule of finance is that the greater the business entity's risk, the greater the return required by investors.

There are many different types of business risk to consider and hundreds of variables that may affect these risks. The combination of these risks and variables define the overall risk/return relationship for a given firm as determined by an investor. The various types of risk include, but are not limited to:

- **Market Entry:** How does the biotechnology firm overcome barriers to entry in the industry, especially the competitive advantages already in place for existing firms?
- **Technology:** Will the new product or technology work? Can it be copied or reverse engineered? What factors will cause the technology to become obsolete? How does the biotechnology company protect its intellectual property and not infringe on the intellectual property of others?
- **Regulatory:** What kind of government approvals will be required? How long will these approvals take to obtain and at what cost?
- **Market Acceptance:** Can the new product be quickly commercialized in sufficient numbers to penetrate the market? How long will it take?
- **Competitive:** What effect will competition have on profitability? What will it take in terms of sales and revenue to secure and sustain market share?
- **Interest Rate:** Will interest rates remain stable or will there be wide fluctuations in interest rates over time? What impact will rates and fluctuations have on operations and on financing alternatives?
- **Currency:** Will fluctuations in foreign currency exchange rates affect the product in foreign markets? Will they have an impact on the cost of materials from foreign sources?

- Economic Structure: What choices need to be made regarding the organizational, legal and capital structure of the firm?
- Financing: Where will the next round of financing come from and in what form? What is the appropriate mix of debt and equity?

Each investor will analyze and consider each of the risk categories and the underlying variables to determine a required return. By understanding its investors' risk/return analyses, a biotechnology firm can more successfully determine the most logical path to securing effective financing for its development and take appropriate steps to reduce real and perceived risks.

B. Industry Variables That Affect Biotechnology Finance

Several factors have a substantial effect on biotechnology finance. Many of these factors conspire to drag out the timeline for the development of the company's product and, consequently, have a negative impact on the ability to successfully obtain necessary financing. Other factors have an impact on risk, early stage development and long-term goals.

Lengthy Development Periods

Developing any new drug, biologic, or medical device for use in humans can be a long, arduous process. Some studies indicate that the creation of a single new drug may involve the research and review of thousands of substances, a ten to fifteen year development and testing process, and a total investment of several hundred million dollars.^{3,4} The timeline is dictated by the nature of developing complex technologies and the extensive regulatory and research requirements that apply to these technologies.

The discovery of deoxyribonucleic acid ("DNA"), the molecule carrying the genetic code for all forms of life, laid the foundation for revolutionary biotechnology advancements. Nevertheless, it took fifty years to develop the computing tools and techniques required to complete the mapping of the human genome in 2003. The complicated manufacture of new biotechnology products often requires the development of new technologies involving ultra-clean production facilities, component assembly techniques and other processes critical to the success of the product. The technology is often complicated and, by virtue of its originality, creativity and inventiveness, can take years to develop.

The regulatory process to bring new technologies to market also presents a daunting challenge to the biotechnology company. According to Standard & Poor's, of the 10,000 substances reviewed and considered for drug development, approximately 250 make it to preclinical laboratory and animal testing.⁵ Within five or more years, approximately five of those substances enter clinical testing on humans, a testing process involving three distinct phases and several more years of study. A Phase I study to determine a drug's safety and level of dosage takes approximately one to two years and involves one hundred to two hundred human volunteers. Phase II involves several hundred human

volunteers and a two to three year process designed to identify potential side effects and the drug's efficacy. Phase III involves testing the drug on several hundred to several thousand volunteers in the hopes of identifying potential adverse reactions and long term effects of the drug. At the end of ten to fifteen years, the Food and Drug Administration ("FDA") will finally approve one drug for the marketplace.

Having the most thorough biotechnology product approval and regulatory process in the world adds significant time and expense to the commercial development of the product. Investors, of course, want to see returns as soon as possible. Typically, there is an expectation of returns or the ability to employ a desirable exit strategy somewhere within three to seven years of investment. As a result, certain products with long development periods may only be undertaken by large, well-established biotechnology and pharmaceutical companies or by partnering with these companies.

The promise and potential of these new products, however, appears to be overcoming investment timidity. Research and development ("R&D") spending in the biotechnology industry segment is among the highest of any U.S. industry group, and it is rising. According to an industry study by Standard & Poor's, R&D spending in the biotechnology industry was \$11.0 billion in 2001, \$12.5 billion in 2002, \$14.5 billion in 2003, and \$10.2 billion through the first half of 2004.⁶ The extreme amount of money required to produce one new product, coupled with a long development period, means investors will have to tie up a substantial amount of capital for a longer period of time. The bottom line is that returns on investment generated by biotechnology companies will need to be higher than those generated from other investments or investors will opt for the other investments.

Reimbursement

The success of many biotechnology products will depend on the ability of the company to secure payment for the product from the insurance companies, health plans and governmental health care programs that provide coverage to the consumer. The ability to sell some products is dependent on an assurance that adequate reimbursement will be available. Obtaining reimbursement can be a time-consuming process. A plan to obtain reimbursement should be established as early as possible for any product that will be dependent on revenue from reimbursement.

Ethical Considerations

In the last 50 years, massive strides in technology have caused an explosion in the development of biotechnology products. The phenomenal advancement in knowledge has also led to deep fears about that knowledge, its potential misuse and ethical considerations scarcely imaginable in the middle of the twentieth century.

One of several examples involves a new form of genetically modified corn, or Bt corn.⁷ This new grain was engineered with a bacterial code that enhanced its ability to repel corn borers and other pests. Sowing Bt corn has the added benefit of reducing the use and

amounts of harmful pesticides required to protect other corn hybrids. But Bt corn has raised genuine practical and philosophical questions such as what are the effects on humans and the environment of products made with Bt corn? These and similar concerns have led many countries to ban the use and production of genetically modified (“GM”) agricultural products.

Stem cell research, cloning and similar cutting edge technologies raise promise, hope and many questions. Some of these questions have led to the development of new laws and regulations governing the use of these technologies, and altering the kinds of biotechnology products that can be produced using these technologies. Fears over the outcome of legislative or regulatory restrictions can have a negative impact on securing financing.

International Law and Import/Export Issues

It may be necessary for a company to introduce a biotechnology product to the global market because of the nature of the product or to generate a sufficient base of revenue to support the costs of development. If so, the company will find itself dealing with a whole new set of challenges. Going into foreign jurisdictions increases the complexity of product development and distribution, particularly in the area of GM foods. International treaties between countries, European Union (“EU”) directives, standards set by the United Nations, country-specific regulations, trade policy, and protectionism all converge to create a complex web of rules for the biotechnology exporter. The governing principle, if there is one, is that biotechnology products will be examined on a case-by-case basis by each country to determine if there is a foreseeable threat to human health, the food supply, or the environment. If a company must be in these markets, financing will be required to endure product testing, multi-agency regulation, and cultural biases against biotechnology, particularly GM foods. Similar concerns arise over importing biotechnology products into the U.S.

Intellectual Property

Intellectual property is fundamental to the financing strategy of a biotechnology company. Among a company’s most valuable assets are the right and ability to develop and exploit existing or new inventions, trade secrets, proprietary information and know-how. To develop an effective financing strategy, a biotechnology entrepreneur must consider the intellectual property it might develop, acquire, or license. It is equally important for the company to develop a thorough knowledge of the competing intellectual property that is or may be owned or under development by other companies or entrepreneurs in the same field. Additionally, before venturing into a discrete area of biotechnology, a company must develop a thorough understanding of government regulations, scholastic research, and information in the worldwide public domain that may have an effect on contemplated developments. The value of existing or proposed intellectual property is contingent both upon the availability of legal protection and upon the immediate and long-term demand for new developments in that area of biotechnology.

Tax and Tax Credits

The tax issues that are relevant to a biotechnology company will typically depend on the stage at which the company is positioned in its life cycle. For example, during its early years, a biotechnology company is likely to make substantial R&D expenditures before it generates significant revenue. The primary tax issues it faces during this period involve identifying and exploiting available tax deductions and tax credits. The Code provides a variety of incentives that may apply to R&D expenditures in the form of both tax deductions and tax credits.

As a biotechnology company progresses in its life cycle, significant tax issues may arise as it commercializes and exploits the patents and technology it develops and owns. These revenue-generating operations will produce another set of tax issues. For example, the decision whether to license or sell a patent may produce fundamentally different tax consequences.

The exit strategy to be used by the company's investors will raise yet another set of tax issues and potential tax liabilities. For example, there are a variety of exit strategies available to investors, ranging from an outright sale of technology to a tax-free reorganization. Each alternative generates different tax consequences, which in turn will have a significant economic impact on the investors.

III. CHOICE OF ENTITY AND CORPORATE LIFE CYCLES

A. Choice of Entity: Determining the Appropriate Business Structure

One of the first strategic financial decisions of a biotechnology business is selecting the most appropriate form of business structure. This choice of entity will affect: how the organization and its owners are taxed; how the organization and the owners may be exposed to or may limit their liability to others; and the ability for the organization to raise capital. Complicating the choice of entity decision is the fact that the optimal form for a start-up stage company may not be the optimal form of entity when the business becomes a mature stage company. Therefore, business owners must consider both the current and the long-term needs of the organization. Altering the form of entity under which a business operates is sometimes difficult from a governance and tax perspective, and sometimes may be accomplished under state law only through a merger or conversion. Consequently, the decision regarding the form of entity must be reviewed carefully and undertaken only after a thorough examination of the short and long term plans of the business.

Types of Ownership – Overview

The primary types of ownership structure include sole proprietorship, general partnership, limited partnership, limited liability partnership, limited liability company, and corporation (both C corporation and S corporation). Each type varies in terms of the formalities required to form the organization, the extent of liability of the owners to others, management and governance requirements, taxation of the organization and its owners and available exit strategies.

The most basic form of business ownership available is the sole proprietorship, which is a business operation owned and managed by a single individual. Very few formalities are required, but the owner is personally responsible for the liabilities of the organization. Similarly, a general partnership can be formed relatively informally between two or more persons intending to carry on a business for a profit. The owners of a general partnership are each personally liable for all obligations of the partnership. In order to limit potential liability of the owners, business owners would need to consider forming a limited partnership (which imposes liability obligations on the general partners but limits the liability of the limited partners), a limited liability partnership (which extends the liability protection to each member of the partnership), a corporation or a limited liability company. A corporation is a separate entity from its owners. Consequently, the owners are generally insulated from liability beyond the capital contributions made to purchase shares of stock of the corporation. The corporation as a separate entity faces additional

taxation, unless a Subchapter S election is appropriately made, in which case the income and expenses of the corporation pass through to the shareholders and profits are taxed at the individual level. The limited liability company is a hybrid which provides members with the liability protections similar to a corporation and the ability to treat the entity, for tax purposes, as a partnership or sole proprietorship.

The chart below summarizes and compares the primary features of each type of business structure:⁸

Sole Proprietorship		
Overview	Business operations are owned and managed by a single individual.	
State or Federal Filings	None required.	
Agreements	Not applicable. Assumed name filing with the Secretary of State if operating under a name different from the owner's name. ⁹	
Limited Liability Protection	None. Owner is personally responsible for all debts of the business.	
Management	Managed by single individual.	
Taxation of Entity and Owners	Income or expenses from the business will be reported on the owner's individual tax return.	
Exit Strategies	Sale of Ownership Interests	Ownership interest is not transferable because no separate interest exists.
	Asset Sales	Sole proprietor may sell the assets of the business. No approvals are required from anyone other than the owner. Gain or loss will be recognized on the owner's individual tax return.
	Mergers	Not available for sole proprietorship.

General Partnership	
Overview	Formed upon an “association of two or more persons to carry on as co-owners a business for profit.” ¹⁰ Because no written agreement is required, a general partnership could be formed unintentionally.
State or Federal Filings	None required. Assumed name filing must be made with Secretary of State if partnership operates under any name other than names of individual partners. ¹¹
Agreements	Many partnerships enter into a written partnership agreement that addresses issues such as: the allocation and distribution of profits and losses; the duties, responsibilities and activities of the managing partner and the other partners; the capital contributions of each partner; the methods for resolving management disputes; and the basis for removing a partner.
Limited Liability Protection	None. Owners are each personally liable for all obligations of the partnership. ¹² The potential liability of each partner is unlimited, regardless of the partner's investment in the partnership or whether the partner was involved in, or consented to, the events giving rise to the liability.
Management	Decentralized management. The partners are entitled to make decisions on matters affecting partnership business (generally by majority vote, but sometimes, unanimous approval is required). ¹³ The right to share in decision-making process can make the management of the partnership cumbersome. As a result, the partnership agreement may centralize some management decisions in a management committee or other smaller group of partners.
Taxation of Entity and Owners	Partnership pays no federal income tax. The income or loss of the partnership is included on each partner's tax return and each partner is required to pay the associated taxes regardless of whether distributions have been made to the partner. Partners are entitled to an equal profit distribution unless the written partnership agreement revises the distribution amounts.

Exit Strategies	Sale of Ownership Interests	<p>A partner is entitled to transfer his or her share of the partnership's profits and losses and his or her right to receive distributions.¹⁴ The right to participate in the governance of the partnership and certain other rights are not transferable.¹⁵ The exchange or termination of interests in a partnership may cause the partnership to dissolve. The transfer of a partner's financial rights will not generally trigger dissolution of the partnership under state law.¹⁶ Partnership agreements generally contain provisions relating to the transfer of interests that may supersede these statutory provisions, including votes required for transfer and providing other partners a right to purchase the interests prior to transfer. When a partner sells his or her ownership interest, he or she will often be required to recognize gain or loss on the sale.</p>
	Asset Sales	<p>Subject to contrary provisions in a partnership agreement, property held may be transferred to a third party by means of an instrument of transfer executed by any partner.¹⁷ If the property is partnership property held in the name of an individual partner, that person generally must assign the property.¹⁸ Gains and losses on sales of assets at the partnership level will generally not be subject to tax at the entity level, but will be passed through to the partners or members for recognition.</p>
	Mergers	<p>A general partnership may engage in a merger with another general partnership, a limited liability partnership or a limited partnership.¹⁹ In order to effect the merger, the parties must enter into a plan of merger that, among other things, sets forth the terms of the merger. The merger plan must be approved by all parties to the agreement, and requires unanimous agreement of the partners or other vote as required under the partnership agreement.²⁰ Following the merger, the surviving partnership must file a statement of merger with the Secretary of State setting forth certain terms of the merger.²¹</p>

Limited Partnership	
Overview	Consists of two type of partners: general partners and limited partners.
State or Federal Filings	File a certificate of limited partnership with the Secretary of State. ²² Name must contain the phrase “limited partnership” or the abbreviations “LP” or “L.P.” ²³ Required to make an annual filing with the Secretary of State. ²⁴
Agreements	Same as General Partnership.
Limited Liability Protection	Partial. General partners are personally responsible for all debts and obligations of the partnership, ²⁵ unless they limit their exposure through a “limited liability limited partnership.” Limited partners do not have the right or power to act for or bind the limited partnership ²⁶ and limited partners are not personally responsible for the obligations of the partnership even if the limited partner participates in management and control of the partnership. ²⁷
Management	General partners are vested with the management responsibility and control and if there is more than one general partner, the decisions are made by a majority vote of the general partners. A unanimous vote of all partners is required to amend the partnership agreement, amend the certificate of limited partnership and to sell or dispose of substantially all of the partnership assets unless the limited partnership agreement revises these requirements. ²⁸
Taxation of Entity and Owners	Limited partnership pays no federal income tax. The income or loss of the partnership is included on each partner's tax return and each partner is required to pay the associated taxes, regardless of whether distributions have been made to the partner. Partners are entitled to receive distributions based upon the value of their respective contributions to the entity. ²⁹

Exit Strategies	Sale of Ownership Interests	<p>Partners in a limited partnership may only transfer their rights to receive distributions.³⁰ This transfer will not constitute an event that would disassociate the partner or cause dissolution of the partnership under state law.³¹ However, a transferee's rights need not be recognized by the limited partnership until the limited partnership receives notice of the transfer. A person receiving an interest in the limited partnership may obtain full rights of a limited partner only after receiving consent of all partners.³² Persons acquiring partnership interests may also be required to assume certain known liabilities of the transferor.³³ Limited partnership agreements generally contain provisions relating to the transfer of interests, such as votes required for transfer and providing other partners a right to purchase the interests prior to transfer, that may supersede these statutory provisions. When a partner sells his or her ownership interest, he or she will often be required to recognize gain or loss on the sale.</p>
	Asset Sales	<p>Unless the partnership agreement provides otherwise, a sale by a limited partnership of all or substantially all of the limited partnership's assets will require the consent of each partner to the limited partnership.³⁴ Gains and losses on sales of assets at the partnership level will generally not be subject to tax at the entity level but will be passed through to the partners or members for recognition.</p>
	Mergers	<p>May merge with an entity pursuant to a plan of merger properly adopted by the constituent entities.³⁵ The plan of merger must be approved by all of the partners of a limited partnership or other vote as set forth in the partnership agreement. Following approval of the plan of merger, articles of merger must be filed by all of the entities prior to the merger.³⁶</p>

Limited Liability Partnership (“LLP”)		
Overview	Extends limited liability protection to each member of the partnership.	
State or Federal Filings	File a statement of qualification with the Secretary of State. ³⁷ Name must contain the term “limited liability partnership” or abbreviations “LLP” or “L.L.P.” ³⁸ Required to make an annual filing with the Secretary of State. ³⁹	
Agreements	Same as General Partnership.	
Limited Liability Protection	Partners in an LLP are relieved of liabilities arising from a wrongful act or omission of other partners or for any other debts of the LLP. ⁴⁰ Each partner's personal assets are shielded from liabilities arising in the course of the LLP's business or obligations from acts or omissions of other partners or employees of the partnership.	
Management	Same as General Partnership.	
Taxation of Entity and Owners	Same as General Partnership.	
Exit Strategies	Sale of Ownership Interests	Same as General Partnership.
	Asset Sales	Same as General Partnership.
	Mergers	Same as General Partnership.

Limited Liability Company (“LLC”)	
Overview	Considered a hybrid form of entity. Provides members with liability protections similar to a corporation and the ability to treat the entity, for tax purposes, as a corporation, partnership or in the case of a single member LLC, a sole proprietorship.
State or Federal Filings	File articles of organization with the Secretary of State. ⁴¹ Name of company must contain the phrase “limited liability company” or abbreviations “LLC” or “L.L.C.” ⁴² Required annual filing with the Secretary of State. ⁴³
Agreements	Usually use “bylaws” (often referred to as “operating agreements”) as an additional agreement to govern the management and financial rights of the entity and its members. Many LLCs use a “member control agreement” to address issues otherwise reserved for the articles of organization. Because this agreement does not need to be filed with the Secretary of State, many LLCs include very few items in their articles of organization and include most provisions relating to the LLC's management and operation in the member control agreement.
Limited Liability Protection	Members of the LLC are not personally liable for debts or obligations of the LLC merely as a result of being a member. ⁴⁴ Members are typically only liable for payment of their capital contributions to the LLC.
Management	Management of the LLC is similar to the management of a corporation. Management is vested in a board of governors that is elected by the members and is responsible for the overall management of the entity. Required to appoint two officers to oversee the day-to-day operations of the business, a chief manager and a treasurer. ⁴⁵
Taxation of Entity and Owners	May be treated as a partnership, an association, or if the LLC has only one member, a disregarded entity. If a disregarded entity, the sole member must include all of the company's income and loss on his or her personal tax return.

Exit Strategies	Sale of Ownership Interests	<p>Membership interests in an LLC are comprised of financial rights and governance rights.⁴⁶ Except as otherwise required under the LLC's articles, bylaws or member control agreement, members may generally transfer the portion of their membership interests constituting financial rights.⁴⁷ The assignment of financial rights will not cause a dissolution of the LLC under state law.⁴⁸ The ability to assign governance rights in an LLC is much more restricted. Members may generally assign their governance rights to other members of the LLC without approval. A transfer of governance rights (or a complete membership interest) to a person who is not currently a member of the LLC, however, requires unanimous written approval of all members.⁴⁹ These provisions may be revised pursuant to the LLC's articles or member control agreement. When a partner sells his or her ownership interest, he or she will often be required to recognize gain or loss on the sale.</p>
	Asset Sales	<p>A sale of substantially all of the assets of an LLC, not occurring in the ordinary course of business, must be approved by a majority vote of the board of governors.⁵⁰ Following board approval, the LLC must receive approval of a majority of the outstanding interests held by its members. Gains and losses on sales of assets will generally not be subject to tax at the entity level but will be passed through to the partners or members for recognition.</p>
	Mergers	<p>May merge or enter into an exchange with another LLC, a corporation, or a cooperative.⁵¹ An LLC must prepare a plan of merger (or exchange) and each party to a merger, and the acquired company in an exchange, must approve the plan of merger. LLCs participating in a merger, or being acquired in an exchange, must have the plan approved by a majority of the board of governors.⁵² Following approval by the board, a majority of the LLC's members must also approve the transaction. Following the member vote, articles of merger or exchange are filed with the Secretary of State.⁵³</p>

“C” Corporation	
Overview	Separate legal entity owned by one or more shareholders. The corporation, and not its shareholders, is generally responsible for its own debts and obligations.
State or Federal Filings	File articles of incorporation with the Secretary of State. ⁵⁴ Name of the corporation must contain one of the following words or phrases: “corporation, “incorporated,” limited,” “company” or an abbreviation thereof. ⁵⁵
Agreements	Certain provisions are required to be in the articles of incorporation such as the corporate name and address, number of authorized shares, and incorporator’s name and address. Other items, if not included in the articles, will be governed by the default statutory provisions and include: cumulative voting rights; that all directors must sign written actions of the board; and preemptive rights for shareholders. Most have bylaws that contain management and operation provisions including election of directors, appointment of officers, meetings of members and directors, and dissolution of the corporation. May also establish rules relating to transfers of interests in the corporation in a shareholder control agreement or buy-sell agreement.
Limited Liability Protection	Shareholders are generally exempt from personal liability for the corporation's debts and, therefore, only risk losing the amount of their investment in the corporation. ⁵⁶ Courts may, however, hold shareholders personally liable for corporate obligations (i.e., “pierce the corporate veil”) if the corporation acted as an “alter ego” of its shareholders. Examples of factors considered by courts include: adequacy of capitalization; observance of corporate formalities; payment of dividends; solvency of the corporation at the time of the transaction; siphoning of funds by the dominant shareholder; function of other directors and officers; presence of corporate records and whether the corporation exists as a façade for individual dealings. ⁵⁷ Shareholders may also be liable for repayment of distributions that were made in a manner not permitted by state statute. For example, Section 302A.551 of the Minnesota Statutes prohibits a distribution of funds to shareholders to the extent the distribution would cause the company to become unable to pay its debts in the ordinary course after making the distribution. ⁵⁸

Management	Management policy of a corporation is governed by a board of directors. ⁵⁹ The board is typically elected by the shareholders. The board appoints at least two officers to run the day-to-day operations: Chief Executive Officer (“CEO”) and Chief Financial Officer (“CFO”). ⁶⁰	
Taxation of Entity and Owners	Taxed under Subchapter C of the Code. Recognizes income and expenses at the corporate level with the corporation paying a tax on income at the applicable corporate income tax rate. ⁶¹ Dividends are generally taxable to shareholders. ⁶² Results in “double taxation” because income received by the corporation is taxed at the corporate level and any profits remaining after taxes are then available for distributions as dividends that are taxed again as personal income to the shareholders.	
Exit Strategies	Sale of Ownership Interests	A transfer of stock by a shareholder does not have a significant effect on the entity and does not generally need to be approved by other shareholders or the corporation’s board of directors. A corporation may, however, impose restrictions on the transfer of its stock in the articles of incorporation, the bylaws, a shareholder resolution or agreement among shareholders. The placement of restrictions on transferability may be used for small corporations to ensure ownership is restricted to a select group of persons. When a shareholder sells stock in a corporation, the shareholder will generally recognize a capital gain or capital loss on the stock sale.
	Asset Sales	Required to receive approval by a majority of the board of directors and a majority of the shareholders to approve a sale of substantially all of the corporation’s assets, unless otherwise provided in the articles or bylaws. ⁶³ Upon the sale of substantially all of the assets, the corporation will recognize a gain or loss at the corporate level. ⁶⁴ Upon distribution of the proceeds, shareholders will also recognize gain or loss on the distribution. ⁶⁵
	Mergers	May merge or enter into an exchange with another corporation or LLC. ⁶⁶ The board of directors must approve, by a majority vote, a plan of merger relating to the transaction and must submit the plan for approval at a special shareholder meeting. ⁶⁷ At the meeting, the plan of merger or exchange must be approved by a majority of the members entitled to vote. The merger will be effective upon filing of the articles of merger with the Secretary of State or upon a later date indicated in the filing. ⁶⁸

“S” Corporation		
Overview	Same as C corporation except that S corporations have different tax treatment and are limited as follows: they may not have more than 100 shareholders; the shareholders must be individuals; the shareholders must be residents of the U.S.; and all shares issued by the corporation must be of the same class. ⁶⁹	
State or Federal Filings	If the corporation meets the statutory requirement under Subchapter S of the Code, the shareholders may elect to be taxed as an S corporation. This filing must be made within 15 days after the third month of the corporation's tax year. ⁷⁰	
Agreements	Same as C corporation.	
Limited Liability Protection	Same as C corporation.	
Management	Same as C corporation.	
Taxation of Entity and Owners	An S corporation files a tax return to report its income and expenses and is generally not taxed separately. Income and expenses of the S corporation “pass through” to the shareholders in proportion to their ownership interest in the corporation and profits are taxed to the shareholders at their individual income tax rates. ⁷¹	
Exit Strategies	Sale of Ownership Interests	Same as C corporation. S corporations often place restrictions on stock transfers so that a transfer will not inadvertently jeopardize the firm’s S corporation status. When a shareholder sells stock in an S corporation, the shareholder will generally recognize a capital gain or capital loss on the stock sale.
	Asset Sales	Same approval requirements as C corporation. Any gain or loss on a sale of substantially all of its assets will be passed to its shareholders. ⁷² A gain will increase the shareholders basis in the stock and a loss will decrease the shareholder’s basis in the stock. However, because the shareholders’ basis in the shares is adjusted for any gain or loss on the asset sale, a shareholder should not be subject to an additional tax or gain when the proceeds from the sale are actually distributed.
	Mergers	Same as C corporation.

Effect on Financing

The type of business structure not only affects how the business will be formed, managed, and taxed, but it will also affect the investor's analysis of whether or not to invest or lend to the entity. The following are just a few examples of how the form of entity affects the financing alternatives available to the business:

- General partnerships and limited partnerships generally cannot effectively issue public securities to raise capital because the investment community typically wants public offerings completed by C corporations.
- S corporations cannot issue public securities because they can have no more than 100 shareholders and those shareholders generally must be individuals.
- Traditional bank debt is not typically made available to general partnerships because of the pass through nature of the personal liability for the general partners. Instead, bank loans will usually be made to the individual general partners who then advance the funds to the partnership.
- Venture capitalists prefer to invest in C corporations. This is because C corporations: are most likely to complete an initial public offering ("IPO") (upon which the venture capitalist will accomplish its exit strategy); are eligible for tax-free reorganizations; and provide flexibility for shareholders to transfer their shares.

B. Corporate Life Cycles

This Guide uses certain terms that are intended to describe the life cycles of the biotechnology company. Corporate life cycles are the generalized descriptions that are commonly accepted to describe the historical stages of an entity. The stages defined below are commonly understood in the business/finance community and will be used throughout this Guide. However, the definitions of these terms are not congruent with any similar terms used in any Statements of Financial Accounting Standards.

Start Up Stage

This is the earliest stage of any business entity. Typically, one has just started a business and there are expenses but no income. This is the riskiest stage in a company's life cycle and as a result, available financing options are extremely limited. The financing alternatives available to a start-up company are one's own personal bank accounts, friends and family, and possibly angel investors. The capital structure of the start-up company will not be complex. Instead, it will typically consist solely of common stock.

Development Stage

The development stage occurs subsequent to the start-up stage and is characterized by the first steps toward development and commercialization of a product. Expenses still exceed

revenues and technology risk remains high. There are ongoing efforts to refine the company's technology and intellectual property. Preliminary business plans begin to take shape and clinical studies of the product are being undertaken. The capital structure of a development stage company is all private. Financing will continue to occur through the personal resources of the founders, friends and family and angel investors. Venture capital ("VC") financing may occur during the development stage and can at times be substantial.

Early Commercialization Stage

This stage is characterized by declining product risks and declining technology risks. The refining of the product is substantially complete and the firm begins to generate revenues from the product. Notwithstanding, expenses continue to exceed revenues. The overriding concern at this stage is usually product acceptance and market penetration. Here, angel investors, venture capitalists and strategic investors are typical financing sources.

Growth Stage

As the name indicates, this stage is characterized by growth of the company resulting from product success in the market. The company is said to be gaining "traction." At this stage, the company typically moves from negative to positive cash flow with revenues continuing to grow. In addition to the financing alternatives already made available, the growth stage company becomes more attractive to a wider range of venture capitalists and strategic investors and may tap the public markets.

Mature Stage

The company has been successful for several years, probably has several product lines and is publicly traded. Mature stage companies have access to bank debt and can readily go to the public markets for equity. Mature stage companies accelerate their growth through mergers and acquisitions.

Comment

Remember, the preceding descriptions are generalizations and exceptions can occur. For example, a company would probably have access to venture and public capital markets as a start-up or development stage company if it developed the cure for cancer. Arguably, one might say that developing the cure for cancer would immediately push the company through the start-up, development and early commercialization stages, thereby depositing the company in the growth stage. In any event, there are no hard and fast rules that dictate when a company is deemed to be at a particular stage. Furthermore, some writers and analysts may use additional stages or combine some of the stages we have described. Notwithstanding, these definitions are more often than not correct, and are the definitions we will use in describing the financing alternatives in this Guide.

IV. BIOTECHNOLOGY FINANCE OPTIONS

A. Introduction

There are many financing alternatives available to the biotechnology company. The selection and availability of any alternative is a function of the life cycle of the company, its form of entity, the various factors presented in this Guide along with the general economic, societal and cultural environments in which the company operates. This section discusses the various financing alternatives available to the biotechnology company and presents them in the order typically encountered as the company matures.

B. Private Capital Formation

Introduction

Private capital formation typically refers to raising equity capital from private individuals and institutions rather than the public equity capital markets. The rules and regulations applicable to fundraising in the private capital arena tend to be more flexible and the terms of transactions are more negotiable than those in the public capital markets. For instance, private investors typically have substantial latitude in negotiating the terms of their investment directly with the company, and the level of regulatory involvement and oversight in the offering process is typically minimal. Notwithstanding the relative lack of regulatory hurdles, state and federal securities laws still play a significant role in all private capital formation. As a result, we begin our discussion of private capital formation with an overview of securities laws, followed by a discussion of seed round financing and finish with VC financing.

Securities and Registration Concerns

Federal and state securities laws have an impact on every type of financing option available to the biotechnology company. The securities laws not only govern mature publicly traded companies, but also affect the very small start-up company that seeks financial contributions from friends and family members. Failure to comply with securities laws can result in civil liability and, in more egregious cases, criminal penalties for the company, its directors and officers.

There are two fundamental rules that directors and officers need to remember regardless of the size of their company. The first rule is that when someone invests in a company, that

person is purchasing a “security.” While it is generally understood that common stock, preferred stock, stock options and stock warrants are all securities, the term “security” is actually much broader in scope and has been interpreted to encompass any investment vehicle that provides the holder with the right to participate in the success (or failure) of an enterprise. The statutory definition of “security” includes: “. . . any note, stock, treasury stock, bond, debenture, evidence of indebtedness, certificate of interest or participation in any profit-sharing agreement, collateral-trust certificate, pre-organization certificate of subscription, transferable share, investment contract, voting-trust certificate of deposit for a security, fractional undivided interest in oil, gas or other mineral rights, any put, call, straddle, option, or privilege on any security, certificate of deposit, or group or index of securities (including any interest therein or based on the value thereof), or any put, call, straddle, option, or privilege entered into on a national securities exchange relating to foreign currency, or, in general, any interest or instrument commonly known as a “security,” or any certificate of interest or participation in, temporary or interim certificate for, receipt for, guarantee of, or warrant or right to subscribe to or purchase, any of the foregoing.”⁷³

The second fundamental rule is that securities require registration at both the federal and state levels unless an exemption from registration under the securities laws is available. A company that intends to access the public capital markets will be required to register its securities. Registration is a time-consuming and expensive process requiring extensive commitments from both the company’s management and outside professionals. In addition, investors in publicly traded securities typically require that the issuer have a successful operating history, growth in revenues, and market acceptance of its product. These hurdles typically discourage start-up, development and early commercialization stage companies from pursuing a registered offering. Furthermore, the ongoing reporting requirements of a publicly traded company add a material continuing expense to the operations of the company. Consequently, biotechnology companies in their start-up, development and early commercialization stages regularly conduct private offerings of securities under various exemptions to avoid the extremely high costs of registration and to avoid the work and expense associated with the ongoing reporting requirements mandated after registration.

Exemptions from Registration

The types of exemptions from registration found under federal and state securities laws vary according to the number and sophistication of investors, the aggregate amount to be raised in the offering, how and where the securities are offered and sold, and several other factors. The number and nature of different exemptions available make it impractical, if not impossible, to comprehensively address the subject in this Guide. The following discussion, therefore, serves only to highlight and summarize a few of the exemptions that are most commonly used by an early stage biotechnology company, and does not describe all of the conditions and restrictions associated with those exemptions. Any company contemplating the offer or sale of its securities pursuant to an exemption from registration is cautioned to consult with an attorney experienced in securities law to ensure the availability of and compliance with an exemption.

Federal Exemptions

Exemptions from registration are available under the federal securities laws for a variety of private securities offerings. When structuring such an offering, it is important to contemplate which exemption best suits the short-term and long-term capital raising goals of the company and to remember that a securities offering may need to be tailored to fit within the requirements of an exemption.

Regulation D of the Securities Act of 1933, as amended (“Securities Act”), is a collection of rules that govern the limited offer and sale of securities without registration. This is a particularly useful set of exemptions because, unlike most other exemptions, Regulation D provides a “safe harbor” for the company’s securities offering, meaning that the company is afforded protection from federal registration requirements if it complies with Regulation D’s requirements. Regulation D includes three exemptions, which are summarized below.

- **Rule 504** provides an exemption for offerings up to \$1 million during the twelve months before the start of and until the completion of the offering.⁷⁴ Purchasers need not meet any suitability test and there is no limit on the number of purchasers to whom the offerer can sell.
- **Rule 505** provides an exemption for offerings up to \$5 million during the twelve months before the start of and until the completion of the offering.⁷⁵ Sales may be made to an unlimited number of accredited investors (defined below), but may not be made to more than 35 non-accredited investors.
- **Rule 506** permits a company to sell an unlimited dollar amount of securities.⁷⁶ Sales may be made to an unlimited number of accredited investors, but may not be made to more than 35 non-accredited investors, each of whom must be a “sophisticated investor.”⁷⁷

For the purpose of Rules 505 and 506, an “accredited investor” includes:

- certain types of financial institutions such as banks, broker-dealers and investment companies;
- entities with total assets in excess of \$5 million (not formed for the purpose of investing in the offering);
- any director, executive officer or general partner of the company;
- any natural person whose net worth (alone or jointly with spouse) exceeds \$1 million;
- any natural person whose individual income exceeds \$200,000 (or jointly with spouse, \$300,000) for each of the past two years, and is expected to exceed that amount in the current year;

- any trust with assets greater than \$5 million that are managed by a sophisticated trustee (and not formed for the specific purpose of investing in the offering); and
- any entity in which all of the equity owners are accredited investors.⁷⁸

The definition of accredited investor is important because Rules 505 and 506 place a limit on the number of non-accredited investors to whom a company can sell securities. Accredited investors are considered to have sufficient financial experience and resources to effectively protect their own interests. As a result, they are not deemed to need the same level of protection as non-accredited investors, who are deemed to be less financially sophisticated and in need of the additional protections afforded by the securities laws. The company must, however, reasonably believe the investor is accredited. To ensure that it has grounds for its reasonable belief, the company is advised to require each investor to certify his, her or its status as an accredited investor prior to selling securities to that investor.

Another commonly used exemption is found under Rule 701, which provides an exemption from registration for offers or sales made to a private company's employees, directors and consultants pursuant to written compensatory benefit plans or contracts.⁷⁹ For an early stage company where cash resources are limited, this exemption provides the company with the opportunity to compensate employees with stock options, which is further discussed in the section below titled "Management Equity Incentive Compensation."

The intrastate exemption provides an exemption from registration for offerings made exclusively to persons residing within the state in which the company is incorporated and has its principal place of business.⁸⁰ This exemption places no limitation on the number or type of investors that a company can sell to or the amount that can be raised. It does, however, place restrictions on the resale of the securities sold under the exemption. That is, they may only be resold to residents of that state for the nine-month period after the date of the last sale made by the company in the offering. While this exemption can be useful to very small, closely-held companies, it is less useful for offerings to a larger number of investors because the exemption is destroyed if any of the securities end up in the hands of someone outside of the state during the restricted period.

Regardless of the exemption a company chooses, extreme care must be taken to structure the securities offering because the exemption can easily be lost if the company fails to comply with the exemption's requirements. For example, a sale to just one non-qualifying investor, even if unintentional, can have the effect of destroying the exemption being relied upon for the entire offering. Once an exemption is destroyed, all offers and sales that were purported to have been made under the "failed" exemption will be deemed to be in violation of the registration requirements unless some other exemption can be found that applies to the offering. In addition to enforcement actions that may be brought by federal and state regulatory agencies as a result of such violations, any investor who purchased a security that was sold in violation of securities laws has the right to rescind the transaction and to receive a refund of the purchase price from the company.

State Exemptions

It is important to understand that in addition to complying with federal securities laws, compliance is required with the securities laws of each state in which the company intends to offer and sell securities. State securities laws, often referred to as “blue sky laws,” vary widely by state, not only as to the types of exemptions available, but also as to the requirements necessary to secure a particular exemption.⁸¹ For example, where one state may require the company to make a pre-sale filing and pay a fee in order to secure an exemption for the offer and sale of securities to a company’s existing shareholders, another state may deem an offer or sale to a company’s existing shareholders to be a “self-executing” exemption, meaning that no filing or fee is required in order to secure the exemption.

Because of the vast number of and variations in exemptions under state blue sky laws, a comprehensive discussion of the available exemptions is not possible here. However, there are some general categories of exemptions that are found in most states, namely: limited offering exemptions, isolated sales exemptions and institutional investor exemptions.

Limited offering exemptions in most states are patterned after the Uniform Limited Offering Exemption (“ULOE”), which was an attempt by state securities regulators to introduce some uniformity to the blue sky laws. The ULOE is intended to correspond with the Rule 505 and 506 exemptions under federal securities laws, and serves to simplify a company’s coordination of federal and state exemptions for a Rule 505 or 506 offering. While most states have adopted the ULOE in some form, the terms and conditions required to secure the exemption vary widely from state to state.

Isolated sales exemptions generally permit a company to make offers and sales to a very small number of purchasers in the state without undertaking a state registration. Most states have some form of isolated sales exemptions, and many do not require the company to make a filing or pay a fee. For example, Minnesota provides an exemption for isolated sales of securities to non-accredited investors, if the company does not make more than ten sales under this exemption in the state of Minnesota during any twelve-month period and complies with other conditions enumerated by the exemption.⁸²

Institutional investor exemptions permit a company to make offers and sales to “institutional investors” without undertaking a state registration. The definition of institutional investor may vary from state to state, but generally will include banks, savings institutions, trust companies, insurance companies, investment companies and other financial institutions or institutional investors. Some states further define “institutional investors” to include accredited investors, as defined by Regulation D of the Securities Act. There are generally no limits on the number of institutional investors a company can sell to and, more often than not, there are no filing requirements at the state level in order to secure this exemption.

In summary, the key for any company when structuring an offering is to be aware of each state in which it will offer and sell securities and to carefully examine the blue sky laws of those states. Failure to comply with state laws can, like federal laws,

subject the company and its officers and directors to civil liability and criminal penalties.

Integration

Another factor that must be carefully considered when attempting to secure an exemption from registration is the concept of integration. Integration imposes limits on an offering by requiring that a sufficient amount of time lapse between the completion of one offering and the beginning of another. It serves to prevent a company from stringing together a series of purportedly “exempt” offerings as a way to evade registration requirements. Integration occurs when two or more separate offerings that may otherwise appear to be exempt are combined and viewed as one continuous offering. For example, integration of a \$1 million Rule 504 offering with a \$5 million Rule 505 offering will destroy both exemptions because the aggregate offering amount of \$6 million exceeds the limitations imposed by Rules 504 and 505. Because most early stage companies seek additional capital on a fairly regular basis, careful planning is required to ensure that the exemptions a company relies upon will not prevent the company from raising additional capital in the near future.

Anti-fraud Considerations

All securities transactions, even those that are exempt from registration requirements, remain subject to the anti-fraud provisions of the federal and state securities laws. Those provisions hold companies and their officers and directors responsible for false, misleading or incomplete statements made in connection with the offer or sale of securities. Federal and state securities laws are designed to ensure that accurate and complete information regarding a company and its financial status and business prospects are provided to potential investors in order to promote efficient capital markets. A misrepresentation or omission of a material fact regarding a security offering is considered securities fraud, even though such behavior may not rise to the level associated with common law fraud. A “material fact” includes any information, whether about the company, its business or the securities being sold, that a reasonable investor would deem an important factor in deciding whether or not to invest in the company. As discussed earlier, civil liability and criminal penalties can be imposed on the company, its directors and officers if the anti-fraud and disclosure rules are not carefully observed.

Disqualification Provisions

In some circumstances, companies may be prohibited from relying on certain exemptions as a result of prior bad acts. Under the “bad boy” provisions, absent a showing of good cause, an exemption will not be available for an offering if the company or one of its officers, directors, 10% security holders, affiliates or other representatives have engaged in certain activities, been convicted of certain crimes or been the subject of injunctive orders relating to violations of the securities laws.⁸³ Rule 505 is one example of an exemption where the bad boy disqualification provisions

apply. Given the serious consequences that can result, companies are encouraged to take adequate precautions to ensure that the individuals with whom they associate will not subject the company to a bad boy disqualification.

Restrictions on Resale of Securities

When securities are sold pursuant to an exemption from registration, the securities will be subject to certain resale restrictions and the shareholder may be forced to hold the securities indefinitely, unless the shares are registered under federal and state securities laws or a sale can be conducted pursuant to an exemption from registration. This is important for both the company and the potential purchaser to understand since resale restrictions will affect the purchaser's decision to invest because an investment in unregistered securities will not be a liquid investment.

Seed Rounds: Initial Financing Sources

Occasionally, an entrepreneur with a strong track record can obtain significant initial financing from institutional sources without a comprehensive business plan or product. Most entrepreneurs and start-up stage companies, however, must rely on less formal, private sources for their initial financing or "seed financing." For biotechnology companies, seed financing is generally raised through three sources: the entrepreneur's personal funds (bootstrapping); friends and family; and angel investors.

Personal Funds: Bootstrapping

Bootstrapping means to promote and develop by use of one's own initiative and work without reliance on outside help.⁸⁴ Everyone has heard the tales of entrepreneurs "maxing out" credit cards, liquidating savings accounts, obtaining home equity loans and cashing in retirement accounts to fund their business ventures. While not necessarily a desirable route, the reality is that most small businesses are started with nothing more than the entrepreneur's own money, hard work and debt. If the company survives the start-up stage and eventually attracts interest from the institutional community, then bootstrapping is actually seen as positive, since institutional investors believe that founders and management who have a significant personal stake in the company will be more committed to continuing to grow the company.

Friends and Family

The aptly-named "friends and family" round of capital is critical to most start-ups, but is typically one of the hardest series of transactions for a start-up to manage. Obtaining financing at this stage usually involves the entrepreneur begging friends and family for financial assistance. The existence of personal relationships between the entrepreneur and the funding source, however, can complicate both business and personal matters. A significant problem with this form of financing is that a friend or family member often invests in the entrepreneur rather than the business and, therefore, may not be able to objectively assess all of the risks associated with an investment in a start-up

company. Additionally, the friends and family round is frequently conducted with less formality than other financing rounds, and parties find themselves making handshake deals that are later open to varying interpretations.

Regardless of whether the funding is in the form of a loan or an equity investment, the key is to be sure that the transaction is documented in a manner that clearly outlines the specific terms of the funding and, if a loan, describes how and when it will be repaid. Taking the time to document a transaction, particularly with the assistance of an attorney, will not only help preserve personal relationships but will also better prepare the company for future financing rounds where an accurate understanding of the company's debt and equity structure will be a critical component to the due diligence of any subsequent lender or institutional investor.

Angel Investors

After tapping one's own personal resources and the resources of friends and family, start-up companies continue to need capital to grow their business and develop their technology. VC groups and institutional investors often refuse to invest in early stage companies because those investors generally require their target companies to have a proven product or technology, solid revenues and a potential for rapid and substantial growth. Early stage companies, therefore, often seek out angel investors.

An "angel investor" is usually a high net worth individual who invests his or her own funds in private companies that are operating in their early stages, and is looking for a higher return on an investment than could be earned on more traditional investments. Angel investors generally look for companies that exhibit high-growth prospects, have a synergy with their own business, or compete in an industry in which the angel investor has already experienced success. In addition to objective criteria, angel investors usually invest based on their "affinity" for a company, its founders, and its technology or business activity. In the biotechnology industry, angel investors include other biotechnology entrepreneurs and executives who have been financially successful in the industry and executives from other life sciences industries who can provide expertise to new biotechnology ventures that they perceive to be the next generation of companies in the industry.

In exchange for their high-risk investment, however, angels often demand significant involvement in the business. Companies seeking equity capital from angel investors must welcome outside ownership and, perhaps, the surrender of some level of corporate control. To successfully attract angel investors, a company must be able to provide a realistic exit strategy for them, such as an eventual public offering, redemption of the angel's equity interest, or a sale of the business.

An angel investor should bring more to the company than just money. Ideally, an angel investor will serve as an advisor or mentor to the entrepreneur and provide additional industry relationships and contacts to aid the business. Because companies in the early stages of development have limited resources, they usually cannot engage the services of professional consultants and advisors. The addition of a knowledgeable, entrepreneurial angel investor with relevant industry experience can be an integral part of the company's growth, and can help pave the way for institutional financing rounds.

Because the quality of angels can run the gamut from the sophisticated to the inexperienced, a company should learn as much as possible about an angel investor's background and track record before accepting their investment.

Because of the individual and private nature of their investments, little information and research is available about angel investors as a group. However, a study conducted by the Center for Venture Research at the University of New Hampshire found that approximately 48,000 entrepreneurial ventures received angel funding in 2004, a 24% increase over 2003. Additionally, the number of active angel investors in 2004 was estimated at 225,000 individuals, an increase of 2.5% over 2003. Investments in biotechnology ventures represented approximately 10% of the total number of angel investments in 2004, with healthcare services, medical devices and medical equipment together representing another 16% of the total angel investments. Although the numbers cannot be precisely confirmed, total investment from angels has been estimated to be anywhere from \$20 billion to \$50 billion annually as compared to the \$3 to \$5 billion per year that the professional VC community is estimated to invest.⁸⁵

Preparing for the Next Level of Financing

While seed round financings are essential in any biotechnology company's growth and development, the research, development and product marketing required to successfully commercialize a product will require significant amounts of cash that must almost always come from venture capitalists, strategic investors, and other institutional investors. A necessary part of a company's preparation for institutional rounds will involve the development of a comprehensive business plan and offering documents.

Business Plan

A comprehensive business plan is a prerequisite to any serious fundraising effort with sophisticated institutional investors. The business plan should serve at least two purposes: (1) establish the development, operations and financial plan by which management will operate and grow the business, complete with risk-reducing milestones; and (2) present an overview of the company that directly addresses the specific needs of and is attractive to the institutional investment community.⁸⁶ The plan needs to clearly and succinctly set forth a description of the company's products, goals, finances and management, including reasonable projections. The major complaints about business plans fall into two categories: they contain too much information along with extended unnecessary narratives and result in certain important details becoming lost to the reader; or they are too short and contain little, if any, understandable information. In preparing a business plan, one needs to strike the perfect balance between too much and too little.

The business plan should be prefaced by a one to two page "executive summary" highlighting the following topics, each of which should be set forth in greater detail in the body of the business plan:

- Company description, location, and history;

- Product(s) to be developed and underlying technology;
- Size and growth rate of the market;
- Competition and the company's competitive advantage;
- Management team;
- Financial summary of projected revenues and income, balance sheets and cash flow statements for five years, with monthly detail for the first two years; and
- Amount and structure of the proposed financing.

The majority of the business plan should focus on issues institutional investors are most interested in: the size and growth rate of the market; targeted customers; competitors and the competitive advantage of the company; and the background of the company's management team.

Offering Documents

Securities laws arose out of the government's desire to protect investors from companies that fail to disclose adequate and accurate information to investors concerning the company, its business and the securities being sold. What constitutes adequate disclosure depends on a number of factors, including the type of investor being targeted and the exemption being relied upon to offer the securities. For example, in a private offering to a limited number of highly sophisticated accredited investors, disclosure requirements may be more informal and less detailed than in an offering to non-accredited investors under Regulation D, which requires a very specific, heightened level of disclosure. As noted earlier, accredited investors are considered to have a certain level of financial sophistication that enables them to make informed investment decisions, while non-accredited investors are deemed to be less knowledgeable and experienced in financial matters and, therefore, in need of the additional protections that the securities laws afford. In either case, the anti-fraud provisions still apply, but it is clear that one set of disclosures may be less onerous for the company than the other.

In a private offering of securities, disclosure is often provided by means of a private placement memorandum ("PPM"). Although disclosure can vary widely among PPMs, a well-prepared PPM can serve many purposes. In addition to satisfying legal disclosure requirements and serving as a record of the disclosures made to investors in the event of litigation, the PPM can serve as a marketing piece to sell potential investors on the attractiveness of the company as an investment.

A PPM should be provided to potential investors well in advance of their investment decision and be accompanied by the opportunity for the investors to ask questions of the company's representatives. While legal counsel should be consulted as to the level of disclosure required for the particular offering, the following subjects are the important disclosure categories that an early stage company would typically include in its PPM:

The Offering - Includes a discussion of the securities being offered, offering price, payment terms, termination of the offering and any other terms of the purchase.

Risk Factors - Describes the principal factors that make an investment in the offering speculative or risky, including the company's lack of operating history or profitable operations, the company's competition in the marketplace, risks concerning patentability of products or technology and patent protections, the company's current and future financial position and any other information that creates risk for the company's business.

Use of Proceeds - Describes the company's anticipated use of the proceeds from the offering, net of expenses incurred in conducting the offering.

Dilution - Provides the investor with a tabular presentation of prior sales of securities and the dilution of the book value of the current investment, if any.

Management's Discussion and Analysis of Financial Condition and Results of Operations⁸⁷ - Discusses the company's liquidity, capital resources, results of operations and any other information necessary for an understanding of the company's financial condition and changes in financial condition.

Description of Business - Discusses the formation and development of the company, the company's business, including principal products/services, markets and distribution, importance of any patents, trademarks or other intellectual property to the company's business, and any dependence on a small number of customers. Additionally, a discussion of the company's R&D activities (to the extent not confidential or proprietary) should be included.

Management - Provides information about the officers and directors of the company, including biographies, ages and positions with the company. In addition, employment contracts and executive compensation should be described.

Principal Security Holders - Discusses the number of issued and outstanding securities held by management and principal owners.

Description of Securities being Offered - Describes the features and the rights and preferences of the security, or if a debt security, the interest rate, maturity, payment terms and any conversion provisions.

Financial Statements/Projections - Includes financial statements for the previous two fiscal years (preferably audited), and management's projections if they have a reasonable basis and would be important for the reader in making an investment decision.

Other Pre-Institutional Rounds

Between the various forms of seed rounds and any significant institutional investment round, biotechnology companies sometimes find themselves in a situation that requires

them to undertake what we will refer to as a “pre-institutional round.” The pre-institutional round is often necessitated as a result of one or more of the following:

- The biotechnology company underestimates the funding required to achieve the milestones necessary to attract institutional investment (e.g., the company doesn’t have enough cash to amass the level of clinical data VC investors demand to determine that the technology is no longer just a “science experiment”);
- The company fails to control expenses, resulting in a cash burn that runs ahead of its original projections;
- The technology is not delivering on its original promise;
- The company’s original business model is not in current favor with the private capital markets and needs to be revised; or
- The company does not have the right leadership team in place.

Whatever the reason, a company in this state needs to raise funds to enable it to either reach the necessary milestones while sticking to its current course, or to correct its course. In either case, the above listed performance and cash shortfalls are not considered compelling enough to attract new money at a higher valuation. Companies finding themselves in such a situation need to prepare themselves for a potentially painful deal structure.

There are several basic structuring scenarios for a pre-institutional round. The first is to simply sell more common stock at or below the valuation used in the last seed round. This is not particularly inviting to non-institutional investors, who typically have no comfort level in valuing a biotechnology company.

Another approach is to attract more sophisticated angel investors using a “plain vanilla” preferred stock, or a security that has some rights senior to the common stock. Typically, the additional rights of this class of equity security might include:

- liquidation preference - the holders of preferred stock are paid first if the company has to be liquidated;
- dividend preference - the preferred stock will include a dividend that, although probably not payable currently, will be in excess of and paid prior to any common dividends;
- anti-dilution protection - if the assumed value of the company is determined at a later time to have been too high, the conversion price of the preferred stock will automatically be adjusted as a result of the issuance of the new shares at the lower valuation; and
- governance rights - certain corporate actions may only be taken if the holders of the preferred stock approve.

A third scenario is to sell convertible notes that serve as a bridge between the seed rounds and the first sizable institutional round. The assumption underlying this approach is that the investors leading the first institutional round will have the necessary expertise to more accurately value the company. A convertible bridge note offering will often include an automatic conversion feature that will be triggered by the closing of an institutional round of a specified dollar amount (a qualified financing). If the convertible bridge note structure is used, the qualified financing round trigger (dollar amount) should be based on the amount of cash necessary to achieve the company's requisite milestones. Investors in a pre-institutional round, whether they are current investors or new investors, will have to be comfortable that this round is truly a "bridge" to an institutional round, and not just a "pier" to more uncertainty, risk, and financial distress.

Two pitfalls the company must avoid in this situation are: underestimating the amount of cash required to achieve the essential milestones that will attract institutional funding; and establishing terms for the pre-institutional round that may be so negative that they deter future institutional investors or make future investors predicate their investment on a substantial renegotiation of the rights of current investors. Although renegotiation may not appear to be problematic, the renegotiation process can be very contentious. It is not unusual for the current investors, whose economic rights will be dramatically diluted in the recapitalized company, to simply refuse to renegotiate their terms, thereby ensuring that prospective investors will walk away from the transaction. Some examples of terms that can prove difficult for institutional investors include:

- deep conversion discounts to the next round (e.g., convertible bridge noteholders have a right to convert the amount due on the note into the securities issued in the qualified financing round at a conversion rate that is significantly less than the price being paid by the institutional investors in the round);
- terms that require the bridge debt be repaid in full out of the proceeds of the institutional round (investors want to see their money used to grow the company, not retire debt);
- excessive warrant coverage (which can really just be another way of providing a deep discount on the conversion rate);
- terms that result in an overly complex capital structure; and
- terms that leave company management with too little equity in the company or that create perverse economic incentives for management to pursue a course of action that may not be in the best interests of all equity holders (e.g., onerous liquidation preferences that drive management to prefer an IPO rather than an outright sale of the company).

VC Investment

VC is high-risk equity investment that typically has a limited time frame between investment and liquidity, which can be problematic for biotechnology companies because of the significant length of time required to go from concept to commercialization. Venture capitalists are searching for substantially above-average returns through investment and

direct involvement with an early stage company that is developing innovative products or services based on proprietary technology (or other meaningful barriers to entry) that will be offered to a market of significant size and growth potential. The actual execution of this type of investing is far more nuanced and complex than simpler forms of private equity investments.

The Venture Capitalist's Perspective

A common question for developing companies is “what makes a VC investor’s money any different than that of other investors?” The answer is, with the right VC investor, the company receives much more than money. It also receives knowledgeable investors who can make meaningful contributions to the development and growth of the company. In addition, sophisticated biotechnology VC investors have a long-term perspective, a very high tolerance for risk, and the willingness to wait for a number of years to liquidate their investment. VC investors are not passive; they are active partners with entrepreneurs in the management of an emerging business.

The primary focus of a VC investor is to receive a significant return on investment within a limited period of time – typically five to seven years. VC investors are not philanthropists or humanitarians, at least in the context of their investments. Their decision to invest will not be made on the basis of the human impact of a company’s product or service (e.g., how many lives might be saved), but on the probability that an investment will generate sought-after returns for the VC fund. VC investors look for companies with advanced technology and engineering innovations that create lower product costs, performance advances, or new markets. In the biotechnology industry, the focus is primarily on new markets, with a strong secondary focus on driving down costs (e.g., reducing the cost of discovering profitable drugs).

VC investors tend to avoid investing in companies that face certain risks such as dominant competitors, commoditized markets (i.e., a market defined by readily substitutable goods and limited or no price competition), or business models that require significant financial resources to successfully develop and commercialize their products. Unfortunately, significant product development and substantial market entry costs characterize much of the biotechnology industry. Consequently, many VC investors are reluctant to invest in the industry. However, many other VC investors have a growing interest in the industry and some VC firms specialize in the biotechnology arena.

The Entrepreneur's Perspective; Advantages of VC

Many start-ups have no alternative but to borrow based on the entrepreneur’s personal assets and credit. Most early stage companies are unable to borrow from banks until they have a substantial track record of revenues. When an entrepreneur’s personal financial limitations make bootstrapping and borrowing impossible, external equity financing must be pursued. Equity financing is attractive from the standpoint that it is “permanent” capital that does not require repayment on a current basis. It also has the advantage of improving a company’s balance sheet and giving the company enhanced credibility with vendors and customers. In certain instances, an equity investment by a

credible industry insider can provide external validation of a company's technology and business plan. An investment by a prestigious VC firm can provide a "seal of approval."

As previously stated, a successful VC investor will also contribute industry knowledge and expertise. These kinds of contributions can be especially important to the biotechnology company where strategic thinking, industry contacts, marketing guidance and technical knowledge can prove to be as or more valuable than the monetary investment. When appropriate, well-connected investors can help a young company ally itself with a larger established corporate partner who might assist the young business through technology exchanges, distribution assistance, customer agreements or even minority investments.

Another quality that the VC investor brings to the equation is a commitment to business planning with a long-range view. During the Internet bubble, many VC investors, as well as the management of the companies they funded, were focused on quick returns and not on building sustainable businesses. This proved disastrous not only for the VC investors, but also for the many who invested in these ill-advised ventures through the public capital markets. Today, successful VC investors focus on investing in companies that have a long-term orientation, with an intent to build a long-lasting business. This is particularly true in the biotechnology industry, where businesses generally require a significant period of time to commercialize their products and achieve market penetration and profitability.

Understand, however, that accepting a VC investment does not guarantee that the company will receive the above-mentioned benefits. Entrepreneurs and company management will experience the disadvantages of VC (discussed below) if they do not undertake the same level of due diligence and analysis in choosing VC investors as the VC investors undertake in deciding to invest. Be selective, focused and analytical. It is all too common for entrepreneurs to take on a posture of desperation, running after any chance of funding, no matter how remote or inappropriate. A VC firm, like any organization, is really only as good as its people.

Disadvantages of VC

The most obvious disadvantage of any external equity investment, not just one from a VC investor, is dilution of existing ownership. Relinquishing some ownership is not necessarily bad, because the new equity provides the opportunity to execute on a business plan, grow the business and increase its value overall. It is always better to own a smaller percentage of a valuable company than 100% of a worthless company. An additional disadvantage is that equity is generally more expensive than debt. To give a simple illustration, suppose your company needs \$1 million to execute on its business plan and has the option of either borrowing that money or taking it in the form of an equity investment in exchange for 25% of the company's capital stock. If the company's value grows to \$100 million and is then sold, the lender would receive only \$1 million plus accrued interest, while the equity investor would receive \$25 million (assuming no additional capital stock has been issued in the interim). In other words, as the value of the company grows, equity holders participate in a pro rata share of that growth, but debt holders are limited to receiving their principal plus accrued interest, no matter how valuable the company becomes.

There are also non-monetary downsides to consider. An equity investment makes the investor a relatively permanent player in the company, at least until a liquid public market develops for the company's stock. It is considerably more difficult to unwind an equity investment than it is to pay off a loan. An associated issue is control. Virtually all VC investments include terms requiring founders and managers to give up a certain amount of control and operating flexibility. These disadvantages, however, do not really manifest themselves as problems unless the relationship between the entrepreneurs and investors sours, but differences of opinion very often develop.

A final disadvantage of a VC investment is the difficulty in obtaining VC. VC firms are inundated with business plans every day. For every one hundred plans a VC firm receives, only ten companies may be granted a meeting with the VC firm. Of those ten companies, only one may receive funding. Moreover, attracting VC takes a considerable amount of time, and if one is successful in closing on a VC equity investment, the related transaction costs can be substantial.

Investment Drivers

Turning back to the VC investor's perspective, there are some key variables that drive the investment decision. The individual VC investor, who brings a unique background of experiences and biases to the negotiating table, ultimately drives the process. There are, however, certain obvious negatives for VC investors, which include:

- business plans that are sloppy or incomplete;
- management that is unwilling to acknowledge business risks or limitations;
- excessive projected salaries, perks and other expenditures;
- entrepreneurs unwilling to engage professional management or fire unqualified friends or relatives in key positions; and
- use of intermediaries such as finders or selling agents to locate early stage funding.

Other potential negatives include biases against engineers or scientists serving as CEO, entrepreneurs with a spotty track record (or no track record), and companies that have been trying to attract funding from too many sources for too long.

The VC process does have some standard operating procedures. An investment is highly unlikely to be made until substantial due diligence has been performed. A VC investor will meet with the key players, such as founders, management and key technical personnel several times. Reference and background checks will usually be conducted. The VC firm will also undertake an extensive program of contacting customers, suppliers, competitors and industry experts. With biotechnology investments, the VC firm will typically have a network of experts who will undertake a detailed review of the company's technology and interview the company's key technical people. If the company has patents, patent counsel for the VC firm may analyze the scope and value of those patents. This process takes at least 60 days,

frequently longer. Compared to many of the VC firms that invested in various Internet business models during the late 1990s without having performed much due diligence, if any, biotechnology investors expend significant time, effort and resources before making a final investment decision. Their goal is to avoid hasty or ill-informed decisions. Each VC investor will move at his or her own pace, so there is no standard timeline for reaching an investment decision. But be cautious of wasting too much time with a prospective investor who seems to suffer from “paralysis by analysis.”

Currently, there are very few VC firms making seed stage investments. A typical VC investor is interested in making larger investments of several million dollars. The size of investment is particularly important with respect to biotechnology companies because of the industry’s significant capital requirements. Another current complicating factor is the increased focus on investments in companies with a more mature operating history. Many VC investors have, ironically, become very risk averse, wanting to invest only in companies that are poised for significant growth that will be fueled by the proposed investment.

Aside from the size of investment and stage of the company’s development, an overriding concern will be the competence and experience of current management. This is often one of the touchiest subjects to address because of the emotional implications of an incumbent management team being told they “don’t have what it takes.” Nothing, however, will kill a possible VC investment faster than an inadequate management team. It is irrelevant that the company’s technology and potential market are incredibly promising. Many VC investors say that they invest in management, not products or market potential. When analyzing whether the incumbent team is worthy of investment, the investors will spend a great deal of time observing management in action before making their investment decision. Even after a term sheet has been presented and the investment transaction is in full swing, any management actions that raise concerns about the quality of the management team may bring the transaction to an abrupt end.

Investment Process Overview

Following completion of the primary due diligence process, if the VC investors have decided to invest, the investment process should move forward quickly. The lead investor (typically the firm making the largest investment if more than one firm), will prepare a term sheet outlining the terms of the proposed investment and present it to the company. The term sheet is typically a detailed outline that sets the stage for a more efficient negotiation of the definitive investment agreements. Bear in mind, though, that every VC deal has a life of its own based on the people involved so there are no standard time lines, deal terms or transaction documents. In other words, negotiating a VC investment is no different than the rest of life. One needs to view it as an adventure.

One of the principal components of the term sheet will be the “pre-money” valuation of the company. This is the investors’ determination of the value of the company prior to their investment. The pre-money valuation for most emerging companies is not based on any classic valuation criteria such as discounted cash flows or comparable companies, because those metrics rarely exist for an early stage biotechnology company. Early stage biotechnology valuation is more art than science, and will be

based in large part on qualitative factors that include, but are not limited to: the strength of the company's intellectual property portfolio; the strength of the existing management team; market validation of existing technology; the amount of progress toward commercialization (including clinical data obtained to date); and estimation of the size of the addressable market and the potential for market penetration.

It is important to have a contextual perspective on valuation. Most entrepreneurs focus almost exclusively on the pre-money valuation, and they do so to their potential detriment. There are many other terms and conditions that affect the ultimate value of the VC investment and the value of the equity interests of the shareholders who were at the table prior to the VC investment. In particular, liquidation preferences, anti-dilution protections and conversion provisions may be structured in such a way that, although an attractive pre-money valuation was ascribed to the company at the time of the VC investment, the investment results in the VC investor capturing a higher percentage of the terminal value of the company than would have been captured if more effort had been dedicated by the company to negotiating and maximizing the structure of these terms and accepting a lower pre-money valuation.

Notwithstanding the execution of a term sheet, the VC investors will continue to conduct due diligence on the company until closing. Because the investors are motivated to maximize their return on investment, not only for themselves but also for the investors in their fund, they will undertake, through their analysts, consultants and attorneys, an exhaustive review of every aspect of the company's history, current status and prospects.

Principal Investment Terms

It is almost universal that VC investors will only purchase preferred stock, which is an equity security with various rights senior to those of common stock. A common mistake companies and their counsel make is to assume that a VC investment is no different than an investment in common stock. That assumption could not be further from objective reality. The terms and conditions of a VC investment are considerably more detailed and complex than an investment in common stock. This means that the terms offered by a VC investor will have to be considered carefully, and in their totality, rather than on a term-by-term basis. There will be some heavy negotiation along the way, the results of which will depend on not only the relative bargaining power of the parties, but also on the sophistication and experience of the company's management and counsel. The principal terms of VC investments are not only complex, but are also subject to constant change due to prevailing economic and industry conditions. While the terms of VC investments are in constant flux, there are many fundamental aspects to preferred stock that will form the basis of a VC firm's investment.

Ranking

Preferred stock is a senior equity security in the capital structure of a company. It is senior to the rights and preferences of the common stock. Just how senior depends on the particular terms of a particular class of preferred stock. Under most state corporate statutes, a company's governing documents, if properly constructed, will

give the board of directors fairly broad latitude in establishing various classes of senior equity securities with varying terms of seniority. The relative seniority as among the common stock and one or more classes of preferred stock will depend on individualized provisions relating to such issues as dividends, liquidation preferences, conversion mechanics, and so forth. Most of these provisions will become a part of the company's articles or certificate of incorporation, which forms the fundamental investment contract between a company and its investors, as well as among the investors themselves.

