FDA Laws, Regulations, and Guidance Documents

SLIDE 1
This presentation will discuss FDA laws, regulations and guidance documents.

SLIDE 2
Let's begin with a very broad brush about the laws, the regulations, and the guidance documents that FDA issues.

This talk will discuss the legal framework under which FDA operates, will give a brief introduction to some of the laws used to do the job at the FDA, and will talk about the regulations and guidance documents.

SLIDE 3
About the legal framework. FDA does what it does because they have the authority to do it, and that authority comes from the United States Constitution. That is the fundamental source of all the United States' laws. The governmental system in the United States is a federal system, where some of the powers are given to the federal government, and others are given to the states. In particular, some of the powers given to the federal government are powers over interstate commerce and foreign affairs.

The federal government is divided into three branches. In the Legislative branch, Congress makes the laws. Then, there is the Executive Branch, which is the President and the federal agencies, such as FDA. The Executive Branch enforces the laws. Last, there is the Judicial Branch, which is the Supreme Court and the other courts. The Judicial Branch makes sure that the Constitution is upheld.

Under the Constitution, there is the authority to enact laws, also called statutes. Congress makes the laws. FDA, as an agency, can then issue regulations and guidance documents as part of the implementation of the laws.

SLIDE 4
You may hear people use the term "law" or "statute." Those terms are interchangeable.

SLIDE 5
The Center for Biologics Evaluation and Research, known as CBER, works with two main statues, the Public Health Service Act, or PHS Act, and the Federal Food, Drug, and Cosmetic Act, or the FD&C Act.

The PHS Act has many, many provisions in it, but there are two key provisions under which CBER works. One is the licensing provision. That is the approval

provision. The other is the communicable disease provisions, which give the authority to issue regulations to prevent the spread of communicable disease.

The other statute under which CBER works is the FD&C Act. It has been amended over 100 times, so, little by little, a regulatory scheme has been put together.

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The Biologics Control Act was enacted in 1902, and was the beginning of federal regulation of medical products, not just of biological products. It is the first time that Congress stepped into the field of regulating medicine products, and they chose biologics.

It happened because of a tragedy where a diphtheria antitoxin was manufactured with materials from a horse that had tetanus. A number of people who received the product died as a result of the contaminated product. Congress stepped in and decided that legislation was needed at a federal level.

This statute was amazing for its time, because it actually required pre-market approval and a resulting license. It also had labeling requirements. The statute provided authority to do inspections of the product manufacturers. And, it provided penalties for those who violated the statute.

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The food and drug law did not come into place until 1906. Although it was fairly comprehensive, it was more of an enforcement statute. It did not require pre-market authorization at that time.

It was mostly focused on penalties, with provisions for criminal penalties, including imprisonment and fines. In addition, it authorized seizures of products. A seizure is a court action against a product, not a person, where a court could require a product to be held in place and not be moved, until the lawsuit is resolved. A decision would be made on what needed to be done with those products that were violative - for example, they might need to be destroyed.

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In 1938, there was another large piece of legislation. This is the Federal Food, Drug, and Cosmetic Act. And this, again, came about as a result of a tragedy involving a drug, specifically elixir sulfanilamide, which contained an unlabeled solvent that resulted in a number of people dying. Congress realized that the existing law did not make illegal the failure to disclose that information. So Congress enacted a new law that extended control over products, beyond drugs, such as cosmetics and therapeutic devices, although the term device was not used. The statute required evidence of safety before a product could be marketed.

It did not require evidence of efficacy, though, at that time. It did allow for inspections. And it added the authority of court injunction, which essentially is a court action ordering a firm to do certain things, such as shut down.

SLIDE 9
You will hear mention of the Public Health Service Act. In 1944, there was a compilation of a number of statutory provisions that had appeared in a variety of different places. These provisions were pulled together into the Public Health Service Act, including the licensure of biologics and the control of communicable diseases.

Under the Public Health Service Act, FDA can issue regulations to prevent the spread of communicable diseases. That includes not just some of the products regulated by CBER, but also the interstate movement of turtles, because of the potential spread of salmonella. FDA has issued regulations in that area.

SLIDE 10
Tragedy struck again. In 1962, Congress enacted additional legislation, following the thalidomide tragedy, where, as a result of a drug, there were many birth defects in babies born in Europe.

