

FDA Basics For Biotech Drugs, Biologics and Devices

I. FDA Overview

- A. FDA has authority over products intended for the diagnosis, treatment or mitigation of human disease or intended to affect a structure or function of the body. These products are regulated as drugs, biologics, medical devices or combinations of these products. Drugs, biologics and medical devices are broadly defined, and include therapeutic and diagnostic biotechnology products.
- B. FDA's authority to regulate comes from the Food, Drug and Cosmetic Act and the Public Health Service Act and the regulations promulgated thereunder. FDA also publishes many informal guidances (most of which can be found at <http://www.fda.gov>) regarding regulatory issues including those pertaining directly to the regulation of biotechnology products.
- C. Classification of a product as a drug, biologic, medical device or combination product depends primarily on that product's intended use and principal mode of action (e.g., drugs and biologics generally function through chemical or metabolic action on or within the body while devices generally function through physical means or *in vitro*.)
 - 1. Biologics are derived from living sources in contrast to most drugs which are chemically synthesized and have a known structure. Biologics regulated by FDA include human blood and plasma and their derivatives, bacterial and viral vaccines, toxin, antitoxin, growth factors, monoclonal antibodies, somatic cells and gene therapy.
 - 2. Biological products are approved for marketing under the Public Health Service Act but, because most biological products also meet the definition of "drugs" under the Food, Drug And Cosmetic Act, they are also regulated under this law.

- D. FDA is charged with ensuring that drugs, biologics and medical devices are safely and thoroughly tested and that commercial products are safe and effective for their intended use.
- E. FDA's regulatory requirements vary somewhat depending on the type of products (e.g., drug, biologic, device or combination of these). However, there are certain FDA requirements and policies applicable to all of these regulated categories.

II. Preclinical Research

- A. Regulations (found at 21 C.F.R. Part 58) pertaining to good laboratory practices ("GLP") must be followed for nonclinical laboratory studies that support, or are intended to support, applications for research or marketing permits for drugs, biologics and devices. Requirements include: testing facility management; facility and equipment requirements; handling of test and control articles; recordkeeping and reporting; written SOPs; and adherence to study protocols.
- B. Preclinical testing can include genotoxicity screening, drug absorption and metabolism, toxicity of drug and metabolites, and speed at which drug and metabolites are excreted from the body.
- C. The purpose of preclinical testing is to develop sufficient data to support a decision to proceed with clinical trials or may be used to support a decision that clinical trials are not necessary.
- D. Testing facilities can be disqualified for failure to comply with FDA requirements (where noncompliance adversely affects the validity of the studies and other FDA actions are not adequate to achieve compliance). FDA may not consider studies performed at violative labs in support of product applications.

III. Clinical Trials

- A. Depending on the product, clinical testing may be required prior to product approval.
 - 1. FDA requirements for clinical studies relate to study sponsors, investigators and institutional review boards. (Primary FDA regulations are found at 21 C.F.R. Parts 50, 56, 312, and 812.)
 - 2. These requirements include: written investigator agreement; investigator training; approval by institutional review board ("IRB"); informed consent; reporting (periodic and special reports including reporting of adverse events); recordkeeping; and study monitoring to ensure compliance with study protocol, investigational plan, FDA and IRB requirements
- B. With some exceptions, FDA approval of an investigational new drug application ("IND") or an investigational device exemption ("IDE") is required before a study can be initiated.

1. Depending on the type of product, such applications include information about product description/composition, stability, product manufacture and control, study protocol, informed consent forms, prior use, safety information, and identification of IRBs.
- C. There are opportunities for early consultation with FDA prior to initiation of a study or during the study.
- D. There are FDA procedures that allow for expanded access to investigational products where there are available data to show that the product may be effective for the target population and that use would not expose patients to unreasonable and significant additional risks. (Other criteria include: the disease is serious or immediately life threatening; a satisfactory alternative therapy doesn't exist; controlled clinical investigations are being conducted or have been completed; and the sponsor is actively seeking product approval and expanded access will not interfere with enrollment in other studies.)
- E. FDA has authority to conduct inspections of clinical study records at the sponsor, investigational site and IRB.
- F. Failure to comply with study requirements can have serious ramifications for the study sponsor, investigator and/or IRB (e.g., product approval problems, warning letters, investigator disqualification, and criminal sanctions).
- G. Examples of FDA clinical study initiatives/issues relevant to biotechnology products.
1. In response to gene therapy trial death, FDA has stepped up inspection of clinical trials, suspended trials that raise concern, issued warning letters citing compliance issues, begun disqualification proceedings against investigator and requested implementation of improved quality assurance measures in gene therapy research.
 2. FDA has proposed a new regulation to allow disclosure of trade secret and confidential commercial information regarding gene therapy and xenotransplantation clinical trials that FDA intends to post on the Internet.
 3. FDA now requires sponsors of gene therapy trials to routinely submit monitoring plans to FDA. Sponsors need to address issues relating to experience and training of monitors and adequacy of monitoring plan.
- H. Related regulation.
1. Gene therapy research that is federally funded or makes use of federal facilities is subject to oversight by the National Institutes of Health ("NIH").
 - a. NIH's Office of Biotechnology Activities ("OBA") is responsible for monitoring progress in human genetics research. The OBA administers the Recombinant DNA Advisory Committee ("RAC"). The RAC reviews gene transfer protocols and recommends changes to NIH.

