Overview of FDA and CBER

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This presentation will give an overview of the Food and Drug Administration and its Center for Biologics, Evaluation and Research, also called CBER.

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Let's start at a high level and drill down from there. The first principles deal with the framework of the U.S. Government. More specifics on how FDA derives its authorities and specific procedures will be covered in a separate presentation. This focus is on the structure of government and where FDA fits into it.

The Constitution establishes three branches in the federal government: the Legislative, which is Congress; the Judicial, which is made up of the federal courts; and the Executive Branch, which is comprised of the President, the President's cabinet and the various federal departments and agencies.

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The President's cabinet is made up of Secretaries, who are the Heads of the various Departments, such as the Department of Defense, the Department of the Interior, and the State Department. The federal agencies are operating units that fall under various departments. The FDA is in the Department of Health and Human Services, which is headed by Secretary Kathleen Sebelius.

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There are a number of operational divisions or Agencies with varying responsibilities under the Department of Health and Human Services. These include the Administration on Aging, the Agency for Health Care Research and Quality, the Centers for Disease Control and Prevention, the Indian Health Service, the National Institutes of Health, and the Food and Drug Administration, among others. The Commissioner of the Food and Drug Administration is Doctor Margaret Hamburg.

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The FDA is the oldest consumer protection agency in the United States. It is just a little over 100 years old. It has both regulatory and law enforcement authorities. It has an incredibly broad set of responsibilities -- not just biologics, but human and animal drugs; food and dietary supplements; animal feeds; medical devices, which include radiation-emitting devices; and cosmetics. The budget for the FDA runs just under 2 billion dollars, and the workforce is close to

10,000 people. While that may not sound like a small organization, by governmental standards, it is.

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This is the most recent version of the organizational chart for the FDA shown on the website, as of April 2011. While the various Offices are correct for the most part, the names of individuals in the chart may have changed. There may also be some omissions. However, the take home message is that the Agency has an Office of the Commissioner; several Offices to support Agency level needs, like the Office of Chief Counsel and Office of Policy and Planning; and a number of Product Centers.

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All of the product centers are operating divisions in their own right and they report to the Office of the Commissioner. These are Biologics Evaluation and Research; Drug Evaluation and Research; Devices and Radiological Health; Food Safety and Applied Nutrition; Veterinary Medicine; Center for Tobacco Products; and the National Center for Toxicological Research.

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The product centers have certain responsibilities in common: Pre-market review. This refers to the evaluation of a product to enter the marketplace. It includes a review for good clinical practice and good laboratory practice where those are applicable.

Post-market safety monitoring refers to the continuous evaluation of the safety of approved products.

Licensing and registration. This includes listing, as well. Basically, it covers knowing which of the approved products are actually being made, where they are being made, and which companies are involved in the distribution and manufacture of which products.

Development of regulatory policy and guidance. Every center is responsible for creating and updating policies and guidance documents that interpret the regulations that apply to their products. There is a discussion in another presentation in this series about how policy and guidance fit in with statutes and regulations to create a complete regulatory approach.

Surveillance priorities and inspection programs. These surveillance priorities are different than the Post-marketing surveillance mentioned before. These deal with the manufacture of the product. They include receiving and reviewing product deviation reports, and, for biologic products, they include the lot release program. There are a variety of different inspection programs. There are inspections of facilities for good manufacturing practice. There are inspections of review sites or research sites to determine whether the data that is being presented to FDA is

actually reliable, what is called bioresearch monitoring inspections. All of these are covered in some detail in other presentations.

Enforcement action clearance responsibility. This refers to interactions between the Office of Regulatory Affairs and the product centers in determining what sorts of enforcement actions are appropriate when deficiencies are identified.

Testing research. FDA does research into new or improved methods for product testing. This also includes what is known as anticipatory research in areas believed to be fertile for new products. This allows FDA to stay current with emerging areas in science, so the best advice possible can be provided to assist sponsors with product development.

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The vision for CBER is innovative technology advancing public health. And what does that mean? For CBER, it means they are committed to protect and improve public and individual health in the U.S., and, anywhere it is feasible, globally. CBER intends to facilitate the development, approval, and access to safe and effective products and promising new technologies. And finally, to strengthen CBER as a preeminent regulatory organization for biologics.

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The mission of the Center is easily stated: To ensure the safety, purity, potency, and effectiveness of biological products, including vaccines, blood and blood products, and cells, tissues, and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury.

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The organization of CBER is straightforward. There is an Office of the Director. Besides the Center Director and Deputy and Associate Directors, there are a number of senior Advisors, who are responsible for various programs.

There are product area offices: The Office of Blood Research and Review, the Office of Vaccines Research and Review, and the Office of Cellular, Tissue, and Gene Therapies. Each of these Offices has primary responsibility for products in their area.

