PRODUCT JURISDICTION

SLIDE 1

This presentation covers product jurisdiction, or how the FDA decides which Center within the agency will have regulatory responsibility for a product. Jurisdiction is often viewed as a black box, so this presentation will try to shed just a little light on that subject. It will also provide you with some important web links that will help identify how the FDA assigns a particular type of product.

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There is a reason why this slide is shown multiple times in this series of training presentations. This is a really unique group of products. If you have pondered this list before, you may have wondered why this diverse group of products is all in one place? Well, there is actually a very good reason. Most are composed of, or generated from, biologically sourced starting materials, and share certain characteristics that the licensure process is designed to address. Each of these products are either specifically listed in the legal definition of a biologic, are analogous to a biologic, or are directly associated with something that is.

The products that are regulated by CBER, the Center for Biologics Evaluation and Research, include vaccines, which may be prophylactic, therapeutic, or both. It does not matter how they are made or what they are made out of. If it is a vaccine, they are most likely with CBER. There are only a very few products that are technically vaccines that are not currently regulated by CBER.

CBER also regulates all of the cell and gene therapies. That includes not only somatic cell therapies, but also stem cell therapies. CBER regulates allergenic extracts both for diagnosis and for treatment. CBER also regulates xenotransplantation products, which are tissues derived from non-human sources and certain biological products that come in contact with living cells, from non-human sources during their manufacture.

CBER regulates human tissue-derived products, but not all of them fall under the licensure process for biologics. There are two very different types of regulatory programs for human tissues, and products fall into one or the other program, based on how the tissues are processed and what they are used for. The two tracks will be discussed a bit more later in this talk.

CBER also has responsibility for certain devices. This may seem a little out of character if you are talking about something that is typically sourced from

biological materials, but some of the CBER devices actually make biologics at the point of care from autologous tissues or cells. CBER regulates them because the device does not perform the therapeutic action, it is the biologic that it creates that does. CBER also regulates devices that are integrally involved in the production or the testing of the human blood supply, which is the final category on this list.

CBER regulates all blood derivatives, whole blood, and blood components and many of the products used to obtain, process and test it.

So there you have a general idea of the product categories that reside in CBER. Let's spend some time on the jurisdiction process in general.

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So what exactly does product jurisdiction mean to the FDA? It is a set of rules that FDA tries to consistently follow to determine what center or agency component is assigned primary responsibility for the review and regulation of a particular product. It is product-specific and sometimes it is even intended use or indication for use-specific.

However, just because a product is assigned to CBER does not mean that it is necessarily a biologic. Center assignment and regulatory path are actually two different questions. A product that comes to CBER could be a biologic, a device that CBER regulates under the device authorities, or even a drug. CBER uses all of the available regulatory authorities.

The Center for Drug Evaluation and Research, or CDER, regulates drugs and a selected group of therapeutic biologics. In 2003 a small group of therapeutic proteins were transferred from CBER to CDER, including things like monoclonal antibodies, and therapeutic recombinant proteins like cytokines and growth factors. So products that are assigned to CDER could be drugs or biologics.

The Center for Devices and Radiological Health, or CDRH, typically only uses one type of regulatory pathway and that is for devices, though they have a variety of options within the device regulatory pathways that they can use.

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A medical product can fall into one of five major classes: It can be a biologic that is regulated under the Public Health Service Act, or PHS Act; it can be a drug under the Food, Drug and Cosmetic Act, or FD&C Act; it can be a device, referred to as things that 'clank' when you drop them; or it can be a combination product. Combination products contain two or more components that normally would be regulated under different regulatory authorities, something like a biologic plus a drug."

There is also a group of products referred to as 361 human cells or tissues, called 361 HCT/Ps, which is Human Cells, Tissues and Cellular and Tissue-Based products. 361 HCT/Ps typically refer to products that are recovered from one person and used in another for the same purpose that it served in the donor. In the case of 361 HCT/Ps, this is talking about products where the only real hazard associated with their use is infectious disease control. Later, this talk will cover when that is not the case, while reviewing the definition for each of these product categories.

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So exactly what is the legal definition of a biologic, since it is such a wide category of products? It was actually defined legally based on the category of products. And that is why, while it is diverse, there is a legal definition that says this is biologic, this is biologic, and this is biologic. The legal definition states that a biologic is a virus, which actually has a very broad meaning, not the more narrow one that is commonly used; a virus is really taken to mean any kind of microorganism.

