



# **Entrepreneur's Resource Guide**

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# Introduction

The BioEnterprise Initiative team has compiled this brief guide to support bioscience entrepreneurs and emerging companies throughout the Cleveland region. In it, the team has cataloged numerous, regional resources that are relevant to developing bioscience business plans as well as growing and operating bioscience companies. In addition, the guide contains links to Web sites that contain additional information on selected aspects of bioscience.

Throughout, the purpose has been to provide basic information on a topic and then assemble the resource information in a manner that is easy to use and find for any entrepreneur, not to re-create materials that already exist or offer specific advice on developing bioscience businesses.

We hope that you find this guidebook a useful tool, and we look forward to your suggestions and additions to make this a more complete resource for the community.

## Legal Disclaimer

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## Intellectual Property

In entrepreneurial growth businesses, a critical factor is the technology around which the company is formed. It is important to know if there is a disruptive innovation or an incremental one, a single product or a platform technology. It is necessary to have a plan to protect the technology and obtain intellectual property (IP) protection as the concept moves to commercialization.

Generally around the globe, the term “intellectual property” encompasses four categories of exclusive rights that may be held in intangible assets: patents, trademarks, copyrights, and trade secret rights. Technology companies, especially early stage or start-up enterprises, often succeed or fail largely on the basis of their ability to establish and protect intellectual property rights related to their core technology assets. Thus a solid understanding of intellectual property-related issues, and a strong program for establishing and protecting IP rights, are fundamental considerations for technology entrepreneurs.

At its core, the concept of property and “ownership” involves the notion of exclusive rights – that is, the right to exclude. An emerging technology company should focus on intellectual property issues for this very simple reason: by establishing and protecting intellectual property rights in the technology, it obtains a competitive advantage. The company is generally able to exclude others from using those technologies, or the company can require others to obtain a license (and pay license fees) for such use.

### **What Is a Patent?**

A patent for an invention is the grant of a property right to the inventor, issued by the Patent and Trademark Office. The term of a new patent is 20 years from the date on which the application for the patent was filed in the United States or, in special cases, from the date an earlier related application was filed, subject to the payment of maintenance fees. U.S. patent grants are effective only within the U.S., U.S. territories, and U.S. possessions.

The right conferred by the patent grant is, in the language of the statute and of the grant itself, “the right to exclude others from making, using, offering for sale, or selling” the invention in the United States or “importing” the invention into the United States. What is granted is not the right to make, use, offer for sale, sell or import, but the right to exclude others from making, using, offering for sale, selling or importing the invention.

## **What Is a Trademark or Servicemark?**

A trademark is a word, name, symbol or device which is used in trade with goods to indicate the source of the goods and to distinguish them from the goods of others. A servicemark is the same as a trademark except that it identifies and distinguishes the source of a service rather than a product. The terms “trademark” and “mark” are commonly used to refer to both trademarks and servicemarks.

Trademark rights may be used to prevent others from using a confusingly similar mark, but not to prevent others from making the same goods or from selling the same goods or services under a clearly different mark. Trademarks which are used in interstate or foreign commerce may be registered with the Patent and Trademark Office. The registration procedure for trademarks and general information concerning trademarks is described in a separate pamphlet entitled “Basic Facts about Trademarks.”

## **What Is a Copyright?**

Copyright is a form of protection provided to the authors of “original works of authorship” including literary, dramatic, musical, artistic, and certain other intellectual works, both published and unpublished. The 1976 Copyright Act generally gives the owner of copyright the exclusive right to reproduce the copyrighted work, to prepare derivative works, to distribute copies or phone records of the copyrighted work, to perform the copyrighted work publicly, or to display the copyrighted works publicly.

The copyright protects the form of expression rather than the subject matter of the writing. For example, a description of a machine could be copyrighted, but this would only prevent others from copying the description; it would not prevent other from writing a description of their own or from making and using the machine. Copyrights are registered by the [Copyright Office of the Library of Congress](#).

General information on patents, trademarks and copyrights are available from the United States Patent and Trademark Office: [www.uspto.gov](http://www.uspto.gov).

## **What Is a Trade Secret?**

Most states have adopted some form of the Uniform Trade Secret Act (UTSA). The UTSA sought to provide some consistency in trade secret law that, until recently, was protected only by state laws. There is now also federal law protection for trade secrets. The UTSA defines a trade secret as, “Information, including a formula, pattern, compilation, program, device, method, technique or process, that a) 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 b) is the subject of efforts that are reasonable under the circumstances to maintain its secrecy.” When you have information that has economic value as a result of its secrecy and you use reasonable efforts to keep it secret, you have a trade secret.

## To protect IP ...

- It is advisable to hire an intellectual property attorney (or an IP search firm) to perform the necessary procedures to secure the concept.
- Be prepared and do plentiful research. Some points to consider while conducting research are:
  - Costs (of patent filings and attorney fees)
  - Basic IP concepts and terms
  - Various scenarios that may arise during the process of patenting a technology.
  - Overview of costs, concepts and scenarios can be found in *An Entrepreneur's Guide to a Bioscience Start-up* ([www.evelexa.com](http://www.evelexa.com))

## For university or other research institution based entrepreneurs:

Entrepreneurs whose innovations are based on research conducted at universities or other federally-supported institutions should contact their Technology Transfer Office. Technology Transfer Offices are generally charged with facilitating the transfer of ideas, inventions and discoveries out of the research lab, through the patent office, and into the commercial sector.

