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FDA Drug Regulation: Investigational New Drug Applications

Summary

- The Food and Drug Administration (FDA)'s primary objective is to ensure safety. Investigational New Drugs (INDs) are focused mainly on safety, and therefore, if applicable, preclinical toxicology, manufacturing, and pharmacology data are very important.
- Take advantage of the FDA's accelerated programs, where applicable, to expedite commercialization.
- Engage with the FDA early on to guide your development program and develop relationships with the FDA.
- Consider global opportunities and plan ahead to meet relevant health authority regulations.
- Academic institutions can offer guidance and regulatory support to faculty investigators.

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FDA Drug Regulation: Investigational New Drug Applications

E. Bike Su Oner,¹ Sergio R. Labra, MS,² and Shelly Fehr³



Topic Relevance by Timeline

Summary

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- Take advantage of the FDA's accelerated programs, where applicable, to expedite commercialization.
- Engage with the FDA early on to guide your development program and develop relationships with the FDA.
- Consider global opportunities and plan ahead to meet relevant health authority regulations.
- Academic institutions can offer guidance and regulatory support to faculty investigators.

Introduction

Congress passed the Pure Food and Drugs Act more than a century ago, and this regulatory framework eventually became the Food and Drug Administration (FDA). Since the FDA was founded, there have been many medical and scientific advancements that have changed our understanding and treatment of numerous medical conditions. This chapter aims to explain the organizational structure of the FDA, discuss the components of an IND, and summarize specific resources available to a small business.

Obtaining a “may proceed” decision from the FDA to conduct clinical trials is a milestone of particular importance for novel compound pharmaceuticals and biologics. The great risks,

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expenses, and prolonged time to bring lead drug candidates to market have pushed the market and regulations to place increasingly greater emphasis and importance on demonstrating solid preclinical development before considering clinical trials. Obtaining IND authorization allows the investigational product and its sponsor (company or organization) to become a significantly more valuable asset that can attract investment, partnership, licensing, and acquisition opportunities.

Becoming well acquainted early on with the intricacies of the IND application and the resources available boosts the chances for authorization by building a compelling application in a time- and cost-efficient manner.

Abbreviations

BLA: Biologics License Applications
CBER: Center for Biologics Evaluation and Research
CDER: Center for Drug Evaluation and Research
CDRH: Center for Devices and Radiological Health
CFDA: China Food and Drug Administration
CFR: Code of Federal Regulations
CISC: Conflict of Interest Standing Committee
CMC: Chemistry, Manufacturing, and Control
CTP: Center for Tobacco Products
DoE: Department of Energy
DoEd: Department of Education
DoD: Department of Defense
DMF: Drug Master File
eCTD: Electronic Common Technical Document
FDA: U.S. Food and Drug Administration
GMP: Good Manufacturing Practice
GO: Office of Global Regulatory Operations and Policy
HF: Hedge Fund
HRAC: Human Research Advisory Committee
IND: Investigational New Drug Application
IRB: Institutional Review Board
NCE: New Chemical Entity
NDA: New Drug Application
NME: New Molecular Entity
NIH: National Institutes of Health
NSF: National Science Foundation
ORA: Office of Regulatory Affairs
OTAC: Office of Translational Alliances and Coordination
PE: Private Equity

PI: Principal Investigator
SBIR: Small Business Innovation Research
STTR: Small Business Technology Transfer
VC: Venture Capital

When Is an IND Needed?

Clinical research requires an IND to ensure that patients are not harmed by a new drug. Any drug, biological product, or device that has not been previously authorized for marketing in the U.S. cannot be used for the purposes of clinical investigation or clinical treatment, even if there are no approved therapies available (Center for Drug Evaluation and Research, “Investigational New Drug (IND) Application”). The FDA defines a drug as any compound or biologic that “affects the structure or function of the body, without regard to whether the compound is intended to influence a disease process” (Center for Drug Evaluation and Research, “Investigational New Drug Applications (INDs) - Determining Whether Human Research Studies Can Be Conducted Without an IND”). Defined as such, an IND is required if any drug or drug-containing combination product where the drug is the primary mode of action does not meet the requirements listed in 21 CFR 312.2 and summarized in Table 1 (Center for Drug Evaluation and Research, “Investigational New Drug (IND) Application”). For any questions regarding IND exemption, the institution’s IRB or regulatory guidance office and/or the FDA should be contacted for guidance.