- b. There are RAC guidelines that include description of facilities and practices intended to prevent unintended release or inadvertent exposure to genetically modified organisms or recombinant DNA. Investigations at institutions receiving NIH funds for research involving recombinant DNA must comply with these guidelines.
- c. There is some overlap and inconsistency between FDA and NIH requirements.

IV. Manufacturing Issues at the Clinical Trial Stage

- A. FDA expects manufacturers of drugs and biologics to comply with good manufacturing practices (“GMPs”) during all clinical product phases, beginning with early Phase I clinical trials. (GMPs cover the manufacture, processing, packaging, holding, testing, and quality control of drugs and biologics.) Companies starting Phase I clinical trials for drugs and biologics must comply with facility and equipment qualification requirements and validate “safety-related processes” (e.g., sterilization, viral clearance) to ensure that the product will consistently meet established specifications. Drug and biologics companies also need to establish and develop quality systems covering all aspects of development, including change controls, failure investigations and software validation.
- B. Medical devices used in clinical trials must comply with design controls established by FDA’s Quality System Regulation (“QSR”). (Design controls are procedures for ensuring that a device is designed to required specifications. This includes procedures for design planning, review, verification, validation, transfer, and changes, all of which must be documented in a design history file.)
- C. After clinical trials have begun, FDA may inspect drug and biologic companies to confirm compliance with GMPs, and may inspect device firms to confirm compliance with QSR design control requirements.

V. Restrictions on Promotion of Investigational Products

- A. There are various FDA rules and policies regarding promotion and advertising of investigational products. A few basics are as follows:
 - 1. FDA generally prohibits promotional materials that claim (or even suggest) that investigational drugs, biologics, or medical devices are safe and effective. (FDA has broad oversight and may look at company websites, detail pieces, direct mail, brochures, press releases, print media, and radio and television advertisements to make determinations of improper promotion.)

2. Sponsors, investigators and those acting on their behalf are not allowed to represent that an investigational device is safe or effective for the purpose(s) for which it is being investigated.
3. Investigational drugs and biologics may be presented in advertisements that are limited to discussion of a therapeutic research area and a manufacturer's name, but do not identify a product ("institutional ads") or simply state the future availability of a specific product, without identifying the use or discussing safety or effectiveness ("coming soon" ads).
4. Continuing medical education ("CME") programs can be used to discuss investigational products as long as they are independent of the manufacturer's influence.
5. Many rules/policies in this area can be confusing and interpretations can change over time. Accordingly, promotion/advertising issues should be evaluated on a case-by-case basis.

VI. Product Approvals

- A. In order to market a new drug or biologic, there must be FDA approval of a new drug application ("NDA") or biologics license application ("BLA"). Most devices must get approval of a premarket approval application ("PMA") or premarket notification ("510(k)") prior to marketing. (Novel devices typically require PMAs while devices that can demonstrate substantial equivalence to a legally marketed device can submit a 510(k) which generally requires less data than a PMA.)
- B. Some biotech drugs are reviewed by FDA's Center for Drug Evaluation and Research ("CDER"). Other biotech drugs, blood products and vaccines are reviewed by FDA's Center for Biologics Evaluation and Research ("CBER"). *In vitro* diagnostic devices and other types of devices are reviewed by FDA's Center for Devices and Radiological Health ("CDRH").
- C. Approved biotech drugs include those for hemophilia, leukemia, hepatitis, transplant rejection, anemia, cystic fibrosis and many types of cancer. A biotech vaccine for hepatitis B has also been approved. *In vitro* biotech diagnostic products include home pregnancy tests and screening tests for HIV and hepatitis.
- D. Product approval applications (depending on the type of product) contain, among other things: product description; preclinical data; clinical data demonstrating safety and effectiveness; description of product manufacture, processing and packaging; stability data; proposed labeling; and patent exclusivity information.
- E. Depending on the product, there may be an FDA inspection of clinical sites and manufacturing facilities before that product can be approved.
- F. There are abbreviated product approval procedures for non-biological drug products and for devices.

