Inspections of CBER Regulated Products

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This presentation will discuss the inspection process for the regulated products of CBER, the Center for Biologics Evaluation and Research.

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This presentation will cover the different types of inspections, when CBER completes the inspections, who is included on the inspection teams, the scope of coverage, and a little bit about the outcomes. The outcomes will also be discussed in the separate presentation entitled, "Compliance and Product Quality".

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There are four basic types of inspections: the pre-license inspections; pre-approval inspections; the biannual or annual good manufacturing practices, or GMP, inspections; and then a little bit about directed and investigational new drug, or IND, inspections.

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The pre-license inspection is performed as part of the "Biologics License Application" review process. There are circumstances when a pre-license inspection can be waived, but generally it's necessary to do one. An applicant can be either a non-FDA-licensed firm coming for their first license, in which case they will definitely get an inspection, OR, an already FDA-licensed firm, coming in with a new product. A licensed firm would submit a new BLA, but their facility could already be licensed for other products. The pre-license inspection may become more complicated if it involves several sites at different locations. A pre-license inspection is necessary for licensure under the CFR, short for the Code of Federal Regulations. The CFR requires that a biologics license application shall be approved only after inspection of the establishments listed in the application and upon determination that the establishments comply with the application's standards and the requirements prescribed in the applicable regulations. This regulation will be discussed a bit later in this talk.

Products that are under drug or device pre-market application are very similar, because they cover new products.

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Pre-approval inspection is slightly different than a pre-license inspection. There are also pre-approval inspections performed for a prior approval supplement. This inspection is for changes to an approved application, which is defined in the

CFR, and covers the general regulation for changes to an approved application. So, specifically for the pre-approval inspection, it could be completed for a new manufacturing facility, a new contract manufacturing facility, or because of significant changes to the manufacturing process.

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GMP inspections are mandated by CFR requirements that each licensed establishment, and any of its additional locations, shall be inspected at least every two years. These facility inspections determine if the establishment is meeting the CFR's minimal requirements for licensed biologics. They also determine if the facility is in compliance with the Public Health Service Act, known as the PHS Act, the Food, Drug and Cosmetic Act, or FD&C Act, and any particular requirements approved in the biologics license application. If the biologics license is for a device regulated by CBER, the CFR regulations cited in the slide establish the minimal requirements, and it must also comply with the PHS Act, FD&C Act, and the BLA. If the device is approved under a device pre-market approval application, called a PMA, it would be subject to the FD&C Act and specific provisions in the PMA.

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Other inspections performed include directed inspections. Generally, in a directed, for-cause inspection, CBER has received information regarding a perceived problem from informants, former disgruntled employees, or even from firms reporting an issue with the suspect firm. CBER does what it can to substantiate the complaint, but many times more information is needed. At that point, CBER can send investigators out to do a for-cause inspection of the facility, to include contacting anyone who might want to talk to the FDA. There are also bio-research monitoring, or BIMO, inspections. The BIMO inspection is part of the investigational stage of product development, and falls within the Investigational New Drug application or IND process. For more information on BIMO, see the presentation entitled, "CBER's Bioresearch Monitoring Program: Clinical and Nonclinical Inspections."

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When are these inspections completed?

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With pre-license and pre-approval inspections, the firm is supposed to be ready for an inspection at the time of their submission. So, in theory, CBER could go out immediately after the application or the supplement is received. But, that is not preferred, because when inspections occur, CBER wants the investigator to see all the pertinent operations at the facility. To ensure this, the firm is contacted so they can check their production schedule to find an appropriate time for the inspection. Because the firm is aware of the pending inspection, it can update CBER if there are any problems requiring a delay with the inspection.

Generally speaking, the timing of inspections is about halfway through the review cycle. For a new BLA, that would be about 5 months after the application was received, since there is a 10-month review time frame. For a prior approval supplement, inspection would happen at about 2 months, because those have a 4-month review time frame.

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Of course there are times when CBER determines that going on an inspection in support of an application or supplement is not necessary. Standard Operating Procedure 8410, also called SOP 8410, is used as a guide in determining when pre-license or pre-approval inspections are necessary. This provides some limited circumstances when an inspection might be waived. The questions that are asked to determine if an inspection should occur include: do differences in the process require an on-site determination of compliance; are the analytical methods accurate and sensitive enough to detect problems; or are different equipment and processes being used? So, generally, if it is the same production or processing area CBER has recently inspected, and the firm has a good compliance history, the inspection might be waived.

