A Brief Overview of the Federal Regulatory Approval Process for Pharmaceuticals, Medical Devices, and Biological Products

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Background

Introduction

This chapter will provide the technology transfer professional with a basic overview of the U.S. federal regulatory approval process for pharmaceuticals, medical devices, and biological products. Please recognize that the laws and regulations that encompass this topic are vast and complex, especially those related to the conduct of human subject-based research. As such, this chapter is only meant to provide the most basic of overviews, while relying heavily on government-related sources.

The FDA's Role: Safety, Efficacy, and Security

Created in 1906, the U.S. Food & Drug Administration (FDA) is currently an agency within the U.S. Department of Health and Human Services and employs more than 11,500 full-time employees. It is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, medical devices, biological products, the U.S.'s food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable, as well as helping the public get accurate, science-based information to appropriately and intelligently use medicines and foods to improve health. Note that this chapter will only address the FDA's role in the regulation of pharmaceuticals, medical devices, and biological products marketed for use in human medicine.

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It is also important to recognize that the Federal Food, Drug, and Cosmetic Act (FD&C Act)—the basic food and drug law of the U.S. originally enacted in 1938—does not give the FDA responsibility to regulate the practice of medicine or to *develop* new drugs, medical devices, or biological products, but rather to oversee the *testing* of new drugs, medical devices, and biological products and their *introduction into interstate commerce*. So, one of the primary roles of FDA physicians, scientists, and other staff is to review test results submitted by drug, medical device, or biological product developers. The FDA then determines whether the drug, medical device, or biological product is safe enough to test in humans and, if so—after all human testing is completed—decides whether the drug, medical device, or biological product can be sold to the public and what its labels should say about directions for use, side effects, warnings, and the like.

The Drug Research Process

The drug research process is complicated, time-consuming, and costly; and the result is never known at the outset. Literally hundreds, and often thousands, of chemical compounds must be made and tested to find one that can achieve the desirable result without causing too serious side effects. Such a complicated process costs vast amounts of time and money. The FDA estimates that, on average, it takes eight-and-a-half years to study and test a new drug before the agency can approve it for the general public, while the cost to the sponsor may approach $1 *billion*. That includes early laboratory research and animal testing, as well as later clinical trials using human subjects.

Building on Good Science

New drug research often starts by studying how the body functions, both normally and abnormally, at its most basic levels. This is conducted via two primary modes of scientific inquiry: *in vitro* (in test tube) studies and *in vivo* (in living organism) studies. The pertinent question is, "If the body's functioning is changed, then will I have a useful drug?" That, in turn, leads to a concept of how a drug might be used to prevent, cure, or treat a disease or medical condition. Once the concept has been developed, the researcher has a target. Sometimes, scientists find the right compound quickly. More often, hundreds or even thousands must be tested. In a series of in vitro experiments (*assays*), compounds are added one at a time to enzymes, cell cultures, or cellular substances grown in a laboratory. The goal is to find which additions show some chemical effect. Some may not work

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well, but may hint at ways of changing the compound's chemical structure to improve its performance. The latter process alone may require testing dozens or hundreds of compounds.

A more high-tech approach is to use computers to simulate an enzyme or other drug target and design chemical structures that might work against it. A computer can show scientists what the receptor site looks like and how one might tailor a compound to block an enzyme from attaching there. Such scientific activity is called research *in silico*—meaning as being performed solely via computer simulation. However, although computers give chemists clues to which compounds to make, they do not give any final answers. That is, compounds made based on a computer simulation still have to be put into a biological system to determine whether they will actually work.

A fourth approach involves testing compounds made naturally by microscopic organisms. Candidates include fungi, viruses, bacteria, and molds, such as those that led to penicillin and other antibiotics. For example, scientists will grow microorganisms in a fermentation broth, one type of organism per broth. Sometimes, 100,000 or more broths are tested to see whether any compound made by a microorganism has a desirable effect.

Early-Stage In Vivo Testing of New Drugs

To this point, the search for a new drug has typically been confined to in vitro studies. Next, scientists have to test those compounds that have shown at least some desired effects in a living system. In initial in vivo testing, drug developers make every effort to use as few animals as possible and ensure their humane and proper care. Note that the clinical health and behavioral well-being of animals used in research and teaching are guaranteed by an interlocking set of state and federal laws, e.g., the Animal Welfare Act of 1966 and FDA requirements and standards (found at 21 Code of Federal Regulations Part 58). Usually, two or more species (such as mice or rats) are tested because a drug may affect one differently from another. Such tests show whether a potential drug has toxic side effects and what its safety is at different doses. The results point the way for testing in humans and, much later, product labeling.

So far, research has aimed at discovering what a drug might do to the human body (called a drug's *pharmacodynamics*). Now, it must also find out what the human body might do

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to the drug (called a drug's *pharmacokinetics*). So, in early-stage human clinical studies (usually in a small number of healthy volunteers and called a Phase I study, see description below), scientists measure how much of a drug is absorbed into the bloodstream, how it is broken down chemically in the body, the toxicity of its breakdown products (metabolites), and how quickly the drug and its metabolites are excreted from the body. Sometimes, such tests find a metabolite that is more effective than the drug originally chosen for development. Such early-stage human testing sets the stage for later human clinical studies in patients who have the disease or condition that the drug is meant to treat.