Technology Transfer Offices facilitate the invention commercialization process, including the protection (through patents and copyrights) and licensing of inventions; the post-licensing oversight of agreement compliance; and distribution of royalties and fees. Technology transfer is accomplished either by a license to an existing company or the creation of a new start-up entity.

The Bayh-Dole Act is the basis for the current practice and success of university technology transfer in the U.S. Bayh-Dole Act pertains to the legalities of rights to technologies developed with federal money (most importantly *NIH grants*). Technologists should familiarize themselves with the act to ensure proper ownership rights. Details can be accessed at: <http://www.cptech.org/ip/health/bd/>

In brief, The Bayh-Dole Act:

- Established a uniform policy governing inventions made at universities using federal research funds;
- Gave universities the right to take title and own such inventions;
- Encouraged universities to forge ties with industry to commercialize these inventions;
- Obligated universities taking title to file patent applications and seek to commercialize the inventions;
- Urged universities to give preference in licensing to small companies;

- Required universities to share a portion of licensing income with faculty inventors; and
- Required universities to use any remaining income, after expenses, to support scientific research and education.

*Crain's Cleveland Business* maintains lists of Professional Services firms: [www.craainscleveland.com/section/craains-lists](http://www.craainscleveland.com/section/craains-lists). The lists are available to download for a small fee.

# Market Opportunity

## Market Opportunity

Successful entrepreneurial growth businesses always have a firm understanding of the market opportunity they are pursuing, their customer needs, and their competition. Businesses develop this understanding through customer/market interactions, market research documents, and a vigilant monitoring of their competitors and new developments/technologies in the field.

## Specifying the Unmet Need

Entrepreneurs must clearly articulate what the unmet needs are in the market that they are addressing. The needs are usually classified as improvements required in the cost, quality, or service for a particular offering. In health care, it is critical to understand the unmet need from multiple viewpoints. For example, a medical device innovation will have implications for patients, physicians (can be multiple physician types), hospitals, and payers. A strong business case assesses the unmet needs and opportunities for each as it relates to the innovation.

The best approach for understanding unmet needs is through interviews with involved parties as well a survey of literature for the relevant application. The business plan should attempt to quantify the unmet need and potential benefit opportunity for the innovation (e.g., extent of savings or profit opportunity, improvement in patient outcomes, etc.) if possible. Most bioscience business plans will need to address payment/reimbursement issues and levels. WebMD ([www.webmd.com](http://www.webmd.com)) and Medscape ([www.medscape.com](http://www.medscape.com)) are examples of sources for news and information on health care technologies. Reimbursement Principles, Inc. ([www.reimbursementprinciples.com](http://www.reimbursementprinciples.com)) is a resource for questions and reimbursement strategies on medical devices.

## Describing the Market Space

Crisp business plans accurately describe the market space. The procedures or patient populations are defined with specificity, not in generalities (e.g., a specific cardiac condition/indication, not cardiac disease in general). And the plans also detail current products or service offerings and expenditures for the specific application area. In many bioscience areas, there will be a mix of treatment approaches and a percentage of cases that go undiagnosed. All of this should be discussed in the business plan.

The best resources for getting data are market research and analyst reports. Some data can be found on a variety of web sites below. It is critical for credibility to parse through gross information to specific numbers as stated above. Finally, the need for global data depends upon the nature of the product/service offering.

## **Competitors/Emerging Technologies**

Successful business people always have a firm understanding on all sources of competition to address the unmet needs that their offerings are targeting. In bioscience areas, this often includes an array of different types of competitors across drugs, devices, and treatment approaches. It is best to assess competition from the point-of-view of the user/consumer, not just competition for similar types of products/services (e.g., stents compete with both drug therapies for patients as well as other surgical procedures such as bypasses). The best sources of information tend to be market research reports and the end consumers themselves.

Furthermore, strong businesses have an eye toward emerging approaches that may increase or decrease their market potential. Web sites such as Medscape and professional society sites and conferences tend to report on new developments that are still in the early stages of development. For drugs and PMA medical devices, the FDA Web sites ([www.fda.gov](http://www.fda.gov)) catalog stage of development of products that are have filed for approval and trials status.

BioEnterprise has compiled a list of Web sites with market data and information on their web site ([www.bioenterprise.com/marketdata](http://www.bioenterprise.com/marketdata)).

# Technology

## Description

A clear, concise description of the technology is an essential component of any well developed Business Plan. The technology should be explained in terms understandable to a layperson that is unfamiliar with the science. Excessive details using highly technical terms may discourage the reader and potential investor.

The Technology Section of the Business Plan should contain an accurate explanation of how the technology addresses an unmet need and justifies the formation of a business (rather than only being suitable as a license).

Many investors will also obtain an opinion from a scientific expert. Consider placing scientific papers and details on the technology in an Appendix to the Plan to facilitate the process.

## Data/Prototype

Data to demonstrate the feasibility, accuracy and efficacy of the technology should be included. Note however, that confidential details which may adversely impact future patent filings should be avoided. Acronyms and the significance of tables, charts and figures should be explained for investors who may not be familiar with the technology. Data should demonstrate the technology's strength as it progresses from proof of concept to pre-clinical (animal) studies to clinical (human) studies.