Dividends

Virtually all classes of preferred stock purchased by VC investors will have a stated dividend. What differs, though, is whether the dividend is payable currently, whether it accrues automatically if not paid currently, or whether it is merely a right to participate in dividends at a particular rate only if and when dividends are declared and paid on the common stock. Most VC investors are not investing for dividend income, they are investing for long-term capital appreciation. So although the dividend issue does have definite economic implications, it is typically not a centerpiece of the deal structure. When it comes to dividend terms, there are basically two schools of VC investors: those who want a fixed, cumulative dividend that will accrue (and may compound) and must be paid before any dividends are paid to common stock holders; and those who merely want to participate in dividends if and when any dividends are declared on the common stock.

Liquidation Preference

To a VC investor, the liquidation preference provision is significantly more important than the dividend structure. In the event a company is liquidated, the VC investors want to be paid immediately after the company's creditors, but before any classes of junior equity. "Liquidation" as defined in the governing documents, however, does not include the classic sort of liquidation that occurs when things have gone badly and it has been decided to "fold the tent" and sell the company's assets. In VC financing, liquidation generally includes such events as a merger or sale of the company or an exclusive license of its technology. Put simply, if things go well and there is real cash on the table, the VC investors want to collect their cut first. Then the question becomes, what is their cut? Determining the answer to that question is where the negotiations become interesting.

In a classic deal, the liquidation preference is equal to 1X the original purchase price paid by the VC for the preferred stock, plus accrued but unpaid dividends. After the payment of that liquidation preference, the VC firm may have "participation rights" which means that it will then share the remainder of the value on a pro rata basis with the holders of all other classes of equity. The pro rata "participation" in the remainder will be calculated as if the preferred stock had been converted to common stock. Here is a simple example of how a 1X liquidation preference can affect the distribution of the sale proceeds, assuming net proceeds of \$100 million. Assume that the pre-money value of the company was agreed to be \$10 million, and the VC purchased \$10 million of Series A Preferred Stock that, on an as-if-converted basis,

amounted to 50% of the outstanding common stock of the company. Starting with the \$100 million net proceeds (and assuming no accrued but unpaid dividends), the VC would receive an initial \$10 million, leaving a net of \$90 million. The \$90 million remainder would then be split equally between the VC firm and the original investors. The end result is that the VC firm would receive 55% of the sale proceeds and the original investors would receive 45% of the proceeds, even though both sides brought the same amount of value to the table when the deal was originally struck (i.e., the original investors contributed a company worth \$10 million and the VC contributed \$10 million in cash).

During some particularly uncertain times, however, it is not uncommon for VC investors to demand “supercharged” preferred stock that has a multiple liquidation preference. Such liquidation preferences have been known to range from 2X to 5X. Let’s revisit the preceding example, but this time use an assumed 3X liquidation preference. Off the top, the VC investor will receive \$30 million and then receive another \$35 million, representing 50% of the remainder. The original investors, on the other hand, would receive only \$35 million. In this example, using the same original contribution values, the VC investor ends up with 65% of the proceeds and the original investors receive only 35%. Add accrued dividends to either scenario and the percentage participation for the original players becomes even worse. The above example demonstrates how the pre-money valuation (say \$8 million vs. \$10 million) may be less important than other terms of the preferred stock structure.

There are also variations on the liquidation preference structure that introduce more creative ways of measuring the preference. Some of these variations introduce concepts such as annual compounding of required returns, or fair market value analysis of various equity interests at the time the preference is triggered.

Conversion

Most preferred stock is convertible into common stock at any time, at the option of the holder. Frequently, preferred stock will automatically convert into common stock if the company completes an IPO that meets certain minimum share price and gross proceeds thresholds. Other triggers for automatic conversion may be based on the company achieving certain objective milestones, or on a supermajority vote of the preferred shareholders. Of course the focus is not solely on the fact that the preferred stock converts, but on how many shares of common stock it converts into. The conversion rate is set by provisions that establish the initial conversion price per share of common stock as it relates to the original purchase price for the preferred stock. Conversion provisions also create triggers that will cause an adjustment to the conversion price upon the happening of specified events in the future. The usual initial conversion structure provides that the conversion price per share of common stock will be equal to the original purchase price for a share of preferred stock. This results in an initial conversion ratio of 1:1. If things don’t go well for the company, then that ratio is likely to shift in favor of the VC investor, which brings us to anti-dilution protection.

Antidilution Protection

Although VC investors are supposed to be risk-oriented, they usually demand some insurance against both a change in the outstanding capital structure of a company and a drop in the company's valuation. This insurance is expressed in provisions that provide antidilution protections. The first aspect of this protection relates to stock splits and recapitalizations and operates to adjust the conversion price to ensure that the effects of a split or recapitalization are neutral with respect to the percentage of the company owned by the VC investor. For instance, if the board of directors was to declare a 10 for 1 split of the outstanding common stock, the conversion price for the preferred stock would be reduced to 1/10th the then-current conversion price, and the number of shares of common stock issuable upon conversion would be increased by a factor of 10.

The other, and more controversial, antidilution protection relates to dilutive sales of common stock or common stock equivalents. This protection is sometimes known as a "ratchet right" and can be structured in several ways. The purpose of a ratchet right is to give the VC investor protection against equity issuances purposefully designed to dilute the VC investor's ownership interest and issuances that place a lower valuation on the company than the value agreed to at the time of the VC investor's original investment (because the company's value has decreased or because the VC firm incorrectly valued the company). A ratchet right will operate to give the VC the right to convert preferred shares into additional shares of common stock if the company sells common stock (or securities exercisable for or convertible into common stock) at a price lower than the then applicable conversion price. The adjustment mechanism will provide for either a "full ratchet," which reduces the VC's conversion price to the lowest price paid for a share of common stock in the dilutive issuance, or a "weighted-average ratchet," which reduces the conversion price based on a weighting between the amount of capital being invested in the dilutive round and the amount of capital previously invested. The weighted average approach is more company friendly. Either approach can be made somewhat more palatable to the company by including a "pay-to-play" provision that requires a VC firm to make an additional pro rata investment in the dilutive round in order to take advantage of the ratchet protection. Any investor subject to a pay-to-play provision that chooses not to invest in the dilutive round will not receive the benefit of the ratchet protection and its ownership interest in the company will be diluted, often substantially.

Governance Rights

Even if a VC investment entitles the investor to less than 50% of the outstanding equity interests in a company, the VC investor will ordinarily not have a minority position when it comes to the governance of the company. VC investors prefer to invest in companies in which they can be active participants in guiding the company. As a result, the deal will require that certain rights be ceded to the VC investors.

At the simplest level, the shares of preferred stock will entitle the investor to a number of votes equal to the number of shares of common stock issuable upon conversion of the preferred stock. The number of shares has the potential to fluctuate

during the term of the investment to the extent the conversion price is adjusted, as discussed above.

The VC investors will also have a contractual right to designate one or more of the company's directors. During early rounds of VC funding, this designation right may constitute a minority of the board, and existing investors may continue to control the makeup of a majority of the board. As the number of rounds, or number of large VC investors increase, the number of investor designees will increase. Entrepreneurs must understand that as institutional money is invested in a company, founder and management influence on the board will decrease substantially, typically to the point where only the sitting CEO will have a seat on the board. It is also not unusual for the VC investors to have a contractual right to designate a majority of the board in the event the company is in default under agreed-upon provisions of the investment agreement. These board designation rights are memorialized in an agreement among the principal shareholders of the company whereby the parties agree to vote their shares to ensure that the director designees are elected to the board during the term of the agreement.

Beyond board designation rights, the most important rights VC investors will receive are what are generally known as "protective provisions." Protective provisions are, essentially, veto rights. The usual approach is that the portion of the company's articles or certificate of incorporation that describes the rights and preferences of a particular class of preferred stock will prohibit the company from taking a series of enumerated actions without the approval of a specified percentage of the outstanding shares of preferred stock. Examples of the actions that are the subject of protective provisions are: (1) changes to the terms of the subject class of preferred stock; (2) issuance of equity securities with rights that are senior or equal to those of the subject class; (3) engaging in major corporate transactions such as mergers, acquisitions, sale or licensing of assets, or issuances of debt; and (4) changing the size of the board of directors. These protective provisions will typically expire when the investors hold less than a minimum percentage of the securities originally issued to them. Protective provisions will also expire when the investor's securities are automatically converted into common shares as the result of the closing of an IPO that meets the criteria for conversion.

Redemption

Another right usually associated with preferred stock purchased by VC investors is the redemption right. Some redemption provisions require a mandatory redemption of the shares after a certain period of time, usually five to seven years. Mandatory redemption, however, is unusual today because accounting rules require that mandatory redeemable shares be classified as debt rather than equity, and nobody wants to make an emerging company's balance sheet look worse than it already is.

The most prevalent structure of this right is what amounts to a "put" option in favor of the VC investors that becomes exercisable after five to seven years. This put right is a product of two VC concerns. The first concern is that, although a good VC investor has the patience to wait for liquidity until the company has successfully executed on its business plan, investors will not wait forever. They need an exit

strategy, and in the off chance one might not be available during the ordinary course of business, the investor wants the ability to force the issue. The other consideration is that most VC funds have a ten-year life span and the fund managers often need to liquidate their investments before the fund terminates.

The redemption price to be paid by the company upon the VC investor's exercise of the put depends on the terms of the preferred stock at issue. In the best scenario, the redemption price will be the original purchase price of the shares, plus accrued but unpaid dividends. However, that hardly ever happens. More often, the redemption price will be based on the higher of the liquidation preference or the then current fair market value of the shares to be redeemed. Sometimes the redemption provision is even more onerous.

All this being said, the reality is that this provision is never implicated. It is more often held like the sword of Damocles over the heads of management and other shareholders. As a practical matter, it is just an issue that will have to be addressed if an exit or liquidity event ends up taking more time than anticipated. It may ultimately force a recapitalization of the company but no investor is going to suddenly show up at the door and ask for its money back.

The Deal Documents

Once the primary terms are agreed to, the deal will be memorialized in the form of a securities purchase agreement, together with one or more related documents that will establish various contractual rights of the VC investors. These documents are not standardized "forms," but complex and sophisticated expressions of the investment contract between the company and the investors. Certain provisions will have a long-range impact on the rights of not only the VC investors and the company, but on the other shareholders as well.

Securities Purchase Agreement

The securities purchase agreement sets forth the primary terms of the purchase and sale of the securities that form the basis of the financing round. While this document will be lengthy, there are certain provisions that are of primary importance. The first portion of the purchase agreement will confirm the pricing and number of shares of the security to be acquired, which will be based on the pre-money valuation established at the time the term sheet was finalized. The company will also provide detailed representations and warranties regarding many of the significant characteristics of the company, including, but not limited to:

- the company's good standing in its state of incorporation;
- that the transaction at hand has been duly authorized;
- the company's current capital structure;

- the accuracy and completeness of certain historical financial statements;
- outstanding debts, liens, liabilities and contingent liabilities;
- material contractual obligations;
- ownership or rights to significant real, personal and intellectual property;
- compliance with various state and federal laws; and
- certain issues of importance to VC investors managing Small Business Investment Company funds, and investors who want to take advantage of Code Section 1202 that permits a partial exclusion of the gain on sale of certain “qualified small business stock” held for more than five years.

The VC funds will also make certain limited representations and warranties to the company, including the nature of their investment intent, and their status as accredited investors. The investor representations and warranties are made primarily for the purpose of providing the company with a basis for complying with exemptions from the registration requirements imposed by federal and state securities laws. The investors will also represent and warrant that they understand that the securities being purchased have not been registered under the Securities Act or any state securities laws, and that the securities must be held unless and until they are appropriately registered or a disposition can be made pursuant to an available exemption from applicable registration requirements.

Each investor’s obligation to purchase the company’s securities will be subject to the satisfaction of several conditions imposed by the purchase agreement. These include: the execution of any agreements that are ancillary to the purchase agreement, including the registration rights agreement and shareholders agreement (discussed below); confirmation of the company’s good standing; certificates of company officers stating that the company’s representations and warranties continue to be true and correct and that the company’s governing documents have not been amended; that all approvals, consents and waivers required to consummate the transaction have been obtained; and delivery of an opinion of the company’s legal counsel regarding various legal issues. There will also be conditions to the company’s obligation to close, though the only meaningful condition will be the receipt of the purchase price.

Amendment of Charter

Another closing condition that should be highlighted is the amendment of the company’s articles of incorporation or charter to establish the principal rights and preferences of the security being sold (see the preceding discussion of “Principal Investment Terms”). This is accomplished through an amendment of the company’s articles or certificate of incorporation that is adopted pursuant to the power of the company’s board of directors, under its existing governing documents and statutory authority, to establish various new classes of equity securities with varying rights and preferences out of authorized but unissued capital stock.

Shareholders Agreement

As if all the preceding were not enough, the VC investors will also require additional contractual rights that will be expressed in an agreement among the company, the investors, and other principal shareholders of the company. This agreement is typically referred to as a shareholders agreement and it will address a variety of issues, including: the makeup of the company's board of directors; restrictions on transferability and sale of company stock; preemptive rights to purchase securities offered in the future; and the right of a majority of VC investors to force a sale of the company.

The first issue covered by a shareholders agreement is the number of seats on the company's board of directors and the power of certain constituencies to fill certain seats. The parties to the shareholders agreement agree to vote their shares in favor of certain candidates designated by specified parties to sit on the board. Major VC investors will almost always have the right to designate one or more directors. Management or founders may also have a similar right. It is also common for the shareholders agreement to dictate that one or more members of the board must be independent of either management or the VCs. The agreement will also provide that the party with designation rights is the sole party with the power to remove and replace its designee.

Additional board issues covered in the shareholders agreement may include: the granting of board observation rights to various parties; the frequency of board meetings; the establishment of committees such as audit, compensation and governance committees; and the reimbursement of expenses incurred by directors in attending board and committee meetings. This section of the agreement may also address indemnification of directors, and impose requirements with respect to the purchase of director and officer liability insurance.

The parties to the shareholders agreement will usually agree to restrict their ability to transfer their shares in the company to any person or entity other than an affiliate, only after first complying with a right of first offer that provides the other parties with an option to first purchase the shares. Along the same lines, the agreement will typically include what is known as a co-sale right or tag-along provision, which gives non-selling shareholders the option of selling a prorated portion of their shares to a third-party purchaser on the same terms as those offered to the selling shareholder.

Preemptive rights are also a very important aspect of the shareholders agreement. This provision is designed to provide investors with a right of first refusal to purchase any new equity securities the company proposes to offer in the future. These rights are usually structured to require that the new securities must be purchased on the same terms as those being offered to third parties, and that each party exercising its rights may buy up to its prorated share of the securities being offered (and often purchase some or all of the shares not purchased by others holding preemptive rights). It is not unusual for this provision to require that, in a "down" or dilutive round, investors must purchase their entire prorated portion of the offered securities in order to obtain the benefits of any ratchet right they may have.

Another significant provision often found in a shareholders agreement is a drag-along provision. A typical construction of this term provides that if some threshold of holders of outstanding preferred stock (typically a supermajority of the outstanding shares) approves a sale of the company, the other parties to the agreement are contractually required to vote their shares in favor of that sale. In other words, the approving VC investors can “drag” the other parties along on the transaction.

Registration Rights Agreement

The last principal agreement governing the VC investment is the registration rights agreement. This highly technical document sets out the mechanics under which the shareholders that are parties to the agreement can force the company to register their shares under federal and state securities laws so that the shares are eligible for public resale.

Registration rights will usually cover the company’s common stock, as well as common stock issuable upon the conversion or exercise of securities such as preferred stock, convertible notes, warrants and options. While excessive detail on the inner workings of this agreement is beyond the scope of this section, it is helpful to have a basic understanding of the principal types of rights granted. The short-form designations of those rights are: demand registration; piggyback registration; and short-form registration.

Demand registration rights allow the holders of some specified minimum number of shares to literally demand and require the company to register their shares by preparing, filing and maintaining an effective registration statement with the Securities and Exchange Commission (“SEC”) and any applicable state securities authorities. A well-drafted registration rights agreement, however, will restrict the circumstances under which such a demand can be made.

Piggyback registration rights give the covered shareholders the opportunity to include their shares in registrations commenced by the company, and sometimes registrations initiated by other shareholders through the exercise of demand rights. This right will typically carve out certain types of registration statements, including a registration relating to the company’s IPO, registrations relating to mergers and acquisitions, and registrations of shares covered by employee benefit plans. Piggyback rights will be subject to the company’s right to exclude any shareholder shares from the registration if the underwriter feels that the inclusion of those shares will have an adverse effect on the marketability of the offering.

Short-form registration rights are rights that are sometimes granted in addition to those described above and which give the covered shareholders limited demand rights if and when the company becomes eligible to register securities on an abbreviated form of registration statement known as Form S-3. Eligibility for registration on Form S-3 is based on certain criteria, including the length of time the company has been public and its market capitalization.

Typically, all of the registration rights discussed here will expire once the subject shares become eligible for resale in the public market pursuant to Rule 144(k) under the Securities Act. Simply stated, Rule 144(k) permits resales without registration for unregistered shares held for at least two years, if the company is current in its periodic filings with the SEC.

C. Management Equity Incentive Compensation

Introduction

While intellectual property is often a biotechnology company's most valuable asset, it is critical for a company to obtain and retain quality managers and scientists. While much of this Guide is dedicated to addressing how one finances the assets and operations of the business, this section addresses alternatives for "financing" the biotechnology company's managers and scientific personnel. We have positioned this section after Private Capital Formation because of the importance that management equity incentive compensation has during the private investment financing rounds, and during the remainder of the biotechnology company's existence.

Stock Options

The most typical form of equity compensation has been stock options, both because of favorable tax treatment of certain options and, until recently, favorable accounting treatment of most options. (See discussion on option expensing below). An option is a right granted to an employee, director, or consultant to purchase a specified number of shares, usually of common stock, at a set price and for a set period of time. Options are similar to warrants except that options are generally provided to persons providing services while warrants are generally provided to investors as additional consideration for their purchase of debt or equity. Options allow the option holder to share in the hoped-for appreciation in the value of common stock over the exercise price without having to invest capital at the time of grant. Among the major variables to consider in the grant of stock options are the following:

Exercise Price

Although the stock purchase or exercise price of an option will generally be at the fair market value of the stock on the date of grant, usually as determined in good faith by the board of directors or Compensation Committee, based on an estimate or upon recent or proposed sales to other investors, the exercise price may be set at a price less than fair market value. Options granted with an exercise price of less than fair market value on the date of grant provide an immediate value to the option holder; however, there is a risk that a discount of more than 50% below fair market value will not be treated as an option for tax purposes. The Internal Revenue Service ("IRS") has recently held that discount options (those issued at an exercise price of less than fair market value) constitute deferred compensation subject to new restrictions under

Code Section 409A that will limit the times at which the discount options may be exercised. The exercise price is not paid until the option holder elects to exercise the option to purchase stock.

Vesting

The right to purchase shares under the option may be exercisable immediately or may be exercisable only after certain events. Typical vesting provisions include: time vesting, in which a portion becomes exercisable annually or monthly if the option holder continues to provide services; and performance vesting, in which a portion becomes exercisable only if certain milestones are achieved, such as additional financing, clinical studies, or governmental approvals. Vesting may accelerate as to all or part of the shares in certain events such as death, disability, termination without cause under an employment agreement, a change in control or similar liquidity event.

Termination of Exercise Period

Most, if not all, options have a termination date. If the option is not exercised by that date, the right to purchase lapses. This allows the company to limit the period during which the shares will be issued at that price. Many options have a term of five to ten years, but certain events such as death, disability or termination of employment require that the option will expire immediately (for example, termination for cause) or within a period of three months or one year from the date of the event (for example, termination without cause or death). Many option plans will also make provision for termination of the exercise period upon a change in control, to avoid having options continue after the company has been purchased and to permit the buyer to design its own equity program.

Rights as Shareholders

Many option plans and option grants will add provisions that limit or affect the rights of option holders after they exercise the option and become shareholders. These restrictions may include a right of the company to repurchase the shares at a fixed price or at the then fair market value if the option holder ceases to provide services. Other restrictions may include: the company's right of first refusal to purchase the shares if the holder attempts to sell the shares to an outside party; the obligation to sell the shares only in a manner that complies with federal and state securities laws; the obligation to sell to a buyer who is acquiring all the shares of the majority shareholders (drag-along rights) and limitations on sales following an IPO (lock-up provisions).

While most VC groups will approve equity compensation to provide an incentive to employees and service providers to increase shareholder value for themselves as well as the VC group, the VC group invariably seeks to limit the rights of these minority shareholders to the extent these rights may affect the ultimate value the VC group receives for its investment. For example, since VC groups put their cash at risk up front, they may want a form of investment, such as preferred stock, that has greater economic

and governance rights than option holders will have. Because option shares will, upon exercise, dilute the percentage ownership of VC groups owning that same form of equity, the percentage of shares available for issuance under an option plan is generally restricted. Discounted options will further dilute the interest of VC shareholders. Finally, VC shareholders may not want all options to vest upon a change in control, since post change in control vesting serves as a means of retaining management and scientific personnel, which may be of great value to a buyer.

Differences Between Options in Corporations and in Pass-Through Entities

The legal structure of the company and whether it is a subchapter C or subchapter S corporation, LLC or limited partnership may be determined based on the tax benefits to early investors, including a VC group. Granting options to employees and service providers of S corporations, LLCs and limited partnerships and communicating the rights and benefits to these option holders involves more complexity than granting options in a C corporation. For example, because LLC and subchapter S corporations are treated as pass-through entities, upon exercise of an option and purchase of an LLC or subchapter S interest, option holders become shareholder-employees, subject to self-employment tax and loss of certain tax-free fringe benefits. An LLC may also provide that prior investors, such as VC groups, retain their priority rights to any existing capital investment and, therefore, grant only a future profits interest to persons providing services. A profits interest grants a right to future appreciation and a right to a pro rata share of any future profits without disturbing the capital accounts existing at the time of grant. At the time of publication of this Guide, the IRS had issued proposed regulations that would allow a grant of a capital or profits interest to be treated as restricted property under Code Section 83, refining the tax treatment of the transfer of vested or unvested LLC and partnership interests and providing a safe harbor method for valuing these interests for tax purposes.⁸⁸

Securities Law

An option grant is a security. The exemptions from registration applicable to the sale of shares generally also apply to the grant of options. The options themselves are not registered, but the shares issuable pursuant to the plan may be registered at or following a public offering of the issuers' common stock, which will allow option holders to sell their shares freely in the public market after exercise. Otherwise, resale restrictions will apply to unregistered securities and to shares held by insiders after an IPO. If the entity has issued options or stock at a significantly discounted exercise price shortly before an IPO (in particular, small offerings not subject to a national market exemption), some state securities commissioners may restrict the right of the entity to sell its shares in that offering in that state. To avoid any claims of misrepresentation on the sale of a security at the time of exercise of the option, companies will also need to consider the availability of material information about the company to option holders, and, more importantly, at the time the shares acquired by the option holders are repurchased by the company, if the option so provides.

Taxation of Options

The previous discussion focused on the non-tax aspects of options. The Code and regulations require in general that property received in exchange for services be taxed as ordinary income at the time the transaction closes, meaning the service provider has received property capable of being taxed. The paying entity is entitled to a corresponding tax deduction only when the provider takes the property into taxable income. The taxation of property, such as restricted stock, is governed by Code Section 83 and the taxation of phantom stock or stock appreciation rights is governed by Code Section 451, and both are discussed in greater detail below. Options are the exception to the rules under Section 83. The tax laws provide generally that the grant of an option that does not have a readily ascertainable fair market value does not result in taxation to the option holder at the time of grant. This feature makes options the preferred equity grant for recipients under current tax laws as compared to an outright sale or transfer of shares, either with or without restrictions.

There are two types of options: *incentive or qualified options* and *non-qualified options*, each of which is taxed in a different manner. The Code favors an option that meets the tax requirements as an incentive stock option because such an option will be taxed only when the stock received is sold or disposed of (except as noted below). In contrast, a non-qualified stock option is taxed at the time of the exercise of the option. To qualify as an incentive stock option, the following conditions must be met:

- the option plan granting the option must be approved by shareholders within twelve months of the date the plan is adopted;
- the option must be granted to and exercised by a person who is an employee (in other words, incentive stock options cannot be granted to non-employee directors or consultants);
- the option must apply to stock of the employer or its parent company;
- the option must be nontransferable except by will or the laws of descent (upon death);
- all the options must be issued within ten years of the date the plan was adopted;
- the option cannot be exercised more than ten years after the date of grant (more than five years after the date of grant if granted to a 10% or greater shareholder);
- the exercise price must be no less than fair market value on the date of grant (no less than 110% of fair market value, if granted to a 10% or greater shareholder);
- incentive stock option treatment only applies to the first \$100,000 in stock value (based on the exercise price), that first becomes exercisable each year, whether or not exercised; and
- the stock cannot be sold until 2 years after the date of the option grant and 1 year after the date of exercise.

If all of these conditions are met, the *spread* (the excess of fair market value on the date of exercise over the exercise price) will not be subject to income tax upon exercise of the option (although the spread is added to the holder's income in determining the alternative minimum tax, which may result in taxation at the time of exercise). Furthermore, when the stock is sold, all of the stock appreciation in excess of the exercise price will be capital gains rather than ordinary income and taxed at the lower capital gains tax rate.

If the holding period is not met, that is, if the stock acquired upon exercise of an incentive stock option is sold within one year from the date of exercise or two years from the date of grant, the spread (the excess of fair market value on the date of exercise over the exercise price) will be taxed at the time of sale as ordinary income and any appreciation after the exercise date will be taxed as capital gains, if the relevant conditions for capital gains treatment are met.

Employees may be granted both incentive stock options and non-qualified stock options, while directors and consultants can be granted only non-qualified options. As noted above, the spread at the time of exercise of non-qualified stock options is taxed at exercise; therefore, non-qualified options exercised by employees must also provide for a means of paying any income tax withholding applicable upon the exercise. (Income to non-employer directors and consultants from the exercise of options is not subject to tax withholding.) This withholding may be satisfied either by the employee by payment of cash at the time of exercise or by the company paying the tax withholding by reducing the number of shares issued upon exercise equal to the withholding, based on the fair market value of the shares at the time of exercise.

While not always the case, often employees granted incentive stock options do not exercise the option except upon termination of employment, or in connection with a liquidity event. In many cases, employees generally sell the shares within a short period of time to convert the appreciation on the stock to cash. Therefore, in many cases, options that are granted as incentive stock options usually are sold before the holding period is satisfied, resulting in the spread on an incentive option being taxed as a non-qualified option.

Accounting for Options

Until recently, in addition to the favorable tax treatment for certain options, accounting rules treated the compensation expense associated with options differently than other forms of compensation, such as salary, bonus or transfers of restricted or unrestricted stock. Because options are not capable of being valued at the time of grant, the accounting profession adopted rules that allowed companies to use the "intrinsic value" of an option granted to employees, which resulted in no expense recorded on the income statement at the time an option was granted, became vested or was exercised (unless certain terms were modified after the date of grant). This treatment allowed companies to grant options without any effect on earnings or profits. On the other hand, a grant of restricted shares that vests over time must generally be recorded as an expense based on the fair market value of the shares at the time of grant amortized over the vesting period, with certain adjustments if shares are forfeited or accelerated.

Because of recent pressure applied by shareholders and government regulators to provide greater clarity and consistency in financial reporting by public companies, the accounting profession has proposed and the SEC has endorsed new accounting standards for public and private companies (Finance Accounting Standards Statement No. 123R; see also, SEC Regulation S-X as amended, 17 CFR 210.4-01(a)(1)). The new standards will require that options be valued and that such value be amortized as a compensation expense on the entity's financial statements. This change has been promoted as providing a level playing field between options and other forms of equity compensation, such as performance shares or restricted stock. However, this change will likely result in companies and VC groups reducing the availability of stock options as a form of equity compensation, primarily because grants of restricted or performance shares result in fewer shares issued to service providers with the same accounting expense as an option for a greater number of shares. Issuers will have some flexibility as to the method of valuing options using a few approved models that take into account expected future growth, return on capital, and the terms of the option. At the time of this publication, the accounting profession is debating changes that would allow non-public companies to retain the intrinsic value method to avoid having to expense options. Companies that continue to grant options may incorporate restrictions in certain terms of option grants to minimize the impact of stock option expensing.

Loan Covenants

The terms of equity compensation grants may also be subject to restrictions under company loan agreements, which may require notice and consent by the lender to any increases in equity compensation, the issuance of new or additional shares, or the issuer incurring any substantial liability related to compensation programs.

Stock Appreciation Rights

Stock appreciation rights represent only the right to the increase in value of a share of stock after the date of grant. This appreciation may be payable either in the form of cash (in which case the tax treatment is similar to that of phantom stock discussed below), or in whole shares of company stock (in which case it is similar to a stock option, but without the payment of an exercise price at the time of exercise). At the time of this publication, the IRS has defined both stock appreciation rights (other than for public companies) and phantom stock plan rights as deferred compensation, subject to restrictions under new Code Section 409A. These restrictions will limit the right to receive payments under a phantom stock or stock appreciation rights plan to a set schedule or certain events such as death, disability, separation from service, or change in control of the company. Under prior tax law, a stock appreciation right could be exercised at any time at the election of the holder.

Restricted Stock

Companies will often issue direct stock ownership to employees and service providers in exchange for their services. Whereas an option represents a right to purchase shares in the future, a stock grant represents the issue of stock currently, either for services performed

in the past or to be performed in the future, at little or no cost to the provider (other than the services provided). Typically, a grant of shares in exchange for future services contains restrictions requiring that the shares be forfeited if the services are not performed. As with options, this vesting may be based upon services performed over a period of time, upon the achievement of performance targets or upon certain events, such as death, disability, termination without cause or change in control. If restrictions are imposed, the certificates representing the restricted shares are retained by the company until the restrictions lapse. Likewise, the shareholder restrictions listed above that may be included in options, such as repurchase of shares upon termination of employment, drag along rights and the right of first refusal, may also be included in the restricted stock agreement. Generally, the equity incentive plan approved by shareholders, under which shares are reserved for issuance upon exercise of stock options, will also authorize the board of directors to grant other types of equity awards, such as restricted stock, performance stock, stock appreciation rights, etc., thereby permitting one or a combination of equity incentives to be awarded to new and existing employees, depending on the needs of the business and the purpose of the incentives.

The taxation of a grant of unrestricted or restricted stock is different than that for options. Under Code Section 61, compensation payable in cash, whether as regular compensation or bonus compensation, is taxable to the employee and deductible to the company at the time of receipt by the employee, director or consultant. Payment of compensation in a form of property other than cash is also taxable at the time of receipt under Code Section 83 (except with respect to an option, as discussed above). Therefore, the fair market value of unrestricted shares issued to a service provider for past services is taxed at the time the shares are issued. With respect to restricted stock, the tax rules provide that the value of the shares will not be taxed as compensation when issued if the shares are subject to a substantial risk of forfeiture. When the risk of forfeiture lapses, however, the value of the shares at the time constitutes taxable compensation. For example, ten shares of restricted stock are granted when the stock's value is \$1.00 per share. Two years later, when the shares vest, its fair market value is \$5.00 per share. The amount of income that is taxable in year two is \$50.00.

Under Code Section 83, which governs the timing and manner of taxation of property received for services, the employee may elect to be taxed at the time of the issuance of restricted shares, rather than later when and if the shares are no longer subject to a substantial risk of forfeiture. Electing to be taxed at the time of issuance is often referred to as a "Section 83(b) election." In the above example, the employee could elect to be taxed on the \$10.00 value of the ten shares at the time of issuance, even though the shares do not vest for two years. Once the value of the shares is taken into income, any increase in value after that date will constitute capital gains (if the applicable holding periods are met) and taxed at the lower capital gains rate. Therefore, the service provider may have to decide whether to make a Section 83(b) election, pay the tax on restricted shares at the time of issuance, and be taxed at capital gains rates on any appreciation after that date, or to wait until the shares actually vest and pay ordinary income tax at that time and then receive capital gains treatment on any future appreciation after the vesting date. The income will be subject to tax withholding for an employee, which will require the employee to pay out of other compensation or assets the amount necessary to cover the withholding obligation. The company may choose to assist the employee in paying the tax by paying a cash bonus or making a loan at the time of taxation to cover the withholding tax due, or may permit the employee to turn back newly vested shares equal to the amount of the tax

withholding. It should be noted that if the company is an SEC-reporting company, then the Sarbanes-Oxley Act of 2002 (“Sarbanes-Oxley”) would prohibit any loans to an officer.

Phantom Stock Rights

Another common form of participation in the growth of a company is phantom equity. As the name implies, phantom equity generally represents only a right to receive a cash payment equal to the appreciation in value and any dividends paid with respect to the actual stock or equity unit. However, the service provider is not entitled to an actual ownership interest in the company and remains only a general creditor of the company with respect to the amount due on the phantom equity. Phantom equity can either be in the form of units representing the equivalent in value to a share of stock or LLC unit or only to the appreciation after the date of grant on a share of stock or LLC unit. The company maintains a book entry accrued liability on its financial statement to account for the increase or decrease in the value of the phantom equity from time to time. The right to receive a payment for the value of the phantom equity can be conditioned on a vesting schedule, either based on time or performance criteria or the occurrence of certain events, and can be payable in a lump sum or in installments upon the happening of certain events such as death, disability or change in control. Because the right represents only a payment of cash, any shareholder rights, such as voting and redemption rights, do not apply to a phantom equity plan.

For tax purposes, the grant of a phantom equity right represents only an unfunded promise to pay money to an employee or service provider in the future. As a result, phantom equity is not taxed to the service provider at the time of grant. The value is taxed only when the payment is actually made to the service provider, at which time the company is entitled to a tax deduction. The payment is treated as ordinary income and no portion is eligible to be taxed at a more favorable capital gains rate. As mentioned above, like stock appreciation rights, phantom equity will be subject to the requirements applicable to a nonqualified deferred compensation plan under new Code Section 409A.

A phantom equity plan is also considered a pension plan, subject to certain requirements under the Employee Retirement Income and Security Act (“ERISA”). Many companies will avoid the requirements of ERISA if the grant of phantom equity (and other similar non tax-qualified deferred compensation plans) is limited to a select group of management and highly compensated employees. For this reason, a phantom equity plan is generally not available to rank and file employees. Stock options, stock appreciation rights and grants of restricted or unrestricted shares of stock are not subject to non-discrimination rules applicable under the Code, nor are they subject to ERISA and, therefore, except for the limitations imposed on grants of incentive stock options, they may be granted to all employees and may discriminate in favor of officers or other highly compensated employees.

Employment and Change In Control Agreements

Most companies and VC groups will consider cash compensation, annual cash bonuses, and grants of equity compensation sufficient incentive for the services to be provided by management and technical employees. Most state courts have held that, in the absence of a written contract or explicit handbook language, all employees are *at-will*, meaning they

can be terminated by the company or quit at any time and for any reason or no reason without liability, (in Minnesota, see *Pine River State Bank v. Metille*, 33 N.W.2d 622 (MN. 1983); however, California and Illinois have exceptions or limitations to the at-will employment rule). Some companies and VC groups will also consider written employment agreements for executives that will provide the executive certain protections against arbitrary termination of employment and may provide for additional benefits, such as salary continuation/severance benefits, continuation of health and other benefits following termination of employment, including protections in the event the executive's job responsibilities, reporting obligations, benefits and other compensation plans are changed following a change in control or liquidity event. These agreements may take the form of individual employment agreements or severance arrangements, or a plan covering a group of executives, and may be limited solely to a termination following a change in control. Often, these agreements include provisions on non-competition, non-disclosure of confidential information and non-solicitation of employees or customers as a condition for any post-termination payments. Severance plans, other than those limited to a select group of management and highly compensated employees, generally are subject to ERISA, which requires certain provisions such as fiduciary obligations, claims procedures and appeal rights, to be set forth in the plan or agreement. Change in control agreements can be negotiated either at the beginning of employment, or only after a serious offer is presented to the company that may result in a change of control.

Summary

All of the factors, including tax, securities, shareholder rights, and accounting rules should be considered carefully in designing an equity incentive plan that results in the issuance of stock to employees, directors or consultants for their services. This design will also be influenced by the choice of entity, the type of liquidity event expected (whether an IPO or the sale or merger of the company with another entity) and the type of equity issued to the VC group.

D. Public Capital Formation

Introduction

The principal public financing alternative is, of course, an IPO. This section explores a biotechnology firm's decision to become public, reviews the advantages and disadvantages of being public, summarizes the steps necessary to prepare a firm for an offering, explores the process involved, describes the ongoing duties once the firm is public and discusses additional public financing alternatives that become available once the firm is public.

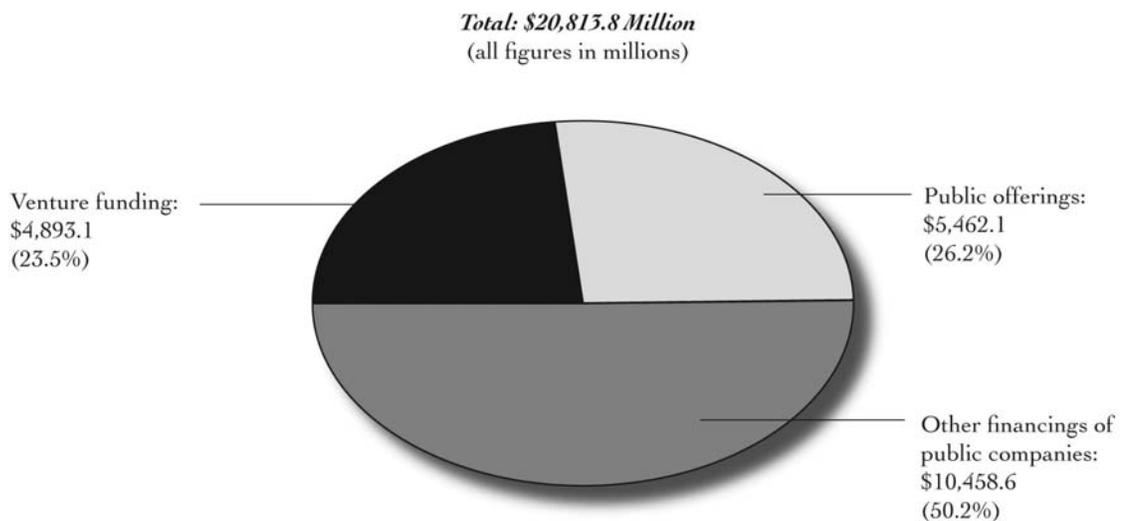
Recent Trends in Biotechnology Public Offerings

An IPO is a widely-known financing alternative for a biotechnology firm. In recent years, the public capital markets have been a great source of capital for the biotechnology

industry with widespread investor interest in life science and health related companies. From 2000 to 2002, over \$70 billion was raised in IPOs by biotechnology firms in the U.S.⁸⁹ In 2002 alone, biotechnology firms raised over \$60 billion in IPOs.⁹⁰ In the years 2000-2002, venture-backed IPOs of biotechnology firms represented between 25-30% of all venture-backed IPOs.⁹¹ These figures suggest that seeking financing from the public capital markets is often a viable financing alternative.

The market for capital in the public sphere is often described as a window. The window can be open for some period of time for certain industries, but then can shut abruptly and remain shut for long periods of time. In 2003, the biotechnology window opened wide, with *The Wall Street Journal* describing the market for public offerings in biotechnology as a “boomlet.”⁹² Because the window can shut as quickly as it opens, a biotechnology company raising capital from the public needs to do so nimbly and expeditiously.

Biotech Industry Financing, 2004



Source: BioWorld

Should the Biotechnology Company Go Public?

The difficult decision of whether to raise capital from the public and become subject to all the duties of a public company is not unique to biotechnology firms. If the firm has a product, technology or business plan that makes it a strong candidate for an IPO, the firm’s board and senior management must also weigh the expense, risk and managerial resources that must be devoted to completing a successful public offering. These are significant, and therefore, a public offering is practical only for a larger biotechnology firm. The decision to go public involves a thorough consideration of many factors including: financing needs; covenants to existing investors that may mandate a public offering; status of products; state of preparedness; risks; market opportunities and valuation; business, tax and estate planning; alternative sources of financing; and the cost of going public.

Advantages to the Biotechnology Firm in Becoming a Public Company

There are many advantages for the biotechnology firm to go public. These include:

Access to Capital Markets

For the biotechnology firm, public capital may be the only source of capital at a reasonable price. Selling equity to the public may be available without giving up significant control or accepting burdensome financial and other covenants that venture capitalists or established companies might impose in exchange for financing. For many biotechnology companies, bank financing is simply not a practical option because the life cycle stage is not mature enough and the risk profile is too aggressive for most banks.

Use of Proceeds

Many biotechnology firms sell shares to the public to satisfy a variety of capital needs including: financing product development expenses such as R&D; funding clinical trials; building out a sales force or engineering team to distribute or develop a product or technology; acquiring or modernizing production facilities; acquiring other businesses or assets including intellectual property or necessary licenses.

Satisfaction of Covenants or Investor Agreements

For many venture-backed biotechnology firms, a public offering may be required to provide an exit strategy for VC investments that carry burdensome liquidation preferences or dividend obligations.

Future Financing

By going public, the biotechnology firm will be able to raise additional capital and to increase its ability to obtain other types of financing. Future investors can be offered new securities with liquidity, and the firm has an ascertainable market value that may help support debt financing.

Mergers and Acquisitions

Public biotechnology firms can create a “war chest” to acquire other assets or businesses by using cash or its securities.

Corporate Reputation

A public offering can enhance a biotechnology firm’s name recognition and strengthen its competitive position in the industry. Media attention accompanies the mere

announcement of a public offering. There is also a certain prominence that accompanies a successful IPO.

Officer, Director, Employee and Consultant Recruiting and Retention

Once a public offering is contemplated or successfully completed, it is often easier to attract and retain key officers, directors advisers and employees through stock options, restricted stock grants, stock purchase plans and stock appreciation rights. This is an important advantage for biotechnology firms because they often need to attract highly sought-after scientists, university or government-funded researchers or executives from larger established biotechnology firms. These professionals often must be convinced to give up the security provided by larger organizations for the promise of financial rewards that come from joining and acquiring an equity interest in a growing biotechnology firm.

Estate Planning

Going public can help diversify founder portfolios. In addition to a primary offering of shares by the issuer, an IPO may include a secondary offering of shares owned by existing shareholders such as founders or early backers of the firm.

Disadvantages to the Biotechnology Firm in Becoming a Public Company

The disadvantages to going public include:

Liability Risks and Regulatory Scrutiny.

Becoming public brings the biotechnology firm wider public exposure and scrutiny by governmental authorities. The public biotechnology firm becomes subject to SEC and stock exchange oversight. The firm will have disclosure obligations to public shareholders. The obligation to timely disclose material developments can create very difficult issues when combined with regulatory or product development issues. Product or technology development challenges such as FDA rejection or disappointing clinical trial results can compound into immediate securities law disclosure issues and risks. Disappointing or unexpected financial results often lead to lawsuits alleging securities law disclosure violations.

Potential for Loss of Control

Depending on the amount of shares sold to the public, controlling shareholders will often lose control of the company at the time of the IPO or in the near future. Going public can also lead to risks of an unfriendly takeover.

Loss of Confidentiality

The biotechnology firm's prospectus and ongoing periodic reporting to the public must disclose previously confidential information about the biotechnology company including, among other things, material agreements, intellectual property, financial data, competitive position, and officer and director compensation.

Reporting and Ongoing Compliance

The public biotechnology firm will be subject to the periodic reporting requirements of the SEC. These requirements include: quarterly reports (Form 10-Q); annual reports (Form 10-K); current reports of material events (Form 8-K); proxy statement disclosures related to the board and officers in connection with shareholder meetings; and reporting ownership in and trading of shares by insiders. These public filings require complex information technology and accounting systems, internal controls, more accounting staff, and increased use of lawyers, accountants, and other outside advisors. Securities analysts and the financial press will also require attention from executives.

Initial and Ongoing Expenses

Going public is a costly and time-consuming endeavor. Legal, accounting and related investor relations expenses will obviously increase on an ongoing basis as a result of a public offering. There are also the costs related to the offering itself. The underwriter of a public offering will charge a commission that can range from 6% to 10% of the offering price. In addition, legal and accounting fees, printing costs, underwriters' expenses and fees will generally add \$500,000 or more to the cost of an offering.

Pressure to Satisfy Shareholder Expectations

Investors will generally expect the biotechnology firm to maintain and continually improve performance with respect to measures such as revenues, earnings, growth, and market share. This can be a significant challenge for a pre-revenue biotechnology company whose fortunes cannot necessarily be measured by revenue or earnings growth but through product or technology development milestones that may or may not pay off in terms of revenue or earnings sometime in the distant future. If investors become disillusioned with the firm's performance, the firm's share price will drop.

Restrictions on Selling Existing Shareholders' Shares

Controlling or major shareholders of a public company cannot freely sell their shares. Additionally, no one with inside information may trade in the company's stock before that information becomes public under penalty of civil and criminal law. Other restrictions include the short-swing profit prohibition which generally bars officers, directors and greater than 10% shareholders from buying and selling company traded securities at a profit in a six-month period whether or not the trading was based on inside information.

Preparing the Biotechnology Firm for an Initial Public Offering

Company Readiness

There is no magic rule to determine whether a company is ready to be public. A variety of factors including market conditions, the right product or technology, financial condition and results, management team and business plan will generally determine whether a company and its advisers can successfully complete a public offering. Many biotechnology firms often require a long gestation period before they are able to generate revenue or earnings. Consequently, with the exception of proven or established companies, underwriters will generally demand that a traditional start-up biotechnology company going public have a strategy that can be easily explained and understood by investors to support a public offering. Biotechnology firms that have no revenues or earnings generally must be developing a very innovative therapy or technology and have in place a strong management team to compensate for the lack of a financial track record.

Board of Directors

Selecting a board of directors for the public biotechnology firm is not that different from selecting directors for a public company in any other industry. The biotechnology firm needs a board that is experienced in the firm's industry and has financial expertise. The expertise of the firm's board in addition to the strength of the management team and business plan is typically an important selling or marketing tool for the underwriters. Additionally, the firm should have a majority of independent directors. Independent directors are those who are not officers of the biotechnology company or its subsidiaries and who do not have a relationship with the biotechnology firm such as a consultant, former employee, vendor or supplier.

Board Committees

The biotechnology firm contemplating an IPO must have independent directors willing to serve on an audit, compensation and governance committee. In response to corporate scandals, the roles of these committees in corporate governance, oversight of management and responsibility to the public shareholders has been magnified. The listing rules of the exchange on which the biotechnology firms will trade must be reviewed to determine whether the biotechnology firm's board can satisfy the independence and governance requirements.

State of Incorporation; Minnesota vs. Delaware

An underwriter for a biotechnology firm contemplating a public offering may ask that the firm reincorporate in Delaware instead of Minnesota. Many national underwriters or their counsel are unfamiliar with Minnesota law and often try to persuade a company to reincorporate in Delaware. There are advantages to incorporating in Delaware, but there are also advantages to incorporating in Minnesota. A significant

number of the largest and most widely known public corporations in this country are incorporated in Delaware. There is, consequently, a widely followed core of Delaware corporate law that has been interpreted over the years. Many directors are also more comfortable serving on the board of a Delaware corporation because indemnification of directors under Delaware law is well developed and more certain compared to most other states, including Minnesota. Disadvantages to incorporating in Delaware include franchise taxes and less protection for minority shareholders. Advantages to incorporating in Minnesota include protections afforded by Minnesota's strong anti-takeover measures that are generally favorable to companies and incumbent boards of directors.

Control Share Acquisition Act

Unless a Minnesota corporation opts out of the statute in its articles of incorporation, the Control Share Acquisition Act⁹³ requires that shareholders of an issuing public corporation approve voting rights for bidders that acquire shares on the market once the bidder crosses certain thresholds. These thresholds are generally 20-33%, 33%-50% and 50% or more. This statute makes a takeover onerous by requiring shareholder approval for the bidder to have voting rights for shares acquired once each of these thresholds is reached.

Business Combination Act

The Minnesota Business Combination Act,⁹⁴ which cannot be opted out of, requires that a disinterested committee of directors approve any shareholder becoming a 10% or greater shareholder of the company in advance of the shareholder crossing the 10% threshold. Without advance approval by the disinterested committee, the shareholder cannot consummate a business combination with the company for four years. This prevents a hostile bidder from acquiring shares on the open market and forcing a takeover without review by the board.

Other Anti-takeover Measures

The start-up biotechnology firm must also consider whether it should adopt other anti-takeover measures. Traditional measures include implementing a staggered board that provides for only part of the board of directors (either one-third or one-half) being up for election each year. As a result, a hostile bidder cannot obtain control of the board of directors during any one board election. The firm may also adopt a poison pill or shareholder rights plan. This measure makes a hostile acquisition of the firm difficult without the approval of the board of directors. Each of these measures have advantages and disadvantages. Some argue that these measures are beneficial to longer-term shareholders because they deter short-term takeover speculative conduct, while others contend that these measures merely entrench the existing board and management.

Underwriters

The underwriter is an investment banking firm or broker-dealer that purchases shares from the firm in the IPO and immediately resells the shares to the public. The selection of the underwriter is one of the key decision points in the biotechnology firm's undertaking a public offering. Often, this decision will be made with input from the venture capitalists, investors, or other significant shareholders that have financed the firm.

In selecting underwriters for a public offering, a biotechnology firm should consider whether the underwriter: is national, regional or local; has experience in the biotechnology industry; is excited about the company's business plan and been successful with biotechnology related IPOs; and, has research and brokerage experience in the biotechnology industry.

The following is a summary of typical underwriting arrangements.

Letter of Intent

An underwriting agreement is signed only after the registration statement becomes effective. The formal underwriting relationship typically begins with a letter of intent.

Offering Size and Price

Underwriters will not guarantee an offering price or total proceeds in advance. In order to meet market conditions, the offering price is set when the registration statement becomes effective. Underwriters will generally estimate a range for the offering price based on market conditions, but these estimates are not binding.

Underwriting Commissions

The underwriting commission, or discount, is the single largest expense in a public offering. The rate has generally been in the range of 6 to 10%.

Underwriter Warrants

Many underwriters will request a warrant to purchase additional securities in addition to the commissions paid to the underwriter. The warrant will generally give the underwriter a five year right to purchase shares at a price equal to 120% of the IPO price.

Reimbursement of Underwriters' Expenses

The managing underwriters will often request reimbursement for some or all of their expenses incurred in the offering, including legal fees. The issuer and underwriter will often agree to limits on reimbursable expenses.

Rights of Refusal

Underwriters also often request a right of first refusal on any future underwritings or other financings by the biotechnology firm. If a right of first refusal cannot be avoided, the issuer should: establish a time limit after which the right expires; restrict the right so that it expires any time it is available but not exercised; and restrict the right so that it applies only to equity public offerings.

Lock-Up Agreements

Underwriters will typically insist that all company shareholders agree to “lock up” or not sell or transfer their shares from the time of the IPO until 6 or 12 months from closing without the express written consent of the underwriters.

Over-allotment Option

The underwriters will also ask for the right to purchase additional shares in an amount up to 15% of the offering for a period of 30 to 40 days after the closing of the initial offering. Whether this option is exercised depends upon the market acceptance of the company’s securities.

Offering Publicity

One of the most important aspects to a biotechnology firm’s public offering relates to the SEC’s restrictions on publicity and communications during the period before, during and after a public offering. The SEC has strict rules on what kinds of communications can and cannot be made during the offering process.⁹⁵ The biotechnology company must be very careful to comply. Specific issues unique to a biotechnology firm may occur if during the course of an offering the firm must make disclosures concerning the status of regulatory filings or approvals. The biotechnology firm would be permitted to issue a brief press release announcing (among other events in the process): its intent to undertake an offering; its filing of a registration statement; and the pricing of an offering. These press releases must contain warnings as set forth in state and federal securities laws and are typically reviewed by counsel for both the company and underwriter.

Starting from the time the biotechnology firm decides to undertake a public offering until a period after closing of the offering, the biotechnology firm is said to be “in registration.” During this “quiet period,” the firm may not tout the offering or the company. The firm may continue to distribute its literature to the types of persons that it has distributed to in the past (e.g., prospective customers and users of the company’s services and products), but a new public relations campaign to promote the company must be avoided. It is critical to comply with these publicity prohibitions of the securities laws. If the SEC determines there is inappropriate publicity or activity in connection with the offering, then the SEC could delay the offering, which could harm the firm if market conditions deteriorate and cause a liquidity crisis. The SEC may require the biotechnology firm to advise investors that they may have a rescission right for unlawful “offers” arising from unlawful publicity that hypes an offering. The SEC could also bring an enforcement action

against the biotechnology firm and one or more of its officers or directors. During recent years, the SEC has undertaken each of these actions against issuers. Additionally, shareholders who bought in the offering could sue the biotechnology firm and its officers and directors under the Securities Act for any oral communication during the quiet period that contained an untrue statement of material fact.⁹⁶

Preparing the Registration Statement

The biotechnology company and its counsel, the underwriter and its counsel, the company's auditing firm, investor relations counsel and scientific consultants including intellectual property counsel and others will meet many times in drafting sessions to prepare the registration statement. The registration statement includes the prospectus that will be delivered to investors. The entire registration statement becomes part of the public record immediately upon filing with the SEC and is available for public inspection. The SEC requires specific line-item information to be contained in the registration statement.⁹⁷ The prospectus is both a disclosure document designed to inform investors and limit liability to the company and its officers and directors by describing risks to investors, and a marketing document telling investors about the exciting investment opportunity that the company represents. These objectives often create conflict among the various constituencies involved in drafting the document and the SEC, which is responsible for reviewing the disclosure and declaring the registration statement effective to permit sales of the relevant securities.

The first step in preparing the registration statement is a general meeting with the company's executives, attorneys, accountants, underwriters, and underwriters' attorneys. At this meeting, responsibility for gathering information and preparing various parts of the registration statement is assigned. Typically, the attorneys plan a coordinating role in directing this team effort, and deadlines are agreed upon for providing the required information and drafts.

Due Diligence Investigation

"Due diligence" is a key aspect of the registration process. Due diligence is the responsibility of all those involved in the preparation of the registration statement to conduct all reasonable investigation to ensure the accuracy of the statements made in the registration statement and to ensure that no material information has been omitted. Of course, the exercise of due diligence with respect to any particular statement or disclosure will imply differing responsibilities depending on the position and role of the individual and the nature of the information.

The biotechnology firm itself is liable, regardless of due diligence, for any material misstatements or omissions in its registration statement. The directors, controlling shareholders, underwriters, experts and corporate officers may, however, avoid liability if they can show that they exercised reasonable or due diligence in examining the facts or relying upon the reports of experts. They cannot avoid liability if "red flags" exist that should have alerted them to investigate an issue further.

Every individual involved in the preparation of the registration statement need not personally verify each statement or disclosure made in the prospectus. It is permissible

for an individual to reasonably rely on statements made by experts such as independent accountants as long as there are no reasonable grounds to not believe and, in fact, the party does believe those statements.

The biotechnology company officers, company counsel, underwriters, underwriters' counsel, and independent auditors will dig deeply into the biotechnology firm and its affairs in carrying out due diligence procedures. Officers and directors should be prepared to candidly answer numerous questions on all aspects of the biotechnology firm and statements made in the prospectus and on the information included on management experience and background, compensation arrangements, and their contracts or transactions with the firm. Underwriters often engage a consulting firm to assist them in evaluating the biotechnology firm's technology, products, risks, FDA compliance and other related technical materials.

In carrying out due diligence procedures, the underwriters will request a "comfort letter" from accountants. This letter details the specific procedures carried out by the company's accountants with respect to the unaudited financial data contained in the registration statement and provides the underwriters with "negative assurance," a statement that nothing came to the accountants' attention that indicated that the unaudited financial statements and other financial data were not prepared in accordance with generally accepted accounting principles ("GAAP") applied on a consistent basis and that there have been no material changes in the financial position or results of operations.

SEC Review

The SEC's Division of Corporation Finance in Washington D.C. reviews all registration statements of IPOs for adequacy of disclosure in accordance with its regulations and other pronouncements. Any deficiencies noted by the SEC staff are generally communicated by a "comment letter."⁹⁸ The areas on which staff comments tend to focus are, to some extent, subject to trends. In many cases, the staff focuses on management's discussion and analysis of the issuer's financial condition and results of operations, transactions between the company and related parties, and areas of weakness in the company, or risks to the company or industry. The SEC may ask the company to support certain claims or statements made in the prospectus by sending the SEC "supplemental information" and to remove the claims or statements if the SEC considers the support inadequate. The SEC also may take issue with a particular choice of accounting policy or may request additional disclosures in the financial statements.

A number of activities begin once a registration statement is initially filed with the SEC. The preliminary prospectus, or "red herring" (so named because the SEC requires the cover page to include legends about the preliminary nature of the prospectus printed in red ink) is used by the managing underwriters to form an underwriting syndicate. Subject to SEC restrictions on the selling efforts that may be employed, the underwriting syndicate begins to deal with prospective investors interested in the offering. Finally, just before the effective date of the registration statement, the underwriting agreement is signed.

Underwriters' Syndication

As soon as the preliminary prospectus is filed with the SEC, the managing underwriters begin their efforts to assemble an underwriting syndicate to sell the company's securities. A copy of the red herring is provided to each prospective investor, who may then "express interest" in the shares. No sales may be made, however, or offers to buy accepted, prior to the effective date of the offering. Allocation of the underwriting commission is first made to the managing underwriters as compensation for managing the offering, with the balance allocated to the underwriting syndicate in proportion to both shares subscribed and shares ultimately accepted for sale to investors.⁹⁹

As already noted, the red herring prospectus may be widely distributed to underwriters and the investing public. No other written sales literature is allowed. The issuer may, however, publish a limited notice of the offering, including the amount of the offering, the name of the company, a description of the security, the offering price, and the names of the underwriters. Known as "tombstone ads" because of their stark appearance, these notices are typically published in newspapers on the effective date of the registration statement and are not considered to constitute sales literature.

Specified oral selling efforts are allowed once the initial registration statement is filed and thus, notwithstanding the comprehensive restrictions imposed by the SEC, most of the underwriters' sales efforts take place during this period.¹⁰⁰ The underwriters will likely take the biotechnology firm's executives on a "road show" to sell the offering. These meetings are designed to give prospective members of the underwriting syndicate and institutional investors an opportunity to understand the biotechnology firm and hear the "story."

Listing Requirements

In consultation with the lead underwriter, the biotechnology firm must decide where to list its securities. Historically, the New York Stock Exchange ("NYSE") has been considered the most prestigious exchange on which to list securities. The National Association of Securities Dealers Automatic Quotations ("NASDAQ"), however, is typically the choice of technology companies including most biotechnology companies undertaking their first offering. Each trading market has its own quantitative listing requirements, which will include market capitalization, price, revenue history, and its own qualitative listing requirements, which will include provisions related to independence of directors, and independence for members of the audit, compensation, governance and nomination committees.¹⁰¹ The markets also have listing fees that can be substantial. The listing rules also require shareholder approval requirements for various actions including adoption of, or material amendments to, equity compensation plans, changes in control and issuances of securities below market in certain instances.

Closing the Offering

If all agree to proceed with the offering, the deficiencies noted by the SEC have been cleared to the SEC's satisfaction, and the final pricing details have been agreed upon, then the registration statement is declared effective by the SEC, the underwriting agreement is

signed and the final prospectus is printed. The closing generally occurs three business days after the effective date and the proceeds are released to the company.¹⁰² If the over-allotment option is exercised, a second closing will be held following that transaction.

Periodic Reporting Requirements

Following the completion of a public offering, the biotechnology company is publicly held. This new status imposes its own significant expenses, burdens and responsibilities on the company and its officers and directors. The following is a summary of the principal requirements of public companies.

Form 10-K

After the biotechnology firm goes public, it must file with the SEC an annual report on Form 10-K within 60 or 90 days of the end of its fiscal year.¹⁰³ Form 10-K must contain audited financial statements for the last three fiscal years, or such shorter period as the company has been in existence, in addition to substantial information regarding the company and its past year's operations. Form 10-K must be signed on behalf of the company by its principal executive officer, its principal financial officer, its principal accounting officer, and by at least a majority of the members of its board of directors.¹⁰⁴ Smaller issuers may use Form 10-KSB (Small Business).

Form 10-Q

In addition to Form 10-K, the company is required to file a quarterly report on Form 10-Q with the SEC for the first three quarters of its fiscal year.¹⁰⁵ A report on Form 10-Q must be filed within 45 days after the end of each quarter (30 days for accelerated filers). No Form 10-Q is filed for the fourth quarter. Form 10-Q must include unaudited quarterly financial statements and must be signed by the appropriate officers, but not the directors, of the company. Smaller issuers may use Form 10-QSB.

Form 8-K

A Form 8-K report is required to be filed with the SEC within four business days following the occurrence of significant corporate events.¹⁰⁶ Events that trigger the Form 8-K reporting requirement include:

- Entering, terminating or amending a material agreement;
- Filing bankruptcy;
- Completing a material purchase or sale of assets;
- Incurring certain direct or off-balance sheet financial obligations;

- Receiving notice of being delisted from a stock exchange or NASDAQ;
- Unregistered sale of equity securities;
- Change in accountants;
- Appointment or departure of officers or directors;
- Amendments to articles of incorporation or bylaws; and
- Amendment or waiver of company code of ethics.

Management Discussion and Analysis

The Company must include the Management's Discussion and Analysis of Financial Condition and Results of Operations ("MD&A") in its Form 10-Q reports and its Form 10-K or its annual report to shareholders, as well as in registration statements under the Securities Act.¹⁰⁷ The MD&A is intended to "provide in one section of a filing, material historical and prospective textual disclosure enabling investors and other users to assess the financial condition and results of operations of the registrant, with particular emphasis on the registrant's prospects for the future."¹⁰⁸ In recent years, the SEC has focused on the importance of the MD&A section as a guide to interpretation of a company's financial statements. Failure to include adequate disclosure may result in enforcement actions and possible civil litigation. The SEC emphasized that a company is required to disclose currently known trends, events, and uncertainties that are reasonably expected to have material unfavorable or favorable effects on a company, such as: a reduction in the company's product prices; an erosion in the company's market share; changes in insurance coverage; or the likely non-renewal of a material contract. The MD&A rules also require a description of short-term liquidity and capital resource needs, covering cash needs up to twelve months in the future, and long-term liquidity and capital resource needs beyond the next twelve months, as well as the proposed sources of funding required to satisfy such requirements.

Exhibits

The exhibits that must be publicly filed include basic documents of the company, consisting of its articles and bylaws, and "material" contracts. Under new SEC rules effective in 2004, when a company enters into a contract or terminates or amends a contract, the company must determine whether the contract would come within the definition of a "material" contract as set forth in Item 601 of Regulation S-K.¹⁰⁹ If so, the company must file a Form 8-K within four business days describing the contract.

Proxy Regulation

Public companies are required to comply with the proxy requirements of the Securities Exchange Act of 1934, as amended ("Exchange Act") and file proxy materials with the SEC in connection with any matter brought to a vote of their shareholders. The final

proxy statement must always be mailed to the SEC concurrently with its mailing to shareholders. It is unlawful for the company to solicit or lend its name to the solicitation of a shareholder vote without compliance with the proxy regulations of the Exchange Act.

Generally, the solicitation is made on behalf of the board of directors and relates to an annual meeting at which directors are to be elected. This proxy statement must be accompanied or preceded by an annual report to security holders containing audited financial statements for the last three fiscal years and other information required by the Exchange Act.

Of interest to officers and directors is the requirement that the proxy statement must disclose the cash compensation, bonus arrangements and stock option information relating to the company's CEO and the company's four most highly compensated executive officers other than the CEO whose total cash and cash equivalent remuneration, during the preceding fiscal year, exceeded \$100,000. Material relationships and transactions between the company and directors, director nominees or executive officers must be disclosed, as well as any involvement in legal proceedings by a director, director nominee or executive officer during the past five years where the proceeding is material to an evaluation of the ability or integrity of the director, director nominee or executive officer. In addition, the proxy must disclose any delinquent filings required to be made by officers, directors and 10% shareholders. These disclosures provide only a small part of the information that must be included in the company's proxy statement.

Accurate Books and Records

In response to "Watergate" and bribes to foreign officials by U.S. corporations, the Foreign Corrupt Practices Act ("FCPA")¹¹⁰ was enacted in December 1977. The FCPA requires public companies to make and keep books, records and accounts that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company.

Public companies must devise and maintain a system of internal accounting controls sufficient to provide reasonable assurances that:

- Transactions are executed in accordance with management's specific authorization;
- Transactions are recorded as necessary to permit preparation of financial statements in conformity with GAAP or other applicable criteria;
- Access to assets is permitted only in accordance with management authorization; and
- The recorded accountability for assets is compared with existing assets at reasonable intervals and appropriate action is taken with respect to any differences.

As described below, the accuracy and reliability of the biotechnology company's systems for recording transactions are critical, and must be certified by the biotechnology company's CEO and CFO and will be attested to by the biotechnology company's independent auditor.

Sarbanes-Oxley

Overview

In response to widely reported corporate fraud and accounting lapses, in July 2002, Congress enacted a series of corporate governance and accounting reforms under Sarbanes-Oxley.¹¹¹ This statute, along with rules and regulations promulgated by the SEC, contain the most significant changes affecting public companies since the passage of the Securities Act and Exchange Act in 1933 and 1934, respectively. Among other things, Sarbanes-Oxley contains important new reforms in accounting, disclosure practices, corporate governance and responsibility, insider trading, audit committees and attorney conduct. In addition to empowering the SEC's regulatory powers, Sarbanes-Oxley reflects an aggressive and active regulatory philosophy toward publicly held corporations in which conservative accounting and transparent disclosure are the guiding principles.

Much of Sarbanes-Oxley responds to widely reported misconduct of large publicly traded companies and their advisers. Unfortunately, with some minor exceptions, the Congressional response embodied in Sarbanes-Oxley applies generally to all companies that are publicly reporting regardless of their size.

One of the important changes brought about by Sarbanes-Oxley is the explicit subjection of a public company's senior officers, including the CEO and CFO, to potential criminal responsibility for the company's failure to complete accurate and truthful disclosure documents, including financial statements and other information contained in SEC reports.

Section 302 Certifications

Section 302 of Sarbanes-Oxley and SEC Rules¹¹² require that the CEO and CFO certify each SEC periodic report. This means that the CEO and CFO must certify, in each quarterly and annual report, among other things, that:

- Each signing officer has read the periodic report;
- The report does not contain any untrue statements of material fact or omit any statements of material fact;
- The financial statements included in the report fairly present the financial condition and results of operations of the issuer; and
- Management is responsible for establishing and maintaining internal controls, that these controls are designed to ensure that material information is made

known to these officers, that the controls were evaluated as of the end of the period covered by the report, that management has reported to the board and audit committee any fraud by employees or management and has reported any deficiencies in controls.

Section 906 Criminal Certifications

Section 906 of Sarbanes-Oxley¹¹³ requires the CEO and CFO to certify, subject to criminal penalty, that each SEC report that includes financial information fully complies with the Exchange Act and is free of material misstatement or omission.

