DIVISION OF PRODUCT QUALITY

SLIDE 1
This presentation will discuss FDA's Division of Product Quality in the Office of Compliance and Biologics Quality, or OCBQ, at the Center for Biologics Evaluation and Research, CBER.

SLIDE 2
Let's review the role of the Division of Product Quality, its development, and how it fits into the CBER operational processes.

This Division is a relatively new entity within CBER. Two major efforts happened which caused the creation of the Division of Product Quality.

The first was a long-term undertaking, over 10 years now, to implement quality management systems within the FDA, and specifically within the Center for Biologics. The effort at CBER was directed specifically to the area of product testing.

Second, at a later point in time, the U.S. Congress initiated a funding appropriations bill with significant money available for pandemic influenza preparedness. With those funds, CBER had an opportunity to create a new Division whose mission was to implement a quality management system focusing initially on the contribution of product testing to pandemic preparedness.

To clarify, this is the Division of Product Quality or DPQ. But there is also DMPQ, or Division of Manufacturing Product Quality, which is also part of CBER Office of Compliance. The Division of Manufacturing Product Quality has a different role, which includes inspectors. DMPQ does pre-licensing inspection and participates to some extent in routine inspections. The Division of Product Quality, the topic of this talk, maintains the testing laboratory. DMPQ has the inspectors and DPQ has the laboratory. The DPQ mission involves the implementation of quality systems, quality management, and has now been ISO accredited for a range of its testing activities.

This presentation will give an overview of the role of DPQ, especially from the standpoint of regulatory review, and with respect to official product testing. Later, it will cover ASS-ay controls, standards and reagents, and some of the current efforts at implementation and improvement of test methods.

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As a new division, the Division of Product Quality was given a charge; to achieve implementation of quality management for in-support testing during licensing, for post-licensing lot release testing, and for Lot Release Protocol review activities.

It was charged to bring controlled, compliant laboratory testing to CBER and charged with seeking accreditation of laboratory testing activities. It was also given the responsibility of management of reference reagents and physical standards, and for maintaining CBER's expertise for performing scientific assessment of test methods and for method validation.

Obviously there is a tremendous amount of expertise in the product divisions, specializing in test methods and method validation. And, from an applications point of view, DPQ brings expertise and consistency to the evaluation of method validation and works to maintain that expertise within CBER.

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The Division of Product Quality provides support services during licensing, during lot release processes, to standards and reagents, and to the transfer, verification and applied use of testing methods. During the licensing process, DPQ looks at and reviews the release tests for the drug substance and drug product. The final bulk is also known as the drug substance, and in the final container, known as the drug product. DPQ looks at methods for transfer and qualification into the laboratory during the licensing process. Validation packages, as submitted, are reviewed. DPQ does the in-support testing and generates testing plans and lot release protocols. You are most likely familiar with lot release protocols. The term “testing plan" may be unique to FDA, so this talk will make clear what the testing plan is in the FDA context.

Finally, during the lot release process, which is managed by the Product Release Branch of OCBQ, the Division of Product Quality contributes with protocol review and confirmatory testing.

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DPQ has an independent Quality Assurance Group whose responsibilities include: document control and issuance; audit of generated testing data; control and review of records created by DPQ; and oversight of sample handling, distribution and compliance with requirements of the testing plans. In other words, DPQ makes sure that the program described in the testing plan is implemented and carried out.

The DPQ Quality Assurance group, or QA group, also helps with the audit of the compliance processes, which include training, preventive maintenance, calibration, environmental monitoring and others according to the requirements of the standard. The QA Group is also part of a Center-level quality team at a higher level, which sets quality policy for CBER, manages internal audit programs, leads senior management review of activities, and thereby facilitates resource allocation as needed to continue to meet the requirements and goals of the program.

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In 2010, DPQ was accredited as meeting the requirements of the ISO-IEC 17025, as revised in 2005. CBER embraces a philosophy of continuous improvement, participates in management review processes at the highest level in the Center, has a strong internal audit program, and the methods are qualified and validated.

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DPQ is really a cross-functional player. It was originally located in the Office of Vaccine. Over time DPQ's responsibilities grew from an influenza focus to a more expanded set of objectives and goals, and its organizational location in the vaccine office was recognized to no longer be a good fit.

A reorganization followed placing DPQ within the Office of Compliance and Biologics Quality. Its current responsibilities include supporting the product divisions by assisting in the chemistry, manufacturing and controls, or CMC, reviews of INDs, or investigational new drugs; biological license applications, called BLAs; and supplements.

