Compliance and Product Quality

SLIDE 1
This presentation will discuss compliance and product quality. This is a follow-on topic to the presentation on inspections of CBER-regulated products, which will cover what happens after the inspection.

SLIDE 2
In this presentation, regulatory actions, recalls and product deviation reports will be addressed.

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After an inspection takes place, FDA expects voluntary compliance by the firm; that is, the firm is expected to voluntarily correct the issues identified during the inspection. FDA will work with firms to implement the needed corrective actions. If voluntary compliance does not work, then FDA will take action to ensure compliance. If there is an immediate danger to health, FDA will take prompt action to protect the public health.

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An FDA Form 483 could be issued to a firm at the time of an inspection if any problems are observed at the inspected site. When the inspection is over, the first order of business for FDA is to write the establishment inspection report, or EIR, which will include a narrative associated with each observation contained in the 483. This process can take some time. One of the roles of the inspection team leader is to obtain and collate their individual assigned portions of what will ultimately be the final report from all the investigators on the inspection team. Timely completion of these sections can be complicated by the fact that routine work has continued to accumulate on the desks of everyone who was on the inspection. This can distract the team members from working on their respective pieces of the EIR. It is up to the team lead to make sure that all the pieces are put together. In addition to a narrative description of each of the 483 observations, the EIR also would include any exhibits, which serve as the evidence to support the findings. Once the team has completed an initial draft of the EIR, compliance officers then perform an evidentiary review. If the firm has submitted their response to the 483 observations since the time of the inspection, these can also be taken into account in the EIR. For CBER regulated products, the EIR is generally reviewed first, by FDA's Office of Regulatory Affairs, or ORA, and then by CBER.

For foreign inspections, the EIR comes directly to CBER for analysis, since CBER acts as the lead district for foreign inspections.

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It is extremely important to FDA that the industry response to the 483 be a thoughtful one. Moreover, the response needs to be complete. It should address all potential product impact issues, including review of other lots affected by the observations, as well as dates for implementation of the corrective actions that have been made, or are to be made. The response should also expand the scope of the 483 observations to cover all products manufactured, or other steps in manufacturing, that could benefit from a more global corrective action and product impact review. A firm needs to look at how the observation may have impacted the rest of their operations. The response often includes an immediate corrective action and proposes long-term fixes to prevent recurrence. Although FDA would like to receive a timely response, speed should be weighed against thoroughness.

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Regulatory actions that FDA can take in response to inspectional findings are defined in the Regulatory Procedures Manual, or RPM, which is available on-line. FDA can choose to have regulatory meetings with a firm, to issue letters as advisory actions, or to take enforcement actions. Enforcement actions are in one of two categories -- either administrative or legal.

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In regulatory meetings, FDA calls a firm, and requests a meeting. At that time, FDA often provides the firm with issues to be addressed. The approach reflects the idea that FDA has concerns, and wants to give the firm an opportunity to alleviate those concerns. Firms should take it quite seriously when they are called for such a meeting.

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There are a few types of advisory actions which take the form of informal advisory letters. The first such advisory letter is the Warning Letter. FDA has no legal responsibility to issue a warning prior to taking an enforcement action, but issuing such a letter allows the agency to state its position without requiring that further action be taken. Again, this step is an effort to get a firm's attention and, hopefully, prompt it into voluntary compliance.

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A Warning Letter requires that the firm respond within 15 working days of receiving the letter. The letters are sent by overnight delivery and are also faxed to the firm. Other government agencies are notified, so if there are contracts being let, other agencies will know the situation. This is another incentive for the firm to come into compliance. The letters are posted on FDA's website. The firm's

response to the warning letter can also be posted, if they request it. Any inadequacies in the 483 response are also addressed in the warning letter. The first section of the warning letter typically addresses the more serious inspectional issues, followed by a section that lists any concerns FDA has with respect to the response to the 483. The warning letter should be viewed as FDA's last attempt to get voluntary compliance before further enforcement action is taken.

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The other form of an advisory letter is an Untitled Letter. The Untitled Letter does not reflect quite the same level of concern as that prompting the Warning Letter. The context of an Untitled Letter is that problems do exist, and FDA wants those concerns communicated to the inspected firm. The letter may ask for a response.

FDA does not advise other federal agencies that the letter is being issued, and there is no warning statement in the letter, hence the name "Untitled Letter". In preparing both the Warning Letter and the Untitled Letter, the Agency procedurally reviews them in the same way.

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This slide shows a chart of the number of both types of letters - Warning and Untitled - that were issued for biological drugs and devices for the fiscal years 2004 through 2009. The numbers have been up and down with no apparent trend one way or the other.

