CBER's Lot Release System: Overview of the Current Process

SLIDE 1

This presentation will cover the CBER lot release system. The CBER Office of Compliance and Biologics Quality, or OCBQ, Division of Manufacturing and Product Quality, or DMPQ, is responsible for the receipt, processing, and release of product lots using this lot release system.

SLIDE 2

This overview will explain the lot release process: what it is, how the system works, what products are covered under lot release, how the system fits different situations, and what changes or enhancements CBER is planning to make.

The lot release system is comprised of product samples and protocols being submitted for review and testing. As part of the review, DMPQ makes sure that everything meets the specifications that were approved at the time of licensing or subsequent updates to the application.

Also covered will be routine lot release. Routine lot release is a term applied to products that are already approved, and the lots are being submitted post-approval. So, the term refers to approved products.

Other presentations have covered the review process for biologics applications and supplements. Note that lot release is part of that process as well, and not only when the lot release protocol gets set up. CBER also gets samples for testing during the approval process.

Does that mean that all products are subject to lot release? No. This presentation will cover some of the alternatives and exemptions to lot release, a bit about product testing, and lastly some of the future directions for lot release.

SLIDE 3

Lot release is covered in the regulations for biological products. The lot release process is initiated during the review process. The protocol is set up, the testing that gets reported is discussed and finalized, and the specifications are agreed upon. These decisions lock the protocol format and information to be included. This lot release protocol will be used for products submitted after approval. Of course, the protocol can be modified later.

You are familiar with pre-license pre-approval inspections from other presentations in this series. DMPQ is the division that goes out and performs the pre-approval and pre-license inspections. DMPQ also takes a look at the supplements that cover changes to facilities and equipment. And, there are a number of things that take place from both the review and compliance side to ensure the quality of the biological products.

The lot release system is one part of that. Reviewing the data that gets submitted as part of the routine lot release post approval is a good way to keep up to date with what the manufacturers are doing. There is selected lot release testing, which will be covered later, as each product has its own test plan that's developed specifically for that product.

SLIDE 4

What are the goals for a lot release? The primary goal is the prevention of substandard lots from reaching the public. By reviewing the analytical methods that the manufacturer used, and the specifications of their own test data, it goes a long way to ensure the quality of lots in commercial distribution.

It also provides for some real-time monitoring of the manufacturing, testing, and product quality. Why? A product could have been approved five years ago, and if there were no major supplements or major changes that would require a new look at the manufacturing process, lot release still gives CBER a chance to look at the lots and the quality of the lots as they are submitted.

But, manufacturing changes are often made as improvements to the process. Examples of manufacturing changes made along the way could be new steps that require process validation, new equipment, or manufacturing at a different scale or even a different facility. So, having product lots tied to significant manufacturing changes gives CBER the ability to look at the impact of those manufacturing changes on product quality. And, this can be done by tying the lot release to certain supplements.

SLIDE 5

Let's cover a brief overview of the regulations that pertain to lot release. The regulations covering lot release are really very short, but have quite an impact for the licensed products. All products that are licensed under the Public Health Service Act may be subject to lot release. There are exceptions for some product classes, such as blood and blood components. Whole blood and other transfusable products are not subject to lot release.

The rest of the licensed products, such as fractionation products and vaccines, are subject to lot release. Even the recombinant products - which are currently exempt from lot release - can be put back on lot release. If a product is subject to lot release, then the lots cannot be distributed until they are released by CBER.

One of the things that comes up, especially when dealing with the H5N1 pandemic and with the H1N1 pandemic: is there a way for different regulatory agencies to trade information and responsibilities, and sign off on releases? At this point, our regulations do not permit that. We as a regulatory agency have responsibility for reviewing and releasing those lots, so that is not something that can be delegated to another regulatory authority.

SLIDE 6

Listed in this slide is a brief overview of the regulations that pertain to lot release. The first bullet point highlights the requirement of the manufacturers. There are really two parts: one, lots cannot be released until the manufacturer's testing is complete, and, two, if there are still ongoing manufacturing processes that may affect the testing, the manufacturer cannot perform that testing until these processes are completed.

The regulations also provide the basis for the manufacturers to submit lot release information to the FDA. That is, the requirement to submit samples and protocols. As a reminder, this is something that is set up as part of the approval process for a biologics product. When a biologics license application, or BLA, is approved, part of that approval letter references lot release. Also, a manufacturer cannot distribute a lot of product until CBER issues the release for that lot. That is not to say that the product will always be on lot release. Later, this talk will cover the mechanisms CBER has for getting products onto a surveillance status.

SLIDE 7

The lot release system has been mentioned in the context of "routine lot release" for approved products, lot release for product submitted in support of an application or supplement, or products that have been put onto surveillance. This slide summarizes lot release at different stages.