DPQ leads test method evaluation, transfer, and qualification from those submissions. DPQ also assists in the evaluation of the acceptability of submitted product specifications, handles test method transfers, verifications and validation of methods that are to be used in lab testing, and participates in development of reference material for use in controlling the testing of new products. DPQ supports the Applications Division by participating in the review process. It prepares and maintains product-specific testing plans, as well as assists in establishing the content of the lot release protocol. DPQ also supports the Compliance Division by performing the lot release protocol review and trending the data. The division performs lot release confirmatory testing and trends the data, and assists with site inspections. A few DPQ staff have been out on inspections, but the majority supports inspections via phone. There may also be quality investigations or testing that is done as part of an investigation or other compliance testing. DPQ also prepares, stores, and distributes testing reagents and reference standards, as needed.

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As this presentation moves through each phase of review and lot release, let's look at the specific activities that the Division of Product Quality participates in. During the IND phase, DPQ spends time with a specific focus on the analytical methods section, looking at final bulk and final container assays, and asking the questions: Is the method scientifically sound? Is it suitable for its purpose? And, DPQ provides guidance as needed for smooth transition to the next phase.

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During a new BLA review, there is, again, a review of analytical methods. The questions are asked: Is the validation package suitable? Is it according to the requirements of applicable guidance? DPQ reviews in-process and final release

specifications with the product reviewers, and helps identify, transfer, qualify, validate and perform testing methods that bring value and address risks when performed in support of the licensing action. Figuring out which tests bring value, where time should be spent, and what should be brought into laboratories is a key role. Please note here that safety, purity, and potency tests are very high on the list of tests that bring value.

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The Division of Product Quality helps draft the product testing plan. This plan describes, supports, and justifies the post-license lot release activities. DPQ helps to finalize the content of the lot release protocol. Remember, DPQ completes the testing according to the testing plan, and reviews lot release protocols for lots that come in for lot release.

After a license is approved, new supplements that come with respect to that license may impact what is in the product testing plan. There may also be an impact on what is in the lot release protocol. So, the job of DPQ is to make sure that the product testing plan is consistent with the proposed changes, and that the lot release protocol also remains consistent with proposed changes.

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Of course the real day-to-day activity that DPQ participates in is the post-license lot release. As mentioned, lot release is managed by OCBQ, and specifically the Product Release Branch. DPQ, however, supports the Product Release Branch by implementing the product testing plan and completing confirmatory testing according to that plan, while reviewing the lot release protocol for every lot that comes in. DPQ is also in the process of establishing a formal data trending process, which hopes to be effective in spotting potential performance drift early.

All decisions are documented in the lot release database. Please refer to the presentation "CBER's Lot Release System: Overview of the Current Process" in this series, which includes information on the computer database used. DPQ interfaces with the lot release database, and enters pass/fail decisions into that database. The Product Release Branch has the ultimate delegated authority for lot release.

If DPQ encounters a result that is out-of-specification, or OOS, either during testing or in review of the protocol, there are certain actions taken. If the OOS is in CBER's testing, then DPQ follows an out-of-specification investigation procedure, and reports the confirmed and valid results to the sponsor, followed by dialogue and work towards a resolution of the issue. But, until resolved, CBER will not sign for lot release.

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Now a description of the testing plan.

These are change controlled and confidential internal documents that specify the following things. They describe the mechanism for performing lot release; meaning, CBER might release on protocol review alone, or on protocol review with testing, or the product may be a product that has been granted surveillance so that it is looked at in a surveillance mode. Or, the product may be exempt from lot release.

The testing plan provides a risk-based rationale and justification for whether or not to perform confirmatory testing. This is why it is called a testing plan. It also includes information that details what samples CBER gets, for example, whether a formulated final bulk, and/or whether final container. It then specifies the test method and the frequency for performing the testing. It also provides appropriate cross-references to current approved product specifications, so it becomes a tool to help CBER with protocol review.

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Testing plans are product specific so that there is one testing plan for each product.

These are confidential pre-decisional documents, and not subject to the Freedom of Information Act. Access could provide a manufacturer with the ability to circumvent this tool, and that is something to be avoided.

The testing plans are change-based and change-controlled, so that with the receipt of a change supplement, or inspectional observations, adverse events, or other factors that would change the risk dynamics, the testing plans might be revised. The testing plans are also on an annual audit cycle.

Looking at a testing plan, you realize it is actually one of the top documents in the CBER document pyramid. They are under the CBER policy documents, but they are a document that contains all the information describing who DPQ is, what tests DPQ has in its arsenal, how often DPQ uses them, and what resources DPQ needs to maintain the program.
It all derives from the testing plans.