The Wrong Road

More often than many scientists care to admit, they just have to give up when a drug is poorly absorbed, is unsafe, or simply does not work. The Pharmaceutical Research and Manufacturers of America (PhRMA) estimates that only 5 in 5,000 compounds that enter preclinical testing make it to human testing, and only 1 of those 5 may be safe and effective enough to reach pharmacy shelves. Occasionally, a tenacious scientist keeps looking and finds a usable compound after others had given up. In other cases, compounds may be put aside because they failed to work on one disease, only to be taken off the shelf years later and found to work on another disease.

The Clinical Trial and FDA Regulatory Process

Overview of Human Clinical Trials

As described above, the process of drug development begins in the laboratory, with years of in vitro and in vivo animal experiments. These stages are known as preclinical research. If successful, then FDA approval is sought to begin clinical trials that involve humans—with later-stage trials involving subjects who have the disease or condition that is to be treated. A description of the various phases of clinical experimentation follows.

Phase I Clinical Trials

Phase I clinical trials, which typically last several months, are primarily designed to determine safe doses and administration methods (i.e., orally, intravenously, inhaled, etc.). These studies investigate how the body metabolizes the drug and side effects that may result from increasing the dosage.

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Phase II Clinical Trials

About two-thirds of drugs tested in Phase I continue to Phase II clinical trials. At this stage, the drug is tested for efficacy, i.e., how well it works for its intended purpose. In most Phase II trials, one group of volunteers may be given the experimental drug while another control group of volunteers will receive a placebo. Safety and effectiveness are examined in these trials. They do not give a final assessment of whether or not a particular drug will successfully treat an illness in the general population, although many patients may report experiencing some therapeutic benefits.

Phase III Clinical Trials

Phase III clinical trials are broken into two segments: Phase IIIa and Phase IIIb. Phase IIIa clinical trials test the drug with several hundred to several thousand subjects to verify efficacy and safety on a larger scale. Generally lasting two to three years, Phase IIIa focuses on regulatory issues and is conducted at a variety of investigative sites.

Once Phase IIIa is complete, the drug's sponsor submits all preclinical, pharmacologic, efficacy, and safety data to local regulatory agencies. Information on the drug's composition and plans for producing, packaging, and labeling are also included. The resulting regulatory review can take up to thirty months to complete, sometimes more, depending on the country and type of drug.

Meanwhile, Phase IIIb clinical trials begin. Involving a large number of patients, Phase IIIb focuses on issues such as cost-effectiveness and efficacy compared with approved drugs in the same therapeutic class or that are used to treat the same disease.

Phase III clinical trials are only performed on the fraction of drugs that demonstrated favorable profiles in earlier trials. Since these studies measure how well a drug works in a large number of people, this helps fine tune dosage amounts and procedures to ensure a drug's safety and effectiveness. For most drugs, Phase III clinical trials involve many health-care centers (i.e., multicenter clinical trials) and hundreds, perhaps even thousands, of patients in the U. S. and around the world. As such, the majority of the funds expended for clinical trials by sponsors are consumed during Phase III. Once these studies are all successfully completed, the FDA can be asked to approve the therapy for the marketplace.

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Phase IV Clinical Trials

After the product has received regulatory approval, Phase IV clinical trials begin. Phase IV trials examine the long-term safety and effectiveness of a previously approved drug. This postmarket phase can include testing for an expanded use, e.g., in pediatric patients.

Investigational New Drug Application

The FDA's Center for Drug Evaluation and Researcher (CDER) performs an essential public health task by making sure that safe and effective drugs are available to improve the health of people in the United States. CDER regulates over-the-counter and prescription drugs, including biological therapeutics and generic drugs. This work covers more than just medicines. For example, fluoride toothpaste, antiperspirants, dandruff shampoos, and sunscreens are all considered drugs. CDER is the largest of the FDA's six centers and employs a staff of about 2,900.

Current federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states to conduct clinical trials of the drug, it must seek an exemption from that legal requirement from the FDA. Submitting an investigational new drug application (IND) to CDER is the means through which the sponsor technically obtains this exemption from the FDA; *however*, its main purpose is to detail the data that provide documentation that it is indeed reasonable to proceed with certain human trials with the drug. In many ways, the IND is the result or culmination of a successful preclinical drug development program.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

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Generally, this includes data and information in three broad areas:

- *Animal pharmacology and toxicology studies*: Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans.
- *Manufacturing information:* Information pertaining to the composition, manufacture, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed as to ensure the company can adequately produce and supply consistent batches of the drug.
- *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 to assess whether they are qualified to fulfill their clinical trial duties.

There are different types of INDs. Commercial INDs are applications that are submitted primarily by companies whose ultimate goal is to obtain marketing approval for a new product. However, there is another class of filings broadly known as *noncommercial INDs* or research INDs. The vast majority of INDs are, in fact, filed for noncommercial research. These types of INDs include investigator INDs, emergency-use INDs, and treatment INDs.

An investigator IND is submitted by a physician, who both initiates and conducts an investigation and under whose immediate direction the investigational drug is administered or dispensed. A physician might submit a research IND to propose studying an unapproved drug or an approved product for a new indication or in a new patient population.