FDA had not allowed marketing of the drug. Congress realized that additional showings were needed before a product could be put on the market, and enacted the Kefauver-Harris drug amendments to require that manufacturers demonstrate the efficacy of the product before it can be marketed.

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Following that, there were the Medical Device Amendments. Although therapeutic devices were included under the previous legislation, Congress specifically addressed devices under the Medical Device Amendments Act. And, they expanded the definition of "devices" and provided more detail in terms of classification of devices.

The statute described a risk-based approach, where there are different levels of oversight depending on what class of product the device was. The higher the class, the more requirements that applied.

And, this statutory provision required either pre-market approval or clearance of the device. Generally, the clearance would be for those products for which another product had already been shown to be safe and effective and the following product was shown to be substantially equivalent.

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Then, there was the Orphan Drug Act in 1983. Congress recognized that there are many patients with diseases that affect only small numbers. Manufacturers often would not choose to study possible treatments for those diseases, because

there was no economic incentive. This act provided incentives to companies to develop products for rare diseases.

There is also the National Childhood Vaccine Injury Act, enacted in 1986. This Act amended the Public Health Service Act. It requires that certain information be made available to patients receiving vaccines, and it gave FDA the authority to recall biological products, not just vaccines. The National Childhood Vaccine Injury Act is a compensation statute. In the United States a number of childhood vaccines are required for children before they attend school. FDA approves medical products based on a decision that the benefits outweigh the risks; medical products are not 100 percent safe. So, there would be times when someone has an adverse event as a result of getting a vaccine. These are really important products from a public health perspective. Congress recognized that it was important that children be vaccinated and it was important that companies continue to exist to make these important vaccines. This statute provides a compensation scheme for certain products that are listed on a vaccine table - for certain adverse events that are associated with those vaccines.

SLIDE 13

In 1992, Congress enacted the Prescription Drug User Fee Act, also called PDUFA. This was the first user fee act for FDA.

At that time, reviews and approvals were taking a long time, and there was a lot of attention on why that was happening. There was much discussion about the lack of adequate resources for FDA to review applications in a timely way. Under this act, the drugs and the biologic manufacturers pay fees for the marketing applications they submit to FDA.

FDA would use those fees for activities in the review process. For example, FDA would use PDUFA fees to hire reviewers to look at applications and safety issues, with a goal of reducing review time.

This act has been reauthorized a number of times. And Congress pays a lot of attention, as does industry and the public, in terms of how FDA is doing. Each time there is a reauthorization of the user fee act, there are goals set.

SLIDE 14

In 1997, Congress enacted the Food and Drug Administration Modernization Act, or FDAMA. FDAMA contains many different pieces. It reauthorized PDUFA. It also states that FDA should make efforts to harmonize between the drug products and biologics products. It created the establishment of the clinical trials database under the Public Health Service Act, which is run by the National Institutes of Health and National Library of Medicine. And it also called for a number of other broad reforms, such as accelerating the review of devices.

SLIDE 15

In 2002, Congress enacted the Public Health, Security, and Bioterrorism Preparedness and Response Act. This followed the terrible events of September 11, 2001. It gave FDA the authority to do more in the area of preventing and responding to emergencies. It also required FDA to issue regulations to have controls over imported and domestically produced commodities.

In addition, this piece of legislation included reauthorization of PDUFA, marking the third time additional revisions to the user fee requirements were made.

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In 2002, the first user fees for medical devices were established. This piece of legislation also had provisions dealing with third parties, who might do inspections of device manufacturers. Though not many became accredited, the legislation's intent was to try to make sure more device firms were getting inspected and also to alleviate burden.

In 2003, Congress passed the Pediatric Research Equity Act, or PREA. At this point, there was attention to the fact that many medicines given to children had not been studied in children. More needed to be known, such as whether these products work the same in children as they do in adults? This statute required sponsors to conduct pediatric testing of certain products. It allows FDA to determine whether or not pediatric testing is appropriate, to waive such testing if it is not appropriate - for example a disease that does not occur in children -- or to defer studies if appropriate.

For example, suppose someone did a clinical trial in adults, and it was ready for approval, FDA would not want to hold up getting an important product to market while the studies in children were done. A main purpose of this statute was to make sure those studies did happen.

SLIDE 17

Then, in 2007, there was the Food and Drug Administration Amendments Act, referred to as FDAAA. This was also another very large bill. It reauthorized a number of existing pieces of legislation.