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Briefly, let's review the types of tests that are currently in the DPQ arsenal. There are compendial tests. In the Code of Federal Regulations, or CFR, you will find minimum requirements tests. In addition to these, there are also standardized tests with methods that are the result of collaborative studies, methods that are published in the literature, or methods that are unique to each license.

There are also tests on blood screening kits. DPQ has absorbed some of the lot release testing that was previously done in the Office of Blood. So DPQ looks to qualify and evaluate the system suitability for each test that is brought into the CBER program.

DPQ demonstrates comparability with data generated by the manufacturers and explores the appropriate validation requirements for each method.

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The list of tests done by DPQ also includes common microbiological tests, some molecular biology tests, some molecular separation and characterization tests, and the important potency tests.

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Analytical chemistry testing includes protein analysis, moisture analysis, and free and conjugated polysaccharides. There are multiple methods used. CBER is evaluating using all kinds of analytical methods for excipients and adjuvants, and is also looking at methods to measure preservatives, including thimerosal.

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This slide describes the lot release protocol.

This is a lot specific record of results, of batch release testing as performed by the manufacturer. It may also include significant in-process testing results and tracking information for seeds, bulks, and other significant materials. As mentioned, the format and content is established during the license review, and data is reviewed during lot release by Division of Product Quality scientists.

Lot release protocols may be revised with each significant supplement to the license.

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That completes an overview from a regulatory point of view. Now, let's talk a bit about assay control, program of development, characterization and supply of reagents, and standards, and their importance. Shortly, rapid methods and other test methods will be discussed, which will be important for the future.

You are probably aware that two important components for controlling biologics are the reference standards and critical reagents. Due to the inherent variability in the biological products and methods, these reagents are critical to ensure safety, potency, and consistency of the products.

DPQ generates certain standards, calibrates them, participates in the calibrations involving international labs, and is involved in distribution as well.

DPQ must maintain the proficiency in its laboratory operations and do so in a demonstrable way, in accordance with the ISO laboratory accreditation process. Programs that support proficiency activities include participation in international collaborative studies, which show whether CBER's results are comparable with

another lab's proficiency program. It also shows if CBER can demonstrate that results are within the inherent variability of the methods.

Not fully realized but moving closer, DPQ is trying to establish a database for comparing CBER test results side by side with the manufacturer's test results, which are received on the lot release protocols. CBER is looking to see if they are getting trends, or if results are equally distributed.

Finally, and most importantly, is CBER's participation with other World Health Organization, or WHO, influenza collaborating centers, known as Essential Regulatory Laboratories, in the calibration of the influenza vaccine potency reagents. This is an annual exercise that gives CBER an opportunity to compare our results with these other labs.

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On to standards, controls, and critical reagents. As mentioned, the Division of Product Quality is responsible for generation and calibration of certain standards. Examples include the reagents for the seasonal influenza vaccine potency test, tetanus and diphtheria antitoxins for potency and flocculation, and reagents for the PPD tuberculosis skin test, or purified protein derivative. There are other product divisions who also participate actively in generation and calibration of many other reagents.

DPQ is not a centralized lab for all the reagents and standards in CBER. Many of these reagents are still maintained, generated, and calibrated in the other product divisions, and serve as the custodians of these reagents. Some of the examples of reagents maintained outside DPQ are mentioned here, including blood typing reagents, serum panels blood screening kits, and many of the blood products like immune globulins and others. Even the reagents for the pandemic influenza vaccine start in the Division of Viral Products in the Office of Vaccines.

All these reagents ultimately come to the DPQ division for distribution. When something becomes routine, for example, H1N1, the responsibility for the reagents is transferred to DPQ. Some other bacterial product reagents are still within their relevant product divisions and those custodians authorize distribution of these reagents. Once they are authorized for distribution, then DPQ is responsible for shipping these reagents.

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Let's move on to how these reagents and standards are distributed.
As mentioned, these reagents and standards are critical in maintaining the consistency in biological products. These are primarily for U.S. licensed manufacturers to release their products, or to prepare their in-house reagents so that they can release their products. These reagents are also very important for developing new products, and though not on the top of the priority list of category of uses for which CBER distributes reagents, based on experience there has not

been a need to refuse to provide these reagents for research purposes. CBER undertakes to make enough reagents to meet its regulatory requirements for the U.S. licensed manufacturers, who are the top priority. There are times when not enough reagents are available for all interested parties, and distribution is then based on a priority system.

