Medical Device Review at CBER

SLIDE 1
This presentation will discuss "medical device review" by the Center for Biologics Evaluation and Research, known as CBER.

SLIDE 2
This presentation will cover some medical device terminology, medical device review at CBER, a quick overview of the laws governing medical devices and their review, medical device classification, and post-approval reporting of problems.

SLIDE 3
The term "medical device" comes from the Food, Drug & Cosmetics Act, or FD&C Act, Section 201(h). The language is listed here on slides 3, 4 and 5 for your reference.

SLIDE 4
In addition to the items listed on slide 3, a medical device must also be something that is covered by the definitions given on this slide.

SLIDE 5
And the definition is continued here on slide 5.

SLIDE 6
Here, the paragraphs of the Act are broken out, and referred to as the plain English language definition of a device. A device can be an instrument, an apparatus, an implement, a machine, a contrivance, an implant, an in vitro reagent, or other similar or related article. It includes any component, part or accessory.

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But, more importantly, there has to be an intention to use that device in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease in man or other animals.

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An in vitro reagent is a special part of the definition of a medical device because it is one of the largest groups of products that are reviewed in CBER as medical devices. In vitro diagnostic products are reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions. But note that this definition goes on to say -- or including a determination of the state of health. It may not necessarily diagnose a disease. It may simply confirm that you are

healthy. Or it may be meant to mitigate, treat, or prevent disease, or its sequelae.

Anything that is intended for use in the collection, preparation, and examination of specimens taken from the human body is also considered an in vitro diagnostic product. The products are regulated as medical devices, as mentioned, under the FD&C Act, and they may also be biological products subject to Section 351 of the Public Health Service Act, or PHS Act.

The presentation entitled, "FDA Regulation of Blood and Blood Components in the United States," talks a bit about the licensure of products under the PHS Act. There are actually some medical devices that are also biologics and, therefore, are also licensed.

SLIDE 9
Here is the plain English definition of an in vitro reagent. In vitro reagents are products for the collection, preparation, or examination of specimens taken from the human body. Again, they may also be biologics.

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Another definition that may be helpful is that of a manufacturer. The regulations that cover the manufacture of medical devices are in the Code of Federal Regulations, in the 800 sections. There is a long list of definitions in that section, one of them being the definition of a manufacturer.

A manufacturer is any person who manufactures, prepares, propagates, compounds, assembles, or processes a device by chemical, physical, biological, or other procedure. You'll notice that the definition of manufacturer is fairly broad. It can encompass multiple people who are included in the process of making one particular device.

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A manufacturer can also be a person who repackages or otherwise changes the container, wrapper or labeling of a device in furtherance of the distribution of the device from the original place of manufacture.

This is often seen in cases where a manufacturer makes a product, knowing that they are going to provide it to one or more distributors, for those distributors to label it, or have it labeled for them and then distributed.

The definition also includes the person who initiates specifications for devices that are manufactured by a second party for subsequent distribution by the person initiating the specifications. One of the most common areas where this applied is in the regulation of software that is also considered a medical device. In many cases, the specification developer is also considered a manufacturer because he is telling a software expert what he needs the software to do.

A manufacturer also can be a person who manufactures components or accessories that are devices that are ready to be used, and are intended to be commercially distributed and used as-is, or are processed by a licensed practitioner or other qualified person to meet the needs of a particular patient. One of the common things that this applies to is surgical instruments that have been packaged and are ready to distribute to someone who will sterilize and relabel them, or will sterilize and use them. They are technically capable of being used even though the manufacturing is not complete. That covers the person who made the instrument as a manufacturer.

Also included in the definition of manufacturer is the person or group of persons who are the U.S. agent of a foreign manufacturer.

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Here is a long list of sources which assists FDA in issuing regulations. The first is the Public Health Service Act of 1912. This is referenced in the medical device presentation, because this is why there are licensed IVDs, or In Vitro Diagnostic, products in CBER. These products were in existence in the early 1940s, and the PHS Act was put into place in 1912. So, the PHS Act does cover those in vitro diagnostic reagents that were manufactured in the early 1940s.

The FD&C Act came along in 1938, but at that time did not yet include medical devices as regulated products. The Medical Device Amendments of May 28th, 1976 are those amendments to the FD&C Act that actually brought medical devices under the purview of FDA.