**Table 1. FDA Criteria for IND Exemption
 (if any of these are not met, an IND is required).**

| |
|---|
| The investigational drug is lawfully marketed in the United States. |
| The investigation is not intended to be reported to the FDA as a well-controlled study in support of a new indication for use of the drug product. |
| The investigation is not intended to support a significant change in advertising to an existing lawfully marketed prescription drug product. |
| The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product. |
| The investigation will continue to be conducted in compliance with the requirements for institutional review set forth in FDA regulations 21 CFR 56, and requirements for informed consent as set forth in FDA regulations 21 CFR 50. |
| The investigation will continue to be conducted in compliance with FDA regulations 21 CFR 312.7, namely the proposed studies should not be used to support the product’s safety, effectiveness, or commercial distribution. |

Working with the FDA

The FDA is a federal agency of the United States Department of Health and Human Services. It protects and promotes public health by regulating food, cosmetics, drugs, and devices. The FDA is the oldest consumer protection agency in the United States, originating in the U.S. patent office in 1848, and later transferred to the Department of Agriculture in 1862. The modern function of the agency was codified in the 1906 Pure Food and Drugs Act, a law that prohibited the commerce of adulterated and misbranded foods and drugs (Hamburg). The FDA's authority has evolved over time with pharmacology advancements, toxicology advancements, and marketplace transformations (see Figure 1) (Junod) (see the chapter "FDA Device Regulation: 510(k), PMA").

Directorates of the FDA

The FDA consists of four directorates:

1. Office of Operations: Provides the agency with services such as information technology, financial management, library services, freedom of information queries, FDA history, and facilities.
2. Office of Medical Products and Tobacco: Specializes in the regulation of drugs, biologics, medical devices, and tobacco products. The Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Center for Tobacco Products (CTP) are considered under this office. The office also oversees the FDA's Office of Special Medical Programs (OSMP). The OSMP is made up of cross-center offices, which are the Office of Combination Products, the Office of Good Clinical Practice, the Office of Orphan Products Development, and the Office of Pediatric Therapeutics (Office of the Commissioner, "Office of Special Medical Programs"). The CDER, CBER, and CDRH are the three main offices with which an academic entrepreneur might communicate.

CDER: Evaluates the risks and benefits of prescription, generic, and over-the-counter (OTC) drug products to ensure they are safe and effective products (Center for Drug Evaluation and Research, "How Drugs Are Developed and Approved"). No drug is absolutely safe, and there is always the risk of an adverse reaction. The CDER approves a proposed drug when its benefits outweigh the risks associated; in addition, the FDA requires that the labeling outlines the risks and benefits reported. The CDER is the largest center of the FDA (Meadows).

CBER: Regulates biological and related products such as blood, vaccines, allergenics, tissues, and cellular and gene therapies. The CBER has the same mission of protecting patient health, however, it is a separate division because biologics are derived from living sources and many are often manufactured using cutting-edge biomedical research. Commercializing biologics requires its own

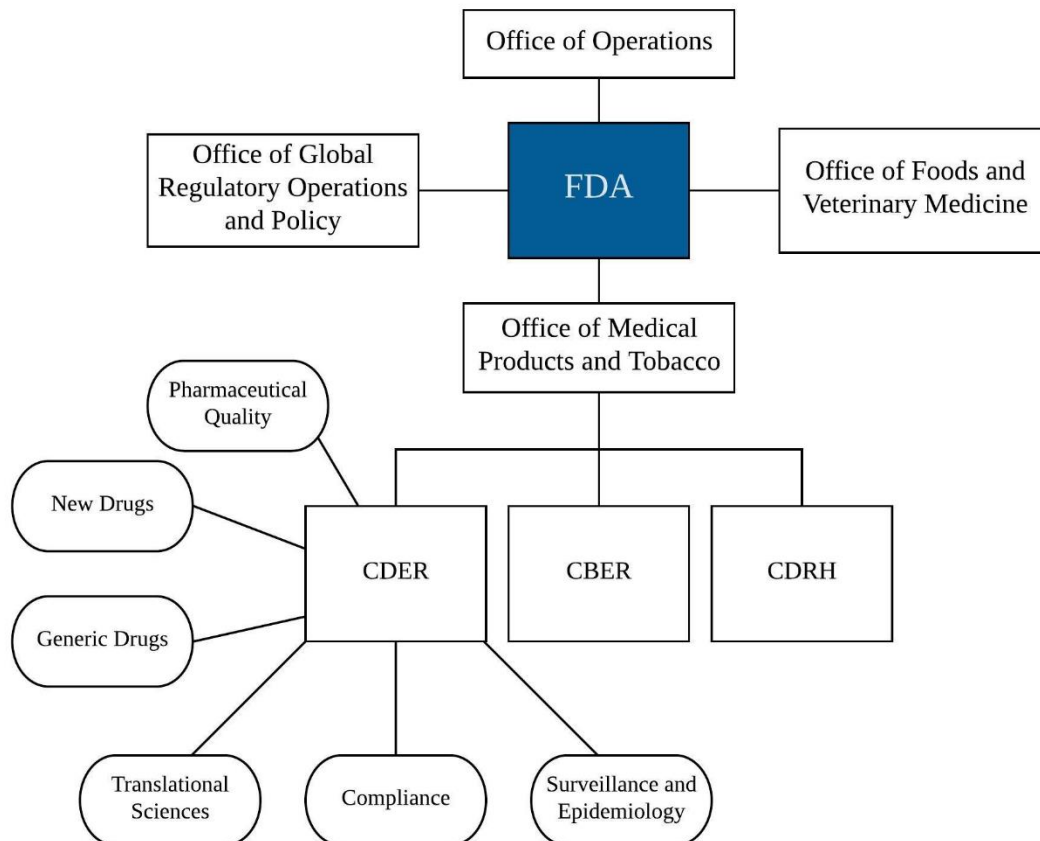
FDA process called Biologics License Application (BLA) (Center for Biologics Evaluation and Research).