Note that regardless of which stage of the process, the same tracking system for lots is used.

For routine lot release with approved products, manufacturers can distribute the lots when they get the CBER release notification. When you see the number of lots later in this presentation, you'll see that this represents the majority of the lots that come into the Center - around 6,000 lots per year.

However, CBER may also get product lots submitted for new products or for supplements for major changes, such as a process change or a new facility. Why? To look at the quality of the product that is manufactured with that change. Note that lots tied to an application or prior approval supplement cannot be released until the submission is approved.

And then there are products on surveillance. Products on surveillance do not get released. However, they go through the same tracking mechanism. Protocols and samples are received, so CBER can complete confirmatory testing.

SLIDE 8

So, let's talk about the lot release process and walk through the process using routine lot release licensed products. With exceptions that will be noted, what will be described here holds true for just about everything else discussed. Routine lot release also represents the greatest portion of the lots received by CBER.

Let's start with samples and protocols. Protocols are a compilation of the manufacturers' test data. There isn't a lot of manufacturing information that is included on a protocol, however they will vary somewhat from product to product. For the most part, the protocol usually contains just the testing data. Remember that the protocol was already set up as part of the initial licensing process. During the BLA review, they determine what tests, and what specifications get reported to CBER, which forms the basis of the protocol. This information -- the product and the manufacturer's license number -- gets entered into the FDA database, the lot release tracking system, which enables the Center to track everything that comes in.

It's a wish to have all protocols in an electronic format because electronic submissions would make things a lot more efficient. At the present time CBER might have 25 to 30 percent of the lot release protocols coming in electronically. A CD is submitted as part of the release which gets uploaded. The advantage is that everyone can review the protocol at the same time, which really helps facilitate the review and getting the lot released. Paper protocols, which still constitute 60 to 70 percent of the releases, have to be physically routed for each reviewer to review the sections that are their responsibility.

SLIDE 9

Continuing with the process overview, once the scientific reviewers look at the information that has been submitted on the protocol, they will look at the data to determine whether the product quality attributes have been met.

This is not a one-way flow of information. The process is set up to give the reviewers a chance to ask questions if there is a problem with the data.

Sometimes it's a simple question - one that just requires clarification - that needs to be requested. Sometimes there are transcription errors on the protocol. However, it may be more involved, such as discovering a whole new test method has been utilized for one aspect of product testing the release. So, this process really gives the reviewers a chance to have some exchanges and discussions with the manufacturer of the product.

SLIDE 10

As noted, CBER gets samples of product lots, and this is an integral part of the lot release process. Product samples - that is, the amount and type received - are set up at the time of licensure. The CBER OCBQ DMPQ Product Release Branch will receive and hold those samples. Then, the scientific reviewers can request samples for confirmatory testing. Please note that DMPQ does not handle research samples - they should be sent directly to the requesting laboratory.

Each lot release protocol might have about 6 to 10 different tests that get reviewed. To facilitate the review, there is a distribution list that gets generated to ensure that each and every product goes to the right review team. After receiving the protocol, each person who is responsible for reviewing a particular test, whether it is sterility testing, preservative testing, heavy metal analysis, or some other test, will determine whether that product needs to be tested according to the testing plan. If so, they would request samples from the Product Release Branch. On occasion, additional samples may be required and requested.

After the reviewer has completed the protocol review and performed any confirmatory testing, they will send the completed protocol back to the Product Release Branch. The Product Release Branch will get all this information back from each scientific reviewer, do a final check to make sure everything has been reviewed and has the appropriate sign off, and ensure that any questions that have come up during this entire process get addressed.

If all the criteria have been met and everything has been found to be acceptable, the official release is generated and signed off by the delegated CBER authority.

SLIDE 11

To continue on the discussion about the lot release process, it would be helpful to get a sense of how many lots get submitted and how this breaks down by product class. As you can see from the Fiscal Year 2008 data, DMPQ released 5,793 products as approved products or the routine lot release mentioned. The three biggest product categories are the ones listed as Blood and Blood derivatives, which are fractionation products, Vaccines, and In-vitro diagnostic tests. Note that the total number of releases processed was 6,313 for the year, as CBER uses the same system for surveillance and other actions. "Other actions" usually means that the lot was tied to an application or supplement.

SLIDE 12

This slide shows the fiscal year 2009 data up to September 15, 2009. This gives an idea of the volume of submissions received from year to year and the throughput of lots that come in. The increase in the vaccine totals are because there were additional lots that came in for H1N1. And those numbers probably grew through the remainder of the year.