1. For drugs, there are abbreviated procedures for Section 505(b)(2) Applications and Abbreviated New Drug Applications (“ANDAs”) for “generic drugs”.
 2. An “Abbreviated 510(k)” can be used when guidance documents exist, a special control has been established or FDA has recognized a relevant consensus standard and the manufacturer demonstrates conformance to this guidance, control or standard. Device modifications can be cleared via a “Special 510(k)” which rely on summary information from the design control process where the modification does not affect the intended use of the device or alter the fundamental scientific technology of the device. (Both of these types of 510(k)s allow for faster approval.)
- G. FDA also has certain other expedited product approval procedures. (Products reviewed on an expedited basis are generally not required fully to demonstrate effectiveness prior to approval.)
1. “Fast track” for drugs and biologics
 - a. FDA standard for “fast track” is when the agency determines the product has an effect on a surrogate clinical endpoint that is reasonably likely to predict clinical benefit. Under this approach, FDA balances the medical need for a new therapy against approving a product with possible unknown risks.
 - b. Intended to facilitate development and expedite review of drugs and biologics for treating a serious or life-threatening condition and that addresses an unmet medical need.
 - c. Manufacturers should request “fast track” status before or after submitting an IND, but before FDA’s review of the NDA or BLA.
 - d. Preliminary review of clinical data may allow FDA to begin its review of the NDA/BLA before the entire application is submitted.
 - e. FDA generally requires post-marketing studies as a condition of approval following expedited review in order to validate the surrogate endpoint or confirm the effect of the clinical endpoint.
 2. Priority review for drugs and biologics
 - a. Drug/biologic applications can get “priority review” if they provide a significant improvement in the safety and effectiveness of treatment, diagnosis or prevention of a serious or life threatening disease.
 3. Expedited review of medical devices.
 - a. Medical devices are considered for expedited review if a device offers a potential for clinically meaningful benefit as compared to existing alternatives (preventative, diagnostic or therapeutic) or when the new medical device promises to provide a revolutionary

advance (not an incremental advantage) over currently available alternative modalities.

- H. There is market protection in the form of market exclusivity for drugs and biologics. (This market protection is independent of, and may be in addition to, patent-related market protection.)
1. Orphan status bars FDA approval of any other application for the same drug or biologic for the orphan indication for a period of seven years. Such exclusivity is available for products intended to treat rare diseases or conditions that affect fewer than 200,000 Americans or for which there is no reasonable expectation that sales would cover the costs of development. Orphan drugs/biologics also get tax credits and eligibility for grants and contracts. (Note that orphan status for devices does not provide market exclusivity, tax credits, etc.)
 - a. Make request for this designation prior to submission of NDA or BLA or for a new, unapproved use of any approved drug.
 - b. Several genomic products have been granted orphan drug status, including gene therapies for the treatment of metastatic melanoma and cystic fibrosis.
 2. New chemical entity exclusivity is available to drugs that contain an active moiety not previously approved by FDA for pharmaceutical use. New chemical entity exclusivity bars FDA from considering the approval of generic drugs and certain other drugs containing the same active moiety for five years.
 - a. Sponsor's market protection is extended to all formulations, dosage forms and indications where the product contains the same active moiety.
 3. Pediatric exclusivity adds six months to other market exclusivity or patent protection that already covers a product. Pediatric exclusivity is available for certain drugs or biologics for which a sponsor conducts a pediatric clinical investigation in response to a written request from FDA.

VII. Post-Approval Issues

A. Establishment registration

1. Drug, biologic and device manufacturers must register their facilities with FDA and list their products.

B. Good Manufacturing Practices/Quality System Regulation.

1. After market approval, drugs/biologics must adhere to GMP requirements and devices must adhere to QSR requirements.
2. The GMP regulations for finished pharmaceuticals (drug or biological products) are found at 21 C.F.R. Parts 210 and 211. The QSR regulations

for medical devices (including *in vitro* diagnostics) are located at 21 C.F.R. Part 820.