Studies and the resulting data should be recorded, dated, signed and witnessed. Data should be recorded in a bound notebook with pre-numbered pages that reduces chances for future alterations. Clear documentation is essential to establish priority dates to acquire and protect Intellectual Property.

Prototypes demonstrate progress toward commercialization. A laboratory prototype (alpha version) is generally constructed for purposes of testing the technology at the research lab bench. It may consist of glassware, instrumentation and electronics assembled from pieces available in the laboratory- to provide proof of the technical concept. A working prototype brings the concept closer to the model which will see commercialization. It may incorporate specially machined or molded items. Electronics may be contained in boxes with realistic displays, with the prototype interacting in a functional way with the user. A Beta test model will be placed in customer environments where the item is expected to be used and will be very similar in function and appearance to the actual item offered for sale.

## **Uniqueness**

The technology description should reinforce the unique advantages of the technology when compared to competing products. In addition to addressing an unmet need, can the technology achieve results quicker, with less cost and more accurately? Will it reduce risk and liability for the customer? What are the competitive advantages? The clinical significance of adopting the technology should be addressed, along with any economic advantages for the insurer, hospital, physician and patient.

# Product Development

## Product Development Plan

Technology-based new ventures of any sort usually require fairly lengthy product development cycles. Because of the added requirements to establish, to the satisfaction of the FDA, proof of product safety and efficacy, the development cycles for bioscience products used in human healthcare are quite complex and can range anywhere from five to more than ten to fifteen years. Such a long delay before sales, revenue generation, and return on investment presents a significant challenge to potential investors. Knowledgeable investors will want to see a carefully thought out and researched development plan that:

- Clearly defines the product;
- Identifies and prioritizes critical steps, identifies decision and branch points and establishes decision criteria;
- Establishes and justifies links between funding events and product milestones;
- Identifies resource needs including contract and collaborative development partners at appropriate points along the development pathway; and
- Demonstrates understanding of the regulatory process.

A sound product development plan is an important tool both to effectively manage the development process internally as well as to attract necessary financial support.

Development pathways will differ depending on a company's product and resources. Bioscience entrepreneurs may find it helpful to approach the planning process from the perspective of the established FDA product categories – device, drug, biological, and combination – which are managed by the FDA Centers for Devices and Radiological Health, Drug Evaluation and Research, and Biologics Evaluation and Research and the Office of Combination Products, respectively (see boxed section below). Regulations and established practices within each FDA division as well as common developmental issues faced by similar product types allow some general product development guidelines to be suggested for each of the different classification groups.

Entrepreneurs are encouraged to consult the FDA web sites to gain a better understanding of the regulatory process and product classification scheme.

## **FDA Centers for bioscience products**

- o Center for Devices and Radiological Health (CDRH)  
[www.fda.gov/cdrh](http://www.fda.gov/cdrh)
- o Center for Drug Evaluation and Research (CDER)  
[www.fda.gov/cder](http://www.fda.gov/cder)
- o Center for Biologics Evaluation and Research (CBER)  
[www.fda.gov/cber](http://www.fda.gov/cber)
- o Office of Combination Products  
[www.fda.gov/oc/combination](http://www.fda.gov/oc/combination)

## **Product Development Process Overview**

FDA regulatory requirements usually dominate bioscience product development strategic planning. Even technical and basic science issues are prioritized within the context of satisfying Agency requirements.

The development process is usually considered in two stages, preclinical and clinical development. The former consists of all the development work that takes place prior to testing of the device or agent in humans, whereas the latter consists of the human trials. The FDA does not regulate preclinical studies *per se* but it does set standards that must be met to enter human trials that strongly impact the preclinical work. Bioscience entrepreneurs seeking to minimize resource use in bringing a new product to market must be well informed of the regulatory requirements for their proposed products and organize their preclinical work to efficiently address key questions and issues that will be raised by the Agency.

The clinical development phase is highly regulated. The goal of this phase is to gain approval by the FDA to market the new product. To win approval the company must demonstrate – following mandated procedures and meeting established criteria – that the product is safe and provides significant health benefits to well-defined patient populations. The rules are many and sometimes complex and the criteria for safety and efficacy can be narrowly defined and relatively inflexible. Experienced, expert regulatory planning and management is critical for success.

The specific steps in each phase depend on the nature of the product – drug, device, biologic, or combination. Generalized development pathways for each are outlined below, following descriptions of two important first steps common to all programs – proof of concept and product definition.

## **Development Pathways – Common Steps**

*Proof of Concept.* An important hurdle to commercializing a product is “proof of concept” or “proof of principle”. Most product ideas that are novel entail unknowns that will need to be resolved during the development process. Some of the unknowns will be of a fundamental nature, reflecting gaps in the current state of knowledge. The product idea may be based on a hypothesis about an unknown, and thus the feasibility of the product idea will depend on the validity of the hypothesis. For example, a biologist may discover a new receptor that is expressed only in certain areas of the brain. Based on existing knowledge of brain functional anatomy, the investigator may propose that a drug that activates the receptor would be a useful therapeutic for depression. The investigator may patent the receptor and form a company to commercialize antidepressants acting at the receptor. However, reasonable investors would hesitate to provide support until the proposed connection between activity at the receptor and the desired clinical outcome is better established. “Proof of concept”, in this case, might entail identification of a compound that has activity at the new receptor and demonstration that it produces effects in animal models that are agreed to generally predict antidepressant activity in humans. The animal experiments do not guarantee human clinical efficacy, but they do provide data that significantly increases the probability and decreases the risk of the commercial venture.