It is important to create internal systems from the bottom up to permit the CEO and CFO to make the appropriate certifications, and permit the external auditor to audit and attest to the efficacy of the internal control systems. Depending on the size of the organization, the CEO and CFO may have to rely on certifications from lower level employees involved in preparing and recording transactions.

Management's Report on Internal Controls and Attestation by Independent Auditor

In addition to the certifications described above, Section 404 of Sarbanes-Oxley¹¹⁴ requires a report of management on internal controls over financial reporting. This report must include:

- A statement of management's responsibility for establishing and maintaining adequate internal control over financial reporting;
- Management's assessment of the effectiveness of internal controls as of the end of the year;
- A statement identifying the framework used by management to evaluate the effectiveness of internal controls; and
- A statement that the company's independent auditors have issued an attestation report on management's assessment of internal controls.

The biotechnology company must work closely with its independent auditors to establish internal controls and develop strategies for creating a Section 404 report that can be attested to by its independent auditors. The expense and effort necessary to satisfy these requirements should not be underestimated.

The SEC's rules implementing Section 404 also require, on a quarterly basis, that management evaluate any change in the company's internal controls over financial reporting that occurred during the fiscal quarter that has materially affected, or is reasonably likely to materially affect, the company's internal controls over financial reporting.

Increased Liability Risk and Forfeiture of Bonuses for Certain Restatements

Sarbanes-Oxley subjects officers and managers to increased exposure for financial fraud and misstatements. In addition, Sarbanes-Oxley provides that if the reporting company is required to restate financial results as a result of misconduct, then any bonuses, incentive or equity compensation paid to the CEO or CFO must be reimbursed to the company.

Audit Committees

As a result of the scandals that led to the passage of Sarbanes-Oxley, the audit committees of publicly held companies are endowed with greater powers and responsibilities. Under Section 301 of Sarbanes-Oxley, the SEC is directed by Congress to approve rules of the NYSE, NASDAQ and other exchanges related to the policies and practices of a public company's audit committee. All issuers must have an audit committee. If an audit committee is not designated, the entire board will serve as the audit committee. Each member of the audit committee must be independent, which means that the member may not accept any compensatory fees from the issuer other than in his or her capacity as a member of the board or a board committee, and the member is not an affiliated person of the issuer. An affiliated person is one who controls or is controlled by the issuer. The SEC rules regarding independence created a safe harbor from the definition of an affiliated person for individuals who own less than 10% of the issuer's voting securities.

Among other things, audit committees must be responsible for the appointment, compensation and oversight of the company's public accounting firm, establish procedures for the anonymous confidential receipt of complaints regarding accounting and auditing matters, and have the authority and funding to engage advisers. In its role of appointing and overseeing the issuer's auditors, the audit committee should keep in mind that a public accounting firm performing the issuer's audit is restricted from performing certain non-audit services that are listed in Sarbanes-Oxley. Even if a non-audit service is not explicitly prohibited by Sarbanes-Oxley, any other non-audit services may only be provided by the issuer's auditor if the service is pre-approved by the audit committee.

Financial Experts

Under Section 407 of Sarbanes-Oxley, the biotechnology company's board must identify whether the audit committee has any "financial experts." A director can be considered a financial expert if he or she has, through education or experience, an understanding of GAAP, experience preparing or auditing financial statements, applying GAAP for estimates, accruals and reserves, experience with internal controls or an understanding of audit committee functions.¹¹⁵

Controls to Ensure Material Transactions are Disclosed

The biotechnology company must have systems in place to ensure that all material transactions are made known to the persons at the company that are preparing SEC

documents.¹¹⁶ These systems are formally called “disclosure controls.” The company’s CEO and CFO must certify the effectiveness of these controls on a quarterly and annual basis within the Section 302 certification described above.

Off Balance Sheet Transactions

Section 401(a) of Sarbanes-Oxley¹¹⁷ requires issuers to disclose all material off-balance sheet transactions, arrangements and obligations (including contingent obligations) in quarterly and annual reports. The types of disclosure required include: the nature and business purpose of the transactions; the importance of the transaction to the issuer in terms of liquidity, capital resources, market risk or credit risk or other benefits; the financial impact and exposure to risk; and any known events, demands, commitments, trends or uncertainties that implicate the issuer’s ability to benefit from its off-balance sheet arrangements.

No Personal Loans

Sarbanes-Oxley forbids a public biotechnology company from directly or indirectly extending or maintaining credit or arranging for the extension of credit in the form of a personal loan to any officer or director. This prohibition includes loans to help recruit an executive such as loans to buy or sell a home and loans to purchase equity.

Code of Ethics for Senior Financial Officers

Sarbanes-Oxley requires that every public company establish a code of ethics for its senior financial officers, or disclose to the public why it does not have a code of ethics. The code of ethics should be written and should generally be designed to deter wrongdoing. At a minimum, the code should promote:

- Honest and ethical conduct, including the ethical handling of actual or apparent conflicts of interest between personal and professional relationships;
- Full, fair, accurate, timely and understandable disclosure in reports and documents that a registrant files with or submits to the SEC and in other public communications made by the biotechnology company;
- Compliance with applicable governmental laws, rules and regulations;
- The prompt internal reporting to an appropriate person or persons that are identified in the code for violations of the code; and
- Accountability for adherence to the code.

Disclosure Issues

The code of ethics may be disclosed on a corporate web site or included as an exhibit to the annual report on Form 10-K. If an officer or director is granted a waiver from the application of the code of ethics, the waiver must be disclosed to the public on the biotechnology company's web site, and filed with the SEC on Form 8-K.

Whistleblower Protection

As described above and pursuant to Section 301, a key reform of Sarbanes-Oxley is the requirement that public companies establish a confidential anonymous system to permit employees to report evidence of financial fraud and other wrongdoing. Section 806 of Sarbanes-Oxley prohibits public companies from demoting, terminating, suspending or harassing any employee that provides information or assists an investigation concerning a violation of SEC rules or statutes or financial fraud.

Counsel's Duty to Report Misconduct Up the Ladder

Outside counsel is required to report evidence of material violations of the securities laws or breaches of fiduciary duty by a public company or its officers or directors to the biotechnology company's chief legal counsel or CEO. If those officers do not appropriately respond to the evidence reported by counsel, then the attorney must report the events to the audit committee. The biotechnology company has the option of establishing a committee of outside managers including one audit committee member - a Qualified Legal Compliance Committee ("QLCC") - to receive complaints and investigate potential violations. Outside counsel may report evidence of violations to the QLCC.

Use of Non GAAP Financial Measures and Quarterly Conference Calls and Earnings Releases

In response to issuers' optimistic portrayals of financial performance not calculated according to GAAP, the SEC has adopted new rules that strictly govern and limit public companies' disclosure of financial measures of performance outside of GAAP measures. Classic examples of non-GAAP financial measures include earnings before interest and taxes ("EBIT"), and earnings before interest, taxes, depreciation and amortization. The SEC and Congress were dismayed at public companies' practice of stretching accounting principles and misleading investors by reporting that they were profitable only if certain items are deducted from the results calculated in accordance with GAAP. Using non-GAAP measures to discuss performance may be important for a biotechnology company because the firm's product, service or technology could be many years away from producing net income according to GAAP and the market may be monitoring non-GAAP measures.

Regulation G and Disclosure in Press Releases and Conference Calls

Under the SEC's Regulation G,¹¹⁸ if the biotechnology company publicly discloses a non-GAAP financial measure in a press release, an oral presentation or other non-SEC filing, then the firm must provide the most directly comparable financial measure calculated and presented in accordance with GAAP, and include a reconciliation schedule showing quantitatively the differences between the non-GAAP financial measure and the most directly comparable measure calculated in accordance with GAAP. For example, if a company discloses an EBIT number, the biotechnology company must disclose net income calculated in accordance with GAAP and include a schedule that shows the differences between the calculations. This reconciliation should accompany any written disclosure and be posted on the company's web site.

SEC Disclosure Under Item 10 of Regulation S-K and S-B

The SEC also added a requirement concerning disclosures of non-GAAP financial measures in filings with the SEC. If the biotechnology company discusses non-GAAP financial measures in an SEC-filed document, the biotechnology company must provide an equally prominent presentation of comparable GAAP calculated performance along with a reconciliation schedule showing the differences between the GAAP calculation and non-GAAP calculation. The company must also explain why the non-GAAP financial measure is useful to investors, and describe any purposes for which management uses the non-GAAP financial measure. A purpose might include calculating compensation or measuring business unit performance.

Under Item 10, the company may not present a non-GAAP financial measure on the face of its financial statements, or in the accompanying footnotes. It is also a violation to adjust a non-GAAP financial measure to eliminate or minimize items identified as non-recurring, infrequent or unusual, if the item is reasonably likely to recur within two years, or there was a similar item within the prior two years.

Earnings Announcements Furnished to the SEC on Form 8-K

Whenever the company publicly reports its quarterly or annual financial results, the company must furnish a copy of the information to the SEC on Form 8-K within four business days unless a conference call is scheduled, and in that case the 8-K must be filed before the conference call as described below. Typically this is accomplished by furnishing a copy of the company's press release for the quarter or year-end period. This 8-K is required even if the press release does not contain any non-GAAP financial measures. If the release contains non-GAAP financial measures, then the release must include the reconciliation and disclosures required by Regulation G and Item 10 described above.

Earnings announcements on Form 8-K are "furnished" to the SEC rather than filed, and that means the information is not incorporated by reference into a registration statement, proxy statement or other report by the company.

Earnings Conference Call Procedures

The following procedures should be followed in connection with a quarterly or other conference call with investors to discuss financial results that have been issued in a press release:

- The earnings announcement press release should be furnished to the SEC on Form 8-K;
- Within 48 hours of the press release, the conference call should be held and its content must be complementary to the information contained in the press release;
- The conference call must be broadly accessible to the public by dial-in conference call, webcast or similar technology and may include a question and answer session;
- The financial information in the press release must be provided on the issuer's web site; and
- The conference call must be widely publicized in advance, and the biotechnology company should disclose instructions on how to access the presentation and indicate where on the web site the earnings information appears.

If these procedures are not followed, or if the conference call content is not complementary to the press release information, then it may be necessary for the company to furnish the conference call transcript on a Form 8-K, in addition to the 8-K that previously furnished the press release.

Enhanced SEC Enforcement Authority and Increased Civil and Criminal Penalties for Securities Fraud

Sarbanes-Oxley greatly expands the SEC's powers and authority in regulating and policing public companies and their officers and managers. The statute provides greater resources to the SEC's enforcement program, and expands the SEC's enforcement powers generally.

Increased Enforcement Remedies

It is now easier for the SEC to permanently bar an individual from serving as an officer or manager of a public company. The SEC need only prove that the individual is unfit, rather than the prior standard of "substantially unfit," to serve a public company. The SEC may also seek to escrow payments that may be made to officers or managers of a public company during the pendency of an investigation. In addition, if an issuer restates its financial results due to material noncompliance with SEC rules as a result of misconduct, the CEO and CFO of the issuer must reimburse the company for any bonuses, incentives, equity based compensation or profits realized on sales of securities during the 12-month period following the issuance of the original results that required restatement.

Increased Criminal Penalties

Sarbanes-Oxley has increased the maximum penalty for violating the Exchange Act to a \$25 million fine and up to 20 years in prison. Sarbanes-Oxley also subjects the CEO and CFO to criminal exposure for falsely certifying financial results. Retaliating against someone that assists an SEC investigation is also a federal offense that could subject an individual to imprisonment. It is also illegal to alter, destroy or mutilate records with the intent to obstruct an investigation of a public company.

Timely and Adequate Disclosure of Corporate News

Publicly held companies are generally expected to release quickly to the public any news or information that might reasonably be expected to materially affect the market. As with most “general rules” there are exceptions. If there are legitimate business reasons for withholding the public disclosure of material corporate information, many corporations (upon advice of counsel) will defer disclosure. If the information leaks into the marketplace or if significant trading activity occurs in the shares of the non-disclosing company, counsel will generally advise public disclosure since most courts have concluded that, where there is selective dissemination of information, the interests of the marketplace outweigh the company’s business reasons for non-disclosure. Accordingly, if the biotechnology company is faced with this conflict, it is important to consider all the legal alternatives available to the company. The biotechnology company should act promptly to dispel unfounded rumors that result in unusual market activity or price variations.

Significant events such as negotiations leading to acquisitions and mergers, stock splits, the making of arrangements preparatory to private or public financing and new contracts, products, or discoveries involve the risk of untimely and inadvertent disclosure of corporate plans. Care must be used in order to keep the information on a confidential basis. Public disclosure of these negotiations has received intense scrutiny by the courts and the SEC. Corporate counsel should be contacted early in the process of any discussions that may lead to a significant corporate transaction in order to assist in evaluating the disclosure issues.

The NYSE has promulgated the following standard: where it is possible to confine formal or informal discussions to a small group of the top management of the company or companies involved, and their individual confidential advisers where adequate security can be maintained, premature public announcement may properly be avoided. In this regard, the market action of a company’s securities must be closely watched at a time when consideration is given to important corporate matters. If unusual market activity develops, a company should be prepared to make an immediate public announcement of the matter.¹¹⁹ Fairness requires that the company make an immediate public announcement as soon as confidential disclosures relating to such important matters are made to “outsiders,” such as appraisers, underwriters or engineers. Where an initial announcement cannot be specific or complete, it will need to be supplemented from time to time as more definitive or different terms are discussed or determined.

Corporate employees, as well as directors and officers, should be reminded as a matter of policy that they must not disclose confidential information they may receive in the course of their duties and must not attempt to take advantage of such information themselves.

Requirements of Officers, Directors and 10% Shareholders

There are three specific requirements of Section 16 of the Exchange Act dealing with “insiders” (executive officers, directors and shareholders with 10% or greater beneficial ownership in the common stock of the company). They are as follows:

- New insiders of the company must disclose their direct and beneficial ownership of the company’s equity securities on Form 3 within ten calendar days of becoming an insider;
- Insiders of the company must report all of their transactions in the company’s securities within two business days on Form 4 and, in some circumstances, must file an annual report on Form 5 to report certain exempt transactions; and
- Insiders of the company may not profit from the purchase and sale or sale and purchase of the company’s securities if both transactions occurred within a six-month period.

Individual Sales of Shares

There are restrictions on resales by the biotechnology firm’s executives or directors who wish to sell some shares to diversify their portfolio or raise cash. First, the underwriters will generally insist that insiders not sell any shares for six or twelve months after the offering without the consent of the underwriters. Once this “lock-up” period expires, insiders must generally sell in compliance with Rule 144 of the Securities Act.¹²⁰

Rule 144

Where any person sells “restricted” or “lettered” stock (stock acquired otherwise than in a public offering), or where an “affiliate,” as defined below, of an issuer sells any stock of the issuer, whether restricted or not, the sales may be subject to the registration requirements of the Securities Act, on the theory that such person is an “underwriter” of the issuer’s securities (i.e., one who has purchased securities with a view to their distribution). Because there is great imprecision in determining when a person is an underwriter in these circumstances, the SEC has developed Rule 144 to provide some guidance. The SEC has taken the position that if restricted securities or securities of an affiliate are sold in strict compliance with Rule 144, the seller will not be deemed an underwriter for purposes of the Securities Act and the transaction will be exempt from its registration provisions.

Under Rule 144, an affiliate of an issuer is defined as “a person that directly, or indirectly through one or more intermediaries, controls, or is controlled by, or is under common control with, such issuer.” While the ability to exercise control of an issuer will vary in each situation, the SEC has taken the position that executive officers, directors and 10% or more shareholders should consider themselves to be affiliates and, when sales of stock (whether the stock is restricted or not) are made by these persons, then the requirements of Rule 144 should be followed.

In order for a sale to be effected in compliance with Rule 144, the following conditions must be met:

Holding Period

The insider must have held restricted securities for at least one year prior to the sale. Shares that were purchased in the market or acquired in a restricted issuance, *e.g.*, shares issued pursuant to a registered stock option plan, are not restricted.

Limitation on Amount of Securities Sold

Rule 144 limits the amount of securities that may be sold by affiliates during any three month period to the greater of 1% of the securities outstanding or the average weekly volume of trading during the four calendar weeks preceding the filing of the notice of the proposed sale on Form 144.

Manner of Sale

Securities sold by affiliates pursuant to Rule 144 must be sold by brokers acting as agents in unsolicited transactions or in transactions directly with a market maker of the securities.

Current Public Information

At the time of sale, there must be available adequate current public information with respect to the issuer, which means the issuer must be current in its SEC reporting.

Notice of Proposed Sale

If the proposed sale is more than 500 shares or for more than a \$10,000 aggregate sale price, the seller must file a notice on Form 144 to be sent to the SEC on the same day the order for sale is placed with a broker. Among other items of information, the Form requires a representation from the seller that the seller “does not know of any material adverse information in regard to the current and prospective operations of the issuer of the securities to be sold which has not been publicly disclosed.” Therefore, affiliates have an obligation to ensure that the representation can be validly given. In the event that such representation is given when the seller knew or should have known that it could not be given, or if all the requirements of Rule 144 are not met, the seller may be in violation of the registration requirements and in some cases the antifraud provisions of the Securities Act and the Exchange Act, thereby giving rise to potential civil liabilities.

Other Public Financing Alternatives and transactions

Once the biotechnology company is public and has been reporting, it can access the public capital markets. The company may, depending upon market demand and success of the company's product, service or technology, undertake a secondary offering in which the company, insiders or other selling shareholders participate. The firm may wish to acquire other companies or assets using its stock as currency. One common transaction that many biotechnology companies rely on as a public financing vehicle is the PIPE transaction.

PIPES

Overview

PIPE is an acronym for private investment in public equity ("PIPE"). This transaction is attractive for many new public companies including biotechnology companies because a PIPE offers relatively fast access to capital. Fast access is often necessary for biotechnology companies that need capital quickly to acquire assets, fund a clinical trial or some other corporate purpose when traditional bank financing is unavailable, and undertaking a follow-on public offering would take too much time. A PIPE transaction can be closed and funding provided to the public biotechnology company generally within ten to thirty days. Consequently, a PIPE transaction can be advantageous because it offers flexibility and speed to issuers and investors. It also is generally less expensive to consummate than a traditional public offering.

Essentially a PIPE involves a private placement of securities by an issuer to a relatively small number of investors. In connection with the PIPE, the issuer commits to file a registration statement to permit the investors to resell the privately placed security (or securities that are converted from the originally issued securities) into the trading market prior to the expiration of the one-year holding period that would be applicable under Rule 144.

Securities Issuable in PIPE Transactions

Many kinds of securities can be sold through a PIPE including common stock, convertible preferred stock, convertible warrants or other equity security. Typically, the security sold in the private placement, or the security into which the privately placed security is convertible, has an existing trading market. That permits relatively expeditious resales by PIPE investors when they choose.

Typical PIPE Terms

The conventional PIPE transaction consists of a private placement to institutions or to a small number of accredited investors through a stock purchase agreement. The investors purchase a fixed number of shares of securities at a fixed price at some

discount to the market. The stock purchase agreement contains typical representations and warranties but relies extensively on the adequacy of the disclosure contained in the biotechnology company's existing SEC reports. Immediately or shortly following the funding of the private placement, the biotechnology company files a resale registration naming the private placement purchasers as selling shareholders in the prospectus. Sometimes, the investors will receive interest on the privately placed security. Often the biotechnology company must pay the investors a penalty interest rate if the resale registration statement is not declared effective by the SEC within a certain time period.

Company Requirements

Typically, a biotechnology firm proposing a PIPE transaction is Form S-3 eligible. Form S-3 is a short-form registration statement that permits established companies to provide less disclosure to investors, and refers investors to publicly available information that becomes a part of the selling document. To be Form S-3 eligible, the biotechnology company must have been public for one year and have filed all required SEC reports in a timely manner and cannot have defaulted on any debt or failed to pay dividends on preferred stock in the past year. A PIPE can be accomplished with companies that are not S-3 eligible, but some of the advantages of speed and cost are lessened because of the time and expense required to comply with longer-form registration statements for the resale by investors.

Unorthodox PIPES, Toxic Conversions and Death Spirals

One PIPE transaction that desperate issuers sometimes succumb to is the "death spiral" or "toxic conversion" PIPE. In this transaction, the privately placed security converts into a variable number of shares of common equity that often is linked to the underlying trading price without a floor or bottom. If the market for the common equity declines, the private purchaser receives more shares. This type of transaction is commonly referred to as a "death spiral" because it is often associated with large declines in stock price and has been linked to price manipulation by short-sellers and others.

Regulatory Approvals

Depending upon the terms, a PIPE transaction may require approval of the exchange on which the company is listed. Also, listing rules of the American Stock Exchange, NASDAQ and NYSE generally require shareholder approval for issuances of securities, including convertible securities, equal to 20% or more of the voting power of the company, subject to certain exceptions and qualifications. In circumstances where shareholder approval is required, the company may close on a portion of the offering and then seek shareholder approval or close into escrow.

E. Debt

Introduction

As the biotechnology company matures, traditional debt from commercial lending institutions will become available as a financing alternative. The ability to obtain debt is a function of the borrower's cash flow, the value of the collateral that the borrower can post and the specific requirements unique to various lenders in the marketplace. In today's environment, competition for commercial lending is robust, which provides unique opportunities for the company to obtain reliable sources of financing at competitive interest rates and under favorable terms.

The process of obtaining commercial credit will be based primarily upon bank policies and procedures and various credit underwriting standards unique to the type of financing that is being obtained. Commercial loans for business purposes are exempt from many of the statutory protections afforded to consumer loans. Minnesota statutes and case law take the approach that as between a lender and a commercial borrower, there is a relatively even playing field.¹²¹ From a practical standpoint, this means that the company's ability to understand and negotiate an advantageous commercial loan will require considerable sophistication.

It is important to remember that banks are conservative lenders interested in two basic fundamentals. First, whether the borrower can afford to pay off the loans from cash generated by the operations of the company. Second, if operations falter, whether the lender has sufficient collateral to foreclose upon and liquidate in order to pay off any outstanding loan balances. Banks do at times extend unsecured credit, but this only occurs as an accommodation to an already existing customer who more likely than not has existing collateralized bank lines in place, or with a borrower whose financial strength is beyond questionable risk. As a result, a company in the development stage or early commercialization stage will find it difficult to obtain traditional debt financing since the lender may perceive the borrower's cash flow and collateral as being risky.

Cost of Credit

In most states, commercial lenders and borrowers are free to negotiate any rate of interest that they may agree upon, subject to applicable usury laws. Unlike consumer loans, which generally involve statutory caps for interest rates and regulated fees and charges, commercial transactions are much less regulated under state law. For example, Minnesota Statutes § 47.59 and § 334.022 provide that if the loan is made to a corporation, LLC, partnership, government or governmental subdivision or agency, trust, estate, joint venture, cooperative, or association, there is no limit on the interest rates, late charges, prepayment penalties, points, commitment fees, expenses, attorney's fees, or other charges.¹²² As a result, commercial lenders generally enjoy more freedom in negotiating acceptable interest rates, fees, charges, and other loan terms that could affect the overall cost of credit. The interest rate to be charged by a lender will be a function of general market interest rates, the lender's cost of funds, the repayment risk of the borrower and various bank policies.

As for the borrower's cost of capital, debt financing through loans and other credit instruments is preferred over equity financing. This is because debt financing offers: tax advantages (through the tax deductibility of interest expense); and cost savings because complex, expensive offering documents do not need to be prepared. While companies would like to use as much debt as possible for financing, lenders will only lend when they believe there has been a sufficient equity investment in the borrower. If a company has too much debt, it will not attract further equity investment. The equity versus debt financing question will continue for the life of the company. The goal for the financial managers of the company is to find the optimal mix of debt and equity.

The Purpose of Credit

Borrowers must be clear about the intended purpose of loan proceeds. Most lenders will focus on the principal use of the credit when determining which loan products are appropriate, and what the basic terms and conditions of those loans should be. Consequently, the company should have a practical understanding of its financial needs before considering debt as a means of financing. For example, if the company needs working capital for day-to-day operations, it may be better suited to a revolving or open-end line of credit where the company can borrow funds, repay funds, and re-borrow under a single agreement with the financial institution. On the other hand, if the company needs to make a substantial acquisition, perhaps for a piece of real estate or a key piece of equipment or technology, then a term loan for a specified amount may be more appropriate. Understanding the company's immediate and ongoing financial needs is critical in determining which loan will be most appropriate for the company.

Common Forms of Commercial Credit

Financial institutions offer various types of commercial credit. The features of the various credit products will change over the corporate life cycle of the borrower. For instance, assuming a stable interest rate environment, the interest and fees charged a borrower should decrease as it moves from a development to a mature stage company because the borrower's credit risk will have decreased. Regardless of the company's life cycle, several key factors will dictate which type of credit product is available to the company.

Unsecured Credit

One of the primary characteristics differentiating loan types is whether the loan is secured by collateral or not. In some cases, depending on the financial integrity of the company or the size of the loan, a lender may be willing to offer unsecured credit. This would simply involve the extension of funds without the need for any corresponding pledge of collateral such as accounts receivable, equipment or real estate. These types of loans are often referred to as signature loans since they simply rely upon the signature of the debtor as the promise to repay. For companies who seek to obtain unsecured credit, lenders will focus on all issues concerning cash flow and profitability.

In the commercial context, unsecured loans are rare. As previously stated, unsecured bank lending only occurs where there is already an existing secured line with the

lender, or where the financial strength of the borrower is beyond questionable risk. More often than not, a company seeking traditional debt financing must be prepared to offer collateral to secure commercial loans.

Secured Credit

Secured credit involves the pledge of corporate assets (or the assets of another person or entity) to the lender as collateral for a loan. Typically, secured loans involve two distinct types of collateralized transactions: asset-based loans and real estate loans.

Asset-based loans involve loans to the company tied to its general corporate assets, both tangible and intangible. The lender will seek a general security interest in the company's equipment, machinery, investments, inventory, patents, trademarks, or other assets where value can be determined. Lenders will require the company to pledge its assets to the bank at the time credit is extended. The lender's security interest will be documented in a security agreement and perfected (the process of establishing one's lien priority rights as against other lienholders) by the lender through the filing of various Uniform Commercial Code ("UCC") financing statements. Depending on the collateral pledged, additional documents, such as assignments may be necessary to properly perfect a lender's interest in the collateral. For biotechnology companies, lenders will want to closely review any patents and licenses being used by the borrower since these are the most valuable assets of the company and, therefore, the lender's best collateral. Failure to appropriately protect one's intellectual property can adversely affect a company's ability to obtain secured credit.

Real estate loans generally involve the lender taking an interest in the company's existing real estate holdings, or the lender financing commercial real estate for acquisition or expansion purposes. Security interests in real property are evidenced by a mortgage (or deed of trust, depending on the state) that must be filed in the appropriate recorder's office.

Lines of Credit vs. Term Loans

Beyond the issue of whether a loan is secured or unsecured, most lenders offer loan products that can generally be divided into two categories: lines of credit and term loans. The suitability of these credit facilities will be tied to various factors, most notably the company's financial needs and the intended purpose of the credit.

In a revolving line transaction, the bank provides the borrower a line of credit upon which it can draw funds, repay and draw again as the borrower's ongoing business needs may require. Most revolving loans are secured and the amount outstanding at any time cannot exceed the lesser of: the maximum loan amount; or the borrowing base (the maximum amount on which the lender will extend credit based upon the value of the pledged collateral times some percentage rate). In most cases, a business line of credit will require the company to pay interest to the lender each month, with the expectation that the principal loan amount will be repaid at the time of loan maturity. Lines of credit are a common form of debt financing and are often used to provide general working capital to a business.

In other situations, a term loan will be a more appropriate financing option. Term loans involve the borrowing of a fixed amount for a specified term and purpose. In most cases, the funds from a term loan are advanced all at once. Term loans for the most part will require monthly, quarterly or annual payments of principal and interest, with a final payment due at maturity. As with most commercial loans, the terms of repayment can be negotiated and the company may find that it can successfully obtain a term loan with monthly payments of interest only, followed by a balloon payment of the principal loan amount.

Letters of Credit

Beyond commercial lines of credit and term loans, the company may find it needs to rely on a bank or other financial institution for a letter of credit. A letter of credit is a written instrument involving three parties whereby the borrower satisfies an obligation of payment to the beneficiary by means of the bank promising to pay the beneficiary when the bank receives specific documents or instructions that are described in the letter of credit. Letters of credit are important tools to reduce risks associated with performance and payment issues on contracts. Letters of credit are frequently used in international sales and purchase transactions. Needless to say, banks will not provide letters of credit on behalf of its customers unless the customer has the financial strength to repay the bank for draws made on any letter of credit.

Working With a Commercial Lender

When approaching a lender for purposes of obtaining commercial credit, the company should be prepared to provide a wide range of information to the lender, both about the company and its business, as well as its owners and principals. Now, more than ever, lenders must conduct extensive due diligence of the company—not only for credit underwriting purposes, but also to comply with numerous federal regulations aimed at preventing illegal business activity. For example, the Bank Secrecy Act requires financial institutions to verify the identity of corporate owners, verify the legitimacy of the business, and review and retain records in accordance with the bank's anti-money laundering policy.¹²³ Recent amendments to this law (as a result of the USA Patriot Act) have increased the banking industry's focus on proper due diligence with all customers.¹²⁴ In addition, financial institutions must comply with the regulations issued by the Office of Foreign Assets Control.¹²⁵ This involves, among other things, the checking of corporate and business names against federally developed lists of suspected terrorists and specially designated nationals.

The lender will commence a thorough review of all aspects of the business including an analysis of corporate structure and formation, an inquiry into the owners and management, and a review of the financial health of the company. In short, the company must be prepared to provide adequate information to the financial institution so that the terms of the commercial lending relationship can be appropriately established.

Corporate Formation Documentation

Lenders will analyze the organization's corporate formation, including documentation regarding the nature of the entity's operations and its underlying owners. Lenders must review these documents in order to verify the company's legitimacy and understand who really owns the business. Beyond these formation documents, the lender will also want to examine corporate authorizations that identify those persons who have the authority to obtain credit on behalf of the company, and have the authority to legally bind the company.

Business and Strategic Plans

The borrower should also be prepared to provide its business plan or other strategic documents to the lender for review and analysis. Most commercial lenders will want to become familiar with the nature of the business, how it is run, and the various business goals and strategies which drive the organization. It is not uncommon for commercial lenders to interview additional members of management in order to obtain a better understanding of the company. The borrower will also need to educate the lender on the technology aspects of the business as well as product development and market acceptance issues.

Asset Quality and Financial Analysis

From a credit-underwriting standpoint, the company will be expected to produce numerous records, including corporate financial statements and tax returns which will paint the financial picture of the company. Credit analysts and underwriters will rely on these documents to determine the company's credit worthiness and to determine the boundaries within which credit will be extended.

A lender will perform a complete analysis of the company's assets and liabilities. For all secured lenders, a major concern will be the quality of the company's assets. For start-up, development and early commercialization stage companies, traditional credit will be extremely difficult, if not impossible, to obtain because the company's expenses exceed income, collateral risk is high and market acceptance risk is unknown. However, where a product has been developed and there is growing market acceptance, the value of the company's assets may be significant and bank credit will become available. Lenders will also determine the "borrowing base" (the percentage of the collateral upon which the lender will advance loan funds), and will establish financial ratios within which the borrower must operate during the term of the loan. The commercial lender will review and analyze all of these financial factors in order to establish a comfort level as to the company's financial adequacy and to better project the type and extent of credit that will be made available to the borrower.

Personal Financial Records

In many cases, depending on the life cycle of the company, it may be necessary to look to the business owners for additional collateral or guarantees to further secure company debt. In the event such collateral or guarantees are required, the lender will demand the personal financial records of the relevant business owners. In order to satisfy the lender's underwriting requirements, business owners should be prepared to submit personal financial documentation including financial statements, tax returns, and more.

Non-Bank Alternatives

There are ever-increasing "asset based" lending products being offered by various non-bank lenders, such as finance and factoring companies. As we have already noted, an asset-based loan is a loan secured by a company's accounts receivable, inventory, equipment, or other non-real estate assets. Alternatively, finance and factoring companies loan on a particular asset or group of assets. Examples would include the lease of a specific piece of equipment or a factoring (effectively a sale) of accounts receivable. In the non-bank asset based lending arena, the lender's primary focus is on the collateral value of the asset in the event the lender must liquidate the asset. As a result, non-bank lenders must ensure that they maintain a first lien security position in the assets they finance. Non-traditional asset based lenders often will advance funds when more traditional sources of debt financing are not available, and for accepting such risk, will charge a higher interest rate and higher fees. Consequently, this type of debt financing may be available to a company in the development stage or early commercialization stage.

Real Estate-Related Lending

For companies interested in acquiring real estate or expanding their operations through the construction of facilities, banks and other financial institutions are common sources of funding. Real estate lending transactions generally involve an additional layer of complexity both for the lender and for the borrower. In addition to providing all the necessary information for purposes of due diligence and loan underwriting, there will be informational requirements associated with the acquisition and development of the real estate involved. This often translates into a lengthier and more complex lending process, as well as increased costs and fees for completing the transaction. In addition to the type of real estate that is the subject of the transaction, the lender will focus on key factors unique to the real estate, such as property valuation, title issues, surveys and environmental issues.

Commercial Loan Documentation

Generally

Most commercial loan transactions involve a long laundry list of documents that are exchanged between the lender and the borrower throughout the course of the

transaction. The appearance of the documents may vary among commercial lenders, but for the most part, the legal impact will be the same. This section lists the important documents a company can expect to encounter when obtaining a commercial loan.

Letters of Intent or Proposal Letters

In some cases, lenders will provide a letter of intent or other form of written proposal that simply sets out projected credit terms being considered by the lender for a possible loan transaction. These letters are generally intended to be nonbinding communications between the lender and the borrower. The letter is intended to establish the parameters of the loan transaction and set a general course for more negotiations without making any firm commitment to lend.

Commitment Letter

Assuming there has been adequate credit underwriting, the lender will issue a commitment letter that will bind the lender to more specific terms of a loan transaction. Some lenders are reluctant to provide this type of letter, since it technically binds them to make the loan at a point in time when every detail of the transaction has not been addressed. Notwithstanding, commitment letters are critical in expansions and in mergers and acquisitions where a third party requires the borrower to produce a lender's commitment letter to confirm that the borrower has in fact secured the financing necessary to complete the contemplated transaction. The commitment letter should include all the key loan terms and conditions in an effort to describe what will later become the actual loan agreement. It will likely have a stated deadline or expiration date before which the company must accept the terms. In most cases, the commitment letter will provide that the borrower will be responsible for the lender's costs and expenses in auditing or otherwise evaluating the business, whether the loan is closed or not.

Credit Agreement

Prior to closing, the company must be prepared to sign a credit agreement, the document that will contain all the important restrictions that the company must follow during the term of the loan. This document usually accompanies the promissory note, and will describe other obligations of the company beyond the obvious expectation to repay the loan. The credit agreement will set forth the numerous loan fees and charges that the lender will impose and the "loan covenants" that must be carefully followed. Many of the provisions contained in the credit agreement will relate to ongoing business obligations of the company. For example, the company will be required to maintain its good standing as a corporate entity, pay its taxes when due, maintain proper insurance, allow for inspection of records and provide regular financial statements. In addition, the company will be expected to comply with numerous financial restrictions, such as borrowing base requirements and financial ratio covenants while the loan is in place. Obtaining additional debt through loans from other lenders will be prohibited or limited, and the company will not be allowed to pledge its assets or encumber any of its property without lender approval. The lender may also restrict payments and distributions to owners and shareholders of the borrower. If the company fails to follow

any provision of the credit agreement, the loan will likely be considered in default. Upon a default, the credit agreement provides for the rights and remedies available to the lender including acceleration of repayment of all outstanding loan balances.

Promissory Note

The promissory note is a negotiable instrument and specifically sets forth the type of credit being extended (e.g., term loan, line of credit), the dollar amount of the loan, and the company's promise as to how and when it will repay all related principal, interest and fees. The note will contain a laundry list of "events of default" which, if they occur, will trigger the lender's right to accelerate the loan and demand immediate payment. Default provisions will cover a wide range of conduct from a breach of the credit agreement to the lender's feeling or belief that the company may be in financial trouble, what is commonly referred to as the "general insecurity clause."

Guaranty

As noted earlier, many commercial loans are routinely secured by guarantees signed by the owner or other key persons within the business organization where the lender believes the borrower's ability to repay the loan or the collateral's liquidation value is risky. Obviously, a guaranty from an owner provides the lender with greater protection against the borrower's risk of default. Most lenders will require a "guaranty of payment," or "unconditional guaranty." This means the lender will be able to collect any indebtedness directly from the guarantor without first having to pursue collection efforts against the borrower. Depending on what the lender requires, the guaranty may cover a single debt or loan amount, or be more broadly worded to cover any present and future debts of the borrower. Guarantors should fully understand the nature and scope of their guarantees prior to signing.

Security Agreement

The security agreement grants the lender a security interest in the collateral securing the loan. The purpose of the document is to clarify the lender's rights to foreclose on the collateral in the event of nonpayment of the promissory note or other default. The document will also contain restrictions on what the company may or may not do with the collateral while it is subject to the lender's security interest. The lender will take steps to perfect its interest in the collateral. "Perfection" is a UCC term referring to the process whereby a secured party protects its lien priority interest in the collateral as against all other lienholders.¹²⁶ Lenders will do this in a variety of ways, depending on the nature of the collateral and the requirements of the UCC.

Mortgage

A mortgage (or deed of trust in certain states) is a security agreement for real estate. Where real estate is pledged to the lender as part of the deal, the lender will require a mortgage signed by all owners of the real estate. The terms of the mortgage will be

governed by state real property laws. Where the real estate involves multiple units or is subject to leases, the lender will also require an assignment of any rental income from those leases.

It is not uncommon for a lender to require that a personal guaranty be secured by a real estate mortgage, typically on the guarantor's home. Common consumer protections, such as the right of rescission, will not be available to a business owner who is asked to pledge his or her home as collateral. Federal Reserve Board Regulation Z (Truth in Lending) provides borrowers with the right to rescind or cancel a loan transaction where their principal dwelling has been pledged as collateral to secure another loan.¹²⁷ However, Regulation Z does not apply to business-purpose loans. As a result, the right of rescission will not protect the business owner who signs a mortgage to secure corporate debt.

Subordination Agreement

Lenders will require a debt subordination agreement when the borrower already has existing debt payable to another creditor. The subordination agreement is a three party agreement between the borrower, the bank as the senior creditor, and the other creditor as the subordinated or junior creditor. The document provides for the junior creditor to subordinate all its rights and remedies against the borrower and the collateral to the interests of the senior creditor. For companies moving from non-bank financing to more traditional debt, these agreements will be common.

F. Strategic Alliances

Introduction

A strategic alliance is a collaboration between two or more companies designed to achieve some corporate objective.¹²⁸ A strategic alliance can be virtually any business relationship between the parties and would include: supply, distribution, manufacturing, marketing and consulting agreements; technology license agreements; mergers or acquisitions; R&D funding agreements; and joint ventures.

Joint Ventures

A joint venture is an agreement involving two or more firms to use some of the assets or resources of each, by way of contracts or transactions, to perform some action providing a payoff to each firm.¹²⁹ It typically refers to instances in which two or more entities contribute assets to a newly formed entity for the purpose of advancing a technology or product. The basic reasons why entities form joint ventures are: each party wants to develop a new product or technology but needs the other party's assets or technology to be successful; each party recognizes an efficiency to combining forces as opposed to "recreating the wheel"; and the operating form provides for the parties to spread their risk of investment. The "efficiencies" could include: access to broader technology; access to broader production, supply and distribution channels; access to a broader customer base;

adding credibility by associating with a reputable entity; and access to regulatory programs and expertise.

A common example of a biotechnology joint venture occurs between a small biotechnology company (“Bioco”), and a large pharmaceutical company (“Pharma”). Typically Bioco has a promising new drug or technology (“Product”) it wants to develop and market but is short on cash for R&D. Bioco holds all the intellectual property rights to the Product and believes that if it can commercialize the Product, the returns will be substantial. As a result, Bioco does not wish to sell all of its rights in the Product. Furthermore, Bioco knows that it takes anywhere between ten to fifteen years at a cost of anywhere between \$800 to \$900 million to bring a new drug to market.¹³⁰ Pharma is interested in the Product for purposes of expanding or complimenting its existing product lines. Pharma could be faced with expiring patents on some of its long-standing product lines and is looking for a new successful drug. Pharma also believes that the returns on the Product will be substantial. Pharma has ready cash for investment in the Product as well as the experience and existing facilities to commercialize the Product. This would include experience with clinical trials and the FDA approval process as well as production, distribution and marketing capabilities. Given each party’s position, it makes sense for the two of them to form a joint venture to develop the Product. Bioco could contribute its technology, patents, research and management to the new entity and Pharma could contribute cash, management and support functions. In return, Bioco and Pharma would each own an interest in the new joint venture. Significantly, some studies indicate that the market value of biotechnology companies who had one or more Pharma equity partners averages 25% higher than those biotechnology companies who had no equity partner.¹³¹ Joint ventures have become so important in technology industries that many venture capitalists do not consider a technology company’s business plan to be complete without identification and discussion of possible corporate partners.¹³²

Joint ventures can be created for virtually any reason, product or technology, and can be between any size and type of entity. While the example of Bioco and Pharma is typical, joint ventures can and do occur between two small companies, or between two large institutions as evidenced by the Minnesota Partnership for Biotechnology and Medical Genomics announced in April 2003 between the University of Minnesota and the Mayo Clinic and sponsored by the State of Minnesota. Other than legal and regulatory limitations including issues such as antitrust, choice of entity, tax, securities and intellectual property (which by no means should be minimized), the joint venture parties are free to agree to any terms. Notwithstanding the benefit of being free to agree to any terms, the parties need to remember that creating and operating a joint venture is very difficult because of differences between the parties resulting from conflicting business cultures and investor expectations. The parties need to be clear with each other about their demands and expectations and reduce their understandings to a formal written joint venture agreement. Since the parties will work closely on an ongoing basis, the parties need to resist the urge to take every possible advantage during initial negotiations of the joint venture and instead leave some “money on the table” to provide continuing incentive for the other party during the course of the relationship.¹³³ The challenge of negotiating joint ventures is to create a structure where the different objectives and concerns of the two parties are compatible and can sustain a long term relationship.¹³⁴

Joint venture transactions are very complex and often involve R&D obligations, complicated technology licensing arrangements, manufacturing and supply provisions,

unique distribution arrangements, sensitive issues regarding technology ownership and rights in future technology and products, and a mixture of equity, debt and R&D financing.¹³⁵ The terms of all the operational issues regarding a joint venture need to be agreed upon by the parties and specifically set forth in a written joint venture agreement. Some of the most important operational issues are:

Investor Responsibilities – The parties need to agree to the common and unique responsibilities each party has to the other party and to the joint venture. This would include the timing and transfer of cash or technology, the method to conduct meetings between the parties, and how the parties may select and remove the management of the joint venture.

Management – The parties should agree on the persons responsible for the management of the joint venture and clearly set forth the responsibilities of those managers. The parties also need to agree as to how managers may be removed or changed. The parties, or the managers, should prepare a clear and comprehensive business plan with financial projections, financial milestones and operational milestones to ensure all parties agree on the expectations and direction of the joint venture.

Choice of Entity – In creating the new entity, the parties must be alert to the concerns and restrictions regarding choice of entity issues.

Rights to Intellectual Property – All parties need to clearly agree who has what rights in any relevant intellectual property developed during the term of the joint venture and at termination, liquidation or merger and acquisition of the joint venture. Furthermore, these agreements need to specifically address the parties' rights in any contributed, acquired, created and derivative intellectual property. The parties need to provide for the terms upon which the joint venture may acquire or dispose of any intellectual property.

Breakup – The parties need to agree on how, when, why and who can terminate the joint venture relationship. Breakup provisions will typically be tied to performance milestones and the business plan of the joint venture.

Mergers and Acquisitions – The parties need to set forth the terms upon which they will allow the joint venture to be merged or acquired by one of the parties or by an unrelated third party. Additionally, the parties need to agree on procedures for allowing the joint venture itself to complete acquisitions.

Accounting - Each party will need to consider the impact that an investment in the joint venture will have on its own financial statements. Specifically, where ownership is by common stock, investments under 20% are generally accounted for on a "cost basis" and are recorded on the investor's balance sheet at the lower of cost or market. This means the investor will be required to write-off part or all of its investment in the joint venture when the investment declines in value. Investments between 20% and 50% are accounted for under the "equity method" which means the investor will be required to recognize its ownership percentage of the joint venture's gains or losses on the investor's income statement. Finally, investments greater than 50% are accounted for on a consolidated basis. This means that all income, loss and balance sheet items are included in the investor's financial statements. The accounting requirements for each investor can, in turn, affect that investor's individual financing capabilities.

On the other hand, the Financial Accounting Standards Board Interpretation No. 46, *Consolidation of Variable Interest Entities, an Interpretation of ARB No. 51* ("FIN 46") established new guidance for the consolidation of variable interest entities (individually a "VIE") for which the voting interest model (common stock ownership) is difficult to apply. Essentially, FIN 46 requires VIE's to be consolidated by their primary beneficiaries if the entities do not effectively disperse risks among the parties involved.

A VIE often holds financial assets (e.g., loans or receivables), real estate or other property. It may be passive or it may engage in activities such as R&D on behalf of another company. FIN 46 defines a VIE as a corporation, partnership, trust, or any other legal structure used for business purposes whose equity, by design, has any of the following characteristics:

- The total equity at risk is not sufficient to finance the entity's activities without additional subordinated financial support (i.e., its equity at risk is less than or equal to the expected losses);
- The equity investors do not have the direct or indirect ability to make decisions about the entity's activities through voting or similar rights;
- The voting rights of equity investors are not proportional to their expected losses or residual returns and substantially all of the entity's activities are on behalf of an investor that has disproportionately few voting rights;
- The equity investors do not have the obligation to absorb the expected losses of the entity (e.g., the equity investors are protected from bearing their share of the entity's potential losses through a guaranteed return); or
- The equity investors do not have the right to receive the expected residual returns (e.g., their return is capped).

If an entity has equity capital of less than 10% of its total assets, the capital generally is considered insufficient to allow the entity to finance its activities without additional subordinated financial support. This presumption can be overcome, however, if: the VIE has demonstrated that it can finance its activities without additional subordinated financial support; the VIE has at least as much equity capital as similar entities that operate without additional subordinated support; or the amount of equity invested in the VIE exceeds the estimate of the entity's expected losses based on quantitative evidence. Although equity capital of less than 10% is presumed to be insufficient, equity capital of 10% or more is not presumed to be sufficient. An enterprise should consider whether the entity with which it is involved needs an equity investment greater than 10% of its assets to finance its activities without subordinated financial support, particularly if the entity is involved with risky activities.

The above accounting analysis is meant to provide general information. The specific facts and circumstances of a transaction must be thoroughly understood and researched before concluding on the proper application of GAAP. The accounting analysis does not include details of the proper accounting for investments in real estate.

Funding – While the venture parties may contribute funds to the new entity in return for debt or equity, the joint venture will also be concerned with the future financing of its

operations. Future funding may continue to be supplied by the venture parties or may be obtained elsewhere. The parties need to agree on how and when such future financings will occur. Any such financings will be affected by and subject to all the issues set forth in this Guide.

R&D Funding Arrangement

An example of an R&D funding arrangement would occur where a large pharmaceutical company provides funding to a small biotechnology company for purposes of advancing and developing the biotechnology company's new drug or technology in return for debt from or equity in the biotechnology company. Unlike a joint venture, the parties do not form a new separate entity. Typically, the contributing party also provides consulting expertise and physical facilities support in an effort to protect its investment. In an R&D funding arrangement, the contributing party will attempt to obtain future buyout rights with respect to the biotechnology company, the product, or the technology. At a minimum, the contributing party will want to acquire some exclusivity arrangement over sales of the product. Many, if not all, of the operational issues discussed under joint ventures also apply to R&D funding arrangements.

Support Agreements

Support arrangements would include any contractual arrangement between a biotechnology company and any other company. They would include, and not be limited to, any of the following types of agreements: research agreements; supply agreements; manufacturing agreements; distribution agreements; marketing and promotion agreements; and consulting agreements. Support agreements can be stand alone agreements, for example, where the biotechnology company outsources its production to an unrelated entity. Alternatively, support agreements can be wrapped into one agreement or one transaction. This occurs in joint venture and R&D funding arrangements where all of the supporting responsibilities can be, but are not required to be, incorporated within the written joint venture agreement or the written R&D funding agreement.

License Agreements

Whether a biotechnology company (collectively for purposes of this section on License Agreements, "Bioco") is small, medium or large, the licensing of its technology, intellectual property rights and products can play a key role in its financing strategy. Licensing encompasses both the grant of license rights to another company, referred to as "out-licensing" as well as obtaining a license from another company or person, referred to as "in-licensing." In financing efforts, out-licensing is used more commonly than in-licensing. Consequently, the primary focus of this section will be on out-licensing. Licensing can be either a stand alone event or a part of another strategic alliance such a joint venture, R&D funding arrangement, support agreement, or a merger or acquisition.

Objectives of “Out-Licensing” as Part of a Financing Strategy

There may be various reasons for Bioco to pursue out-licensing as a part of its financing strategy. Bioco may grant a license in its technology, products or intellectual property in order to obtain cash to fund further development of products or technology, or to reimburse itself for expenses for past development. Alternatively, Bioco may be seeking a partner that may be able to develop or commercialize the out-licensed product or technology better or more rapidly than Bioco is able to achieve on its own. The licensee may achieve more rapid proof of concept of Bioco’s core technology in a particular application, thereby enhancing the value of the core technology for other applications. Out-licensing of certain technology or products, or specific applications or fields of use for the technology or products, may allow Bioco to focus its resources and cash on other opportunities, such as other applications of the out-licensed product or technology. Offering to license technology or products in combination with the issuance of Bioco securities may enable Bioco to secure a strategic partner that is interested in an equity investment in Bioco, in exchange for rights in Bioco’s products, technology or intellectual property.

Scope of License

A critical consideration of out-licensing is the scope of rights to be licensed. Questions of scope affect the value that the license may command, as well as the rights and opportunities that remain for Bioco to pursue outside the scope of the license, which may affect subsequent rounds of financing. Bioco must consider what product or technology will be licensed, and what products or technology of Bioco will remain outside the scope of the license. For example, the licensee’s rights in the licensed product or technology may extend to all applications and fields of use for the particular licensed product or technology, or the license may be limited to specified applications or fields of use. Bioco must clearly define any limitations on fields of use or applications to avoid conflicting expectations and possible dispute if it licenses the same product or technology to more than one licensee. Bioco also must consider whether any limitations are, in fact, practical or enforceable once the product is commercialized. For example, a product licensed for a particular application or indication may possibly be used or dispensed by an end-user who could also use the product for another application outside of the licensed field. In this scenario, Bioco may be undercompensated if the consideration paid or payable to Bioco under the license is based only on the value of the opportunity within the licensed field.

The geographic scope of the license may also be critical. A licensee’s rights may be limited to certain countries or areas of the world. Bioco may need to analyze the value of the opportunity for commercialization of the license in a variety of countries and determine if the value is reflected in the consideration. One relevant issue is whether a particular licensee is capable of exploiting the licensed product or technology in each of the countries that are covered by the license, or whether the licensee will need to engage local “partners” as sublicensees in certain of the countries in order to realize the commercial value of the license in those other countries.

This leads to the consideration whether the license includes the right to sublicense. Most often, a license is deemed not to include the right to sublicense without the

licensor's consent unless the license expressly grants the licensee a right to do so. The exception to this general rule is that a license "to manufacture" generally includes the right "to have manufactured" unless the license expressly excludes this right or requires the licensor's consent.

The right to sublicense should be carefully considered. Bioco must be diligent in selecting a licensee it believes is capable and motivated to vigorously exploit and commercialize the licensed technology or products. Concern would naturally arise whether the full value of the licensed opportunity will be realized if the licensee is able to pass off to a sublicensee, without input from Bioco, the development, manufacture or commercialization of the licensed product or license. For example, a sublicensee that performs poorly with regard to regulatory compliance (whether in regard to manufacture or sale) may taint the product in other countries, undermining the value of the product altogether. To address these concerns, Bioco may want to condition the licensee's right to sublicense upon prior notice to and consent of Bioco. Whether to require this as a condition is not, however, always a "black and white" issue. For example, Bioco may be comfortable permitting the licensee to grant a sublicense without consent for marketing and sales, but require consent for a sublicense that is broader, including development, obtaining and maintaining regulatory approval and manufacture.

A related issue is whether the scope of the license should include the right to manufacture all components of the licensed product. Sometimes, Bioco will retain the manufacture of the licensed product or some key component or ingredient of that product. Perhaps Bioco will manufacture the product in bulk and supply product to the licensee for final packaging and labeling. Alternatively, the license may reserve for Bioco the production of some key ingredient for use in the licensee's production under the license agreement. This arrangement may facilitate more efficient utilization of Bioco's facility or afford Bioco an additional source of revenue in the form of the transfer price for the bulk product or ingredient supplied. Sometimes this arrangement is necessary because production of the ingredient is a part of Bioco's core technology that Bioco does not wish to disclose and teach to a licensee, or perhaps the processes involved in such production are beyond the technical capabilities of the licensee.

If the scope includes the right to manufacture and the licensee will undertake additional development, including development and testing in support of obtaining regulatory approval, Bioco must consider who will own rights in the resulting data and results, or any innovations or improvements to the licensed technology or product. Each of the licensor and licensee may want to "use" the data or improvement. If the rights are owned by the licensee, Bioco should receive a "license back" to use the data, results, improvements and innovations outside the scope of the license. The issue would arise whether that license back to Bioco from the licensee would be royalty-free or royalty-bearing. At a minimum, the licensee will generally want rights in the data, results, innovations and improvements as necessary to be able to fully exploit the licensed technology or product. For its part, Bioco will not want the licensee to hold any rights that would bar Bioco from pursuing opportunities outside the scope of the license, or bar any activities of Bioco whatsoever in the event the license is terminated.

Similarly, Bioco must consider whether the scope of the license includes rights in any later-developed intellectual property, enhancements or improvements of Bioco. The licensee may argue that it should not "have to pay for the same rights twice" if during

the term of the license Bioco develops enhancements to the licensed product or technology. It is common to include later-developed or acquired enhancements and improvements within the scope of the licensed rights. Bioco should give careful thought, however, as to the extent of future developments that will be included within the scope of the initial license. It may be suitable, for example, to include rights in ordinary course “tweaks” and improvements, but not “new generation” technology or products that are beyond the realm of ordinary course improvements to the initially licensed technology or product.

Valuing the License Rights

Once the scope of the license is defined, it is important to address the value of the licensed rights. Valuation will require consideration of a number of factors, including the market opportunity represented by the licensed product or technology within the field of use covered by the license, as well as whether there are particular synergies relative to the technology or products of a particular licensee that enhance the value of the license for that particular licensee.

A more general consideration is how preliminary or advanced the development of the licensed product or technology is relative to commercialization. This involves consideration of the stage of testing, clinical study, and regulatory approval and an analysis of what it would cost in dollars, resources and time for the licensee to pursue this opportunity in the absence of the license. There may be market-timing considerations such as whether the license grant at this particular time would permit the licensee to beat all or certain competitors to market enabling it to garner a greater market share.

Other factors relevant to addressing of valuation include the nature of any intellectual property rights that are being licensed. The licensor needs to consider whether its patent claims are broad and strong, or narrow and weak. The licensor needs to also consider whether it would be difficult for the licensee to pursue the commercial opportunity independent of the license without infringing the patents as well as the scope of the exclusionary effect afforded by the patents to create barriers to entry by third parties.

In addition, in valuing the licensed rights, the licensor should consider whether the grant of the license will, as a practical matter, foreclose other opportunities that are technically outside the scope of the license, and what will be the value of those lost opportunities.

Realizing Value for the License Rights

In connection with addressing valuation, the licensor needs to determine how to structure the license to realize its value. Often licenses involve payments upon signing, milestone payments and earned royalty payments. The product or technology whose development is more advanced with shorter time to commercialization often can command higher signing fees and earlier and higher milestone payments. This is because the opportunity that is closer to commercialization offers enhanced value, with

potentially reduced risk, and permits the licensee to incur fewer expenses to develop and achieve a quicker return on capital. Higher signing fees and earlier and higher milestone payments are also sometimes achieved if there is a very strong market opportunity and there would be substantial barriers to the licensee in pursuing this opportunity in the absence of the license (*e.g.*, due to expense, time or intellectual property rights).

Occasionally, a licensee seeks to obtain a license for “defensive purposes.” For example, if the licensee is pursuing alternative avenues of development for a potential product in an emerging area, it may be uncertain which path offers the best opportunity for commercial success and it may want to establish an intellectual property position blocking competitors from as many alternatives as possible. In that situation the licensee may be uncertain whether it, in fact, intends to commercialize the licensed technology, or whether it is securing the rights primarily to make those rights unavailable to competitors. In that circumstance, it is important that the licensor secure the value of the opportunity in non-contingent payments, because the licensee may never commercialize the product or technology. This may warrant a “paid-up license” under which the licensor receives a single signing fee, or a combination of a signing fee and other non-contingent installment payments.

In a payment structure involving milestone payments, it is important that milestone events be stated with clarity to avoid confusion and dispute. The milestone events should be clear, measurable and objective. Milestone events that are based upon “satisfactory completion” or “satisfactory results” of pre-clinical testing, for example, without stating an objective standard for “satisfaction” (such as achieving pre-stated end objectives for the testing) are ripe for conflict. The licensor needs to consider carefully the consequences if milestone events are not achieved as anticipated. For example, will the licensee be obligated to pay the milestone payment if the milestone event is not achieved by a certain date? Alternatively, will the licensor be permitted to terminate the license if the milestone payment is not paid by a certain date. Whether termination is a suitable remedy in this situation depends upon whether the opportunity is subject to a limited market window, and whether the licensor could readily secure another licensee to pursue the opportunity. If termination is a suitable remedy, it is important that it be accompanied by an obligation that upon the termination the licensee transfers all data, results, regulatory filings and the like to licensor to enable the licensor to pursue the opportunity as expeditiously as possible.

A significant goal of the payment structure is to compel the licensee to have a substantial financial investment in the license in terms of payments to licensor, as well as expenses incurred in development, regulatory approval and commercialization. This motivates the licensee to pursue development and commercialization aggressively in order to recover its “return on capital.” The licensor needs to create objective standards for the licensee’s development and commercialization efforts. Minimum royalty obligations are often an important tool for the licensor in establishing these standards. The licensor also needs to ensure that the licensee has the capacity and motivation to realize the full value of the commercial rights licensed. This includes technical and regulatory expertise, financial wherewithal, experience in commercial scale-up, and marketing experience and capabilities throughout the geographic territory.

Recovering the Opportunity If “Things Don’t Work Out”

Sometimes, things don’t work out with a particular licensee. Perhaps the licensee has a change of priorities, or the individual who was the project champion with the licensee changes positions or leaves the company. Alternatively, perhaps the results of testing or clinical study were unexpected or disappointing. To protect against these situations, the licensor should consider providing prompt “exits” if there are unanticipated delays or challenges in development, regulatory approval or commercialization. The goal is to minimize any adverse impact on the technology, product and opportunity so as to reduce the stigma that may attach if the licensor subsequently tries to proceed with another license partner. Make no mistake, when a license terminates and the licensor seeks to proceed with another licensee partner, it will be necessary to explain to the new partner what previously happened. Perhaps the initial licensee’s protocol or analytical methods were flawed. In all events, it is important that the license agreement contemplate the possibility of these delays and permit the licensor to obtain the return to it of all rights, data, regulatory filings, clinical study results, regulatory approvals, manufacturing know-how, market intelligence, as well as product or technology enhancements or improvements, upon termination of the license.

“In-Licensing” as Part of a Financing Strategy

While “out-licensing” has been the focus of this section, “in-licensing” may also play a role as part of Bioco’s financing strategy. Some financing objectives of in-licensing technology, products or intellectual property may include obtaining patent rights to clear the path to commercialization of Bioco’s own technology or enhancing Bioco’s ability to restrict or reduce competition. Also, in-licensing third party rights in “enabling” or synergistic technologies or products may strengthen or distinguish Bioco’s technology or products, or expand its product line and thus strengthen its financing strategy.

Clarity is critical with respect to rights acquired, and the respective obligations of Bioco and the licensor. These considerations mirror the considerations with respect to “out-licensing” mentioned above, and include clarity as to scope of rights, rights in future developments, enhancements, data, regulatory filings and approvals, and licensor’s responsibility for technical assistance and transfer of know-how to enable Bioco to exploit the licensed technology or product.

Due diligence is critical to understanding the stage of development of an in-licensed technology or product and should include all communications with regulatory authorities. Careful due diligence will identify unrealistic expectations on the part of the licensor or licensee concerning the efforts required to complete development, regulatory approval, and commercialization, or concerning the scope of the market or the barriers to competition. These are all important factors to identify in order to properly evaluate any in-license opportunity.

As part of a financing strategy, in-licensing can be very expensive both in terms of milestone payments to the licensor and expenses incurred in clinical development, regulatory approval and commercial scale-up. In evaluating an in-licensing opportunity, one must consider the resources that Bioco will need to commit to realize

value and whether committing those resources to the pursuit of that opportunity may foreclose other opportunities, or create more accelerated demands on Bioco for capital. On the other hand, in-licensing may provide Bioco with products or technology that otherwise would take years and significant capital to develop and may, therefore, accelerate implementation of Bioco's business strategy.

Mergers and Acquisitions

Mergers and acquisitions (“M&A”) refers to a variety of transactions involving the acquisition by one party of one or more business entities or lines of business of another party by means of: a purchase and sale of assets; a purchase and sale of ownership interests; or a merger. M&A transactions are considered the ultimate strategic alliance since complete ownership of the acquired party or complete ownership of a business line or technology is the end result.

Many M&A transactions evolve out of prior strategic alliances, especially joint ventures and R&D funding arrangements. Option, call and put rights are often included in strategic alliance agreements, anticipating a future M&A event. Even when these terms are not specifically provided, the ongoing close relationship of a strategic alliance often leads to the financial decision to merge with or acquire the other party.

Why Use Mergers and Acquisitions

The reasons for deciding to enter into an M&A transaction can vary and are different between the buyer and the seller. A seller may be seeking liquidity for its owners, a strategic partner to purchase an ownership interest in its enterprise, or an exit from a business it no longer wishes to pursue. Historically, IPOs and M&A transactions have been the two primary exit strategies for corporate founders and venture capitalists. However, as financial markets have tightened and private placement offerings and IPOs have become increasingly more difficult to complete, there has been a renewed emphasis on M&A as an exit strategy, especially in the biotechnology industry. As for the buyer, it is looking for either a “strategic” opportunity that will enhance or complement the buyer’s existing operations, or a “financial” opportunity to acquire, grow and eventually sell the acquired entity or asset at a profit.

Many large pharmaceutical companies complete strategic acquisitions because they have extensive production, distribution, marketing and financial resources, but may lack sufficient creativity to enter into new fields in order to expand and complement their existing product lines. In the biotechnology industry, large pharmaceutical companies routinely acquire small developing organizations to jump start new, innovative products to replace mature ones that are facing patent expirations. The managed care revolution has also accelerated M&A activity among large pharmaceutical companies. This is because of the need to constantly reduce or control costs which many corporate directors and officers believe can be accomplished by creating larger, more diversified and efficient business entities. The globalization of research, technology and finance has also fueled international M&A transactions. Developing biotechnology companies may likewise strategically use M&A transactions to gain access to financial, distribution, production, marketing, clinical and information resources of more established entities.

Given the overwhelming cost of R&D, clinical trials and regulatory compliance, biotechnology related acquisitions often occur at stages earlier than originally envisioned by biotechnology company founders and venture capitalists.

As previously stated, financial opportunity buyers are strictly in the market to quickly grow an acquired entity and sell the entity for a profit. They search for sellers that they believe have an identifiable problem or business roadblock that can be remedied by the buyer. This usually means the buyer has sufficient cash to push the seller beyond the problem or roadblock or that the buyer has expertise or can acquire the expertise to solve the problem or circumvent the roadblock.

Structuring the M&A Transaction

Regardless of the parties' reasons for undertaking an M&A transaction, they will generally use one of the following structures to complete the deal:

- a purchase and sale of assets;
- a purchase and sale of stock (while this section refers to a purchase and sale of stock, the principles discussed likewise apply to the sale of any ownership interest in a business organization); or
- a statutory merger (conducted according to statutory requirements) of the entity to be acquired with and into a newly-formed subsidiary of the acquiring entity (or a merger directly with and into the acquiring entity).

These three structural alternatives are discussed in greater detail below, and the exact structure ultimately used will depend on a number of factors. The tax treatment for any gain realized by the acquired entity and its owners will likely be one of, if not the most, important factor to consider in structuring a transaction. Use of net operating loss ("NOL") carry forwards is yet another factor, but recent limitations on the use of NOLs under Section 382 of the Code have somewhat lessened the significance of this issue. Other key considerations include, but are not limited to: successor liability issues; whether the acquired entity is a privately-held or a public company; whether the acquiring entity is seeking to purchase all or only part of a business; the extent to which the acquired entity operates in a regulated industry; and contract assignment limitations and the necessity for obtaining third-party consents.

Asset Purchase

In an asset purchase transaction, the buyer purchases all or substantially all the assets of the seller or purchases a line of business of the seller, and the buyer generally assumes only those liabilities of the seller that the buyer specifically agrees to assume. Unlike a stock purchase or merger transaction, the buyer in an asset transaction has the opportunity to pick and choose which of the seller's liabilities it will assume. In fact, one of the most important reasons for structuring an acquisition as an asset purchase transaction is the desire of the buyer to limit or avoid responsibility for liabilities of the seller. That having been said, so-called "successor liability" doctrines can require a

buyer to be responsible for certain liabilities of the seller even if the asset purchase agreement provides otherwise. In addition, there are federal and state environmental laws that impose strict liability for environmental problems on successor owners.

The asset purchase agreement will contain numerous representations, warranties and covenants addressing, among other things, the business and operations of the seller. The agreement will also contain indemnification provisions that require the seller or its shareholders to indemnify the buyer for any breach of a representation, warranty or covenant. The scope and duration of the indemnity can vary significantly depending upon the perceived risks involved in the transaction.

Approval of the boards of directors of both the buyer and the seller will generally be required to consummate an asset purchase transaction. Approval of the shareholders of the seller is also generally required under state law when all or substantially all of the seller's assets are being sold. State law typically does not require the approval of the buyer's shareholders to consummate an asset purchase transaction.

Stock Purchase

In a stock purchase transaction, the acquiring entity ("buyer"), buys the stock or other outstanding ownership interests in the acquired entity ("target") from the holders of those interests ("shareholders"). In a stock purchase of a closely held business, the buyer will enter into one or more purchase agreements directly with the shareholders, all or most of whom are generally involved in negotiating the transaction. The stock purchase agreement will typically contain numerous representations, warranties and covenants, and the shareholders will be required to indemnify the buyer for any breach of those representations, warranties and covenants. Again, the scope and duration of these indemnification obligations can vary depending upon the perceived risks inherent in the transaction.