An emergency-use IND allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND using normal IND submission procedures. It is also used for patients who do not meet the criteria of an existing study protocol or if an approved study protocol does not exist.

A treatment IND is submitted for experimental drugs showing promise in clinical testing for serious or immediately life-threatening conditions while the final clinical work is conducted and the FDA review takes place.

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New Drug Application (NDA)

When the sponsor of a new drug believes that enough evidence on the drug's safety and effectiveness has been obtained to meet the FDA's requirements for marketing approval, the sponsor submits a new drug application (NDA) to the FDA. The application must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics. If the NDA is approved, then the product may be marketed in the United States. For decades, the regulation and control of new drugs in the United States has been based on the NDA. In fact, since 1938 (the year that the FD&C Act was passed), every new drug has been the subject of an approved NDA before U.S. commercialization. The data gathered during the in vivo animal studies and human clinical trials of an IND become part of the NDA.

Abbreviated New Drug Application

An abbreviated new drug application contains data that, when submitted to CDER's Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. A generic drug product is a drug that is shown to be comparable or *bioequivalent* to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use. Generic drug applications are called abbreviated because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness, just scientific proof of bioequivalence. Once approved, a generic drug manufacturer can then market the generic drug product to provide a lower cost alternative to the American public.

Using bioequivalence as the basis for approving generic copies of drug products was established by the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Act). This act expedites the availability of less-costly generic drugs by permitting the FDA to approve applications to market generic versions of brand-name drugs without conducting costly and duplicative clinical trials. The same act permitted the brand-name companies to apply for up to five additional years of patent protection for the new medicines they developed to make up for time lost while their products were going through FDA's approval process (called p*atent term extension*). Brand-name drugs are subject to the same bioequivalence tests as generics upon reformulation.

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Note that all approved products, both innovator and generic, are listed in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations,* which is also called the Orange Book after its original distinctive orange-colored hard-bound cover.

Regulation of Medical Devices

The FDA's Center for Devices and Radiological Health (CDRH) develops and implements national programs to protect the public health in the fields of medical devices and radiological health. These programs are intended to assure the safety, effectiveness, and proper labeling of medical devices; to promote quality in mammographic services; and to control unnecessary human exposure to potentially hazardous radiation and to ensure the safe, efficacious use of such radiation.

The basic framework governing the regulation of medical devices was established in 1976, via specific medical device-related amendments to the FD&C Act.

CDRH's Office of Device Evaluation is responsible for the program areas through which medical devices are evaluated or cleared for clinical trials and marketing.

Device Classification

The FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as *panels*. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device, i.e., Class I, II, and III.

The class to which the device is assigned determines, among other things, the type of premarketing submission/application required for FDA clearance to market. If the device is classified as a Class I or a Class II device, and if it is not exempt, then a 510(k) will be required for marketing (see discussion below). All devices classified as exempt (from the requirement to submit a 510(k)) are subject to the limitations on device exemptions. Limitations of device exemptions are covered under 21 CFR Parts 862-892. For Class III devices, a premarket approval application (PMA) is usually required (see discussion below).

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Device classification depends on the intended use of the device and also upon indications for use. For example, a scalpel's intended use is to cut tissue. A subset of intended use arises when a more specialized indication is added in the device's labeling such as, "for making incisions in the cornea." Indications for use can be found in the device's labeling, but may also be conveyed orally during sale of the product.

In addition, classification is risk-based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Class I includes devices with the lowest risk and Class III includes those with the greatest risk.

Note that the baseline requirements of the FD&C Act apply to all medical devices: Class I, II, and III.

Premarket Notifications (510(k)s)

This process is somewhat analogous to a generic drug concept in that premarket notification is used to obtain marketing clearance for a device that is substantially equivalent in safety and effectiveness to another lawfully marketed device or to a standard recognized by the FDA when used for the same intended purpose (e.g., if there is no available lawfully marketed comparator device). At least ninety days before placing a medical device into commercial distribution, the registrant must submit a premarket notification to the FDA, commonly known as a 510(k) in reference to the relevant section of the FD&C Act. The exception to this is if the device is exempt from the 510(k) requirements of the FD&C Act by separate statute or FDA regulation.

In addition to other information concerning the device, e.g., a description of the device (called a 510(k) summary or a 510(k) statement), the 510(k) submitter must include information to substantiate that the device is *substantially equivalent* to a legally marketed device (that is not subject to premarket approval) or otherwise compared to an FDA standard for similarly used devices. Such information may include a summary of the safety information related to the device. A substantially equivalent device is marketed subject to the same regulatory controls as the device or standard to which it is found to be substantially equivalent. A device may not be marketed pursuant to a 510(k) until the submitter receives written clearance from the FDA; that is, a successful submission is said to have been cleared, rather than *approved*.

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Premarket Approval Applications

Under the FD&C Act and FDA regulations, a manufacturer or others must submit a PMA for FDA review and approval before marketing certain new Class III 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; or are new and present unknown safety or effectiveness issues or risks, e.g., an artificial heart or a hip or knee implant. The PMA submitter must provide reasonable assurance that (1) the device is safe and effective for its intended use and (2) that it will be manufactured in accordance with current good manufacturing practices. As to item (1), the data is usually collected first from preclinical animal studies and then from human clinical trials. PMA clinical studies are akin to drug studies in their complexity and expense, but not their size, i.e., a Phase III device-related clinical trial usually involves a much smaller number of study subjects, e.g., approximately 200 or less.

