Blood Screening IVDs (OBRR)

SLIDE 1
This presentation will discuss Blood Screening IVDs or in vitro diagnostics.

SLIDE 2
For blood safety in the U.S., this slide shows what is referred to as the "five layers of safety" related to collection. First are donor selection criteria. Second is the use of registries that would avoid the use of collections from previously unsuitable donors, tracking the donors after they have been tested. The third is laboratory testing for infectious disease markers. Fourth are quarantining collections pending the determination of whether or not the donors are suitable. And finally, monitoring and investigating any adverse events to ensure appropriate responses and corrective actions. This presentation will concentrate on number three - laboratory testing for infectious disease markers.

SLIDE 3
If you are involved in blood donor screening, there are two basic types of tests. There are donor screening tests, which are typically immunoassays. These could be enzyme immunoassays or more recently, the chemiluminescent immunoassays that have come to market, which detect antibodies to HIV, HTLV, the hepatitis B virus and the hepatitis C virus. There are also tests that detect HIV and HBV proteins, for example, with hepatitis B surface antigens, tests that have played a very important role in blood safety, and tests that detect HIV, HBV, HCV and West Nile virus nucleic acid or the so-called NAT tests.

There are also supplemental tests. The screening tests will give you a preliminary idea about whether someone is positive or not. Each of these tests typically has to be confirmed by an additional, more specific test. These will be the supplementals, and these are such things as your Western blots, recombinant immunoblot assays or RIBAs, chemiluminescence assays, and again these would be for the confirmation of repeatedly reactive screening test results.

SLIDE 4
Tests that are used to screen blood donors undergo the licensing process. These applications are reviewed in, and the policies for use are set by, the Center for Biologics Evaluation and Research, or CBER. These are in vitro diagnostics with an indication for the screening of blood, or blood components, for transfusion or further processing. These go through the licensing process and are called licensed biologics. While not going into the regulations and laws for this, the term is really "licensed", as opposed to "cleared devices". The 5-10(k) process is

another way to bring products to market. Generally, a less-stringent review is required, and typically, software instrumentation and external control material used for blood donor screening go through the 5-10(k) process. These are called cleared devices.

SLIDE 5
The path toward licensing. Before the clinical studies are performed, there is a series of events that take place.

CBER meets with sponsors to let them know what is required for the licensure of a test, so that CBER can try to get the best information up front. Then they file a formal document which would allow the test to be used in clinical trials to generate performance data.

SLIDE 6
You may be familiar with the IND, or the investigational new drug application. It may be a bit confusing, because CBER is not dealing with a drug in this instance, but rather is dealing with a device. Nevertheless, the use of the term applies in this case. It allows the device to be marketed or sold to investigators across state lines, for the purpose of conducting an investigation. That is a lot of what FDA does. The federal laws control interstate commerce, so that the device will not be allowed to be used in clinical trials unless it has this formal permission from FDA.

Otherwise, the investigator would be breaking the law. This slide shows the Contents of an IND and what is expected. There are a number of different components which are outlined in the regulations. Biologics are covered in the Code of Federal Regulations or CFR part 21, in the 600s.

The contents of an IND would be an investigational plan and a detailed protocol. The protocol is critical in the IND. CBER needs to understand exactly what the investigators are going to be doing, and the investigators need to know exactly what they are going to be doing. Investigator information includes who will be conducting the trial, and other things such as investigator financial disclosure statements, and Investigational Review Board, or IRB approvals. This is critical to make sure that the safety and rights of the test subject are taken care of, as well as informed consent documents.

Other contents of an IND include limited information on manufacturing of the device, so that CBER has an idea of what this device is and how it works. And any previous experience which can give CBER a sense of whether it actually does what it is supposed to do.
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ND annual reports are filed with CBER to show how the device has been used over the past year, how many devices have been used, and any significant findings resulting from the use of the device.

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There are two actions that can be taken with and IND once it is received. The first action is to allow the IND to proceed. This means that the clinical studies can proceed as specified in the IND.CBER does not actually "approve" IND's.

However, if there are concerns about the safety for patients, or if the studies that are proposed are going to be insufficient to support approval of the test, CBER can place the IND on clinical hold. CBER must respond within thirty days if the IND is to be put on hold.

SLIDE 8

After the studies have been conducted under the IND, an application is filed with CBER to allow the test to be marketed. This is called a biologics license application, or BLA. This results in a license for a facility to manufacture a product.

Software instrumentation is covered by the 5-10(k) process, also called the premarket notification process. The buzzword, or benchmark for this is "substantial equivalence". This means it is substantially equivalent to something that has been on the market already or something that was marketed before 1976.