If the shares of capital stock of the target are held by a large number of shareholders, or if the target is a public company, the buyer may make a friendly "tender offer" (with the approval of the seller's board of directors) to purchase all of the shares of the target. If not all shareholders respond favorably to the tender offer, the buyer may undertake a second-step "squeeze-out" merger of the non-tendering minority shareholders, usually at the same price the buyer paid for the shares in the tender offer. In the "squeeze-out" merger, the buyer would cause the target to merge into a newly formed, wholly owned subsidiary of the buyer. In exchange for the shares of the target, the minority shareholders would receive cash and the buyer would own all of the outstanding shares of the subsidiary. The rules governing tender offers can be complex and often require significantly more documentation than a stock acquisition not involving a tender offer.

If the target is publicly traded and declines to engage in negotiations with the buyer regarding a potential acquisition, the buyer may put pressure on the management of the target to consider the buyer's proposal through the use of a "hostile" tender offer and proxy fight. The target's board of directors has a fiduciary duty to consider all reasonable business offers and is, therefore, prevented from altogether ignoring proposals that have the potential of enhancing shareholder value.¹³⁶

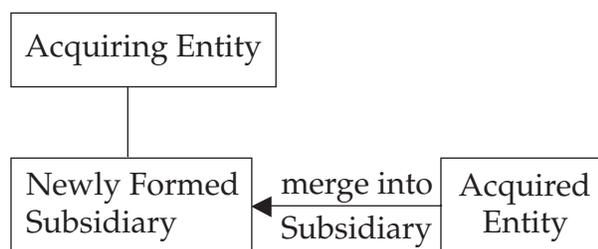
When stock is acquired, the liabilities of the target remain with the target after the shares have been transferred. This is because the legal form of the target and its assets and liabilities have not changed, only the equity ownership of the target has changed. By virtue of purchasing the target's capital stock, the buyer is effectively taking on the target's liabilities.

Merger

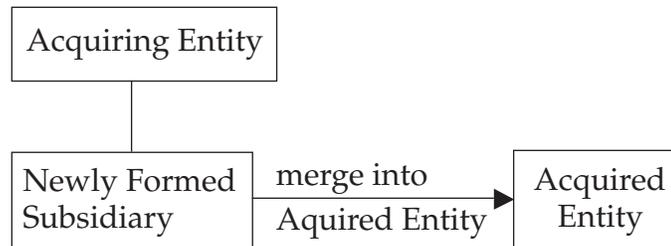
A statutory merger is the combination of two or more business entities into one of the entities, which becomes the "surviving entity." Legally, there are "constituent entities" and a surviving entity in a merger. Practically, however, one of the parties is taking the role as the "acquiring entity" while the other party (or parties) is taking the role as the "acquired entity." Under state law, the surviving entity automatically retains or acquires all the properties, rights and powers, as well as all of the debts, liabilities and obligations of all of the constituent entities. Upon effectiveness of the merger, the legal existence of the non-surviving entity ceases and the shareholders of the non-surviving entity receive consideration (typically, cash or shares of stock in the acquiring entity) in return for relinquishing their equity interests in the non-surviving entity.

Generally, state law requires approval of the board of directors and the shareholders of each of the constituent corporations to a merger. To effectuate a merger, the acquiring entity typically forms a new wholly-owned subsidiary to conduct the transaction, thereby only requiring the approval of the subsidiary's sole shareholder – the acquiring entity. Most state statutes allow for "appraisal" or "dissenters" rights that entitle shareholders of the acquired entity to vote against the merger and to receive a judicially determined "fair value" for their shares instead of the merger consideration. The procedure is very detailed and must be strictly complied with in order for a shareholder to be entitled to this alternate consideration. Typically, the merger agreement will contain a termination provision allowing the acquiring entity to terminate or be released from the transaction if more than a specified percentage of shareholders of the acquired entity exercise appraisal rights.

There are two mechanical variations to a merger – the forward subsidiary merger and the reverse subsidiary merger (sometimes also referred to as forward and reverse triangular mergers). In a forward subsidiary merger, the acquired entity is merged with and into a newly-formed subsidiary of the acquiring entity, and the newly-formed subsidiary is the surviving corporation.



In a reverse subsidiary merger, the newly-formed subsidiary of the acquiring entity merges with and into the acquired entity, with the acquired entity surviving as a wholly-owned subsidiary of the acquiring entity.



The result after each merger is that the surviving entity will be wholly owned by the acquiring entity. The main benefit in consummating a reverse subsidiary merger over a forward subsidiary merger is the manner in which the reverse subsidiary merger addresses the problem of contract assignments. More specifically, many supplier, vendor, consulting, lease and licensing agreements that the acquired entity has in place may contain clauses preventing their assignment without certain third party approvals. Because the form of the acquired entity does not change in a reverse subsidiary merger, the need for third party consents for assignment of agreements is often eliminated by conducting a reverse subsidiary merger.

Spin Out

Where an acquiring entity does not wish to acquire all the lines of business of an acquired entity in a merger or where an acquired entity desires to retain certain product lines, it may be necessary to segregate certain assets of an acquired entity before conducting a merger. One possible mechanism to accomplish this is to “spin out” those assets into a separate legal entity prior to the merger. The acquired entity’s shareholders are then issued some form of security in the entity into which the assets are spun out.

Transaction Consideration

Generally, under any of these M&A transaction structures, the consideration paid by the acquiring entity will be cash, promissory notes or other debt instruments, stock of the acquiring entity, or some combination of the foregoing. Any time securities are being issued as consideration in connection with an M&A transaction, the issuance will require registration under the Securities Act and applicable state laws or require an exemption from such registration. Although registration can be costly and time-consuming for the acquiring entity, registered securities that are given as consideration by a publicly-traded acquiring entity provide the benefit of a liquid asset to the shareholders of the acquired entity and, except for registration related costs, does not deplete the acquiring entity’s cash. If in a transaction the acquiring entity issues securities that exceed 20% of the acquiring entity’s outstanding

securities, NYSE and NASDAQ rules may require the acquiring entity to obtain shareholder approval for the issuance.

The amount of consideration in an M&A transaction may be fixed or it may vary based on events occurring after the closing. If the purchase price is based on the net asset value of the acquired entity, there may be an adjustment to the purchase price based on a closing date balance sheet that is prepared after closing of the transaction. The parties may also negotiate an “earn-out” as part of the total consideration in cases where: it is difficult to value the asset being acquired and more time will add clarity to the value; the buyer is willing to share with the seller a part of the upside which is expected to result after the transaction; or the buyer cannot pay a lump sum purchase price and the seller is willing to finance the transaction over some limited time period. In an earn-out, the buyer pays the seller some amount over time based on some agreed upon operating results of the acquired business such as: a portion of the post-closing net sales of the product sold by the acquired business; a portion of post-closing net income of the acquired business; or a multiple of the post-closing net income achieved by the acquired business. The parties often agree to hold back a certain portion of the consideration in escrow for a period of time (typically 12 to 18 months) to satisfy any potential indemnification obligations of the acquired entity or its shareholders.

As explained in the Tax and Tax Credits section of this Guide, tax considerations play a major role in determining the structure of any M&A transaction. Generally, the tax laws encourage parties to sell stock (as opposed to assets) because shareholders pay only one level of tax (capital gains) at capital gains tax rates when stock is sold, and capital gains rates are lower than ordinary income tax rates. On the other hand, buyers generally seek the tax treatment afforded by a purchase of assets (as opposed to stock). Upon a purchase of assets, the buyer may benefit from a step up in basis of the acquired assets attributable to the new cost of the assets, and thereafter enjoy greater depreciation write-offs. Because depreciation is a non-cash expense, a taxpayer has the benefit of deducting an expense without incurring the related cash outflow. Therefore, any increase in a depreciable asset’s tax basis is a benefit to the acquiring entity. The primary disadvantage of structuring an M&A transaction as an asset purchase, at least from the seller’s perspective, is that the buyer and its shareholders can be exposed to two levels of tax, once at the corporate level on any gain on the assets sold, and again when the proceeds of the transaction are distributed to the seller’s shareholders. However, this double taxation issue will not arise where the seller is an LLC or is otherwise taxed as a partnership.

Many parties mistakenly believe that “tax free” treatment is readily available in M&A transactions. Section 368 of the Code provides for three primary types of reorganizations to qualify for what is commonly referred to as tax free treatment – when in fact it is tax deferred treatment.¹³⁷ If the Code specified requirements are met, the sellers are not required to pay tax at the time of the transaction. Instead, the tax basis of any new stock received will be the tax basis of stock relinquished by the taxpayer in the merger. Gain would then be deferred until such time as the new stock is sold. The provisions of Code section 368 are very restrictive and require that stock be the primary consideration and that the payment of cash or other property, referred to as “boot,” be limited.

Understanding the M&A Process

Professional Assistance

The process of completing an M&A transaction can be difficult, complicated, and time-consuming. It is critical for all parties to assemble an experienced team of professionals to develop strategy, locate the right partner, structure the transaction, negotiate the deal and facilitate the process. Investment bankers with expertise in the industry can be used for these purposes and are considered essential to conducting a thorough analysis of the value of the acquired entity. Investment bankers can also provide fairness opinions, which have become an increasingly important component for larger M&A transactions. A fairness opinion may be prepared at the request of the board of directors of the acquiring entity or the acquired entity and used as an independent evaluation to determine whether a given transaction is “fair from a financial standpoint” to either the shareholders of the acquiring entity or the acquired entity, or both, as the case may be. A board of directors will then use the fairness opinion as support for its decision to approve or reject a transaction in the event a shareholder suit challenges that decision.

Each of the parties will also engage its own team of counsel experienced in the industry and having experience with corporate, securities, intellectual property, regulatory, tax, employment, environmental, real estate and other matters legally necessitated by the transaction. Industry-experienced accountants can also provide critical assistance with structuring the transaction in a tax efficient manner, assisting with the preparation of pro forma financial models and with completing the financial due diligence.

Confidentiality Agreements, Term Sheets and Letters of Intent

Before parties to a potential M&A transaction begin speaking with each other and providing confidential and proprietary information about their technology and business, they should enter into a confidentiality or nondisclosure agreement (“CDA”). CDAs in M&A transactions need to carefully and broadly describe the type of information that will be exchanged. The acquiring entity will want to review any and all public and non-public information about the acquired entity, including information related to items such as technology, employment, litigation, environmental, tax, intellectual property, finance, accounting, research, regulatory, marketing, production, and distribution. The fact that the parties are in discussions about a potential transaction, and the terms of those discussions, should also be treated as “confidential information” subject to the agreement. Typically, there is no expiration date on the confidentiality obligation in an M&A transaction. Acquired entities should also demand a non-solicitation clause as part of their CDAs, prohibiting the prospective acquiring entity from soliciting or hiring the other entity’s employees for a period of one to two years after the date of the CDA (other than in connection with closing the subject transaction).

After initial investigation of the acquired entity, the acquiring entity will typically generate a term sheet or letter of intent covering the principal business points of the

deal so that the parties can develop a mutual understanding of the primary elements of the transaction. Letters of intent are rarely used in transactions involving public companies because they raise disclosure issues under SEC and stock exchange rules. To avoid any SEC and stock exchange requirements regarding the making of a public announcement about a transaction that is still preliminary, non-binding and may not ultimately be concluded, public companies prefer to use preliminary term sheets to identify the key elements of the deal and then move straight to drafting definitive documents.

Whether using a letter of intent or a term sheet, the document is generally non-binding, except for any obligations to: negotiate in good faith; maintain confidentiality of the terms of the transaction and the information disclosed between the parties; and comply with any non-solicitation or no-shop provisions. The term sheet or letter of intent will serve as the road map for negotiating and drafting the more detailed definitive agreements.

Because pricing might very well be the most important factor in determining whether or not the parties agree to consummate an M&A transaction, the question of when the parties fix a purchase price becomes a matter of strategy. As noted above, structure directly affects the net value of the transaction to the acquired entity, the acquiring entity and their respective shareholders. Acquired entities may choose to defer negotiating a purchase price until after the acquiring entity has completed its preliminary due diligence investigation (the due diligence process is described in greater detail below). Acquired entities should realize that once they have tentatively agreed to a price, the likelihood of the acquiring entity negotiating price decreases if any blemishes are discovered during due diligence is far greater than the acquired entity negotiating price increases because the due diligence was clean. This is largely attributable to the fact that acquiring entities begin the M&A process with the assumption that any due diligence investigation will not reveal anything sufficiently material to justify a change in price.

The acquiring entity will generally demand an exclusivity period of at least 60 to 90 days in order to commit to spending the resources to undertake its due diligence investigation, which can be time-consuming and expensive. Acquired entities are sometimes compensated by the acquiring entity for providing exclusivity, and for keeping the company off the market during the due diligence period.

Due Diligence

After a confidentiality agreement or letter of intent is signed, the acquiring entity will complete a detailed legal and financial investigation, of the acquired entity to determine (or confirm) the value of the entity, business or product line being acquired, and to analyze and allocate post-closing risks and responsibilities. While the nature and scope of the information sought will depend upon the type of business being acquired and the industry in which it operates, the acquiring entity will typically request that the acquired entity provide access to, and copies of, all relevant information concerning:

- finance and tax, including financial statements, audit reports, supporting schedules, inventory and cost information, debt instruments and tax returns;

- corporate organization such as articles and bylaws, capitalization information, shareholder lists, minutes of all shareholder and board of directors meetings;
- intellectual property such as registered patents, applications and invention disclosures, trademarks and copyrights, technology licenses, assignments from employees and consultants;
- R&D initiatives;
- products, sales and marketing including customer lists, manufacturing and supply contracts, distribution agreements, marketing plans and programs;
- material contracts such as those with suppliers, customers and consultants;
- employment, contractor and labor matters such as employment or consulting contracts, employee benefits and ERISA plans, payroll information and benefits claims history;
- facilities including real estate title or lease documentation;
- environmental items such as Phase I and Phase II environmental assessment reports and claims history depending on the nature of the business activity;
- manufacturing and operations including regulatory compliance, production processes, quality assurance procedures and files, including device or drug history files;
- regulatory and clinical information including all approvals and applications, correspondence with the FDA and foreign authorities, third party audit information and reports, and adverse event reporting;
- insurance coverage; and
- litigation including pending and threatened litigation.

Gathering this data can be very intrusive upon the acquired entity, especially when it is attempting to keep its operations running smoothly and keep the potential transaction confidential from employees, customers and vendors. Often a data room will be compiled offsite, such as at counsel's office, to avoid disruption of the acquired entity's business activities. Technology exists to assemble electronic data rooms that facilitate review by multiple parties, or by parties that are geographically distant.

Intellectual property is the key asset for most companies in the biotechnology industry. Significant time and resources should be spent assessing the status of the acquired entity's intellectual property including its patents, formulations, processes and other trade secrets. This may include analysis of the validity of patents and non-infringement of third-party rights, as well as assurance that title to all inventions has been properly assigned to the acquired entity from all employees, consultants or inventors. Any prior research agreements with consultants and universities should

be reviewed to ensure that the acquired entity owns all rights to such property and to determine whether any future royalties may be owed post-closing.

A regulatory due diligence review is also critical. The acquiring entity will need to conduct adequate due diligence to satisfy concerns such as whether the acquired entity's clinical trials have been conducted in accordance with applicable requirements, and whether the acquired entity has adequate compliance procedures in place. The scope of the due diligence should be suitably detailed to answer all of the acquiring entity's questions.

If the acquired entity is marketing products that are covered by Medicare, then an analysis of the marketing practices should be conducted to ensure compliance with and avoid successor liability under the fraud and abuse laws which generally include state and federal anti-kickback statutes, civil and criminal false claims acts, the Stark laws, and the federal Civil Money Penalties Act.¹³⁸ In undertaking due diligence, particular attention should be given to the acquired entity's internal compliance program and business conduct standards (or lack thereof), to its sales and marketing practices particularly in the area of pricing terms, customer sales incentives, and payments to physicians or physician organizations, and to the advice given by reimbursement specialists to existing or potential customers. Additionally, any promotion of off-label uses for the seller's products, *i.e.*, those not covered in the product's FDA approval, deserve special scrutiny.

All material contracts of the acquired entity must be reviewed to determine whether there are pricing terms and performance obligations that may be unacceptable to the acquiring entity, or whether there are change of control or assignment limitations or termination rights that may deprive the acquiring entity of the ability to continue the contract after closing.

Planning for Success

Two of the key reasons cited for failure of acquisitions to achieve the strategic goals envisioned are lack of integration planning and poor integration execution. Integration planning should begin early in the transaction. Parties should carefully consider the cultural fit of the organizations when locating potential suitors. Integrating the entrepreneurial spirit of a biotechnology start-up into a large, inflexible organization can present many challenges and needs to be considered carefully as the deal is consummated.

G. Federal Grants Through SBIR/STTR Programs

Introduction

An often overlooked financing alternative for small businesses are federal grants through the Small Business Innovation Research Program ("SBIR") and the Small Business Technology Transfer Program ("STTR"). The SBIR program is a highly

competitive three-phase award system that provides qualified small business concerns with opportunities to propose innovative ideas meeting the specific R&D needs of the federal government. SBIR grants of up to \$100,000 (Phase I) and \$750,000 (Phase II) per topic are available for U.S. small businesses to allow them to engage in federal R&D activities that have the potential for commercialization. The STTR program is designed to facilitate cooperative R&D efforts between small business concerns and U.S. research institutions. STTR grants of up to \$100,000 (Phase I) and \$750,000 (Phase II) are available for small businesses that will work with research institutions on R&D that has the potential for commercialization. Small businesses may be awarded multiple SBIR/STTR grants for separate and distinct research topics. To date, over \$12 billion has been awarded by the SBIR program to various small businesses across the country and over \$2 billion is available under the SBIR/STTR programs in fiscal 2005.¹³⁹

It is important to understand that the SBIR/STTR programs are aimed at funding the development of new ideas and technology, and SBIR/STTR grants are generally not available to fund the development of technology for which a patent has been applied. That is not to say that award recipients do not retain ownership rights in the technology developed through SBIR/STTR awards or that patents cannot be sought by award recipients with respect to such technology. Award recipients do retain ownership and the right to patent, but may be asked to grant limited licenses to the federal government with respect to their innovations funded by the federal government.¹⁴⁰ Award recipients may also be required to make data developed through SBIR/STTR awards available to the scientific community.¹⁴¹ The ownership of innovations and technology developed through STTR awards must be addressed in a written agreement between the small business and its research institution partner prior to an STTR Phase I award.

Historical Background/Policy Objectives

The SBIR program began in 1982, when Congress passed the Small Business Innovation Development Act (“SBIR Act”).¹⁴² The SBIR program was reauthorized in 1992¹⁴³ and 2000,¹⁴⁴ extending the program until September 30, 2008. The SBIR Act requires federal agencies that receive a certain level of federal funding for outside R&D to funnel a specific percentage of that funding (currently 2.5%) to “small businesses,” as defined by the SBIR Act and related regulations. The policy objectives of the SBIR Act include: using small businesses to stimulate technological innovation; strengthening the role of small business in meeting federal R&D needs; increasing private sector commercialization of innovations developed through federal SBIR R&D; increasing small business participation in federal R&D; and fostering and encouraging participation by socially and economically disadvantaged small business concerns and women-owned business concerns in the SBIR program. Both the SBIR and STTR programs are aimed at stimulating high-tech innovation in the marketplace, while meeting specific R&D needs of the U.S. government. These programs fund the critical start-up and development stages of a company and encourage the commercialization of the technology, product or service, which, in turn, stimulates the U.S. economy.

The STTR program was established by the Small Business Technology Transfer Act of 1992.¹⁴⁵ It was reauthorized in 1997¹⁴⁶ and again in 2001,¹⁴⁷ extending the program until September 30, 2009. Federal agencies with extramural R&D budgets over \$1 billion are required to administer STTR programs using an annual set-aside of 0.30%. The goals of the STTR program are similar to those of the SBIR program, with the added objectives of

requiring cooperation between small businesses and research laboratories, and moving ideas from the laboratory to the marketplace.

The SBIR and STTR programs differ in two major ways. First, under the SBIR program, the Principal Investigator affiliated with the small business concern must have his or her primary employment with the small business concern at the time of the award and for the duration of the project period, while the STTR program does not stipulate primary employment. In fact, the Principal Investigator can be affiliated with the research institution. Second, the STTR program requires research partners at universities and other non-profit research institutions to have a formal collaborative relationship with the small business concern. At least 40% of the STTR research project is to be conducted by the small business concern and at least 30% of the work is to be conducted by the single, “partnering” research institution.

Structure of SBIR/STTR Programs

Both the SBIR and STTR programs are organized in three phases. Phase I is a feasibility study to evaluate the scientific and technical merit of an idea. Phase I awards are for periods of up to six months (or one year for STTR) in amounts up to \$100,000. Phase II awards are designed to expand on the results of the Phase I study and pursue the development of the technology, product or service evaluated in Phase I. Phase II awards are for periods of up to two years in amounts up to \$750,000, although certain participating agencies will sometimes accept proposals for greater amounts or time periods if necessary for the completion of the project. Phase II awards are only granted to Phase I awardees. Phase III is for the commercialization of the results of Phase II and requires the use of private sector or non-SBIR/STTR federal funding. In some federal agencies, Phase III may involve follow-on non-SBIR/STTR funded R&D or production contracts for products, processes or services intended for use by the federal government.

Eligibility Requirements

A small business must pass several eligibility standards to be considered for SBIR or STTR awards.¹⁴⁸ It must be an organized for-profit U.S. business entity,¹⁴⁹ at least 51% of the ownership of which must be held by individuals who are citizens of, or permanent resident aliens in, the U.S. or another for-profit entity that is at least 51% owned and controlled by one or more of such individuals.¹⁵⁰ The business must be independently operated, located in the U.S. and have 500 or fewer employees, together with its subsidiaries and affiliates. Grant requests must identify a Principal Investigator and for SBIR companies, the Principal Investigator’s primary (greater than 50% of time) employment must be with the small business during the project. The Principal Investigator need not have a Ph.D., but is required to have expertise to oversee the project scientifically and technically. Eligibility is determined at the time of the award.

Participating Agencies

Each year, federal agencies and departments receiving extramural federal R&D funding in excess of \$100 million are required by the SBIR program to reserve 2.5% of their R&D

funds for award to small businesses. Currently, that includes the following eleven agencies and departments: Department of Agriculture (“USDA”), Department of Commerce (including the National Institute of Standards and Technology), Department of Defense, Department of Education, Department of Energy, Department of Health and Human Services (“HHS”) including the National Institutes of Health (“NIH”), Department of Homeland Security, Department of Transportation, Environmental Protection Agency (“EPA”), National Aeronautics and Space Administration (“NASA”) and National Science Foundation (“NSF”). These agencies designate R&D topics and accept proposals.

With respect to the STTR program, federal agencies and departments with at least \$1 billion in budgeted extramural federal R&D funds are required to provide at least 0.30% of their funding to small business concerns. There are currently five federal agencies that participate in the STTR program, the Department of Defense, Department of Energy, NASA, HHS (including NIH) and the NSF.

Small Business Administration Role

The U.S. Small Business Administration (“SBA”) is a coordinating agency for the SBIR and STTR programs. It directs the implementation of the SBIR and STTR programs by the participating agencies, reviews their progress and reports annually to Congress on its operation. The SBA is also the information link to SBIR/STTR, collecting solicitation information from the participating agencies and publishing such information quarterly in a Pre-Solicitation Announcement (“PSA”). Current PSAs can be found at www.sba.gov/sbir, as well as links to the participating agency SBIR and STTR program solicitations. The PSA is a single source for the topics and anticipated release and closing dates for each agency’s solicitations. The SBA does not, however, become involved in selecting topics or award recipients. The participating agencies have unilateral authority and responsibility to: select SBIR/STTR topics, release SBIR/STTR solicitations, evaluate SBIR/STTR proposals, and award SBIR/STTR funding agreements on a competitive basis.

Biotechnology Topics

Topics related to biotechnology can be found in many of the agencies participating in the SBIR and STTR programs, but the most likely places are the NIH within HHS and the National Institute of Standards and Technology within the Department of Commerce. The NIH awarded a total of \$631 million in SBIR/STTR awards in fiscal 2004 (\$564 million of which were SBIR grants). Examples of current areas of interest for the NIH include: nanotechnologies, bioinformatics, biodefense, proteomics/genomics, genetically engineered proteins, biosensors, biosilicon devices, biocompatible materials, acousto-optics and opto-electronics, imaging technologies, education/communication tools, computational biology and behavioral research.¹⁵¹

Application Process

The standard Phase I application process starts with participating agencies describing R&D topics in solicitations. Small business concerns then prepare short proposals (usually

25 pages or less, with no attachments allowed). Unsolicited proposals are not accepted. Participating agencies then review the proposals and evaluate them based on technical merit, the firm's qualifications, and the potential for commercialization and societal benefit. The participating agency then makes the awards and enters into funding agreements with the award winners. The entire process can take up to nine months from the time proposals are due.

Each participating agency establishes procedures for developing and announcing topic areas, setting dollar amounts of awards, application deadlines, the number and timing of solicitations, the proposal review process, and the type of award (contract or grant). Certain participating agencies are "contracting agencies," that have highly focused topics, carefully established plans, protocols and requirements and often provide for a procurement mechanism. These include the Department of Defense, NASA, EPA, Department of Commerce/National Institute of Standards and Technology and the Department of Transportation. Other agencies are "granting agencies," which have less specific topics, more flexibility and allow the Principal Investigator to establish the approach. These include the Department of Energy, NSF and the USDA. Some agencies, including HHS, NIH and the Department of Education, use both approaches. Visit the websites of the participating agencies for further information.¹⁵² Note that proposals for awards may be made at multiple participating agencies, but awards may not be accepted from multiple agencies for the same topic.

Subcontracting

For Phase I SBIR awards, a minimum of two-thirds of the research or analytical effort must be performed by the proposing firm, and for SBIR Phase II awards, a minimum of one-half of the research or analytical effort must be performed by the proposing firm. With respect to STTR Phase I and II awards, either the proposing firm or the non-profit research institution may subcontract, although the small business must perform at least 40% of the work and the research institution must perform at least 30%.

Additional Information and Assistance

For more information, visit the websites of the SBA at www.sba.gov/sbir, National Institutes of Health, Office of Extramural Research at www.grants.nih.gov/grants/funding/sbir, and the National Institute of Standards and Technology at <http://www.nist.gov/tpo/sbir/index.cfm>. Another helpful website is www.zyn.com/sbir, which provides tools for easily searching open SBIR/STTR solicitation topics. In addition, the Minnesota Department of Employment and Economic Development ("DEED") has established an SBIR/STTR assistance program to coordinate funding opportunities between Minnesota companies and participating federal agencies with respect to the SBIR/STTR programs. DEED's website can be found at <http://mn.gov/deed/>.

V. FACTORS THAT INFLUENCE BIOTECHNOLOGY FINANCE

A. Introduction

As previously stated, there are many factors that affect the financing strategies and options available to the biotechnology company. Different factors can have different consequences on the company throughout its life cycle. Furthermore, many of the factors can affect each other during the life of the company. This section presents a collection of factors that are likely to materially affect the financing of any biotechnology company. An understanding of these factors will provide a strong foundation for understanding the availability and restrictions on the financing options that were presented in the previous section.

B. The Impact of the FDA

Introduction

FDA considerations will significantly affect the financing strategy of a biotechnology company. FDA regulatory approval can be expensive, lengthy and sometimes unpredictable. The biotechnology company's value will likely increase significantly as the company advances through the process of obtaining regulatory approval. Given the length of time and significant expense of the regulatory approval process, and increases in entity value that occur as the company progresses through the regulatory process, a more staged approach to financing may both reduce unnecessary dilution and prove to be a more realistic approach to financing.

If the company's product requires FDA approval for commercial sale in the U.S., the approval is typically the lynch pin to positive cash flow. Achieving regulatory approval may also increase barriers to competition. Once regulatory approval is obtained, issues of ongoing compliance also involve significant expense. Compliance considerations range from manufacturing, labeling, and quality assurance to promotion and sales. This section will focus primarily on the regulatory framework and the FDA approval process. It will also offer an overview of adverse event reporting requirements because these considerations may impact the scope of the market, or the perception of a product in the market.

Overview of FDA Regulation of Drugs, Biologics, Devices, Veterinary Additives and Drugs

Different divisions or centers of the FDA are responsible for regulating human drugs, biologics, devices and veterinary additives and drugs. The Center for Drug Evaluation and Research ("CDER") regulates human drugs, including over-the-counter and prescription drugs. The Center for Biologics Evaluation and Research ("CBER") regulates blood products, vaccines, cellular and gene therapy, tissue and medical

devices used in collecting, processing, testing, manufacturing and administration of licensed blood, blood components and cellular products. CBER also regulates all HIV test kits used both to screen donor blood, blood components and cellular products and to diagnose, treat and monitor persons with HIV and AIDs.

On October 1, 2003, the FDA transferred certain product oversight responsibilities from the CBER to the CDER. This consolidation was intended to provide greater opportunities to further develop and coordinate scientific and regulatory activities between CBER and CDER, leading to a more efficient, effective, and consistent review program for human drugs and biologics. Under the new structure, the biologic products transferred to CDER that were already approved as biologics under Biologic License Applications (“BLA”) before that transfer will continue to be regulated as licensed biologics under their then-existing BLAs. The approval process for new products in categories transferred to CDER will be the New Drug Application (“NDA”), rather than the BLA that applied prior to the transfer of those biologic product categories to CDER. The categories of therapeutic biological products now under CDER’s review include: monoclonal antibodies for in-vivo use; cytokines, growth factors, enzymes, immunomodulators and thrombolytics; proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors); and other non-vaccine therapeutic immunotherapies.

The Center for Devices and Radiological Health (“CDRH”) is responsible for regulating firms who manufacture, repackage, relabel, or import medical devices sold in the U.S. In addition, CDRH regulates radiation emitting electronic products (medical and non-medical) such as lasers, x-ray systems, ultrasound equipment, microwave ovens and color televisions.

The Center for Veterinary Medicine is responsible for ensuring that animal drugs and medicated feeds are safe and effective and that food from farm animals is safe to eat.

The Center for Food Safety and Applied Nutrition (“CFSAN”) is responsible for promoting and protecting the public’s health by ensuring that the nation’s food supply, including nutritional and dietary supplements, is safe, sanitary, and honestly labeled, and that cosmetic products are safe and properly labeled.

Getting to Market – Regulatory Approval

The first question for the biotechnology company to consider relative to the regulatory framework is whether its product is subject to FDA review or approval prior to commercial sale in the U.S.¹⁵³ If the product is subject to FDA review, the company needs to determine which regulatory review and approval process applies. Even if the product is not subject to FDA review or approval prior to commercial sale in the U.S., the company must determine if the product is otherwise subject to FDA regulation (e.g., with respect to labeling or reporting).¹⁵⁴

Although vitamins and dietary supplements generally do not require FDA approval for commercial sale in the U.S., their labeling is subject to FDA regulation.¹⁵⁵ Drugs and biologics, in contrast, require FDA approval prior to commercial sale in the U.S. and are also subject to FDA regulation with respect to their labeling.¹⁵⁶

Biological products or biologics include a wide range of items such as vaccines, blood and blood components, allergenics, somatic cells, gene therapies, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources – human, animal, or microorganism – and may be produced using biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research, and may be used to treat a variety of medical conditions for which no other treatments are available. In contrast to most drugs that are chemically synthesized and whose structure is known, many biologics are complex mixtures that are not easily identified or characterized.

The Approval Process

The approval process for “new drugs” and most biologics is the NDA.¹⁵⁷ Although there are still certain categories of biologics that require approval through the BLA process, the NDA is the vehicle through which sponsors of new drugs and most biologics formally propose that the FDA approve the new drug or biologic for sale and marketing in the U.S. The NDA is designed to provide enough information to permit an FDA reviewer to address the following questions: whether the drug or biologic is safe and effective in its proposed use(s), and whether the benefits of the drug or biologic outweigh its risks; whether the proposed labeling (package insert) for the drug or biologic is appropriate, and what it should contain; and whether the methods used in manufacturing the drug or biologic and the controls used to maintain the quality of the drug or biologic are adequate to preserve the identity, strength, quality, and purity of the drug or biologic.¹⁵⁸ The documentation required in an NDA is intended to tell the whole story of the drug or biologic, including what happened during the clinical tests, what the ingredients of the drug are, the results of the animal studies, how the drug or biologic behaves in the body, and how it is manufactured, processed and packaged. Clinical testing to gather data to support the NDA is undertaken using an Investigational New Drug Application (“IND”), and data gathered during the animal studies in support of the IND, as well as data from the human clinical trials of an IND, must be submitted as part of the NDA.¹⁵⁹

The main purpose of an IND application is to provide sufficient data to demonstrate that it is reasonable to permit tests of a new drug or biologic on humans. During the early preclinical development of the new drug or biologic, the company’s primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the company then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies. The IND allows the company to conduct investigational clinical trials in accordance with the protocols submitted under the IND.¹⁶⁰ The IND is not an application for marketing approval and does not allow the company to use the drug or biologic in patients outside of the approved clinical protocols.

The clinical studies undertaken for new drugs and biologics pursuant to an IND in support of the NDA are undertaken in three distinct phases, known as Phase I, Phase II,

and Phase III.¹⁶¹ Phase I studies provide for the initial introduction of an IND or biologic into humans.¹⁶² These studies are closely monitored and may be conducted in patients, but are usually conducted in healthy volunteer subjects. These studies are designed to determine the metabolic and pharmacologic actions of the drug or biologic in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence regarding effectiveness. During Phase I, sufficient information about the drug's pharmacokinetic effects should be obtained to permit the design of well-controlled, scientifically-valid, Phase II studies. In addition, if there is an adequate disease model and well-defined pharmacology, there may be additional Phase I studies to consider the drug's pharmacological effects. Also, additional Phase I studies, such as pharmacokinetic studies with patients with renal or hepatic impairment, may be required. The total number of subjects included in all Phase I studies varies with the drug or biologic, but is generally in the range of one hundred to two hundred.

Phase II studies are early, controlled clinical studies conducted to obtain some preliminary data on the safety and effectiveness of the drug or biologic, or the dosage ranging, for a particular indication or indications in patients with the disease or condition.¹⁶³ This phase of testing also helps determine the common short-term side effects and risks associated with the drug or biologic. Phase II studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people.

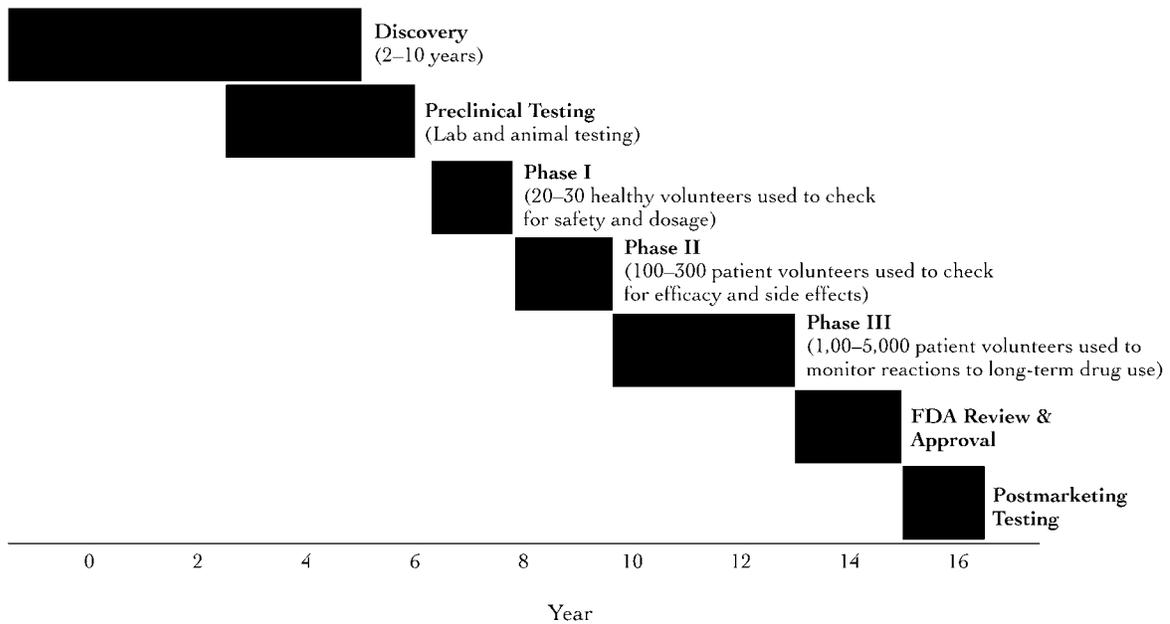
Phase III studies are expanded controlled and uncontrolled trials.¹⁶⁴ These studies are performed after preliminary evidence suggesting safety and effectiveness of the drug or biologic has been obtained in Phase II, and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall risk/benefit relationship of the drug or biologic. Phase III studies also provide an adequate basis for extrapolating the results to the general population, the results of which are included in the product labeling. Phase III studies usually include several hundred to several thousand people. The controlled studies would require a placebo control group, unless ethical or medical considerations would prohibit use of a placebo control in the patient population.

The FDA sometimes requires, or sponsoring companies (i.e., the biotechnology company) sometimes agree to, post-marketing clinical studies, known as "Phase IV clinical studies." These studies typically require the sponsor to demonstrate the clinical benefit of a product following accelerated approval.¹⁶⁵ The FDA uses post-marketing study commitments to gather additional information about a product's safety, efficacy, or optimal use. Agreements with sponsors to conduct post-marketing studies can be reached either before or after the FDA has granted approval to a sponsor to market a product. The number of patients involved in post-marketing studies can range anywhere from several hundred to several thousand, depending on the issue to be addressed in the post-marketing study.

For those categories of biologics that still require BLA approval,¹⁶⁶ the process is very similar to the NDA process. Following initial laboratory and animal testing, a biological product is studied in clinical trials in humans under an IND. If the data generated by the studies demonstrate that the product is safe and effective for its intended use, the data are submitted to CBER as part of a BLA for review and approval for marketing. After a license application is approved for a biological product, the product may also be subject to official lot release. As part of the manufacturing process, the manufacturer is required

to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by CBER, the manufacturer submits samples of each lot of product to CBER together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. CBER may also perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, CBER conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

Biotech Drug Discovery Process



Source: Ernst & Young LLP, *Biotechnology Industry Report: Convergence*, 2000

[As described in the text, the number of patients/volunteers in a Phase may vary significantly from the levels set forth in this chart. — Editor]

Generic Drugs and the Abbreviated New Drug Application

Unlike “new” drugs, which are subject to the NDA process and require clinical study under an IND, “generic” drugs are subject to approval under the Abbreviated New Drug Application (“ANDA”) process.¹⁶⁷ A “generic” drug is one that is comparable to an innovator drug product (i.e., a drug that has been approved under an NDA) in dosage form, strength, route of administration, quality, performance characteristics and intended use. Unlike an NDA, ANDAs are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, they must scientifically demonstrate that their product is bioequivalent to the innovator drug (i.e., performs in the same manner as the innovator drug). The generic version must deliver the same amount of active ingredients into a patient’s bloodstream in the same amount of time as the innovator drug.

Currently there is no biologics counterpart for the ANDA. All biologics must be approved by means of an NDA or, as applicable for certain categories of biologics, a BLA.

Medical Device Approval Process

If the biotechnology company has a product that is a medical device, unless the device is deemed “exempt,” the FDA will classify the company’s device into one of three classes that identify the level of regulatory control that is necessary to ensure the safety and effectiveness of a medical device.¹⁶⁸ The classification of the device will identify the marketing process (either premarket notification (“510(k)”) or premarket approval (“PMA”)) that the company must complete in order to obtain FDA clearance or approval for marketing the device in the U.S.¹⁶⁹ Class I are those devices requiring general controls, Class II are those devices requiring special controls, and Class III are those devices generally requiring PMA.

PMA

The PMA is the most stringent type of device marketing application required by the FDA. The approval is based on a determination by the FDA that the PMA contains sufficient valid scientific evidence to ensure that the device is safe and effective for its intended uses. As previously stated, Class III devices generally require PMA. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which by their use present a potential, unreasonable risk of illness or injury.¹⁷⁰

510(k)

The 510(k) is a premarket notification that must be cleared by the FDA prior to marketing a medical device. A 510(k) premarketing submission must demonstrate that the device to be marketed is substantially equivalent to a “legally marketed” medical device, known as the “predicate device.” A “predicate device” is a device that was legally marketed before May 28, 1976, or a device that subsequent to that date was cleared under a 510(k) submission, or a device that has been reclassified as a Class I or Class II device. The submission must include descriptive data and, when necessary, performance data to support that the device is substantially equivalent to the predicate device.¹⁷¹

Investigational Device Exemption

The Investigational Device Exemption (“IDE”) is the medical device counterpart of the IND in the drug approval process. An IDE allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data required to support a PMA application or a 510(k) submission to the FDA. Clinical studies are required to support a PMA. In addition, all Class III devices and the majority of Class II devices requiring clinical data to demonstrate the substantial equivalence in support of a 510(k) require an IDE application prior to initiation of the clinical trials. Clinical trials on low

risk medical devices are exempt from filing an IDE as long as they receive approval from an Institutional Review Board.¹⁷²

Adverse Event Reporting to the FDA

Post-Marketing Adverse Drug Experience Reporting

Prescription drug manufacturers, prescription drug packers, and private label distributors of prescription drugs are required to submit post-marketing Adverse Drug Experience (“ADE”) reports to the FDA. Post-marketing ADE surveillance is designed to obtain information on rare, latent or long-term drug effects not identified during pre-market testing. Sponsors, manufacturers, packers and distributors are required to report all serious, unexpected (i.e., not listed in the drug product’s current labeling) ADEs to the FDA within 15 calendar days. A serious ADE is one that is fatal or life threatening, is a persistent or significant disability/incapacity, requires inpatient hospitalization, or is a congenital anomaly. A serious ADE also includes prolongation of existing hospitalization. For ADEs that do not meet the criteria for “serious ADEs,” periodic reports must be submitted to the FDA quarterly during the first three years following approval of the drug and annually thereafter.¹⁷³

Medical Device Adverse Event Reporting

The Medical Device Reporting (“MDR”) regulation¹⁷⁴ requires that user facilities must submit medical device adverse event reports to the FDA and to the device manufacturer whenever the facility becomes aware that a device used at the facility may have caused or contributed to a patient death. User facilities must also report adverse events to the device manufacturer or to the FDA (if the manufacturer is unknown) whenever they become aware that a device may have caused or contributed to a serious injury to a patient of the facility. In addition, user facilities are required to submit an annual report summarizing the reports submitted by the user facility during the reporting period.

The MDR regulation also requires that device importers must submit medical device adverse event reports to the FDA and the device manufacturer whenever they become aware that one of their imported devices may have caused or contributed to a death or serious injury. In addition, device importers must submit adverse event reports to the device manufacturer whenever they become aware that one of their imported devices has malfunctioned and the malfunction would be likely to cause or contribute to a death or serious injury if it were to recur.

C. Intellectual Property Rights

Intellectual property is fundamental to the financing strategy of a biotechnology company. The right and ability to develop and exploit existing or new inventions, trade secrets, proprietary information, and know-how are the company’s most valuable assets. To develop

an effective financing strategy, a biotechnology company must consider the intellectual property it might develop, acquire, or license. It is equally important for that company to develop a thorough knowledge of the competing intellectual property that is or may be owned or under development by other companies or entrepreneurs in the same field. Additionally, before venturing into a discrete area of biotechnology, a company must develop a thorough understanding of government regulations, scholastic research, and information in the worldwide public domain that may have an effect on contemplated developments. The value of existing or proposed intellectual property is contingent both upon the availability of legal protection and upon the immediate and long-term demand for new developments in that area of biotechnology.

There are four broad categories of intellectual property: patents, copyrights, trademarks and service marks, and trade secrets. All intellectual property is international in scope, and no effective financing strategy can disregard international regulation and protection. Although a number of international treaties and conventions allow for some degree of international protection, there is no “worldwide patent” or “worldwide trademark” governed by a uniform, universal statute. For illustrative purposes, this section will primarily address U.S. intellectual property law.

In the U.S., patents and copyrights are authorized by the U.S. Constitution¹⁷⁵ and are exclusively creatures of federal law.¹⁷⁶ Although the individual states do not issue patents or copyrights, trademarks are governed by an amalgam of state and federal laws as well as the common law.¹⁷⁷ In about three-quarters of the states, trade secrets are governed by a version of the Uniform Trade Secrets Act.¹⁷⁸ Those states that have not enacted trade secret statutes recognize other statutory or common law protection for proprietary confidential information.

There is an unavoidable nexus between trade secrets and patents. While a new invention is under development, information about it is a trade secret and must be protected from public disclosure. In the U.S. and most other countries, patent applications are published 18 months after the filing date, unless the application has been abandoned or the applicant certifies that the application will not be filed in another country that requires publication. The U.S. Patent and Trademark Office (“USPTO”) publishes copies of issued and expired U.S. patents, and both the patents and the prosecution history of each patent are matters of public record.

Copyright registration certificates identifying a work by title, brief description, author, and owner are publicly available from the Register of Copyrights at the Library of Congress. Registration is not mandatory, however, and many copyrighted works are not registered until they become the subject of a dispute or a transaction. The USPTO also publishes copies of issued and expired trademarks, as well as abandoned or rejected applications and marks. Most states also publish lists of state-registered marks. For obvious reasons, trade secrets are not published, although references to their existence and general descriptions of their competitive impact may be found in the public record, such as published court decisions, filings with the SEC, public offerings, and financing materials.

The first step in evaluating intellectual property for financing purposes is to determine the demand for the invention or technology that a company seeks to protect or develop. This analysis requires an investigation not only of the availability of a patent or patents in the U.S., but also an understanding of international patents. The analysis also requires a review of the relevant worldwide literature, a survey of academic projects and activities, and full knowledge of information generally available to the industry. Products and processes that

have been on the market for many years may not be subject to patent protection, but may be protected by trade secret law. A well-guarded trade secret may be protected by significant legal barriers that will endure well beyond the life of a patent in any country.¹⁷⁹

In evaluating the commercial potential for new and existing intellectual property, it is also essential to determine what R&D is being performed by universities, colleges, and private research organizations by means of reviewing publications and presentations in the field. The unrestricted public dissemination of information may destroy the trade secret protection for which that information might otherwise qualify. Moreover, publication of patentable ideas becomes “prior art” and may negatively affect the availability of patent protection for even the most significant breakthroughs. Under the doctrine of “inherent anticipation,” even an unintentional disclosure may be “prior art.”

The first step in evaluating any new development is to determine if it is in fact new, and thus protectable, or if the idea has already made its way into the public domain. The “value” of an idea in a scientific sense may far exceed its “value” as intellectual property, if the idea has been publicized in sufficient detail to commit it to the public domain before it can be legally protected. Conversely, the fact that an idea is not “new” does not mean that it is no longer valuable. Identification of a product with a famous trademark may allow that product to retain some of its value even after the patent for that product expires.¹⁸⁰ As noted above, a trade secret may outlast a patent by many years and provide its owner with a virtual monopoly.

Patents

There are three types of patents in the U.S. Utility patents cover machines, articles of manufacture, compositions of matter, and processes.¹⁸¹ Plant patents cover asexually reproduced plants,¹⁸² and design patents apply to the ornamental appearance of articles of manufacture or machines.¹⁸³ Ideas, products of nature, and laws or principles are not patentable.

For patent applications that were filed on or after June 8, 1995, the term of an issued U.S. plant or utility patent will be 20 years from the effective filing date of the application.¹⁸⁴ For applications filed before June 8, 1995, the term is either 17 years from the date the patent was or is granted, or 20 years from the effective filing date, whichever is longer.¹⁸⁵ Design patents have a term of 14 years from the date of issuance.¹⁸⁶

Utility, Novelty and Non-Obviousness

To be eligible for patent protection, an invention must be useful,¹⁸⁷ “novel,”¹⁸⁸ and “not obvious.”¹⁸⁹ “Usefulness” may be a difficult burden to meet for a biotechnology invention; a chemical formulation or process with no present practical application may be of scientific interest but cannot be protected by a U.S. patent. The USPTO does not formally handle biotechnology inventions any differently than inventions in other areas of technology, but as a practical matter the burden of disclosing specific utility or usefulness apparent to others in the field may be more difficult to meet for a biotechnology invention. That statutory requirement also creates a risk for investors, in

that it requires public disclosure of the idea to potential competitors, often before the patent has been issued and protection is in place.

An invention's utility "must be definite and in currently available form."¹⁹⁰ Under the USPTO Guidelines for Examination, if an applicant asserts a credible utility for the claimed invention, or if utility is apparent to a person of ordinary skill in the art, then the patent examiner should not reject the claims based on a lack of utility. An applicant who fails to identify a specific useful application for an invention, or who fails to disclose adequate information about the invention by failing to make its usefulness immediately apparent to those familiar with the technological field of the invention, will not satisfy the statutory "usefulness" requirement. Under those circumstances, a patent would not issue.

In addition, the inventor is required to disclose the best mode for practicing the invention that is known to the inventor at the time the application is submitted.¹⁹¹ Thus a patent applicant cannot disguise the true anticipated value of the invention by failing to disclose the preferred embodiment of the invention until after the patent has issued.

In patent parlance, "novel" means that, before invention by the applicant, the idea disclosed and claimed was not: known or used by others in the U.S.; patented or described in a printed publication anywhere in the world; invented by someone else in the U.S. who has not abandoned, suppressed, or concealed the invention; or described in a patent application filed by a different person (if that application later issues as a U.S. patent).¹⁹² If the proposed invention was described in print in the U.S. or a foreign country at any time more than one year before a patent application has been filed, or if a version of the invention has been the subject of public use or sale in the U.S. for more than one year before filing, no patent can be issued.¹⁹³ A trivial or "obvious" modification of an existing invention or state of the art (whether or not protected by a patent) will not be granted patent protection if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art at the time the invention was made.¹⁹⁴

The "novelty" requirement presents special difficulties in biotechnology because inventions in the field often relate to discoveries of already existing natural biological compositions or mechanisms. Discovery of an existing natural biological composition or mechanism fails to meet the novelty requirement of Section 101 of the U.S. Patent Act. To obtain a patent for a biological composition that already exists in nature, the inventor must distinguish the claimed composition from the naturally-occurring one by claiming that the composition has been isolated, or purified, or produced through recombinant DNA.

In making that distinction, the inventor must take into account the Doctrine of Inherent Anticipation, which can be fatal to a patent application, and its sibling, the Doctrine of Accidental Anticipation, which might in some cases rescue the same application. Under the Doctrine of Inherent Anticipation, even when a prior art reference fails to disclose explicitly the entire subject matter of a patent claim, the reference may inherently anticipate the claim if it is the "natural result flowing from" the disclosure of the prior art reference.¹⁹⁵ Under the judicially-created Doctrine of Accidental Anticipation,

however, inherent anticipation does not apply if the prior art accidentally discloses the claimed subject matter.¹⁹⁶

The Doctrine of Inherent Anticipation prevents the removal from the public domain of features or properties that inherently exist, but are unknown and not taught in the prior art.¹⁹⁷ Discovery of a necessary and inevitable feature or characteristic that is inherent or otherwise implicit in a prior art reference, even if unrecognized or unappreciated, does not make it novel for the purposes of patentability.¹⁹⁸ Under the Doctrine of Accidental Anticipation, the Doctrine of Inherent Anticipation does not apply in cases of accidental or unwitting anticipation.¹⁹⁹ In *Tilghman v. Proctor*,²⁰⁰ for example, the Supreme Court held that the previous unintended and unappreciated practice of a process to separate fats and oils was insufficient to anticipate a subsequent patent for that purpose. The contradictory and possibly overlapping meanings of these two doctrines have given rise to much litigation and to confusing judicial decisions.

In *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, a group of generic drug companies challenged the validity of Schering's patent in descarboethoxyloratadine ("DCL"), a compound for non-drowsy antihistamines.²⁰¹ Schering previously had obtained a patent for loratadine, the active component in CLARITIN®, which is formed naturally in the human body upon ingestion.²⁰² In its pre-clinical studies Schering determined that DCL was an active metabolite for loratadine. Although there was no prior art teaching concerning DCL, the Federal Circuit Court of Appeals²⁰³ held that Schering's prior art patent for loratadine inherently anticipated its later patent claims for DCL because DCL necessarily and inevitably forms when loratadine is administered to a patient.²⁰⁴

The significance of the *Schering* decision was the Federal Circuit's rejection of the argument that inherent anticipation requires recognition of the inherent characteristic or result in the prior art.²⁰⁵ Although DCL was not recognized in the prior art, it was a necessary and inevitable consequence. Elimination of the recognition requirement makes sense; by their very nature, inherent properties or results are typically not disclosed or described in a patent. From a legal standpoint, however, *Schering* may have undermined the Doctrine of Accidental Anticipation.

The *Schering* court addressed the Doctrine of Accidental Anticipation and concluded that it survived elimination of the recognition element from the Doctrine of Inherent Anticipation.²⁰⁶ In other decisions, the Federal Circuit has considered a number of factors to determine if Inherent Anticipation or Accidental Anticipation applies to a patent: Did the prior art intend the claimed composition or process? Did the prior art include knowledge of the claimed composition or process or of the newly discovered function of the composition or the newly discovered result of the process? Did the prior art include knowledge of a claimed component or function of the claimed process? Did the prior art perform the claimed process or make or use the claimed composition for a different purpose? Was the claimed composition useful in the prior art? Was the claimed process useful to achieve the claimed result in the prior art?²⁰⁷

Observed biological results and underlying mechanisms of biological actions often are not understood until after the publication of experimental findings. As a result, the early publication of an experimental finding may inherently anticipate, and therefore preclude, issuance of a patent based on a subsequently achieved understanding of the earlier publication. For a biotechnology investor, a determination of whether the prior

art necessarily and inevitably reveals a composition or process is essential to an evaluation of both patentability or, conversely, of freedom to pursue use of a process or composition because the prior art has committed information, perhaps unintentionally, to the public domain.

Patent Infringement

In biotechnology finance, it is essential to analyze competing patents to protect against investing time and resources into development of a product or process that cannot be marketed legally because it infringes upon an existing patent. A qualified patent attorney should provide an opinion regarding relevant patents in the field. That opinion should: meaningfully discuss the file history of each competitive patent; present any legal and factual analysis for the basis for the opinions; and specifically address all claims and interpret them. Infringement analysis requires consideration of literal infringement and the “doctrine of equivalents.”

A new device may literally infringe an existing patent if it follows the claims in the patent as written and interpreted by a court according to their meaning and scope.²⁰⁸ Under the “doctrine of equivalents,” if a device performs the same overall function in substantially the same way to obtain substantially the same result as the claimed invention, then infringement may be found even if the device does not literally infringe each element of a patent claim.²⁰⁹ An opinion letter obtained should: discuss the limits of existing patents to assist an inventor of a new biotechnology product in designing around existing patents; analyze information previously considered by the USPTO if the opinion relies on an obviousness or anticipation defense against infringement; link prior disclosures to claim limitations if the opinion deals with obviousness or anticipation; assess secondary indications of non-obviousness if the opinion deals with obviousness; and explain the burden of proof on accused infringers involving invalidity or unenforceability.

Pharmaceutical Patents

Pharmaceutical patents and patents in living matter are of special significance to biotechnology companies. Pharmaceutical patents are regulated in part by an addendum to the U.S. Patent Act, the Drug Price Competition and Patent Term Restoration Act of 1984,²¹⁰ known as “the Waxman-Hatch Act” after its respective chief sponsors in the U.S. House of Representatives and Senate. Waxman-Hatch creates a separate but related body of law that applies exclusively to pharmaceutical patents.

Waxman-Hatch was established to restore effective patent terms that had eroded substantially over the years. The FDA subjects new pharmaceuticals to a complicated and time-consuming approval procedure, and one purpose of Waxman-Hatch was to permit the patent holder to enjoy the full term of the patent, or as much of the full term as possible, even if FDA approval were delayed beyond the issuance date. Thus, the term of patents on processes and composition of matter subject to FDA approval may be extended due to FDA caused delays in distribution.

Waxman-Hatch provides for patent term extensions for pioneering drugs but also provides exemptions for generics that otherwise might infringe patents. Waxman-Hatch provides that it is not an act of infringement to make, use, offer to sell, or sell within or import into the U.S. a patented invention that is primarily manufactured using recombinant DNA, hybrid technology, or other processes involving site specific genetic manipulation techniques solely for uses reasonably related to the development and submission of information under a federal law that regulates the manufacture, use, or sale of drugs or veterinary biological products. This “safe harbor” allows generic drug manufacturers to enter the marketplace as soon as the patent in a corresponding pharmaceutical product expires, thereby eliminating the unwarranted extension of the drug’s patent term.

As a result of a recent decision by the U.S. Supreme Court, a limited “research exemption” exists under Waxman-Hatch for drug manufacturers who later seek to obtain FDA approval. In *Merck KgaA v. Integra Lifesciences I Ltd.*,²¹¹ a unanimous Court determined that a statutory exemption from patent infringement exists “for uses reasonably related to the development and submission of information” to federal regulatory agencies. In an opinion by Justice Scalia, the Court determined that Waxman-Hatch creates a broad safe harbor for the use of patented pharmaceuticals by those who may wish to develop medications that may be subject to regulation by the FDA or other regulatory approval processes.

The case arose from the efforts of scientists at the Scripps Research Institute, who discovered that blocking the receptor on certain cells inhibits new blood vessel generation, thereby showing promise for a means to halt cancerous tumor growth and treat other diseases. Merck hired Scripps to identify potential drugs that would inhibit blood vessel generation. Scripps chose the cyclic RGD peptide EMD 121974, which had been patented by Integra, and tested it to assess the action of the peptides and the proper mode of administering them therapeutically.

Integra sued, claiming that use of the patented RGD peptide was patent infringement. In its defense, Merck relied on the “safe harbor” provision of Waxman-Hatch,²¹² which states:

It shall not be an act of infringement to . . . use . . . a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

Merck argued that its research was intended to produce a drug that eventually would be submitted to the FDA for approval and that denying the exemption would delay the availability of the drug for medical treatment. The Supreme Court accepted that argument, eliminating the judge-made distinction between “clinical” and “pre-clinical” trials for the purposes of the Section 271(e)(1) safe harbor. The safe harbor “extends to all uses of patented inventions that are reasonably related to the development and submission of any information” to the FDA.

Although the scope of the *Merck* decision has yet to be determined, it is clear from the Supreme Court’s decision that the safe harbor extends even to the results of experiments that ultimately are not submitted to the FDA. The exemption is sufficiently

broad to cover any research reasonably related to the process of developing information for submission under any federal law regulating the manufacture, use, or distribution of drugs.

Basic research that is not done with the intent of identifying possible candidates for future FDA approval is not covered by the Waxman-Hatch safe harbor, however. Moreover, the Supreme Court provided that certain patents on substances used only as “research tools” would not fall within the Section 271(e)(1) safe harbor, although it was clear from the record in *Merck* that the RGD peptides patented by Integra were not used as such research tools.

From the perspective of biotechnology finance, it is essential to determine the expiration date of any competitive patent, and when possible to exploit the newly-broadened “safe harbor” provision of Waxman-Hatch as part of the process of developing generic pharmaceuticals. Generic equivalents may be submitted to the FDA approval process in advance in order to allow the generic manufacturer to enter the market with an equivalent product at the earliest possible time following expiration of the pharmaceutical patent. Conversely, owners of patents in pharmaceuticals must monitor ANDAs filed with the FDA by generic manufacturers to ensure that generic pharmaceuticals that might otherwise infringe its patents will not be introduced into the market prior to expiration of the patents.

Patents In Living Matter

Patents in living matter have been available in the U.S. since 1980, when the U.S. Supreme Court decided in *Diamond v. Chakrabarty* that “a patent can be granted on anything under the sun which can be made by man.”²¹³ Chakrabarty genetically engineered a bacterium enabling it to break down crude oil. At first, the product was rejected because it was considered a “product of nature.” However, as the enhanced bacterium was not naturally occurring, it was considered a “product of man,” and the Supreme Court ordered the USPTO to issue the patent.

Chakrabarty opened the portal for the issuance of numerous U.S. patents and genetically engineered life forms, including transgenic animals and biological materials. Human cells and tissues, including embryos and stem cells, remain unpatentable products of nature. These materials may be patentable subject matter, however, if they are modified in some way that transforms them into man-made material.

For much of the public, patents in living matter or modifications of embryos or stem cells raise moral and ethical questions. The courts have recognized these moral and ethical concerns in several older patent cases. The USPTO or the courts may deny patentability to inventions that are deemed to be “immoral, mischievous, contrary to public policy, or injurious to the well being of society.”²¹⁴ This so-called “moral utility doctrine,” first articulated in the nineteenth century, rests on the notion that, if an invention is evil, it cannot be useful, and if it is not useful, it cannot be patentable. Opponents of cloning and stem cell research have argued that patentability for those practices could and should be denied based on the moral utility doctrine.

To date, neither the USPTO nor the courts have denied patentability to controversial inventions based on the “moral utility” doctrine. The USPTO has articulated a policy, however, that denies patentability to any claim that could encompass a human being. Of course, under *Chakrabarty*, unmodified human cells and tissues, including embryos and stem cells, are already considered unpatentable products of nature. As decisions in this area develop, however, they may have a significant impact on biotechnology development in controversial fields and will necessarily affect the financing strategy and decision-making of the biotechnology company.

European Patents

Patentability in the U.S. does not ensure patentability internationally. Under European rules, a patent must have industrial applicability, be novel, and involve an inventive step.²¹⁵ Unlike the USPTO, the European Patent Office (“EPO”) incorporates certain non-technical concerns into its examination of biotechnological inventions. The EPO will not issue patents that violate public policy or morality when commercially exploited.²¹⁶ For example, the EPO has identified as unpatentable in Europe processes that include cloning for human beings and uses of human embryos for industrial or commercial purposes. In Europe, like the U.S., the human body at the various stages of its formation and development is unpatentable.

Differences in the patent laws in the U.S. and Europe were highlighted in the “Harvard Mouse” case.²¹⁷ A patent was issued to Harvard College for a mouse genetically engineered to make it more susceptible to cancer – it was useful for research purposes even if not useful to the mice involved. In Europe, the patent application for the same invention was initially rejected for failure to constitute patentable subject matter. Following appeal, the invention was found not to violate the European morality provision, and a patent could be maintained in amended form directed to transgenic rodents.

Compulsory Licensing of Patents

Like other patents, biotechnology patents also may be subject to compulsory license, in which the government removes some of the patentee’s control over the patent in exchange for compensation. A national government may force a patent holder to license the patented invention to other companies, which may or may not be competitors, for a reasonable royalty or license fee. The U.S. government has the power to require compulsory licensing of patents obtained through federally funded research under certain circumstances.²¹⁸ Compulsory licensing is rarely done in the U.S., however, and licenses are normally only granted when a supplier of a critical patented product cannot meet the needs of the public.

On the international side, however, the international agreement on Trade-Related Aspects of Intellectual Property²¹⁹ (“TRIPS Agreement”), to which the U.S. is a signatory, provides for compulsory licensing or governmental appropriation under certain specified circumstances. The EU does not have general compulsory licensing provisions. Instead, compulsory licensing and other government intervention regarding inventions are typically handled on a national basis.

Governmental Appropriation of Patents

Outright appropriation is a more direct approach by which a national government may take control over patent rights. The U.S. government has the power to use, or commission another to use, any patented technology, but the government is then liable for reasonable and full compensation for the taking of these rights. Under U.S. law, whenever an invention described in or covered by a U.S. patent is used or manufactured by or for the U.S. without a license from the owner, the owner's remedy is against the U.S. and is limited to "recovery of his reasonable and entire compensation for such use and manufacture."²²⁰ The patent owner may sue the federal government for a reasonable royalty but cannot obtain an injunction against infringement and cannot prevent its competitors from infringing the patent to the extent that the federal government directs the infringement.

The TRIPS Agreement also provides guidelines for government appropriation in member countries. Under British law, for example, the Crown may use, or authorize the use of, any patented invention if the patentee is compensated for lost profits due to appropriation.²²¹

Research Exemption

Most international law recognizes a "research exemption" that allows use of a patented invention for experimentation with the intent to improve upon the invention. The U.S. "research exemption" was recently defined by the Supreme Court in the *Merck* decision under Waxman-Hatch.

Even in those countries that do have a "research exemption," it is generally only applicable to those who have no intent to use or sell the improvement. In the U.S., an "experimental use" exemption applies for research done solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry.²²² Most academic research does not fall under the experimental use exemption, nor does most private research. State universities are immune from federal patent infringement lawsuits under the sovereign immunity granted by the Eleventh Amendment to the Constitution. State universities therefore enjoy a sort of *de facto* research exemption not available to private colleges and universities.

The European Patent Convention does not contain rules regarding an experimental use or research exemption. General defenses exist, however, for acts done for experimental purposes related to the subject matter of the patented invention and for non-commercial private acts. International laws generally allow for more freedom for experimental research than U.S. law. As a result, experimental research will often be immune from patent infringement in Europe, even if done for commercial purposes.

Competitor Patents

It is essential for a biotechnology company to inventory and evaluate the patents in the portfolios of its competitors. An analysis of the scope of those patents and the

technology they cover is essential, as well as the territories and nations in which the patents apply. In evaluating competitor patents, investors in a biotechnology company must determine if it is financially worthwhile to design around existing patents, or to wait for the expiration date before introducing a competing product. Licensing opportunities may be more attractive than designing around a patent, risking an infringement lawsuit, or challenging the validity of the patent.

Copyrights

Copyrights are of considerably less value than patents to biotechnology companies. Copyrights protect expression in tangible form and do not protect ideas.²²³ The intellectual property most valuable to biotechnology is specifically excluded from copyright protection, which by statute does not “extend to any idea, procedure, process, system, method of operation, concept, principle, or discovery, regardless of the form in which it is described, explained, illustrated, or embodied.”²²⁴ Copyright protection is not available for procedures for: doing, making, or building things; scientific or technical methods or discoveries; business operations or procedures; or mathematical principles; formulas, or algorithms.

A copyright is the exclusive right granted to the author of original literary or artistic works to reproduce, publish, or sell them for a limited period of time. In the U.S. and around the world, that “limited period of time,” is extremely long – the life of the creator plus 70 years,²²⁵ and for works made for hire, anonymous, or pseudonymous works,²²⁶ the shorter of 95 years from publication or 120 years from creation. The value of a copyright to a biotechnology company is in the protection of its marketing materials, manuals, or advertisements. Copyright protection extends to a description, explanation, or illustration of an idea or system, but only to the particular literary or pictorial expression chosen by the author. The copyright owner – which in the case of a work prepared by an employee would ordinarily be the biotechnology company – has no exclusive rights in the idea, method, or system described in the work.

Suppose, for example, that an author writes a paper explaining a new system for creating a transgenic mouse. The copyright in the book, which comes into existence at the moment the work is fixed in a tangible form, will prevent others from publishing the text and the illustrations describing the author’s ideas for creating and using the new creature. The copyright alone will not give the copyright owner any rights to prevent others from adopting the ideas for commercial purposes or from developing or using the machinery, processes, or methods described in the book. Copyright law, therefore, could be used to prevent, or obtain compensation for direct copying but could not be used to protect against the use or dissemination of the ideas.