As part of the review process, the FDA may present the PMA to an expert advisory panel for its recommendations. After obtaining the panel's recommendations, the FDA makes a determination to (1) approve the PMA, (2) deny it, or (3) request additional information. When the FDA either approves or denies the PMA, it must publish a notice in the Federal Register to inform the public of the decision and make available a summary of the safety and effectiveness data upon which the decision is based. This publicly available summary does not include proprietary data or confidential information submitted by the applicant.

PMA Supplements

After a PMA is approved, the PMA holder may request FDA approval of changes to be made. For example, it may request changes to the device, its labeling or packaging, or the manufacturing processes used in its production. Unless prior approval is expressly not required by the PMA regulation, changes that affect the safety or effectiveness of the device require that the FDA's PMA process be followed again. The FDA's review of a PMA supplement may be easy or difficult depending on the type of device, the significance of the change, and the complexity of the technology. Some PMA supplements can be as complex as the original application. Although the statutory timeframe is 180 days for PMA supplements, the FDA is committed to reviewing these in shorter timeframes and has reduced review timeframes through the use of real-time supplement process, thirty-day notices, and expedited reviews.

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Investigational Device Exemptions

Under the FD&C and FDA regulations, an individual, institution, or company can sponsor the clinical investigation of a medical device to establish its safety and effectiveness. Before conducting such a clinical trial, however, the sponsor must first obtain the approval of an investigational review board (IRB), as well as informed consent from the study subjects at the time of their enrollment in the study. If the investigational device study presents a significant risk to the subjects (e.g., the study involves the testing of a Class III device), then the sponsor must also obtain the FDA's approval of an investigational device exemption application (IDE) pursuant to 21 CFR Part 812. The IDE must contain information concerning the study's investigational plan, report of prior investigations, device manufacture, IRB actions, investigator agreements, subject informed-consent form, device labeling, cost of the device, and other matters related to the study (also see the previous PMA discussion). The FDA has thirty calendar days from the date of receipt of the application to approve or disapprove an IDE submission. In sum, in the case of Class III medical devices, a sponsor would first need to file an IDE to facilitate obtaining the clinical data necessary to later file a PMA.

IDE Amendments and Supplements

Although not provided for in the IDE regulations, all submissions related to an original IDE that has been submitted, but not approved, are referred to as *IDE amendments.* After an IDE is approved, related submissions are called *supplemental applications* under the regulations. Identification of IDE amendments enables the FDA to track each IDE from the time it is originally submitted until the time it is approved.

The IDE regulation requires the sponsor of an investigation of a significant risk or Class III device to submit a supplemental application for any of several specified reasons. For example, a sponsor must submit a supplement if there is a change in the investigational plan when such a change may affect the scientific soundness of the study or the rights, safety, or welfare of the subjects. Supplemental applications also are required for the addition of investigational sites. This regulation also requires the submission of various reports, which are logged in as supplements to IDE applications. These include reports on unanticipated adverse effects of the device; recall and device disposition; failure to obtain informed consent; and annual progress reports, final reports, investigator lists, and other reports requested by FDA.

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Product Development Protocols

The 1976 medical device amendments to the FD&C Act allows for two product approval pathways for a Class III (significant risk) device: the PMA (as described above) or, with *prior* FDA permission, the notice of completion of a product development protocol (PDP). The PDP process is based upon early consultation between the sponsor and the FDA leading to a device development and testing plan acceptable to both parties. It minimizes the risk that the sponsor will unknowingly pursue (with the associated waste of capital and other resources) the development of a device that the FDA will not approve. The PDP plan incorporates four discrete stages of FDA review during the device design process: (1) a PDP summary outline; (2) an FDA/advisory panel review of the full PDP; (3) consideration and, where appropriate, preapproval of design modifications and protocol revisions made during execution of the PDP; and (4) action on the sponsors notice of completion of the PDP. FDA review of the PDP summary may take up to thirty days, the review of the full PDP may take up to 120 days, and the FDA must declare the PDP completed or not completed within ninety days of receiving the notice of completion. If the FDA finds that the notice of completion—together with other information previously submitted—shows that the requirements of the PDP have been met, then the FDA will declare the PDP complete.

Humanitarian Device Exemptions

A humanitarian use device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. A humanitarian device exemption (HDE) application is essentially the same as a PMA in both form and content but is exempt from the effectiveness requirement of a PMA. Even though the HDE is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose, the application must contain sufficient information for the FDA to determine, as required by statute, that the device does not pose an unreasonable or significant risk of illness or injury to patients and that the probable benefit to health outweighs the risk of injury or illness from its use. A HDE application must also contain information that will allow FDA to make the other determinations required by the FD&C Act. An approved HDE authorizes marketing of the HUD.