What constitutes “proof of concept” is, to a degree, subjective and dependent on expert knowledge and judgment. It is clearly different from proof of efficacy which is only established after human clinical trials. Both investors and innovators will rely in part on expert opinions from third parties and consensus rather than individual opinion. Innovators should seek input from those familiar with the investment community and be prepared to use resources such as personal finances or basic research grants from government or private sources to develop their ideas to the point where equity investors are comfortable with the remaining technological uncertainty.

*Product definition.* Product definitions should include meaningful and realistic operational specifications that are as precise and specific as possible. Such specifications may be enhanced over time as development efforts refine the underlying technology, but it is important to begin the product development process with targets for cost and performance that address market needs and alternative solutions. Developing specifications is usually more straightforward for devices than for drugs and biologics, with parameters such as size, accuracy, and so on sometimes an integral part of the product concept. In the case of drugs and biologics, it can be advantageous to develop a product definition and specifications that go beyond “a cure for” and demonstrate knowledge of differences between patient populations, sensitivity to reimbursement policies, understanding of physician preferences and practices, appreciation of the limitations imposed by production, and so on.

## Development Pathways - Devices

*Regulatory Issues.* As part of developing a device's product definition, entrepreneurs should identify the appropriate CDRH classification. FDA assigns devices to one of three categories – Class I, II, or III – which describe the degree of hazard to a patient inherent in the device (or, as described by FDA, “the level of control necessary to assure the safety and effectiveness of the device”). As an informative introduction see “Getting to Market with a Medical Device” at the CDHR web site [www.fda.gov/cdrh/devadvice](http://www.fda.gov/cdrh/devadvice)

The safety class determines, among other things, the type of application required for FDA clearance. If a device is categorized as Class I or II, and *if it is not exempt* (see below), a **510(k)** application will be required for marketing. For Class III devices, a pre-market approval application (**PMA**) is usually required.

- **510(k)** – “A 510(k) is a premarketing submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, *substantially equivalent* [italics added; see adjacent boxed text], to a legally marketed device that is not subject to premarket approval (PMA). Applicants must compare their 510(k) device to one or more similar devices currently on the U. S. market and make and support their substantial equivalency claims.”

“Substantial equivalence”, as defined by the FDA, means that a device has the same intended use as the predicate device; and has the same technological characteristics as the predicate device; or has different technological characteristics that do not raise new questions of safety and effectiveness, and the sponsor demonstrates that the device is as safe and effective as the legally marketed device. Detailed information on how FDA determines substantial equivalence can be found in the Premarket Notification Review Program 6/30/86 (K86-3) blue book memorandum.

- **PMA** – “Pre-Market Approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.”

The FDA recognizes that many new devices are improved versions of existing technologies, performing essentially the same function in much the same manner as previously approved devices. The Agency allows companies to simplify the regulatory process by referring to the existing, or “predicate device”, as evidence for the basic safety and efficacy of the common elements. Companies thus do not need to expend resources on redundant studies but they may focus on what is novel or different in the new configuration. Until the applicant receives an order declaring a device SE, they may not proceed to market the device

### **Predicate devices**

The FDA maintains a searchable database of devices with current marketing approval. To obtain information on products which may serve as predicate devices,

- o Search the device classification database using key words, for example, infusion pump, [www.accessdata.fda.gov/scripts/cdrh](http://www.accessdata.fda.gov/scripts/cdrh)
- o Obtain the product code for that class of device (infusion pumps = FRN)
- o Search the 510(k) database [www.accessdata.fda.gov/scripts/cdrh](http://www.accessdata.fda.gov/scripts/cdrh) for products with the same code. Note the 510(k) numbers (start with K) of the products which may be predicate devices.
- o Enter the 510(k) number to access additional information on a specific product

### **Device Classifications – Examples**

Class I – elastic bandages, examination gloves, hand-held surgical instruments

Class II – powered wheelchairs, infusion pumps, surgical drapes

Class III – heart valves, silicone gel-filled breast implants, implanted cerebella stimulators

### **Additional Requirements**

Introduction of some devices to the market does not require either a 510(k) or PMA application; these devices are classified as *exempt*. Most devices so classified were in production and use prior to passage of certain regulations in 1976; a more complete account can be found at the FDA/CDRH web site “Device Advice – Class I/II Exemptions” at [www.fda.gov/MedicalDevices](http://www.fda.gov/MedicalDevices) (7/13/04). Exemption in this context does not mean freedom from regulation; all devices, regardless of the approval process, must conform to additional requirements concerning:

- registration – establishments involved in the production and distribution of medical devices intended for commercial distribution in the US are required to register with the FDA

- listing – medical device establishments required to register with FDA must list the devices they have in commercial distribution including devices produced exclusively for export
- labeling – medical devices must be labeled with the name and place of business of manufacturer, intended use, adequate directions, and other information described by law
- Good Manufacturing Practice – GMP regulations require that domestic or foreign manufacturers have a documented, quality system for the design, manufacture, packaging, labeling, storage, installation, and servicing of finished medical devices intended for commercial distribution in the U.S.