There are a number of cross-cutting offices. The Office of Compliance and Biologics Quality is responsible for both compliance issues and manufacturing facility issues across the product scope of the Center.

The Office of Biostatistics and Epidemiology houses our biostatisticians and epidemiologists, who deal with statistical analysis of clinical data, preclinical data in some cases. They're also involved in post-marketing assessment of adverse events.

The Office of Management is the administrative group charged with keeping the wheels running.

CBER has an Office of Communications, Outreach, and Development. Their responsibilities include internal training and external communications, including managing the CBER web site, answering consumer questions and responding to manufacturer inquiries, among other things.

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How do biological products differ from conventional drugs? There are a number of ways. Traditional small molecule drugs are fairly simple, straightforward syntheses, although they have gotten far more complex in the modern era. But generally, the concept of an Active Pharmaceutical Ingredient, called API, that can be obtained from a chemical supply company, has a certificate of analysis, and is then formulated into a drug product, does not translate well to a biologic product.

The vast majority of biologics are derived from living sources: Humans, animals, microorganisms. Most biologics are complex mixtures that are not easily characterized. In actual fact, there are still some licensed biologics where the active moiety is not clearly identified and the mode of action is not completely understood. Many Biologics have multiple effects, and are mixtures of various forms of the substance. One can tell you how a product is made, what it looks like, or give some characterization criteria, but may not be able to say, with certainty, that this is the active moiety, and this is how it works. It's one of the problems of dealing with a biologic.

Biologics tend to be heat-sensitive, and they are incredibly sensitive to microbial contamination. Manufacturing can be a problem. Terminal sterilization is not usually possible. Consequently, it is necessary to use aseptic principles from initial manufacturing steps. For these and other reasons, the manufacturing process for a biologic tends to be more important to its function than is the case for small molecule drugs.

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Consequently the manufacturing process starts at a much earlier point than is usually the case with small molecule products. Rather than obtaining a chemical from a supplier, it starts at the chicken or the egg, or both, to work forward. The process starts with the original microbe or cell line, and so on.

Since biologics are made using, or derived from, living cells, tissues, or organisms, there are inherent risks that just are not a problem for small molecule products, an example being live virus vaccines. Yes, you may have an adverse event with a small molecule drug that you have given to a person, but you usually do not worry about that small molecule drug going from that person to some

other person, and causing an adverse event in the innocent bystander. However, that is a possibility with a live virus vaccine.

There are also risks from new and emerging threats, both natural and manmade. Hepatitis B vaccine is a case in point. The first hepatitis B vaccines were made from human plasma, which was isolated from human donors. A problem arose when AIDS was first seen in people. AIDS and hepatitis B tended to be found together at an alarming rate. It made donor screening far more important for the plasma-derived vaccines. It made it far more important to move to a recombinant DNA-derived vaccine.

As mentioned, the manufacturing of biological products tends to be complex. Small changes in manufacturing can result in incredible changes in the ability of the biologic to do what it is supposed to do. It means that you have to pay a lot of attention to the facilities, materials, processing, and products. There are products where manufacturing flow is absolutely critical. For example, in the production of a killed virus vaccine, you must be sure that you are not crossing product streams pre- and post-inactivation. Otherwise you risk contamination of your killed product with live virus.

There are other reasons to be careful about manufacturing changes. A relatively minor change in the manufacturing process of a licensed, inactivated, virus vaccine could allow virus to escape inactivation, and be released into the final product. Instead of protecting people from the disease, in this scenario, the vaccine could cause the disease.

Another interesting thing about biologics is that there are multiple mechanisms of action, and those multiple mechanisms are not always predictable. Many of these products are heterogeneous mixtures of subtypes of the product. It makes it far more important that you control your manufacturing process, so that you do not make a change that causes a significant change in the distribution of subtypes. You want to avoid the possibility of an increase in a subtype that is associated with an undesirable action.

The last point here is the concern about the safety of critical products. All products are approved based on an evaluation of risk-of-use versus benefits-from-use. Once that is established, you must be vigilant to see that the risk-benefit profile is not shifted in the wrong direction. While this is true of all products, it assumes special meaning for CBER vaccine products. Many of these are given not just to healthy individuals, but also to healthy infants. Safety is absolutely critical.

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Biological products have a somewhat unique role in health care and national preparedness. With pandemics, wars and disasters, and bioterrorism -- there are biological products that can be used to counter the effects of these events.

There are also biological products that can be used to prevent the worst outcomes of some of these events.