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Regulatory Process Relating to Biologics

The FDA's center for biologics evaluation and research (CBER) regulates biological products for human use under applicable federal laws, including the FD&C Act. Note that CBER's activities also encompass medical devices associated with blood collection and processing procedures as well as those associated with cellular therapies. CBER protects and advances the public health by ensuring that biological products are safe and effective and available to those who need them. CBER also provides the public with information to promote the safe and appropriate use of biological products.

CBER regulates an array of diverse and complex biological products (biologics), both investigational and licensed as *not drugs,* including:

- *Allergenics*: Patch tests used to diagnose the causes of contact dermatitis; extracts used to diagnose and treat rhinitis (hay fever), allergic sinusitis and conjunctivitis, and bee stings.
- *Blood*: Blood and blood components used for transfusion, such as red blood cells, plasma, and platelets; pharmaceutical products made from blood and used as clotting factors and immunoglobulins.
- *Devices*: Medical devices and tests used to safeguard blood, blood components, and cellular products from HIV, hepatitis, syphilis, and other infectious agents; reagents used to type blood; machines and related software used to collect blood and blood components.
- *Gene therapy*: Gene therapy products used to replace a person's faulty or missing genetic material, such as treatments for cancer, cystic fibrosis, heart disease, hemophilia, diabetes, and infectious diseases such as AIDS.
- *Human tissues and cellular products:* Human tissues used for transplantation, such as skin, tendons, ligaments, and cartilage; and cellular products, such as human stem cells and pancreatic islets, used to treat cancer, Parkinson's disease, hemophilia, anemia, diabetes, and other serious conditions.
- *Vaccines*: Vaccines used for the prevention of infectious diseases, such as mumps, measles, chicken pox, diphtheria, tetanus, influenza, hepatitis, smallpox, and anthrax; vaccines used to treat HIV and to treat or prevent non-infectious conditions, including various cancers.

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- *Xenotransplantation products:* Xenotransplantation products, such as live animal cells, tissues, or organs, used to treat human diseases such as liver failure and diabetes, where human materials are not always available.

Biological Products

Biological products include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, nucleic acids, or complex combinations of these substances or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources—human, animal, or microorganism—and may be produced by biotechnology methods and other cutting-edge technologies. Gene-based and cellular biologics, for example, often are at the forefront of biomedical research and may be used to treat a variety of medical conditions for which no other treatments are available.

In contrast to most drugs that are chemically synthesized and their structure is known, most biologics are complex mixtures that are not easily identified or characterized. Biologics, including those manufactured by biotechnology, tend to be heat sensitive and susceptible to microbial contamination. Therefore, it is necessary to use aseptic principles from initial manufacturing steps, which is also in contrast to most conventional drugs.

Biologics often represent the cutting-edge of biomedical research and, in time, may offer the most effective means to treat a variety of medical illnesses and conditions that presently have no other treatments available.

Biologics Approval Process

Biologics are approved for marketing under provisions of the Public Health Service Act (PHS Act). However, because many biologics also meet the definition of drugs under the FD&C Act, those that do are also subject to regulation under FD&C Act provisions that relate to drugs.

The PHS Act requires individuals or companies who manufacture biologics for introduction into interstate commerce to hold a license for the products. CBER issues these licenses. Biological products intended for veterinary use are regulated under a separate

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law, the Virus, Serum and Toxin Act, which is administered by the U. S. Department of Agriculture.

Licensing of biologic products under the PHS Act is very similar to the new drug approval process for human drugs. Following initial laboratory and animal testing, a biologic is studied in clinical trials in humans under a biologics-related investigational new drug application (IND). If the data generated by the studies demonstrate that the product is safe and effective for its intended use, then the data are submitted to CBER as part of a biologics license application (BLA) for review and approval for marketing. The BLA is essentially a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce. That is, the BLA serves the same purpose for biological products as an NDA does for (nonbiologic) drugs.

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

In Vitro Diagnostic Devices

In vitro diagnostics (IVDs) are medical devices that analyze human body fluids, such as blood or urine, to provide information for the diagnosis, prevention, or treatment of a disease. IVD manufacturers are required to follow the same regulatory procedures as are followed by other manufacturers of medical devices, e.g., submission of IDEs, 510(k)s, etc.

Clinical Laboratory Improvement Act of 1988

In addition to FDA regulation under the FD&C Act, IVD devices are also subject to the Clinical Laboratory Improvement Amendments of 1988. This law established quality standards for laboratory testing and an accreditation program for clinical laboratories.

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The requirements that apply vary according to the technical complexity in the testing process and risk of harm in reporting erroneous results. The regulations established three categories of testing on the basis of the complexity of the testing methodology: (1) waived tests, (2) tests of moderate complexity, and (3) tests of high complexity. Laboratories performing moderate- or high-complexity testing or both must meet requirements for proficiency testing, patient test management, quality control, quality assurance, and personnel. These specific requirements do not apply to tests in the waived category.

CDRH Office of In Vitro Diagnostic Device Evaluation and Safety

The CDRH's Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) regulates all aspects of in-home and clinical laboratory IVDs. The OIVD was formed November 17, 2002, in order to consolidate all regulatory activities for IVDs. The OIVD has a dual charge to foster the rapid transfer of new IVDs into the marketplace while preventing marketing of unsafe or ineffective devices. To accomplish this, the OIVD combines the functions of all the offices within CDRH into one organizational unit for cradle-to-grave regulation of IVDs.