The Safe Medical Devices Act of 1990 expanded on that amendment, and required that devices have to be safe.

This was further amended by the medical device amendments of 1992.

In 1996 the FDA Export Reform and Enhancement Act was enacted. The FDA Modernization Act of 1997 brought a number of changes that were intended to make the review process a little bit smoother and a little more transparent to industry.

The Medical Device User Fee and Modernization Act of 2002 allowed FDA to collect user fees to support hiring and training of reviewers, and to facilitate review of medical devices.

The presentation "FDA Regulation of Blood and Blood Components in the US" mentions the Food and Drug Administration Amendments Act of 2007 (also known as FDAAA). This one has less of an impact on medical devices than it does on drugs and biologics, but there are some aspects of it that have also affected the way FDA conducts business.

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The other presentation points out that there is a difference between the laws or the acts and the regulations. The regulations that have been promulgated to allow FDA to carry out its business of regulating medical devices are in the Code of Federal Regulations, Part 800. And for the licensed IVDs, which are biologics, there are additional regulations in Part 600. The slide has the web site link to those regulations.

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Now, to why CBER reviews devices. As mentioned, the reagents used in typing blood were in widespread use early on. In the 1940s, many of those products were licensed as biologics for two reasons.

First, they met the definition of a biologic, because they are a product containing an antibody.

Second, they were also being used to test another licensed product, that being blood and blood components. So, historically, licensed IVDs have been reviewed since the early forties.

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But, as things got more complex, more products were being recognized as devices, and there was more focus on where they were being used and what they were being used for.

There was an agreement reached in 1991 called the Intercenter Agreement between CBER and the Center for Devices and Radiological Health, or CDRH.

That document is still available on the FDA web site at the link in the previous slide.

This document says that CBER is designated as the lead center in FDA for regulating certain medical devices that are utilized or indicated for the collection, processing, testing, storage, or administration of biological products to ensure their safety and effectiveness.

CBER will use the authorities under the PHS Act, which allows FDA to license devices, and the FD&C Act, as well as any other authorities delegated to CBER.

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The Intercenter Agreement restates this concept in several different ways, several different times, trying to describe the areas that they thought at that time may come into question. So, the agreement goes on to say that CBER has the lead responsibility for medical devices associated with blood and blood components. This is also where CBER gets the authority to regulate anything that is used in testing blood and blood components.

You will note that it spells out screening or confirmatory clinical laboratory tests associated with blood banking practices and other process testing procedures.

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The Agreement addresses two different groups of reagents that are licensed under the PHS Act; immunohematology reagents, which includes blood grouping reagents, reagent red blood cells and anti-human globulins, and blood-borne pathogen tests.

The list of blood-borne pathogen tests is not complete, but at the time the agreement was signed, it included HIV 1 and 2, HIV antigen, HBS Antigen, HB core, HCV and HTLV I and II. As new blood-borne pathogens are identified, tests for those agents are also reviewed in CBER as licensed biologicals.

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The agreement goes on to state that CBER also has the responsibility for regulating all in vitro tests, including diagnostic tests that are not performed in association with blood bank practices, intended for HIV and all other retroviruses. This part is the unusual part because, normally, if a device is intended for use in diagnostic testing or a use that is not associated to the blood bank, it is normally going to be reviewed at CDRH. But, this is the one exception where all medical devices intended for use for HIV and other retroviruses are reviewed at CBER. That is why some of the medical devices for predicting which drugs will work for particular HIV variant, for a particular patient, are regulated in CBER.

The presentation entitled, "Blood Screening IVDs," refers to these devices.

These devices include but are not limited to collection devices, specimen containers, test kit components or support materials, and devices used or indicated for the inactivation of these viruses. To date, there has not been much in the way of products for inactivation of these viruses, but, if there were any that were developed, they would come to CBER.

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While it is not specifically mentioned in the agreement, the term biologic product does include those products regulated by the Office of Cellular, Tissue and Gene Therapies, or OCTGT, as well as the Office of Vaccines Research and Review, or OVRR.

There are some things that are reviewed as devices, either alone by OCTGT or in conjunction with Office of Blood Research and Review, known as OBRR. That includes IVDs for testing cadaveric samples, bags for collecting stem cells, devices for processing peripheral blood stem cells, just to name a few.