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There are recurring citations that occur in our Warning Letters. The five most frequent ones specific to drug product manufacturing can be seen on this slide. They are cross-referenced with the specific regulatory requirement detailed in the Code of Federal Regulations, or CFR, under Part two-eleven, which addresses drug product manufacturing. The most frequent citation, two-eleven point 192, is the failure to thoroughly investigate any unexplained discrepancy or failure of a batch, or any of its components, to meet any of its specifications. This is always a serious issue. The next one, the two-eleven point 22 citation, is specific to the quality control unit and its deficiencies.

The deficiencies are described in the Warning letter, and reflect that the quality unit is not fulfilling its responsibility. Next is the two-eleven point 160 citation, the failure to establish a file of scientifically sound, appropriate specifications and assuring that such specifications are reviewed and approved by the quality control unit. Next is two-eleven point 100, where the firm fails to establish and follow written procedures, or to justify deviating from those procedures. And finally two-eleven point 113b, where a firm has failed to establish and follow appropriate procedures designed to prevent microbial contamination. Since most of CBER's products are aseptically processed, this is a very important issue.

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While Part two-eleven in the CFR regulations applies to drug product, FDA is also concerned with the upstream portions of the production process. If the agency identifies concerns in the upstream processing, there are additional CFR citations that can be invoked that are specific to drug intermediates and substances, and which revolve around product production, and process controls. Additionally, citations can be directed at failure investigations, building and facility inadequacies, cleaning or maintenance issues, laboratory controls and, again, as with the drug product, the general quality unit deficiencies.

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For biological devices, the top five citations on Warning letters are actually very similar. Though the regulations are different, the language is very similar to the drug product language, for example, the failure to establish and maintain control procedures that describe process controls.

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Now let's move on to enforcement actions. So, what is considered in the decision to take an enforcement action? Well, a range of things are looked at. First, is the compliance history of the company. Are the current violations similar or repeats to what has been seen before? Sometimes the same violation is seen on multiple inspections. Did the firm fail to implement commitments that they made or sustain those commitments? Were any of the current violations intentional or a flagrant violation? Do any of the violations present a reasonable possibility of injury or death? No single consideration is determinative, except if the violation presents a reasonable possibility of injury or death.

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Now to administrative actions. These administrative actions are in fact considered enforcement actions.

Administrative actions for CBER fall under two categories - those for licensed products, and those for human cells, tissues and cellular and tissue-based products or HCT/Ps. For licensed products, a license suspension would be sought if there were an immediate danger to health. For continued violations of licensed requirements and current good manufacturing practices, or CGMPs, a license revocation could be sought. Generally, before a license is revoked, a notice of intent to revoke would be sent. This notice tells the recipient that FDA intends to revoke the firm's license because of continued non-compliance. This letter usually gets the attention of a firm. For HCT/Ps, if there are significant violations of the HCT/P regulations, an order to retain, recall, and/or destroy product can be issued. If there are significant violations and a danger to health, an order to cease manufacturing of the HCT/Ps can be issued.

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Here are some examples. 2006 was a busy year for tissue manufacturers. The Biomedical Tissue Services, or BTS, was issued an order to cease manufacturing on January 31, 2006. Donor Referral Services, or DRS, was issued one on August 18, 2006. Although tissues already distributed were of concern and had been recalled, FDA determined that the serious nature of the firms' violations constituted a danger to health, and thus led to these unprecedented actions.

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For the BTS order, the firm was inadequately screening donors for risk factors of relevant communicable disease. FDA found numerous instances where the death certificates were at variance with the death certificates obtained from the state health authorities, including the cause, place, time of death, and the identity of the next of kin.

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The BTS case resulted in a number of individual criminal convictions prosecuted by various authorities. Guilty counts included body stealing, forgery, grand larceny and enterprise corruption, with sentences ranging from 6 and a half to 58 years in prison. FDA worked cooperatively with federal, state, and local authorities in these prosecutions.

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The DRS Order was very similar to the BTS Order. Numerous instances were found where the information provided by DRS was at variance with the death certificates obtained by the FDA, from the State where the death occurred. For example, the cause, place of death, or time of death did not match the State death certificate. This case also resulted in the prosecution of individuals.

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And with these orders, FDA did contact our foreign regulatory counterparts in the countries that had received HCT/Ps that were implicated in the orders, and provided updates as they became available. For BTS, there was something in the neighborhood of 25,000 items that were shipped to foreign sites, which was quite extensive. For the DRS, the shipments abroad were significantly less.