Not long ago, one of the difficulties with biological products was that they did not make much money. There was very little profit margin in them. It was one of the reasons for the loss of vaccine manufacturers. One response was the passage of the Vaccine Injury Act, which was intended to keep the vaccine manufacturers from just shutting down because they could not afford to keep going. Now there are a number of biologics that actually do have a good profit margin. And, in fact, in current times, even those that maintain a low profit margin are being found by industry to be worth having in their portfolio. Although they do not make profits on a "blockbuster" scale, they continually generate a low level of profit, which can sustain their manufacture and contribute to a company's overall profitability.

And finally, many of the new therapeutic technologies are in the area of biologics. The new technologies are highly visible, and generate a lot of interest. These technologies hold the potential for great benefit, but there are complex risks associated with them. It is important to stay abreast of the science to properly regulate these products.

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What products does CBER cover? A number of them have been mentioned already. There is a wide range of both investigational and licensed products: allergenics; blood products; a subset of devices; gene therapies: human tissues and cellular products; vaccines, both preventive and therapeutic; and xenotransplantation products.

Details about all product areas will be covered in other presentations, so this presentation will give only an overview.

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Allergenics. There are really two big areas for allergenic products. The first is the patch test to diagnose the causes of contact dermatitis. The other is allergenic extracts. These are used to diagnose and treat such things as allergic-rhinitis, sinusitis, conjunctivitis, and bee stings.

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There is a wide array of BLOOD products. They include both blood and blood components for transfusion, like red blood cells, plasma, and platelets. They also include pharmaceutical products that are made from blood, like clotting factors, and immunoglobulins. Finally, related recombinant products, such as anti-hemophilic factors, are blood products as well.

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The devices. Remember, this is a small subset of the universe of medical devices. The vast majority of devices are regulated in the Center for Devices

and Radiological Health. However, there are devices that actually are biologics. CBER also covers devices that are regulated within the biologics paradigm. These include devices for collection, processing, testing, manufacture, and administration of blood and blood products and cellular products, as well as, re-agents to type bloods, all HIV test kits used to screen donors of blood and blood components and to diagnose, treat, and monitor persons with HIV.

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Gene therapy. This is an area that covers a wide variety of products. Their common feature is that they introduce genetic material into the body to replace faulty, missing, or inactive genetic material to have their beneficial effect.

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Tissues and cellular products. This includes human tissues for transplantation, like skin, tendons, ligaments, and cartilage. The cellular products include such things as human stem cells, pancreatic islet cells, and the like.

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Vaccines may be preventive or therapeutic. They may target infectious diseases, such as measles, mumps, or polio vaccines, or be intended to treat or prevent non-infectious conditions, including cancer.

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The xenotransplantation products comprise a range of treatments. They may be live, non-human cells, tissues, or organs. They may also be human cells that have been cultured, or otherwise been in ex vivo contact with non-human cells. Whichever of those it may be, it is introduced into the human body to achieve its purpose. There is a potential benefit here where human materials are limited, but it does pose special infectious disease concerns.

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Investigational biological products. The statute forbids introduction of a biological product into interstate commerce unless it is licensed. For a product to be licensed, you must submit data to support safety and efficacy. But, in order to do that, the product needs to be moved between states, which cannot happen unless it is licensed. In order to break this vicious circle, there are regulations that permit a product to be shipped interstate for investigational purposes. As with Investigational New Drugs, or INDs, these same regulations and same approaches are used. Biologic product development begins with initial laboratory and animal testing, and then human clinical trials. If the human trials are done in the U.S., they are done under an IND application. Generally, there is considerable interaction between the IND sponsor and CBER during the development of a biologic product. Sponsors conducting studies outside the U.S. are not required to have an IND, but they may apply for one, if they wish. Studies not conducted IND may be used in support of licensure, if they meet the appropriate criteria, specifically things like good clinical practices, and so on.

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In order to get a license for a biological product, there must be a showing of safety and efficacy. To do this, the company submits an application containing non-clinical, clinical, product, and manufacturing data including facility information. There may be a pharmacovigilance plan submitted. CBER reviews the data and other information that has been supplied, and will complete a pre-license inspection. There will be a bioresearch monitoring inspection to assure that the clinical data submitted actually resembles the clinical data that were collected. As necessary, CBER will ask questions, request further information, and then make a determination as to the safety and efficacy of the product.

When the product is approved, it is licensed. There will be a number of post-approval activities, for instance, lot release, biennial facility inspections -- these are manufacturing inspections -- and adverse event surveillance. There may be Phase 4 IND studies to extend datasets or clarify specific points.

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Other presentations in this series will cover legal authority for regulating biological products; research and science in CBER; product-specific considerations; inspection programs; safety surveillance; and combination product review.

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This slide shows the CBER internet home page. You can go to this page to look for whatever might interest you.

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This concludes the presentation, "Overview of the Food and Drug Administration and the Center for Biologics Evaluation and Research".

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