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Some of the specific devices that CBER reviews include the apheresis machines used to collect and process blood for transfusion or for further manufacture, some of the blood filters, blood refrigerators are regulated, although they have actually been exempted from the need for any submission to FDA, bone marrow collection and transfusion kits, blood warmers, plasma thawers, and stem cell concentrators.

Interestingly, what is excluded from review is administration sets, and that is most likely because that is considered something used with the patient. So, the administration sets are reviewed at CDRH. Therapeutic devices are also reviewed at CDRH, for example, dialysis machines and, interoperative blood salvage devices, interestingly, are reviewed at CDRH, not at CBER.

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There are some other reagents that are reviewed at CBER. They are intended for use in the processing of licensed biologicals and analogous products. Some of these are lectins, protectins, bovine albumin, and potentiating media.

Leukocyte typing sera or other types of HLA kits intended for determination of tissue type are reviewed in OBRR, primarily because at one point they were being used for determining compatibility for purposes of platelet and white cell transfusions.

Quality assurance reagents intended for use in conjunction with a licensed biological reagent or in vitro test are also reviewed in CBER.

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Other reagents over which CBER has review involvement include clinical laboratory devices with separate blood bank claims. Often, a manufacturer will have a product that has been developed with the intent to be used in the diagnostic arena, but then as that agent becomes of concern in blood transfusion, they look at it to determine if there is any utility in testing donated blood. So, sometimes a product will have had a diagnostic claim for some period of time, and then the manufacturer will want to add a claim of being able to use that product for donor blood.

Software programs for data management in blood establishments, abbreviated as BECS, Blood Establishment Computer Software, are reviewed in CBER because of the integral role they play in preventing the release of unsuitable units of blood. In many countries, this type of software is not considered a medical product, but in the United States it is believed that it meets the definition of a device. So, CBER regulates them as such.

Dosimeters and thermal indicators were often first used in clinical practice. As irradiation of blood became popular, CBER began to regulate dosimeters and thermal indicators used in the processing of blood.

CDRH reviews microwave ovens because they emit radiation. However, if a microwave is marketed for thawing blood products, then CBER will also participate in the review.

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Since CBER regulates both the therapeutic product and the devices used to test them, this creates some unique situations. In many cases, the results of in vitro tests are key to ensuring the safety and efficacy of biological therapeutic products, for example, blood components and derivatives, the management of donors through temporary deferrals and subsequent reentries or permanent deferrals and counseling, if necessary. FDA is also faced with having to rapidly respond to emerging infectious agents, and some of those that have come to FDA in the very recent past are the TSEs, West Nile virus, SARS, pandemic flu, monkey pox, and Chagas. The list is ever changing.

If after release for distribution of those products, the in vitro reagents used in the testing and release are recalled, CBER must then evaluate whether or not the products tested with those in vitro reagents should also be recalled. CBER must also use the results of the in vitro tests to determine whether or when a donor should be turned away from donating, to protect the blood supply.

As new infectious agents emerge, CBER is expected to react rapidly to determine whether or not the agents can be transmitted by blood.

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Some would ask if the review of devices at CBER is any different than the review of devices at CDRH. The key difference is that most of the products that are reviewed at CDRH in terms of in vitro diagnostics are intended for the detection or diagnosis of disease in a patient showing signs and symptoms of the disease, whereas those devices that come to CBER are being used to test normal, healthy adults who wish to give blood. They likely have no signs or symptoms of a disease, but they may be carrying some sort of disease. So, you have different populations that are being tested in these instances.

In general, when you are testing well individuals, looking for those who maybe have the initial stages of a disease, you are normally going to need higher numbers of clinical trial samples to assure statistical significance of the study.

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A little bit about pathways to market: Some devices may be exempt from pre-market review by FDA. Those that are not, come to FDA through a number of pathways. One is the pre-market notification, or 510(k). Another is a pre-market approval, or PMA.

Significant risk devices, which can be Class II or Class III, do require an

investigational device exemption prior to their distribution.

A product can come to market through a product development protocol, or PDP. There are also humanitarian device exemptions, or HDE, which are similar to orphan drug status.

There are analyte specific reagents, or ASRs. These are single entities that can be used for a laboratory to develop a test of their own, in-house. In this case, CBER will require a biologics license application or BLA.