Other products that are considered to be biologics are:
- a therapeutic serum;
- a toxin or an antitoxin;
- again a vaccine;
- a blood or blood component or derivative;
- an allergenic product;
- a protein or analogous product.

And this last category is a really important part of the definition. Because of the many products not envisioned when this original definition was created, they are now assigned using this category. So anything that's alive, with very few exceptions, is in CBER for review.

For cell and gene therapy, you are probably wondering how did that category end up in CBER? Most of the early cell products investigated for clinical use were derived from blood. Blood cells are a blood component, which is explicitly listed in the definition of a biologic. Somatic and stem cell therapies derived from other sources are analogous to blood cells, so cellular therapies as a group are biologics.

It's a similar story for the gene therapies… most of the original ones were, in fact, virally vectored. A virus is specifically listed in the definition of a biologic, so if you take the term "virus" literally, again, they are biologics.

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Given that background, what is a drug and what is different about it? Drug is a much, much broader definition. In fact, all biologics are drugs. They are articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of

disease in man or other animals. Also, articles other than food, though there are a few medical foods as well, that are intended to affect the structure or function of the body of man or other animals. So, you can see that is a pretty broad definition, and biologics fits under this broad umbrella, as do devices.

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What exactly is a device? A device is an instrument or an apparatus, implement, machine, contrivance, implant, in vitro reagent, or some other related article, many of which, as stated earlier, tend to clank if you drop it. It is something that is actually an instrument or an implement, something generated in a consistent manner. It is also intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and it is -- or it is intended to, affect the structure and/or function of the body of man or other animals. An important distinction between a device and the broader category of a drug or a biologic is this: a device cannot achieve its primary intended purposes through chemical action within or on the body of man. This is the case, for example, with an implant.

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Devices do meet the definition of drugs, but they also have to meet this caveat that says they are not dependent on chemical processes and they are not dependent on being metabolized to achieve their primary intended purposes.

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Given all of that, what is a human tissue? Well, knowing where they came from, an HCT/P is something that has been recovered from a human donor, either a living or cadaveric. They are human cells, tissues, cellular, or tissue-based products, and they can be regulated solely under Section 361 of the PHS Act if the material is basically taken out of the donor, minimally processed -- that is no significant changes made to the tissue that would affect its use-- and then used in the recipient for the same purpose the original owner used it for. This is called a homologous use.

It cannot be combined with a drug or a biologic or any other kind of regulated article; it has to be used by itself. And it cannot be intended to have a systemic effect.

It also cannot be dependent upon the metabolic action of a living cell for its function unless it happens to be used in an autologous manner, that is in the same person that it came from, or in an allogeneic manner in a first- or second-degree blood relative, or for reproductive use. That is a very narrow range of products.

The concern about 361 HCT/Ps is the risk of transmitting a disease from one individual to another. The concern is not about whether the cells or tissues work, because they worked in the original owner. There should not be concern about how it is manufactured, because in order to be regulated solely under section

361 of the PHS Act, the processing that takes place should not alter the product's utility for repair or regeneration. That is, it should not change the way that tissue works in the body in a significant way.

When all of these criteria are met for an HCT/P, then the Agency oversees the product by inspection to ensure that the risk of infectious disease transmission is controlled.

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So, there are basically five categories of products that come into the agency for medical use. How does one figure out where they go?

The first thing to ask is what is this thing? Meaning, the first question should be: Is the product one "thing" in terms of the FDA regulatory scheme, is it more than one thing, or it is not known what it is?

It is possible that the product is composed of a single entity, but that does not mean one active ingredient. What it means is that the product is composed of articles or a single article that would all normally be regulated as, for example, a drug; or a group of biologics that would all be regulated as biologics; or perhaps a kit of a bunch of different devices; or individual ones that are just drugs, just biologics, or just devices. These are single entity products. And FDA assigns those in one way because, even if there are multiple components, they would all normally be regulated under the same pathway.

The other type of product is when there is more than one component part in the product, and the parts would not normally be regulated under the same type of regulatory path. That is a combination product. For example, a device combined with a biologic, a biologic plus a drug, or a drug plus a device.

Then the other big bucket that a product might fall into is the human tissue products. The first question asked for the human tissue products is not "is it single entity or is it a combination"? The question asked is… "does it meet the four criteria mentioned earlier"? Can it be regulated as a 361 or is this something else?