CDRH: Facilitates medical device innovation by regulating the safety of medical devices and radiation-emitting products (Office of the Commissioner, “Intercenter Agreement Between CDER and CDRH”).

3. Office of Foods and Veterinary Medicine: Ensures the safety of foods for humans (including dietary supplements such as vitamins), by ensuring food labels contain reliable information that consumers can use, and setting a science-based standard to prevent foodborne illnesses.

4. Office of Global Regulatory Operations and Policy (GO): This office consists of the Office of Regulatory Affairs (ORA) and the Office of International Programs. The ORA helps support the FDA with rapid modernization and globalization of the FDA’s regulated products and new legislative authorities provided by Congress. The ORA advises and assists key officials on compliance-related topics that have an impact on policy development and execution. The ORA also coordinates and evaluates the FDA’s overall compliance efforts. The deputy commissioner of the GO provides oversight and directs the FDA’s policies on domestic and international product quality and safety. This office is also responsible for the FDA’s globalization initiatives. It directs global collaboration and global data sharing, development, and harmonization of standards. The functional statements for the ORA and the GO can be found in the FDA’s “Staff Manual Guides” (Office of the Commissioner, “Staff Manual Guide Table of Contents”).

Figure 1. Organizational Structure of the FDA.



FDA Expedited Development Programs

The FDA has four primary expedited development and review programs for drugs—Fast Track, Accelerated Approval, Breakthrough Therapy, and Priority Review—intended to accelerate the market launch of drugs addressing unmet needs (Center for Drug Evaluation and Research, “Expedited Programs for Serious Conditions—Drugs and Biologics”). Only the first three are applicable to the development stages concerning an IND application, and they are summarized in Table 2. (Priority Review designation only accelerates the final commercialization approval after all clinical data has been produced). Take advantage of these designations if the product could first target a medical need meeting the FDA’s criteria. Drugs treating life-threatening or severely debilitating diseases, for example, can be approved quickly via the Fast Track designation or via the Accelerated Approval pathway using surrogate endpoints as measures of clinical efficacy, allowing for potentially much cheaper and shorter clinical trials (Center for Drug Evaluation and Research, “Emergency Investigational New Drug (EIND) Applications for Antiviral Products”). Studies have shown that orphan drugs are likely to be approved with what would normally be insufficient data for other drugs (Kesselheim et al.) (see the chapter “Orphan Drugs: Understanding the FDA Approval Process”). A single IND application may benefit from multiple programs.

Using FDA Resources

It is critical to engage early with the FDA as the product nears the development maturity. It is worthwhile to request a meeting with the FDA early on to start building a relationship with them and to address specific questions. To that end, have a specific plan to make the most out of meeting with the FDA. Note that the pre-IND briefing package, consisting of background necessary data, is submitted to the FDA at least four weeks prior to the meeting date (Center for Drug Evaluation and Research, “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Pr”). The FDA has three different meeting types:

Type A: A meeting with the purpose of helping a stalled product development program proceed (e.g., dispute resolution, special protocol assessment, etc.). It is held within 30 days of request.

Type B: All milestone meetings like the pre-IND meeting, granted within 60 days of request.

Type C: A meeting for any other purpose. It is granted within 75 days of request.

The pre-IND meeting provides the best opportunity to determine if the collected nonclinical, clinical, manufacturing, and safety data up to that point are enough to support a Phase 1, Phase 2, or Phase 3 (less frequently) study in humans and to discuss the scope and design of the study (Center for Drug Evaluation and Research, “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Pr”).

Filing an IND

Clinical investigations for investigational drugs are filed by a sponsor, who is responsible for the conduct of the investigation. The sponsor must obtain a “may proceed” from the FDA before conducting a protocol study. This process starts when the sponsor files an IND with the FDA. The sponsor provides the FDA with all the necessary information to evaluate the safety and efficacy of the drug and the intended research, and the FDA ensures the safety of the subjects who participate in clinical trials.

Table 2. FDA’s Expedited Programs Applicable to Early Clinical Studies.

| FDA Program | Fast Track Designation | Breakthrough Therapy Designation | Accelerated Approval Pathway | Orphan Drug Designation |
|--|--|---|---|---|
| Qualifying Criteria | Drug intended to treat a serious condition AND data (including nonclinical) demonstrates the potential to address unmet medical need OR Drug has been designated as a qualified infectious | Drug intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available | Drug that treats a serious condition AND provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint likely to predict clinical benefit | Drug intended to treat a condition affecting 200,000 people or less in the US. |
| When to apply | With the IND application or during open IND | With the IND application or during open IND | Discuss early on the development point | At any time in its development process |
| Features | Development and review are expedited, including the use of rolling review (FDA starts reviewing portions of application before it is completed) | Intensive guidance on efficient drug development, Proactive involvement of senior management, rolling review, and consideration for Priority Review | Approval based on an effect on the surrogate endpoint or intermediate clinical endpoint. | Marketing application fee is waived and other financial development incentives. |
| References for more details (See the resources) | Section 506(b) of the FD&C Act | Section 506(a) of the FD&C Act | 21 CFR parts 314, 601, and Section 506(c) of the FD&C Act | 21 CFR parts 316.20 - 316.30 |

Source: (Center for Drug Evaluation and Research, “Expedited Programs for Serious Conditions—Drugs and Biologics”; Office of the Commissioner, “Designating an Orphan Drug or Biologic”).