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Now let's move on to legal actions. The legal actions FDA can employ are seizure, injunction, consent decree, and prosecution.

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A seizure is essentially a warrant for arrest of a property, so FDA can seize property from the firm. And an order is issued by a judge or magistrate in U.S. Federal Court. FDA presents a sworn affidavit and other evidence to establish probable cause for FDA's determination that there has been a violation of the Food, Drug and Cosmetic Act. The company is unlikely to receive any notice

that a seizure is about to happen. CBER's goal is to be able to initiate a seizure within three days of receiving a recommendation from the field.

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In a seizure, the subject goods are usually seized by U.S. Marshals, who could be accompanied by FDA agents or investigators. The goods are thereafter under Federal Court jurisdiction, so they cannot be released to the company or to the FDA.

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An injunction is a court order that commands a company to do something or to stop doing something. It must have approval of and be filed by the Office of Consumer Litigation in the Department of Justice. The company will receive advance notice prior to this filing. It grants FDA the power to inspect the facilities at the firm's expense, to shut down operations, and to dispose of the goods. Violations of the terms in the injunction can result in civil or criminal contempt.

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A consent decree is a step down from an injunction. It is a court order agreeable to both parties. It may be permanent or limited. It can be precise or broad. And importantly, it allows the manufacturer to continue manufacturing and distributing medically necessary products, if certain conditions are met.

There may be some products that may not be allowed to be distributed, but FDA can carve out those products that are medically necessary and, under certain conditions, may continue to be manufactured and distributed. A consent decree may also cite the names of individuals specifically.

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Civil prosecutions can lead to civil penalties because of false statements or interference with an investigation. For example - destroying documents while FDA is on an inspection; knowingly failing to disclose issues; obstructing FDA investigators; and providing services while debarred. If an individual is debarred, and continues to provide services, they are subject to civil prosecution.

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Criminal prosecutions. A criminal prosecution may be preceded by a section 305-hearing, for contempt of a civil order. Criminal prosecutions may result from a Title 18 violation. An assault on federal employees performing their duty, such as investigators while on inspection, is such a violation. Also, conspiracy to defraud the U.S., or mail fraud, are other examples of Title 18 violations.

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Recalls. Recalls are defined in the Code of Federal Regulations as a voluntary action in lieu of FDA-initiated court action for product removal or correction. It is a voluntary action by the firm to carry out its responsibility to protect public health.

Recalls are classified as Class I, Class II, or Class III. Class I represents the most significant health hazard. The vast majority of CBER recalls are voluntary.

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Here is a breakdown of the recalls of CBER products by numbers of lots between fiscal years 2005 and 2008. Though these numbers show that blood clearly has had the greatest number of recalls, this is somewhat misleading inasmuch as a unit of blood is considered to be one lot of product. For the non-blood products, one lot could be made up of hundreds, thousands or tens of thousands of units. So these numbers tell only part of the story.

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For HCT/Ps, in Fiscal years 2006 and 2007, there were 13 and 7 Class I recalls respectively. The vast majority were related to the BTS and DRS cases discussed previously. For example, 9 of the 13 in 2006 and 5 of the 7 in 2007 were BTS or DRS related. CBER had 4 Class I recalls in fiscal year 2008, three of which were HCT/P recalls

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Biologic Product and HCT/P deviation reports are required to be submitted by the regulations. For biologic products and blood, the regulation was implemented in 2001. These reports must be submitted no later than 45 days from the date the deviation was discovered. For HCT/Ps, the rule was implemented in 2005.

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What is reported in a BPDR? Very specifically, it represents a deviation from CGMP, the regulations, standards, or specifications that may effect safety, purity, potency or it represents an unexpected or unforeseeable event, which may affect safety, purity, potency and it occurs in a facility or a facility under contract and involves a distributed product. If the product has not left the control of the manufacturer, and has not been distributed, a BPDR does not have to be submitted.

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And for HCT/Ps, what is reported? First, an event that represents a deviation from applicable regulations that relate to prevention of communicable disease, transmission, or contamination. Second, an unexpected and unforeseeable event that may be related to transmission or potential transmission of communicable disease -- or may lead to HCT/P contamination. Or third, deviations from core CTGPs and distributed HCT/Ps. Once again, a firm must report those that occurred in its facility, or a facility that performed a manufacturing step for the firm under contract agreement or other arrangement. These also have the reporting requirement within 45 days of discovery.

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FDA has a wide range of enforcement strategies and tools to ensure compliance with the law, ranging from communication of concerns, to criminal prosecution by the Department of Justice.

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This concludes the presentation, "Compliance and Product Quality".

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