Combination Products

Combination products are those containing a combination of drugs, medical devices, and/or biologics that are physically, chemically, or otherwise combined, e.g., drug-eluting stents or drug-infused bone implants. Clinical trials for combination products are more comprehensive, costly, and complicated than those required for individual drugs, medical devices, or biologics as the individual properties of each component must be investigated, as well as the properties of the components when used in combination. The FDA's Office of Combination Products assigns an FDA center (i.e., CDER, CBER, or CDRH) to have primary jurisdiction over the review of combination products and also coordinates reviews involving more than one FDA center.

Medical Products that Incorporate Nanotechnologies

In August of 2006, the FDA formed a Nanotechnology Task Force (NTF) that was charged with determining regulatory approaches that encourage the continued development of innovative, safe, and effective FDA-regulated products that use nanotechnology materials.

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The NTF continues to identify and recommend ways to address any knowledge or policy gaps that exist so as to better enable the FDA to evaluate possible adverse health effects from FDA-regulated products that use nanotechnology materials.

In 2007, the NTF released a report that recommended that the FDA consider developing guidance and taking other steps to address the benefits and risks of drugs and medical devices using nanotechnology.

Then Commissioner of the FDA Andrew von Eschenbach, M.D., endorsed the *NTF Report* and its recommendations: "Nanotechnology holds enormous potential for use in a vast array of products," he said. "Recognizing the emerging nature of this technology and its potential for rapid development, this report fosters the continued development of innovative, safe and effective FDA-regulated products that use nanotechnology materials."

The *FTR Report* stated that FDA experts believed that nanotechnology products presented and would continue to present challenges similar to those FDA faces for products of other emerging technologies; however, product safety and effectiveness profoundly changed as size went up or down within the nanoscale, thereby adding additional complexity to product reviews.

The *NTF Report* also stated that many of the nanotechnology products that the FDA would regulate would span the regulatory boundaries between drugs, medical devices, and biologics and that these, then, would likely be regulated under the rules established for combination products (see previous discussion).

Summary and Exhibits

The field of regulatory oversight of pharmaceuticals, medical devices, and biological products is vast and complex. By design, this chapter has only provided the most basic of information. If a technology transfer professional finds himself or herself in a situation in which FDA oversight may be triggered, e.g., a spin-off wants to begin in vivo testing of a new medical device, then the author strongly recommends contacting a regulatory professional for advice.

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The appended exhibits are meant to provide additional educational information to assist the technology transfer profession in increasing his or her familiarity with the subject matter of this chapter. Exhibit A provides an stepwise listing of the drug review process, Exhibit B provides a description of the three regulatory classes of medical devices, Exhibit C provides a glossary of key terms and abbreviations, and Exhibit D provides additional sources of information. Note that the best starting point is the FDA's homepage (www.fda.gov).

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Exhibit A: Drug Review Steps

1. Preclinical in vitro and in vivo testing.
2. An investigational new drug application (IND) outlines what the sponsor of a new drug proposes for human testing in clinical trials.
3. Phase I studies (typically involve twenty to eighty people): In general, early-stage trials include several Phase I studies: (1) a single ascending dose study (or first dose in human study), (2) a multiple ascending dose study, (3) possible drug and/or food interaction studies, and (4) a proof-of-concept study, which is sometimes called a Phase I/II or Phase IIa study. The principal goals of early Phase I studies in human volunteers are usually safety, tolerance, and dose escalation, often to define the maximal tolerated dose.
4. Phase II studies typically involve a few dozen to about 300 people and are intended to preliminarily address efficacy.
5. Phase IIIa/Phase IIIb studies typically involve several hundred to about 3,000 people and are intended to address safety and efficacy under conditions mirroring how the drug will be used commercially.
6. The pre-NDA period, just before a new drug application (NDA) is submitted, is a common time for the FDA and drug sponsors to meet.
7. Submission of an NDA is the formal step asking the FDA to consider a drug for marketing approval.
8. After an NDA is received, the FDA has sixty days to decide whether to file it so it can be reviewed.
9. If the FDA files the NDA, then an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness.
10. The FDA reviews information that goes on a drug's professional labeling (information on how to use the drug). Such information is found primarily in what is termed the package insert.
11. The FDA inspects the facilities where the drug will be manufactured as part of the approval process.
12. FDA reviewers will approve the application or find it either approvable or not approvable.

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Exhibit B: Regulatory Classes of Medical Devices

Medical devices are divided into three classes, each with different regulatory requirements based on risk stratification as outlined below.

Class	Risk	Regulatory Requirements
Class I	Present minimal potential harm to the user.	Mostly exempt from testing. Does not require regulatory approval.
Class II	More complex, higher risk that are not life-sustaining.	Regulatory clearance required: 510(k). Based on demonstration of substantial equivalence to marketed devices or recognized FDA standards for devices used for a substantially equivalent (i.e., a standard-conforming purpose).
Class III	Support or sustain human life.	Regulatory approval required: premarket approval (PMA). Based on the results of clinical studies.