An IND can be sponsored by a pharmaceutical company, faculty investigator, or research institution (in some cases, the NIH also can sponsor these) (*4.1.16 Investigational New Drug Applications-Investigational Device Exceptions*). Sponsors are responsible for selecting qualified investigators and ensuring proper monitoring of the investigation, to guarantee it is conducted in accordance with the investigational plan and protocols submitted in the IND, per 21 CFR 312.50. An investigator is the individual who actually conducts the clinical investigation. In academic research settings, an investigator IND by a researcher is usually submitted on behalf of the institution. When an academic research investigator holds an IND, the academic researcher is the sponsor. The academic researcher communicates and reports directly to the FDA. The investigator, in this case, will both initiate and conduct the investigation. The regulatory sponsor is also required to register the trial on [ClinicalTrials.gov](https://clinicaltrials.gov).

At the University of Pennsylvania, for example, a sponsor is required to be a member of the school of medicine faculty, to not have a significant conflict of interest, and to obtain training. In some cases, a University of Pennsylvania faculty member without a medical/dental license can be a sponsor if they assign the review of information relevant to the safety of their study product to a University of Pennsylvania faculty member who is currently licensed. Different policies may apply at other academic centers (“Responsibilities & Qualifications of IND/IDE Sponsors”).

IND applications require the sponsor to provide information on data regarding clinical and/or nonclinical data, manufacturing information (such as composition, manufacturer, stability, and controls), the clinical protocol, and the investigators.

There are two categories of INDs: commercial and research. These differ mainly in terms of the purpose of the research and who is submitting the application. Commercial INDs are generally submitted by companies or other entities, including the NIH, with the intent of bringing a new compound to market. Research INDs are often submitted by physician researchers.

All new drug applications are reviewed by a committee or a division specializing in the therapeutic area. An IND application has ten required sections (see Figure 2), which cover topics such as investigative plan, clinical protocol, manufacturing and quality testing information, pharmacology, and toxicology. Commercial INDs must be submitted via the Electronic Submissions Gateway (see Resources below), but research INDs are not required to be submitted via the Gateway. Do consider submitting in eCTD submission format via the Gateway for faster processing (Center for Drug Evaluation and Research, “Electronic Common Technical Document (eCTD)”).

Figure 2. Contents of an Investigational New Drug (IND) Application.

Further information on important and complex sections of an IND submission is provided below.

1) Cover Sheet (FDA Form 1571)

This form can be found on the FDA's website. It serves to identify the sponsor, investigational drug, phase of investigation, and parties responsible for monitoring the conduct of the study.

2) Introductory Statement and General Investigational Plan

This section describes the general investigational plan, for example, what are the cohorts, how are subjects randomized, and dosing information. This section is brief, often two–three pages. It mentions the name of the drug, active ingredients, mechanism of action, human experience with the drug (if there is any—in which case the section might reference previous INDs), publications, and the experience of other countries, if such information is available.

3) Investigator's Brochure (IB)

This is a compilation of clinical and preclinical data on the investigational product(s) and the study product(s) that is relevant to human subjects' research. Risk summary and expected adverse events (AEs) are listed in the IB. For this reason, a medically qualified professional should contribute to and review the IB. The sponsor is responsible for keeping the Investigator's Brochure up-to-date. An IND is a living application; it can be modified and expanded upon throughout the clinical investigation process.

4) Protocols

A protocol for each proposed clinical trial is required. Detailed activities of the investigation, number of subjects, and detailed time frame are included in the protocol. The principal concern for a Phase 1 protocol is safety, therefore only elements critical to subject safety should be explained in detail.

5) Chemistry, Manufacturing, and Control Information (CMC)

In a Phase 1 CMC submission, emphasis should be placed on information that will allow evaluation of the safety of the subjects. Insufficient evaluation of product safety can be a basis for a clinical hold. A description of the product(s), name and address of the manufacturer, and detailed production, testing, labeling, and storage information are required.

6) Pharmacology and Toxicology Information

Pharmacokinetics and toxicology information from preclinical and clinical data, information to support the stability of the drug (and methods used to monitor it), and the quality assurance process should be presented in this section. While performing preclinical studies, a sponsor should evaluate what experiments are needed to demonstrate the safety and toxicology profile of the product(s). For further information on Phase 1 IND protocols, refer to “Guidance for Industry: Content and Format of INDs for Phase 1 Studies” (see Resources).