SLIDE 9

Contents of a BLA. CBER expects to see clinical data that show the test kit meets its prescribed requirements for safety and efficacy. For blood donor screening tests, this would involve clinical data from sites of intended use. This is important because CBER wants to know how well this test performs in precisely the type of site where it would be used, which would usually be a blood bank.

CBER expects that the trials will be conducted across a broad geographic area. It is expected that the data be primarily from the U.S., because, again, that is where the test is going to be used. With the use of multiple kit lots to show that the test is manufactured with consistent quality; and that there will be a number of data points to evaluate sensitivity and specificity which are the two numbers typically dealt with.

CBER also makes a point to have statisticians on the review committees for these products, to make sure that the numbers and statistics are correct and that they support the safety and efficacy claims.

Also during the course of clinical trial, testing is done in parallel with another licensed or approved test, so the clinical decisions are made on the basis of the test that has already been licensed, as opposed to using an investigational test where results could be incorrect. That is the purpose of the investigational study, to determine how well this test actually performs. With tests that are the first of its kind, there are some special conditions that CBER applies.

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In terms of the contents, CBER is also looking for what is referred to as nonclinical data, to show that the manufactured product again meets its prescribed requirements for safety, purity, and potency. This is to assess the relative analytical sensitivity and specificity compared again to a licensed test.

Some examples of the sort of data that CBER is looking for are seroconversion panels, dilution panels, the effect of potentially interfering substances or unrelated medical conditions, to see if any of these conditions might interfere with the ability of the test to give a correct answer.

For example, would someone who is infected with the hepatitis B virus give either a false positive or a false negative result on an HIV test? If so, that limitation should be specified in the package insert.

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CBER expects the BLA to give a full description of the manufacturing methods. This includes all of the standard operating procedures for the manufacturing of this test kit, as well as batch records, which would be a record for three manufactured kit lots to show that the manufacturing is consistent.

CBER expects to see stability data, all the labels, enclosures, containers, and advertising and promotional material -- everything that has to do with this test. CBER needs to see this information up front to make sure the test works, and that it can be produced consistently.

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As part of the preapproval process, there are inspections that take place for the manufacturing facilities. This is to assess conformance not only to good manufacturing practices, but also to the quality system regulations, or QSRs, which are in a different part of the Code of Federal Regulations. Specifically, QSRs are in 21 C.F.R. section 820.

The QSRs require information on quality systems for devices, including in vitro diagnostics. During the inspectional process, CBER assesses the manufacturing process and procedures.

CBER expects to see the product being manufactured during the inspection, so CBER can observe whether everything is done properly. CBER looks at the manufacturing facility's recordkeeping, design controls, and corrective and preventive action procedures, when there have been deviations and problems, to make sure that they have been adequately addressed.

Design controls are something you may not have heard about. This is part of the Quality System Regulations. Design controls are a formal process by which

quality is built into a product. Among other requirements, maintenance of a design history file is needed to document all changes to the product. Design Controls follow the life cycle of the product from its inception, or from the idea which generated the products, through the development process, and ultimately to the point where it transfers from research to manufacturing.

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Another type of inspection is bioresearch monitoring, or BIMO. The purpose of BIMO is not to look at the manufacturing process, but to look at the clinical trials. This is to ensure that the quality and integrity of the data submitted to FDA in support of the BLA are appropriate, and to ensure that the rights of the human research subjects are protected so that BIMO is focused on the clinical trials themselves at the clinical trial site.

FDA inspectors will go to the clinical trial sites, audit data, investigate complaints, offer answers to questions about good clinical practices, and help evaluate concerns about data integrity. There have been a number of situations in which the data have been compromised through some practices which were not appropriate.

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Let's look at what happens after licensing. This will cover changes that are made to tests by manufacturers, the lot release process, biennial inspections, response to complaints, and monitoring programs.

SLIDE 15
As for lot release, the CFR states that no lot of any licensed product will be released by the manufacturer before completion of tests for conformity with standards applicable to such product. Here is what that means.

SLIDE 16
A company will submit to CBER a lot of the test kit along with a protocol, which is a summary of their own test results. CBER reviews the protocol and tests the lot using lot release panels. CBER makes those panels available to manufacturers, so they can do pretesting before they send in their lots to make sure their tests are set up appropriately, and the tests are working.

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In most cases, all kit lots must undergo testing at FDA prior to release, although there are situations in which lots can go under surveillance, and not every lot has to be tested. Generally the blood donor screening test kits do not go on surveillance, because it is necessary that every kit lot used for donor screening pass the panel testing.

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This slide shows the panels used for lot release. There are antibody panels for HIV-1 and HIV-2, antibody panels for HTLV-1 and HTLV-2, panels for hepatitis B surface antigen, panels for hepatitis C virus, and also panels for the NAT tests, which include HIV RNA, HCV RNA and West Nile virus RNA.