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Exhibit C: Select Glossary and Common Abbreviations

adverse event (AE): Any untoward medical occurrence in a patient or clinical-investigation subject administrated a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

biologicals license application (BLA): A set of documents submitted to the FDA to gain authorization to commercially market a new biological product for use in humans.

blinding/masking: A procedure in which one or more parties to a clinical trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the study subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor(s), and, in some cases, data analyst(s), being unaware of the treatment assignment(s).

case report form (CRF): A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the study sponsor on each study subject.

Center for Biologics Evaluation and Research (CBER): CBER's job is to ensure that biologics are safe and effective. CBER has a staff of about 950.

Center for Drug Evaluation and Research (CDER): CDER's job is to ensure that drugs are safe and effective. CDER is the largest of the FDA's six centers, with a staff of about 2,900. It has responsibility for both prescription and over-the-counter drugs.

clinically significant: Referring to a patient test result that is clinically important and should be brought to the attention of the patient's physician for decisions regarding treatment and/or evaluation.

compliance (in relation to clinical trials): Adherence to all the clinical-trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

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contract research organization (CRO): A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of the sponsor's study-related duties and functions.

clinical trial/study: Any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product or products; and/or to identify any adverse reactions to an investigational product or products; and/or to study adsorption, distribution, metabolism, and excretion of an investigation's product or products with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

establishment inspection report (EIR): FDA inspector's letter documenting an inspection visit and his or her observation(s) regarding it that is sent to the principal investigator when an FDA Form 483 is not issued.

FDA Form 1572 (statement of investigator): A legal agreement between the FDA and the clinical investigator that must be signed prior to beginning a research study involving an investigational new drug. Form 1572 outlines the investigator's responsibilities for the study.

FDA Form 482: Notice of FDA inspection to assess study compliance with appropriate regulations and guidelines to determine whether the data submitted are accurate.

FDA Form 483 (notice of FDA inspectional observations): A list of inspectional observations and discrepancies found in the investigation at the conclusion of the FDA inspection of a clinical investigational site and followed by an exit interview to review findings. The principal investigator will be given a list of the findings.

FDA Guidelines: A set of recommendations that governs the FDA's interpretation of federal regulations.

federal wide assurance (FWA): A promise by institutions to federal agencies to protect research subjects participating in research.

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510(k): A 510(k) is a premarket submission made to the FDA to demonstrate that a medical device to be marketed is at least as safe and effective as, that is, substantially equivalent to, a legally marketed device that is not subject to a PMA. Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalency claims. 510(k) refers to Section 510(k) of the FD&C Act.

good clinical practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the right, integrity, and confidentiality of study patients are protected. Most often meaning the actual and documented compliance with the FDA's good clinical practice guidelines as specified in Title 21 of the Code of Federal Regulations (especially Part 312) and/or the ICH Harmonised Tripartite Guideline for Good Clinical Practice. Further, compliance with the regulations governing the protection of human subjects (45 CFR Part 46) should also be considered integral to good clinical practice.

good laboratory practice (GLP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of preclinical studies that provides assurance that the data and reported results are credible and accurate. Most often meaning the actual and documented compliance with the FDA's good laboratory practice guidelines as specified in Title 21, Part 58, of the Code of Federal Regulations.

human subject: Any individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A human subject may also be interchangeably called a *research patient* or a *study patient* or a *study subject* or a *trial subject* or a *research subject.*

Institutional Animal Care and Use Committee (IACUC, usually pronounced EYE-ah-cuck): A constituted body whose role is to protect the welfare of animals used in research.

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investigational device exemption (IDE): An IDE refers to the regulations specified in Title 21, Part 812, of the Code of Federal Regulations. An approved IDE means that the IRB (and FDA for significant-risk devices) has approved the sponsor's study application and all the requirements under 21 CFR 812 are met.

investigational new drug application (IND): A set of documents submitted to the FDA to gain authorization to test a new drug.

informed consent: A process by which a potential trial subject voluntarily confirms his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to his or her decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form (ICF).

institution: Any public or private entity or agency (including federal, state, or other agencies).

investigational (or institutional) review board (IRB): An independent body constituted of medical, scientific, and nonscientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a clinical trial by, among other things, reviewing, approving, and providing continued review of the clinical trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the clinical trial subjects.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Globally recognized guidelines regarding the conduct of a clinical trial recognized by the FDA.

investigational drug: A drug permitted by the FDA to be tested on humans, but not yet determined to be safe and effective for a particular use in the general population and not yet licensed for marketing. An investigational drug is also referred to as a test article.

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investigator: An individual who conducts a clinical investigation.

investigator drug brochure (IDB or IB): Material and documents prepared by a sponsor that summarizes the preclinical (animal studies) and clinical results of trials using the investigational drug.

medical ethics committee: An entity made up of institutional officials, physicians, legal advisers, and patient advocates whose role it is to ensure that all interactions with patients are conducted in an ethical manner.

minimal risk: The probability and magnitude of harm or discomfort anticipated in the research is not greater in and of itself above that is ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

new drug application (NDA): A request for FDA approval to market a new drug.

open-label drug: A study drug or drugs whose administration in a research study is not blinded or hidden from the investigator and/or patient.

patient confidentiality: The legal concept that information provided by the study patient or about the study patient will not be disclosed to others without the patient's permission or knowledge.

premarket approval (PMA): Premarket approval is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. Class III medical devices are those that support or sustain human life, that are of substantial importance in preventing impairment of human health, or that present a potential, unreasonable risk of illness or injury.

premarket notification (PMN): See definition of 510(k) above.

principal investigator (PI): The individual conducting the clinical investigation as indicated on the FDA Form 1572. This individual agrees to take ultimate responsibility for the conduct of the clinical trial.