Some background: Sometimes when Congress enacts a law, they put it in place only for a set period of time. Other times, there is no time limit on the legislation. So, certain statutes are put in place until Congress changes the law. An example is the general provisions of licensing a biological product. But for some others, like the user fee provisions or the Pediatric Research Equity Act, Congress put time limits in place.

For example, PDUFA and PREA are in place for five years. Congress then has to reauthorize them, if they think it is appropriate. And so, every five years, PDUFA's provisions are re-negotiated. Discussions may include: What is appropriate? Is more money needed? It is a lot of work.

In general, the revisions have enhanced the authorities, and have enhanced public health.

FDAAA reauthorized a number of provisions, both the Prescription Drug User Fee Act and the Medical Device User Fee Act. It also reauthorized the Best Pharmaceuticals for Children Act, which has to do more with products regulated by the Center for Drugs, products approved under the FDCA, and generic products. It did not apply to biologics.

It also reauthorized the Pediatric Research Equity Act - including a provision to include new pediatric information in labeling. So, the reauthorization strengthened the existing requirements.

The Pediatric Research Equity Act required the agency to form a Pediatric Review Committee, or PeRC, to look at what the agency was doing, for example, regarding waiving or deferring studies in children. The PeRC is an internal committee consisting of people from the commissioner's office, CBER, and CDER. And the committee provides recommendations for the review divisions' considerations. Part of the purpose of the PeRC is to ensure a more consistent application across the agency in the area of pediatrics.

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This slide provides additional information about FDAAA. FDAAA has a section on pediatric devices, to enhance the devices used in children. It also created a foundation called the Reagan-Udall Foundation, to support areas of research that would be critical to getting products to market. FDAAA expanded the existing requirements about clinical trials, with regard to the existing database that contains information on ongoing clinical trials.

FDA is working closely with the National Institutes of Health in terms of the information to go in a database. There is a provision about putting results information in the database. FDA participated with NIH in a public meeting on this topic.

FDAAA contains a provision on conflicts of interest. This provision has to do with advisory committee meetings, where FDA consults with outside experts on many issues, including issues related to product approvals. Some people have raised concerns about the number of people on the advisory committees who have conflicts and this provision contains restrictions in terms of selection of advisory committee members.

Title IX of FDAAA contains new safety provisions. Some of these provisions give FDA the authority to require post-marketing studies in certain instances. So, for instance, if in looking at the adverse events for a product, there is a signal suggesting that the product may be causing the adverse event, then FDA can

require a post-marketing study or a post-marketing trial. Again, the threshold has to be met, but it is new authority for FDA.

SLIDE 19

Section 351 of the Public Health Service Act is where FDA gets the authority to approve biological products. This statute defines what a biological product is, and it actually uses all these words found on the slide, rather than saying "biological product." A key word, besides those specific ones, is "analogous product." For a product to be a biological product, it has to be applicable to preventing disease, treating disease, or curing diseases or conditions in people.

SLIDE 20

In 1972, FDA became the agency that regulated biological products. Before then, it was at NIH. These products are licensed under the Public Health Service Act.

In some other countries, people use the word "license" to refer to something different than premarket approval. FDA uses the term to mean pre-market approval. Biological products, also, either meet the definition of drug or device under the Food, Drug, and Cosmetic Act. So, there is additional statutory authority to regulate them.

For instance, a vaccine also meets the definition of "drug" because it is a product that is given to people to prevent disease. Thus, the provisions in the FD&C Act also apply such as the requirement that manufacturers need to follow good manufacturing practices. The products need to be labeled appropriately under those provisions of the law. They are subject to the sanctions in the PHS Act and in the FD&C Act.

SLIDE 21

To distribute a biological product in interstate commerce, a manufacturer needs pre-market approval. The standard used to license a product is that the product needs to be shown to be safe, pure, and potent. The facility has to meet appropriate standards. Manufacturers have to agree to be inspected.

FDA has the power to suspend or revoke a license. Administratively, FDA can do that itself; it does not have to go to court. And, FDA has the power to recall products.

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Under the PHS Act, in addition to the licensing provisions, FDA can also take actions to prevent communicable diseases. This statutory provision does not say it is forbidden to ship something in interstate commerce that might cause communicable disease. Instead, it says that the Secretary of Health & Human Services can issue regulations to prevent the spread of communicable disease -- it requires FDA to issue a regulation to make something forbidden.