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There are also a number of panels that are in development as the landscape changes. There are emerging agents that are coming, and there are subtypes to be aware of. Panels should be able to pick up those subtypes.

So, an HIV subtype RNA panel has been developed, as well as an HBV DNA panel. These have not been implemented yet, but FDA has now licensed a couple of HBV NATs. There is also an antibody panel for T. cruzi.

SLIDE 20

Some other aspects of post-approval activities include biennial inspections, inspections that take place every 2 years. When problems arise, FDA has the ability to do inspections more frequently. These are called "for cause" inspections. Warning letters or untitled letters can be issued, and judicial actions may be sought, including injunction and seizure. Ultimately, FDA can suspend the license or revoke the license if it is felt that the company is not cooperating and is providing a product which is a threat to public health.

There can also be a recall. The recall is voluntary on the part of the manufacturer. This would be done to carry out the manufacturer's responsibility to protect public health with respect to its own products. Generally manufacturers are very good about doing recalls, if they are made aware of a problem by FDA, or if they become aware of a problem by themselves.

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A quick note about software and instrumentation. As mentioned, they can be submitted separately in what is called a 5-10(k), or they can be submitted as part of the BLA, so the whole test system can be reviewed. CBER prefers to have the instrumentation included as part of the entire BLA. This allows a look at the whole system. Also, any changes made to the instrument, or changes made to the assay, are easier to evaluate in the context of one whole system, as opposed to an instrument-versus-a-test, and coordinating those reviews.

SLIDE 22

Let's conclude with a discussion of what tests are required in the U.S., some of the licensed tests that are available, and finally, an assessment of the effectiveness of donor screening.

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The regulations specify that blood be tested for a number of agents, including HIV-1 and HIV-2, HTLV-2, hepatitis B virus, and hepatitis C virus.

SLIDE 24

The tests available now are anti-HIV-1 only, anti-HIV-1-2 only, combination tests for HIV-1 and 2 together, and two tests that screen for HIV-1, HIV-2 and HIV-1 group O. The second of the HIV-1 group O assays was just licensed around mid-2009.

Currently there are two HTLV-1-2 tests. There are of course tests for Hepatitis B Surface Antigen, anti-HB core, anti-HCV, and one assay for anti-T. cruzi.

In terms of supplemental tests, there are supplementals for HIV-1 and HCV, and a number of nucleic acid tests for HIV-1, HCV, HBV and West Nile. One of the more recent tests that FDA licensed will detect five agents at once, HIV-1 and 2, HIV-1 Group O, hepatitis B and hepatitis C.

SLIDE 25

This graph gives a sense of the decreasing risk of viral infection from transfusion. In 1983, before testing was implemented, there was a 1-in-100 risk of contracting HIV as a result of a transfusion. On the X axis are years, and then the different types of tests that came into being. Between 1984 and 1985, screening for HIV antibody began. You can see the risk is gradually going down. At one point, HIV P24 antigen testing appeared. Then nucleic acid testing appeared in 1999, and the risk continues to go down. Similarly, with HBV, the risk was about 1 in 2000 to 1 in 3000 in 1984. With the implementation and licensure of additional tests which were more sensitive, the risk is also coming down. There is a very dramatic drop with the implementation of new technologies.

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To put some numbers on this, you can see that this is the residual risk for HIV infection, HCV infection and HBV infection using serology testing by itself, pooled nucleic acid testing, and single-unit nucleic acid testing. What you see in yellow and underlined is the risk for the type of testing which is now done routinely. For example, HIV pooled NAT is routinely done, and so the risk of HIV infection at this point is about 1 in 2 million. The residual risk most likely comes from window period donations before the appearance of any detectable nucleic acid. For HIV, the risk drops from 1 in 1.3 million down to 1 in 1.9 million, or about 1 in 2 million. So, there is some gain to be made. Moving to single-unit NAT, the risk would drop further to 1 in 3 million. The reason this is not being used routinely now is strictly because of technology. It has not quite caught up yet.

For HCV there is a very, very dramatic gain in safety. Using serology, the risk is 1 in 230,000. But, using pooled NAT, which is now the standard, the risk drops to 1 in 1.6 million, with a slight decrease in the risk moving to single-unit NAT.

For HBV, there is not too big a difference between serology testing, which is currently being done, versus pooled NAT, which drops to 1 in 210,000. But, the

risk is cut in half moving to single-unit NAT. Implementing HBV NAT has been an interesting area for FDA, because there are discussions ongoing now as to whether HBV NAT should be recommended as routine for blood donors.

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This is a table of all the licensed donor screening assays for infectious agents, and also a listing of all the HIV diagnostics. This reference also has hyperlinks for most of the tests, which will take you to the package insert, the approval letter, and some other review material that went toward the licensure of the test.

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This concludes the presentation, "Blood Screening IVDs".

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