Depending on the product type, there are different types of samples; some products get released as a bulk, some as the final product. Flu is a good example of releasing on bulk. Why? Because there may be multiple fillings. And so, once it's a formulated trivalent, the formulation doesn't change, and that's what is released.

Other products may be released at different points, such as product made up of many serotypes, a serotype to be blended later. Each particular serotype may be released initially, then release the final containers once all the serotypes have been blended. So what gets released is somewhat product-dependent. The samples are under constant monitoring, stored properly, and available for the review team and the CBER scientists who are on that distribution to review the testing for the specific product.

SLIDE 13

Now a side trip, to cover the other uses for the lot release system. Primarily, the discussion has talked about routine lot release. These are the products that are already licensed. What happens with lots that are submitted in support of applications and supplements? And by "supplements" it means the prior approval supplements, the major changes, a facility change, a brand new facility, or brand new process. For most of the minor supplements, one would not expect lots to be tied to those particular submissions.

As for lots submitted as part of the application review and approval process, until the application is approved, the product is not approved, and therefore lots cannot be released until the application is approved.

SLIDE 14

Certainly for applications there is an expectation that lots will be submitted as part of, and in support of that application review. In some cases, it's a novel product and CBER wants to gain some experience with it. In some cases, such as a supplement, it represents a significant change.

During the application review process, the information that is going to be submitted in a protocol, and the protocol format, need to be determined. As mentioned, the reviewers need to determine what tests are going to be reported, what are the specifications, and the format for how the test data is going to be reported. Those are all determined here during the review process and set. So, once that product is licensed, that same format will be used subsequent for the lot release protocols.

SLIDE 15

Testing plans may have been mentioned in another presentation, but it is worth covering. For new products that are being approved, testing plans have been

developed. They are based on the risk, CBER expertise, and the resources that are available. It provides a system to determine which lots the Center will test.

Lots that are submitted in support of a prior approval supplement, just like they are for an application, cannot be released until that supplement is approved. That is the one difference between routine lot release and those that are tied to supplements or applications. The routine lot release lots are ready to be distributed. For the lots that are tied to either applications or supplements, the submissions have to be approved first. And, there is a way to track which lots are linked to submissions in the CBER system, which is one of the reasons that this database is so helpful.

SLIDE 16

Some lots or some products can be exempted from lot release. This is referred to as "placing lots on surveillance". Periodically, manufacturers submit lot samples and lot protocols, but the distribution of lots does not require CBER's release. So, everything discussed in terms of sending samples, sending protocols, tracking and storage, is all the same. The difference for products on surveillance is that, at the very end of the process, DMPQ does not sign off on a release. Once manufacturers submit the protocol they are able to distribute product.

SLIDE 17

Let's talk about the process to go from routine lot release to be put on surveillance.

If a company wants their product to go on surveillance, they should follow the process that is posted in the Federal Register Notice of 1993. In this FR Notice, there are proposed alternatives to lot release - or what is termed "putting products on surveillance". This request would have to come in as a supplement. This type of change, from release to surveillance, would be a prior approval supplement.

What should be in the submission? Well, there would have to be an acceptable lot release history. So if CBER saw lots that had failed or had problems meeting specs, or for some other reason, it would probably not be something that would be approved without a lot of additional information. If, on the other hand, you have a history of a couple hundred lots that have not had problems, then one could consider that to be an acceptable lot release history. The manufacturer needs to demonstrate continued control of the manufacturing process and facility. Using the same processes and the same manufacturing facility over time helps establish consistency and control. If there have been major process changes, CBER certainly would want to evaluate how these changes may have impacted the product quality attributes, also taking into consideration complaints and any corrective actions that have been taken with lots that have been manufactured.

Surprisingly, a lot of manufacturers do not go through this route. Only a handful of products have applied under this mechanism, but it does exist.

The reverse is also true. If CBER sees problems, lot release can be reinstated, and that has been done on occasion. There was a manufacturer that was having problems controlling moisture for one of its products that was exempt from lot release, and CBER put them back on lot release for a couple years until it was under control.

SLIDE 18

The other way that products can be exempted from lot release is by product class. Back in December of 1995, CBER published the Federal Register Notice that basically exempted all the well-characterized biotech products from lot release. So, the recombinant DNA-derived proteins and the monoclonal antibodies, as product classes, were exempt from lot release requirements.

Does this mean they could be put back on lot release? Yes. If you look at the regulations, there is a provision that any lot of any licensed product may be, at any time, subject to lot release. So, if there is a for-cause reason, these could essentially go back on lot release.