Although a copyright comes into existence as soon as a work is committed to a tangible medium of expression, federal registration is required to enforce copyright rights in the U.S.²²⁷ Notice – the familiar © – is no longer a statutory requirement but is permitted²²⁸ and a recommended best practice.

International Copyright

There is no “international copyright” that will automatically protect works in every country throughout the world. Protection against unauthorized use in a particular country depends on the national laws of that country. However, most countries offer protection to foreign works under certain conditions that have been greatly simplified by international copyright treaties and conventions. There are two principal international copyright conventions, the Berne Union for the Protection of Literary and Artistic Property and the Universal Copyright Convention.

An author who seeks copyright protection for his or her work in a particular country should first determine the extent of the protection available to works of foreign authors in that country. If possible, this should be done before the work is published anywhere because protection may depend on the facts existing at the time of first publication.

In general terms, a work may be protected in a country in which protection is sought, if that country is a party to one of the international copyright conventions, by complying with that convention. Even if the work cannot be protected under an international convention, protection under the specific provisions of the country’s national laws still may be possible. There are, however, some countries that offer little or no copyright protection to any foreign works.

Trademarks

Trademarks and service marks comprise the third category of intellectual property. Trademarks typically identify products and service marks identify services. It is important in the biotechnology field to obtain and maintain international trademark protection for valuable products. For example, the trademark “NUTRASWEET®” is associated throughout the industry, and among consumers worldwide, as an artificial sweetener for human consumption. Although the patent for the artificial sweetener has long expired, the product itself is well known by its trademark.

A trademark is a word, symbol, device or design, slogan or any combination of those used by its owner to distinguish a good or service from those of another. A service mark is used in the sale or advertising of services. Trademarks are valuable to foster competition and prevent consumer confusion, identify and distinguish products, identify the source of goods, indicate the quality of goods, build consumer loyalty, and leverage advertising investment. The stated purpose of the Lanham Act, the federal trademark law in the U.S., is to regulate commerce by making actionable deceptive and misleading use of marks in commerce.²²⁹

In the U.S., trademark rights are established by using the mark in commerce in connection with particular goods.²³⁰ Registration is not required to maintain trademark rights, although registration is available by filing an application with the USPTO.²³¹ Federal registration serves as constructive notice to all others that a mark is registered by its owner in connection with specified goods or services,²³² and no subsequent user may in good faith use the same goods or services. The registration is *prima facie* evidence of the owner’s exclusive right to use the mark,²³³ and after five years the registration may become incontestable.²³⁴ Federal registration is required before the trademark owner is permitted

to use the registration symbol – ®.²³⁵ By recording the registered trademark with the Department of Homeland Security, the trademark owner can exclude importation of goods bearing infringing marks.²³⁶ If the company is involved in litigation, specific statutory remedies such as recovery of profits, attorney fees, and treble damages become available following registration.²³⁷

In most other countries, trademark rights are established through registration. Before beginning to sell biotechnology products in foreign countries, it is important to first apply for and register the trademarks. It is essential to conduct a thorough national and international search in all countries where the biotechnology company might conceivably have a market to determine that the mark is available before adopting a product mark. Registration must be made in advance of entry in most countries. In many countries, a trademark may not be used without registration. Failing to register a trademark in a foreign country may require the trademark owner to re-brand or forego that market altogether.

The strongest trademark is that which has the least literal relationship to the product to which it is attached. For example, the coined term “PREMARIN®” is a very strong trademark for a hormone replacement drug;²³⁸ similarly, the arbitrary term “AMAZON®” is very strong for on-line book sales, because although it is an ordinary word, it appears out of its usual context. A suggestive term such as “NUTRASWEET” is also strong, particularly after it has been used effectively over a long period of time.

Descriptive terms, such as “NATIONAL CASH REGISTER™” for cash registers, are weak unless they have acquired “secondary meaning” by use in the public. Generic terms, such as “book,” “ice cream,” or “estrogen” are not trademarks at all – merely descriptive terms.

Trade Secrets

In evaluating a biotechnology company’s intellectual property assets, or those of its competitor, it is also crucial, although sometimes difficult, to include an assessment of trade secrets. If properly protected, trade secrets can be more valuable than patents. The value of a trade secret derives in part from the fact that, unlike a patent, a properly protected trade secret will never enter the public domain.

Most states have adopted the Uniform Trade Secrets Act, which defines a trade secret as “information, including a formula, pattern, compilation, program, device, method, technique, or process, that: (1) derives independent economic value, actual or potential, from not being generally known to, and not being readily ascertainable by proper means by, other persons who can obtain economic value from its disclosure or use; and (2) is the subject of efforts that are reasonable under the circumstances to maintain its secrecy.”²³⁹ In the remaining states, the most common definition is that a “trade secret may consist of any formula, pattern, device, or compilation of information which is used in one’s business, and which gives him an opportunity to gain an advantage over competitors who do not know or use it.”²⁴⁰ Both at common law and under the Uniform Trade Secrets Act, a trade secret may be a formula for a chemical compound, a process for manufacturing, treating or preserving materials, a pattern for a machine or other device, or a list of customers.²⁴¹ A trade secret can even be a practice of doing something “wrong” – not following generally

accepted practices and procedures in the industry – if doing so it provides a competitive advantage.²⁴²

A recent example of the value of a trade secret as a sort of “super-patent” involved a lawsuit brought by Wyeth Laboratories.²⁴³ Wyeth had acquired the rights to a secret chemical process used to extract estrogen from the urine of pregnant mares in order to make a hormone therapy replacement drug known as PREMARIN. The only “naturally” derived hormone therapy replacement drug, PREMARIN had been sold in the U.S. since 1942, when the FDA first approved it. Wyeth and its predecessors had obtained a number of patents, all of which had expired, in connection with estrogen extraction research. Because none of the patents covered the process actually used to create PREMARIN and because Wyeth and its predecessors had maintained that process as a trade secret, the Court prohibited a competitor from manufacturing a generic equivalent. The process had been in use for more than 60 years, and many competitors, including Wyeth, which purchased the process after failing to reverse engineer it, had tried unsuccessfully to duplicate it. The court concluded that the secret PREMARIN manufacturing process remained a valid trade secret and could not be used by a competitor who obtained it through improper means.

In order to protect trade secrets, a biotechnology company must take affirmative steps to identify those secrets and adopt procedures to protect them. These procedures may include: adopting physical security procedures, such as locks and guarded entrances, visitor and employee badges, and limiting access to facilities where trade secrets might be kept; instituting a formal document handling policy; using confidentiality and non-competition agreements with employees; using non-disclosure agreements with vendors, customers and prospects; keeping track of copies of materials; limiting computer access to information, and observing the use of passwords to access computer data. It is also important to avoid inadvertent publication of trade secrets in sales materials and at academic conferences.

D. Tax and Tax Credits

Introduction

The tax issues that are relevant to a biotechnology company will typically depend on the life cycle stage of the company. For example, during its early years, a biotechnology company is likely to make substantial R&D expenditures before it generates significant revenue. The primary tax issues it faces during this period involve identifying and exploiting available tax deductions and tax credits in the Code.

As a biotechnology company progresses in its life cycle, significant tax issues will arise as it begins to commercialize and exploit the patents and technology it develops and owns. These revenue-generating operations will produce another set of tax issues. For example, the decision whether to license or sell a patent may produce very different tax consequences.

The exit strategy to be used by the company’s investors will raise yet another set of tax issues and potential tax liabilities. For example, there are a variety of exit strategies available

to investors which range from an outright sale of technology to a tax-free reorganization. Each alternative generates different tax consequences that will have a significant economic impact on the investors.

To thoroughly discuss all the tax issues impacting the various types of biotechnology companies would require a restatement of a large portion of the Code. Instead, we have summarized those issues which are most important to the operations and financing of a biotechnology company. Tax advice and tax planning are an integral part of any firm's financial strategy. As a result, every biotechnology company would be well served to engage appropriate tax counsel for advice, planning and reporting of both state and federal taxes.

Tax Deductions and Credits

Product Development

Under federal income tax law, certain expenditures incurred in the development or acquisition of technology are granted favorable tax treatment in the form of deductions or credits. In general, items that are allowed as deductions decrease taxable income by an amount equal to the amount of the deduction times the taxpayer's effective tax rate.²⁴⁴ In contrast, items that are allowed as tax credits generally decrease taxable income on a dollar-for-dollar basis.²⁴⁵ For example, assuming a 35% federal income tax rate, a dollar of deductions would reduce a taxpayer's taxable income and corresponding tax liability by \$.35 while a dollar of tax credits would reduce a taxpayer's tax liability by \$1.00.

With respect to the timing of various deductions, current expenses are business expenditures that produce no significant benefit beyond the end of the year in which they are incurred and are deductible in that year.²⁴⁶ Inventory costs are deductible under "first-in-first-out" or "last-in-first-out" inventory accounting conventions only when the inventory is sold.²⁴⁷ Capital expenditures incurred to create or acquire assets that produce significant benefits beyond the end of the year of acquisition must be capitalized, and are not deducted currently.²⁴⁸

Where the costs of capital expenditures are not deducted in a current year, these costs generally are depreciated or amortized over the useful life of the asset, where that useful life is prescribed by law or empirically determinable.²⁴⁹ Where an expenditure may not be expensed in a current year or deducted over the asset's useful life, the taxpayer's investment is held in abeyance and offset against future sales proceeds if the asset is sold, or deducted as a loss if the asset becomes worthless or is abandoned.²⁵⁰

Exceptions Applicable to Intellectual Property

A significant expense for biotechnology firms is R&D. Section 174 of the Code provides two methods for treating research or experimental expenditures paid or incurred by a taxpayer in connection with a trade or business. Taxpayers may elect to either: currently deduct research and experimental expenditures; or defer and amortize these costs over a period of at least sixty months beginning with the month in which benefits

from the cost of the project are first realized.²⁵¹ Therefore, Section 174 allows a new business to elect to deduct research and experimental expenditures even though it is not engaged in a trade or business when the costs are incurred. In one case, the U.S. Supreme Court found that a business formed to develop an incinerator could deduct research expenses incurred in the years before it produced and marketed the incinerator.²⁵² While a taxpayer is not required to conduct a trade or business at the time the research expenses are incurred, the taxpayer must have a realistic prospect of entering into a trade or business based on such research if the research is successful. One court has enunciated the test as whether the taxpayer can demonstrate an objective intent to enter into the trade or business and the capability to do so.²⁵³

The term "research or experimental expenditures" means expenditures incurred in connection with the taxpayer's trade or business that represent R&D costs in the experimental or laboratory sense.²⁵⁴ Expenditures represent R&D costs in the experimental or laboratory sense if they are for activities undertaken to discover information that would eliminate uncertainty concerning the development or improvement of a product.²⁵⁵ In general, this uncertainty exists if the information available to the taxpayer does not establish the capability or method for developing or improving the product or the appropriate design of the product.²⁵⁶ For these purposes, a product includes a pilot model, process, formula, invention, technique, patent, or similar property that is either used by the taxpayer in its trade or business or held for sale, lease or license by the taxpayer.²⁵⁷ Whether expenditures qualify as Section 174 research or experimental expenditures does not depend on the nature of the product being developed; rather, the issue is the nature of the activity to which the expenditures relate and whether that activity is intended to eliminate uncertainty concerning the development or improvement of the product.²⁵⁸

For example, the following items give rise to qualified research and experimental expenditures: costs of designing and developing an automatic manufacturing system; costs of designing, developing, fabricating, and testing a super sonic transport prototype aircraft; and attorney's fees incurred to obtain foreign patents for which the taxpayer owned U.S. patents.²⁵⁹ In contrast, the following activities are specifically excluded from research and experimental expenditures: quality control testing of materials or products, efficiency surveys, management studies, consumer surveys, advertising or promotions, and acquisition of another's patent, model, production or process.²⁶⁰

Section 174 applies to research or experimental expenditures only to the extent that the expenditures are reasonable under the relevant circumstances.²⁶¹ In general, the expenditure is considered reasonable if it would ordinarily be incurred for similar activities by similar enterprises under similar circumstances.²⁶² The treatment of research or experimental expenditures also applies to expenditures paid or incurred for research or experimentation carried on by another person or organization such as a research institute, foundation, engineering company, or similar contractor.²⁶³

Finally, research and experimental expenditures previously deducted under Section 174(a) are not subject to recapture upon the sale of the technology to which the deductions relate. Accordingly, if the capital gains requirements are otherwise met, the entire gain upon the sale of the technology may be treated as capital gain without regard to the benefits previously received from the earlier deductions claimed under Section 174(a).²⁶⁴

Section 197 Intangibles

Section 197 of the Code allows a deduction with respect to the capitalized costs of certain intangible property (“Section 197 Intangible”) that is acquired by a taxpayer in connection with the acquisition and conduct of a trade or business.²⁶⁵ Taxpayers may amortize the cost of Section 197 Intangibles on a straight-line basis over a 15-year period beginning in the month in which the property was acquired.²⁶⁶

Section 197 Intangibles are property included in any one of the following categories: (1) goodwill and going concern value; (2) intangible property that relates to workforce, information base, know-how, customers, suppliers, or other similar items; (3) any license, permit, or other right granted by a governmental unit; (4) any covenant not to compete entered into in connection with the direct or indirect acquisition of an interest in a trade or business; and (5) any franchise, trademark, or trade name.²⁶⁷ Therefore, under Section 197, patents, copyrights, formulas, processes, designs, know how, or similar items have a 15-year amortization period if acquired as part of a trade or business. If acquired separately and not as part of the acquisition of a trade or business, then the acquired patents and similar property are amortized over their remaining useful life.²⁶⁸ In contrast, patents created by the taxpayer and self-created know-how are eligible to be currently expensed under Section 174(a), discussed above.

The practical effect of the rules imposed by Section 197 is that taxpayers generally favor acquiring the assets of a trade or business in order to obtain a purchase price cost basis and corresponding deductions over 15 years, rather than acquiring the capital stock of a trade or business and assuming the existing historic tax basis in such assets.

Credit for Research and Development Expenses

Section 41 of the Code provides a credit against tax for certain types of research expenses paid or incurred in a tax year.²⁶⁹ Congress included the research credit to serve as an incentive to taxpayers to conduct product development research activities and basic research.

As explained above, a credit is more valuable than a tax deduction because it will reduce income tax liability dollar for dollar. The research credit is an incremental credit, meaning that it is allowed on annual growth in qualified research spending over historical levels. Companies most likely to use the credit are those with a growth rate in research expenses in excess of their growth rate in sales. The research credit is unfortunately very complex – it involves numerous definitions and calculations. The following discussion is intended to provide general guidance on its application to a biotechnology company.

Eligibility

To claim the research tax credit, a taxpayer must determine that it is performing qualified research and that it is claiming expenses only for qualified research. To constitute “qualified research,” a cost must be deductible under Section 174.²⁷⁰ In addition, an activity must be undertaken for the purpose of discovering information

that is technological in nature (patents are presumed to meet this test). The application of the technological information must also be intended to be useful in a new or improved business component. Finally, substantially all of the activities (at least 80%) related to the research effort must constitute elements of a process of experimentation.²⁷¹

Certain types of activities are expressly excluded from qualified research.²⁷² These include research conducted after the beginning of commercial production, research that adapts an existing product or process to a particular customer's needs, duplication of an existing product or process, surveys or studies, or research funded by another person.²⁷³

In general, qualified research expenses are the same as those defined in Section 174, discussed above, with minor adjustments. Qualified research expenses include both in-house expenses for the taxpayer's own research (such as wages paid and supplies used in the conduct of qualified research), as well as a percentage of amounts paid or incurred for qualified research done by a person other than an employee of the taxpayer.²⁷⁴

Amount of the Research Credit

The research credit is only allowable to the extent of a portion of a company's incremental research expenses. There are two permissible methods for computing the credit, the standard method and the alternative incremental method. The standard method applies unless a taxpayer elects to use the alternative incremental method.²⁷⁵

Under the standard method, the research credit is based on the historical relationship between research expenses and sales and the average gross receipts of the four most recent years. The base amount is the product of the fixed base percentage and the average gross receipts for the four years immediately preceding the computation year.²⁷⁶ The fixed base percentage is the ratio of research expenses to gross receipts.²⁷⁷ The credit is equal to the sum of: 20% of the excess of qualified research expenses for the current year over the base period amount; and 20% of the basic research payments made to a qualified organization.²⁷⁸

An alternative three-tiered research tax credit is available to generate higher research credits for companies that have increasing sales figures or otherwise level research expenditures. The credit is equal to the sum of an increasing percentage of the amount of qualified research expenses in excess of a percentage of the base amount, and is divided into three tiers.²⁷⁹

In the case of entities in which income is passed through to the owners (such as S corporations or partnerships), any allowable credit cannot exceed the amount of tax attributable to the individual's taxable income allocable to that individual's interest in the entity.²⁸⁰

The credit has expired in the past, although Congress has renewed it periodically. As of the date of this publication, the research credit is set to expire for expenditures incurred after December 2005.²⁸¹

Orphan Drug Credit

In certain circumstances, taxpayers are eligible to receive a tax credit for a portion of their clinical testing expenses to develop drugs to treat rare diseases and conditions.²⁸² An election to receive the credit is made by filing Form 8820.

A rare disease or condition is one afflicting 200,000 or fewer persons in the U.S., or afflicting more than 200,000 persons in the U.S. but for which there is no reasonable expectation of recovering the cost of developing and making available a drug from sales in the U.S.²⁸³

“Clinical testing” means human clinical testing only if the testing: (1) is carried out under an exemption for a drug being tested for a rare disease or condition under Section 505(i) of the Food, Drug and Cosmetic Act of 1938, as amended (“FDC Act”); (2) occurs after the drug is designated under the FDC Act and before the drug is approved; (3) is conducted by or for the taxpayer; and (4) relates to the use of the drug for the rare disease or condition for which it was designated under the FDC Act.²⁸⁴ The credit is generally not allowed for testing conducted outside the U.S.

In general, the allowable credit equals 50% of the taxpayer’s qualified clinical testing expenses.²⁸⁵ Qualified clinical testing expenses typically include amounts paid or incurred that would be described as “qualified research expenses” under Section 41.²⁸⁶

General Business Credit Limitations

The research credit and orphan drug credit are both components of the “general business credit.”²⁸⁷ These credits are non-refundable and may not exceed a specified portion of a taxpayer’s tax liability. They are also subject to limitations and to carry-back and carry-forward rules. When the credit exceeds the limitation in any year, the unused portion may be carried back one year and forward twenty years, subject to various limitations, and thereafter deducted to the extent not fully utilized.²⁸⁸

Credit for Nonconventional Fuel Production and Biomass.

Section 29 of the Code provides a tax credit for qualified fuel produced and sold by a taxpayer, including gas produced from biomass. In general, the credit is three dollars, adjusted for inflation, multiplied by the barrel-of-oil equivalent of the qualified fuel. The credit is reduced proportionately to the extent a facility or the equipment was financed with grants, subsidized energy loans, or tax-exempt financing.

For purposes of the credit, biomass is any organic material other than oil, natural gas, and coal (including lignite), or any product derived from them.²⁸⁹ Taxpayers generally

are entitled to the credit in proportion to their ownership interest in the facility or the fuel production.

Unlike the general business credit, the Section 29 credit cannot be carried forward or back – it is a "use it or lose it" credit.

Tax Issues Arising from Commercialization

A primary business goal of a biotechnology firm is to commercialize and exploit the technology it develops and owns. Commercialization often will take the form of the sale or licensing of technology. Each approach gives rise to distinct federal income tax consequences. Of course, exploiting technology can also take the form of an outright sale of the company, a merger or consolidation, or a joint venture.

Taxable Dispositions

Patents and know-how are often transferred on a contingency of use basis where payments are received over a period of time based on revenue. For tax purposes, a technology transfer must be analyzed to determine whether there has been a sale of the technology or a license of the right to use the technology. By controlling the rights that are conveyed in a technology transfer, a company may in some cases control whether the proceeds received from the transfer will be taxable as capital gain or as ordinary income.

Achieving capital gains for non-corporate taxpayers is an important tax objective because long-term capital gains are subject to more favorable tax rates than ordinary income.²⁹⁰ For corporations, the issue is less significant because the same corporate tax rate applies to both capital gains and ordinary income.²⁹¹ All taxpayers, however, are affected by capital losses and capital loss carry-forwards because of limitations on their use.²⁹²

If the transfer of a patent constitutes a sale for tax purposes, in most cases the sale will result in capital gain to the extent the amount realized exceeds the taxpayer's adjusted basis in the patent.²⁹³ Long-term capital gains arise from the sale of capital assets held for more than one year. For patents and know-how, the holding period commences when the patent or know-how is purchased or, if it was developed, when it is reduced to practice.

If a transfer constitutes a sale, when one or more payments is received in more than one tax year, a seller generally will recognize gain under the installment method, which means gain will be recognized over time as payments are received.²⁹⁴ Where the face amount of an installment obligation exceeds \$5 million, an additional tax may be imposed based on the amount of tax liability on the deferred gain.²⁹⁵ This additional tax may eliminate much of the benefit provided by the installment method. In addition, a portion of installment payments received in subsequent tax years will constitute imputed interest and constitute ordinary income.²⁹⁶

If a transfer does not constitute a "sale" for tax purposes, payments received will be treated as royalties whether in the form of a lump sum or contingent payments.

Royalty payments generally constitute ordinary income and are deductible by the payor.

The substance of a transfer rather than its form controls its federal income tax treatment. For non-individual patent holders such as corporations, whether the transfer of a patent constitutes a sale depends on certain tax common law criteria. A transfer of know-how is determined under a similar set of rules.²⁹⁷ For individual patent-holders, a transfer of a patent is not a “sale” unless it falls under Section 1235 of the Code.

In the case of non-individual taxpayers such as corporations, whether a transfer constitutes a sale or a license depends on criteria determined under case law. At a minimum, a sale requires the transfer of the right to make, use and vend a patent. A sale should also convey to the transferee the right to sue for infringement. An assignment that contains field of use fragmentation and geographical segregation within the country of issuance may qualify as a sale, although the IRS is likely to challenge this treatment.²⁹⁸ Limitations that give the transferor unconditional right to terminate the transfer or that transfer rights for a period of less than the useful life of the patent will cause a transfer to be a license, not a sale.²⁹⁹

Section 1235 applies to transfers of patents by individuals. Section 1235 provides favorable tax treatment for individuals because payments received are taxed as long-term capital gains, although there is no holding period requirement and the imputed interest rules do not apply. Section 1235 requires that there be a transfer “of all the substantial rights to a patent.”³⁰⁰ Generally, a patent holder must transfer the entire right to exclude others (including the patent holder) from making, using and selling the invention.³⁰¹

Certain types of transfers are expressly excluded from a transfer of “substantial rights” under Section 1235. For example, the following transfers will not qualify under Section 1235: a transfer limited geographically within the country of issuance; a transfer limited in duration to a period less than the remaining life of the patent; a transfer which grants fields of use within trades or industries, which are less than all the rights covered by the patent, or which exist and have value at the time of the grant; and a transfer which conveys less than all the claims or inventions covered by the patent which exist and have value at the time of the grant.³⁰²

Tax Free Dispositions

It may also be possible for a taxpayer to exchange its rights in a patent or other technology in a manner that qualifies as a tax free exchange under Section 1031 of the Code. Section 1031(a) provides that neither gain nor loss is recognized if qualifying property is exchanged for other qualifying property of a “like kind.” For example, a cross-license of like kind technology may qualify as non-taxable under Section 1031(a).

Whether intangible personal property is of a like kind to other intangible personal property generally depends on the nature or character of the rights involved (e.g., patent or a copyright), and also on the nature or character of the underlying property to which the intangible personal property relates. Although not entirely free from doubt, regulations under Section 1031 suggest that all patents (regardless of the underlying technology) are like kind.³⁰³

Tax Issues Arising from Exit Strategies

Investors will ultimately seek to exploit technology and exit their investment through the sale of the company. There are a variety of structures available for disposing of the enterprise, ranging from a taxable merger or stock sale to a tax-free reorganization. The tax consequences of each structuring option are likely to have a significant economic impact on both the buyer and seller.

Taxable Sales or Reorganizations of the Company

Owners of a biotechnology company may choose to sell the company itself. There are a variety of structures available for a sale that are discussed in more detail in the Mergers and Acquisitions section of this Guide. For federal income tax purposes, however, a taxable disposition – whether by merger or sale – will generally be treated under one of two scenarios: a sale of ownership interests in the company; or, a sale by the company of its assets followed by a distribution of net proceeds to the owners.

Sale of Ownership Interests

If a transaction is treated as the sale of stock, the selling shareholder will generally recognize gain based on the difference between the amount realized and his or her tax basis (usually the cost).³⁰⁴ Because stock generally constitutes a capital asset, gain from the sale of stock held for more than one year is long-term capital gain taxed at favorable rates.³⁰⁵

A similar tax treatment applies to the sale of partnership interests or membership interests in an LLC taxed as a partnership,³⁰⁶ although there is a potential to recognize ordinary income under partnership tax rules.³⁰⁷

The buyer of stock in a corporation will take a tax basis in the stock equal to its cost. In the case of a corporation, the company whose stock is acquired will generally retain its historic tax attributes, such as its tax basis in assets. On the other hand, a company that is taxed as a partnership may make a tax election to provide the seller with a special basis adjustment arising from the purchase.³⁰⁸

Sale of Assets

Owners of a company may instead choose to sell the assets of the company then distribute the proceeds in liquidation of the company. A sale of assets of a corporation is generally subject to two levels of income tax: the corporation is taxed on gain or loss arising from the asset sale at corporate rates; and shareholders are subject to tax at individual rates when they receive the proceeds of the sale in a distribution. One of these levels of tax may be avoided in the case of a sale of assets by a corporation taxed under subchapter S or by a partnership or LLC taxed as a partnership.

The structure of the sale may have a substantial impact on the economics – often a structure that is advantageous to one party will be disadvantageous to the other. For

example, a seller will typically want to sell stock of a corporation because gain from the sale of stock generally constitutes capital gain subject to favorable tax rates. On the other hand, a buyer will typically want to purchase assets because the buyer's tax basis in the acquired assets will generally equal the cost of these assets as paid by the buyer.³⁰⁹ A buyer can then depreciate or amortize the acquired assets using the increased cost basis.

Joint Ventures

A joint venture provides a biotechnology company with the ability to exploit its technology by partnering with one or more other companies, each of which provides a valuable resource or service. The benefits of a joint venture include access to technology, access to new markets, financing sources and new customers. For example, one of the members could contribute to the joint venture (via a license) its technology, while a second member could contribute sales, marketing services and a customer base.

Joint ventures are often structured in the form of a partnership or an LLC that is taxed as a partnership. This type of entity provides maximum flexibility with respect to the sharing of profits and losses and distributions among the owners.³¹⁰ It also provides flexibility on termination of the joint venture, because (unlike corporations) assets may generally be distributed from the entity without causing adverse tax consequences.³¹¹

Exit Strategies that Avoid Taxable Recognition of Gain or Loss

It may be possible in some cases to achieve the business goals of a disposition of the biotechnology firm by using a structure that is not currently taxable. For example, certain types of mergers, sales of stock or sales of substantially all of a company's assets qualify as tax-free or partially tax-free.³¹² Generally, in a tax-free transaction the seller's gain or loss does not disappear altogether. Instead, it is deferred until a later taxable transaction.

Section 368 of the Code identifies certain types of mergers and sales that qualify as tax-free "reorganizations." These include mergers, stock sales and asset sales. Each type of reorganization has a variety of technical requirements, the particular details of which are beyond the scope of this discussion. Other Code sections may also be available to structure a tax-free transaction.³¹³

The tax-free reorganization rules generally apply to corporations, not to partnerships or limited liability companies taxed as a partnership. In addition, a tax-free reorganization requires, among other things, that the buyer use its own stock (or in some cases stock of its parent) as a substantial portion of the consideration received by the shareholders of the company that is sold.³¹⁴ For example, shareholders of a biotechnology corporation may be able to exchange their stock for the stock of a purchasing corporation in a manner that is not subject to current taxation.

To the extent a selling shareholder receives stock in a tax-free reorganization, the seller takes a tax basis in the stock of the acquiring corporation equal to its basis in the stock of the corporation that was sold.³¹⁵ In that way, the seller's gain is deferred until there is a subsequent taxable disposition of the stock received in the transaction.³¹⁶ It is usually

possible to structure a tax-free reorganization so that a portion of the consideration received by the shareholders is cash, although receipt of cash is generally taxable in the year of receipt.

In a tax-free reorganization, a buyer obtains the assets with their historic tax basis as carried over from the seller. This carry-over basis rule will prevent the buyer from depreciating or otherwise recovering the cost of the assets based on the purchase price of the company, and often is a disincentive to the buyer.

Finally, the tax-free reorganization rules require that the buying corporation be willing to use its own stock (or in some cases the stock of its parent) as consideration, and that a good portion of the selling corporation's shareholders be willing to become shareholders of the buying corporation. If these various general requirements are satisfied, it is often possible to structure a transaction in a manner that qualifies as tax-free under the federal income tax rules.

E. U.S. Import/Export Considerations

This section begins a discussion of biotechnology products in the global marketplace. It deals with the global trade in biotechnology from a U.S. perspective by looking at imports into and exports from the U.S. The following section moves beyond the U.S. borders to consider the international perspective. Global treaties, regional directives, country-specific regulations, and cultural biases all combine to make the international biotechnology landscape a complex one. At the current time, the global regulatory sphere is often more intensely concerned with biotechnology in agriculture, such as GM foods, plants, or seeds, rather than pharmaceuticals. While a number of countries seem to accept the idea of the creation of drugs and devices, they strongly resist the idea of creating or modifying organisms. This increased concern about agricultural products makes global trade in biotechnology products increasingly complex.

Starting with the U.S. perspective, import and export concerns are the responsibility of various agencies that govern biotechnology products, each of which has the task of protecting people from the potential hazards posed by biotechnology. On the import side, all import items are subject to the same certification and registration processes regardless of whether they originate from friendly countries, biotechnology partners, or even foreign subsidiaries of the U.S. importer. On the export side, fewer agencies are involved, but concerns of national security deepen the potential pitfalls for the unwary exporter.

Imports into the U.S.

It may be necessary for a U.S.-based company to import biotechnology products from foreign countries for use in experiments or for production and development of another product. In each case, an agency of the Department of Homeland Security, the Customs and Border Protection ("CBP," formerly the U.S. Customs Service), will examine products and documentation at the point of entry and apply the appropriate U.S. laws and regulations. CBP acts on behalf of the FDA (in connection with consumables and devices), the USDA (in connection with feed and seed items), and the EPA (in connection with

substances considered potentially hazardous to the environment). Sometimes more than one of these agencies asserts regulatory jurisdiction over a given imported item. Each agency has a different focus and different approval processes that may affect biotechnology imports.

Items that interact with the human body such as food, medicine, or a medical device are subject to regulation by the FDA. The importation scrutiny means that the items must be shown to be safe for use or consumption, and in the case of devices, be both effective and properly labeled. FDA approval procedures, discussed earlier in this Guide,³¹⁷ apply to imported as well as domestically produced items. FDA approval may take anywhere from a few months to several years to complete. In addition to the formal approval process, the FDA has a pre-market consultation procedure. For bioengineered plants, the FDA becomes involved when the plants are to be offered as foods or animal feeds, just as it would in the case of plants developed through more traditional means. As previously discussed, the FDA involves itself in pre-market consultation and screening of a developer's research information rather than conducting the research on its own.³¹⁸

The USDA oversees the safety of biotechnology plants and seeds through extensive testing by its Animal and Plant Health Inspection Service ("APHIS"). APHIS offers plants and seeds two methods of entry into the U.S. agricultural environment: a formal method of inspection or permits, and a method of consultation following certain guidelines. This second method of consultation or "notification" is available for imports as well as for domestically bioengineered plants. The importer (like the domestic producer) must meet any safety requirements. The requirements are not numerous, but they may be difficult to meet for some newly developed organisms. Among the requirements are: the plants are not certain specified noxious weeds; the introduced genetic material is "stably integrated"; the function of the introduced material is "known"; and the material does not give rise to an infectious entity, encode substances "likely" to be toxic to nontarget organisms associated with the plant, or encode products for pharmaceutical use.³¹⁹ The process of notification will require close consultation with APHIS on the applicable standards as a means of clarifying those standards not previously defined in the regulations.³²⁰ Pharmaceuticals and other products outside the standards of the notification method are dealt with through the more complex approval process of examination and permits.

Finally, the EPA is charged with regulating pesticides and toxic chemicals in the environment. The EPA considers its jurisdiction to encompass both pesticides and toxic chemicals, and it has identified a biotechnology element in each of these areas. Under the Federal Fungicide, Insecticide, and Rodenticide Act,³²¹ the EPA regulates not only manufactured chemical pesticides but also those produced by a designed organism. "Registration," the process of securing EPA approval for insecticides, is complex, time-consuming, and strictly monitored. Issuance of any permits for field-testing can be subject to considerable restriction. Similarly, in the EPA's other area of biotechnology concern, toxic substances in the environment, the EPA considers its authority under the Toxic Substances Control Act ("TSCA")³²² to extend not just to chemicals, but also to organisms (all of which are at least to some extent chemical in nature or activity). Biotechnology regulation under the TSCA is primarily a matter of pre-release screening based on a detailed notice to the EPA.³²³

In light of the above, the obvious word of caution for the U.S. importer is that the ready availability of foreign components and products should not be assumed, but should be

checked against the regulations of the appropriate agency or agencies. Qualification, registration, or at least detailed “notification” may be required before the desired items can be imported for further use.

Exports from the U.S.

U.S. export regulations with respect to bioengineered items are not as detailed or restrictive as U.S. import regulations. This asymmetrical approach to import/export regulations is not unique to the U.S., but is shared to some degree by all countries, and so a biotechnology exporter would be well advised to check for restrictions before planning an export program. Products and technology may be subject to export licensing requirements and possible restrictions from the Department of Commerce. The concern for export clearance is not necessarily shared by other departments or agencies of the U.S. government or required by their governing legislation. For example, the TSCA generally does not apply to substances being prepared in the U.S. for export.³²⁴ In circumstances involving potential hazards, however, the U.S. government is required to notify the intended destination country.

In addition to the export issues specific to biotechnology, a U.S. exporter is subject to all of the ordinary rules of possible export control. For the biotechnology developer, these rules can be grouped into three categories: universal concerns; technology export concerns; and domestic “deemed” exports. The universal concerns carry the caution that all companies and individuals must observe strict prohibitions against transacting business with, or exporting to, certain embargoed countries, listed individuals, or specified companies.³²⁵ Under the second category, technology exports, each item proposed for export from the U.S. must be considered on a case-by-case basis with respect to product classification and proposed destination to determine whether the U.S. prefers not to share the technology with all or some other countries. Where protection of technology is deemed necessary, an export license is required – and may be denied.

Finally, the rules of “deemed exports” mean that for each item requiring an export license to a given country, some of the technology related to the item (through the design, manufacture or composition of the item) may also require an export license for export to that country. Alternatively, technology may be even more tightly restricted than the tangible item to which it applies. While these extensions of export controls to technology may be obvious, the potentially surprising corollary of this license requirement is that an “export” of technology can occur by disclosure to a national (or permanent resident) of the country in question, even though the disclosure is made to the foreign person within the U.S. through a technical briefing, or even through mere access to technical documentation.³²⁶ In other words, a technical sales presentation to a foreign visitor, or more likely, the involvement of a foreign scientist in R&D within the U.S., may require an export license. Conducting the unlicensed “export” is a serious violation of federal law. At the time of publication of this Guide, lawful permanent resident status is sufficient for treatment of the holder as a U.S. citizen under the export laws. The rules of “deemed exports” are in flux, however, so consultation with legal counsel is recommended for this and other questions that may arise in connection with technology or product exports.

F. International Regulations and Barriers

In the biotechnology realm, moving beyond the U.S. borders increases the complexity of product development and distribution, most visibly in the area of GM foods. As this section describes, international treaties between countries, directives of the EU, standards by the United Nations, country-specific regulations, trade policy, protectionism, and fear (rational or irrational) all come together to create a complex web of rules for the biotechnology exporter. In the case of drug and device biotechnology, country-by-country regulations create a patchwork of application and market entry regulations for biotech developers. On the other hand, in the areas of agricultural organisms and seeds, there has been greater progress towards multinational cooperation. As a result, this section focuses on biotechnology in the agricultural trade, rather than drugs or biomechanical devices. Emerging trends in the areas of drugs and devices point to opportunities for multinational cooperation similar to the protocols developed for agriculture.

The governing principle, if there is one, can be stated as: biotechnology products will be examined on a case-by-case basis by each country to determine if there is a foreseeable threat to human health, the food supply, or the environment. Beyond that, the biotechnology exporter should be prepared to endure product testing, multi-agency regulation, and cultural biases against biotechnology, particularly GM foods. The prudent exporter should have a thorough understanding of his or her product in order to appropriately educate foreign government officials and citizens.

Background

Each country has different rules and regulations that apply to genetic engineering and other biotechnology initiatives. Furthermore, personal, social, and religious beliefs tend to affect the willingness of foreign governments and societies to accept genetic engineering practices or the resulting products. Consequently, success in the international market depends on favorable laws and regulations, as well as consumer and societal acceptance of new biotechnology.

As noted above, biotechnology regulation is a patchwork of national and quasi-national restrictions and requirements. In the case of drugs and devices, most countries have their own equivalent of the FDA. Some countries permit access to their markets with relatively little proof of efficacy, while others apply very serious roadblocks that take many months and many millions of dollars to overcome. Within the EU, there are procedures such as the process of obtaining a CE mark (the manufacturer's declaration that the product complies with the essential requirements of the relevant European health, safety and environmental protection legislation implementing certain Directives of the EU) that simplify or eliminate the country-by-country filings for devices. There is also an increasing willingness of national regulatory bodies to recognize, at least to some degree, the approval of a drug or device in another country. Indeed because FDA process for devices is so complex, a number of device manufacturers introduce products in European countries prior to obtaining FDA approval. Despite the clearly identifiable trends, however, the fields of drug and device biotechnology remain very fragmented and very much in flux. As a result, a comprehensive discussion on a country-by-country basis would seem to be premature at this point, and multinational efforts to address issues of drugs or devices seem to be limited to those banning narcotics.

In contrast, the field of agriculture, holding the public's attention as it does, has shown substantial progression and significant multinational cooperation. In agricultural trade, the four largest markets for U.S. farm products in 2001 were: Japan, at \$8.9 billion; Canada, at \$8.1 billion; Mexico, at \$7.4 billion; and the EU, at \$1.1 billion.³²⁷ Unfortunately for U.S. farmers and proponents of genetically engineered agricultural products, the governments and consumers of these and many other foreign countries have serious concerns with respect to such technology and the resulting products. Even if a government joins an international agreement or otherwise indicates a willingness to accept GM foods, a U.S. developer of biotechnology products must recognize that international agreements and national laws at any given time are not necessarily the final answer to the questions of market entry.

Often a national population, or groups within the national population, will influence the government's attitude or will render the final decision in the marketplace. As a result, changing or guiding foreign opinion will become a major focus of the developer's effort. Regardless of legal permission for imports, such as the increasingly permissive European Directives discussed below, substantial blocs of consumers in many countries are highly resistant to any form of genetically engineered foods.³²⁸ European consumers have rejected GM crops and foods for several years, and now other foreign populations such as Chinese consumers are speaking out and taking action against such products, both domestic and foreign.

The bases for these concerns has been the subject of much investigation over the past several years, but the underlying attitudes remain largely as described in a 2001 paper prepared by the USDA which thoroughly examined consumer acceptance of GM foods.³²⁹ That research indicated that public wariness remained regarding GM foods that did not have a long history of use.³³⁰ Although there has been general respect around the world for the benefits that scientific R&D can offer, there has also been an abiding concern for the unknown. In the U.S., a survey indicates that GM foods reached a point of widespread acceptance in 2004.³³¹ U.S. consumers reached a point of "indifference," with half or more of the consumers polled recognizing no difference between GM foods and others.³³² Nevertheless, even in the U.S. there remains skepticism by the public in some areas.

In Japan and the EU, citizens are concerned that foods should be proven safe rather than relying on the absence of proof that they are unsafe. Indeed, the same report that showed Americans largely indifferent showed more than half of the Europeans feared the environmental impact of GM foods and over 70% believed that living organisms should not be modified. Governments, through their treaties and regulations, often articulate this overarching theme of "proving safety" versus the "absence of unsafety." In the EU, this guiding caution is known as the "precautionary principle." It permeates the laws and regulations with respect to genetically modified organisms (individually a "GMO") holding that all genetically engineered crops and foods are considered unsafe until proven otherwise.³³³

The effects of public attitudes on trade can be substantial and can vary dramatically. As an example, China, potentially one of the most promising future markets for GM crops, the fourth largest producer of GM crops and in the past a supporter of biotechnology³³⁴, has begun to delay its adoption of transgenic plant cultivation. In recent years, China has banned virtually all imports and exports of GM crops.³³⁵ Meanwhile, in Japan, the largest market for U.S. food products and an obviously large potential market for biotechnology

food products, biotechnology food is being subjected to extensive legally mandated testing and verification under developing international standards and procedures.³³⁶ Canada, another major producer of biotechnology food products, participates in a different system. Like the U.S., Canada does not ban such items outright, but has various regulations concerning prior notification and screening of foods and crops that are to be presented to the Canadian market.³³⁷ Mexico in recent years has both embraced and banned biotechnology foods.³³⁸

International Structures for Legal Control or Standardization

Beyond the social and cultural issues that biotechnology presents in foreign markets are the governments themselves. Typically, agreements between foreign governments take the form of treaties. Treaties are usually signed by a country's executive, ratified by its congress or parliament, and enacted through enabling legislation that brings the requirements of the treaty into force within the country. The Cartagena Protocol on Biosafety ("Cartagena Protocol") discussed below, is an adjunct to just such a treaty and requires the same process for implementation. In addition to treaties, economic trading areas, such as the EU, may issue directives that to a considerable degree bind their member states. Directive 2001/18/EC of the European Parliament and of the Council ("Directive 2001/18"), is such a directive in the area of biotechnology and GMOs. Finally, another international player, the United Nations, has entered the biotechnology discussion with its own standards, the Codex Guidelines on Food Derived From Biotechnology ("Codex Guidelines"). Each of these international accords has the potential to make foreign exports of biotechnology easier, but country-specific challenges remain.

European Directive 2001/18

The prolonged and intense public resistance to genetic engineering has been reflected in legislation, regulations and international agreements³³⁹ that now generally accept some presence of biotechnology food and feed products, subject to varying degrees of qualification, registration, or examination. The clearest example of regulation at the international level is that of the EU, where the main framework for the regulation of GMOs is contained in Directive 2001/18³⁴⁰ and the Regulation (EC) No. 1830/2003 of the European Parliament and of the Council ("Regulation 1830/2003").³⁴¹ Unless imports containing GMOs comply with Directive 2001/18, they will not be admitted into the EU. In accordance with the precautionary principle, Directive 2001/18 requires that the risk associated with each product be evaluated on a case-by-case basis prior to the product's release or placement on the market.³⁴² For the importer to be in full compliance, certain disclosure requirements must be met, including the clear labeling of genetically engineered products.³⁴³ Labeling exports from the U.S. to comply with these requirements would be extremely costly and difficult, because of the problems with identity preservation and traceability.³⁴⁴

Directive 2001/18 is binding on all EU states with respect to the results to be achieved. However, each EU member state enjoys considerable latitude in implementing Directive 2001/18. Historically, the latitude was even wider, as seen in the case of Europe's early acceptance of Bt corn. In early 1998, a directive had approved the use of Bt corn, but several member states responded with legislation to prevent the

genetically engineered corn from being introduced into their own territories.³⁴⁵ The reluctance to follow the earlier directives has continued. Most recently Hungary banned GM corn, while Germany enacted a strict GM crop law holding planters of GM crops liable for economic damages to adjacent non-GM fields that are contaminated by those crops.³⁴⁶

U.S. exporters have contributed to the creation of import barriers by failing to comply with the requirements of an earlier, more extensive directive.³⁴⁷ Following adoption of Directive 2001/18, however, the moratorium by individual member states was to have ended, in favor of the new, Europe-wide standards of testing. Labeling requirements for foods were to have been loosened under Regulation 1830/2003 as long as only specified trace amounts of GM products were present. In April 2005, to address the continuing reluctance of five member states to comply with the new directive and regulation, the EU had even gone so far as to warn them of legal action if they did not end their moratorium.³⁴⁸

Despite the legal progress in requiring more openness toward imports, the U.S. position was set back considerably by circumstances occurring early in 2005. Revelations of “pollution” of some U.S. corn stock with Bt corn resulted in a sudden and full European moratorium on U.S. feed corn until the percentage content of Bt corn had been determined.³⁴⁹ Despite the temporary halt to corn exports from the U.S., currently reaching half a billion dollars per year, there are no expectations that the U.S. position will be permanently damaged, if in the near future the levels of Bt corn in U.S. feed corn stocks can be adequately demonstrated.

The Cartagena Protocol and the Codex Guidelines

In addition to Directive 2001/18, two international agreements respond to genetic engineering initiatives: the Cartagena Protocol³⁵⁰ and the Codex Guidelines. Each is an emerging standard in its own way. The Cartagena Protocol has been adopted and ratified by 119 nations as of April 30, 2005, but not yet by the U.S. The Cartagena Protocol attempts to strike a balance on trade in GM crops. The Cartagena Protocol contains a number of features and provisions that could have a major impact on whether trade in genetically engineered crops is encouraged or discouraged.

Like Directive 2001/18, the Cartagena Protocol employs the “precautionary principle,” a feature of the treaty that will likely have the most impact on the sustainable development of GM crops. The precautionary principle is invoked when a party makes a decision to import new GMOs that are capable of reproduction, such as GM seeds. In this event, the Cartagena Protocol established an Advanced Informed Agreement procedure, under which an exporting nation must inform an importing nation in detail as to the facts of a new form of GMO before the first shipment of the organism.³⁵¹ The importing nation must acknowledge receipt of the notice in writing and then decide to accept or reject the shipment.³⁵² As with Directive 2001/18, each Cartagena Protocol signatory is free to decide for itself whether it will accept or reject a specific import. This freedom to decide creates additional work and uncertainty for U.S. biotechnology companies that are considering the export market. For example, the government of Zambia cited the Cartagena Protocol for its decision to reject food aid from the U.S. because it contained GM corn.³⁵³

This freedom to consider human health and other effects raise the issue whether the Cartagena Protocol arguably conflicts with the principles of the World Trade Organization (“WTO”), which is dedicated to free trade and “most favored nation” principles. Under the WTO, the inquiry is whether the product is like other items being permitted entry into the country, and if the answer is affirmative, then the entry should be permitted. Simply put, under the WTO, science and current practice answer the question of whether to permit importation. Under the Cartagena Protocol, in contrast, the receiving nation can rule out importation based on the science of environmental protection. Furthermore, if the science would tend to permit the product to pass, the Cartagena Protocol permits the nation involved to consider the human health risks and socioeconomic factors that may have an impact within the nation’s borders.

The Cartagena Protocol is concerned with standards, information, and cooperation, but not enforcement, and so it has no real enforcement mechanism. The Cartagena Protocol has provisions on liability and redress, but these provisions focus on entry without national permission (e.g., illegal or accidental entry), rather than refusal to permit entry.

In addition to adopting the precautionary approach as noted above, the Cartagena Protocol introduces a common, international bank of knowledge on living modified organisms and establishes a system for sharing information. The Biosafety Clearing-House stores and provides information on laws, regulations, decisions, standards, illegal transboundary movements, international agreements, and contact details for national authorities. Given the richness and practical value of this information, the Biosafety Clearing-House website³⁵⁴ can be expected to become a major reference tool for the importers and exporters of GM foods in the coming years.

The other major international effort for regulation of food products, known as the Codex Guidelines,³⁵⁵ is a set of United Nations developed standards for food items, providing detailed specifications for foods possibly involved in international trade. In these guidelines, the United Nations has considered a position similar to that of the EU, that is, before any GM product is put on the market, it should be subject to a pre-market safety assessment conducted on a case-by-case basis.³⁵⁶ Again, there would be some variation permitted for national adoption of the guidelines. So, depending on the manner in which various provisions of the Cartagena Protocol are implemented by each signatory, and if the Codex Guidelines are adopted and followed by each country, there could be a significant impact on U.S. exports. Final determination of guidelines is pending.

Country-Specific Implementations of the Cartagena Protocol

The Cartagena Protocol has at its core a principle of national assessment. This means that in addition to procedural issues such as signing, ratifying, and implementing the Cartagena Protocol, a given country’s internal regulations play a large part in how the Cartagena Protocol functions. Because of their important status as key trading partners of the U.S., the countries of Japan, Mexico, Canada, and China will be considered at in more detail.

Japan

Japan, with its enormous consumption of U.S. food products, has recently adopted and implemented the Cartagena Protocol.³⁵⁷ Under the implementing law, for importation, informed consent of the importer must be demonstrated, and the packaging must be adequately marked and supplemented with detailed documentation. The Japanese statute provides a complex system of risk assessment, followed by Japanese ministry (agency) review and determination of acceptance for importation.

Standards abound, including:

- characteristics that will qualify or disqualify a person for undertaking the testing procedures for organisms (Article 18);
- requirements of qualification and reporting placed on “Registered Testing Bodies” (Article 19); and
- a “requirement” for approval by the relevant ministry after a consultation with experts has shown “no adverse effect that could pose an unacceptable risk” to biodiversity (Article 4.4).

In the end, the Cartagena Protocol’s principle of national assessment is maintained, and Japan can make its own determination, regardless of expectations. Importing is likely to be, at least for the near future, a matter of case-by-case determination.

Mexico

Mexico has signed and ratified the Cartagena Protocol. The Cartagena Protocol entered into force under Mexican law in 2003. Consequently, Mexico would have been expected to pursue a policy of examining and admitting imports of GM food products. However, historical factors have delayed implementing legislation.

Mexico’s basic standard for the importation and domestic handling of GMOs was established ten years ago,³⁵⁸ granting authorization for experimental planting of GM crops. The General Directorate of Plant Health administered this experimental planting. Examinations of Mexico’s indigenous corn crops and subsequent reports suggested contamination of the indigenous crops by some GM varieties. These reports led to calls for an outright ban on GM foods. As a result, a moratorium on imports was instituted in 1998. Many safety concerns have subsequently been allayed and new legislation, due in 2005, is expected to establish a formal framework for implementing the Cartagena Protocol and permitting entry of GM items, subject to evidence of safety and fully informative labeling.³⁵⁹

Canada

Canada has not yet ratified the Cartagena Protocol despite being the Cartagena Protocol’s location of initial signature, the site of the current administration of the Cartagena Protocol, and a major producer of GM crops. Although Canada supports

the objectives of the Cartagena Protocol and intends to ratify it at some point, the Canadian government believes that matters concerning accidental violation, rules for non-parties and interaction with the WTO, must first be settled before ratification can occur.³⁶⁰ Again, the question of conflict with the free-trade and consistency principles of the WTO have contrasted with the national authority of the Cartagena Protocol.

Canada has noted, however, that it has in place a well-developed system of examination and regulation of imports of GMOs, and in particular GM food. That system shares some characteristics with the U.S. import restrictions, in that the control of imports of GM foods falls within the jurisdiction of the Food and Drug Regulations of Health Canada³⁶¹ and the method of clearance for importing or use inside Canada is “notification.” An extensive list of information is required, including items such as the name under which the food will be sold, the location of the manufacturer, and a description of the food. The description of the food product must include “information respecting its development,” “details of the method by which it is manufactured,” and information on its intended use, and history of use in another country, if any.³⁶² Health Canada has the authority to request further information after the initial notification, and no sale may occur until approval is given.

China

China signed the Cartagena Protocol in 2000 and instituted an extreme regulatory regime on imports of GM crops, alleging safety concerns. Many observers, however, concluded that its real intention was to allow China more control over imports than would have been possible under its recently acquired WTO obligations.³⁶³ When China ratified the Cartagena Protocol in May of 2005, the official news release emphasized labeling and control aspects of the Cartagena Protocol more than any expected increase in imports and exports.³⁶⁴

After signing the Cartagena Protocol in 2000, imports of GM products were essentially banned, commercialization of GM rice was halted, and from 2002 to 2005, the government’s “Catalogue for the Guidance of Industries for Foreign Investment” prohibited foreign companies from conducting GM seeding within the country.³⁶⁵ Seeding by domestic companies, and seeding of previously planted crops by some foreign companies present in China for many years, may still be possible. Even those foreign companies with a long-term presence in China are facing difficulties expanding to other GM crops. Overall, the interruption in import and development efforts by foreign sources of GM crops has been significant.

In the meantime, research within China has continued. It has been reported that GM rice has been widely sold within the country and possibly, undeclared as such, for export.³⁶⁶ In early 2004, for the first time since the start of its import ban, China granted its first “safety certificates.” The certificates allowed the importation of three import GM foods, all from the U.S., two strains of corn and one of soybeans. Unfortunately, the approval process remained less than transparent.³⁶⁷

The actual framework of Chinese regulation has been in place in large part since at least 2001, when the Ministry of Agriculture issued its “Regulations on Safety Control of

Agricultural GMOs,” and the resulting regulations created a typically labyrinthine approval process.³⁶⁸

- The Regulations on Safety Assessment define four classes of safety to be applied by the Ministry of Agriculture in a process requiring several months.
- The Regulations on Safety of Import require an approval from the Ministry of Agriculture for entry into the country, followed by testing at progressive levels (in a medium, in environmental release, and in production), and possibly further safety approval by the GMO Safety Administration Office.
- Finally, under the Regulations on Labeling of Agricultural GMOs, the Ministry of Agriculture requires labeling of certain GMOs (soybeans, corn, rapeseed, cotton seed, and tomatoes), as well as products derived from them, regardless of whether the products no longer contain the GMOs.
- GM foods are regulated by the Ministry of Health, which requires a safety assessment by a Health Ministry commission dedicated to this task. Safety and nutritional quality are examined, and any approval is to be issued within six months, after which the food must be labeled to identify its GM nature.

This complex regulatory scheme is presented to the world and the WTO as a question of safety, but others have regarded it as a rather blatant attempt to control imports for economic reasons.³⁶⁹

Conclusion

Amidst controversy and resistance from consumer and industry groups, some countries are beginning to accept GM crops and even encourage this development. For example, India, which traditionally has not allowed the importation of GM seeds, stated that it might allow such importation to meet a domestic shortfall of its food supply. The government noted, however, that any decision to permit importation of GM seeds would continue to keep the interests of local farmers in mind.³⁷⁰ Mexico, on the other hand, may allow imports to occur more freely but would require genetically engineered products to be labeled.

As nations continue to impose labeling requirements for products containing genetically engineered organisms or even outright bans on the importation of such products, U.S. producers will face difficult challenges to their continued profitability, potentially rendering considerable damage to the biotechnology industry and its beneficiaries.³⁷¹ If the U.S. cannot sell genetically engineered seeds, crops and foods into these countries, a large part of the market for these products disappears. For example, the ban on the importation of GM food items by EU countries has had a significant impact on the sales and practices of local farmers. The ban has also prevented U.S. companies from using ingredients from transgenic crops in their products that are marketed in Western Europe.³⁷²

Rejection of genetically engineered foods by foreign countries also affects a company's ability to obtain financing for its genetic engineering initiatives. In one well-publicized case, from 2000 to 2002, Monsanto's stock price fell almost 50% in part because of the

rejection of GM products by the EU and the countries influenced by it.³⁷³ Thus, a shift in policy and practice with respect to genetically engineered products may need to occur at the international level to improve the ability of U.S. companies to obtain financing for these products. A company engaging in biotechnology R&D would be well advised to remain apprised of developing laws and regulations in potential markets around the world.

G. Genetic Engineering

Introduction

Genetic engineering encompasses many different applications and is defined in many different ways. In general, genetic engineering is the intentional production of new genes and alteration of genomes by the substitution or addition of new genetic material.³⁷⁴ Under Minnesota law, genetic engineering has been defined as the introduction of new genetic material to an organism or the regrouping of an organism's genes using techniques or technology designed by humans.³⁷⁵

Genetic engineering applications for human health include the production of vaccines and somatic and germline gene therapy. Gene therapy replaces defective or missing genetic material and can be employed to help fight diseases such as cancer, diabetes, high blood pressure and heart disease. For patients with diseases that are currently incurable (e.g., cystic fibrosis, hemophilia, and other genetic disorders), gene therapy offers relief and hope for a cure. Genetic engineering also encompasses broader applications as it relates to human health such as monoclonal antibody R&D and tissue engineering. Based on the scope of this Guide, these and other genetic engineering applications may not be specifically addressed.

In the past, agricultural genetic engineering was performed through the use of selective breeding, heredity and reproduction.³⁷⁶ Today genetically engineered crops or GMOs are produced by taking a gene from one organism and inserting it into the genetic makeup of another organism.³⁷⁷ In this context, genes are moved not only between plant species, but also between plants and animals.³⁷⁸ By controlling the insertion of one or two genes into an organism, scientists can give the organism a specific new characteristic without transferring undesirable traits. This section will focus primarily on plant products because most agricultural biotechnology activity occurs in this area.³⁷⁹

Laws, Regulations and Government Initiatives Affecting Finance

Developers of genetically engineered products encounter regulation domestically at the federal and state level, and internationally on a country-by-country basis. Thus, the success of genetic engineering, which relies on a favorable or accommodating legal system for profitability, depends in part on favorable legislation continuing to be passed at each of these levels.³⁸⁰ In addition, success and even survival in the biotechnology market is

dependent on numerous legal agreements, acquisitions, licenses and associations with manufacturers of complementary products and technology.³⁸¹

Federal Laws, Rules and Regulations

Human Applications

Gene therapy products must be tested extensively before they can be sold in the U.S. The FDA is the principal federal agency responsible for regulating gene therapy products. While the NIH Recombinant DNA Advisory Committee (“RAC”) previously asserted regulatory responsibility over gene therapy, RAC is now an advisor to NIH for the purpose of reviewing novel gene therapy protocols.³⁸² In addition to FDA regulations, any publicly funded gene therapy research is still subject to NIH oversight.³⁸³ Failure to comply with NIH’s strict guidelines could result in the withdrawal of NIH funding.³⁸⁴

FDA’s sub agency, CBER, regulates the majority of gene therapy products³⁸⁵ through the use of the Public Health Service Act and the FDC Act.³⁸⁶ In October 2003, regulation of some categories of Therapeutic Biological Products was transferred to the CDER.³⁸⁷ The approval process for products regulated by CDER is the NDA, while products regulated by CBER require approval through a BLA.

Under either process, a manufacturer who is considering marketing a gene therapy product in the U.S. must first notify the FDA, test the product in the laboratory and then conduct extensive research in animals. The manufacturer must obtain an IND before it may study the gene therapy product in humans. The IND requires the manufacturer to explain how it will conduct the study, the possible risks involved, the steps it will take to protect patients, and to provide data in support of the study. As part of the IND process, a committee of scientific and medical advisors and consumers (called an Institutional Review Board) must approve the study.³⁸⁸ Researchers must also inform the persons who may be part of the study about the study’s potential risks and benefits, and obtain their consent.³⁸⁹ There are three phases of clinical study associated with this process.

The FDA has not yet approved for sale any human gene therapy product.³⁹⁰ The FDA is scrutinizing gene therapy research closely and has suspended several gene therapy experiments as the result of the deaths of several human subjects.³⁹¹ In spite of these setbacks, gene-related R&D is growing. The FDA has received more than 300 requests from manufacturers and researchers to study gene therapy products. As of 2000, the FDA was overseeing approximately 210 active IND gene therapy studies.³⁹²

Agricultural Applications

There is no single U.S. federal statute that governs the regulation of genetically engineered plants and crops and no single federal agency with overall responsibility. Instead, genetically engineered plants and crops are regulated through a Coordinated Framework (defined below) of agencies that are each charged with

monitoring different aspects of genetically engineered organisms.³⁹³ At present, no fewer than three major federal agencies have significant roles in regulating the use of genetically engineered organisms (collectively, the “Coordinated Framework”): the EPA; the USDA and APHIS; and the FDA. The FDA ensures that foods made from genetically engineered plants are safe for humans and animals to eat, USDA makes sure they are safe to grow, and EPA ensures that pesticides introduced into the plants are safe for human and animal consumption. While the three agencies act independently, they have a close working relationship because many products come under the review of all three.³⁹⁴ For example, a bioengineered food that is the subject of a consultation with the FDA may contain an introduced pesticidal substance known as a plant-incorporated protectant that would be subject to review by the EPA.³⁹⁵ Fortunately, this Coordinated Framework of agencies is predicated on the principal that GM crops and foods are safe until proven otherwise and that they should be regulated in the same manner as traditional crops or foods.³⁹⁶ Thus, even though proponents of genetically engineered agricultural practices and products are forced to navigate this confusing maze of laws and regulations (which can result in inefficiencies, needlessly steep economic and opportunity costs and delays for industry and the general public, as discussed in detail below), they do not have to face legislation that simply prohibits such practices or products.³⁹⁷

The EPA regulates transgenic crops under three separate statutory schemes: the TSCA,³⁹⁸ the Federal Insecticide, Fungicide and Rodenticide Act (“FIFRA”);³⁹⁹ and the FDC Act.⁴⁰⁰ Under the TSCA, the EPA ensures that pesticides, including genetically engineered pesticides, introduced into plants are safe for human and animal consumption.⁴⁰¹ A person who intends to manufacture or process a new pesticide is required to first submit formal notice to the EPA detailing the structure, proposed use, production amount, byproducts, disposal methods and all existing data concerning the environmental and health effects of the pesticide.⁴⁰² The EPA has ninety days to evaluate a premanufacture notification and to determine whether the pesticide poses an unreasonable risk to health or to the environment.⁴⁰³ There are two reporting vehicles that have been specifically designed for genetically engineered microorganisms: the Microbial Commercial Activity Notice (“MCAN”); and the TSCA Experimental Release Application (“TERA”). The MCAN is required when persons intend to use intergenetic microorganisms (featuring genes from two or more different genera) for commercial purposes in the U.S.⁴⁰⁴ Submissions must include extensive information as to the characteristics of the genetically engineered microorganism, including health and environmental effects data.⁴⁰⁵ The TERA is used to report results of testing new microorganisms in the environment through advance submission and EPA evaluation of detailed information about genetically engineered microorganisms and their effects.⁴⁰⁶ The EPA has sixty days to evaluate TERA applications to determine whether the microorganisms pose a risk.⁴⁰⁷ If the EPA finds that a pesticide does pose a risk, it may limit production of the pesticide either permanently or temporarily.⁴⁰⁸ In addition, the EPA can promulgate rules requiring further testing of the pesticide if it deems such additional testing necessary.⁴⁰⁹

While the procedural rules discussed above are burdensome, the substantive rules of TSCA also pose a risk to persons trying to bring new genetically engineered organisms to market as these rules leave regulators a great deal of discretion to approve or not approve a new genetically engineered pesticide. For example, two key factors the EPA uses in determining if further testing is required (“unreasonable

risk,” and release of “substantial quantities” into the environment), remain undefined.⁴¹⁰ Thus, depending on the inclination of regulators, this subjectivity and discretion could cause inappropriate levels of intervention. If regulators impose additional testing requirements in cases where there may be little actual need for them, it would be costly and time-consuming and would unduly burden the biotechnology industry, perhaps resulting in failure to bring some products to market.⁴¹¹ These deficiencies are magnified by the deferential approach courts bring to bear in reviewing EPA decisions. Because EPA decision-making involves determinations of scientific and technical data thought to be within the expertise of the agency, judicial review is limited to the arbitrary and capricious standard, under which agency decisions are rarely disturbed.⁴¹² Thus, a person who, in trying to bring a genetically engineered product to market, receives an unfavorable decision from the EPA, is not likely to find relief in the courts. Fortunately, TSCA requires a cost-benefit analysis whereby the EPA must take into account the environmental, economic and social impact of any action taken under TSCA.⁴¹³ In addition, it has been suggested that TSCA is structured in such a way as to be biased in favor of product approval to avoid impeding technological innovation.⁴¹⁴ In particular, the limited amount of time allotted to evaluate the notices submitted to the EPA exerts great pressure in favor of rubber-stamp approval of the submissions.⁴¹⁵

In addition to TSCA, the EPA uses FIFRA to regulate the distribution, sale and use of pesticide products.⁴¹⁶ FIFRA mandates the registration of pesticides, including genetically engineered pesticides and the pesticidal substance produced by pest-protected plants, before distribution or use.⁴¹⁷ In order to secure registration, an applicant must obtain an experimental use permit and conduct field studies to demonstrate that the pesticide will not cause “unreasonable adverse effects on humans or the environment, when used according to widespread and commonly recognized practices.”⁴¹⁸ Once a registration is secured, FIFRA requires the labeling of registered pesticides and training and certification requirements for applicators.⁴¹⁹ The process can be time-consuming and costly, particularly for pesticides featuring a previously untested active ingredient.⁴²⁰ Because very little formal guidance is available to the industry concerning the type of data and information required to support EPA registration of the pesticidal substance produced by pest-protected plants, the EPA imposes data requirements on a case-by-case basis. Registration of a pesticide may be denied at the outset or, once granted, may be suspended or cancelled upon EPA determination that it appears a pesticide generally causes unreasonable adverse effects on the environment, considering the economic, social and environmental costs and benefits of the use of the pesticide.⁴²¹

Similar to TSCA, the substantive rules of FIFRA are inadequate to cover the difficult issues presented by genetically engineered organisms, which results in regulators obtaining a great deal of discretion to approve or not approve a new genetically engineered chemical substance. However, FIFRA does not allow the EPA to deny registration of a pesticide or experimental use permit unless the EPA evaluation of the proponent’s initial data submission results in a finding of “unreasonable adverse effects” on the environment.⁴²² Although lacking in detailed guidance, this is a difficult standard for regulators to meet as scientific risks must be balanced against profit and other factors in a cost-benefit analysis before the regulators can deny, suspend or cancel registration. Essentially, FIFRA is set up to encourage technological innovation and eliminate excessive impediments on commerce.⁴²³

If a substance is deemed to be a pesticide under FIFRA, it is automatically subject to regulation, inspection and enforcement under the FDC Act if it is used on a food or feed crop or if residues of it are otherwise expected to occur on a food or feed crop.⁴²⁴ The EPA has the authority to issue regulations that permit pesticide residues in or on food under the same “reasonable certainty of no harm” standard that the FDA applies to food additives.⁴²⁵ However, additional data related to dietary exposure must be submitted to the EPA in connection with the registration of a food-use pesticide.