U.S.-licensed manufacturers get first priority. The next or second priority is for cases when a company has a pending regulatory action, such as a supplement to change methods. The next priority is to support and supply sponsors of INDs who are developing new products. CBER also provides reagents and standards to other national regulatory authorities through the World Health Organization and other regulatory authorities, as well as to researchers in academia or other government agencies like NIH, so they can develop new products. Though there is a rather large number of recipients overall, and there are supply constraints at times, CBER has so far been able to provide to anyone who has asked for reagents.

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For the influenza vaccine reagents, these activities are carried out every year. As mentioned, CBER collaborates with the W-H-O by serving as an Essential Regulatory Laboratory, or ERL. There are a total of four ERL's. In addition to CBER, there is the NIBSC in the U.K., the TGA in Australia, and NIID in Japan. These four labs get together in the early part of the year once the currently circulating influenza strains have been identified and begin working on the generation and procurement of materials to prepare the associated reagents. The process starts with the generation and procurement of the purified hemagglutinin, or HA, for inoculation of sheep, because that is the part of the process that takes about 8 to 10 weeks to generate antibodies specifically for hemagglutinin. Simultaneously, work is started on getting a virus preparation to designate as a primary liquid standard. The primary liquid standard is the one which is sent across the four labs in Australia, Japan, the U.K. and CBER to be calibrated.

The lab which first initiates this calibration collects all the results and assigns a potency to the primary liquid standard. Simultaneously, CBER is working on the sheep antibodies to HA. As the sheep antibodies are produced, CBER begins optimizing its dilutions for the single radial immuno-diffusion test. Also simultaneously, CBER starts working on generation of a lyophilized secondary antigen. Once that is obtained, it is also distributed to the other ERLs, along with the sheep antibodies. All these labs calibrate the secondary lyophilized antigen against the primary liquid standard to assign HA content in terms of microgram per vial.

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The final subject to be discussed here is DPQ's work on alternate methods or the methods which have been optimized in the product divisions. These methods

can be implemented for routine use in manufacturing operations. When methods are optimized in product Divisions, DPQ begins discussion with the product divisions, to bring these to the DPQ division for its own optimization, by including, for example, appropriate controls, method design, number of replicates, and standards.

Once this is done, DPQ completes preliminary studies to see whether a given method is appropriate for lot release purposes. Then, DPQ completes validations of the methods. Once successful through these stages, the methods are then provided to manufacturers to complete collaborative studies or go to other international regulatory authorities, if they are interested in the methods.

Here are a couple of examples on the methods currently being worked on. One method is the rapid sterility method. As you know, sterility is done at multiple stages during the manufacture of biologics, and takes 14 days. There is a need for a method which can more rapidly test for sterility, for two reasons: to save 7 days at the final stage of testing, but also to save time during all the manufacturing steps during a pandemic when availability of vaccine is urgent. Availability of this method in the H1N1 pandemic would have been extremely helpful.

CBER is also working on a rapid Mycoplasma detection test which was developed in the Division of Viral Products. Scientists in that division came up with a very promising method in which they could get results in 5 days, instead of 4 to 5 weeks with the classical test. So, the method was transferred to DPQ for optimization. DPQ is now doing equivalence studies with the test referenced in the CFR.

There are significant efforts underway with the influenza reagent preparation, because as mentioned, influenza reagents are prepared every year with the seasonal influenza strains changing. This annual change translates into the pressing need to generate the reagents in a timely manner, and have the vaccine available by July or August. This is a short window of time, so DPQ is always looking for more rapid methods or better alternate methods.

One of the methods being looked at is the protein determination. It looks very simple, but routinely DPQ has been doing the Hjeldahl method, which requires a sizeable sample in terms of milligrams - sometimes the quantity is not available. The method also takes a relatively long period of time. DPQ is working on some potential alternative analytical methods using Mass spectrometry to identify different components. This effort is one being undertaken in collaboration with the different divisions in CBER's Office of Cellular, Tissue and Gene Therapies and Office of Vaccines. DPQ is also looking at the reverse phase HPLC, or High Performance Liquid Chromatography, for the potency test, as well as working on alternate approaches to generate antibodies, again with collaboration from scientists within the Division of Viral Products.

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Like the rapid sterility method, which is in the advanced stage, we are working on different options with rapid microbial methods. This slide summarizes the current options for the rapid microbial methods, that is, those methods used to isolate, identify, or even detect a microorganism, mostly bacteria. There are a number of other technologies being used. These can be put into four broad categories.