The emphasis in this section has been on FDA requirements since they pose the primary regulatory burden. Devices may also be subject to regulations or oversight by other government agencies and additional organizations. Clinical laboratory systems may, for example, come under OSHA jurisdiction in matters of operator safety, under EPA jurisdiction in matters of material output, and may be subject to UL design specifications. However strong the medical value of the proposed device, failure to recognize and meet all regulatory concerns during product development can significantly delay commercialization and revenue generation.

*Prototyping & Preclinical Development.* Device development is an iterative process of building, testing, and modifying. the pathways for development and resources required vary widely. The best advice to an entrepreneur may be to carefully determine which capabilities are fundamental core competencies and provide a competitive advantage and which may be outsourced.

As an example, a device producer may choose to contract for some product testing. A company with core expertise in MEMS production may find it better to outsource *in vivo* testing of an implantable drug delivery device than to try to develop the capability inhouse. Options for outsourcing include not only commercial providers, such as those listed in this resource, but also sponsored work in academic labs. In considering the latter route, the entrepreneur need be aware of both the larger objectives and motivations of potential academic collaborators as well as the possible intellectual property ownership issues that may arise.

## Development Pathways – Drugs & Biologics

The development pathways for drugs and biologics are quite similar – not surprising since the basic difference between the classes is simply the source. Drugs, generally, include well-defined combinations of smaller molecular weight, single compounds of synthetic origin whereas biologics usually include potentially complex mixtures of compounds, often of relatively high molecular weight, which are obtained from natural sources or biological processes such as fermentation.

The commercialization process for pharmaceuticals (drugs & biologics) is usually divided into a preclinical and clinical development stages as was the case for devices. Drug development often includes an additional stage, “discovery”, which is the organized search for suitable molecular candidates which have a target biological activity.

Preclinical development of a drug candidate (or “biological product”) includes:

- 1) collection of relevant biological data that suggest the active compound and will prove safe and effective in human trials;
- 2) identification of a production process for the active agent, characterization of intermediates and impurities, and development of in-process and final specifications for purity;
- 3) development of a formulated drug including analytical methods to adequately determine its composition and purity;
- 4) development of a clinical research plan through Phase IIa (see below); and
- 5) preparation of initial clinical supplies.

The IND application must contain information in three broad areas:

- o *Animal Pharmacology and Toxicology Studies* - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans.
- o *Manufacturing Information* - Information on the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.
- o *Clinical Protocols and Investigator Information* - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Also, information on the qualifications of clinical investigators--professionals (generally physicians) who oversee the administration of the experimental compound--to assess whether they are qualified to fulfill their clinical trial duties. Finally, commitments to obtain informed consent from the research subjects, to obtain review of the study by an institutional review board (IRB), and to adhere to the investigational new drug regulations.

From “Investigational New Drug (IND) Application Process”, CDER, [www.fda.gov/Drugs](http://www.fda.gov/Drugs) (7/13/04).

The preclinical work should satisfy FDA requirements for advancement to human clinical trials. When ready to initiate trials, a company will summarize and present the preclinical data to the Agency in an Investigational New Drug Application (the “IND” or “INDA”) (see following text box). The request will be denied, and commercialization of the product delayed, unless the IND meets FDA specifications for form, content, and documentation.

”Relevant” biological data to suggest a candidate compound will prove safe and effective in human trials depends on the particular product. FDA does not mandate specific tests but evaluates each application in light of the proposed indication and prior experience. The trend has been to provide a greater variety of studies addressing a range of potential issues. Some studies are required for marketing approval but not for clinical trial approval. Typical pre-INDA safety studies are listed in Table 1 below. It is as important to provide assurance of data quality as it is to provide data. This is accomplished through strict adherence to Good Laboratory Practice (GLP) guidelines (see adjacent text box) throughout the preclinical research stage for any studies providing data that will be used to support the IND. Since relatively specialized facilities and procedures are required to complete many of the basic safety studies in compliance with Agency requirements, new and smaller drug companies often contract out GLP safety studies.

### Good Laboratory Practice (GLP)

The two foundations of GLP are consistency and documentation. Standard protocols must be developed – and followed diligently – for laboratory operations, including not only particular assays or production steps but also supporting activities such as calibration of critical equipment. Thorough and consistent record keeping is required at all times – production batches must be tracked, data kept in an organized fashion, input materials tested and labeled, and so on and on. Not all the information collected is submitted to FDA, but the Agency reserves the right to inspect the documents and facilities at any time; failure to meet the required standards can result in rejection of any associated data.