Under the Federal Plant Pest Act, APHIS determines whether a transgenic crop or plant is likely to have a negative agricultural or environmental effect before its release into the environment or its movement in commerce.⁴²⁶ This determination is made through a process that requires developers to obtain permission from APHIS if they plan to import, transport or field test a transgenic plant.⁴²⁷ Before APHIS will grant a permit to a developer, that developer must demonstrate that: the transferred gene is “well characterized” and would not induce disease in the host plant; the introduced gene material is firmly integrated into the DNA and introduces no infectious material or material toxic to non-targeted organisms; the genetic material does not pose a significant risk of creation of any new plant virus; and the plant contains no functional genes derived from human or animal pathogens.⁴²⁸ Based on its experience with the permit program, APHIS has begun to develop several exemptions of articles that it has determined do not pose a plant pest risk. One of the most important exemptions allows the introduction of certain regulated articles without a permit so long as APHIS is notified in advance and so long as certain performance standards are met.⁴²⁹ Once notice is given, APHIS has thirty days to review the notification and confirm that the notification is appropriate or inform the applicant that no release may take place without a permit.⁴³⁰ In addition, before a genetically engineered crop plant can be produced on a wider scale and sold commercially, its developers must petition APHIS for a determination of “non-regulated status” based on information supplied by the developer.⁴³¹ APHIS grants petitions upon a finding that the new plant is as safe to use as more traditional varieties.⁴³²

Fortunately, for proponents and developers of genetically engineered organisms, APHIS does not mandate any individual environmental evaluations be performed under its notification procedure.⁴³³ In addition, similar to the EPA, APHIS regulations do not appear to provide adequate guidance to regulators. Thus, the regulations lend themselves to being pro-industry as regulators are more apt to rely on the assurances offered by the proponent of a new crop variety and to adopt whatever scientific and technical data are furnished in support of the crop’s introduction.⁴³⁴

For its part, the FDA is charged with ensuring the safety and effectiveness of foods (including genetically engineered foods) for humans and animals, including foods derived from bioengineered plants under the FDC Act.⁴³⁵ The FDA operates on the policy that genetically engineered foods should be regulated in the same manner as conventional foods unless they contain substances or demonstrate attributes that are unusual for the particular product.⁴³⁶ The FDA specifically requires a developer to notify the agency of its intent to market food or animal feed from a bioengineered plant and submit to the FDA a summary of the developer’s scientific and regulatory assessment of the food at least 120 days before marketing.⁴³⁷ In addition, the FDA and

the producers of transgenic foods typically engage in a consultation process to identify and discuss relevant safety, nutritional and other regulatory issues regarding bioengineered foods prior to the distribution of these foods.⁴³⁸ After reviewing the company's submission, the FDA will issue a letter to the firm describing its conclusion about the regulatory status of the food or animal feed.⁴³⁹ The FDA has also drafted guidelines to assist manufacturers who wish to voluntarily label their foods being made with or without the use of bioengineered ingredients.⁴⁴⁰ While the Union of Concerned Scientists has urged the FDA to require labeling to identify which foods are genetically engineered, the FDC Act provides the FDA a limited basis on which to require labeling. Generally, there must be something tangibly different about the food product, not the process by which it is made, for the FDA to require labeling.⁴⁴¹ In addition, if special labeling were to be required by the FDA, a system for "identity preservation" would need to be established to ensure that genetically engineered products were kept separate from non-genetically engineered products at all stages of production. Because this identity preservation system was not put in place when GMO development began, it would be almost impossible to implement now because of the costs and logistics involved.⁴⁴² Finally, with respect to drugs, biologics and medical devices derived from bioengineered plants for use in humans and animals, more rigorous testing such as pre-clinical and clinical testing for the FDA regulated products and pre-license testing for USDA regulated products may be required.⁴⁴³

While currently there is no federal legislation in the U.S banning agricultural genetic engineering practices or products, there appears to be a trend toward greater regulation of genetically engineered species. As the tools and techniques used in biotechnology become more complex and a broader range of species are researched for a wider variety of uses, new regulatory challenges and increased regulation will emerge, thus creating more difficult challenges for the companies trying to bring such products to market.

Federal Government Initiatives

Perhaps one of the most important federal government initiatives in recent years was the Human Genome Project ("HGP"). The HGP was a 13-year international project coordinated by the Department of Energy and the NIH.⁴⁴⁴ The project's goals included identifying the 20,000 to 25,000 genes in human DNA, determining the sequences of the 3 billion chemical base pairs that make up human DNA, storing the information obtained in databases, improving tools for data analysis, and transferring related technologies to the private sector. The HGP is finished, but analysis of the data will continue for many years.⁴⁴⁵

The Technology Transfer Office ("TTO") at the National Human Genome Research Institute ("NHGRI") assists in the transfer of the technology developed at NHGRI to the private sector for further development. The TTO negotiates material transfer agreements and other legal documents enabling the sharing of research resources between NHGRI and the private sector. The TTO also facilitates agreements used when NIH's industry collaborates to further develop a technology for commercialization.⁴⁴⁶

Another federal resource is the National Institute of General Medical Sciences' ("NIGMS") human genetic cell repository. NIGMS, a component of NIH, announced in

December 2004 that the Coriell Institute for Medical Research in Camden, New Jersey, would continue operating the NIGMS human genetic cell repository.⁴⁴⁷ The repository provides cells and DNA for use in human genetic and genomic research. The repository also houses panels of cell lines and DNA representing nearly all the variants of certain diseases. The repository's web site lists all available cell lines and DNA collections along with detailed background information on their characteristics.⁴⁴⁸

Many federal agencies also provide funding and partnership opportunities for genetic engineering initiatives. One such source is the Department of Energy's Joint Genome Institute Community Sequencing Program, which provides scientists across the country with worldwide access to advanced genome sequencing equipment and expertise for projects the agency believes have significant scientific merit. In 2005, the DOE is supporting two such projects encompassing agricultural and industrial applications.⁴⁴⁹ Federal lawmakers have also established an Agricultural Genome Initiative to encourage agricultural genomic research.⁴⁵⁰ Under this initiative, the Secretary of Agriculture has the authority to make grants or enter into cooperative agreements with individuals and organizations.⁴⁵¹ While the government initiatives appear to be more heavily aimed at scientists and researchers, this is arguably an avenue of funding for any person or company that meets the criteria set forth by the government. Additional agencies and programs include: NIH Office of Extramural Research SBIR and STTR programs;⁴⁵² NIH's National Institute of Biomedical Imaging and Bioengineering;⁴⁵³ The NSF's SBIR and STTR programs;⁴⁵⁴ and The Department of Defense SBIR and STTR programs.⁴⁵⁵ Additional information regarding these programs and the application process can be obtained directly from each agency.

State Laws, Rules and Regulations and Initiatives

In addition to U.S. federal regulations, genetic engineering practices are also regulated on a state and local level. Although at this time genetically engineered products relating to human health are not regulated in Minnesota, regulations may vary from state to state and anyone engaging in the development of these products should consult state and local laws.

State Initiatives in Human Genetic Engineering

One major initiative in Minnesota is The Minnesota Partnership for Biotechnology and Medical Genomics. This partnership, which includes the Mayo Clinic, the University of Minnesota and the State of Minnesota, seeks to position Minnesota as a leader in biotechnology and medical genomics applications.⁴⁵⁶ Taken together, Mayo and the University of Minnesota manage \$700 million in major research projects, and have already invested nearly \$500 million dollars in their respective biotechnology and medical genomics programs.⁴⁵⁷

In June 2005, the University of Minnesota opened the McGuire Translational Research Facility on the Minneapolis campus. The Facility provides space for state-of-the-art research in many biotechnology areas, including gene therapy.⁴⁵⁸ In 2003, the University of Minnesota and the City of Saint Paul, Minnesota launched University Enterprise Laboratories, a 125,000 square foot research facility that

provides wet lab space for start-up, small and medium size life science companies. In January 2005, University Enterprise Laboratories announced it landed \$24 million in funding from investors.⁴⁵⁹

Nationwide Trends in Agricultural Genetic Engineering

In addition to federal regulation of transgenic crops, some states, including Minnesota, have regulatory structures that are similar to the federal regulatory structure.⁴⁶⁰ The difference at the state level, however, lies in the fact that there is significant tension between proponents and opponents of agricultural genetic engineering. As a result, certain U.S. states, cities and counties have or are considering bans, moratoriums and tighter regulations on planting of biotechnology crops, while others are adopting resolutions and legislation in favor of genetic engineering practices. For example, while California's Mendocino County was the first county in the U.S. to ban GM crops and animals, political leaders in California's Fresno and Kings Counties, among the largest agricultural counties in the U.S., have adopted resolutions favoring biotechnology crops, and other California counties are poised to do the same.⁴⁶¹ Vermont is also considering a moratorium on genetically engineered seeds and became the first state to require labeling of GM seeds, which will be a very cumbersome if not impossible requirement for seed manufacturers to meet.⁴⁶² Developments such as these are now occurring on a weekly if not daily basis. The most recent example of restrictive legislation in Minnesota was a bill introduced in the Minnesota legislature in March of 2005 that called for a prohibition against the release, planting, cultivation, harvest and sale of genetically engineered wild rice.⁴⁶³ In addition, legislative measures are being considered in several states, including Vermont, Montana and Hawaii, that would make seed makers liable for damages from genetically engineered seeds or crops, so that traditional farmers know they can grow crops and not be liable to a seed maker for licensing fees if they find they are infiltrated by some genetically engineered drift.⁴⁶⁴ Unfortunately, for farmers and companies who are proponents of genetically engineered crops, if this legislation carries, it will likely have a chilling effect on the production and sale of genetically engineered seeds in these states. North Dakota lawmakers on the other hand have rejected a bill that would make seed manufacturers liable for biotechnology wheat cross-pollination because the bill would have harmed the state's biotechnology industry and discouraged investment in R&D.⁴⁶⁵

Thus, it appears that even if the federal government does not impose tighter restrictions on the planting, production and sale of GM plants and crops, some individual state and local governments may take it upon themselves.

Minnesota's Regulatory Structure for Agricultural Genetic Engineering

In Minnesota, GM crops are regulated under a structure similar to the federal structure. A permit must be obtained before a GMO can be released into the environment.⁴⁶⁶ Permit applications must include, among other things, any EPA, USDA, or other federal agency regulatory application or approval document that is required under federal law.⁴⁶⁷ In addition, all permit applications are subject to an

environmental review that may add significant time to the application process.⁴⁶⁸ The Commissioner of Agriculture may issue a permit if it is determined that the proposed release does not have the potential for unreasonable adverse effects on the environment.⁴⁶⁹ However, the Commissioner may also place terms and conditions on the permit including, but not limited to, the period of use, the amount or number of genetically engineered organisms or products that can be used, monitoring activities, department inspections, reporting of experiment results and experiment termination procedures.⁴⁷⁰ This process can be cumbersome in that more than one permit may be required for a specific release, and a new permit is required for each release of a genetically engineered organism until the Commissioner determines that the proposed use of the genetically engineered organism is no longer subject to special regulation.⁴⁷¹

Minnesota law does, however, provide an exemption to the permit requirement for the release of genetically engineered organisms where substantial evidence has shown that the organism can be released without adverse effects on humans and the environment, or can be released under the supervision of a federal regulatory agency without adverse effects to humans and the environment.⁴⁷² Thus, a person proposing a release for which a federal authorization is required may apply for an exemption from the state permit requirement by filing a written request that includes a copy of the federal application and the information necessary to determine if there is a potential for significant environmental effects. The Environmental Quality Board⁴⁷³ or appropriate state agency must grant or deny the exemption within 45 days after the receipt of the written request.⁴⁷⁴ If the board determines the federal program is adequate to meet only certain state law requirements, the board may exempt these releases from only those specific requirements.⁴⁷⁵

Consequently, in Minnesota and likely other states with a similar regulatory structure, companies or persons involved in bringing GM agricultural products to market may be subject to two levels of regulation unless an exemption from state regulation can be obtained.

Intellectual Property Laws and Issues

In the biotechnology industry, intellectual property protection is a key to survival, as the patentability or non-patentability of genetically engineered subject matter affects investors' willingness to provide financing.⁴⁷⁶ While no specific regulations have been developed for human applications, in the agricultural context various legal means have been established to protect plant inventions such as the Plant Variety Protection Act ("PVPA")⁴⁷⁷ and the Plant Patent Act. Unlike a standard patent, in order to receive protection under PVPA, the plant breeder must apply to the USDA for a Certificate of Protection and show that the plant is: new and distinct; novel; and uniform and stable. While a PVPA certificate confers a legal right to exclude others from reproducing, selling, importing or exporting the protected plant variety for a period of 20 years, there are two exceptions: farmers retain the right to save seeds; and researchers retain the right to use the protected plant for further development. Consequently, as the agricultural industry has become highly focused on transgenically modified plants, standard patent protection is now preferred because it is thought to provide the broadest coverage.⁴⁷⁸

The first patent for genetically engineered subject matter was granted in the U.S. in 1980.⁴⁷⁹ Since then over 1,800 patents have been issued despite the fact that it has become more difficult to obtain a patent covering genetically engineered organisms.⁴⁸⁰ Although these patents continue to be granted, many of the public patents in living matter raise moral and ethical concerns. Thus, the question remains in the mind of many whether genetically engineered subject matter should be considered patentable subject matter.⁴⁸¹ Neither the U.S. courts nor the USPTO have denied patentability to controversial inventions. The USPTO has, however, articulated a policy that denies patentability to any claim that could encompass a human being. In addition, the Supreme Court has interpreted the statutory range of what constitutes patentable subject matter to be quite broad, but hardly universal.⁴⁸² For example, the laws of nature, natural phenomenon and abstract ideas are not patentable, as “such discoveries are manifestations of...nature, free to all men and reserved exclusively to none.”⁴⁸³

The critical distinction guiding inquiries into the patentability of subject matter in the U.S. is that human made or synthetic products or processes are patentable while products and processes of nature are not.⁴⁸⁴ Thus, where such synthetic products such as genetically engineered crops and plants can reproduce with no human intervention, the line becomes blurred between a natural process, which is not patentable, and a human made product, which is patentable.⁴⁸⁵ Outside of the U.S. moral and ethical considerations are given greater weight. For example, the EU Biotechnology Directive of 1988 on legal protection of biotechnological inventions defines several categories of technologies that are not patentable because they are either contrary to the public order or because of their moral implications.⁴⁸⁶ In addition, the EPO will not issue patents that violate public policy or morality when commercially exploited.

In addition to the issue of patentability, many unique challenges arise when GMOs are patented, especially those that can reproduce without human intervention. When a patented organism is capable of reproduction after release into the wild, it can lead to unintentional but inevitable infringement.⁴⁸⁷ For example, if the wind blows seeds from a GM corn crop, protected by a patent, into a neighboring corn field, the harvest from that neighbor’s field would contain at least some of the patented variety, thereby turning that farmer into an unintentional, yet inevitable, infringer.⁴⁸⁸ Given current scientific trends, the belief that patents may protect genetically engineered products that spread and reproduce by natural processes could easily lead to misdirected research investments and to a widespread crippling of an industry whose participants learn that even their best efforts to respect patent rights may not save them from liability as inevitable and unintentional infringers.⁴⁸⁹ Genetic drift and subsequent GMO invasion could also lead to a concentration in power in the agriculture industry.⁴⁹⁰ For example, Monsanto’s patent provides that the offspring of a cross between a patented plant and a conventional plant is also afforded patent protection if the progeny contains the patented gene. If the farmer is unable to insulate himself from the drift of GMOs, a significant potential monopolization problem exists as each invaded crop will be controlled by the patentee.⁴⁹¹ Monopolization of this nature could easily chill innovation, inquiry, experimentation and commercial development and thus, investment.

Another unique problem lies in the ownership of biological resources when the ownership affects economies based on regional crops. In fact, attempts by U.S.

companies to patent crops native to developing countries have been met with strong international protest. For example, in 1997 a U.S. company, RiceTech, Inc., patented a form of jasmine rice that would grow in the U.S. and trademarked it "jasmati." Thailand, the world's top exporter of rice, responded by accusing RiceTech of stealing the genetic material of its rice without its permission and of using a trademark that would intentionally confuse consumers thereby threatening their local rice economy.⁴⁹² Thailand was joined by India and Pakistan in fighting the patent and trademark protection granted to RiceTech.

In addition to utilizing patents to protect their investments, because the cost of R&D associated with producing genetically engineered seeds is increasing, seed companies are becoming more aggressive in their desire to limit farmers' rights to save seeds to use from one year to the next. To further protect their investments, seed companies are using licensing agreements that, among other things, place restrictions on farmers and prohibit them from saving seeds.⁴⁹³

Legal Arrangements

In addition to other funding sources, agricultural biotechnology companies will try to grow by means of mergers, acquisitions, and alliances with seed distributors and chemical manufacturers.⁴⁹⁴ For example, Monsanto recently agreed to pay \$1 billion in cash for Seminis, Inc., a California-based supplier of more than 3,500 seed varieties to commercial fruit and vegetable growers, dealers, distributors and wholesalers in more than 150 countries.⁴⁹⁵ Because seed companies ultimately decide which biotechnology to incorporate into their product lines, without a captive seed company, there is no guarantee that an agricultural biotechnology company will be able to bring its technology to market which may chill investment in the technology.⁴⁹⁶

International Issues; Trade Barriers Affecting Finance

Overview

At the international level, developers of genetically engineered subject matter face regulation on a country-by-country basis as well as public resistance to such initiatives and the resulting products. Thus, the success of genetic engineering initiatives depends in part on favorable legislation being passed in each of these countries and in part on social acceptance of these products and practices.⁴⁹⁷

Human Applications

In the realm of human genetic engineering applications, the EU has provided guidance to its member countries with respect to how genetic engineering issues should be addressed. Member nations are not bound by any specific laws, rules or regulations unless and until they adopt and ratify the same. The United Nations Education Science and Culture Organization's Universal Declaration on the Human Genome and Human

Rights was adopted by 186 member states in 1997.⁴⁹⁸ The declaration is not binding, but provides guidance to member states on such issues as genetic discrimination, genetic reductionism, informed consent, confidentiality, non-peaceful use of genomic data and equitable access to treatment. The declaration encourages research into genetically-based and genetically-influenced diseases. The only biological procedure it does not permit is reproductive cloning.

The Council of Europe Convention for the Protection of Human Rights and the Dignity of the Human Being with Regard to the Application of Biology Medicine specifically bans human genetic modification that is not for preventive, diagnostic or therapeutic purposes and germ-line genetic modification.⁴⁹⁹ By signing the Convention, a country expresses its interest in the treaty and its intention to become a party to the treaty. Although the country is not bound by the signature until it ratifies the convention, it has the obligation not to defeat the object and purpose of the treaty until it has made its intention clear not to become a party to the treaty. Currently 32 of the 46 member nations have signed and 19 have ratified the Convention.

Agricultural Applications

Rules and regulations that apply to genetic engineering initiatives differ from country to country as do the human and social beliefs surrounding such practices and the resulting products. Regulations range from outright bans of GM crops in some countries to voluntary labeling of GM foods in others.⁵⁰⁰ For example, the EU applies a guiding factor known as the “precautionary principle” in its laws and regulations relating to GMOs. The precautionary principle states that genetically engineered crops and foods are unsafe until proven otherwise.⁵⁰¹ Thus, in the EU and the countries influenced by it, genetically engineered products are often rejected, or acceptance of these products by a particular country is often opposed by that country’s residents and consumers. Unfortunately for U.S. farmers and other proponents of genetically engineered agricultural products, the four largest markets for U.S. farm products are: Japan, Canada, Mexico and the EU.⁵⁰² If U.S. farmers cannot sell genetically engineered products into these and other foreign countries, a large part of the market for such products disappears.⁵⁰³ In addition, rejection of genetically engineered products by foreign countries affects the ability of U.S. companies to obtain financing for their genetic engineering initiatives. For example from 2000 to 2002, Monsanto’s stock price fell almost 50% in part because of the rejection of GM products by the EU and the countries influenced by it.⁵⁰⁴

This prolonged and intense public resistance to genetic engineering is reflected in various international rules, regulations and agreements.⁵⁰⁵ While these rules, regulations and agreements are becoming increasingly permissive in their acceptance of the presence of biotechnology food and feed products, they make the acceptance subject to varying degrees of qualification, registration, or examination. The clearest examples of regulation at the international level are set forth in legislation that stems from the EU and the United Nations. While the legislation stemming from each of these governing bodies has the potential to ease restrictions on GM crops and foods, country-specific challenges remain.

The main framework for the legislation governing the regulation of GMOs in the EU is contained in Directive 2001/18⁵⁰⁶ and Regulation 1830/2003.⁵⁰⁷ Although Directive

2001/18 is binding on all EU member states with respect to the results to be achieved, each EU member state enjoys considerable latitude in implementing Directive 2001/18. Unless imports containing GMOs comply with Directive 2001/18, they will not be admitted into the EU. To be in full compliance, certain disclosure requirements must be met, including the clear labeling of genetically engineered products.⁵⁰⁸ Because of the difficulties with identity preservation and traceability, labeling exports from the U.S. to comply with these requirements would be extremely costly and difficult.⁵⁰⁹ While the labeling requirements were to have been loosened under Regulation 1830/2003 as long as only trace amounts of GMOs were present, certain countries continue to be reluctant to comply with the relaxed requirements. In fact, the USDA has recently issued two reports on agricultural biotechnology that cover the evolving world requirements for the traceability and labeling of agricultural biotechnology products and the complexities of predicting the use of these products in the future. The reports are titled: Global Traceability and Labeling Requirements for Agricultural Biotechnology-Derived Products - Impacts and Implications for the U.S.; and Preparing for the Future.⁵¹⁰ The first report considers: the proliferation of mandatory biotechnology traceability and labeling requirements in other countries; how different segments of the U.S. food and feed supply chain are addressing those requirements; and marketplace issues and tools that are relevant to these developments. The second report identifies broad trends and factors, such as global labeling and traceability requirements that will shape the use of biotechnology in the future. Companies engaged in genetic engineering initiatives should monitor any developments and initiatives that stem from these reports.

In addition to Directive 2001/18, two additional sets of standards are responsive to genetic engineering initiatives, the Cartagena Protocol⁵¹¹ and the Codex Guidelines.⁵¹² The Cartagena Protocol attempts to strike a balance on trade in GMOs by requiring an exporting nation to inform an importing nation in detail as to the facts of a new form of GMO before the first shipment of such organism.⁵¹³ The importing nation must then acknowledge receipt of the notice in writing and decide whether to accept or reject the shipment.⁵¹⁴ As with Directive 2001/18, the Cartagena Protocol employs the "precautionary principle," which will likely have the most impact on the sustainable development of GM crops. In addition, like Directive 2001/18, each Cartagena Protocol signatory is free to decide for itself whether it will accept or reject a specific import, which creates additional work and uncertainty for U.S. biotechnology companies.⁵¹⁵ Similarly, according to the Codex Guidelines, before any GM product is put on the market it should be subjected to a pre-market safety assessment conducted on a case-by-case basis.⁵¹⁶ Consequently, depending on the manner in which various provisions of the Cartagena Protocol are implemented by each signatory, and if the Codex Guidelines are followed or adopted by each country, there could be a significant impact on U.S. exports. For example, if nations continue to impose labeling requirements for products containing genetically engineered organisms or ban the importation of such products altogether, U.S. producers will face difficult challenges that will result in damage to the profitability of the U.S. producers as well as the biotechnology industry.⁵¹⁷

Conclusion

Despite the general resistance to GM products, some countries, amidst controversy and resistance from consumers and industry groups, are beginning to accept this

technology and even encourage the development of genetically engineered products.⁵¹⁸ However, other countries continue to ban products containing GMOs or impose labeling requirements for such products. Thus, U.S. producers continue to face challenges to continued profitability, rendering damage to the U.S. market for GM crops. If U.S. producers cannot sell GM crops and foods into foreign markets, a large part of the U.S. producers' market for these products would disappear.

Thus, a shift in foreign policy and practice with respect to GM crops and foods would have a positive effect on U.S. companies' ability to obtain financing for their efforts. Because of the rapidly changing nature of the landscape in this area, a company engaging in genetic engineering would be well advised to remain fully informed of the laws and regulations that are developing in markets around the world.

Ethical and Social Issues Affecting Finance

Although genetic engineering may be technologically promising, if the public is morally opposed or there exists excessive concern about the safety of the technology and the resulting products, then the technology may go nowhere. As a result, there will be no market for genetically engineered products and no funding for additional R&D.

Many social and moral issues have been raised in connection with the human applications of genetic engineering, most visibly gene therapy. Questions have been raised such as who should determine what constitutes a disability or disorder; who will have access to gene therapy; and who will pay for it.⁵¹⁹ Germline therapy is especially controversial in that the alteration of germ cells introduces the possibility of passing genetic alterations down to future generations.⁵²⁰ Because ethical issues are so prevalent in biotechnology, in 2001, President Bush created the President's Council on Bioethics to advise him on bioethical issues that emerge as a result of advances in biomedical science and technology and to inquire into the human and moral significance of these developments.⁵²¹

Another factor affecting public perception of the safety of gene therapy is its effect on individuals participating in the human trials of the product. In a well-publicized case in 1999, 18-year-old Jesse Gelsinger died less than a week after entering a gene therapy trial.⁵²² More recently, the FDA suspended several gene therapy experiments after learning that a child in France developed cancer as a result of his participation in a gene therapy experiment.⁵²³

Consumers are also concerned about maintaining the privacy of information obtained through genetic testing. To address this concern, at least 26 states have passed laws related to genetic discrimination.⁵²⁴ Minnesota's genetic discrimination laws, which are similar to laws in other states, prohibits discrimination related to genetic testing by health plan companies and employers.⁵²⁵

On the agricultural front, there has been little evidence of a counterrevolution in the U.S., as most consumers have been relatively unaware of the presence of GM crops and foods. In fact, recent indications show that in the U.S., GM foods reached a point of widespread acceptance. However, consumer resistance and various acts of protest by non-government organizations have surfaced in the past and continue to surface today.⁵²⁶ Some opponents

of GM crops and foods urge mandatory labeling of genetically engineered products, some advocate for more stringent testing of these products before marketing and still others urge an outright ban of such products.⁵²⁷ During the latter half of 1999, environmentalist groups such as Future Farmers and Reclaim The Seeds, destroyed genetically engineered crops across the country on a weekly basis.⁵²⁸ More recently, five environmental groups sued the USDA over its policies of allowing field testing of GM plants in Hawaii.⁵²⁹ The Center For Food Safety, which has ongoing lawsuits with the FDA and EPA concerning the safety of these foods, has called for the establishment of stringent pre-market safety testing and mandatory labeling for genetically engineered foods.⁵³⁰ Even award winning chefs have launched anti-genetically engineered food campaigns, beginning with banning such foods in their own exclusive restaurants.⁵³¹

This public opposition to GM products appears to stem from: concern for the environment and the disruption of the natural ecosystem into which these products are released or inadvertently escape; and concern about unknown health risks that may result from consumption of genetically engineered food. For example, there is widespread concern that genes from crops grown as biopharmaceuticals may cross over to normal crops thereby contaminating the food supply, and that GM foods may introduce into foods allergens that can be hazardous for unsuspecting consumers. In February 2003, the Grocery Manufacturers of America recommended that the FDA restrict the biopharmaceutical industry in order to protect the food supply from contamination.⁵³² Similarly, a study released by the Union of Concerned Scientists on December 15, 2004, declared the nation's food supply at risk from crops that are genetically engineered to create pharmaceuticals and reported the group would press the USDA to restrict the biopharmaceutical industry to prevent contamination of the food supply.⁵³³ Fears such as these could prevent consumer acceptance of genetically engineered foods, which will ultimately impede the ability of companies to obtain financing for these products. Unfortunately for those in the industry, such fears are not unfounded. In the late 1990's Brazil nut genes were inserted into soybeans to increase the protein content of the beans. However, consumers allergic to nuts experienced allergic reactions when they ate the beans. Fearing litigation, the R&D of the soybeans was suspended.⁵³⁴ In March of 2005, news that tainted biotechnology corn seeds may have entered the food supply again fueled the concern of those opposed to biotechnology products.⁵³⁵

For a variety of reasons, many consumers also have difficulty with the concept of plant foods created using genes from animals. For example, the first engineered true food approved by the FDA for the U.S. consumer market was the Calgene FlavrSavr® Tomato, introduced in the early 1990's. The tomato, created by inserting a gene from a pig into the tomato's genome, was designed to have a prolonged shelf life. While the FlavrSavr Tomato was a production success, it was a marketing disaster because producers did not consider how the public would respond to learning the gene responsible for the tomato's resilience came from a pig.⁵³⁶ For a variety of reasons, including religious, cultural, dietary, and general "awareness," the public rejected the FlavrSavr tomato and the idea of creating an enhanced vegetable using a pig gene.

Such negative publicity takes a toll, as it forces companies to expend money in public relations campaigns and settling lawsuits rather than on R&D to bring products to market, which in turn affects the willingness of the investment community to fund such efforts. For example, StarLink Logistics, Inc., a subsidiary of Aventis AS and Avanta USA, agreed to pay \$110 million in 2003 to settle a lawsuit filed by farmers who claimed

they were injured by consumer fears generated when unapproved biotechnology corn that contained a potential human allergen was discovered in the food supply. Avenits and Avanta were also part of a \$9 million settlement to consumers who said they suffered allergic reactions from eating foods that contained StarLink® corn.⁵³⁷ In addition to the costs of the lawsuit, the planting of the StarLink corn had to be stopped after the recall of the contaminated food products.⁵³⁸ More than four years after the incident occurred, its impact is still being felt throughout the industry. For example, South Korea, one of the largest importers of corn still requires certification from suppliers that the corn it is buying does not contain StarLink corn.⁵³⁹ Such mishandling of biotechnology products will continue to cause consumers to mistrust the technology and possibly reject genetically engineered products.

Agricultural genetic engineering also has industry opposition from organic and traditional pesticide, seed and pharmaceutical manufacturers, plant breeders and farmers, all of whom promise their customers that their products are free of GM material. Such organic and traditional farmers are concerned that uncontrolled gene flow will result in trace amounts of GMOs being found in non-genetically engineered crops. Based on labeling requirements overseas, even trace amounts of GM material in claimed non-genetically engineered crops would affect organic and traditional farmers' ability to sell in foreign markets. For example, California rice farmers, concerned that Japanese customers will boycott their products if the genetic engineering of rice is allowed into the state have called for a ban on genetically engineered rice in California.⁵⁴⁰ In Hawaii, organic papaya farmers are outraged because trace amounts of genetically engineered papaya are showing up in their harvest.⁵⁴¹

The concern for proponents of genetically engineered products is that uninformed, or poorly informed, public and industry opinion has and will continue to spark onerous legislation and restrictions and with opposition to genetic engineering becoming a trendy cause, there will likely be additional increases in public concern that could put pressure on elected officials to impose further restrictions. Consumer and industry acceptance of genetically engineered products is critical to the survival of the industry and materially affects a biotechnology company's ability to obtain financing for genetic engineering efforts. Without consumer acceptance, there is no market for the products.

Conclusion

The retention and adoption of favorable legislation at the federal, state and international level will help biotechnology companies obtain financing for their genetic engineering efforts as it will expedite bringing such products to market. However, consumer acceptance of genetic engineering will establish the rate of adoption for these products as well as the viability of the market from an investment perspective. Many biotechnology companies have not performed as well as anticipated because their products have been banned in some countries, which chills investment opportunities. On a positive note, government funding and initiatives remain strong, consumer acceptance is growing, and as the technology develops and stabilizes, there will be fewer reasons to distrust the technology.

H. Stem Cells

Introduction

There is currently widespread debate, both at the federal and state levels, regarding the extent to which stem cell research should be permitted and the extent to which public money should be used to fund such research. The details in this area of the law are constantly changing. This section addresses federal and state restrictions on stem cell research that are currently in place or being proposed as of the date of this publication, as well as issues related to stem cell research funding.

Despite the fact that scientists and doctors have been working with stem cells and using stem cells for therapeutic purposes (i.e., bone marrow transplants), since the 1960's,⁵⁴² the current debate surrounding stem cell research primarily arose in 1998 when scientists at the University of Wisconsin and Johns Hopkins University developed a technique to isolate and grow human stem cells.⁵⁴³ The current debate relates not to the research of stem cells generally, but to a primary source of the stem cells, human embryos.

Human stem cells can be derived from a number of sources, including: adults (bone marrow, skin, muscle, blood and the brain); the placenta; umbilical cord blood; unborn/aborted fetuses; and embryos.⁵⁴⁴ Stem cells may also be derived from plants and animals, but state and federal restrictions on stem cell research and funding relate almost entirely to human stem cells derived from unborn/aborted fetuses and embryos. Unless otherwise stated, the restrictions discussed in this section relate exclusively to the research, and funding of research, on human stem cells derived from unborn/aborted fetuses and embryos.

Embryonic stem cells are generally derived from embryos remaining after in vitro fertilization.⁵⁴⁵ However, embryos may also be created by somatic cell nuclear transplantation ("SCNT") or cloning.⁵⁴⁶ Generally the restrictions discussed in this section would apply equally to all embryos, regardless of the manner of their creation. Additional restrictions exist that are specific to the cloning of human embryos, whether for reproductive or therapeutic purposes.

Legal Restrictions on Stem Cell Research

Restrictions in Minnesota

Minnesota law does not prohibit or restrict research on already existing stem cells. Also, there are no limitations on state funding of research related to stem cells. Minnesota's support for stem cell research is perhaps best demonstrated by the presence of one of the world's leading research centers in the field of stem cell research, the Stem Cell Institute at the University of Minnesota. The Institute is internationally recognized for its work in bone marrow transplantation, umbilical cord blood, and adult stem cell research.⁵⁴⁷

While stem cell research is widely supported in Minnesota, state law does prohibit the derivation of new stem cells from a living human embryo or fetus, and violation of this prohibition carries a criminal penalty.⁵⁴⁸ This prohibition applies to research on any human

organism, conceived either in the human body or produced in an artificial environment other than the human body, from fertilization through the first 265 days thereafter.⁵⁴⁹

Legislation has been introduced in both the House of Representatives and Senate for Minnesota's 2005-2006 legislative session that would set the state policy with respect to stem cell research.⁵⁵⁰ The legislation would expressly permit stem cell research and the derivation of embryonic stem cells from any source, including SCNT, with appropriate review by an institutional review board.⁵⁵¹ In addition, the legislation would specifically appropriate state funds to be used to further the purposes of the legislation.⁵⁵²

Federal Restrictions

Federal law does not restrict stem cell research, regardless of the source of the stem cells. Federal law does restrict federal funding of certain types of stem cell research. See the discussion titled Public Funding of Stem Cell Research below for more information on these restrictions.

Other States

Several states restrict research on live embryos and unborn/aborted fetuses. The following table lists the states that have enacted restrictions and the type of restrictions currently in place.⁵⁵³

State:	Prohibits Research Using:
Arizona Statutes §§36-2302, 2303	Aborted living/non-living embryo or fetus
Arkansas Statutes §20-17-802	Aborted live fetus
California Health and Safety Code §§ 123440, 125300-320	Aborted live fetus
Florida Statutes §390.0111	Aborted live fetus
Illinois Statutes 720 ILCS §§510/6, 510/12.1	Aborted living/non-living fetus
Indiana Statutes §§35-46-5-1, 16-34-2-3, 16-34-2-6	Aborted living/non-living embryo or fetus
Kentucky Statutes §§ 436.026, 311.715	No state-supported medical facility may conduct research in which an embryo is intentionally destroyed
Louisiana Statutes §§14:87.2, 9:121, et. seq	Fetus/embryo in utero, viable embryo can't be destroyed, embryos cannot be created for research
Maine Statutes 22§1593	Fetus/embryo born or extracted alive, only applies to in vitro fertilized embryos post-implantation
Massachusetts Statutes 112§12J	Live embryo or fetus before expulsion from womb
Michigan Statutes §§ 333.2685, 2687	Live or dead embryo/fetus, cloned embryo

Missouri Statutes §§188.036, 037	Fetus alive pre-abortion
Montana Statutes §50-20-108(3)	Live fetus
Nebraska Statutes §§28-342, 346, 71-7606	Aborted live fetus, state funds for research on aborted fetal tissue, state funds for embryonic stem cell research
New Hampshire Statutes §§168-B-1, 15	Embryo may not be maintained ex utero past 14 days after fertilization unless cryopreserved; embryo donated for research may not be implanted
New Mexico Statutes §24-9A-1, 3, 5	Fetus/embryo born or extracted alive
North Dakota Statutes § 14-02.2-01, 02	Fetus/embryo born or extracted alive, cloned embryos
Ohio Statutes §2919.14	Living/non-living embryo or fetus
Oklahoma Statutes 63 §1-735	Fetus/embryo
Pennsylvania Statutes 18§§3203, 3216	Live embryo or fetus, no non-therapeutic research on unborn child
Rhode Island Statutes § 11-54-1	Fetus/embryo born or extracted alive
South Dakota Statutes § § 34-14-16, 17, 20; 34-23A-17	Living or non-living embryo or fetus; embryo outside of a woman's body; research on cells or tissues derived from an embryo outside a woman's body
Utah Statutes § § 76-7-301, 310	Live fetus, fertilized embryo post-implantation; live unborn child
Virginia Statutes § 2.2-2233.2	No public money to entity conducting embryonic stem cell research

This table shows the variety of restrictions that the states have placed on the derivation of new stem cells from existing embryos. Note, however, only one state, South Dakota, has specifically outlawed stem cell research. To date, only California, New Jersey, Massachusetts and Connecticut have laws specifically permitting research on embryos.⁵⁵⁴

Public Funding of Stem Cell Research

Funding in Minnesota

Minnesota law does not specifically support or restrict the funding of stem cell research. Minnesota is actively seeking to provide a supportive environment for all types of biotechnology. As discussed above, legislation is currently being introduced that would set aside state money to be used specifically for stem cell research. While there is no specific state funding for stem cell research, the Minnesota Department of Trade and Economic Development can provide guidance on the resources, financial and otherwise, that are available to Minnesota businesses.

Federal Funding

Federal funding for embryonic-based research has had a varied past dating back to the 1973 *Roe. v. Wade* decision, when people became concerned about the use of aborted fetuses in research.⁵⁵⁵ Shortly thereafter, Congress enacted the first restrictions on funding of research that utilized “a living human fetus.”⁵⁵⁶ More recently, in 1995, Congress attached language to the appropriations bill funding HHS and the NIH providing that no federal funds could be used for any research that destroys human embryos or subjects them to serious risk of destruction.⁵⁵⁷

After the isolation of embryonic stem cells at the University of Wisconsin in 1998, which was funded by private capital, the General Counsel of the HHS decided that based on the wording of the 1995 funding restriction, federal funding could be made available for stem cell research.⁵⁵⁸ He based this determination on the fact that, once isolated from the embryo using private funds, subsequent research on the resulting stem cells did not involve or endanger any embryos.⁵⁵⁹ The Clinton administration adopted this position and developed specific guidelines to enact this policy. These guidelines were never put into practice due to the end of Clinton’s term as president.⁵⁶⁰

On August 9, 2001, President Bush announced the policy that remains in effect today.⁵⁶¹ Essentially, federal funding is only available for stem cell research performed on stem cell lines created before August 9, 2001.⁵⁶² Initially the administration asserted that there were more than 60 stem cell lines available for research.⁵⁶³ In truth, closer to 20 stem cell lines are available, all of which may be unsuitable for many types of research because they were established on mouse feeder cells and, as a result, may have become contaminated.⁵⁶⁴

In May 2005, the U.S. House of Representatives approved a bill that would ease restrictions on federal funding of embryonic stem cell research, sending the bill on to the Senate.⁵⁶⁵ President Bush has threatened to veto the bill if it is approved by the Senate and presented to him to sign.⁵⁶⁶

Other State Funding

While many states have proposals for state funding of stem cell research, only four states have made specific funding commitments to stem cell research.

California

In November 2004, California voters approved Proposition 71, which authorizes the sale of \$3 billion in general obligation bonds over ten years to provide funding for stem cell research and research facilities.⁵⁶⁷ In addition, the proposition amends the state constitution to establish a right to conduct stem cell research and to establish the “California Institute for Regenerative Medicine” to regulate stem cell research and funding in California.⁵⁶⁸

Currently the legality of Proposition 71 is being challenged by opponents in courts.⁵⁶⁹ Recently the state Supreme Court refused to rule on the issues presented.⁵⁷⁰ The state

is contemplating bringing its own suit to obtain a judicial determination of the legality of the program.⁵⁷¹

New Jersey

New Jersey formally legalized embryonic stem cell research in January 2004, and since then has committed \$9.5 million dollars for the creation of the Stem Cell Institute of New Jersey.⁵⁷² In addition, the governor has introduced legislation to spend \$150 million to build and equip a facility to house the institute, and to invest an additional \$60 million to build biomedical research facilities.⁵⁷³

Massachusetts

The Massachusetts state lawmakers recently overturned a veto by the state's governor and approved a bill that specifically permits researchers to conduct research on embryonic stem cells.⁵⁷⁴ The bill became law in May 2005.⁵⁷⁵

Connecticut

The Connecticut legislature approved a bill establishing a 10-year \$100 million plan to fund stem cell research, which was signed into law on June 15, 2005.⁵⁷⁶

Private Funding

By far the leading biotechnology company supporting stem cell research is Geron Corporation located in California.⁵⁷⁷ Geron funded the University of Wisconsin and Johns Hopkins research teams that first isolated stem cells.⁵⁷⁸ Geron also supports a research team at the University of California, San Francisco.⁵⁷⁹ Through its support, Geron essentially controls several stem cell lines and holds a portfolio of 240 stem cell patents.⁵⁸⁰ In addition, Geron has acquired exclusive rights to develop certain stem cell products based on the University of Wisconsin's holdings, which include patents affecting 64 stem cell lines.⁵⁸¹ In addition, some large companies are gradually becoming involved in stem cell research programs, including Becton, Dickinson & Co., Invitrogen Corp., Johnson & Johnson, General Electric Co., and a research division of Novartis AG.⁵⁸²

Current Trends

The status of federal funding of embryonic stem cell research has left the states to compete for a share of the biotechnology industry. Many states are scrambling to pass laws that expressly permit stem cell research and provide state funding for that research. Other states are moving to further restrict stem cell research. In general terms, the split between the states runs largely along political lines.⁵⁸³ States carried by Bush in the 2004 presidential election, if not restricting research, are rejecting legislation that would support stem cell research. For instance, Virginia recently rejected legislation that would have created a research fund of public and private money, and Texas is considering a ban on

stem cell research.⁵⁸⁴ New Jersey is considering a bond measure to raise \$230 million for research,⁵⁸⁵ and Delaware's Senate has approved a bill allowing the use of embryonic stem cells in research.⁵⁸⁶ Maryland's legislature is also currently voting on a bill that calls for spending state money, \$23 million per year, on embryonic stem cell research.⁵⁸⁷ Various proposals are being circulated in New York supporting stem cell research, but in the face of a considerable deficit, the provision for state funding in any resulting bill is less clear.⁵⁸⁸ Illinois, Wisconsin, Michigan, Washington and Pennsylvania are also looking at, or preparing to propose, legislation permitting and funding stem cell research.⁵⁸⁹

As the states battle for supremacy in the biotechnology industry, the landscape of state regulation changes on virtually a daily basis. Not many states are dormant on the issue of stem cell research and funding.

I. Cloning

Introduction

Cloning is the process of creating a genetic copy of an existing organism. The latest technology used in cloning is SCNT and involves the transfer of the nucleus from a somatic cell to an egg whose nucleus has been removed. This is the method that was used to clone Dolly the sheep in 1996.

The concept of cloning has sparked a great deal of ethical debate and regulation on an international, federal and state level. The following discussion of cloning is divided between the cloning of human beings and the cloning of agricultural products. The regulations in these areas are constantly changing, therefore, the laws of the federal government and the particular state where the cloning project is to take place should be researched prior to its commencement.

Primary Types of Cloning

There are two types of cloning that are primarily discussed at the current time: reproductive cloning and therapeutic cloning. Reproductive cloning involves technology used to generate an organism that has the same nuclear DNA as a currently existing or previously existing organism. The end result of reproductive cloning is a genetic copy of the existing organism. Therapeutic cloning involves the creation of cloned cells of an organism not for the creation of an entirely new organism, but to harvest the stem cells for other uses. The primary difference between the reproductive cloning and therapeutic cloning is the end result.

Cloning of Humans

Although the cloning of human beings has been the subject of many debates, there has been no federal legislation prohibiting the cloning of humans. There are, however, certain

federal restrictions on human cloning and some state legislatures have enacted legislation restricting human cloning. Of the states that have addressed the issue, some have prohibited reproductive cloning and therapeutic cloning while others have only prohibited reproductive cloning. The international community is also addressing the issue of human cloning.

Federal Regulation

Although several attempts have been made, there is currently no federal legislation that prohibits the cloning of a human being in the U.S. Even though there is no prohibition, it does not mean that human cloning is without regulation. In 1993, the FDA stated that creating a human being with cloning technology is subject to FDA regulation under the Public Health Service Act and the FDC Act.⁵⁹⁰ To stress its oversight, on October 26, 1998 and March 28, 2001, the FDA issued “Dear Colleague” letters reminding researchers of its authority to regulate human cloning.⁵⁹¹ These letters stressed that no one can use SCNT to create a human being unless an IND application is in effect.⁵⁹² This means that anyone involved in the cloning of human beings must not only incur the cost relating directly to the cloning process, but must also incur the cost of complying with FDA regulations.

Human cloning is also limited by an additional financial barrier: on March 4, 1997, President Clinton issued a Memorandum prohibiting the use of federal funds for the cloning of human beings.⁵⁹³ Note, these regulations do not prohibit researchers from financing the cloning of human beings through private funding sources.

Regulation by States

Several states have adopted legislation relating to the cloning of human beings. The legislation in each state varies, with some states prohibiting both reproductive cloning and therapeutic cloning and others only prohibiting reproductive cloning. The chart below contains a list of states that have addressed the issue and which activities the states have prohibited.⁵⁹⁴ The penalties for violating the statutes of each state vary but in many instances can result in criminal penalties and fines. Prior to engaging in any type of human cloning, the laws of the state where the cloning is intended to take place should be reviewed to ensure compliance.

State	Statute	Prohibition of Reproductive Cloning	Prohibition of Therapeutic Cloning
Arkansas	Ark. Code Ann. § § 20-16-1001, 1002, 1003, 1004	Yes	Yes
California	Cal. Bus. & Prof. Code § 16004, 16105 Cal. Health & Safety Code § § 24185 and 24187	Yes	No
Iowa	Iowa Code § § 707B.1 to 4	Yes	Yes
Michigan	Mich. Comp. Laws Ann. § § 333.26401-06, 333.16274, 333.16275, 333.20197, and 750.430a	Yes	Yes

State	Statue	Prohibition of Reproductive Cloning	Prohibition of Therapeutic Cloning
Missouri	Mo. Ann. Stat. § § 1.217 and 196.1127	Prohibits the use of state funds	No
New Jersey	N.J. Stat. Ann. § 2C:11A-1	Yes	No
North Dakota	N.D. Cent. Code § § 12.1-39-01 and 12.1-39-02	Yes	Yes
Rhode Island	R.I. Gen. Laws § § 23-16.4-1 to 4-4	Yes	No
South Dakota	S.D. Codified Laws § § 34-14-26 through 28	Yes	Yes
Virginia	Va. Code Ann. §§32.1-162.22	Yes	Unclear

International Regulation

In March 2005, the General Assembly of the United Nations approved Resolution 59/280, a *non-binding* declaration requesting that all member states ban all forms of human cloning.⁵⁹⁵ As of July 2004, thirty countries had adopted legislation prohibiting the reproductive cloning of human beings.⁵⁹⁶ The adoption of Resolution 59/280 will likely result in several other countries adopting such prohibitions, potentially including the U.S. Since Resolution 59/280 did not specifically carve out therapeutic cloning, member countries may also enact prohibitions on the therapeutic cloning of human beings.

Effect on Corporate Finance

Obtaining financing for a project involving the cloning of human beings is more difficult because of federal, state and international restrictions. Because federal funds cannot be used for such research, funds must be obtained from a private source or from a state that permits its funds to be used in such a manner. In addition, obtaining these funds becomes more tenuous as a result of the ongoing ethical debate surrounding the issue of human cloning. Although at the current time cloning is not prohibited federally or by many states, there is risk that cloning will become prohibited and therefore, any knowledge, gains, or products obtained from human cloning performed prior to the prohibition will not be able to be used or marketed in the U.S.

Agricultural

The cloning of agricultural products involves both plant and non-human animal cloning. Although there does not appear to be a prohibition of the cloning of plants and non-human animals, this cloning is also subject to regulation. Although the extent of such regulation is unclear at this time, it is likely the FDA and the USDA will be the primary agencies in charge of such regulation.

Plant Cloning

Plant cloning is likely to be regulated by the UDSA's APHIS under the Plant Protection Act.⁵⁹⁷ If the USDA finds that a cloned plant is a "regulated article," a permit must be

obtained before the plant is imported, transported interstate, or released into the environment.⁵⁹⁸

Non-Human Animal Cloning

The FDA has regulatory authority over non-human animal cloning under the FDC Act.⁵⁹⁹ In addition, the EPA has stated that it has regulatory authority over GM animals under the TSCA.⁶⁰⁰ However, it has not applied the TSCA to GM animals.⁶⁰¹ If the EPA applies the TSCA, it is likely to argue that the TSCA also applies to cloned animals.

Use of Cloned Plant and Non-Human Animals

Both the FDA and the USDA have regulatory authority over the use of cloned plants and non-human animals as food products. Depending on how the agencies classify the cloned animal and plant products, such products may be regulated by the FDC Act⁶⁰² the Meat Inspection Act,⁶⁰³ the Poultry Products Inspection Act,⁶⁰⁴ or other acts.

Regardless of the potential regulation, the FDA has put into effect a voluntary moratorium preventing the sale of animals cloned using SCNT until the FDA can research issues concerning: food safety, the effect on the animals, and the environmental impact of bringing cloned animals to market. Although the FDA has released a draft risk assessment summary indicating that there is no significant risk to animal health or food safety, the moratorium remains in effect.⁶⁰⁵

Effects on Corporate Finance

In summary, there is a great deal of potential oversight by the federal government relating to the cloning of plants and animals in agriculture. In addition, there may be additional regulation at the state level. A party participating in cloning for agricultural purposes will not only incur the costs related to cloning, but also the cost of complying with the applicable regulations. There is also the potential that the funds spent on the cloning of non-human animals to be released in the food supply may be wasted if the FDA does not lift the existing moratorium. The cloning of agricultural products also raises certain ethical issues that may deter private funding sources.

J. Reimbursement

Introduction

Reimbursement refers to the process of securing payment for a product from insurance companies, health plans and governmental health care programs. It is a subject that should be a part of every medical product company's business plan. Savvy investors will want assurances that the products of the companies in which they are investing will be salable, and salability is heavily affected by the availability of adequate reimbursement.

Because obtaining reimbursement can be a time-consuming process, it is important to develop an early reimbursement strategy for any medical product.

In 2002, Johnson & Johnson effected a brilliant strategy by obtaining from Medicare an “accelerated incremental reimbursement” for its new drug-eluting stent even prior to securing marketing approval from the FDA. Johnson & Johnson was able to convince Medicare to extend coverage by showing “consistent clinical outcomes in two important randomized, double-blind, controlled clinical trials . . . for nearly two years, sharing clinical and health economic data for drug-eluting stents.”⁶⁰⁶ In recognition of the significance and cost of the product, HHS created two new Diagnostic Related Group (“DRG”) codes for reimbursing procedures involving the new stent. As a result, Johnson & Johnson was able to bring a new, expensive product to market with additional reimbursement already established. Johnson & Johnson’s approach underscores the significance of having a well thought out reimbursement strategy, and in particular, the importance of early attention to targeted data collection and early communication with HHS.

Most medical devices and pharmaceutical products are ultimately paid for by third-party payors, such as private insurance companies and government healthcare programs, including Medicare, Medicaid and TriCare. To be successful, a new product must appeal both to consumers, that is the patient or the ordering physician or facility, and to payors. While the adequacy of reimbursement is certainly not the only factor affecting purchasing decisions, inadequate reimbursement can deter use of even the most attractive product and will exert a downward pressure on pricing.

Identifying the path to optimal reimbursement involves a complex analysis, focusing on the nature of the product, how it will be used, by whom and in what setting. The answers to these questions determine the reimbursement system appropriate to the new product, which in turn determines the applicable coding system. If the product is adequately described in the relevant coding system (i.e., generally, when it is analogous to an existing product, or is an insignificant part of an established procedure), coverage and the rate of reimbursement is easily determined by reference to established payor practices. It may be necessary to seek expanded coverage, however, if the product is to be used for a novel population. It may also be possible to enhance the payment rate through the use of new technology add-on payments. If the product is sufficiently innovative or is used in what amounts to a new service, there may not be an applicable code and a new code may be desirable. In this case, coverage and the rate of payment must also be established.

A product may enjoy reimbursement advantages or disadvantages relative to a competitive product or modality of treatment. If, for example, reimbursement for drug-eluting stents and the associated procedure is capped at a rate that results in a per-case loss to hospitals while reimbursement for an alternative modality of treatment such as coronary artery bypass grafts yields a profit, then all other things being equal, hospitals may resist adopting the new technology. When a similar discrepancy affects the reimbursement for the services of an ordering physician, the resistance may have a more pronounced effect on treatment choices.⁶⁰⁷ For example, a new capital-intensive technology may allow a procedure historically performed in an inpatient setting to also be performed in an office setting. If no additional reimbursement is available to the physician to finance the acquisition of the technology, however, physicians may elect to forgo purchasing the equipment and continue to perform the procedure on an inpatient basis.

Of course, some products can result in cost savings for purchasers even when reimbursement is not available to cover the cost of acquisition. Thus, for example, an imaging technology that reduces the time spent in surgery, or an after-care technology that reduces complications and the average length of stay, might be appealing to a provider even when no additional reimbursement is available in connection with the purchase or use of these technologies. So long as the purchaser has an economic incentive to manage costs, as is the case under prospective payment and capitated systems of reimbursement, the absence of reimbursement for a cost-reducing product may not be significant. If a product is to be marketed as a cost reduction tool, however, data substantiating the cost effectiveness of the product is essential.

Having a comprehensive reimbursement strategy greatly enhances the probability of success of a product. While this section will focus on U.S. rules, formulating a reimbursement strategy should include a review of the other countries where the product will be sold because reimbursement rules can vary greatly from country to country.⁶⁰⁸ The strategy should also include an analysis of the applicable payors. In the U.S., Medicare tends to be the engine that drives the train and, consequently, this section will concentrate on Medicare reimbursement. Private payors and other public payors often follow Medicare, but may also use different approaches. Failing to recognize the importance of reimbursement can result in delays in bringing a product to market and a reduction in profitability. Taking reimbursement into account from the outset allows a product to be positioned for optimal reimbursement treatment and provides a realistic basis for economic forecasting.

Overriding Considerations

There are several overriding themes to consider when formulating a reimbursement strategy. First, a comprehensive strategy requires attention to three elements – coding, coverage and payment. Codes describe the items or services used, coverage deals with the question of whether a coded service is within a payor’s benefit set, and payment deals with the rate of reimbursement. These three elements are discussed in greater detail below.

Second, obtaining new codes, coverage and payment requires the submission of data supporting various propositions. For example, to obtain a new Health Care Common Procedure Coding System (“HCPCS”) code, the sponsor must provide six months of marketing data. More importantly, payors may not grant coverage without adequate efficacy and efficiency data. Recall that Johnson & Johnson’s success was predicated on its ability to show HHS compelling clinical and economic data demonstrating the utility of the new stents.

Third, the reimbursement process involves many stakeholders including hospitals, doctors, patients and payors. Patient advocacy organizations, physicians’ specialty societies and even politicians may assist efforts to secure reimbursement. The involvement of these groups can help underscore the importance of providing adequate reimbursement rates and an appropriate scope of coverage. Broad-based public demand goes a long way to securing coverage and payment.

Fourth, many new products will be unable to secure an immediate change in reimbursement. If a product falls within an existing code, in the absence of an add-on payment, then no additional reimbursement will be immediately available from Medicare on

account of the use of the product. Instead, the user will continue to be paid the same amount as before the introduction of the new technology. Eventually, through periodic annual recalibrations based on cost and claims data, the payment for the code should be adjusted to reflect the additional costs of the new technology. These adjustments may take several years in the best of circumstances, may be diluted if other cheaper items or services are considered as is the case where generics are allocated the same J-code (as defined in the table below) as brand name drugs or may never be included by Medicare due to reporting problems.

An immediate change in reimbursement can be obtained by securing a new code and related payment. For example, the Johnson & Johnson stents were allocated new DRG codes that were specific to the use of the new drug-eluting stent. An immediate change in reimbursement can also be obtained in limited circumstances where additional, immediate “add-on” or “pass-through” payments may be available for certain inpatient⁶⁰⁹ and outpatient⁶¹⁰ items and services.

Reimbursement Systems

There are a number of different reimbursement systems in use. The nature of the product as well as the setting in which it will be used determines the applicable system. That system will then have implications for coding, coverage and payment. There are different reimbursement systems for: professional services, such as physicians’ services; facility services, such as inpatient and outpatient hospital stays; and for items such as durable medical equipment and drugs. Reimbursement systems also typically draw distinctions between places of service, for example, between hospitals, physicians’ offices and ambulatory surgery centers.⁶¹¹ Therefore, some procedures may be ineligible for reimbursement in ambulatory surgery centers but eligible for reimbursement in hospitals. Also, a single procedure may be reimbursed at a different rate depending on where it is performed. Other considerations include limitations on who may bill for certain types of services.

Some of the reimbursement methodologies in current use by Medicare are:

EXAMPLES OF MEDICARE REIMBURSEMENT METHODOLOGIES			
Type of Service	Type of Reimbursement	Coding System	Method for Accounting for Costs of New Technology
Inpatient Hospital Stay	<u>Prospective Payment System (“PPS”).</u> Hospitals receive a predetermined, fixed amount calculated with reference to the patient’s primary diagnosis. The capped payment gives hospitals an incentive to manage costs.	ICD-9-CM International Classification of Diseases 9th Revisions, Clinical Modification. ICD 9 codes are used to group patients into DRGs.	Periodic adjustments to DRGs, based on cost and charge data. Add-on payments. New DRGs.
	<u>Cost Based.</u> A minority of hospitals and some parts of PPS hospitals are reimbursed on a “reasonable cost basis.” Cost-based providers are able to pass-through new costs and have little incentive to restrict costs.	Cost Report.	Actual costs reported.

EXAMPLES OF MEDICARE REIMBURSEMENT METHODOLOGIES			
Type of Service	Type of Reimbursement	Coding System	Method for Accounting for Costs of New Technology
Outpatient Hospital Visit	<u>Outpatient Prospective Payment System</u> . Hospitals receive a predetermined, fixed amount calculated with reference to the group of services provided to the patient during an outpatient visit. ⁶¹²	Current Procedural Terminology (“CPT”)-4 codes are used to group services into Ambulatory Payment Classifications (“APCs”). HCPCS C-codes are used to identify transitional new technologies not yet adequately reimbursed by an APC.	Periodic adjustments to APCs, based on cost and charge data. New technology APCs. Pass-through payments. New APCs.
Physicians’ Service	<u>RBRVS Fee Schedule</u> . The Resource-Based Relative Value Scale establishes relative values for physicians’ services. The relative value of each service is set with reference to the relative value units representing physicians’ work, practice expenses, and the cost of professional liability insurance.	CPT.	Periodic updates reflecting practice expenses picked up in survey data. ⁶¹³
Drugs	<u>Fee Schedule</u> .	HCPCS J-codes	Average sales price (“ASP”) or invoice pricing. Drugs and biologicals are generally paid at ASP plus 6% with ASPs updated on a quarterly basis. Some drugs may be paid on the basis of average wholesale price, published acquisition cost or invoice pricing. All of these methodologies are predicated on the costs of the drugs.

The above chart does not set forth all of the different methodologies used by Medicare. Medicare also has separate fee schedules for ambulance services; durable medical equipment; prosthetics/orthotics and supplies; clinical lab services; skilled nursing facilities; home health services; and some ambulatory surgical center services. Private payors may use these and additional methodologies, such as capitation (a per head payment intended to cover a package of services that may or may not be used by the beneficiary) and negotiated rates.

Coding, Coverage & Payment

As previously stated, reimbursement for a new product depends on three factors – coding, coverage, and payment.

Coding

Coding is the language of reimbursement. The most commonly used coding systems are set forth on the foregoing schedule. By requiring providers to bill using particular codes representing diagnoses, procedures and items, payors are able to standardize payment for similar items and services. An item or service without a code is typically billed under a miscellaneous or unclassified code until a new code is assigned. Using a miscellaneous or unclassified code generally makes reimbursement uncertain (there is no set price), slower (it requires manual, rather than electronic submission), and requires the provision of additional documentation supporting and explaining the claim. Consequently, providers do not favor miscellaneous or unclassified codes.

A coding analysis begins with assessing whether there are existing codes that appear to cover the item or service in question. Note that products are more likely than services to be subsumed in existing codes. Depending on the situation, a manufacturer may or may not want its product to fit within an existing code. As discussed above, there are reasons to prefer an established code to a miscellaneous or unclassified code. If reimbursement under an existing code is inadequate or if there are restrictions on the setting in which the code may be used, however, then a manufacturer may want to establish a new code with an adequate rate of reimbursement.

Overreaching and underreaching with respect to coding can also be damaging. For example, if a manufacturer takes an expansive view of the application of an existing code, it may be accused of procuring false claims when providers, relying on the analysis, later submit for reimbursement using the suggested code. An expansive view of an existing code could also preclude a manufacturer from seeking a new code for a distinct product.

Payors may decide to require that a product or procedure use an existing code while the manufacturer may prefer that a new code be established. For example, some new implanted devices may be coded so that they are grouped into DRGs that pay for procedures that historically have not involved implantable devices. Many brand name drugs are grouped under J-codes that also cover generics. Inappropriate grouping is most likely to happen when payors have insufficient information about the new product.

If there is an existing, applicable code, there will be an established rate of reimbursement. If there is no applicable code, a manufacturer may choose to rely on the miscellaneous or unclassified codes, or to seek a new code. Obtaining a new code is a time-consuming process, involving multiple parties, such as physician specialty groups, the American Medical Association (“AMA”) and the Center for Medicare Services (“CMS”).

Coverage

Identifying the correct code does not guarantee reimbursement. The decision by a payor to reimburse for a particular item or service is called a coverage decision. A coverage decision typically involves consideration of the following issues:

- Whether a particular item or service is reimbursable at all;
- Whether there are circumstances that negate coverage;
- Who may provide a particular service;
- Who may receive a reimbursable service; and
- How frequently may the service be provided.

Coverage may vary with payors, jurisdictions, and even when payment is being sought from a single payor in a single jurisdiction, on a case-by-case basis.⁶¹⁴ Many products are reimbursed without any formal coverage decision. Products that fit within existing codes will be routinely reimbursed based on prior coverage decisions and the payor's particular coverage criteria. New products, whether billed under miscellaneous, unclassified or new codes, may be the subject of case-by-case or of categorical coverage decisions. Medicare's coverage decisions occur at three basic levels. These levels are set forth below in ascending order of frequency of occurrence:

- **National Coverage Determinations**—CMS makes formal coverage decisions through the Medicare National Coverage Determination (“NCD”) process. CMS maintains a comprehensive data base of NCDs.⁶¹⁵ Either the public or CMS may request an NCD. Manufacturers are often reluctant to request an NCD because a negative decision will apply program-wide. There is a formal and time-consuming process for obtaining a new NCD.⁶¹⁶ Because CMS uses an evidence-based approach⁶¹⁷ to evaluate items and services for coverage, a request for an NCD must be accompanied by, among other things: the rationale for how the evidence selected demonstrates the medical benefits for the target Medicare population; information that examines the magnitude of the medical benefit; reasoning for how coverage of the item or service will help improve the medical benefit to the target population; and a description of any clinical trials or studies currently underway that might be relevant to a decision regarding coverage of the item or service. CMS refers most NCD requests to outside impartial groups, such as the Medicare Coverage Advisory Committee for assistance in evaluation.
- **Local Medical Review Policies**—Medicare contracts with local contractors, called carriers and intermediaries, for claims processing and other services. The Medicare contractors are empowered to make coverage decisions that are effective only for their particular jurisdiction. Although these decisions have historically been referred to as Local Medical Review Policies, the reference is being changed to Local Coverage Decisions or LCDs. The process is similar to that outlined above with respect to NCDs.
- **Medicare Policies and Procedures**—Medicare policies and procedures, as outlined in the Medicare Manuals and other Medicare communications, may also serve to restrict coverage. The absence of a formal NCD does not mean that Medicare has no policy on point.

- Case by Case Claims Processing—Payors applying their own criteria for coverage may determine whether to extend coverage for an item or service in the particular instance.

Clinical Trials

Clinical trials normally present two distinct coverage issues: whether coverage is available for the product being tested and whether the costs of the clinical trial itself will be covered.⁶¹⁸ Many clinical trials involve items and services for which coverage is not an issue. For example, the fact that data is collected in a trial involving the implantation of a covered device should not negate coverage for the device or associated covered services. Other trials that involve new products, however, may be considered experimental or investigational in nature and, therefore, may be excluded from coverage under basic coverage principals. Under Medicare policy, certain products will be reimbursable notwithstanding their newness. Trials may also involve items and services that are not related to the provision of medically necessary treatment, such as cosmetic surgery and, therefore, would not normally be covered by Medicare under its benefit set.

Payment

Payment for an item or service is set with reference to the applicable code. The government programs have complex systems for gathering cost and charge data and factoring that data into payment rates. Manufacturers can assist the government by identifying deficiencies in the data and providing alternative data supporting higher rates of reimbursement. Ultimately, the amount available for reimbursement is determined by the program's budget. Private payors may simply pay billed charges or, particularly in the managed care setting, negotiate rates with providers in advance.

Communicating About Reimbursement

While Medicare supports the dissemination of accurate billing advice, it:

- Does not tolerate the dissemination of false billing advice, and may prosecute these cases under the False Claims Act;
- Questions those who provide extensive reimbursement support services suspecting that certain services amount to valuable benefit given as an illegal kickback for the purchase of product;
- Is uncomfortable with "economic selling" – the practice of selling a product on its profit-making potential, although it has not established a viable legal theory for pursuing these cases; and
- Requires that invoicing be accurate and transparent, and that data reported to the government be accurate.

Conclusion

Reimbursement is a very complex area. The pitfalls for the unwary or uninformed are many but the return on a successful approach can be significant. A thoughtful reimbursement strategy may attract investors and ease the product's introduction into the market. Failure to address reimbursement from the start may cause an otherwise valuable product to fail. A reimbursement strategy should be an early part of any biotechnology company's business plan.

K. Regulatory and Law Enforcement Oversight of Biotechnology Firms

Whether they are privately or publicly funded, all biotechnology companies will come within the regulatory and compliance authority of two groups of federal agencies.⁶¹⁹ First, biotechnology by its nature falls within the purview of HHS and its constituent agencies, the FDA, NIH and CMS. Second, financing for biotechnology firms is subject to scrutiny by federal law enforcement agencies, such as the SEC and FBI, and by state law enforcement agencies charged with protecting investors. These dual functions have resulted in coordinated efforts by the FDA and the SEC to protect the investing public from claims made by biotechnology firms regarding FDA reviews and approval proceedings.⁶²⁰ This increased collaboration by the FDA and SEC to protect the public from pre-approval promotional statements highlights the need for every biotechnology company to appreciate the responsibilities of the agencies and the risks associated with noncompliance.