A Form 3674 is also necessary. This is an attestation that the sponsor will register the trial on ClinicalTrials.gov or has determined that the law does not require registration (for example, with Phase 1 or single-patient expanded access protocols) (Office of the Commissioner, “Form FDA 3674 - Certifications to Accompany Applications/Submissions”).

Once an IND application is submitted, the sponsor must wait 30 days before starting a clinical trial, or until they receive an FDA “may proceed” decision. These 30 days allow the FDA time to review the prospective study. The FDA may respond to an IND application with suggestions or mandatory change requirements. If the sponsor fails to make the required changes, the FDA places a “clinical hold” on an investigation. A clinical hold may also interrupt a clinical trial if problems occur during the study. There is no deadline to resolve the issues that caused a clinical hold.

There are different INDs, depending on the goals of the proposed clinical investigation, the specific human testing proposed, and the expected risks. There are two other subcategories of INDs that are relevant to academic research: treatment IND (or expanded access IND) and exploratory IND applications. Treatment IND applications ask to use an experimental drug that proves beneficial and promising in clinical studies before the completion of the research, FDA review, and approval. This kind of IND is also called an “expanded access” IND or “compassionate use” IND. Expanded access is required when it is determined that there is no comparable or satisfactory therapy available to diagnose or treat a patient’s condition, and the patient is unable to participate in a clinical trial or obtain the investigational drug under another IND. Further information can be

found under the “Expanded Access” link included in the Resources (Office of the Commissioner, “Expanded Access”).

In addition to commercial and research INDs, there are also exploratory INDs, which are intended for a clinical trial that has very limited human exposure and has no therapeutic or diagnostic intent, such as screening studies, microdose studies, etc. These exploratory INDs are conducted prior to the dose escalation, safety, and tolerance studies that are ordinarily major components of an IND (Center for Drug Evaluation and Research, “Exploratory IND Studies”). Almost nine out of ten new drugs will then fail the human testing phase (Van Norman). A promising candidate for an IND application is often selected using *in vitro* testing in animal models, and the information on any risks anticipated based on the pharmacologic and toxicology data collected is submitted to the FDA as part of the IND. These studies are designed to select a safe starting dose for human studies. However, collecting preclinical data requires significant investment of resources and time, and, even so, animal testing does not always predict performance in humans. Existing regulations allow flexibility on the amount of data that needs to be submitted with an IND application. Exploratory INDs are first-in-human studies, or single, and low-dose studies conducted on 1–15 healthy volunteers (Center for Drug Evaluation and Research, “New Drugs at FDA: CDER’s New Molecular Entities and New Therapeutic Biological Products”).

FDA Assistance to Small Businesses

The FDA provides additional support for small businesses through the CDER Small Business & Industry Assistance (SBIA). The mission of the SBIA is to help small pharmaceutical businesses understand the regulation of human drug products, and to assist them in finding the resources they need for an efficient IND application process. A “small business” means a business employing fewer than 500 full-time employees. SBIA assistance is open to all, including those in academia. The SBIA hosts webinars and offers web-based learning tutorials. According to section 736(d) of the Federal Food, Drug, and Cosmetic Act, the FDA will waive or reduce one or more user fees if the applicant is a small business submitting its first-in-human drug application (Office of the Commissioner, “Application User Fees for Combination Products: Guidance”).

The FDA works with the Small Business Administration (SBA) to determine and qualify the applicant for a small business waiver. If a small business waiver is granted, the applicant has one year to submit their human drug application, as the circumstances supporting the waiver may change. An example would be if an applicant merged with a larger company or if a small business purchased an NDA from an unaffiliated company, in which case they would have an approved human drug product and they would no longer qualify for the waiver. It is possible to ask the FDA to extend the one-year limit; in this case the applicant would be reevaluated to confirm that they still meet the criteria for a small business waiver.

Additionally, the federal government’s Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs are the largest seed-stage funding sources in the

world, with more than \$2.2 billion distributed each year (Marek) (see the chapter “SBIR/STTR Grants: Introduction and Overview”). The NIH Office of Translational Alliances and Coordination (OTAC) helps to accelerate the translation of new scientific discoveries and coordinates the SBIR and STTR programs. The mission of the SBIR and STTR programs is to support scientific excellence and stimulate technological innovation through the investment of federal funds in small U.S. businesses (at least 51% U.S.-owned). Choosing a program should be based on the company’s situation and needs. SBIR and STTR grants are attractive to small businesses due to their non-dilutive nature. It should be noted that VC/HF/PE-owned companies will be eligible for up to 25% of NIH, NSF, and DoE funds, and 15% for all other agencies. For both funding opportunities, the applicant is always the small business.

Resources Provided by Academic Centers

Conducting a clinical research study at an academic center comes with the benefit of regulatory support and guidance from the university. For example, at the University of Pennsylvania, the Office of Clinical Research (OCR) is designed to support the conduct of clinical research and ensure compliance. The OCR provides the university’s sponsors, investigators, and Penn vendors with tools, resources, and training, such as IND, IDE, and CTA application templates, assistance in preparing for an FDA inspection, and more. The OCR staff may assist with clinical trial data management systems as well.