CDER – Division of Scientific Investigations  
[www.fda.gov/AboutFDA/](http://www.fda.gov/AboutFDA/)

### Table: Typical Preclinical Safety Studies, Drugs & Biologics

<u>Test</u>	<u>Comments</u>
Acute toxicity	Typically LD <sub>50</sub> in 2 species, 1 non-rodent, 2 routes of administration
Chronic toxicity	Typically 1X dosing daily for 2-4 weeks; animals observed for acute toxicity, tissues examined for pathology at end of study. Dosing regime can depend on acute toxicity and expected therapeutic usage.
Mutagenicity	Typically Ames assay; also <i>in vitro</i> mouse lymphoma and chromosomal aberration
Distribution, metabolism, and elimination	A broad range of <i>in vitro</i> assays ( <i>e.g.</i> hepatic microsomal enzymes – CYP450), cell-based assays ( <i>e.g.</i> CACO cell adsorption) and whole animal tests ( <i>e.g.</i> distribution & elimination)
Efficacy	Depends on target indication

The FDA provides a simplified regulatory submission option to those seeking to market drugs or biologics equivalent to existing products. Such products include the “generic drugs”. In the case of drugs the doctrine of “substantial equivalence” simplifies to chemical identity of the active ingredient. Once a composition of matter patent covering an important active pharmaceutical agent expires, competitors are free to use it. The competitors are freed from the costly and time-consuming requirements of proving the agent’s safety and efficacy. Instead, the FDA requires only that they submit proof that the proposed formulated drug, which includes excipients as well as the active agent, delivers the active agent in essentially the same manner as the marketed product.

## Development Pathways – Combination Products

Combination products are usually comprised of both a device and a drug or biologic, such as a drug eluting stent. Development pathways for combination products include elements from both component pathways. At present the FDA requires that regulatory submissions for such products be sent first to the Office of Combination Products. There a determination is made whether the product presents more drug-like, biologic-like, or device-like regulatory issues and the Office forwards the application to the appropriate section of CDER, CBER, or CDRH. The recipient takes primary responsibility for regulatory oversight. Combination product innovators should discuss potential regulatory issues in advance with the FDA.

Consider the example of a generic drug, previously taken orally, which is redeveloped in a transdermal patch delivery system. The patch, which includes no significant new technology, is subject to relatively simple 510(k), Class III device requirements. However, existing data for the oral formulation of the drug cannot be used to support safety and efficacy claims when the active agent is administered transdermally. The combination, patch + formulated drug, is subject to the more extensive clinical trial requirements of a new drug.

## Clinical Trials

The regulatory requirements for clinical trials are generally beyond the resource capabilities of small organizations. The standard model for most small companies is to establish partnerships with large pharmaceutical or device companies which provide the expertise and resources required for large scale clinical development. Innovators with very novel technologies that address significant markets may attract strategic partners at a relatively early stage of development (preclinical). However, it is most often necessary to obtain preliminary clinical proof of efficacy (a Phase IIa trial; see below) before they can attract the interest of a large partner. Clinical development is normally done by a contract research organization (CRO); the company management should include a very experienced clinical research and regulatory expert able to monitor and manage the outsourced work.

FDA classifies clinical trials into four Phases, labeled I – IV. On an informal basis and depending on the indication, these standard Phases are sometimes combined or subdivided. Brief descriptions of the Phases are:

- Phase I – basic safety studies. PI trials for drugs traditionally employ a very small (10-25) number of healthy volunteers. Such studies can usually be completed in 6 - 12 months. Costs vary considerably depending on the indication; \$1M provides an average, order-of-magnitude estimate. The studies are designed only to provide information concerning safety (acute responses) and not to provide any information concerning efficacy.

- Phase II – preliminary efficacy studies. PII trials usually include a significant number (10’s to 100’s) of patients. The studies are designed to provide information concerning efficacy as well as drug pharmacokinetics and optimum dosing. For development purposes, PII studies are often divided into PIIa and PIIb. PIIa studies may require up to several hundred patients, 1 – 2 years, cost 3-5 times or more than PI trials, and are intended to provide only the most basic efficacy information. PIIb trials are usually of somewhat larger magnitude.
- Phase I/IIa – for certain agents, a traditional PI trial in healthy volunteers is undesirable (certain relatively toxic cancer drugs, for example, or gene therapy agents). Safety studies may be conducted in patients in such cases. Such trials often include monitoring of efficacy-related clinical endpoints. However, the design of the trials including the number of patients enrolled is inadequate to provide statistically acceptable proof of efficacy.
- Phase III – definitive efficacy trials using planned commercial dosing. Such studies may range from 100’s to 1000’s of patients, require 3-5 years, and cost tens of millions of dollars. PIII studies provide the bulk of the clinical information used by FDA to approve a drug candidate.
- Phase IV – includes “post-marketing” studies undertaken after approval and market introduction. Such studies may be used by drug companies to obtain comparative data between market competitors, to support extended marketing claims, and so on. In some cases FDA approves drugs on an expedited basis because of significant clinical need with a requirement for PIV studies to further substantiate relatively limited pre-marketing data.

# Funding Sources

A critical item for all entrepreneurial companies is the funding necessary to advance a technology to a commercial product. Investors all seek to invest in companies that offer one or more of the following: (1) new and rapidly growing companies (2) the development of new products and services (3) risk that carries the expectation of high reward and (4) a long term opportunity for growth and success.

The dollars needed can be significant, for example \$10-25MM to bring a device to market, and \$25-100MM+ to bring a new drug into the marketplace. Entrepreneurs need to know where to go to get the money; what will be done with the money; and how to pay the money back i.e. know their company and how to explain it; have a good business plan/model; make a convincing value proposition.