There are two categories of devices at CBER. There are those that are exempt from the requirement to submit an IND, or investigational new drug application, and those that would be the immunohematology reagents. That is primarily because there is not going to be a significant impact to the person who provided the blood sample if there are discrepant results during the clinical trial. Whereas with the viral marker tests, if one test gives a negative result, and one test gives a positive result, there is a significant decision-making process that has to go on to decide what happens with that person, if they will be told they have a disease or if they do not have a disease. Those products do require an IND prior to submission of the BLA.

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Our processes are risk-based. So, there is a device classification process. This applies to those devices that are not just a biologic, but are also placed into three classes based on risk: Class I, Class II and Class III. In this case, Class I is the least risky. Class III is the highest risk.

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Class I devices are described in both the FD&C Act and in the Code of Federal Regulations. The regulations state for Class I devices that general controls alone are sufficient to provide reasonable assurance of safety and effectiveness. Or it is not clear if general controls alone are sufficient but the device is not life-supporting, life-sustaining or of significant importance in preventing impairment of human health.

These two definitions both reference general controls. So, it is important to know that general controls include establishment registration, which is simply the manufacturer saying this is who I am and where I am located, product listing which is that manufacturer telling us all of the products that they manufacture. They are required to conform to the quality system regulation, which was formerly known as the Good Manufacturing Practice Regulation. They have to conform to device labeling requirements, and, if applicable, they have to submit a 510(k). There are other controls in the act as well.

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Most Class I devices are now exempt from the requirement for pre-market or

510(k) notification, unless they are designated as reserved. Reserved devices still require submission of a 510(k). Most Class I devices are not subject to the design control provisions of the quality system regulation or QSR, but they are subject to the rest of the QSR.

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Class I is the least risky, so it is the least stringent regulatory category. One common example in the blood bank world would be a blood grouping view box, the box that is used for examining serologic tests on a slide.

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Class II devices are also described in the Act and in the CFR. Specifically, general controls alone are insufficient to provide reasonable assurance of safety and effectiveness, but there is also sufficient information to establish some special controls.

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Special controls can include performance standards. In some cases, FDA has promulgated and included in the CFR certain performance standards for devices. Special labeling requirements are a form of special control. Most recently, FDA has been using guidance documents to convey things that should be considered as special controls. Also, other things that can be used as special controls are the requirement for the manufacturer to have patient registries, post-market surveillance and other actions deemed appropriate by the commissioner.

There is some leeway in deciding what other things to put in place to assure safety and effectiveness. You need to know that these are in addition to the general controls, not instead of.

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Again, Class II devices are generally moderate-risk devices. They may be life-supporting or life-sustaining, and some have been exempted from the requirement to submit a 510(k).

One of the Class II devices seen most often is the automated blood grouping and antibody test systems. These are not exempt from the requirement to submit a 510(k).

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The 510(k) process is probably the one that is most difficult for both users and manufacturers to grasp fully. It is described in Section 510(k) of the FD&C Act, and it is intended to demonstrate substantial equivalence or that the device is substantially equivalent. This means that it is as safe and effective as a legally marketed device of the same type, and it considers the intended use, the technological characteristics and whether or not any of those differences raise new issues of safety and effectiveness.

There is a 90-day review clock on 510(k)s, and there are some limitations in the review. It is a paper review. FDA does not get to see the product. There is no inspection. There is no hands-on testing.

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In a 510(k), the major elements of the submission are the intended use and indications for use statements, a description of the performance characteristics and the labeling, in particular, the package insert. There is not a requirement in the regulations that there be clinical trials for medical devices that come in through 510(k), but CBER has the ability to ask for them if felt there's a need. For devices reviewed at CBER, in most cases there is some sort of field testing and data from those studies provided to CBER.

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Substantial equivalence is a comparison of a new device to one that is or was already legally on the market, which is known as the predicate device. But it is also important to know what substantial equivalence is not. It is not a determination that a new device is exactly the same as the one that is or was already legally on the market, nor is it an FDA approval. It is simply a determination that the devices are very similar to each other, both in their intended use and in their performance.

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For Class III devices, there is insufficient information that general or special controls will provide reasonable assurance of safety and effectiveness, and the device is life-supporting, life-sustaining, or of substantial importance in preventing impairment of human health, or they presenta potential unreasonable risk of illness or injury.