Sponsors and investigators at most academic centers are required to complete training on Human Subject Protections and Good Clinical Practice (GCP) every three years, and Health Insurance Portability and Accountability Act (HIPAA) training every year. It is also required that conflict-of-interest training is completed prior to engaging in research activities, and periodically afterwards (*Faculty | Office of Clinical Research | Perelman School of Medicine at the University of Pennsylvania*).

Academic centers also usually have an Institutional Review Board (IRB), which is an independent committee that follows federal regulations and oversees the protection of human subjects involved in research studies (see the chapter “Resources at Academic Entrepreneurship Centers”). Studies involving human subjects cannot begin their investigations without IRB review and approval. Central and private IRBs (fee-for-service) also exist.

Global Market

In terms of pharmaceuticals (including both small-molecule and biologics), the U.S. currently comprises about 49% of global market sales, with the European Union’s Big 5 (Spain, Germany, Italy, France, and the U.K.) and Japan comprising 21.5% and 8.3% of the market, respectively, as of 2016 (Mikulic). These and other rapidly growing markets like China provide significant commercialization opportunities. Depending on the innovative product, it may better fit a different

country's market or it may at least be worth expanding its commercialization abroad. Just as it is important to consider the protection of intellectual property (IP) outside the U.S., the regulatory differences from country to country must not be neglected (see the chapter "Intellectual Property: Ownership and Protection in a University Setting"). In general, each country maintains its own sovereignty in the requirements and process through which they approve novel drugs or devices. Fortunately, the second largest market after the U.S., Europe, is relatively centralized under the same agency, the European Medicines Agency (EMA). Other potentially relevant regulatory bodies to consider are the CFDA in China and the PMDA in Japan.

The current private healthcare system in the U.S. allows the free pricing of products by the manufacturer, which often means higher prices than those possible in most other countries, where the price is regulated by their health authorities. Commercializing in the United States first sets up an initial price benchmark that other countries use as an external reference point for setting their own prices. Thus, unless the product addresses conditions found much more prominently in different countries (e.g., tropical infections or diagnostics in low-income countries), it is usually a good development strategy to first seek approval in the U.S. through the FDA and commercialize there before pursuing approval in other countries. Submitting an application to one or more of these regulatory bodies will carry additional costs to plan for, especially considering that outside the U.S. multiple protocols will each need an application. Nonetheless, should local sponsors or funders be secured in those regions, it could significantly increase market penetration.

When planning to apply to other regulatory bodies besides the FDA, one should design the proposed studies with International Conference on Harmonisation (ICH) GCP guidance, to satisfy all global regulatory bodies where there is the intention to apply in the future. The FDA, like the rest of the world's major health regulatory bodies, accepts global clinical trial (GCT) results from studies done in foreign countries, which often can significantly reduce study costs and development time and are therefore worth considering.

Finally, it should be noted that one should not expect the regulatory process outside the U.S. to be necessarily cheaper or involving lower approval standards. For example, the EMA can be even more stringent than the FDA in how it evaluates a novel product against their standard of care. Furthermore, most foreign health authorities require proof of the cost-effectiveness of the novel product, in addition to proof of safety and efficacy. Lastly, fast-track approval requirements and "rare disease" definitions can vary as well. As always, due diligence is the best advice.

Costs

Since the Prescription Drug User Fee Act of 1992, a fee is charged when an IND application is submitted (Darrow et al.). This fee is the responsibility of the IND sponsor. The fee rates change every year, so it is best to check the applicable fees on the FDA website provided in the Resources. Combination products can often be described within a single IND and would then require a single

fee. The preferred payment method is online, on pay.gov, through an electronic check (Automated Clearing House (ACH) payment). Lawyers' and consultants' expenses should also be considered, if applicable. The FDA has several fee exemption designations that could be helpful as well. For example, if the product is of orphan designation or the sponsor is submitting their first application as a small business, the IND submission fee is waived (Center for Drug Evaluation and Research, "User Fee Waivers, Reductions, and Refunds for Drug and Biological Prod").

Conclusion

It is vital to understand what is required in each section of an IND. The university has teams focusing solely on the regulatory aspects of clinical research, therefore the university provides a lot of guidance to produce a successful IND, whether the sponsor outsources IND activities to a regulatory department or works on the activities themselves, with the assistance available from the university.

It is key to understand and utilize federal grants available for small businesses. These applications provide non-dilutive capital, peer review, and validation of technology, and they enable the early transfer of technology and the establishment of startup companies. Whether funding is granted or not, the applications can also provide feedback to improve the project.