3. The GMP/QSR regulations include requirements pertaining to: equipment qualification; process validation; design controls; change and document controls; personnel responsibilities; production and process controls; purchasing controls; acceptance activities; and corrective and preventative actions.
4. Important early stage issues include: facility design review; establishing/developing systems; and conducting assessments to verify status against FDA requirements.
5. The GMP/QSR regulations are not prescriptive, and manufacturers are given some discretion in interpreting and applying the requirements.
6. Companies must develop their own procedures and controls for manufacturing processes that meet the GMP/QSR requirements.

C. Promotion/Advertising Issues

1. There are many FDA regulations and policies (often unwritten) regarding post-approval promotion and advertising. Each circumstance must be evaluated on a case-by-case basis. Following are some basics:
 - a. Promotion of FDA regulated products cannot be false or misleading and must be presented with fair balance.
 - b. A prescription drug is misbranded if all advertisements and other descriptive printed material do not contain a true statement of information or brief summary relating to side effects, contraindications, and effectiveness as required by FDA regulations.
 - c. A restricted device (this includes all Class III PMA devices) is misbranded if all advertisements and other descriptive printed materials do not contain a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.
 - d. Scientific journal articles distributed by a manufacturer's representative that contain "off label" information can be used to contend that the product is misbranded.
 - e. A manufacturer can be responsible for unapproved claims made by a physician or other third party if the manufacturer encouraged or provided financial support for these claims to be made.
 - f. Product-specific press releases may be subject to FDA scrutiny. Press releases must be accurate and consistent with approved labeling or indications that have been approved for a product.
 - g. FDA pays close attention to the Internet, and applies traditional rules and policies to Internet promotion as well as Internet-specific

policies e.g., device uses that are not approved in the U.S. should be presented under separate country icons.

D. FDA Inspections

1. FDA can enter and inspect any factory, warehouse or establishment where drugs, devices, or biologics are manufactured, processed, packed or held for interstate commerce or after introduction into interstate commerce.
2. FDA can inspect the establishment, equipment, finished and unfinished materials, containers and labeling. FDA has even greater inspectional authority over prescription drugs, nonprescription drugs for human use and restricted devices.

E. Recordkeeping and reporting requirements

1. Examples of post-approval recordkeeping and reporting requirements include:
 - a. MedWatch reporting of deaths, serious injuries, reportable defects and malfunctions to FDA.
 - b. Reporting to FDA where postmarket surveillance studies are required.
 - c. Reports to FDA regarding product recalls.
 - d. Reports/new product submissions for changes to approved products or manufacturing procedures.

F. Importing-Exporting Products

1. Various FDA import and export laws apply to drugs, biologics and medical devices.

G. FDA Enforcement Authority

1. FDA's enforcement authority over non-compliant products, companies and individuals includes: untitled letters/warning letters; adverse publicity; corrective advertising; suspension/revocation of product approval; application integrity policy; seizures; injunctions; mandatory recalls; disgorgement of profits; civil penalties; and criminal penalties.
 - a. The Food, Drug and Cosmetic Act is a "strict liability" statute. This means that it doesn't matter whether the individual knew about the violations if that person had responsibility and authority to prevent or promptly correct the violation complained of. Accordingly, responsible corporate officials may be held responsible for the acts of employees.
2. Under the Public Health Service Act there is authority to immediately suspend licenses where there is a danger to public health.

VIII. Regulation By Other Agencies

- A. The laws and regulations of other Health and Human Services (“HHS”) divisions/federal agencies may impact on decisionmaking by companies that manufacture FDA-regulated drugs, biologics and medical devices. For example:
1. Health Care Financing Administration - Reimbursement issues for Medicare and Medicaid; patient privacy, security and electronic transactions under Health Insurance Portability and Accountability Act of 1996 (“HIPAA”).
 2. National Institutes of Health - Oversight over federally funded/supported gene therapy research.
 3. Public Health Service - Guideline for conducting xenotransplantation procedures.
 4. Federal Trade Commission - Antitrust concerns and authority over advertising of consumer products including drugs, biologics and devices.
 5. Securities and Exchange Commission - Law requires public companies to disclose meaningful financial and other information to the public.