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In this case, the submission is a pre-market approval. This is an application that undergoes scientific and regulatory review to ensure the safety and effectiveness of the device.

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Class III devices, as mentioned, are high-risk devices. It is the most stringent regulatory category, and general controls still also apply to these devices.
An example of a Class III device is an electromagnetic blood and plasma warming device.

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The PMA process is described in Section 515 of the FD&C Act. Approval of a PMA is based on reasonable assurance of safety and effectiveness, and that is based on valid scientific evidence.

There is a 180-day review clock for these, as opposed to a 90-day review clock for a 510(k). The limitations in review are the fact that, in most cases, these are new devices, so there is not a whole lot of historical information. Also, again, CBER does not get to see the device itself.

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The major elements of a PMA submission are the intended use and indications for use statements, the performance characteristics, descriptions, the labeling, and clinical or field trial data. And, there is the opportunity to perform a pre-approval inspection in this case.

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The BLA process has been covered in the presentation, "FDA Regulation of Blood and Blood Components in the United States". As mentioned, some of the IVDs have been licensed since the early 1940s. The BLAs are described in the PHS Act, and you are looking for safety, purity and potency of the product. A standard application for a BLA is a 10-month review. If the product is determined to be important enough to get a priority review, they are done in 6 months.

Also mentioned in the referenced presentation are Supplements, and that much of this work is on Supplements to existing BLAs. The type of supplement dictates what the review timeframe is; it can be between four and ten months.

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The major elements of a submission are very similar to those for a PMA: The intended use and indications for use statements, the performance characteristics, the labeling, clinical or field trial data. In this case, CBER gets conformance lots, if it is an IVD. CBER actually gets samples and a summary of the testing that the manufacturer has done.

CBER has the opportunity to perform those same tests on those reagents, to see if the results are the same as the manufacturer. Again, CBER has a pre-license or pre-approval inspection.

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Post-approval requirements for medical devices are similar, but not identical for all medical devices. For those that are 510(k) and PMA, the main requirements are that they report any corrections and removals to the FDA, and that they file medical device reports.

For licensed IVDs, it is possible to get a bit more from the manufacturers. Again, they are required to submit reports of corrections and removals, and medical device reports. Because they are licensed products, submission of biologic product deviation reports can also be required.

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A medical device report is specifically related to the use of a medical device, the failure of which may have resulted in an adverse event, which is defined as death or serious injury. In all cases, there is at least a suspicion that the medical device malfunctioned.

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Medical Device Reports, or MDRs, are required reports. They must be reported to the FDA as soon as possible, but no later than 10 days from becoming aware. Becoming aware is defined in the CFR - seen in the slide in quotes -- and there are several ways a manufacturer may become aware that their device has been involved in a failure requiring a medical device report.

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MDR's are reported through FDA's MedWatch. The website is listed in the slide. MedWatch is FDA's system for reporting adverse events. Manufacturers can submit MDR's through MedWatch.

Although reporting is voluntary for others, such as Physicians and users, manufacturers are required to submit reports.

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This slide breaks down what other groups are required to report or may do so voluntarily.

User facilities are required to report. Health professionals and consumersmay report voluntarily.

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So, one might ask, why does FDA collect the information on these reports and what does FDA do with it?

FDA does this to collect quality information on these safety reports, to promote consistency in the collection of the information, and to have a routine format for collecting similar types of information. This helps expedite FDA's review of critical safety information. It helps to strengthen FDA's ability to monitor the safety of human drugs, devices, and biologic products. It enables the agency to protect and promote public health.

Using these reports, FDA can detect trends with a particular device type or a particular device manufacturer, and intercede to prevent future problems.

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There are many medical devices used in the process of collecting donor blood. If there are adverse events in collection or in transfusion, FDA can perform trend analyses to determine if there are any trends that can help FDA take appropriate actions to protect the blood supply. Trend analysis also assists FDA in

determining whether scientific and regulatory policies are working, or if they need revision.

It helps to ensure the safety, purity, and potency of blood and blood components for administration to patients, since the devices being reviewed are related to blood transfusion. And, it helps identify defects in products used to collect blood.

SLIDE 50
For additional information, this slide includes links to information on devices regulated by CBER and the CDRH device advice web site.

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This concludes the presentation, "Medical Device Review at CBER".

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