Resources

1. The U.S. Food and Drug Administration Website
 - a. The U.S. FDA maintains all its resources and guides on its website. One should find the most up-to-date information there.
 - b. In particular, the academic entrepreneur may find most valuable their sections on:
 - i. Educational resources, including presentations by their officials: <https://www.fda.gov/Training/learningportal/ucm417363.htm#humandrug>
 - ii. Development & Approval Process (Drugs): <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm>
 1. Investigational New Drug (IND) Application: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm>
 2. This is an official resource to request advice regarding the evidence support and protocol design for studies specifically treating infections: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/default.htm>

- iii. Information and Resources for Industry (Drugs):
<https://www.fda.gov/Drugs/ResourcesForYou/Industry/default.htm>
 - iv. Guidances (Drugs):
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>
 - v. Prescription Drug User Fees:
<https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee/default.htm>
 - vi. The Electronic Submissions Gateway
 - 1. This is the FDA’s central electronic regulatory transmission portal, where the IND may be submitted:
<https://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm>
 - vii. Orange Book:
 - 1. Database of all FDA-approved drugs and their related patent and exclusivity details:
<https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm>
2. The Electronic Code for Federal Regulations (e-CFR)
- a. Rules published in the *Federal Register* by the departments and agencies of the federal government. All definitions and details will be found in Title 21, Chapter 1 of the CFR. Some particular sections that may be valuable are:
 - i. The IND Application regulations found in Part 312:
<https://www.ecfr.gov/cgi-bin/text-idx?SID=e09c55087458aadb6c203352c7ebd4f7&mc=true&node=pt21.5.312&rgn=div5>
 - ii. The Institutional Review Boards provisions can be found in Part 56, while the Good Laboratory Practice for Nonclinical Laboratory Studies provisions can be found in Part 58: <https://www.ecfr.gov/cgi-bin/text-idx?SID=14178553f774254bb8f07142651bf67c&mc=true&node=pt21.1.58&rgn=div5>
 - iii. For any other particular inquiries, this is the current Title 21 outline, and below are the relevant subchapters: <https://www.ecfr.gov/cgi-bin/text-idx?gp=&SID=e09c55087458aadb6c203352c7ebd4f7&mc=true&tpl=/ecfrbrowse/Title21/21chapterI.tpl>
 - 1. Subchapter A: General (Parts 1–99)
 - 2. Subchapter C: Drugs: General (Parts 200–299)
 - 3. Subchapter D: Drugs for Human use (Parts 300–399)
3. ClinicalTrials.gov
- a. The U.S. National Library of Medicine’s searchable database of private and public clinical studies conducted around the world. Containing over 200,000

trials—past and present—it is a great resource for finding example studies before and at the investigational plan development stage:

<https://clinicaltrials.gov/>

4. FDA Staff Manual Guide
<https://www.fda.gov/about-fda/reports-manuals-forms/staff-manual-guides>
5. Office of Special Medical Programs
<https://www.fda.gov/about-fda/office-medical-products-and-tobacco/office-special-medical-programs>
6. FDA Regulatory Procedures Manual
<https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-manuals/regulatory-procedures-manual>
7. Guidance for Industry: Content and Format of INDs for Phase 1 Studies
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074980.pdf>
8. Good Clinical Practice Addendum E6(R2)
<https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf>
9. Expanded Access
<https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm# Requirements for All Expanded Access Uses>
10. Exploratory IND Studies: Guidance for Industry, Investigators, and Reviewers
<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078933.pdf>
11. Penn Manual for Clinical Research
<https://www.med.upenn.edu/pennmanual/secure/>

References

- 4.1.16 *Investigational New Drug Applications-Investigational Device Exceptions*. Oct. 2018,
https://grants.nih.gov/grants/policy/nihgps/html5/section_4/4.1.16_investigational_new_drug_applications-investigational_device_exceptions.htm.
- Center for Biologics Evaluation and Research. “Biologics License Applications (BLA) Process (CBER).” *U.S. Food and Drug Administration*, 2 Feb. 2018,
<http://www.fda.gov/vaccines-blood-biologics/development-approval-process-cber/biologics-license-applications-bla-process-cber>.
- Center for Drug Evaluation and Research. “Electronic Common Technical Document (eCTD).” *U.S. Food and Drug Administration*, 17 July 2019,
<http://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd>.
- . “Emergency Investigational New Drug (EIND) Applications for Antiviral Products.” *U.S. Food and Drug Administration*, 26 July 2018,