FDA has used this authority in a number of areas. For instance, some of the blood regulations about communicable diseases have been written partly under this authority. In addition, the tissue regulations were also issued under this authority. For some of the tissue products, such as skin and bone, FDA does not require pre-market approval. Instead, FDA requires that there be provisions in place to prevent the spread of communicable diseases. These provisions include testing the donors, screening them, and asking them questions for high-risk behavior.

SLIDE 23
This slide lists a number of other laws that affect the FDA. But this is just a small piece of other laws that affect the FDA. The FDA works with some laws on a regular basis. For instance, the Administrative Procedure Act influences the rulemaking that FDA does.

The Federal Advisory Committee Act has to do with transparency. This cannot all be done behind closed doors. In consulting outside experts, FDA often needs to have public meetings when seeking advice from others.

There is the National Environmental Policy Act. Here, the FDA takes into account what effect the products might have on the environment. In some cases, companies may need to do an assessment of what effect their product might have on the environment.

The Freedom of Information Act addresses how to respond to requests for information from the public and the disclosure of information.

Without going into details, these slides make you aware of many of the reasons why FDA does or does not do certain things.

SLIDE 24
FDA issues regulations. Sometimes you will hear people use the word "rule" instead. Both are correct. A regulation is binding. It is a requirement that an agency issues under statutory authority.

SLIDE 25
Rulemaking within FDA typically means "notice and comment" rulemaking. This is actually a requirement of Congress. This requirement comes from the Administrative Procedure Act.

FDA wants to get input from people so informed decisions can be made. Notice and comment rulemaking includes publishing a notice of the proposal in the Federal Register, which is online and in print.

The Federal Register is issued on a daily basis for all federal agencies, and covers many topics, including rulemaking. This notice provides an opportunity for public comment. Following FDA's assessment of the public comments, a final rule would then be issued. FDA takes into account all the comments received. Comments from the public, including from people anywhere in the world, are really important, and make a difference. Many of the rules FDA staff have worked on have changed from proposal, to draft, and to final stage. So, the comments are very important.

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What does a final rule consist of? The specific requirements are included in the Code of Federal Regulations. In the Federal Register, not only is there the regulation itself, but there is the whole story about why FDA did what it did.

When FDA puts out a proposal, it explains the rationale. And, when FDA issues the final rule, it addresses the comments. That is in the preamble -- the background information.

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In addition, in rulemaking, impact on small businesses and the impact on the environment is assessed. FDA is required to figure out how much paperwork is being required of people, and also what impact it might have on states and local governments. FDA also does an economic analysis. Rulemaking is a big undertaking and takes time.

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The next few slides list some of the regulations that FDA works with regularly.

The FDA regulations are contained in Title 21 of the Code of Federal Regulations. The first parts, 1 through 99, are general provisions. For example, there are regulations about advisory committees and information about financial disclosure.

SLIDE 29
Then you have regulations that address investigational studies. Part 50 and Part 56 contain the human subject protection provisions, as well as provisions related to institutional review boards. Sections numbered in the 200s and 300s have a lot of information about drugs, which may be applicable to CBER products, because many biologics are drugs. So you have the labeling provisions in parts 200 and 201. The good manufacturing practice provisions in Parts 210 and 211 also apply to CBER products. And, the investigational new drug provisions in Part 312 apply to clinical investigations of biological products.

SLIDE 30
Then you have the 600s - the specific biologics regulations. Part 600 contains a number of provisions, including standards for establishments, and requirements

to report adverse experiences. The 601s are about the licensing provisions. There are specific regulations on good manufacturing practices for blood and blood components in Part 606.

Because CBER regulates some devices, this slide shows some device regulations. They are in the 800s. The tissue regulations are contained in Part 12-71.

SLIDE 31
This series presents another talk on Guidances and Good Guidance Practices, so this slide will only mention it briefly.

FDA works with statutes, regulations, and guidance documents. And each one really gets more specific. Guidance documents are documents put out to provide a little bit more information about what people can do to comply with existing requirements. They represent FDA's current thinking on matters, but they are not binding.

SLIDE 32
This slide shows websites where the different guidance documents in the agency can be found.

SLIDE 33
And this slide is a list of helpful acronyms.

SLIDE 34
This concludes the presentation, "FDA Laws, Regulations, and Guidance Documents".

We would like to acknowledge those who contributed to its development. Thank you.