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If something appears to be a single entity, what are the decisions behind what the product is, and where it belongs?

For single entity products where all parts appear to be regulated under a single type of path, you have to figure out what path that is. For example, if there are a bunch of instruments that come together in a pack and they are used to splice and dice in surgery, you would say that it's a device kit. If it is a cellular product and the cells are being used to transmit some type of gene therapy, that is a

biologic. So, the first thing is to classify the product as a biologic, drug, or device. FDA does that based on the legal definition of what those products are.

Once you know that it is a biologic, for example, let us say it is a virus that is used as a vaccine, look at where that type of product usually goes. You may recall from one of the first slides that vaccines go to CBER. If it is not obvious, how do you know what biologics go to CBER and what might belong in CDER? FDA has a transfer agreement between the two Centers that is posted on the web. It explains what therapeutic proteins went to CDER and what things stayed in CBER. There is also past precedent to guide the assignment process.

What if the product meets the definition of a device? As mentioned earlier, not all of the devices are in CDRH. So ask, what kind of device is this and is it the one that CBER might normally regulate, or is this one of the majority of devices that goes to CDRH? Again, there is an intercenter agreement that can help guide the device assignment. While they are fairly old, some of the information there is still accurate because the general categories of devices that are reviewed by CBER have remained fairly consistent through the years.

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You have already seen the list of single entity products that are assigned to CBER, but just as a reminder, here it is again. If a product falls into one of these categories, that is products that meet the definition of a biologic, including cell and gene therapy, vaccines, whole blood etc, they come to CBER for review.

In addition to the biologics, CBER has those devices that are intended to make a biologic at the point of care. This is a device that is used at the patient bedside or ambulatory treatment facility, that takes a piece of human tissue or some other patient-derived source of material, and processes it in some way to make a therapeutic article. The device itself is not the therapy, it is the output of the device. Then, as mentioned earlier, CBER also regulates some devices that are directly involved in the production or the testing of human blood for transfusion.

Finally, CBER also regulates a small number of drug products. This category includes things that are used in the collection and processing of blood or cellular products.

This presentation has talked about how FDA assigns a product in which all the parts fall under the umbrella of a single regulatory scheme. But, what happens when the parts are really very different and would not normally be regulated under the same pathway? That is called a combination product.

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So, what exactly is a combination product? There are several variations on a theme, but the type that most people think of initially is when two distinct components are combined to create a single, composite product. For example,

you might grow cells, which are a biologic, right onto a synthetic scaffold, which is a device. That is a combination product. The two components would normally have been regulated differently -- one is biologic, one is a device -- but they have been physically or chemically combined such that they are inseparable. In this case, the two components are shipped together and usually have a single application that covers the entire product.

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Combination products do not have to be physically or chemically combined. They can also be two or more separate things that are packaged together and shipped. For example, you might have a cellular product and a scaffold that is shipped together in the same refrigerated package, but not physically combined until the doctor is ready to use them.

The two components can also be packaged separately and shipped separately, but cross-labeled for use together. Using the cell and scaffold example again, the cells might have to be shipped in a frozen state while the scaffold can be shipped at room temperature in a sterile package. Their label specifies that they are intended for use only with each other, and both of them have to be present in order to achieve the intended therapeutic effect. That is also a combination product.

Finally, it is also possible for two investigational products to meet the definition of a combination product, and be eligible for development under a single application, for example, a single Investigational New Drug application or IND, or an Investigational Device Exemption or IDE.

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How is something like this assigned? You cannot just say, this is a biologic and biologics go to CBER or CDER, because there is also a device in there or a drug, or perhaps even all 3.

For combination products, the Agency created an assignment algorithm. The first question asked is: can the primary mode of action of this product as a whole be defined? What is it intended to do?

In some combination products, the answer to this question is really straightforward, one of the components is clearly the powerhouse. For example, if you talk about a syringe to inject a cytokine, the syringe is a delivery system. The cytokine is doing the work in the body. In that combination, the cytokine is the primary mode of action.

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What is meant by primary mode of action? For products that contain more than one component, it is possible there is also more than one mode of action.

The primary mode of action is defined as the means by which a product as a whole achieves its intended therapeutic effect or action. If one component of the combination is clearly responsible for most of that action, then the combination product is assigned to the Center that usually regulates that dominant component.