- <http://www.fda.gov/drugs/investigational-new-drug-ind-application/emergency-investigational-new-drug-eind-applications-antiviral-products>.
- . “Expedited Programs for Serious Conditions—Drugs and Biologics.” *U.S. Food and Drug Administration*, Sept. 2017, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics>.
- . “Exploratory IND Studies.” *Biotechnology Law Report*, vol. 25, no. 2, Aug. 2018, pp. 167–74, doi:10.1089/blr.2006.25.167.
- . “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry.” *U.S. Food and Drug Administration*, Dec. 2017, <http://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry>.
- . “How Drugs Are Developed and Approved.” *U.S. Food and Drug Administration*, 7 Jan. 2019, <https://www.fda.gov/drugs/development-approval-process-drugs/how-drugs-are-developed-and-approved>.
- . “Investigational New Drug Applications (INDs)—Determining Whether Human Research Studies Can Be Conducted Without an IND.” *U.S. Food and Drug Administration*, Sept. 2013, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-new-drug-applications-inds-determining-whether-human-research-studies-can-be>.
- . “Investigational New Drug (IND) Application.” *U.S. Food and Drug Administration*, 5 Oct. 2017, <http://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application>.
- . “New Drugs at FDA: CDER’s New Molecular Entities and New Therapeutic Biological Products.” *U.S. Food and Drug Administration*, 2 Feb. 2018, <http://www.fda.gov/drugs/development-approval-process-drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products>.
- . “User Fee Waivers, Reductions, and Refunds for Drug and Biological Prod.” *U.S. Food and Drug Administration*, Jan. 2015, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/user-fee-waivers-reductions-and-refunds-drug-and-biological-products>.
- Darrow, Jonathan J., et al. “New FDA Breakthrough-Drug Category—Implications for Patients.” *The New England Journal of Medicine*, vol. 370, no. 13, Mar. 2014, pp. 1252–58, doi:10.1056/NEJMhle1311493.
- Office of Clinical Research | Perelman School of Medicine at the University of Pennsylvania*. <https://www.med.upenn.edu/ocr/faculty.html>. Accessed 9 July 2019.
- Hamburg, Margaret A. “Shattuck Lecture. Innovation, Regulation, and the FDA.” *The New England Journal of Medicine*, vol. 363, no. 23, Dec. 2010, pp. 2228–32, doi:10.1056/NEJMsa1007467.
- Junod, Suzanne. “FDA and Clinical Drug Trials: A Short History.” *A Quick Guide to*

- Clinical Trials*, edited by Madhu Davies and Faiz Kerimani, Bioplan, Inc, 2008, pp. 25–55, <https://www.fda.gov/media/110437/download>.
- Kesselheim, Aaron S., et al. “Trends in Utilization of FDA Expedited Drug Development and Approval Programs, 1987-2014: Cohort Study.” *British Medical Journal*, vol. 351, Sept. 2015, p. h4633, doi:10.1136/bmj.h4633.
- Marek, Kurt W. “The National Heart, Lung, and Blood Institute Small Business Program: A Comprehensive Ecosystem for Biomedical Product Development.” *JACC: Basic to Translational Science*, vol. 1, no. 7, Dec. 2016, pp. 660–65, doi:10.1016/j.jacbts.2016.08.001.
- Meadows, Michelle. “Promoting Safe and Effective Drugs for 100 Years—FDA.” *FDA Consumer*, vol. 40, no. 1, Jan-Feb 2006, <https://www.fda.gov/files/Promoting-Safe-and-Effective-Drugs-for-100-Years-%28download%29.pdf>.
- Mikulic, Matej. “Distribution of global pharmaceutical market revenue from 2010 to 2018, by region.” *Statista*, 1 Nov. 2018, <https://www.statista.com/statistics/275535/distribution-of-global-pharmaceutical-market-revenue/>.
- Office of the Commissioner. “Application User Fees for Combination Products: Guidance.” *U.S. Food and Drug Administration*, Apr. 2005, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/application-user-fees-combination-products>.
- . “Designating an Orphan Drug or Biologic.” *U.S. Food and Drug Administration*, 26 July 2018, <https://www.fda.gov/industry/developing-products-rare-diseases-conditions/designating-orphan-product-drugs-and-biological-products>.
- . “Expanded Access.” *U.S. Food and Drug Administration*, 6 May 2019, <http://www.fda.gov/news-events/public-health-focus/expanded-access>.
- . “Form FDA 3674—Certifications to Accompany Applications/Submissions.” *U.S. Food and Drug Administration*, June 2017, <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/form-fda-3674-certifications-accompany-drug-biological-product-and-device-applicationssubmissions>.
- . “Intercenter Agreement Between CDER and CDRH.” *U.S. Food and Drug Administration*, 16 Feb. 2018, <http://www.fda.gov/combination-products/classification-and-jurisdictional-information/intercenter-agreement-between-center-drug-evaluation-and-research-and-center-devices-and>.
- . “Office of Special Medical Programs.” *U.S. Food and Drug Administration*, 28 Mar. 2018, <https://www.fda.gov/about-fda/office-medical-products-and-tobacco/office-special-medical-programs>.
- . “Staff Manual Guide Table of Contents.” *U.S. Food and Drug Administration*, 1 Feb. 2018, <http://www.fda.gov/about-fda/reports-manuals-forms/staff-manual-guides>.
- “Responsibilities & Qualifications of IND/IDE Sponsors.” *Penn Manual for Clinical Research*, Perelman School of Medicine at the University of Pennsylvania, <https://www.med.upenn.edu/pennmanual/secure/responsibilities-and-qualifications->

of-ind/ide-sponsors.html. Accessed 3 Aug. 2019.

Van Norman, Gail A. “Drugs, Devices, and the FDA: Part 1: An Overview of Approval Processes for Drugs.” *JACC: Basic to Translational Science*, vol. 1, no. 3, Apr. 2016, pp. 170–79, doi:10.1016/j.jacbts.2016.03.002.

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