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For biologics, the FD&C Act and the PHS Act gives the authority for inspections, and states when inspections should happen. The FD&C Act says registered firms should be inspected biannually. For CBER products, the CFR says that each licensed establishment shall be inspected biannually. For human cell and tissue establishments, there is a risk-based approach in prioritizing inspections. There is no statutory or regulatory requirement regarding inspectional frequency for Human Cells, Tissues, and Cellular-Based Products, known as HCT/Ps. For the flu vaccine manufacturers, inspections happen annually and early in the manufacturing cycle, so problems or issues can be detected and resolved in a timely fashion, to ensure an adequate supply of vaccine for the upcoming flu season.

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Who is on the inspection team?

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For the pre-license or pre-approval inspections of biologic drugs and devices, the Division of Manufacturing and Product Quality in CBER's Office of Compliance and Biologics Quality, or OCBQ, serves as the lead on these inspections. An investigator from the local district office at the firm's location is invited, and a product specialist is encouraged to join and go on inspection.

For blood and blood products, the Division of Blood Applications in CBER's Office of Blood Research and Review acts as the lead for the inspection, and they also invite the local district office to participate in the inspection.

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For the GMP inspections of Biological Drugs and Devices, there is "Team Biologics." This is a core group of investigators from various districts in the Office of Regulatory Affairs, or ORA. They reside in their home districts, but they are really on the same team. They are specially trained for CBER products, and perform annual or biannual GMP inspections. The team invites the participation of a product specialist, that is, someone from an appropriate Products Division, whether the Office of Blood Research and Review, Office of Vaccines Research and Review, or Office of Cellular Tissue and Gene Therapies. There may be more than one product specialist on an inspection, depending on the products produced at the firm.

As an example, there could be vaccine manufacturers, which manufacture both bacterial and viral vaccines. An inspection could potentially involve two different product specialists. Product specialists are expected to attend either on-site or off-site. This is intended to provide the Team Biologics investigators someone with specific knowledge of the products being inspected. If the product specialists are not able to attend in person, they will be available by phone. In this way if the investigator has a specific question, they can contact the assigned product specialist by e-mail or by phone. For blood and blood products, and for human cells and tissues, we have a group of investigators in the local districts who are specially trained in blood and tissue inspections to handle blood and tissue GMP inspections.

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What is the scope and coverage of these inspections?

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With respect to pre-license and pre-approval inspections, as per the CFR, CBER will make a determination of compliance with the application and applicable standards, including GMP standards, in order to approve the application or supplement. The product to be introduced into interstate commerce has to be available for inspection during all phases of manufacturing. That is why the FDA contacts the firm and sets up the pre-license or pre-approval inspection to make sure that they are in these stages, and in particular the manufacturing stages of interest.

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It is also necessary to verify the authenticity and accuracy of the data submitted in the application, and to focus on the subject product; including verification that the process has been validated, and observing the manufacturing of the product.

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For routine GMP inspections, the coverage is of current good manufacturing practices, or CGMPs, for all products or of the high-risk products manufactured at the location. Again, for the flu manufacturers, that is done every year. The

production processes are inspected for all high-risk products manufactured at that location. Additionally, a review is performed of the complaints that the firm has received; any adverse event reports that the firm has received; A\any trends that they see, for example, in their environmental monitoring; all Biological Product Deviation Reports the firm has submitted to CBER; medical device reports, which are similar to the Adverse Event Reporting System, or Airs, but specific to devices; the recalls that they have had; and any changes that they have made since the last inspection.

If the manufacturer has had to change their process, it is important to make sure that they have submitted appropriate supporting documentation, as outlined in the CFR.

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The investigators follow different compliance programs for each program area. Here is the list of compliance programs that are available on-line, if you would like to access them to see what CBER focuses on. The list includes guidance for inspection of Biological drugs, blood and blood products, source plasma, in vitro diagnostics, and human cells and tissue.

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What are the potential outcomes?

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For any of the inspections discussed, documentation of observations, known as an FDA Form 483, could be issued. If the investigators have not observed any problems at the firm, they will not issue a Form 483. A response by the firm to a Form 483 is not a regulatory requirement. So, if a Form 483 is issued, the firm does not have to respond, but it is generally in the best interest of the firm to do so. For pre-license and pre-approval inspections, if the firm wants to get licensed or have their supplement approved, they will need to respond to the observations and mitigate the concerns raised by the inspectors. This is part of the review process and is essentially the same as an information request letter based on CBER's review of the supplement or application. These concerns need to be addressed before the application or supplement can be approved.

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Basically, the Form 483 lists observations made by the representatives during the inspection. They do not represent a final agency determination regarding their compliance. And if the firm has an objection regarding an observation, or has implemented or plans to implement corrective action, then the firm may discuss the objection or action with the FDA representatives during the inspection, or submit this information to FDA to the address on the Form 483.

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A discussion of a violative inspection is discussed in the presentation entitled, "Compliance and Product Quality".

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This concludes the presentation, "Inspections of CBER Regulated Products".

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