One is the growth-based method that measures biochemical or physiological parameters that reflect growth of organisms - DPQ is working on a couple of examples. Another is the ATP bioluminescence technology developed by Millipore. The advantage of this technology is that if you are familiar with the sterility test, one of the methods to do a sterility test is by membrane filtration. So, this method can adapt to the membrane filtration readily.

DPQ is also evaluating another two technologies, BACTEC and BacT-Alert; these are two systems you might have heard about in the field of clinical microbiology. These two are used in clinical labs to isolate the organisms when somebody is sick, and to get fast isolation, detection, and antibiotic sensitivity results to start the treatment. These look very promising for sterility also.
Then there are viability-based methods based on the viability of organisms.
Some are artifact-based depending on detection of products of the organisms.
The last category is the genomics based method, based on the advances in gene sequencing and PCR. DPQ also intends to consider one of the systems from the ABI.

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Next are more specifics about the four systems just mentioned. First is the ATP bioluminescence system from Millipore. It is compatible with the current membrane filtration technology. You filter the samples, take the membrane, put it on the media for a very short period, maybe a day, and then treat with a mixture which releases the ATP, and then measures the ATP. Depending on the growth of the organisms, you detect these. Some organisms are very slow growing. CBER was able to detect the slowest-growing organisms within 5 days, where the traditional sterility method took about 10 days to see the growth.

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The BacT-Alert method is based on the detection of the carbon dioxide produced by the organisms. At the bottom of the media bottle shown on this slide, there is an indicator with the carbon dioxide generation. It changes the color from blue/greyish to yellow.

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The BACTEC method is also based on a similar technology, detection of carbon dioxide, but with a different detector. This is a fluorescent-based CO2 detector, and has a similar level of sensitivity.

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Here is a method which DPQ has been investigating and seemed very promising. Even one single bacterium can be identified and detected from the sample. This is based on the PCR, where you take the sample, prepare it, and based on the PCR product, you sequence it. So, PCR primers are in the 16-S ribosomal region of the bacteria, 16-S RNA for the bacteria and D2 region of the fungi.

Once you have the PCR product, then the system sequences that. The sequences have certain differences which are unique for the different species. CBER has a big database. Once you sequence it, you run through the database and get the identification of the organism. One of the requirements for the sterility test is that you not only have to detect the organism, but you have to isolate and identify it as well, so that this system can simultaneously do both things. It can detect it, and by sequencing it, can identify it. This can be done in a day.

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Then as mentioned DPQ is working on the Mycoplasma detection method. There is the traditional CFR method or the European Pharmocoepia method, based on the growth in media, which takes 4 to 5 weeks, with a minimum of 4 weeks. Then the Indicator cell culture method, which takes 5 days, but it does not detect all of the Mycoplasma. So, DPQ is working on a rapid method, which can detect all the organisms, and, preferably, do it within 7 days. These methods are based on detection of nucleic acid in the organisms.

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DPQ has also been investigating a hybrid method, which was described by BioReliance, a contract testing lab. DPQ started with the standard culture method, which, per the CFR, requires14 days for initial incubation. After 14 days, you subculture on a solid medium for another 2 - 3 weeks. In this method, however, instead of subculturing on a solid medium, BioReliance started doing the PCR, so that you get results in 14 days. DPQ is evaluating this method, and comparing this with the method developed by scientists in the Division of Viral Products using MDCK cells and PCR detection. The approach DPQ is using includes spiking the MDCK cells with different Mycoplasma species at different levels, then sampling at different days and detecting with PCR. For this method, a lot of work has already been published.

This method has the potential to detect a large number of almost all the mycoplasmas which have been identified so far. CBER is going to verify this method and validate it and hopefully initiate a collaborative study on this method. CBER held a workshop on Rapid Mycoplasma detection methods with a large

number of participants from different manufacturers and other regulatory agencies. CBER received valuable input on how to should proceed in a collaborative study.

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Just to summarize on DPQ activities, much is done with pre-licensing activities, which means that before licensing of a product, DPQ assists with the BLA review of test method sections, the method validation section, and also the product release specifications. Based on those reviews, DPQ recommends and works with the CMC reviewers to come up with a list of tasks needed to perform in support of the license application. Then, DPQ assists in negotiation of the contents of the lot release protocol, and also develops a product testing plan as described. After the licensure of the application, DPQ performs a lot release protocol review, implements and maintains the product testing plan, and also completes supplement reviews particularly related to methods. As mentioned, DPQ also does ASS-ay quality control, manages the standards and reagents, and is working on bringing the new test methods for lot release purposes.

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This concludes the presentation, "Division of Product Quality".

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