As the preceding sections of this Guide readily attest, biotechnology applicable to food, nutritional supplements, and pharmaceutical uses is subject to heavy regulation, oversight and clearance. With FDA review taking up to ten to twelve years for certain products,⁶²¹ and with the financial and practical risks and rewards of biotechnology development already so high, developers and entrepreneurs must understand in advance where they could be exposed to claims by the government and by investors. All biotechnology firms must avoid baseless allegations of fraud, abuse, and promotional application offenses, or face disaster.⁶²² Having a regulatory compliance plan in place and employing or engaging a regulatory compliance person or firm along with appropriate legal counsel, should assist any biotechnology company in navigating through the regulatory complexities. Failure to successfully navigate these complexities can result in material claims being assessed against and violations being imposed upon the company and, in certain cases, the principals of the company.

Fraud and Abuse in the HHS Context

The General Accounting Office estimates that fraud and abuse costs the Medicare system ten cents of every dollar spent.⁶²³ During 2000 alone, \$239.8 billion was expended by the Medicare system. Fraud and abuse losses within the Medicare system total approximately \$65 million every day of the year.⁶²⁴ Fraud is an intentional deception or misrepresentation known to be false or not believed to be true and made for the purpose of realizing an unauthorized benefit. Abuse, as applicable to Medicare, is comprised of incidents or

practices by providers, which although not considered fraudulent, are inconsistent with accepted sound medical, business or fiscal practices that directly or indirectly create unnecessary costs to Medicare.⁶²⁵

Anyone who provides health care goods or services under Medicare or Medicaid, or under any health care program administered by a state that has been funded by the U.S., is subject to sanctions under the statutes that establish, regulate and protect these programs. Similarly, the application of biotechnology to food products, while not subject to the claims and reimbursement processes inherent in the health care system, is also monitored and evaluated by the FDA.

Pharmaceutical products, such as those developed through biotechnology, are typically charged to and paid for by third parties such as insurance companies or government funded programs. Biotechnology firms that look to federal or state dollars for funding or reimbursement for health care products must comply with the statutes, regulations and rules, or they will incur the risk of financial liability, civil money penalties, assessments, exclusions from government-funded programs, and in egregious cases, criminal prosecutions.

The laws and rules applicable to Medicare and Medicaid are exceedingly complex and the penalties are severe. All biotechnology firms operating in the pharmaceutical, drug delivery or food products fields should have a written regulatory compliance plan in place.

Health and Human Services Office of Inspector General

Pursuant to Congressional mandate, legal and regulatory compliance regarding health care programs is policed and investigated by the HHS Office of Inspector General (“OIG”).⁶²⁶ OIG’s mission is to identify and eliminate fraud, waste and abuse in HHS programs, and to promote efficiency and economy in HHS operations. OIG accomplishes its statutory mission through audits, inspections and investigations, by excluding from program eligibility individuals and entities who have engaged in fraud or abuse, and by imposing civil money penalties for certain types of misconduct.⁶²⁷ OIG also has the authority to refer or to participate in criminal investigations conducted by the U.S. Department of Justice, which is the only agency empowered to prosecute federal criminal health care fraud and abuse cases. OIG regularly teams with other federal law enforcement agencies such as the Federal Bureau of Investigation, the U.S. Postal Inspection Service, and the IRS, in order to investigate and prosecute individuals and business organizations.

The HHS programs affected by the biotechnology industry that are subject to OIG oversight, protection, exclusion and investigation include: the FDA; Centers for Medicare and Medicaid Services; NIH; Office of Disease Prevention and Health Promotion; Administration on Aging; and Substance Abuse and Mental Health Administration.

Federal authority to investigate and combat fraud was consolidated and strengthened pursuant to the Health Insurance Portability and Accountability Act of 1996 (“HIPAA”).⁶²⁸ HIPAA established the federal Health Care Fraud and Abuse Control Program (“HCFAC”), which operates pursuant to the joint oversight of the U.S. Attorney General

and OIG. HCFAC coordinates federal, state and local law enforcement efforts regarding health care fraud and abuse. By coordinating these functions, the many regulatory and law enforcement agencies are able to share information and resources more effectively and efficiently.

OIG holds the authority to exclude providers convicted of a health care offense so that Medicare and Medicaid will not pay the provider for services or goods. Exclusion is mandatory for Medicare-program related convictions and patient abuse⁶²⁹ and permissive for others.⁶³⁰ OIG is also authorized to commence proceedings to impose civil monetary penalties and collect damages for incorrect claims and other abuses of the Medicare system.⁶³¹ OIG is authorized to perform its investigative functions without notice to health care providers or others that fall within its authority. Indeed, individuals and business organizations may not even know that they are the subject of covert investigations until the matters are prepared for submission in a criminal or civil judicial proceeding.

Statutory Bases For Liability and Exposure for FDA Fraud and Abuse

False Statements and Fraudulent Claims

Biotechnology firms seek regulatory clearance and approvals from the FDA. In doing so, the firms, their principals and representatives make representations regarding the technology and its health and safety implications to the public. These representations must be truthful and complete.

18 U.S.C. § 1001 provides that:

[W]hoever, in any matter within the jurisdiction of the executive, legislative, or judicial branch of the Government of the United States, knowingly and willfully— (1) falsifies, conceals, or covers up by any trick, scheme, or device a material fact; (2) makes any materially false, fictitious, or fraudulent statement or representation; or (3) makes or uses any false writing or document knowing the same to contain any materially false, fictitious, or fraudulent statement or entry, shall be fined under this title or imprisoned not more than 5 years, or both.

In addition to Section 1001, additional federal criminal statutes address “false, fictitious, or fraudulent” claims,⁶³² any “scheme or artifice” undertaken “to defraud the United States [or] to obtain money or property by means of false or fraudulent pretenses, representations or promises,”⁶³³ and false statements or concealments “involving a health care benefit program.”⁶³⁴

Taken together, these federal criminal statutes penalize false statements, schemes and claims to mislead Medicare and Medicaid, and HHS and any of its subsidiary agencies such as the FDA or the NIH.⁶³⁵ Misleading representations, including “puffery,” to CDER regarding biotechnology human drugs, to CBER regarding biotechnology blood products, vaccines, gene therapies and cellular products, or to CFSAN regarding food supply and nutritional supplements, may result in OIG inquiries and administrative action and, when appropriate, referral to the Department of Justice for federal grand jury investigations and criminal prosecutions.

Tension arises between the need for complete disclosure to regulators and the desire to maintain the confidentiality of intellectual property that might not yet be protected by patents. When torn between disclosure and silence, all doubts must be resolved in favor of full disclosure. Half-truths to the FDA are unacceptable because nondisclosures or partial disclosures may constitute concealments under Section 1001 when an individual or entity has a legal duty to disclose,⁶³⁶ as is the case when seeking FDA approvals.

All of the federal statutes discussed in this section require that the purportedly false information or concealment pertain to material information. Individuals or entities rarely find solace in contending that the information at issue was not material because the government is only required to prove that a false statement, representation or omission “has a natural tendency to influence, or is capable of influencing, the decision of the agency.”⁶³⁷ In other words, materiality is present even when the information is not relied upon by the agency or even when the agency already knows the truth.

Title 42 Crimes

Congress has promulgated specific statutes directly addressing false statements in connection with health care programs or actions undertaken by manufacturers that cause false statements. The statutes directly apply to statements made to obtain reimbursement for the application of biotechnology from any federally administered or funded health program. Anyone who knowingly and willfully makes a false statement or representation of material fact in an application for payment,⁶³⁸ in determining a right to payment,⁶³⁹ or who conceals facts that affect the initial right or continued right to payment⁶⁴⁰ is in violation of these laws.

Anti-Kickback Act

The Federal Health Care Program Anti-Kickback Act (“Anti-Kickback Act”) imposes criminal liability for the knowing and willful payment, solicitation, or receipt of remuneration in return for referring an individual to a person for, or in return for purchasing, leasing, ordering or for arranging for or recommending purchasing, leasing or ordering items or services reimbursable by a federal health care program.⁶⁴¹ The Anti-Kickback Act is violated even when the intention to induce referrals is one among other legitimate activities. Offering entertainment, free or reduced price products, loans or grants, or less than fair market value charges for anything of value, may violate the law if undertaken knowingly and willfully.

Careful practitioners will evaluate the application of the Anti-Kickback Act whenever Medicare providers form joint ventures to develop products or deliver services. When, for example, physicians invest in laboratories and share in their profits, the primary inquiry will be whether the purpose of the arrangement is to obtain a source of referrals or to raise funds. The former may violate the Anti-Kickback Act.

Because the Anti-Kickback Act is breathtakingly broad, Congress requires that OIG issue a number of regulatory “safe harbors.” Conduct falling within the safe harbors “shall not be treated as a criminal offense . . . and shall not serve as the basis for an

exclusion.”⁶⁴² OIG is also authorized to issue “advisory opinions” that serve as formal guidance regarding the Anti-Kickback Act, the safe harbor provisions, and the application of remedies, penalties and exclusions by OIG. Advisory opinions may be relied upon by the parties requesting and obtaining them and are a highly persuasive authority upon which to base a defense to fraud and abuse allegations.

Conspiracies and Schemes to Defraud

18 U.S.C. § 371 criminalizes conspiracies to violate any federal criminal law whether articulated within Title 18 or not, and agreements to defraud the U.S. In addition, 18 U.S.C. § 1347 prohibits any “scheme or artifice—(1) to defraud any health care benefit program, or (2) to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any health care benefit program.”

Although conduct directed to or against HHS or any of its agencies may be covered by less serious provisions of law, nothing hinders the government from charging individuals and business organizations with felony conspiracy, health care fraud, and mail or wire fraud for precisely the same conduct also covered by misdemeanor offenses.⁶⁴³ In other words, the government is authorized to charge any statute that it believes applies. It makes no difference that conduct addressed in a Title 18 felony prosecution also might be criminalized by misdemeanor offenses that carry less serious penalties.⁶⁴⁴

False Claims Act, *Qui Tam* cases and Whistleblowers

The False Claims Act penalizes health care providers or others who knowingly submit false claims to Medicare by subjecting defendants to triple damages and fines.⁶⁴⁵ Private individuals are authorized to file *qui tam* actions pursuant to the False Claims Act on behalf of the U.S. *Qui tam* relators – the private parties who initially sue on behalf of the U.S. government – have initiated cases resulting in huge financial liabilities owed by pharmaceutical manufacturers such as the \$430 million paid by Warner-Lambert for marketing Neurontin® to address ailments that were beyond the FDA’s approved uses.⁶⁴⁶ After the initial filing by a private *qui tam* relator, the federal government has the option to intervene and assume control of the litigation.⁶⁴⁷

Individuals who know of false claims may be rewarded for disclosing information regarding Medicare fraud that leads to the recovery of money from wrongdoers under the False Claims Act.⁶⁴⁸ Civil proceedings under the False Claims Act may be referred for criminal investigation and prosecution. Private *qui tam* plaintiffs may become witnesses in parallel federal criminal investigations. When firms under investigation learn of the government’s interest, they unwisely may be tempted to punish, pressure or interfere with witnesses, thereby simultaneously providing evidence of the conduct under investigation and creating new grounds for exposure. Anyone who “willfully prevents, obstructs, misleads, [or] delays . . . the communication of information or records relating to a violation of a federal health care offense to a criminal investigator. . .” commits a felony.⁶⁴⁹

Whistleblowers may find other resources and assistance from public interest groups. For example, The False Claims Act Legal Center is a nonprofit organization dedicated to combating fraud through the promotion of the False Claims Act, by bringing suits under its qui tam provisions, and by pursuing state law false claims cases.⁶⁵⁰

Recent Developments Regarding Securities and Investor Fraud

Recent developments in the business of biotechnology have promoted collaboration among federal agencies that previously would have had little interaction with one another—the FDA and the SEC. On February 5, 2004, the FDA and the SEC jointly announced improvements to the procedures for policing biotechnology disclosures.⁶⁵¹ The joint efforts of the FDA and SEC reflect a confluence of the FDA approval/clearance process and representations that are made by biotechnology companies to investors. The joint efforts arise because companies “played with their stock price by the way they spun updates on their regulatory processes.”⁶⁵²

Pursuant to the initiative, the FDA agreed to provide technical assistance to the SEC’s Division of Corporate Finance and to provide documents and information to the SEC’s Division of Enforcement when it appears that false or misleading information regarding FDA approvals has been disseminated to the public. The FDA now has a centralized procedure for referring suspected instances of securities fraud to the SEC when, for instance, companies disseminate misleading information to investors regarding the FDA’s regulatory process. As FDA Commissioner Mark McClellan put it, “We will protect the confidential information you give us, but that doesn’t mean you can feel free to mislead the investment community.”⁶⁵³ Notwithstanding the positive publicity, however, there is doubt in the investment community as to whether the inter-agency cooperation between the SEC and the FDA has rendered the expected results.⁶⁵⁴

Federal scrutiny over biotechnology firms has also been greatly enhanced by Sarbanes-Oxley, which was passed to bolster public confidence in the financial markets. Sarbanes-Oxley requires heightened reporting requirements and increases the penalties to executives, directors, auditors and attorneys who violate its provisions. It also requires that auditors must have greater independence and that members of the board of directors must exercise their own informed judgment. Most of Sarbanes-Oxley, however, applies only to public companies and their agents, not to private or closely held firms. With respect to nonpublic companies, the older and staid offenses of mail fraud, wire fraud, common-law fraud and theft remain good law today.

The new federal diligence regarding biotechnology finance follows on the heels of a rise in private biotechnology lawsuits brought by investors. The claims run the gamut from concealing communications with the FDA to poor forecasts of future performance. This increase in private securities lawsuits has received more publicity since the insider trading scandal at ImClone Systems, Inc. At ImClone, company executives and others traded securities on non-public information that ImClone’s star experimental cancer drug would not receive FDA approval based upon the data that had been submitted.⁶⁵⁵

Although federal mandates and oversight of disclosure and accountability have increased, the ability of private plaintiffs to press claims against companies recently

suffered a setback. In *Dura Pharmaceuticals, Inc. v. Broudo*, investors alleged that a pharmaceutical company misrepresented the future FDA approval of a new device and claimed that those misrepresentations had artificially inflated the price of the company's securities. The U.S. Supreme Court ruled that the investors had failed to adequately allege "loss causation," because other factors could have affected the difference between the inflated price and later losses.⁶⁵⁶ Thus, current U.S. law provides that plaintiffs no longer may merely allege that a misrepresentation or omission inflated the price of a security. Instead, plaintiffs now must prove both a decline in the value of the security and that the misrepresentation or omission, and not something else, was a substantial cause of the financial harm.⁶⁵⁷ This new loss causation rule will reduce the number and value of claims against biotechnology firms.

Conclusion

The preceding discussion represents a sampling of the most important regulatory and law enforcement issues that biotechnology companies must consider. Because of the complexity of regulatory issues and the penalties which can be imposed for failure to comply, all biotechnology companies should have a compliance plan and appoint or engage a designated compliance officer or firm along with appropriate legal counsel.

L. Distress Stage

Introduction

The Bankruptcy Code, as well as bankruptcy practice and proceedings, have a material impact on all operating entities, including biotechnology firms. While we hope the reader does not need to heavily rely on the materials presented in this section, we recommend having a general knowledge of workout and bankruptcy issues for purposes of effective financial planning and business operations. We have summarized what we consider to be the most important underlying themes as well as specific issues concerning bankruptcy and its impact on both debtors and creditors. Most bankruptcy issues are generic to all entities, whether they are biotechnology firms or not. However, special attention should be paid to the discussion regarding intellectual property licenses due to the importance of licensing in the biotechnology industry.

Potential Liability for the Board of Directors

General

The board of directors of a corporation has the ultimate responsibility for managing the business and affairs of the organization.⁶⁵⁸ The board owes fiduciary duties to the corporation and its shareholders that principally consist of the duties of care and loyalty.⁶⁵⁹

Duty of Care

The duty of care requires directors to exercise reasonable care in discharging their responsibility for the management of the corporation.⁶⁶⁰ Directors fulfill their duty of care when they make informed decisions, consult professionals to the extent necessary and use reasonable diligence in gathering and considering information.⁶⁶¹ The “business judgment rule” typically protects directors by affording deference to board decisions that are made on an informed and good faith basis with a reasonable belief that the actions taken will benefit the corporation.⁶⁶² Directors are generally protected from liability for the consequences of their decisions when those decisions were made on an informed and disinterested basis.⁶⁶³

Duty of Loyalty

The duty of loyalty, by contrast, requires directors to act in the best interests of both the corporation and its shareholders.⁶⁶⁴ This duty requires directors to refrain from advancing their personal interests at the expense of the corporation by, for example, not usurping corporate opportunities or by participating in self-interested transactions.⁶⁶⁵ Courts, in the wake of Sarbanes-Oxley⁶⁶⁶ and Enron, have in recent years given increased scrutiny to corporate governance and board duties. The duties of care and loyalty are enforceable by a derivative action commenced by shareholders for the benefit of the corporation and, indirectly, the shareholder body.⁶⁶⁷

Zone of Insolvency

Board Has No Duty to Creditors of Solvent Corporation

It is well established that directors owe no fiduciary duties to the corporation’s creditors when the corporation is solvent.⁶⁶⁸ The rights of creditors are fixed by the terms of their contractual relationship with the corporation and, in the case of tort claimants and other involuntary creditors, other applicable law.⁶⁶⁹ As such, a board of directors is not generally required to consider the best interests of creditors when arriving at corporate decisions. Unlike shareholders, creditors cannot typically enforce claims against the corporation’s directors for breaches of fiduciary duties where the financial condition of the business is positive.

Board Has a Duty to Creditors of Insolvent Corporation

Many courts have held that when a corporation becomes insolvent,⁶⁷⁰ the board of directors owes a fiduciary duty to its creditors,⁶⁷¹ even if formal insolvency proceedings have not been commenced. There have been two rationales identified for shifting/expanding the fiduciary duties owed by directors of an insolvent corporation to creditors. The first is predicated upon a “trust fund” theory of the directors’ role after insolvency. The courts reason that when liabilities exceed

assets, directors become trustees for the corporation's creditors and hold the corporate assets in trust for their benefit.⁶⁷² The second rationale is based upon the notion that creditors are increasingly put "at risk" as a consequence of corporate actions (viz. director decisions), when the enterprise approaches insolvency. Where creditors are unnecessarily exposed to high-risk strategies adopted by directors in order to enhance the value of the enterprise for the interests of shareholders, a creditor may be able to maintain a cause of action against directors for breach of fiduciary duty.⁶⁷³

Board's Duties to Shareholders

Courts are divided on the issue of whether directors continue to owe fiduciary duties to shareholders when the corporation is insolvent or in the zone or vicinity of insolvency. Some courts have found that directors no longer have duties that run to the shareholders in such circumstances, because all duties have shifted to the corporation's creditors.⁶⁷⁴ The justification for this position is that the directors are managing the company whose equitable owners are no longer the shareholders, but the creditors. The shareholders are "out of the money." Under both state law and federal bankruptcy law, creditors have a claim on the corporation's assets that is superior to that of the shareholders. Other courts have taken the view that directors of a corporation that is insolvent or approaching the zone or vicinity of insolvency have expanded fiduciary duties that are owed to both constituencies—creditors and shareholders.⁶⁷⁵ This standard is predicated upon the notion that a director's fiduciary duties are best served if business judgment is exercised in favor of all stakeholders.

Strategies for Addressing Fiduciary Duties and Avoiding Liability

Directors and officers are increasingly becoming the targets of personal liability claims based upon actions taken or not taken while the corporation is in financial distress. These claims are typically brought by creditors whose claims remain unsatisfied when the business fails and are based upon breaches of fiduciary duties. While it may not be possible to eliminate the risks of director liability altogether, there are a number of steps that can be taken to minimize the risks, including the following:

Observance of Fiduciary Duties

The most complete protection for directors can perhaps be obtained by a strict adherence by the board of its fiduciary duties—understanding the duties and recognizing to whom these duties are owed. Because insolvency alters the duties and risks of directors, it is incumbent upon the board to determine if the corporation is insolvent, will be rendered insolvent by a particular transaction or is operating within the zone or vicinity of insolvency.

Ensure Disinterestedness

It is essential that the directors involved in making decisions for the corporation be disinterested and independent. Avoiding any potential conflicts of interest and the appearance of self-dealing is critical especially when a corporation is insolvent or enters the zone or vicinity of insolvency.

Scrutinize Insider Transactions

It is important to recognize that any transactions between the corporation and “insiders” (i.e., officers, directors, shareholders and affiliates) must be carefully scrutinized and justified by the board, as these transactions will certainly be given special and thorough attention by creditors and shareholders who are looking for recovery on account of their unsatisfied claims. The amount and timing of compensation, dividends or other payments made to or for the benefit of directors, officers, shareholders and other insiders may become subject to avoidance as preferential or fraudulent.

Compliance with Regulatory Obligations

A board should ensure that the corporation is strictly complying with all laws and regulations and, if necessary, rectify any noncompliance as soon as possible. A violation of environmental and tax laws, for instance, may give rise to personal liability for directors. For example, the failure of a corporation to ensure that its trust fund taxes (i.e., withholding taxes), and similar obligations are not paid on a timely and current basis may result in personal liability for such obligations.

Appropriate Review of Significant Transactions

Any significant transaction approved by the board of directors may be subject to scrutiny and challenge by creditors and other outside parties, and should be approved only after careful and documented consideration. The advice of qualified outside counsel and financial advisors should be sought in such circumstances whenever possible. The advice of professionals is particularly important in the context of a financial restructuring, as the corporation will likely be presumed insolvent. A report prepared in good faith by officers of the corporation or outside experts and duly considered by the board will maximize the protections offered by the business judgment rule for director decisions.

Avoid Payments that Operate to Favor Select Creditors in Final Hour

When considering the corporation’s debt structure, it is important to understand that payments made to creditors in preference of payments to other similarly situated creditors may pose particular problems. A corporation that is insolvent or approaching insolvency (i.e., the handwriting is on the wall) often makes

payments to a select group of creditors (critical vendors, insider indebtedness, third-party debt guaranteed by directors and officers) while others go unpaid. These types of payments can often be set aside as preferential or fraudulent and give rise to potential claims against directors.

Maintain Adequate Directors' and Officers' Insurance

While directors' and officers' liability insurance coverage provides certain protections, it does not protect against all potential liabilities. Directors should assure themselves that adequate insurance coverage is maintained and that all premium payments have been made.

Consider Costs and Benefits of Bankruptcy

Although bankruptcy is not advisable for every company in financial distress, it should always be considered as one of the many available alternatives. Legal counsel and financial advisers with bankruptcy experience should normally be consulted to advise the board on costs, rights, obligations and benefits of a bankruptcy proceeding.

Alternative Responses to Distress

Companies are often in serious financial problems before management even identifies or realizes that problems exist. Several alternatives are available to distressed companies once management recognizes the company's financial problems and concludes that steps must be taken to address the problems. Outside legal and management professionals are often engaged to assist in selecting and following through with a response to a financial distress situation.

Out-of-Court Restructuring

One of the inescapable challenges for a company with financial problems is whether to attempt a voluntary out-of-court workout or file Chapter 11. All things being equal, a business should not file for Chapter 11 if the same potential result can be achieved in a voluntary workout. It would be difficult, however, to successfully accomplish a voluntary workout if there are more than a dozen major unsecured creditors or if there are one or more uncooperative secured or unsecured creditors. If a debtor is nevertheless able to convince its unsecured creditors to voluntarily accept extended payment terms, and if it is able to convince its secured creditors to provide the necessary leeway to work through a reorganization period, then an out-of-court restructuring may be successful.

Regardless of whether one attempts an out-of-court workout, a Chapter 11 reorganization, or a Chapter 7 liquidation, it is often advisable to employ a workout consultant/financial advisor. This is particularly true where creditors are questioning management's credibility, integrity or competence. Financial projections and business

plans endorsed by an advisor may be more credible and effective in dealing with secured and unsecured creditors, trade creditors, landlords, bondholders and the court.

Prior to commencing a workout or filing bankruptcy, management and other professionals must spend considerable time: evaluating the company's business; identifying the reasons why its financial condition is precarious; considering the implementation of a plan of extensive, tough cuts through all levels of the company to reduce costs and overhead; determining whether the company can withstand a Chapter 11 filing; and determining whether to continue operations or liquidate. The company must candidly identify its problems and its core business and answer the question of whether it can become profitable. Next, it must develop a credible business plan for the future and project as accurately as possible the cash flows of the company. The cash flows from the future business plan may dictate whether to reorganize or liquidate and the amount of debt that the company can service. The nature of the proposed reorganized balance sheet will suggest what negotiations need to be conducted with which constituencies and in what order. For example, some creditors may find their rights completely unaffected while at the other end of the spectrum, some equity holders or creditors may find that they will receive little or nothing from the reorganized company. Other creditors will be somewhere in between. Obviously, creditors whose claims are unaffected can be counted upon to support any reorganization while equity holders and creditors who receive nothing can be expected to oppose any reorganization.

Receivership

Receiverships are legal proceedings authorized by state law, as compared to federal bankruptcy law, and involve the appointment by a state court of an individual to serve as a receiver to replace management and manage the assets of a company. In certain circumstances, receivers may be appointed prior to a creditor obtaining a judgment, but are more likely to be appointed by a court once a creditor has obtained a judgment and is seeking to have that judgment satisfied. While receivers have the authority to continue to operate the distressed business, a receiver will normally proceed to sell or liquidate the assets of the business, and use those proceeds to pay secured and other creditors. The Minnesota receivership statute is a very flexible statute that allows the creditors and the court substantial latitude in determining how the receivership conducts operations and navigates through the receivership proceeding. However, one of the disadvantages of a receivership proceeding in Minnesota is that a receiver does not have the authority to commence and pursue "preference" claims against parties paid prior to the commencement of the proceeding, the proceeds of which would be available for creditors in a federal bankruptcy proceeding. Statutory receiverships are not typically used as a means to recover assets for unsecured or judgment creditors in Minnesota.

Chapter 7 Bankruptcy

Chapter 7 refers to that chapter of the Bankruptcy Code entitled "Liquidation." A company can end up in a Chapter 7 bankruptcy proceeding either by filing a voluntary

Chapter 7 bankruptcy petition, by being the subject of an involuntary Chapter 7 bankruptcy proceeding commenced by its creditors, or by converting, either voluntarily or involuntarily, from a Chapter 11 bankruptcy proceeding to a Chapter 7 bankruptcy proceeding. When a Chapter 7 bankruptcy proceeding is filed, a trustee is appointed by the bankruptcy court, and all operations of the company cease. A Chapter 7 trustee's role is to liquidate and turn into cash all assets and claims of the company and then to distribute those proceeds to creditors of the company pursuant to a priority scheme established by the Bankruptcy Code. Secured creditors usually recover their collateral or substantially all of the proceeds of their collateral upon a liquidation. Unencumbered property, the value of collateral in excess of a secured creditor's claim, and the proceeds of certain avoidance claims pursued by the trustee generally represent the assets available to pay for the operation of the bankruptcy estate and to distribute to the unsecured creditors. It often takes one to two years or longer to complete a Chapter 7 bankruptcy proceeding. While it is possible for unsecured creditors to be paid in full in a Chapter 7 bankruptcy proceeding, it is certainly the exception for this to happen. Unsecured creditors typically recover a small percentage of their total claim in a Chapter 7 proceeding. Shareholders are only entitled to be paid in a Chapter 7 proceeding once unsecured creditors are paid in full. Therefore, shareholders usually recover nothing.

Chapter 11 Bankruptcy

Chapter 11 refers to that chapter of the Bankruptcy Code entitled "Reorganization." While Chapter 11 does not suddenly cure financial problems, it does provide a formal procedure for reorganizing a company, partnership or individual and for dealing with its creditors in an organized fashion. After a Chapter 11 is filed, most creditors are held at bay for a period of time to give the debtor "breathing room" to formulate a reorganization plan. For the uninitiated, the 12 to 18 month or longer period that companies are generally in a contested reorganization can be analogized to an Antarctic expedition: unfamiliar territory; difficult and strenuous conditions; and what appears to be the whole world against you. Chapter 11 has, however, provided many companies their last opportunity to reorganize and has produced many success stories.

Selected Bankruptcy Topics

Involuntary Bankruptcy Proceeding

Most companies in bankruptcy choose to file bankruptcy voluntarily. However, an involuntary bankruptcy proceeding may be filed by three or more holders of claims against a company, unless there are fewer than twelve such holders, in which case one creditor can commence an involuntary proceeding. The aggregate amount of the debt required under the bankruptcy laws to be held by the petitioning creditors changes periodically, but is less than \$20,000. An involuntary bankruptcy petition is a creditor's tool to collect on claims against the debtor when standard collection remedies are inadequate. It may be particularly advantageous for creditors to put a company into an involuntary bankruptcy proceeding when the company is preferring certain unsecured

creditors, the company is engaging in fraud and improper disposition of assets, the debtor's management is not responding to financial problems or when another creditor may have levied upon the assets of the company to satisfy its claim, all of which precludes an equal distribution of the company's assets to other creditors. After a bankruptcy court enters an order for relief that the involuntary proceeding was proper, then the company will either proceed under the Chapter 11 scenario, or it will be liquidated under a Chapter 7 proceeding.

Debtor-in-Possession

Upon filing a Chapter 11, the debtor becomes a debtor-in-possession ("DIP"), and remains in that role unless the case is converted to a Chapter 7 liquidation, or unless a trustee is appointed to manage the company. As a DIP, the principals can continue to operate the business through the reorganization period, subject however, to certain statutory requirements. Management is expected to act in a fiduciary capacity not just for the members or shareholders during this period, but also for the creditors and other parties in interest to the bankruptcy estate. Failure to act properly jeopardizes the debtor's chances of reorganizing, could cause present management to be ousted, and could result in the court invoking its powers against the offending parties.

Automatic Stay

Upon filing Chapter 11, an automatic stay is imposed that stops most actions, harassment and legal proceedings against the company that would be otherwise permissible outside of bankruptcy. Although the automatic stay stops actions against the company, courts have differing opinions as to whether the automatic stay should be extended to principals, guarantors, parties holding letters of credit and other non-debtors. The extent of the automatic stay depends upon the particular judge assigned to the case and the specific facts and circumstances of the proposed extension. An important exception to the automatic stay is the requirement that the business continue to operate in accordance with applicable state law. Accordingly, governmental entities may proceed with criminal investigations and prosecutions, and continue to enforce their police and regulatory powers.

The automatic stay can be terminated, modified or conditioned upon the proper request of an interested party – usually a secured creditor. Out of respect for apparent due process concerns, the Bankruptcy Code imposes strict time limits on relief from stay proceedings, e.g., the court must convene at least a preliminary hearing within 30 days after the date the request for relief is filed. Relief is to be granted for "cause," including the lack of "adequate protection" of an interest in property or if the property is not necessary for an effective reorganization.

Proceeds from Inventory or Collateral Cannot be Used Without Court Approval

A DIP cannot use money from the sale of inventory or collateral subject to a secured creditor's mortgage or security agreement, without court approval. The Chapter 11

debtor usually obtains authority to use the “cash collateral” in the ordinary course of business, either by voluntary agreement with the secured creditor or by order of the court. The DIP will usually be required to maintain assets at certain levels, and to limit the use of cash collateral to some degree. Without court approval and adequate protection of the secured creditor, however, proceeds of collateral cannot be used.

Transactions Must Generally be in the Ordinary Course of Business

Running a business in Chapter 11 is complicated because court approval (following appropriate notice to interested parties) is needed before certain management decisions, previously made and executed on a short fuse by management, may be implemented. The approval process may take days, weeks or even months, depending upon the proposed action and the level of opposition. As a general proposition, a DIP may use its property, manage its assets in the ordinary course of business, and incur credit in the ordinary course of business, free from court supervision. As a rule of thumb, any agreements, arrangements, or other contracts or transactions should always be discussed with bankruptcy counsel to determine whether they are in the ordinary course of business and can be entered into without court approval. Completing a transaction without court approval will void the transaction and may cause appointment of a trustee if the transaction required approval. A good faith mistake is no defense. In the absence of fraud, however, court approval protects the directors from any liability for the decision.

Preferential Transfers

Payments on old debt to unsecured creditors made within 90 days of the bankruptcy filing can generally be recovered by the debtor after filing Chapter 11, if the payments were not made according to ordinary business terms or if the creditor did not provide credit exceeding the amount of payment after the payment was made. To the extent that a secured creditor is undersecured (i.e., the value of its collateral is less than the amount of debt owed), payments to the creditor within the 90-day preference period may also be recovered, if the payments allow the secured creditor to improve its position over other creditors during that period. The preference period is expanded to one year with respect to payments or transfers by the debtor to its insiders (generally, those in a control position, affiliated entities or relatives). The recoveries are not automatic but require a lawsuit with all attendant costs and delays.

Fraudulent Transfers

Transfers made with actual intent to hinder, delay or defraud creditors within one year prior to a bankruptcy filing are, as one would expect, voidable in bankruptcy. In addition, transfers by the debtor for less than fair value made within such one-year period are voidable if made while the debtor was insolvent or had unreasonably small capital to continue its business, or at a time when the debtor believed it could not repay its debts. While this may sound extremely broad, the Bankruptcy Code protects transferees in these circumstances if they act in good faith and give reasonable value to

the debtor in return for the transfer. If a fraudulent transfer occurred outside the one-year period prior to filing, that transfer may still be set-aside under applicable state law.

Contract or Lease Terminations

Chapter 11 provides a debtor with some breathing room to determine whether to cure obligations such as defaulted leases, contracts, franchise agreements, and license agreements, or to allow those agreements to remain in default or expire. Alternatively, where the leases or agreements have been terminated prior to the Chapter 11 filing, or where the other party to a contract has issued prior and proper notice that the contract terminates of its own accord at some specific point in time, the company may lose its rights to maintain those leases or contracts. A Chapter 11 filing should occur before non-remedial termination actions occur if the company wants to maintain the lease or contract. The filing protects only the contracts of the entity in bankruptcy, not subsidiaries or affiliates not in bankruptcy.

Intellectual Property Licenses in Bankruptcy

General

Contractual rights to intellectual property are very important to companies in the biotechnology industry. The filing of a bankruptcy case by or against a licensor or licensee has the potential of depriving the counterparty to the license agreement of contractual rights, leaving it with perhaps nothing more than a general unsecured claim for breach of contract. As a general proposition, a debtor or trustee in bankruptcy has the right to assume or reject executory (partially performed) contracts such as license agreements.⁶⁷⁶ The consequence of a debtor's (or trustee's), decision with respect to a license agreement can have significant consequences on the counterparty to the agreement.

Debtor as "Licensor"

A number of courts have historically held that a debtor's (or trustee's) rejection of an intellectual property license agreement has the effect of nullifying the licensee's right to continued use of the licensed property. The rejection, which relieved the debtor of both its ongoing affirmative performance obligations and its passive obligation to permit the continued exploitation of the licensed property rights, often had devastating consequences to licensees that devoted substantial resources in reliance upon the rights granted under the agreement.⁶⁷⁷ The Bankruptcy Code was amended in 1988 in an attempt to safeguard the interests of licensees of "intellectual property"⁶⁷⁸ and ensure that a licensee receives the benefit of its bargain.

A licensee has two choices when the bankrupt licensor elects to reject the license agreement. The licensee can elect to treat the contract as terminated and assert a general unsecured claim against the bankruptcy estate for breach of contract damages.⁶⁷⁹ Alternatively, the licensee may elect to retain its existing contract rights

including the right of exclusivity, as well as any supplementary agreement (e.g., third-party escrow arrangement).⁶⁸⁰ In the event that the licensee elects to retain its rights in the license, it will be obligated to continue making all royalty payments due under the contract and waive any right of setoff that may otherwise arise by virtue of the rejection.⁶⁸¹

One common approach for a licensee to protect its license with a faltering licensor is to require the licensor to place the intellectual property, together with all upgrades and modifications, into an escrow that may be accessed by the licensee under enumerated circumstances. These technology escrow agreements, subject to certain constraints, are generally enforceable in bankruptcy. A frequent pitfall with these escrow arrangements is the failure by the licensee to properly monitor the details of the arrangement to ensure that the escrowed materials have been updated. Upon the occurrence of an insolvency event, a licensee frequently discovers that the escrow contains outdated or incomplete information. This obviously presents significant challenges for a licensee whose business is dependent upon the intellectual property that was originally thought to be securely placed into escrow.

From the licensor's perspective, care should be taken to ensure that any escrow agreement is narrowly tailored to allow access to the escrowed materials only if the licensor ceases business operations or fails to support its products for a specified time. Likewise, caution is suggested with respect to waivers and other contractual provisions that a licensee attempts to bargain for as part of the arrangement that are directed at vitiating the protections afforded debtors in bankruptcy.

Debtor as "Licensee"

While the bankruptcy laws now provide special protections for "licensees" when a licensor is subject to a bankruptcy proceeding, there is no unique statutory protection for licensors when a licensee enters into bankruptcy. When the debtor-licensee is in bankruptcy and desires to "reject" the license agreement and stop performing, the same rules apply as to any other contract. It's often a matter of unilateral business judgment and discretion. One of the challenges for a licensor in the event of a licensee's or trustee's rejection of the license is to ensure that all tangible materials and proprietary information that has been delivered to the debtor-licensee or developed in connection with the agreement remain confidential and are not transferred to a third party in an asset sale or otherwise.

A licensee in financial distress that desires to "assume" (*i.e.*, retain) the benefits and accept all of the burdens of an intellectual property license agreement has significant issues that should be considered in advance of a bankruptcy filing. There is a substantial body of law that stands for the proposition that a licensee-debtor is precluded from assuming its obligations under a license agreement in a bankruptcy proceeding over the objection of the licensor.⁶⁸² The fact that there is no existing default under the license agreement and the licensor may be receiving the full benefit of its bargain is of no consequence in jurisdictions that have elected to follow this view. It is critical that a licensee in financial trouble solidifies its relationship with its licensor, or at the very least understands the probable motivations of its licensor, before entering into bankruptcy.

Bankruptcy Clauses

It is typical to include provisions in contracts and license agreements that specifically purport to address insolvency and bankruptcy. Notwithstanding, the bankruptcy laws expressly invalidate a large number of these clauses. For instance, clauses in a license agreement providing for a right of termination or modification based upon the debtor's insolvency, financial condition or bankruptcy filing, are inoperative in a bankruptcy case.⁶⁸³ Similarly, clauses that condition continued rights under a license agreement upon the satisfaction of certain penalties are unenforceable in bankruptcy.⁶⁸⁴ The bankruptcy laws disfavor forfeitures and contractual provisions that operate to impair a debtor's ability to receive the full benefit of a contract.

Assignments

Many contracts, including license agreements, contain express provisions prohibiting, restricting or placing conditions on assignments to third parties. The bankruptcy laws invalidate these anti-assignment clauses in most agreements in order to permit the debtor's estate to reap the economic value of the asset (*i.e.*, contract) through its transfer to a third party.⁶⁸⁵ There are, however, special rules with respect to contracts that are not assignable under applicable nonbankruptcy law. For instance, federal law precludes the transferability of patent and copyright licenses absent the consent of the licensor.⁶⁸⁶ The bankruptcy laws recognized the applicability of other law and accordingly do not allow a debtor or trustee to assign these licenses over the objection of the licensor.⁶⁸⁷ While there is no federal law prohibiting transfer of trade secret licenses, these licenses should likewise be considered ordinarily non-assignable.⁶⁸⁸ A trickier question is whether the policy against transferability applies to cases where no transfer of the contract is contemplated, but there is a change in ownership of the licensee company. At least one court has decided that a change in ownership of a business does not constitute an impermissible assignment of the contract that is precluded in bankruptcy.⁶⁸⁹ The law is not yet fully developed in this area and may be affected by balancing the express terms of the operative agreement with the bankruptcy policy of maximizing creditor recovery. As such, a licensor may be well advised to consider expressly defining a prohibited assignment under the agreement to include "change of control."

NOTES

- ¹ WEBSTER'S II NEW COLLEGE DICTIONARY 419 (Houghton Mifflin Company 2001).
- ² GRETCHEN MORGENSON & CAMPBELL R. HARVEY, PH.D., THE NEW YORK TIMES DICTIONARY OF MONEY AND INVESTING (Henry Holt & Co. 2002).
- ³ Frank DiLorenzo, Survey, *Biotechnology* (Standard & Poor's, Dec. 23, 2004).
- ⁴ Tufts Center for the Study of Drug Development, *Post-Approval R&D Raises Total Drug Development Costs to \$897 Million*, 5 IMPACT REPORT (May/June 2003).
- ⁵ *Id.* at 18.
- ⁶ DiLorenzo, *supra* note 3, at 14.
- ⁷ Bt corn is a corn variety genetically modified to express the insecticidal protein that occurs naturally in *Bacillus thuringiensis* (Bt). University of Minnesota Extension Services, *Bt Corn & European Corn Borer* (2002), at <http://www.extension.umn.edu/distribution/cropsystems/DC7055.html>.
- ⁸ The specific characteristics of each structure may vary from state to state. The following charts reference Minnesota law.
- ⁹ MINN. STAT. § 333.01 (2004).
- ¹⁰ *Id.* § 323A.0101.
- ¹¹ *See id.* § 333.01.
- ¹² *Id.* § 323A.0306.
- ¹³ *Id.* § 323A.0401.
- ¹⁴ MINN. STAT. § 323A.0502 (2004).
- ¹⁵ *Id.* § 323A.0503.
- ¹⁶ *See id.*
- ¹⁷ *Id.* § 323A.0302.
- ¹⁸ *See id.*
- ¹⁹ MINN. STAT. § 323A.0905 (2004).
- ²⁰ *See id.*
- ²¹ *Id.* § 323A.0907.
- ²² *Id.* § 321.0201 (West Supp. 2005).
- ²³ *Id.* § 321.0108.
- ²⁴ MINN. STAT. § 321.0210. (2004)
- ²⁵ *Id.* § 321.0404.
- ²⁶ *Id.* § 321.0302.
- ²⁷ MINN. STAT. § 321.0303 (West Supp. 2005). Prior to January 1, 2005, if a limited partner participated in the management or control of the business, the limited partner could have lost its limited liability protection.
- ²⁸ *Id.* § 321.0406.
- ²⁹ *Id.* § 321.0503.
- ³⁰ *Id.* §§ 321.0102, 321.0701.
- ³¹ *Id.* § 321.0702.
- ³² *See* MINN. STAT. §§ 321.0702, 321.0301 (West Supp. 2005).

³³ *Id.* § 321.0607.
³⁴ *Id.* § 321.0406.
³⁵ *Id.* §§ 321.1106, 321.1107.
³⁶ *Id.* § 321.1108.
³⁷ *Id.* MINN. STAT. § 323A.1001 (2004).
³⁸ *Id.* § 323A.1002.
³⁹ *Id.* § 323A.1003.
⁴⁰ *Id.* § 323A.0306.
⁴¹ *Id.* § 322B.115.
⁴² MINN. STAT. § 322B.12 (2004).
⁴³ *Id.* § 322B.960.
⁴⁴ *Id.* § 322B.303.
⁴⁵ *Id.* § 322B.67.
⁴⁶ *Id.* § 322B.03, subd. 31.
⁴⁷ MINN. STAT. § 322B.31 (2004).
⁴⁸ *Id.*
⁴⁹ *Id.* § 322B.313.
⁵⁰ *Id.* § 322B.77.
⁵¹ *Id.* § 322B.70.
⁵² MINN. STAT. § 322B.72 (2004).
⁵³ *Id.* § 322B.73.
⁵⁴ *Id.* § 302A.111.
⁵⁵ *Id.* § 302A.115.
⁵⁶ *Id.* § 302A.425.
⁵⁷ 9 DUNNELL MINNESOTA DIGEST CORPORATIONS § 15.11 (5th ed. 2003).
⁵⁸ MINN. STAT. §§ 302A.551, 302A.557 (2004).
⁵⁹ *Id.* § 302A.201.
⁶⁰ *Id.* § 302A.301.
⁶¹ I.R.C. § 11 (2004).
⁶² *Id.* § 61.
⁶³ MINN. STAT. § 302A.661 (2004).
⁶⁴ I.R.C. § 1001 (2004).
⁶⁵ *Id.* § 331.
⁶⁶ MINN. STAT. § 302A.601 (2004).
⁶⁷ *Id.* § 302A.613.
⁶⁸ *Id.* § 302A.615.
⁶⁹ I.R.C. § 1361(b) (2004).
⁷⁰ *Id.* § 1362(b).
⁷¹ *Id.* § 1366.
⁷² *Id.*
⁷³ Securities Act of 1933 § 2(a)(1), 15 U.S.C. § 77b(a)(1) (2004).
⁷⁴ 17 C.F.R. § 230.504 (2005).
⁷⁵ *Id.* § 230.505.
⁷⁶ *Id.* § 230.506.

- ⁷⁷ *Id.* § 230.506(b)(2)(ii), provides:
Each purchaser who is not an accredited investor either along or with his purchaser representative(s) has such knowledge and experience in financial and business matters that he is capable of evaluating the merits and risks of the prospective investment, or the issuer reasonably believes immediately prior to making any sale that such purchaser comes within this description.
- ⁷⁸ 17 C.F.R. § 230.501(a) (2005).
- ⁷⁹ *Id.* § 230.701.
- ⁸⁰ Securities Act of 1933 § 3(a)(11), 15 U.S.C. § 77c(a)(11); 17 C.F.R. § 230.147.
- ⁸¹ Consider, for example, that unlike most states, the State of New York generally does not register or regulate securities, rather it regulates the persons (or entities) that sell the securities. Accordingly, prior to any offering of securities in New York, the issuer will be required to register itself with the State of New York.
- ⁸² MINN. STAT. § 80A.15, subd. 2(a)(1) (West Supp. 2005).
- ⁸³ Securities Act of 1933 § 262, 15 U.S.C.A. § 230.262 (2004).
- ⁸⁴ AMERICAN HERITAGE DICTIONARY OF THE ENGLISH LANGUAGE (4th ed. Houghton Mifflin Co.).
- ⁸⁵ Center for Venture Research, University of New Hampshire, 2004, at <https://paulcollege.unh.edu/cvr>.
- ⁸⁶ GREGORY C. SMITH, *START-UP & EMERGING COMPANIES: PLANNING, OPERATING AND FINANCING THE SUCCESSFUL BUSINESS* (Law Journal Press 1997).
- ⁸⁷ In the case of a start-up, this section may be of little value given the lack of historic financial statements. In this case, a section titled “Management’s Plan of Operations” is more appropriate to disclose the company’s plans for the next six to nine months.
- ⁸⁸ I.R.S. Notice 2005-43, 2005-26 I.R.B. 1376.
- ⁸⁹ BRYAN BERGERON & PAUL CHAN, *BIOTECH INDUSTRY: A GLOBAL, ECONOMIC, AND FINANCING OVERVIEW* 87, 98 (2004).
- ⁹⁰ *Id.*
- ⁹¹ *Id.* at 211.
- ⁹² *Heard on the Street*, WALL STREET JOURNAL, Aug. 22, 2003.
- ⁹³ MINN. STAT. § 302A.671 (West Supp. 2005).
- ⁹⁴ *Id.* § 302A.673.
- ⁹⁵ See 12 C.F.R. § 230.135 (2005); see also Securities Act Release No. 33-5009 (Oct. 7, 1969).
- ⁹⁶ The SEC recently proposed amendments to the pre-offering communication procedure that generally liberalizes communications for large companies known as “well-known seasoned issuers. “These are already public firms that have a market capitalization of greater than \$700 million. The proposed rules would offer non-reporting companies, including those filing an IPO, some new leeway in written communications prior to the effectiveness of a registration statement as long as the written communication is contemporaneously filed with the SEC and a preliminary prospectus accompanies the written communication. Securities Act Release 33-8501 (Nov. 3, 2004).
- ⁹⁷ Form S-1 is the SEC Form used by most issuers in connection with an IPO. Form S-1 requires the issuer to disclose information about a number of matters including: its business, properties, legal proceedings, market for its common stock, financial statements, directors and officers, executive compensation, security ownership, related-party transactions, and the issuer’s securities.
- ⁹⁸ The SEC comment letter is generally mailed and faxed to the issuer. The issuer’s correspondence to the SEC is transmitted electronically through the SEC’s EDGAR (Electronic Data Gathering and Retrieval) System and does not become publicly available until after the offering. The registration statement and amendments to the registration statement are also filed electronically but become publicly available on the SEC’s website (<http://www.sec.gov/answers/edgarletters.htm>) immediately upon filing.
- ⁹⁹ See LOUIS LOSS ET AL., *FUNDAMENTALS OF SECURITIES REGULATION* 66 (4th ed. 2001).

- ¹⁰⁰ *Id.* at 99; CHARLES J. JOHNSON, JR. & JOSEPH MCLAUGHLIN, CORPORATE FINANCE AND SECURITIES LAW 191-95 (3d ed. 2004).
- ¹⁰¹ See, e.g., National Association of Securities Dealers, Rules of the Association: Marketplace Rules (4000-7000), available at http://finra.complinet.com/en/display/display_main.html?rbid=2403&element_id=3771 (last visited June 4, 2005).
- ¹⁰² JOHNSON & MCLAUGHLIN, *supra* note 100, at 106.
- ¹⁰³ “Accelerated filers” must file their 10-K within 60 days while non-accelerated filers have 90 days. An accelerated filer is a company in which the aggregate market value of non-voting common equity held by non-affiliates is \$75 million or more. 17 C.F.R. § 240.12b-2 (2005). Affiliate is defined to mean, “a person that directly or indirectly through one or more intermediaries, controls, or is controlled by, or is under common control with, the person specified.” *Id.* Affiliates are generally officers, directors and controlling or significant shareholders.
- ¹⁰⁴ The registration statement forms and Forms 10-K and 10-KSB are frequently amended by the SEC and do not appear in the Code of Federal Regulations. Copies of these forms are available on a number of websites, including <http://www.merrilldirect.com>.
- ¹⁰⁵ Forms 10-Q and 10-QSB are frequently amended by the SEC and do not appear in the Code of Federal Regulations.
- ¹⁰⁶ For a detailed description of Form 8-K, see Securities Act Release 33-8400 (March 16, 2004).
- ¹⁰⁷ For a detailed discussion of Management’s Discussion and Analysis, see Commission Statement about Management’s Discussion and Analysis of Financial Condition and Results of Operations, SEC Release Nos. 33-8056, 34-45321 (Jan. 22, 2002) (*available at* <http://www.sec.gov/rules/other/33-8056.htm>) and Disclosure in Management’s Discussion and Analysis about Off-Balance Sheet Arrangements and Aggregate Contractual Obligations, SEC Release Nos. 33-8182, 34-47264, 68 Fed. Reg. 5982 (Jan. 28, 2003) (*available at* <http://www.sec.gov/rules/final/33-8182.htm>). *See also* JOHNSON & MCLAUGHLIN, *supra* note 100, at 150-64.
- ¹⁰⁸ *See Management’s Discussion and Analysis of Financial Condition and Results of Operations; Certain Investment Company Disclosures*, Securities Act Release No. 6835 (May 18, 1989) n. 14 and accompanying text.
- ¹⁰⁹ 17 C.F.R. § 229.601 (2005).
- ¹¹⁰ 15 U.S.C. ch. 2B, § 78m (2004).
- ¹¹¹ Pub. L. No. 107-204, 116 Stat. 745 (2002).
- ¹¹² 17 C.F.R. § 240.13a-14 (2005).
- ¹¹³ Section 906 has been codified as 18 U.S.C. § 1380.
- ¹¹⁴ Pub. L. No. 107-204, § 404.
- ¹¹⁵ 17 C.F.R. § 240.13a-15 (2005).
- ¹¹⁶ 17 C.F.R. § 240.13a-15. *See* Securities Act Release No. 33-8238 (June 5, 2003).
- ¹¹⁷ Pub. L. 107-204 § 401(a) (codified at 15 U.S.C. ch. 2B § 78m (2004)).
- ¹¹⁸ 17 C.F.R. § 244 (2005).
- ¹¹⁹ New York Stock Exchange, NYSE Rules 202.01 (2005), available at <http://nyserules.nyse.com/NYSE/Rules/>.
- ¹²⁰ 17 CFR § 230.144 (2005).
- ¹²¹ MINN. STAT. § 334.022 (West Supp. 2005); *Bichel Optical Labs. v. Marquette Nat’l Bank*, 336 F. Supp. 1368 (D. Minn. 1971).
- ¹²² MINN. STAT. §§ 47.59, 334.022.
- ¹²³ 31 U.S.C. §§ 5311-5330 (2002).
- ¹²⁴ Uniting and Strengthening America by Providing Appropriate Tools Required to Intercept and Obstruct Terrorism Act of 2001 (USA PATRIOT Act), Pub. L. No. 107-56, 115 Stat. 272, tit. III (2001) (International Money Laundering Abatement and Anti-Terrorist Financing Act of 2001).
- ¹²⁵ *See* OFFICE OF FOREIGN ASSET CONTROL, REGULATIONS BY INDUSTRY, *at* <http://www.treas.gov/offices/enforcement/ofac/regulations/> (last visited May 26, 2005).
- ¹²⁶ *See* U.C.C. §§ 9-308 to 9-316 (2003).

- ¹²⁷ See 12 CFR §§ 226.15 (open-end credit), 226.23 (close-end credit) (2005).
- ¹²⁸ MORGENSON & HARVEY, *supra* note 2.
- ¹²⁹ Charles A. Schaffer, *Joint Ventures and the Entrepreneurial Small Firm: A Cautionary Note*, 1 MINN. J. BUS. LAW & ENTREPRENEURSHIP (No. 2 2002).
- ¹³⁰ Tufts Center for the Study of Drug Development, *Outlook 2005* (2005), at <http://csdd.tufts.edu/InfoServices/OutlookPDFs/Outlook2005.pdf>; Tufts Center for the Study of Drug Development, *Outlook 2004* (2004), at <http://csdd.tufts.edu/InfoServices/OutlookPDFs/Outlook2004.pdf>.
- ¹³¹ Tyzoon Tyebjee & Jill Hardin, *Biotech-pharma alliances: Strategies, Structures and Financing*, 10 J. COMM. BIOTECHNOLOGY 329-39 (June 2004).
- ¹³² Thomas F. Villeneuve & David M. Kaufman, *Creating Successful Technology-Based Corporate Partnering Agreements*, PRACTICING LAW INSTITUTE (July-Aug. 2002).
- ¹³³ *Id.*
- ¹³⁴ *Id.*
- ¹³⁵ *Id.*
- ¹³⁶ MINN. STAT. § 302A.251, subd. 5 (West Supp. 2005) (acknowledging that corporate interests may best be served by “the continued independence of the corporation”).
- ¹³⁷ I.R.C. section 368 describes seven types of corporate reorganizations. I.R.C. § 368(a)(1)(A)-(G) (2005). The three major types of reorganization described by the Code are: (1) a statutory merger or consolidation provided for by state law; (2) an acquisitive stock reorganization, where the purchasing corporation acquires controlling interest in the target corporation stock in exchange for voting stock of the purchasing corporation; and (3) an acquisitive asset reorganization, where the purchasing corporation receives a transfer of all or substantially all of the assets of the target corporation in exchange for purchasing corporation stock. *Id.* § 368(a)(1)(A)-(C).
- ¹³⁸ 42 U.S.C. §§ 1301A-7b (2005) (Civil Money Penalty Act, containing anti-kickback provision); 42 U.S.C. § 1395nn (2005) (Stark law); MINN. STAT. § 256B.064 (West Supp. 2005) (state anti-kickback and civil false claims statute); *Id.* § 609.465 (criminal false claims statute).
- ¹³⁹ See generally United States Small Business Administration, Office of Technology, at <http://www.sbir.gov>.
- ¹⁴⁰ The Bayh-Dole Act of 1980 and the related Executive Order number 12591 (April 10, 1987) provide incentives for the practical application of research supported through federal funding agreements. See Pub. L. No. 96-517, 94 Stat. 3015 (1980). To be able to retain rights and title to inventions made with federal funds, so-called “subject” inventions, the grantee must comply with a series of regulations that ensure the timely transfer of the technology to the private sector, while protecting limited rights of the federal government. The regulations apply to any subject invention—defined as any invention either conceived or first actually reduced to practice in the performance of work under the federal award—and to all types of recipients of federal funding, including SBIR/STTR awards.
- ¹⁴¹ See, e.g., NATIONAL INSTITUTES OF HEALTH, GRANTS POLICY STATEMENT (Dec. 2003), available at <http://grants.nih.gov/grants/policy/policy.htm> (last visited June 4, 2005).
- ¹⁴² Pub. L. No. 97-219, 96 Stat. 217 (1982).
- ¹⁴³ The Small Business Research and Development Enhancement Act, Pub. L. No. 102-564, 106 Stat. 4249 (1992).
- ¹⁴⁴ The Small Business Reauthorization Act of 2000, Pub. L. No. 106-554, 114 Stat. 2763 (2000).
- ¹⁴⁵ The Small Business Research and Development Enhancement Act, tit. II.
- ¹⁴⁶ The Small Business Reauthorization Act of 1997, Pub. L. No. 105-135, 111 Stat. 2592 (1997).
- ¹⁴⁷ The Small Business Technology Transfer Program Reauthorization Act of 2001, Pub. L. No. 107-50, 115 Stat. 263 (2001).
- ¹⁴⁸ See 13 C.F.R § 121.702 (2004).
- ¹⁴⁹ This includes sole proprietorships, partnerships, limited liability companies, corporations, joint ventures, associations, trusts and cooperatives.

- ¹⁵⁰ Upon request, the Office of Government Contracting makes formal “size determinations” as to whether a business qualifies as an eligible small business for SBA programs. SMALL BUSINESS ADMINISTRATION, OFFICE OF GOVERNMENT CONTRACTING, OFFICE OF SIZE STANDARDS, *at* <https://www.sba.gov/content/what-are-small-business-size-standards>.
- ¹⁵¹ NATIONAL INSTITUTES OF HEALTH, THE SBIR AND STTR PROGRAMS AT THE NATIONAL INSTITUTES OF HEALTH: GENERAL INFORMATION AND NUANCES, *at* http://www.grants.nih.gov/grants/funding/nih_sbir_sttr_overview.ppt (PowerPoint) (last visited June 4, 2005).
- ¹⁵² *See* SBIR-STTR Agency Solicitations, *at* <http://www.sba.gov/sbir/indexprograms2.html>. Supplemental resources are also available for applicants. & “a” “SBIR/STTR at <http://www.sbir.gov>; SBIR Gateway, <http://www.zyn.com/sbir/>; Small Business Technology Coalition, *at* <http://www.sbtcc.org/>; ASSEts *at* <http://www.inknowvation.com>.
- ¹⁵³ Regulations pertaining to food, drugs, and medical devices are found in the Title 21 of the Code of Federal Regulations (Food and Drugs).
- ¹⁵⁴ *See, e.g.*, 21 C.F.R. § 201 (2004).
- ¹⁵⁵ *Id.* §§ 101.1-101.108.
- ¹⁵⁶ *Id.* §§ 201.1-201.311.
- ¹⁵⁷ *Id.* § 314.
- ¹⁵⁸ *Id.*
- ¹⁵⁹ 21 C.F.R. § 312 (2004).
- ¹⁶⁰ *Id.*
- ¹⁶¹ *Id.* § 312.21.
- ¹⁶² *Id.* § 312.21(a).
- ¹⁶³ *Id.* § 312.21(b).
- ¹⁶⁴ 21 C.F.R. § 312.21(c) (2004).
- ¹⁶⁵ *Id.* § 312.85.
- ¹⁶⁶ *Id.* §§ 601.2-601.90.
- ¹⁶⁷ *Id.* §§ 314.92-314.99.
- ¹⁶⁸ *Id.* § 860.
- ¹⁶⁹ 21 C.F.R. § 814 (2004).
- ¹⁷⁰ *Id.*
- ¹⁷¹ *Id.* §§ 807.81-807.100.
- ¹⁷² *Id.* § 812.
- ¹⁷³ *Id.*
- ¹⁷⁴ 21 C.F.R. § 803 (2004).
- ¹⁷⁵ U.S. Constitution, Article I, Section 8, Clause 8 provides that: “The Congress shall have the power . . . To promote the progress of science and the useful arts, by securing for limited times to authors and inventors exclusive right to their respective writings and discoveries.”
- ¹⁷⁶ The statutory patent system is set forth in the U.S. Patent Act, 35 U.S.C. section 101. Copyrights are governed by the Copyright Act of 1976, as amended, 17 U.S.C. section 101. Some states have “inventor” statutes to protect employees from unknowingly surrendering to their employer ownership rights to personal inventions. *See, e.g.*, MINN. STAT. § 181.78 (2004).
- ¹⁷⁷ The federal trademark statute is the Trademark Act of 1946 (commonly referred to as “the Lanham Act”), as amended, 15 U.S.C. section 1051, and arises under the commerce clause, U.S. Constitution, Article I, Section 8, clause 3. All 50 states have adopted trademark registration statutes. Trademark rights also may be acquired and protected in the United States as a matter of common law.

¹⁷⁸ Thirty-eight states, including Minnesota, have adopted the Uniform Trade Secrets Act, although some have modified the statute with language that may be significant in individual cases.

¹⁷⁹ See the discussion *infra* of the Wyeth Laboratories secret process for manufacturing PREMARIN®.

¹⁸⁰ A well-known example is NUTRASWEET® artificial sweetener, which remains a vital brand name nearly a decade after the patent in the chemical formulation went into the public domain.

¹⁸¹ 35 U.S.C. § 101 (2004).

¹⁸² *Id.* § 161.

¹⁸³ *Id.* § 171.

¹⁸⁴ *Id.* § 154.

¹⁸⁵ *Id.* § 154(c)(1).

¹⁸⁶ 35 U.S.C. § 171 (2005).

¹⁸⁷ *Id.* § 101.

¹⁸⁸ *Id.* § 102.

¹⁸⁹ *Id.*

¹⁹⁰ *Id.* § 101.

¹⁹¹ 35 U.S.C. § 112 (2004).

¹⁹² *Id.*

¹⁹³ 35 U.S.C. § 102(b).

¹⁹⁴ 35 U.S.C. § 103.

¹⁹⁵ Schering Corp. v. Geneva Pharm., Inc., 339 F.3d 1373, 1379 (Fed. Cir. 2003) (quoting Eli Lilly & Co. v. Barr Labs., Inc., 251 F.3d 955, 970 (Fed. Cir. 2001)).

¹⁹⁶ *Id.* at 1378.

¹⁹⁷ HERBERT F. SCHWARTZ, PATENT LAW AND PRACTICE § 4.I.C, at 68-69 (4th ed. 2003).

¹⁹⁸ 1 DONALD S. CHISUM, CHISUM ON PATENTS § 3.03, at 67 (2003).

¹⁹⁹ *Id.*

²⁰⁰ 102 U.S. 707 (1881).

²⁰¹ 339 F.3d at 1376.

²⁰² *Id.* at 1375.

²⁰³ The Federal Court has exclusive jurisdiction over patent appeals.

²⁰⁴ Schering Corp. 339 F.3d at 1378-79.

²⁰⁵ *Id.* at 1377.

²⁰⁶ *Id.* at 1378.

²⁰⁷ Anne Brown & Mark Polyakov, *The Accidental and Inherent Anticipation Doctrines: Where Do We Stand and Where Are We Going?* (March 30, 2004) (presented at the Third Advanced Forum on Biotech Patents: The Tactical and Practical Guide to Today's Most Complex Issues, Boston, MA).

²⁰⁸ Elkay Mfg. Co. v. Ebco Mfg. Co., 192 F.2d 973 (Fed. Cir. 1999).

²⁰⁹ Graver Tank & Mfg. Co. v. Linde Air Products, Co., 339 U.S. 605 (1950).

²¹⁰ 35 U.S.C. § 271 (2004).

²¹¹ 125 S.Ct. 2372 (2005).

²¹² 35 U.S.C. § 271(e)(1).

²¹³ 447 U.S. 303 (1980).

²¹⁴ Lowell v. Lewis, 15 F. Cas. 1018, 1019 (C.C. Mass 1817).

²¹⁵ Convention on the Grant of European Patents, Oct. 5, 1973, Munich, Article 52(1).

²¹⁶ WTO Agreement on Trade-Related Aspects of Intellectual Property Rights.

²¹⁷ Ex parte Harvard, Case V-6/92, 1992 O.J. E.P.O. 589 at Part 2 (Examining Div. 1992).

²¹⁸ 35 U.S.C. §§ 200-212 (2004).

²¹⁹ Pub. L. No. 103-465, 108 Stat. 4809 (1994) (codified as amended by 35 U.S.C. § 154 (West Supp. 2005)).

²²⁰ 28 U.S.C. § 1498(a).
²²¹ Patents Act of 1977, §§ 55-59.
²²² *Madey v. Duke Univ.*, 307 F.3d 1351 (Fed. Cir. 2002).
²²³ 17 U.S.C. § 102(a) (2004).
²²⁴ *Id.* § 102(b).
²²⁵ *Id.* § 302(a).
²²⁶ *Id.* § 302(c).
²²⁷ *Id.* § 411(a).
²²⁸ 17 U.S.C. § 401(a) (2004).
²²⁹ 15 U.S.C. § 1127 (2004).
²³⁰ *Id.*
²³¹ *Id.* § 1051(a)(1).
²³² *Id.* § 1072.
²³³ *Id.* § 1057(b).
²³⁴ 15 U.S.C. § 1065 (2004).
²³⁵ *Id.* § 1111.
²³⁶ *Id.* § 1124.
²³⁷ *Id.* § 1117.
²³⁸ As will be discussed in more detail *infra*, “PREMARIN®” may arguably be characterized as “suggestive.”
²³⁹ *See, e.g.*, MINN. STAT. § 325C.01 (2004).
²⁴⁰ Restatement (First) of Torts § 757, cmt. b (1939).
²⁴¹ *Id.*
²⁴² In *Mangren Research & Development Corp. v. National Chemical Co.*, 87 F.3d 937 (7th Cir. 1996), the valuable trade secret was routine use of a chemical component widely regarded in the industry as unsuited for the very application for which it was used.
²⁴³ 2003 WL 22282371, No. Civ. 98-2469 (D. Minn. Oct. 2, 2003), *aff’d* 395 F.2d 897 (8th Cir. 2005).
²⁴⁴ I.R.C. § 63 (West Supp. 2005).
²⁴⁵ *Id.* §§ 21-55.
²⁴⁶ *Id.* §§ 162, 263, 441, 446.
²⁴⁷ *Id.* §§ 471, 472.
²⁴⁸ *Id.* § 263; Treas. Reg. § 1.263A-1 (2000).
²⁴⁹ I.R.C. § 167 (West Supp. 2005).
²⁵⁰ *Id.* § 1001.
²⁵¹ *Id.* § 174(a)-(b).
²⁵² *Snow v. Commissioner*, 416 U.S. 500 (1974).
²⁵³ *Kantor v. Commissioner*, 998 F.2d 1514 (9th Cir. 1993).
²⁵⁴ Treas. Reg. § 1.174-2(a)(1) (1994).
²⁵⁵ *Id.*
²⁵⁶ *Id.*
²⁵⁷ *Id.* § 1.174-2(a)(2).
²⁵⁸ *Id.* § 1.174-2(a)(1).
²⁵⁹ Rev. Rul. 73-275, 1973-1 C.B. 134; Rev. Rul. 69-484, 1969-2 C.B. 38; Rev. Rul. 68-471, 1968-1 C.B. 109.
²⁶⁰ Treas. Reg. § 1.174-2(a)(3) (1994).
²⁶¹ *Id.* § 1.174-2(a)(6).
²⁶² *Id.*
²⁶³ *Id.* § 1.174-2(a)(8).