SLIDE 19

Lot release and testing: All the laboratories have procedures for their lot release testing and this is getting more standardized as things move forward with the testing plans for all CBER-regulated products. Over-layered on top of this is the Center's Laboratory Quality Policy Manual, which really describes the system used to ensure that the procedures in place are all standardized and followed. And, as things move forward on this, CBER is trying to incorporate some of the products that may have been licensed, say, 10, 15 years ago, and bring them into the same testing plan system.

SLIDE 20

The lot release system has been in place for quite some time in some current form, and if you look back through the history of lot release, similar regulations have existed for decades. The majority of testing that is being conducted is, for the most part, in the Division of Product Quality. There are other divisions that are currently doing the protocol review as well as testing. They are using scientifically sound methods. The test methods that are validated by the manufacturers get reviewed by CBER as part of the BLA or supplement review process. And sometimes even that work goes back into the IND stage. If it is a new product, there may be collaboration at a very early stage.

If there are problems, and occasionally something will come up, CBER will participate in collaborative studies to ensure that product quality is met. The staff performing the testing has gone to manufacturers labs, and the manufacturers

have come into CBER laboratories, just to work out particular issues. Sometimes there is an issue with the reagents. Sometimes it is just interpretation of test methods. And certainly, with the CBER staff, the tests are performed and supervised by experts in their particular field.

SLIDE 21

Where is the future going? The overall goal for the Center is getting accredited to ISO standards. In 2010, the Center was accredited for a number of standards and continues to pursue accreditation in others.

There is certainly a lot of work that the laboratories are doing to maintain their proficiency with performing the assays and developing additional quality documentation that define the testing requirements.

The oversight of the lot release process and harmonized approach for all laboratories is also occurring. It is a huge endeavor to move all the laboratories into one over-arching system. And, you saw the number of lots received per year and the number of products, so you can imagine getting this many products and several testing laboratories all thinking the same as things move forward.

SLIDE 22

As mentioned, CBER is developing the testing plans for the products already under review. These testing plans get signed off by the offices involved with review and testing the particular product. For the new products CBER develops the testing plans as part of the approval process. For the products that were licensed some time ago, CBER is still working on these plans to determine what makes sense for them in terms of CBER confirmatory testing.

The testing plans have been developed to be flexible. There are a number of criteria that are built into each one of the testing plans. Therefore if problems arise or there is another pressing need, CBER can shift and reduce or increase the amount of testing done, either lot by lot, or product class by product class.

SLIDE 23

The laboratory accreditation is something that CBER has been targeting for some time. The CBER Lab Quality System was successfully accredited to ISO 17025 in October of 2010. There had been a couple of dry runs along the way to reach this point. For example, the World Health Organization came in to complete an assessment and provided some guidance to help CBER along.

SLIDE 24

The tracking system has been mentioned a few times. This lot release system is the tracking system used to track the lots. All samples and protocols are tracked in the lot release system. To give you an idea of what information is captured, CBER starts with the sample and protocol received dates. Why is that important? There are no official time frames for release. You would be surprised

how many times CBER gets inquiries regarding the timelines for the releases. So, this is very helpful, because CBER can try to get review and sign off in a timely fashion. It also shows whether the staff has performed the tests, if they've entered the data, and any issues that could impact on lot release. Remember, this system is also being used for products submitted under application, or for a major process change under supplements. There is a way to link this information, as well.

The system can also be used to track the status of the review and testing for a particular lot. Samples and protocols can also be tracked separately. An example where this came in handy is for the H1N1 lots, as there was a need to expedite their release. Imagine the delay if the samples and protocols were submitted at the same time, and the product had to undergo a 14-day sterility test. In such cases, CBER can perform concurrent testing. The manufacturer can submit the samples to CBER even though it has not completed all its tests. And CBER can undertake its testing concurrently. Once the manufacturers' testing is complete, they can submit the protocol to CBER. This can save quite a bit of time, and worked well for the H1N1 lots.

SLIDE 25

Record retention is often an issue in lot release submissions. A substantial number of records are generated. CBER's Document Control Center, or DCC, is the main repository for these records. They have a standard record retention schedule, which is based on the federal government's retention system. The Product Release Branch stores paper and electronic submissions for two months and then sends them to the DCC.

The testing information is still maintained, however, by the laboratory performing the test. This information is kept separate from the information submitted by the manufacturer.

SLIDE 26

In summary, all licensed products go through the lot release process, unless they are specifically exempted or approved to be on surveillance.

CBER does not perform confirmatory testing on every lot, but does review all protocols submitted by the manufacturer. Testing plans for when CBER conducts these confirmatory tests are being implemented for all CBER products.

CBER does have a mechanism for corrected protocols, especially for taking care of minor issues. The manufacturer can fax the correction, which makes for a smoother process.

Slide 27

This concludes the presentation, "CBER's Lot Release System: Overview of the Current Process."

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