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protocol: A document that describes the objective(s), design, methodology, statistical considerations, organization of a trial, and the background and rationale for the trial.

randomization: The process of assigning clinical trial subjects to treatment or control groups using an element of chance to determine the assignments to reduce bias.

regulatory compliance file: Each clinical study should have a regulatory compliance file associated with it. At a minimum, it should contain:

(a) stamped, approved, informed consent form;
(b) letter from IRB, dated and signed, indicating approval of clinical study;
(c) IRB membership list;
(d) signed protocol approval signature page;
(e) completed FDA Form 1572;
(f) CVs for all individuals listed on the FDA Form 1572;
(g) financial disclosure forms for all individuals listed the FDA Form 1572;
(h) verification of the study site's FWA;
(i) evidence that a study site selection visit was performed for any study site not used within the past six to twelve months (may depend on the standard-operating-procedures (SOPs) of the sponsor); and
(j) evidence that a study site initiation visit took place.

research: A systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to general knowledge. Activities that meet this definition arguably constitute research, whether or not they are conducted or supported under a program that is considered research for other purposes.

research patient identity: Identifying features, such as name or medical record number, that must be masked or otherwise hidden on copies of any source document given to representatives of any non-institutional entity. It is highly recommended that source documents that identify research patients by name, Social Security number, medical record number, etc., be stored separately from the associated case report form.

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serious adverse event (SAE): An untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of exiting hospitalization, results in persistent significant disability/incapacity, or is a congenital anomaly/birth defect.

significant risk device: A significant risk device is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (2) is for use in supporting or sustaining human life and represents a potential for serious risk to the health, safety, or welfare of a subject; (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or (4) otherwise presents a potential for serious risk to a subject.

site: The institution or facility where research is conducted.

source document: The record in which data concerning a research patient is first captured. Examples: original documents, data, records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the trial).

sponsor: The entity (individual, company, institution, or organization) that holds the IND or which otherwise takes responsibility for the initiation, management, and/or financing of a clinical trial.

standard operating procedures (SOPs): A statement of principles governing the institution in the discharge of its responsibilities for protecting the rights and welfare of human patients participating in research conducted at or sponsored by the institution, regardless of whether the research is subject to federal regulation. This may include an appropriate existing code, declaration, or statement of ethical principles or a statement formulated by the institution itself.

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study drug disposition record: Documents that record adequate disposition of the study drug, including dates, quantity, and use by study patients. If the investigation is terminated, suspended, or discontinued or completed, then the PI is usually required to return the unused supplies of the study drug to the sponsor or otherwise provide for disposition of the unused supplies of the study drug.

study records: Two basic types of records kept regarding clinical investigation: (1) case history documentation and (2) the study protocol and related documents. Case history documents record all observations and data pertinent to the research study about each research subject treated with the test article or enrolled as a control. Study protocol documents consist of correspondence sent to or received from the study sponsor and its monitor(s), including any protocol modifications and records of IRB approval and of other communications/actions pertaining to the research study.

trial site: The location(s) where trial-related activities are actually conducted.

vulnerable subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, or nursing students; subordinate hospital and laboratory personnel; employees of the pharmaceutical industry; members of the armed forces; and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving informed consent.

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Exhibit D: Useful Citations and Web Sites

FDA's home page: www.fda.gov

Federal Food, Drug and Cosmetic Act: 21 United States Code (U.S.C.) Sections 301-399
The FDA's portion of the Code of Federal Regulations (CFR) interprets the Federal Food, Drug, and Cosmetic Act and related statutes. Title 21 of the CFR contains most of the regulations pertaining to food and drugs. Key parts include:

- Part 50 covers the protection of human subjects.
- Part 54 covers financial disclosures for clinical investigators. This regulation is intended to ensure that financial interests and arrangements of clinical investigators that could affect reliability of data submitted to FDA in support of product marketing are identified and disclosed by the sponsor.
- Part 56 covers institutional review boards (IRB).
- Part 58 covers good laboratory practice (GLP) for nonclinical (animal) studies.
- Part 312 covers investigational new drug application (IND) regulations, including regulations for clinical investigators.

Title 45 (Public Welfare, Department of Health and Human Services) CFR Part 46 - Protection of Human Subjects

Advanced Medical Technology Association (AdvaMed): www.advamed.org

Association of Medical Diagnostics Manufacturers (AMDM): www.amdm.org

European Medicines Agency (EMEA): www.emea.eu.int/Inspections/GCPgeneral.html

International Conference on Harmonisation: www.ich.org

Medical Device Manufacturers Association (MDMA): www.medicaldevices.org

Model Agreements and Guidelines International (MAGI): www.magiworld.org

Pharmaceutical Research and Manufacturers of America (PhRMA): www.phrma.org

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