## Who finances startups?

**Angel Financing** – Capital raised for a private company from independently wealthy investors. This money is generally used as seed financing, the first round of capital for a start up business. This is the money is typically used to prove a concept, develop a business plan, or pay for the initial patent filing. This money usually takes the form of a loan or an investment in preferred stock or convertible bonds. Angel investments generally range from \$50-500K with amounts both larger and smaller not uncommon.

**Venture Capital (VC) Financing** – An investment in a startup business that is thought to have excellent growth prospects but can't access traditional capital markets. The initial VC financing, the A round, is in a company that was previously financed by founders and/or angels. The name comes from the fact that investors receive Series A Preferred stock in the company. The normal investment range for such a round is \$2 – 5 million, though it can be larger for biopharmaceutical opportunities in particular. While some VC funds may get involved with a company at a very early stage, most prefer both a business plan and an experienced team be in place prior to considering an investment.

As the company achieves defined operational milestones and needs additional growth capital, it may seek additional funds from the VC community, Rounds B, C, D, etc. Such rounds can range from a few million dollars to in excess of \$50 million.

**Mezzanine Financing** – Stage of financing for a company immediately prior to an Initial Public Offering (IPO). It is available from institutions that generally won't get involved in the earlier, higher risk financings. It can be structured as preferred stock, convertible bonds (a security that can be converted to another type of security, generally common stock, at a pre-stated price) or subordinated debt (debt that has inferior liquidation privileges and therefore carries a higher interest rate).

**Debt or Asset Financing** – Obtained from banks or other lending institutions. Cannot usually be obtained until the company is profitable and/or has assets to provide as security.

**Initial Public Offering (IPO)** – This is the sale or distribution of stock in a company to the public for the first time. They generally occur after a company has developed into a profitable business and is relatively stable (except in the case of some biotech or IT offerings). It provides capital with less additional dilution than private equity offerings and also can provide liquidity for earlier investors in the company. It also carries with it significant securities regulations and reporting requirements to the government and all share holders.

An overview of each type of financier can be found on [www.evelexa.com](http://www.evelexa.com) *The Entrepreneur's Guide to a Biotech Startup: Raising Money*.

### **Incentive Programs: City of Cleveland**

Cleveland provides a variety of incentives for businesses locating in the city limits:

- Empowerment Zones/Enterprise Communities- exemptions on property improvements for up to 10 years, for businesses that invest in designated areas.
- Fixed rate loans for projects that help to create or retain jobs in participating “small city” communities. A majority of jobs must be for persons in low or moderate income households.

Many City of Cleveland incentive programs must include an application to and approval from the Ohio Dept. of Development. For more information, contact Michael Dealoia at the City of Cleveland.

### **Incentive Programs: State of Ohio**

Information on business incentive loans and tax credits is available from the Ohio Dept. of Development: [www.odod.state.oh.us](http://www.odod.state.oh.us) . Follow the link “for Businesses” to “Business Incentives”.

Ohio’s Technology Investment Tax Credit (TITC) program may be of particular interest to entrepreneurs starting a new business. This program offers benefits to Ohio taxpayers who invest in small, research and development, and technology-oriented firms. Through the TITC program, Ohio investors may reduce their state taxes by up to 25 percent of the amount they invest in qualified, technology-based Ohio companies. Specific types of investments (purchase of common stock, preferred stock, membership interest, partnership or other equity position) are eligible and the investment must not exceed \$250,000 in any single company. The program's credit may be applied to personal income tax, corporation franchise tax, public utility excise tax or the tax on dealers in intangibles.

Investors and companies must meet a variety of requirements as specified by Ohio law to qualify for the program.

Technology Investment Tax Credit Program: [www.odod.state.oh.us/tech/titc](http://www.odod.state.oh.us/tech/titc). The TITC program also maintains an email box at: [titc@odod.state.oh.us](mailto:titc@odod.state.oh.us)

### **Funding Sources: State**

#### *Third Frontier Action Fund*

This project is the state's largest commitment to expanding Ohio's high-tech research capabilities and promoting innovation and company formation that will create high-paying jobs for generations to come. The 10-year, \$1.1 billion initiative is designed to:

- Build world-class research capacity
- Support early stage capital formation and the development of new products
- Finance advanced manufacturing technologies to help existing industries become more productive

Third Frontier related projects and programs include:

- Wright Centers of Innovation: Grants to support large scale R&D development platforms to accelerate Ohio commercialization efforts. Wright Centers are collaborations among Ohio academic research institutions, non-profit research organizations and Ohio businesses in five focused areas: advanced materials, bioscience, power and propulsion, information technology, and instruments, controls and electronics.
- The Biomedical Research and Technology Transfer Partnership: Grants to support biomedical/biotechnology research leading to Ohio commercialization and improvement to the health of Ohio's citizens. Collaboration between two or more organizations (Ohio higher education institutions, non-profit research organizations and/or Ohio companies) is a program requirement.

<http://www.thirdfrontier.com>

### **Funding Sources: Federal**

#### *SBIR/STTR*

The Small Business Innovation Research (SBIR) and State Technology Transfer Research (STTR) programs are federally mandated programs in which certain government agencies reserve a portion of their R&D funding to award to small businesses. Under a competitive process, small business can receive awards to engage in federal R&D projects with commercial potential. The set aside portion for the SBIR program is 2.5% of a participating agency's budget, while the portion for the STTR program is 0.03%. Government agencies provide information on solicitations for proposals and the funding process on their agencies' web sites.