²⁶⁴ Rev. Rul. 85-186, 1985-2 C.B. 84.

²⁶⁵ I.R.C. § 197(a), (c) (West Supp. 2005).

²⁶⁶ *Id.* § 197(a).

²⁶⁷ *Id.* § 197(d).

²⁶⁸ Treas. Reg. § 1.167(a)-14(c)(4) (2003).

²⁶⁹ I.R.C. § 41.

²⁷⁰ *Id.* § 41(d)(1)(A).

²⁷¹ *Id.* § 41(d).

²⁷² *Id.* § 41(d)(4).

²⁷³ *Id.*

²⁷⁴ I.R.C. § 41(a)(1) (West Supp. 2005).

²⁷⁵ *Id.* § 41(c)(4)(B).

²⁷⁶ *Id.* § 41(c).

²⁷⁷ *Id.* § 41(c)(3).

²⁷⁸ I.R.C. § 41(a) (West Supp. 2005).

²⁷⁹ *Id.* § 41(c)(4). The credit is the sum of three amounts: (i) 2.65% of the portion of the taxpayer's qualified research expenses for the tax year that exceeds 1%, but does not exceed 1.5%, of the taxpayer's average annual gross receipts for the four tax years preceding the tax year for which the credit is being computed; (ii) 3.2% of the portion of the taxpayer's qualified research expenses for the taxable year that exceeds 1.5%, but does not exceed 2%, of the taxpayer's average annual gross receipts for the four prior taxable years; and (iii) 3.75% of the portion of the taxpayer's qualified research expenses for the taxable year that exceeds 2% of the taxpayer's average annual gross receipts for the four taxable years preceding the taxable year for which the credit is being computed. *Id.*

²⁸⁰ *Id.* § 41(g).

²⁸¹ *Id.* § 41(h)(1).

²⁸² I.R.C. § 45C (West Supp. 2005).

²⁸³ *Id.* § 45C(d).

²⁸⁴ *Id.* § 45C(b)(2).

²⁸⁵ *Id.* § 45C(a).

²⁸⁶ *Id.* § 45C(b)(1).

²⁸⁷ I.R.C. § 38 (West Supp. 2005).

²⁸⁸ *Id.* § 196.

²⁸⁹ *Id.* § 29(c)(3).

²⁹⁰ *Id.* § 1(h).

²⁹¹ *Id.* § 11(b).

²⁹² I.R.C. § 1212 (West Supp. 2005).

²⁹³ *Id.* § 1001; Treas. Reg. § 1.1221-1(c) (1975).

²⁹⁴ I.R.C. § 453.

²⁹⁵ *Id.* § 453A(c).

²⁹⁶ Treas. Reg. § 1.1275-4(c)(4)(i) (2004).

²⁹⁷ Rev. Rul. 64-56, 1964-1 C.B. 133.

²⁹⁸ *See, e.g.,* *Watson v. United States*, 222 F.2d 689 (10th Cir. 1955); *United States v. Carruthers*, 219 F.2d 21 (9th Cir. 1955).

²⁹⁹ *Bell Int'l Corp. v. United States*, 381 F.2d 1004 (Ct. Cl. 1967).

³⁰⁰ I.R.C. § 1235(a) (West Supp. 2005).

³⁰¹ *See Taylor v. Commissioner*, 29 T.C.M. (CCH) 1488 (1970).

³⁰² Treas. Reg. § 1.1235-2(b)(2), (3) (1980).

³⁰³ Treas. Reg. § 1.1031(a)-2(c)(1) (2005).

³⁰⁴ I.R.C. § 1001.

³⁰⁵ *Id.* § 1221(a).

³⁰⁶ *Id.* § 741.

³⁰⁷ *See, e.g.*, I.R.C. § 751 (West Supp. 2005).

³⁰⁸ *See id.* § 754.

³⁰⁹ *Id.* § 1012.

³¹⁰ *Id.* § 704(a).

³¹¹ *Id.* § 731.

³¹² Qualifying structures are generally described as “reorganizations” under section 368 (a)(1). *See* I.R.C. § 368(a)(1) (West Supp. 2005).

³¹³ *See, e.g., id.* § 351.

³¹⁴ Treas. Reg. § 1.368-1(e) (2005).

³¹⁵ I.R.C. § 354.

³¹⁶ *Id.* § 358.

³¹⁷ *See supra* Part V.B.

³¹⁸ *See generally* <http://usbiotechreg.nbii.gov/roles.asp> (discussion of U.S. agencies’ responsibility concerning bioengineered foods, presented through a joint effort of the FDA, EPA, and USDA). A more detailed discussion of the FDA examination and approval processes is found above in Section V.B.

³¹⁹ 7 C.F.R. § 340.3 (2004) (notification for the introduction of certain regulated articles).

³²⁰ For example, the term “stably integrated” is covered in the relevant regulation as a demonstrable standard, namely that, “[t]he cloned genetic material is contiguous with elements of the recipient genome and is replicated exclusively by mechanisms used by recipient genomic DNA,” but many of the terms are yet to be standardized. 7 C.F.R. § 340.1 (2004).

³²¹ 7 U.S.C. § 135 (1972).

³²² 15 U.S.C. § 2601 (1976).

³²³ See the EPA website for details on regulations and practices: <http://goo.gl/7b9m8U>

³²⁴ 15 U.S.C. § 2611 (2004).

³²⁵ The several agencies and departments that list prohibited persons, companies and countries publish their respective lists, which unfortunately are not available in one place. Please check with your legal advisors regarding the current lists, but generally at least the following website should be consulted: <http://www.cbp.gov/trade/trade-community/programs-outreach/blocked-denied-debarred>. This website provides links to the appropriate lists from the Bureau of Industry and Security the Office of Foreign Assets Control, and the Office of Defense Trade Controls.

³²⁶ Both the International Trade in Arms Regulations (ITAR) at 22 C.F.R. § 120.9(2) and the Export Administration Regulations (EAR) at 15 C.F.R. § 734.2(b)(2)(ii) (2004). A detailed discussion with questions and answers is on the Bureau of Industry and Security website <http://www.bis.doc.gov/index.php/policy-guidance/deemed-exports/deemed-exports-faqs>

³²⁷ BERGERON & CHAN, *supra* note 89, at 87, 98.

³²⁸ *Id.* at 24, 98.

³²⁹ ROBBIN SHOEMAKER ET AL., ECONOMIC ISSUES IN AGRICULTURAL BIOTECHNOLOGY 28-35 (Economic Research Service Agriculture Information Bulletin No. (AIB762), March 2001), *available at* http://www.ers.usda.gov/media/564963/aib762_1_.pdf.

³³⁰ *Id.*

³³¹ Kynda R. Curtis et al., *Consumer Acceptance of GM Food Products in the Developing World*, 7 *AGBIOFORUM* 70-75 (1&2 2004), *available at* <http://www.agbioforum.org/v7n12/v7n12a13-mcluskey.htm>.

³³² *Id.*

- ³³³ Mystery Bridgers, *Genetically Modified Organisms and the Precautionary Principal: How the GMO Dispute Before the WTO Could Decide the Fate of International GMO Regulation*, 22 TEMP. ENVTL L. & TECH. J. 171, 172 (2004).
- ³³⁴ Curtis, *supra* note 331.
- ³³⁵ Anand Krishnamoorthy, *China Drags Its Heels On GM Rollout* (Jan. 20, 2005), available at <http://www.foodnavigator-asia.com/Policy/China-drags-its-heels-on-GM-rollout>.
- ³³⁶ Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Law No. 97 of 2003) (Japan). available at https://www.env.go.jp/en/laws/nature/law_ccsubdrmo.pdf.
- ³³⁷ See, e.g., the Canadian regulation on “Novel Foods” and their notification and clearance for sale in Canada, available at www.hc-sc.gc.ca/fn-an/gmf-agm/fs-if/novel-foods-aliments-nouveaux-eng.php.
- ³³⁸ See EL FINANCIERO (THE ECONOMIST, Mexico) Aug. 13, 2002, at https://www.organicconsumers.org/old_articles/gefood/mexico081602.php.
- ³³⁹ BERGERON & CHAN, *supra* note 89, at 98.
- ³⁴⁰ Parliament Directive 2001/18/EC, Official Journal L 106/1.
- ³⁴¹ Regulation 1830/2003/EC, 2003, Official Journal L 268/24.
- ³⁴² Parliament Directive, *supra* note 340 at 1, 2, 4.
- ³⁴³ Bridgers, *supra* note 333, at 179.
- ³⁴⁴ *Id.* See also GENOMICS & GENETICS WKLY., GENETIC ENGINEERING; TRACEABILITY OF GENETICALLY MODIFIED ORGANISMS IN THE FOOD CHAIN DISCUSSED, 73, 2004 WL 65357741 (Aug. 20, 2004) (discussing a new package of legislation that would make the labeling requirement more cumbersome).
- ³⁴⁵ John Charles Kunich, *Mother Frankenstein, Doctor Nature and the Environmental Law of Genetic Engineering*, 74 S. CAL. L. REV. 807, 847 (Mar. 2001); see also Susan Boensch Meyer, *Recent Developments, Genetically Modified Organisms*, COLO. J. INT’L. ENVTL. L. & POL’Y 102, 103 (1999).
- ³⁴⁶ Kunich, *supra* note 345; Ned Stafford, *GM Law A Blow For Science*, THE SCIENTIST, December 1, 2004, available at <http://www.the-scientist.com/?articles.view/articleNo/23191/title/GM-law--a-blow-for-science/>
- ³⁴⁷ Council Directive 90/220/EEC, Official Journal L 117/15.
- ³⁴⁸ See EurActiv.com, Commission Warns Five Member States to Lift GMO Bans or Face Legal Action (April 27, 2005), available at <http://goo.gl/Sgjzgz> (including a note that the European Health and Consumer Commissioner suggests system similar to that of the EU on labeling and traceability).
- ³⁴⁹ Press Release, European Union, Commission requires certification of U.S. exports to stop unauthorized GMO entering the EU (April 15, 2005), available at http://europa.eu/rapid/press-release_IP-05-437_en.htm?locale=en.
- ³⁵⁰ Cartagena Protocol on Biosafety to Convention on Biological Diversity, opened for signing, January 29, 2000, 39 I.L.M. 1027 (entered into force September 11, 2003).
- ³⁵¹ *Id.* at art. 8, para. 1; *Id.* at Annex I, 26-27.
- ³⁵² *Id.* at 7 art. 9, 8 art. 10, para. 6 and 10 art. 12 (noting that any rejection must be based on scientific findings).
- ³⁵³ See *Genetic Engineering: Traceability of Genetically Modified Organisms In The Food Chain Discussed*, 73 GENOMICS & GENETICS WKLY., 2004 WL 65357741 (Aug. 20, 2004) (discussing a new package of legislation that would make the labeling requirement more cumbersome).
- ³⁵⁴ Available at <http://bch.cbd.int/>.
- ³⁵⁵ Issued by CODEX Alimentarius, which was created in 1963 under the auspices of the United Nations’ World Health Organization and Food and Agriculture Organization. The official website of the CODEX is at http://www.codexalimentarius.net/web/index_en.jsp.

- ³⁵⁶ Daniel M. Krainin, *Biotech Crops, Biosafety Protocol: Genetically Modified Sustainability?*, NAT. RESOURCES & ENV'T 63, 67 (2004).
- ³⁵⁷ Law Concerning the Conservation and Sustainable Use of Biological Diversity through Regulations on the Use of Living Modified Organisms (Law No. 97 of 2003) (Japan). Available at http://www.bch.biodic.go.jp/download/en_law/en_Law.doc.
- ³⁵⁸ NOM-056-FITO-1995 (Mexico).
- ³⁵⁹ Morgan Lee, *Mexico's President to Sign New Regulations on Genetically Modified Crops*, FOOD, February 18, 2005, available at <http://legacy.utsandiego.com/news/mexico/20050218-1500-mexico-biotech.html>.
- ³⁶⁰ Press Release, Environment Canada, *Canada's Position on Ratification of the Cartagena Protocol on Biosafety* (November 18, 2003), available at http://www.ec.gc.ca/media_archive/press/2003/031118_n_e.htm.
- ³⁶¹ Canada Food and Drug Regulations, § B.28.001 (Jun. 10, 1999), available at http://laws-lois.justice.gc.ca/eng/regulations/c.r.c.,_c._870/index.html.
- ³⁶² *Id.* § B.28.002(c).
- ³⁶³ Phelim Kyne, CHINA WATCH: China Biotech Barriers Reflect Turf War, DOW JONES NEWSWIRES, May 12, 2002, available at <http://www.organicconsumers.org/patent/china060702.cfm>.
- ³⁶⁴ Foodnavigator-asia.com, *GMO issues Step up in China* (May 23, 2005).
- ³⁶⁵ Jia Hepeng, *GM Rice May Soon Be Commercialized*, CHINA BUSINESS WEEKLY (Jan. 27, 2005), available at http://www.chinadaily.com.cn/english/doc/2005-01/27/content_412646.htm.
- ³⁶⁶ BBC News, *GM Rice 'Sold Illegally in China'* (Apr. 13, 2005), available at <http://news.bbc.co.uk/1/hi/world/asia-pacific/4440817.stm>.
- ³⁶⁷ *Debate over GMOs Simmers in China*, CHINA DAILY (Apr. 6, 2004), available at <http://www.organicconsumers.org/ge/china041304.cfm>.
- ³⁶⁸ See generally, Heike Baumüller, *Domestic Import Regulations of Genetically Modified Organisms and their Compatibility with WTO Rules - Some Key Issues 11-12* (International Centre for Trade and Sustainable Development 2003), available at http://www.ictsd.org/pubs/TKN/tkn_domestic_regs.pdf.
- ³⁶⁹ See *Biotechnology and Biosafety Certificates*, in 2004 WHITE PAPER - AGRICULTURE AND FOOD (American Chamber of Commerce in Beijing 2004), at <http://goo.gl/G0W2mV>.
- ³⁷⁰ *India May Import Genetically Modified Oil Seeds*, EXPRESS INDIA, REUTERS, Jan. 20, 2005.
- ³⁷¹ Kunich, *supra* note 345, at 857-858.
- ³⁷² Hilary Preston, *Drift of Patented Genetically Engineered Crops: Rethinking Liability Theories* 81 TEX. L. REV. 1153, 1162 (2003) (noting that the U.S. grain industry has lost virtually all of the \$200 million annual export market for sale of corn to the EU as a result of the EU's restrictions on the importation of GM corn); Kunich, *supra* note 345, at 814-815; K.T. Arasu, *Kraft CEO Sees Nutrition Role for Biotech Foods*, REUTERS, March 14, 2005.
- ³⁷³ BERGERON & CHAN, *supra* note 89, at 225.
- ³⁷⁴ MCGRAW-HILL DICTIONARY OF SCIENTIFIC AND TECHNICAL TERMS 892 (6th ed. 2003).
- ³⁷⁵ MINN. STAT. § 18F.02 (2005); *id.* § 18B.01.
- ³⁷⁶ Kunich, *supra* note 345, at 808-09.
- ³⁷⁷ Hilary Preston, *Drift of Patented Genetically Engineered Crops: Rethinking Liability Theories*, 81 TEX. L. REV. 1153, 1155 (2003); see also Lisa Rathke, *Sale of GE Seeds Rises in Vermont*, ASSOCIATED PRESS, January 18, 2005.
- ³⁷⁸ Preston, *supra* note 377, at 1155 (noting that this movement of genes from one organism to another is often labeled "transgenic," which term is interchangeable with "genetically engineered," or "genetically modified").

³⁷⁹ BERGERON & CHAN, *supra* note 89, at 87.

³⁸⁰ *Id.* at 103.

³⁸¹ *Id.*

³⁸² W. Christopher Matton & F. Scott Thomas, *The Continuing Balance: Federal Regulation of Biotechnology*, 44 JURIMETRICS J. 283, 311 (Spring 2004).

³⁸³ Wilder J. Leavitt, *Regulating Human Gene Therapy: Legislative Overreaction to Human Subject Protection Failures*, 53 ADMIN. L. REV. 315, 325-26 (Winter 2001).

³⁸⁴ *Id.*

³⁸⁵ Matton & Thomas, *supra* note 382; see also CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, CELLULAR GENE THERAPY, at <http://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/default.htm>

³⁸⁶ Matton & Thomas, *supra* note 382, at 312, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, *supra* note 385.

³⁸⁷ CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, TRANSFER OF THERAPEUTIC PRODUCTS TO THE CENTER FOR DRUG EVALUATION AND RESEARCH, at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133463.htm>

³⁸⁸ CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, *supra* note 385; see also, 21 C.F.R. §§ 312.20, 312.22, 312.23 (2002).

³⁸⁹ CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, *supra* note 385.

³⁹⁰ *Id.*

³⁹¹ Rick Weiss, *Boy's Cancer Prompts FDA to Halt Gene Therapy*, WASHINGTON POST, available at <http://www.washingtonpost.com/wp-dyn/articles/A3926-2005Mar3.html>.

³⁹² CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, HUMAN GENE THERAPY AND THE ROLE OF THE FOOD AND DRUG ADMINISTRATION, at <http://www.fda.gov/biologicsbloodvaccines/cellulargenetherapyproducts/default.htm>.

³⁹³ Kunich, *supra* note 345, at 823; Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23301 (June 26, 1986) (hereinafter Coordinated Framework).

³⁹⁴ Linda Bren, *Genetic Engineering: The Future of Foods?*, FDA CONSUMER MAGAZINE (Nov.-Dec. 2003).

³⁹⁵ U.S. FOOD AND DRUG ADMINISTRATION, CENTER FOR FOOD SAFETY AND APPLIED NUTRITION, LIST OF COMPLETED CONSULTATIONS ON BIOENGINEERED FOODS (March 2005), at http://www.foodsafety.wisc.edu/assets/pdf_files/genetic_engineering_future.pdf.

³⁹⁶ Kunich, *supra* note 345, at 823-824; BERGERON & CHAN, *supra* note 327, at 88 (noting that once plants and/or crops are cleared by the EPA, USDA and FDA, they are treated like any other plant or crop).

³⁹⁷ Kunich, *supra* note 345, at 823.

³⁹⁸ 15 U.S.C. §§ 2601-2692 (2005).

³⁹⁹ 7 U.S.C. §§ 136-136y (2004).

⁴⁰⁰ 21 U.S.C. §§ 301-399 (2004).

⁴⁰¹ See *supra* note 398; see also Kunich, *supra* note 345, at 825 (noting that the EPA and the EPA's TSCA Biotechnology Program have asserted authority over genetically engineered organisms and microorganisms by defining them as chemical substances).

⁴⁰² 15 U.S.C. §§ 2604(d), 2607(a)(2).

⁴⁰³ 15 U.S.C. § 2601(c).

⁴⁰⁴ 40 C.F.R. § 725.105 (2005).

⁴⁰⁵ *Id.* §§ 725.155-725.160.

⁴⁰⁶ *Id.* §§ 725.250, 725.255.

⁴⁰⁷ *Id.* § 725.270(a).

⁴⁰⁸ 15 U.S.C. § 2604(f)-(e) (2005).

⁴⁰⁹ *Id.* § 2603(a)(1)(A).

⁴¹⁰ *Id.* § 2603(a)(1)(A)-(B).

⁴¹¹ Id.

⁴¹² Baltimore Gas & Elec. Co. v. Nat'l Res. Def. Council, 462 U.S. 87, 97-98 (1983); Chem. Mfrs. Ass'n v. EPA, 859 F.2d 977 (D.C. Cir. 1998); see also Devra Lee Davis, The "Shotgun Wedding" of Science and Law: Risk Assessment and Judicial Review, 10 COLUM. J. ENVTL. L. 67, 97 (1985).

⁴¹³ 15 U.S.C. § 2601(c) (2005).

⁴¹⁴ Kunich, *supra* note 345, at 830.

⁴¹⁵ Id.

⁴¹⁶ See 7 U.S.C. §§ 136(a), 136(u); see also Plant Pesticides Subject to the Federal Insecticide, Fungicide and Rodenticide Act and the Federal Food, Drug and Cosmetic Act, 59 Fed. Reg. 60,496 & 60,506-07 (EPA Nov. 23, 1994) (the definition has been interpreted to include plant hormones).

⁴¹⁷ Kunich, *supra* note 345, at 831; GENETICALLY MODIFIED PROTECTED PLANTS: SCIENCE AND REGULATION 33 at 150-151 (Comm. on Genetically Modified Pest-Protected Plants, Nat'l Research Council eds. 2000), available at <http://www.nap.edu/openbook.php?isbn=0309069300&page=R1> (hereinafter NRC 2000).

⁴¹⁸ 7 U.S.C. § 136a(c)(5)(D), (bb) (2005). This standard is intended to take into account the economic, social and environmental costs and benefits of the pesticide. 40 C.F.R. §§ 158, 162, 172 (2000) (noting that there is a presumption that an Experimental Use Permit is not required for experimental use in a contained facility (laboratory or greenhouse) or for some types of small-scale tests conducted on a cumulative total of no more than ten (10) acres); see also 7 U.S.C. § 172.3(b)(1)(i), (c)(1).

⁴¹⁹ 7 U.S.C. §§ 136a(c)(9), 136i(a).

⁴²⁰ 40 C.F.R. § 158.65(2); see also Judith E. Breach, No "Killer Tomatoes": Easing Federal Regulation of Genetically Engineered Plants, 53 FOOD & DRUG L.J. 181, 189-90 (1998) (describing the FIFRA process and discussing the attendant transaction costs).

⁴²¹ *Env'tl Def. Fund v. EPA*, 548 F.2d 998, 1003 (D.C. Cir. 1976) (suspension also requires a showing that the pesticide constitutes an imminent hazard to humans or to the environment); *Nat'l Coalition Against the Misuse of Pesticides v. EPA*, 867 F.2d 636, 643-44 (D.C. Cir. 1989) (in order to initiate cancellation proceedings at least a "substantial question of safety" must be found).

⁴²² 7 U.S.C. §§ 136a(c)(5), 136(bb).

⁴²³ Kunich, *supra* note 345, at 836.

⁴²⁴ NRC 2000, *supra* note 417, at 151 (noting that EPA's jurisdiction under FFDCA applies even if the pesticide has been exempted from regulation under FIFRA).

⁴²⁵ Id.

⁴²⁶ 7 U.S.C. §§ 150aa-150jj (2005); *id.* §§ 151-164, 166-67; NRC 2000, *supra* note 417, at 146; see also Final Policy Statement for Research and Regulation of Biotechnology Processes and Products, 51 Fed. Reg. 23,336 & 23,342 (June 26, 1986).

⁴²⁷ 7 C.F.R. § 340.0-340.9 (2005); see Bren, *supra* note 394 (noting that most bioengineered plants are considered "regulated articles" under the regulations of the APHIS).

⁴²⁸ 7 C.F.R. § 340.3(b).

⁴²⁹ *Id.* § 340.3(c); NRC 2000, *supra* note 417, at 145.

⁴³⁰ 7 C.F.R. § 340.3.

⁴³¹ *Id.* § 340.6; see FDA, *supra* note 395.

⁴³² 7 C.F.R. § 340.3(b)(2) (2005).

⁴³³ Kunich, *supra* note 345, at 840; Genetically Engineered Organisms and Products; Notification Procedures for the Introduction of Certain Regulated Articles and Petition for Nonregulated Status, 58 Fed. Reg. 17,044 & 17,054 (Mar. 31, 1993) (stating the APHIS has determined that the constraints imposed by the eligibility criteria and the performance standards are sufficient).

⁴³⁴ Kunich, *supra* note 345, at 841.

⁴³⁵ 21 U.S.C. §§ 301-395 (1994); 42 U.S.C. §§ 262-263a (1994); Bren, *supra* note 394 (noting that if a food does not meet FDA standards FDA has the right to take it off the market); see *infra* Chapter V.B. of this Guide for a more in depth discussion of FDA regulations.

- ⁴³⁶ Kunich, *supra* note 345, at 842; see also Statement of Policy: Foods Derived From New Plant Varieties, 57 Fed. Reg. 22,894 & 22,991 (May 29, 1992).
- ⁴³⁷ Press Release, U.S. Dept. of Health & Human Services, FDA to Strengthen Pre-Market Review of Bioengineered Foods (May 3, 2000).
- ⁴³⁸ *Id.*; see also David R. Nicholson, Agricultural Biotechnology and Genetically Modified Foods; Will The Developing World Bite?, 8 VA. J. L. & TECH. 7, 28 (2003).
- ⁴³⁹ See HHS, *supra* note 437.
- ⁴⁴⁰ *Id.*
- ⁴⁴¹ *Id.*; Statement of Policy: Foods Derived From New Plant Varieties, 57 Fed. Reg. 22,894 & 22,991 (May 29, 1992).
- ⁴⁴² Bridgers, *supra* note 333.
- ⁴⁴³ U.S. FOOD AND DRUG ADMINISTRATION, GUIDANCE FOR INDUSTRY; DRUGS, BIOLOGICS, AND MEDICAL DEVICES DERIVED FROM BIOENGINEERED PLANTS FOR USE IN HUMANS AND ANIMALS (draft guidance distributed for comment purposes only), available at <http://www.fda.gov/> (last visited March 13, 2005).
- ⁴⁴⁴ HUMAN GENOME PROJECT INFORMATION, ABOUT THE HUMAN GENOME PROJECT, http://web.ornl.gov/sci/techresources/Human_Genome/index.shtml.
- ⁴⁴⁵ *Id.*
- ⁴⁴⁶ NATIONAL HUMAN GENOME RESEARCH INSTITUTE, TECHNOLOGY TRANSFER OFFICE, <http://www.genome.gov/10001152>. More information on the TTO can be obtained at www.genome.gov.
- ⁴⁴⁷ Press Release, National Institute of General Medical Sciences, New Contract Allows NIGMS Cell Repository to Continue Providing Key Genetic Research Resources (December 14, 2004), available at www.nigms.nih.gov/news/releases.
- ⁴⁴⁸ The Coriell Institute's website address is <https://www.coriell.org/>.
- ⁴⁴⁹ DOE Approves Research of Evolutionarily Important Organisms, PURDUE UNIV. NEWSWISE, available at <http://www.newswise.com> (last visited January 20, 2005).
- ⁴⁵⁰ 7 U.S.C. § 5924 (2005).
- ⁴⁵¹ *Id.*; *id.* § 5921 (discussing grants for environmental assessment to analyze the relative impacts of animals, plants and microorganisms modified through genetic engineering); *id.* § 5925 (discussing national specialty crop research program providing grants for the purpose of improving the efficiency, productivity and profitability of specialty crop production in the United States).
- ⁴⁵² See *infra* Section V.G. of this guide, which provides more detail on the SBIR/STTR Programs.
- ⁴⁵³ National Institute of Biomedical Imaging and Bioengineering, 6707 Democracy Blvd., Suite 202, Bethesda, MD 20892-5477, (301) 451-6768; website: <http://www.nibib.nih.gov>.
- ⁴⁵⁴ National Science Foundation, Small Business Innovation Research & Small Business Technology Transfer (SBIR/STTR), 4201 Wilson Blvd., Arlington, VA 22230, (703) 292-5111, website: <http://www.nsf.gov/funding>.
- ⁴⁵⁵ Department of Defense Small Business Innovation Research Small Business Technology Transfer Fast Track, website: www.acq.osd.mil/sadbu/sbir/; SBIR/STTR Help Desk (866) 724-7457.
- ⁴⁵⁶ MAYO CLINIC, MEDICAL GENOMICS AND BIOTECHNOLOGY: SEEDING THE FUTURE OF MEDICINE, <http://www.mayoclinic.org> (last visited April 3, 2005).
- ⁴⁵⁷ *Id.*
- ⁴⁵⁸ UNIVERSITY OF MINNESOTA, CAPITAL PLANNING & PROJECT MANAGEMENT, <http://www.cppm.umn.edu> (last visited April 3, 2005).
- ⁴⁵⁹ *U of M Biotech Incubator Lands \$24M in Funding*, THE BUSINESS JOURNAL (MINNEAPOLIS/ST. PAUL), (Jan. 24, 2005), available at <http://www.twincities.bizjournals.com/twincities/stories/2005/01/24/daily2.html>.

- ⁴⁶⁰ MINN. DEPT. OF AGRIC., REGULATION OF GENETIC ENGINEERING IN MINN., available at <http://www.mda.state.mn.us/licensing/licensetypes/biotechnology.aspx> (last visited April 3, 2005); see also COLO. STATE UNIV. DEPT. OF SOIL & CROP SCIENCES, TRANSGENIC CROPS: THE REGULATORY PROCESS FOR TRANSGENIC CROPS IN THE U.S., available at <http://cls.casa.colostate.edu/transgeniccrops/index.html> (last visited April 3, 2005).
- ⁴⁶¹ Harry Cline, Kings, Fresno Supervisors Pass Pro-Biotech/Agriculture Resolutions, WESTERN FARM PRESS, Feb. 15, 2005 (noting that while the resolutions favoring biotech crops are not legally binding, they are a signal to opponents of the technology that they will have difficulty enacting a ban at least at the county level).
- ⁴⁶² Rathke, *supra* note 377.
- ⁴⁶³ Genetically Engineered Wild Rice Release, Planting, Cultivation, Harvesting, or Sale Prohibition, 2005 WLNR 3724834, S.F. No. 1566, 84th Sess. (Minn. 2005) (introduced).
- ⁴⁶⁴ *Id.*; Curt Woodward, Resistance To Biotech Wheat Still Prompting Legislative Debate, GRAND FORKS HERALD, ASSOCIATED PRESS, February 13, 2005.
- ⁴⁶⁵ *Id.*; see also North Dakota Senate Rejects Ban On Biotech Wheat, GRAND FORKS HERALD, ASSOCIATED PRESS, Feb. 15, 2005.
- ⁴⁶⁶ MINN. STAT. § 18B.285(1)(a) (West Supp. 2005) (governing use, distribution and release of genetically engineered pesticides); *id.* § 18C.310(1) (governing release of genetically engineered fertilizer, soil amendments and plant amendments); *id.* § 18F.01 (governing the release of genetically engineered organisms). Where the permits requested are related to livestock and domestic animals, the Board of Animal Health must also be consulted. *id.* § 18F.04.
- ⁴⁶⁷ *Id.* §§ 18B.285(2), 18C.310(3), 18F.07(3).
- ⁴⁶⁸ *Id.* §§ 18F.12, 116D.04(1)(a), (c), 2(a), 3(a) (discussing the process and time provided for environmental review).
- ⁴⁶⁹ MINN. STAT. §§ 18B.285(1)(b), 18C.310(2), 18F.07(2) (West Supp. 2005).
- ⁴⁷⁰ *Id.*
- ⁴⁷¹ *Id.* §§ 18C.310(1), 18F.07, 18F.12.
- ⁴⁷² *Id.* §§ 18F.13, 116C.94, 116C.97.
- ⁴⁷³ *Id.* §§ 116C.92, 116C.93. The Environmental Quality Board is the state coordinating organization for regulatory activities relating to genetically engineered organisms.
- ⁴⁷⁴ MINN. STAT. § 116C.97(2)(c) (West Supp. 2005). See *id.* § 116C.91-116C.96 for a discussion of the state environmental requirements.
- ⁴⁷⁵ *Id.* § 116C.97(2)(b).
- ⁴⁷⁶ BERGERON & CHAN, *supra* note 89, at 156, 158 (stating that most biotech companies in the U.S. contend that no one will invest in genomic research and development without the protection afforded by patents); see *infra* Section V.C. of this Guide for a more in depth discussion of intellectual property laws and issues.
- ⁴⁷⁷ 7 U.S.C. §§ 2402, 2422 (2005); Nicholson, *supra* note 438, at 15.
- ⁴⁷⁸ Nicholson, *supra* note 438, at 15.
- ⁴⁷⁹ Diamond v. Chakrabarty, 447 U.S. 303 (1980); J.E.M. Ag. Supply v. Pioneer Hi-Bred Int'l, 534 U.S. 124, 130 (2001) (confirming the result in *Chakrabarty*).
- ⁴⁸⁰ BERGERON & CHAN, *supra* note 89, at 158 (noting that the U.S. Patent & Trademark Office is more likely to grant a patent for genetically engineered organisms than the European Patent Office, which represents approximately 27 countries).
- ⁴⁸¹ Smithkline Beecham Corp. v. Apotex Corp., 365 F.3d 1306, 1329 (Fed. Cir. 2004); see also BERGERON & CHAN, *supra* note 89, at 158 (noting that the application of patent law to the human genome is a source of fierce debate).

- ⁴⁸² Animal Legal Def. Fund v. Quigg, 932 F.2d 920 (N.D. Cal. 1991).
- ⁴⁸³ *Chakrabarty*, 447 U.S. at 309; *J.E.M. Ag. Supply*, 534 U.S. at 130.
- ⁴⁸⁴ *Chakrabarty*, 447 U.S. at 313.
- ⁴⁸⁵ *Smithkline*, 365 F.3d at 1330; *see also Chakrabarty*, 447 U.S. at 309 (stating that a natural reproduction process whether sexual or asexual is ineligible for patent protection).
- ⁴⁸⁶ BERGERON & CHAN, *supra* note 89, at 159-160.
- ⁴⁸⁷ *Smithkline*, 365 F.3d at 1330.
- ⁴⁸⁸ *Id.*; *see also Preston*, *supra* note 377, at 153.
- ⁴⁸⁹ *Smithkline*, 365 F.2d at 1333; *Preston*, *supra* note 377, at 153.
- ⁴⁹⁰ *Preston*, *supra* note 377, at 162; *Monsanto Canada, Inc. v. Schmieser*, [2001] F.C.T.D. 256 (Sask.) (establishing troublesome precedents that individuals could be held liable for innocently growing or helping reproduce genetically modified crops and that genetically modified crops would still be covered by the intellectual property rights of whoever patented them even if they result from natural, random mutations).
- ⁴⁹¹ *Preston*, *supra* note 377, at 162.
- ⁴⁹² *Preston*, *supra* note 377, at 160-61.
- ⁴⁹³ *Nicholson*, *supra* note 438, at 15.
- ⁴⁹⁴ BERGERON & CHAN, *supra* note 89, at 101; *see infra* Section IV.F. of this Guide (discussing strategic alliances and joint ventures in greater detail).
- ⁴⁹⁵ *Monsanto Grows Globally Despite Biotech Criticism*, ASSOCIATED PRESS Mar. 20, 2005.
- ⁴⁹⁶ BERGERON & CHAN, *supra* note 89, at 101.
- ⁴⁹⁷ BERGERON & CHAN, *supra* note 89, at 103.
- ⁴⁹⁸ UNESCO, *The Universal Declaration on the Human Genome and Human Rights* (Nov. 11, 1997), available at <http://unesdoc.unesco.org/images/0010/001096/109687eb.pdf>.
- ⁴⁹⁹ *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Council of Europe, Convention on Human Rights and Biomedicine*, opening of Treaty April 4, 1997, entry into force January 12, 1999, available at <http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm>.
- ⁵⁰⁰ BERGERON & CHAN, *supra* note 89, at 24, 98.
- ⁵⁰¹ *Bridgers*, *supra* note 333, at 172.
- ⁵⁰² BERGERON & CHAN, *supra* note 89, at 98.
- ⁵⁰³ *Preston*, *supra* note 377, at 1162 (noting that the U.S. grain industry has lost virtually all of the \$200 million annual export market for sale of corn to the EU as a result of the EU's restrictions on the importation of genetically modified corn); *Kunich*, *supra* note 345, at 814-15; *K.T. Arasu*, *supra* note 372.
- ⁵⁰⁴ BERGERON & CHAN, *supra* note 89, at 225.
- ⁵⁰⁵ *Id.* at 98; *see supra* Part V.F. for a more complete discussion of the international laws and regulations surrounding genetic engineering initiatives.
- ⁵⁰⁶ *Parliament Directive 2001/18/EC*, 2001 O.J. (6106) 1.
- ⁵⁰⁷ *Commission Regulation 1830/2003/EC of July 2003 on Traceability and Labeling*.
- ⁵⁰⁸ *Bridgers*, *supra* note 333, at 179.
- ⁵⁰⁹ *Id.*; *see also Genetic Engineering: Traceability of Genetically Modified Organisms In The Food Chain Discussed*, 73 *GENOMICS & GENETICS WKLY.*, 2004 WL 65357741 Aug. 20, 2004 (discussing a new package of legislation that would make the labeling requirement more cumbersome).
- ⁵¹⁰ *USDA Issues Two Biotechnology Reports*.
- ⁵¹¹ *Cartagena Protocol*, *supra* note 350.

- ⁵¹² Daniel Mikrainin, *Biotech Crops, Biosafety Protocol: Genetically Modified Sustainability?*, NAT. RESOURCES & ENV'T 63, 67 (2004).
- ⁵¹³ Cartagena Protocol, *supra* note 350, at art. 8, ¶ 1; *id.* at Annex I, 26-27.
- ⁵¹⁴ *Id.* at 7 art. 9, 8 art. 10 ¶ 6, 10 art. 12 (noting that any rejection must be based on scientific findings).
- ⁵¹⁵ *Id.*
- ⁵¹⁶ Mikrainin, *supra* note 512, at 67.
- ⁵¹⁷ Kunich, *supra* note 345, at 857-858.
- ⁵¹⁸ EXPRESS INDIA, *supra* note 370; Morgan Lee, *supra* note 359; see *supra* Part V.F. for a more complete discussion of consumer and industry developments surrounding international genetic engineering initiatives.
- ⁵¹⁹ Human Genome Project Information, *Ethical, Legal, and Social Issues*, available at http://www.ornl.gov/sci/techresources/Human_Genome/elsi/elsi.shtml (last modified Sept. 6, 2004).
- ⁵²⁰ Human Genome Project Information, Gene Therapy, available at <http://ghr.nlm.nih.gov/handbook/hgp?show=all> (last modified Oct. 19, 2004).
- ⁵²¹ Press Release, The White House Office of the Press Secretary, Executive Order: Creation of the President's Council on Bioethics (Nov. 28, 2001).
- ⁵²² Saving Amy, CBS NEWS.COM (Sept. 7, 2000), available at <http://www.cbsnews.com/stories/1999/12/29/48hours/main144255.shtml>.
- ⁵²³ WASHINGTON POST, *supra* note 391.
- ⁵²⁴ Kourtney L. Pickens, Don't Judge Me By My Genes: A Survey of Federal Genetic Discrimination Legislation, 34 TULSA L. J., 161, 170 (Fall 1998).
- ⁵²⁵ MINN. STAT. § 72A.139, subd. 3 (2005) (prohibiting health plan companies from determining eligibility for coverage, establishing premiums, limiting coverage, renewing coverage, or any other underwriting decision, by (1) requiring or requesting an individual or a blood relative of the individual to take a genetic test; (2) making any inquiry to determine whether an individual or a blood relative of the individual has taken or refused a genetic test, or what the results of any such test were; (3) taking into consideration the fact that a genetic test was taken or refused by an individual or blood relative of the individual; or (4) taking into consideration the results of a genetic test taken by an individual or a blood relative of the individual.); *id.* § 181.974.
- ⁵²⁶ Kunich, *supra* note 345, at 814-815.
- ⁵²⁷ Bren, *supra* note 394.
- ⁵²⁸ John J. Miller, Against The Grain: Enviro-Terrorists Target Farms, NAT'L REV. 22-24 (March 6, 2000).
- ⁵²⁹ USDA Sued Over Clearance For Field Tests Of Genetically Modified Crops, 23 BIOTECHNOLOGY L. REP. 55 (Feb. 2004).
- ⁵³⁰ Kunich, *supra* note 345, at 817-818.
- ⁵³¹ *Id.*
- ⁵³² BERGERON & CHAN, *supra* note 89, at 26.
- ⁵³³ Agriculture Study Funds Oversight of Modified Crops, says Food Supply Faced Contamination Risk, BIOTECH WATCH (Dec. 20, 2004) (citing Union of Concerned Scientists, A Growing Concern: Protecting the Food Supply in an Era of Pharmaceutical and Industrial Crops).
- ⁵³⁴ BERGERON & CHAN, *supra* note 89, at 26.
- ⁵³⁵ Joy Powell, Tainted Biotech Corn Seeds May Have Circulated, STAR-TRIBUNE (MINNEAPOLIS) Mar. 23, 2005, available at <http://www.startribune.com>.
- ⁵³⁶ BERGERON & CHAN, *supra* note 89, at 22.
- ⁵³⁷ *Id.* at 104.
- ⁵³⁸ *Id.*

⁵³⁹ Arasu, *supra* note 372.

⁵⁴⁰ *Genetic Engineering: Biotech Grass "Gene Flow" Underscores Growing Concern*, 73 GENOMICS & GENETICS WKLY., 2004 WL 743069 (October 15, 2004).

⁵⁴¹ *Id.*

⁵⁴² NATIONAL INSTITUTE OF HEALTH, *Frequently Asked Questions*, available at <http://stemcells.nih.gov/info/faqs.asp> (last modified Jan. 7, 2004).

⁵⁴³ John A. Robertson, *Causative vs. Beneficial Complicity in the Embryonic Stem Cell Debate*, 36 CONN. L. REV. 1099 (2004).

⁵⁴⁴ Charity Schiller, *Stem Cell Research and Conditional Federal Funding: Do State Laws Allowing More Extensive Research Pose a Problem for Federalism?*, 31 PEPP. L. REV. 1017, 1025-1026 (2004).

⁵⁴⁵ *Id.* at 1026.

⁵⁴⁶ *Id.*

⁵⁴⁷ Stem Cell Institute at the University of Minnesota, at www.stemcell.umn.edu.

⁵⁴⁸ MINN. STAT. § 145.422 (2005).

⁵⁴⁹ *Id.* § 145.421.

⁵⁵⁰ H.F. 13, S.F. 730, Reg. Sess. (Minn. 2005).

⁵⁵¹ *Id.*

⁵⁵² *Id.*

⁵⁵³ NATIONAL CONFERENCE OF STATE LEGISLATURES: STATE EMBRYONIC AND FETAL RESEARCH LAWS (2004), available at <http://www.ncsl.org/research/health/fetal-homicide-state-laws.aspx> (as updated via state statutes March 20, 2005).

⁵⁵⁴ *Id.*; *Legislators in Conn., Mass. Approve Stem Cell Bills*, ASSOCIATED PRESS, June 1, 2005; *Governor Rell Signs Law Establishing Stem Cell Research Fund, Ban on Human Cloning*, PR NEWSWIRE, June 19, 2005.

⁵⁵⁵ *Id.*

⁵⁵⁶ *Id.*

⁵⁵⁷ *Id.*

⁵⁵⁸ *Id.*

⁵⁵⁹ *Id.*

⁵⁶⁰ *Id.*

⁵⁶¹ *Id.*

⁵⁶² *Id.*

⁵⁶³ Rick Weiss, *House Leaders Agree to Vote on Relaxing Stem Cell Limits*, WASHINGTON POST, Mar. 25, 2005.

⁵⁶⁴ *Id.*; *see infra* note 580.

⁵⁶⁵ David Stout & Timothy Williams, *House Votes to Reverse Ban on Funding for Stem Cell Research*, NEW YORK TIMES, May 24, 2005.

⁵⁶⁶ *Id.*

⁵⁶⁷ Attorney General of California, *Summary of Proposition 71*, available at <http://vigarchive.sos.ca.gov/2004/general/propositions/prop71-title.htm>.

⁵⁶⁸ *Id.*

⁵⁶⁹ Bob Egelko, *State Supreme Court Refuses to Hear Challenge to Stem Cell Research Program*, SAN FRANCISCO CHRONICLE, Mar. 24, 2005.

⁵⁷⁰ *Id.*

⁵⁷¹ *Id.*

⁵⁷² Lorraine McCarthy, N.J. Governor Proposes \$380 Million in State Funding for Stem Cell Research, BIOTECH WATCH, Jan. 18, 2005.

⁵⁷³ *Id.*; *Governor introduces measure for stem cell site, park work*, STAR LEDGER, June 10, 2005.

- ⁵⁷⁴ *Legislators in Conn., Mass. Approve Stem Cell Bills*, ASSOCIATED PRESS, June 1, 2005; Steve LeBlanc, *Massachusetts OK's Stem Cell Bill*, DAILY BREEZE, Apr. 1, 2005.
- ⁵⁷⁵ *Legislators in Conn., Mass. Approve Stem Cell Bills*, ASSOCIATED PRESS, June 1, 2005.
- ⁵⁷⁶ *Id.*
- ⁵⁷⁷ Sylvia Kim, *Embryonic Stem Cell Research Controversy: Focus on the Private Sector and International Sphere*, 14 HAST. WOMEN'S L.J. 89, 102-103 (Winter 2003).
- ⁵⁷⁸ *Id.*
- ⁵⁷⁹ *Id.*
- ⁵⁸⁰ Kingsley Taft, Sharon Webb, *Stem Cells: Their Promise, Their Problems*, MONDAQ BUSINESS BRIEFING, Mar. 9, 2005.
- ⁵⁸¹ *Id.*
- ⁵⁸² Antonio Regaldo, *Big Companies Quietly Pursue Research on Embryonic Stem Cells*, WALL STREET JOURNAL, Apr. 12, 2005.
- ⁵⁸³ Mitch Frank, *Stem Cell Struggles*, TIME, Mar. 28, 2005.
- ⁵⁸⁴ *Id.*
- ⁵⁸⁵ *Id.*
- ⁵⁸⁶ *Delaware Senate Passes Stem Cell Research Bill*, ASSOCIATED PRESS, Jun. 14, 2005.
- ⁵⁸⁷ John Wagner, *House Agrees To Funding on Stem Cells: Approval Seen as Backing for Md. Biotech Industry*, WASHINGTON POST, Mar. 29, 2005.
- ⁵⁸⁸ *The Stem Cell Race*, NEW YORK TIMES, Mar. 20, 2005.
- ⁵⁸⁹ Chris Nolan, *Stem-Cell Gold Rush Spreads Beyond California*, EWEEK, Jan. 19, 2005; Ed Silverman, *Legislating Stem Cells*, THE SCIENTIST, Mar. 28, 2005; Karen Pierog, *U.S. States Eye Bonds to Boost Scientific Research*, REUTERS, Apr. 22, 2005.
- ⁵⁹⁰ Application of Current Statutory Authority to Human Somatic Cell Therapy and Gene Therapy Products, 58 Fed. Reg., 53248-9 (Oct. 14, 1993).
- ⁵⁹¹ Letter from Stuart L. Nightingale, M.D., Associate Commissioner, FDA (October 26, 1998), available at <http://www.fda.gov>; Letter from Kathryn C. Zoon, Ph.D, Director Center for Biologics Evaluation and Research to Associations Cloning Technology (March 28, 2001), available at <http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm105853.htm>.
- ⁵⁹² *Id.*
- ⁵⁹³ Memorandum on the Prohibition on Federal Funding for Cloning of Human Beings, 33 Weekly Comp. Pres. Doc. 281 (Mar. 4, 1997).
- ⁵⁹⁴ NATIONAL CONFERENCE OF STATE LEGISLATURES, STATE HUMAN CLONING LAWS (Mar. 12, 2004), available at <http://www.ncsl.org>.
- ⁵⁹⁵ UN NEWS CENTER, General Assembly Approves Declaration Banning All Forms of Cloning (2005), available at <http://www.un.org/apps/news/story.asp?NewsID=13576&Cr=cloning&Cr1=>.
- ⁵⁹⁶ UNITED NATIONS EDUCATIONAL, SCIENTIFIC AND CULTURAL ORGANIZATION, NATIONAL LEGISLATION CONCERNING HUMAN REPRODUCTIVE AND THERAPEUTIC CLONING (2004).
- ⁵⁹⁷ 7 U.S.C. § 7701 (2004).
- ⁵⁹⁸ *Id.* § 7712(c).
- ⁵⁹⁹ 21 U.S.C. § 301 (2004).
- ⁶⁰⁰ 15 U.S.C. § 260.
- ⁶⁰¹ PEW INITIATIVE ON FOOD AND BIOTECHNOLOGY, GUIDE TO U.S. REGULATION OF GENETICALLY MODIFIED FOOD AND AGRICULTURAL BIOTECHNOLOGY PRODUCTS (2001).
- ⁶⁰² 21 U.S.C. § 301 (2004).
- ⁶⁰³ *Id.* § 600.
- ⁶⁰⁴ *Id.* § 451.
- ⁶⁰⁵ FOOD AND DRUG ADMINISTRATION, ANIMAL CLONING: A RISK ASSESSMENT (2003).

- ⁶⁰⁶ Press Release, Cordis Corporaton, Drug-eluting Stents to Receive Incremental Reimbursement (July 31, 2002).
- ⁶⁰⁷ See, e.g., the analysis set forth in Deborah Pan & Jeffrey Su, Stents: Marketing Considerations, May 12, 2003, available at <http://www.docstoc.com/docs/164627308/Boston-Scientific>.
- ⁶⁰⁸ A summary of the reimbursement systems of a number of different countries may be found at <http://www.advamed.org/>.
- ⁶⁰⁹ As of 2005, CMS had approved pass-through payments for only four new technologies. MEDICARE PAYMENT ADVISORY COMMISSION, REPORT TO CONGRESS: MEDICARE PAYMENT POLICY, MEDICARE PAYMENT ADVISORY COMMISSION 78 (Mar. 2005).
- ⁶¹⁰ Payments for new technologies used in outpatient department can be procured through new technology APCs, of which those are roughly 80 granted a year, or via pass-through payments added to the base APC payment. *Id.*
- ⁶¹¹ With the advent of computer-assisted technology, the location of the service may not be entirely clear.
- ⁶¹² Some hospitals continue to provide outpatient services on a cost basis.
- ⁶¹³ See, e.g., AMERICAN MEDICAL ASSOCIATION, RBRVS: RESOURCE BASED RELATIVE-VALUE SCALE, available at <http://www.ama-assn.org/> (last updated June 7, 2005).
- ⁶¹⁴ See, e.g., AETNA, CLINICAL POLICY BULLETIN: DRUG-ELUTING STENTS 0621 (Jan. 11, 2005), available at http://www.aetna.com/cpb/medical/data/600_699/0621.html.
- ⁶¹⁵ See <http://www.cms.hhs.gov/>.
- ⁶¹⁶ See <http://www.cms.hhs.gov/>; see also MEDICARE PAYMENT ADVISORY COMMISSION, REPORT TO CONGRESS: MEDICARE PAYMENT POLICY, APPENDIX B: AN INTRODUCTION TO HOW MEDICARE MAKES COVERAGE DECISIONS (2003), available at http://www.medpac.gov/documents/reports/mar14_entirereport.pdf?sfvrsn=0.
- ⁶¹⁷ In reviewing coverage, CMS weighs the medical and scientific evidence in accordance with a fairly standardized hierarchy that ranks the relative authority given to various types of studies. See <http://www.medpac.gov/>.
- ⁶¹⁸ For more information on Medicare coverage of clinical trials, <http://www.cms.gov/Medicare/Medicare.html>. For a copy of the pre-MMA NCD on routine costs of clinical trials, <http://www.cms.gov/Medicare/Medicare.html>.
- ⁶¹⁹ See Donald G. McNeil Jr., New Ideas in Global Health Get a \$437 Million Assist, N.Y. TIMES, June 28, 2005, at D1.
- ⁶²⁰ See www.sec.gov/news/press/2004-13.htm; see also Amy Tsao, Feds to Biotech: No More Fibbing!, BUSINESSWEEK, Feb. 20, 2004.
- ⁶²¹ See Dennis S. Fernandez & James T. Huie, *Strategic Balancing of Patent and FDA Approval Processes to Maximize Market Exclusivity* 1.
- ⁶²² See, e.g., Press Release, Department of Justice, Warner Lambert to Pay \$430 Million to Resolve Criminal and Civil Health Care Liability Relating to Off-Label Promotion (May 13, 2004), available at <http://www.justice.gov>.
- ⁶²³ NATIONAL HERITAGE INSURANCE COMPANY, CENTERS FOR MEDICARE AND MEDICAID SERVICES, FRAUD AND ABUSE GUIDE 3 (Aug. 2004).
- ⁶²⁴ *Id.*
- ⁶²⁵ *Id.* at 4-5.
- ⁶²⁶ 5 U.S.C. app. 3 (2005).
- ⁶²⁷ 5 U.S.C. app. 3, §§ 2(1) & (2), 3(a), 4(a)(3), 9(a)(1)(D).
- ⁶²⁸ Health Insurance Portability and Accountability Act of 1996, Pub. L. No. 104-191 (1996).
- ⁶²⁹ 42 U.S.C. § 1320a-7 (2005).
- ⁶³⁰ FRAUD AND ABUSE GUIDE, *supra* note 623, 18.
- ⁶³¹ 42 U.S.C. § 1320a-7a(a) & (b) (2005).

⁶³² 18 U.S.C. § 287 (2005).
⁶³³ *Id.* § 1031.
⁶³⁴ *Id.* § 1035.
⁶³⁵ See *United States v. Sarin*, 10 F.3d 224 (4th Cir. 1993) (regarding false statement to NIH).
⁶³⁶ *United States v. Olin Mathieson*, 368 F.2d 525 (2d Cir. 1966); *United States v. Larson*, 796 F.2d 244, 246 (8th Cir. 1986).
⁶³⁷ EIGHTH CIRCUIT MANUAL OF MODEL JURY INSTRUCTIONS, CRIMINAL, § 6.18.1001A (2003).
⁶³⁸ 42 U.S.C. § 1320a-7b(a)(1) (2005).
⁶³⁹ *Id.* § 1320a-7b(a)(2).
⁶⁴⁰ *Id.* § 1320a-7b(a)(3).
⁶⁴¹ *Id.* § 1320a-7b(b).
⁶⁴² 42 C.F.R. § 1001.952 (2005).
⁶⁴³ See *United States v. Augustine Med., Inc.*, No. 03-3211-8, 2004 WL 256772 (D. Minn. Feb. 10, 2004); *United States v. Adler*, 623 F.2d 1287, 1290 (8th Cir. 1980).
⁶⁴⁴ *United States v. Batchelder*, 442 U.S. 114 (1979); *Adler*, 623 F.2d at 1290 (Sections 287 and 1001 not rendered inoperative regarding false claims and statements to Medicare and Medicaid by corollary Title 42 misdemeanors).
⁶⁴⁵ 31 U.S.C. §§ 3729-3731 (2005).
⁶⁴⁶ See Press Release, Department of Justice, *supra* note 622.
⁶⁴⁷ 31 U.S.C. § 3730.
⁶⁴⁸ 42 C.F.R. § 420.405 (2005).
⁶⁴⁹ 18 U.S.C. § 1518 (2005).
⁶⁵⁰ See <http://www.taf.org>.
⁶⁵¹ See Press Release, United States Securities and Exchange Commission, SEC and FDA Take Steps to Enhance Inter-Agency Cooperation (Feb. 5, 2004), available at <http://www.sec.gov/news/press/2004-13.htm>.
⁶⁵² Tsao, *supra* note 620.
⁶⁵³ *Id.*
⁶⁵⁴ See Ross Kerber, Regulators Seen Failing to Cooperate—FDA, SEC has vowed to unite on drug firms' disclosures, THE BOSTON GLOBE, June 6, 2005.
⁶⁵⁵ See Bernadette Tansey, Rise in Biotech Lawsuits, S. F. CHRON., Jan. 26, 2004, available at <http://www.genet-info.org>.
⁶⁵⁶ *Dura Pharm., Inc. v. Broudo*, 125 S. Ct. 1627 (2005).
⁶⁵⁷ *Id.*
⁶⁵⁸ See MINN. STAT. § 302A.201 (2004).
⁶⁵⁹ See, e.g., *United States v. Byrum*, 408 U.S. 125, 141-42 (1972); *Great Rivers Coop. v. Farmland Indus., Inc.*, 198 F.3d 685, 701-02 (8th Cir. 1999); *Revlon, Inc. v. MacAndrews & Forbes Holdings, Inc.*, 506 A. 2d 173, 179 (Del. 1986).
⁶⁶⁰ *Graham v. Allis-Chalmers Mfg. Co.*, 188 A.2d 125, 130 (Del. 1963) (finding the degree of care to be that "which ordinarily careful and prudent men would use in similar circumstances").
⁶⁶¹ *Smith v. Van Gorkem*, 488 A.2d 858, 872 (Del. 1985).
⁶⁶² "A board of directors enjoys a presumption of sound business judgment, and its decisions will not be disturbed [or second guessed] if they can be attributed to any rational business purpose. A court under such circumstances will not substitute its own notions of what is or is not sound business judgment." *Sinclair Oil Corp. v. Levien*, 280 A.2d 717, 720 (Del. 1971). Accord *In re Bidermann Indus. U.S.A., Inc.*, 203 B.R. 547, 552 (Bankr. S.D.N.Y. 1997).

- ⁶⁶³ See *Aronson v. Lewis*, 473 A.2d 805, 812 (Del. Super. Ct. 1984); *But see, e.g., Brandt v. Hicks, Muse & Co. (In re Healthco Int'l, Inc.)*, 208 B.R. 288, 306 (Bankr. D. Mass. 1997) (finding that the directors failed to fulfill their “duty to inform themselves, prior to making [the] business decision, of all material information reasonably available to them”).
- ⁶⁶⁴ Myron M. Sheinfeld & Judy Harris Pippitt, *Fiduciary Duties of a Corporation in the Vicinity of Insolvency and After Initiation of a Bankruptcy Case*, 60 BUS. LAW. 79, 80 (2004).
- ⁶⁶⁵ See, e.g., *Demoulas v. Demoulas Super Markets, Inc.*, 677 N.E.2d 159, 179 (Mass. 1979) (indicating that directors “are bound to act with absolute fidelity and must place their duties to the corporation [and its shareholders] above every other financial or business obligation”); *Clements v. Rogers*, 790 A.2d 1222 (stating that “the duty of loyalty is implicated when conflicted directors propose a self-dealing transaction”).
- ⁶⁶⁶ Sarbanes-Oxley Act of 2002, Pub. L. No. 107-204, 116 Stat. 745 (2002).
- ⁶⁶⁷ Shareholders, as the holders of the residual interest in the corporation, may maintain a derivative action against the corporation’s board of directors for breaches of fiduciary duties and indirectly benefit from any recovery obtained on behalf of the corporation. See *MAXXAM Inc./Federated Dev. S’holders Litig.*, 698 A.2d 949, 956 (Del. Ch. 1996).
- ⁶⁶⁸ See *United States v. Jolly*, 102 F.3d 46, 48 (2d Cir. 1996).
- ⁶⁶⁹ *Katz v. Oak Indus., Inc.*, 508 A.2d 873 (Del. Ch. 1986). See James Gadsden, *Enforcement of Directors’ Fiduciary Duties in the Vicinity of Insolvency*, 24 AM. BANKR. INST. J. 16 (Feb. 2005).
- ⁶⁷⁰ Courts have employed two principal definitions of “insolvency”: the “equitable” insolvency test and the “balance sheet” insolvency test. Under the equitable insolvency definition, the courts consider whether a corporation is generally able to pay its debts as they come due. The balance sheet standard, by contrast, considers whether the fair market value of the corporation’s assets is worth less than its liabilities. Courts have also found transactions that render the corporation insolvent or on the brink of insolvency subject directors to heightened scrutiny. See, e.g., *Brandt v. Hicks, Muse & Co. (In re Healthco Int'l, Inc.)*, 208 B.R. 288 (Bankr. D. Mass. 1997). While these are legal definitions, they are similar to the accounting definition of a going concern: a business with the ability to realize its assets at recorded amounts and to extinguish its liabilities in the normal course of business. See American Institute of Certified Public Accountants, *The Auditor’s Consideration of an Entity’s Ability to Continue As A Going Concern (Statement on Auditing Standards No. 59) AU § 341.02*, available at <http://www.aicpa.org>.
- ⁶⁷¹ *Unsecured Creditors Comm. v. Noyes (In re STN Enters.)*, 779 F.2d 901, 904 (2d Cir. 1985); *Geyer v. Ingersoll Publ’ns Co.*, 621 A.2d 784, 787 (Del. Ch. 1992).
- ⁶⁷² See *Helm Fin. Corp. v. MNVA R.R., Inc.*, 212 F.3d 1076, 1081 (8th Cir. 2000).
- ⁶⁷³ See *Credit Lyonnais Bank Nederland, N.V. v. Pathe Communications Corp.*, Civ. A. No. 12150, 1991 WL 277613 (Del. Ch. Dec. 30, 1991) (opining that directors of a corporation that is in the vicinity of insolvency should view the corporation as a “community of interests”).
- ⁶⁷⁴ See, e.g., *FDIC v. Sea Pines Co.*, 692 F.2d 973, 977 (4th Cir. 1982), cert. denied, 461 U.S. 928 (1983).
- ⁶⁷⁵ See, e.g., *Geyer*, 621 A.2d at 789.
- ⁶⁷⁶ See 11 U.S.C. § 365 (2004). In the context of “rejection,” the non-debtor counterparty is typically left with only a general unsecured claim for breach of contract. See *id.* § 365(g).
- ⁶⁷⁷ See, e.g., *Lubrizol Enters., Inc. v. Richmond Metal Finishers, Inc.*, 756 F.2d 1043 (4th Cir. 1985).
- ⁶⁷⁸ See 11 U.S.C. § 101(35A). Notably, the Bankruptcy Code’s definition of “intellectual property” is restrictive in scope and does not include trademarks, trade name rights or service marks. See *id.*
- ⁶⁷⁹ 11 U.S.C. § 365(n).
- ⁶⁸⁰ *Id.*
- ⁶⁸¹ *Id.* § 365(n)(2).
- ⁶⁸² See, e.g., *Perlman v. Catapult Entm’t, Inc. (In re Catapult Entertainment, Inc.)*, 165 F.3d 747 (9th Cir. 1999). Accord *In re Hernandez*, 285 B.R. 435 (Bankr. D. Ariz. 2002); *In re Access Beyond Techs., Inc.*, 237 B.R. 32 (Bankr. D. Del. 1999).
- ⁶⁸³ 11 U.S.C. § 365(e) (2004).

⁶⁸⁴ *Id.* § 365(b).

⁶⁸⁵ *See id.* § 365(f).

⁶⁸⁶ *See In re CFLC, Inc.*, 89 F.3d 673 (9th Cir. 1996).

⁶⁸⁷ *See* 11 U.S.C. § 365(c)(2004).

⁶⁸⁸ *See generally* *Rockwell Graphic Sys., Inc. v. DEV Indus., Inc.*, 925 F.2d 174 (7th Cir. 1991).

⁶⁸⁹ *See, e.g.*, *Institut Pasteur v. Cambridge Biotech Corp.*, 104 F.3d 489 (1st Cir. 1997) (finding that the sale of 100% of the debtor's stock pursuant to a Chapter 11 plan did not constitute a de facto assignment of the debtor's licenses to the new parent corporation). *But cf. Perlman*, 165 F.3d at 747.

GLOSSARY OF DEFINED TERMS

510(k)	FDA premarket notification classification for marketing clearance process of certain medical devices in the United States
ADE	Adverse Drug Experience
AMA	American Medical Association
ANDA	Abbreviated New Drug Application
Anti-Kickback Act	The Federal Health Care Program Anti-Kickback Act
APC	Ambulatory Payment Classifications
APHIS	Animal and Plant Health Inspection Service
ASP	average sales price
BLA	Biologic License Applications
Cartagena Protocol	Cartagena Protocol on Biosafety
CBER	Center for Biologics Evaluation and Research
CBP	Customs and Border Protection (formerly U.S. Customs Service)
CDA	confidentiality or non-disclosure agreement
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CEO	Chief Executive Officer of the company
CFO	Chief Financial Officer of the company
CFSAN	Center for Food Safety and Applied Nutrition
CMS	Center for Medicare Services
Code	Internal Revenue Code of 1986, as amended
Codex Guidelines	Codex Guidelines on Food Derived From Biotechnology
CPT	current procedure terminology
DCL	descarboethoxyloratadine
DEED	Department of Employment and Economic Development for the State of Minnesota
DIP	debtor-in-possession
Directive 2001/18	Directive 2001/18/EC of the European Parliament and of the Council on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC
DNA	deoxyribonucleic acid
DRG	Diagnostic Related Group
EBIT	earnings before interest and taxes
EPA	Environmental Protection Agency

EPO	European Patent Office
ERISA	Employee Retirement Income and Security Act
EU	European Union
Exchange Act	Securities Exchange Act of 1934, as amended
FCPA	Foreign Corrupt Practices Act
FDA	Food and Drug Administration
FDC Act	Food, Drug and Cosmetic Act of 1938, as amended
FIFRA	Federal Insecticide, Fungicide and Rodenticide Act
FIN 46	Financial Accounting Standards Board Interpretation No. 46, <i>Consolidation of Variable Interest Entities, an Interpretation of ARB No. 51</i>
GAAP	generally accepted accounting principles
GM	genetically modified
GMO	genetically modified organisms
HCFA	Health Care Fraud and Abuse Control Program
HCPCS	Health Care Common Procedure Coding System
HGP	Human Genome Project
HHS	Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act of 1996
IDE	Investigational Device Exemptions
IND	Investigational New Drug
IPO	initial public offering
IRS	Internal Revenue Service
LLC	limited liability company
LLP	limited liability partnership
M&A	mergers and acquisitions
MCAN	Microbial Commercial Activity Notice
MD&A	Management's Discussion and Analysis of Financial Condition and Results of Operations
MDR	Medical Device Reporting
NASA	National Aeronautics and Space Administration
NASDAQ	National Association of Securities Dealers Automated Quotations
NCD	National Coverage Determination
NDA	New Drug Application
NHGRI	National Human Genome Research Institute
NIGMS	National Institute of General Medical Sciences
NIH	National Institutes of Health
NOL	net operating loss
NSF	National Science Foundation
NYSE	New York Stock Exchange
OIG	HHS Office of Inspector General
PIPE	private investment in public equity

PMA	FDA premarket approval classification for marketing approved process of certain medical devices in the United States
PPM	private placement memorandum
PPS	Prospective Payment System
PSA	Pre-Solicitation Announcement
PVPA	Plant Variety Protection Act
QLCC	Qualified Legal Compliance Committee
RAC	Recombinant DNA Advisory Committee
R&D	research and development
Regulation 1830/2003	Regulation (EC) No. 1830 of the European Parliament and of the Council of the European Union, of 22 September 2003, concerning the traceability and labeling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms and amending Directive 2001/18/EC
Sarbanes-Oxley	Sarbanes-Oxley Act of 2002
SBA	U.S. Small Business Administration
SBIR	Small Business Innovation Research Program
SBIR Act	Small Business Innovation Development Act
SCNT	somatic cell nuclear transplantation
SEC	Securities and Exchange Commission
Section 197 Intangible Securities Act	certain intangible property as defined by Section 197 of the Code Securities Act of 1933, as amended
STTR	Small Business Technology Transfer Program
TERA	TSCA Experimental Release Application
TRIPS Agreement	Trade-Related Aspects of Intellectual Property Agreement
TSCA	Toxic Substances Control Act
TTO	Technology Transfer Office
UCC	Uniform Commercial Code of any relevant state, as amended
ULOE	Uniform Limited Offering Exemption
U.S.	United States of America
USDA	U.S. Department of Agriculture
USPTO	U.S. Patent and Trademark Office
VC	venture capital
VIE	variable interest entity
WTO	World Trade Organization

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