Unfortunately, you can not always tell if one or another component plays the greatest role and in some cases there are distinct therapeutic effects that need to be taken into account, for example a physical barrier effect and a pain killer. So, if there is not a clearly dominant component, what is the product assignment?

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The first question asked is: Has this same product already been assigned before? Meaning, does the Agency have something that is virtually identical? If so, then FDA tries to send the new version to the same place.

If not, then FDA looks at the components and asks if one of these is really considerably more complex in terms of either safety or efficacy considerations. And if one really stands out as being more complex or more difficult, that combination product is assigned to the center which has the expertise with those questions of safety and/or efficacy.

If neither of those circumstances apply, you look at unique regulatory requirements. This is a rare circumstance to get to step three. Usually with new products, one or the other is going to have more difficult questions of either safety and/or efficacy.

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You may recall from a previous slide that Center assignment does not necessarily indicate what regulatory path may be used for a given product.

Combination products give some options in terms of how they are regulated because usually, if you say something is a biologic, then it is a single entity biologic, and would be regulated under the PHS Act. But with a combination product, you may have a biologic and a device, for example, that could be regulated in combination with one another as either a biologic under the PHS Act or a device under the device authorities. Regulatory pathways are usually decided by the center which gets the product, that is, the one which has the lead for the product. Combination products are typically regulated under a single application, but FDA also has the ability to choose one particular regulatory path then blend in elements of another. This helps make sure that all the safety issues or all of the efficacy issues that are specific to that specific product are covered.

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Obviously, product jurisdiction can be a complicated thing, but there are a variety of paths that a sponsor can take if they have questions about what their product is or where it belongs.

There is a number of staff in CBER and in the other centers that deal with this all the time, and those staff talk. If one sees a product inquiry from a sponsor or gets a question from a review team, it can be circulated by e-mail or discussed by telephone between staffs. If the answer is straightforward and everyone is in agreement, the question is answered informally. If it is not, it is taken to the Office of Combination Products and evaluated as a group to figure out where it goes.

If it happens to be a human tissue and the big question is "does it meet the four criteria for regulation solely under section 361 of the PHS Act?", the place it is sent first is the Tissue Reference Group. Their job is to look at the tissue, look at past precedent and the way the tissue rules have been interpreted, and determine if this is in fact a 361 human tissue, or if there is something different about it that requires a premarket review of some sort. Remember that all 4 criteria have to be met in order to be considered a 361 HCT/P. So, human tissues are not eligible for regulation solely under section 361 if they are more than minimally manipulated, not intended for homologous use, mixed with something else, or are allogeneic and dependent on the activity of a living cell. Products that have one or more of these characteristics can be a biologic or a device, or sometimes even a combination product, depending on what it is mixed with. The Tissue Reference Group makes the decision as to whether a product meets the criteria for regulation solely under section 361. If the product does not, the product is assigned to the Center that normally regulates that type of product.

Finally, there is an opportunity to get a formal opinion on what a product is through something called a Request for Designation, or RFD. FDA oftentimes gets this from sponsors who are very, very early in the development stage and do not really know much about their product. Sponsors get a maximum of 15 pages to describe the product, how it is made, its intended use, and any background research they have that contributes to the understanding of how the product is supposed to work. FDA looks closely at this information and relevant data from the open literature, then applies the applicable set of rules to figure out what it is.

A formal RFD results in a legally binding decision. The agency has a 60-day clock to review the submission and make a determination. If the submission provided by the sponsor does not contain sufficient information to make a decision, the Office of Combination Products will not file it. OCP will let the sponsor know what is missing but then it is up to the sponsor to correct whatever deficiencies exist then refile if they would like to have an official determination.

FDA also has the ability to engage in this discussion process in an informal way, but due to the time involved in the review, typically the informal process for complex or controversial products is not used.

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For questions, there is documentation on the FDA website that describes the process and the assignment algorithm in a little more detail for the combination products.

The website also provides jurisdiction updates. These are single line descriptions of past decisions that do not provide detailed product information, but do serve as general examples that can help you get a better idea about how FDA applies the rules. For example, FDA might say something like processed human tissue that retains live cells for the purpose of treating diabetic ulcers are considered to operate by a biological mode of action and are assigned to CBER.

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This concludes the presentation, "Product Jurisdiction."

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