The SBIR/STTR program consists of three parts:

- Phase I (feasibility studies)- awards of up to \$100K (over time frames of 6 12 months) to support
- Phase II (research)- awards of up to \$750K (over 2 years)
- Phase II continuation—awards of up to \$1 million a year for 3 years
- Phase III (commercialization)- no support from SBIR/STTR funds

To qualify for SBIR funding, the company must:

- Be a US for-profit business, owned at least 51 % by individuals and operated independently
- Be located in the US
- Have 500 or fewer employees

In addition, the Principal Investigator's primary employment during the project must be with the company.

The STTR program facilitates collaboration between US business and US research institutions on projects with commercial potential. Qualifications for STTR funding include:

- The business must be a US concern.
- The business must be engaged in a formal research collaboration (certain percentages of involvement apply) with a US research institution (college, university, non-profit research organization or US government research center).
- The parties must have an agreement that allocates IP rights and rights for future R&D and commercialization.
- The principle researcher does not have to be employed by the business.

Eleven government agencies issue SBIR solicitations: the Department of Agriculture, the Department of Commerce, the Department of Defense, the Department of Education, the Department of Energy, the Department of Health and Human Services, the Department of Homeland Security, the Department of Transportation, the Environmental Protection Agency, the National Aeronautics and Space Administration, and the National Science Foundation.

The Small Business Administration, Office of Technology, ([www.sba.gov/sbir](http://www.sba.gov/sbir)) and the National Science Foundation ([www.nsf.gov](http://www.nsf.gov)) web sites provide general information on the programs and links to specific agency solicitations.

# Business Infrastructure

## Legal

One of the earliest decisions an entrepreneur must make is the form of organization in which to conduct business. There are more choices than most people realize, including not only decisions on the form of organization, but also in which state to organize. Without careful consideration, the law will sometimes imply a form of organization (i.e., a partnership) when the parties have failed to affirmatively choose one. Since this can have serious unintended consequences, entrepreneurs should give early attention to this issue.

The correct form of business organization depends on competing business, legal, and tax considerations. The relative importance of each category depends on several factors, including the nature of the business, the profile and number of owners, the financial strategy for building the business (e.g., attracting venture capital or growing internally) and tax considerations. Thus, the first job is to understand your business strategy, goals, and objectives, with attention to the key criteria relevant to the appropriate form of organization.

## **Financial**

### Accounting

In addition to professional legal support, early-stage bioscience companies need to establish good accounting and financial control processes early to give confidence to future investors.

Crain's Cleveland Business maintains lists of professional services firms, including accounting firms: [www.crainscleveland.com/section/crains-lists](http://www.crainscleveland.com/section/crains-lists). The list may be downloaded for a small fee.

## Insurance

Insurance is a necessary but sometimes overlooked piece of new business formation. The entrepreneur should meet with an insurance broker to discuss his/her individual situation and purchase the appropriate insurance.

Crain's Cleveland Business maintains a list of professional services firms, including those offering business insurance: [www.craainscleveland.com/section/craains-lists](http://www.craainscleveland.com/section/craains-lists). The list may be downloaded for a small fee.

## **Facilities**

For a startup, it is almost always advisable to lease space rather than to tie up scarce funds in the purchase of real estate. In addition, unless future space needs can be accurately forecast (which is rare), the company should look for the most flexible lease terms possible that would let the company expand or contract as it goes through its development cycle without being locked into unneeded fixed costs.

Incubators nurture small technology businesses during the start-up stage. The incubators provide a variety of business development assistance including below-market space, shared office services, and managerial and technical assistance in an environment conducive to new small businesses. Incubators offer entrepreneurs the ability to concentrate on the development of a product/service without the typical problems that affect such start-up ventures and often result in their premature demise.

Incubators offer a variety of administrative support to tenant companies, including: rental space, laboratories, "clean rooms," conference rooms, telephone answering, bookkeeping, access to specialized equipment, manufacturing and assembly areas, offices, reception areas, access to business equipment including copy and fax machines, word processing, and break rooms.

## **Permits**

In addition to other regulatory issues relating to the product or employment, companies may also be required to obtain special permits or licenses for the type of research or development considered. A list of permits and licenses required by the state of Ohio can be accessed at: [business.ohio.gov](http://business.ohio.gov)

Other important agencies that regulate permits include the Ohio EPA (waste disposal) [www.epa.state.oh.us](http://www.epa.state.oh.us) and the Ohio Department of Health (especially for toxic and radioactive materials) [www.odh.ohio.gov](http://www.odh.ohio.gov).

## **Equipment and Instrumentation**

Development of a new technology may require substantial investments in expensive, specialized equipment and/or facilities; expenses that may not be affordable for a cash-strapped entrepreneur. In addition to purchase and lease of equipment and instruments, underutilized equipment/instruments and facilities may be available on a fee-for-service basis at local institutions. The entrepreneur should thoroughly investigate any fee-for-service contracts to ensure no loss of IP if work is conducted through an outside party. Work which is collaborative in nature (rather than fee-for-service) may generate shared IP which can be problematic at a later date.