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MONTHLY UPDATE–JULY 2010

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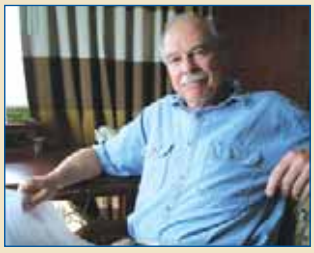

Bill Paulson, Editor-in-Chief

EDITOR's NOTE: Welcome to the inaugural issue of IPQ's "Monthly Update" on key CMC/GMP developments in the US, Europe, and internationally. The IPQ family of publications has been expanded this Spring to include breaking stories "In the News" on our web site, "Weekly News Alerts" sent via e-mail, and the "Monthly Update." These now accompany our uniquely valuable in-depth "Special Reports" on emerging areas of concern drawing particular attention from industry and regulators. IPQ's new offerings will bolster our mission of helping readers understand, engage in and respond to the dialogue and developments around evolving and harmonizing the regulation of pharmaceutical and biologic quality and manufacturing. Subscribers and license holders to IPQ have access to all of these sources of cutting-edge news and in-depth analysis as well as to the full IPQ archives. Visit IPQpubs.com for further information.

UNITED STATES

USP Upgrading Bioassay Coverage; FDA Weighs In on Bioassays at AAPS' National Biotech Meeting

The US Pharmacopeia (USP) is upgrading its coverage related to bioassays to keep pace with the evolving science and technology.

In the July/August *Pharmacopeial Forum*, USP is proposing revisions for public comment to General Chapters <1032>, <1033>, and <1034>, which address the design, validation, and analysis of bioassays respectively.

> **In its announcement of the proposed changes, USP explained that three *ad hoc* advisory panels have created "a comprehensive suite of bioassay guidance chapters that have emanated from USP's core compendia bioassay standards."**

In March 2008, USP had proposed a comprehensive revision to its General Chapter <111>, which covers the analysis of biological assays. The proposed revision elicited three primary concerns: 1) the evaluation of curve similarity, 2) the utility of equivalence testing as an effective statistical method in several areas of bioassay data analysis, and 3) the best means for combining data from multiple assays.

Based on the comments received, USP shifted its focus to creating a new General Chapter <1034> to focus specifically on the analysis of biological assays and address the concerns raised about Chapter <111>. A new General Chapter <1032> to address the design of biological assays is also being proposed.

The revision to USP's existing Chapter <1033> on the validation of biological assays reflects the comments received on an original proposal to revise the chapter released in March 2009. The new general bioassay chapters will be accompanied by a minor revision to the currently official <111> to bring it into alignment with them. A more comprehensive revision of <111> is planned, once all product- and monograph-specific references in the chapter have been addressed.

The entire suite of the four chapters (<111>, <1032>, <1033>, and <1034>) will eventually be accompanied by a new General Chapter <1030> that will provide a "roadmap" to the chapters including a unifying glossary of terms. The chapters will ultimately be accompanied by example data sets that would be made available on USP's website.

USP is making the proposed chapters available for download and comment earlier than in the past "in order to solicit the widest possible stakeholder input." The public comment period ends October 15th, 2010. Comments and inquiries regarding these chapters should be directed to Tina Morris, at tsm@usp.org.

USP is holding its third annual bioassay workshop on August 11-12 at its headquarters in Rockville, MD focused on bioassay development, guidance, changes and case studies to help advance its compendial initiative.

Bioassays Important in Comparability

The importance of good bioassays and their uses and limitations was highlighted at the AAPS National Biotech Conference in San Francisco in May by CDER Office of Biotechnology Products (OBP) Biochemistry Lab Chief Emily Shacter.

Speaking on the role of bioassays in comparability studies of biologics, Shacter emphasized that "bioassays are very important. You can inject a protein into the body, but is it active or not, or to what degree is it active? This is very important for knowing that you have the correct dosing of a protein."

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She pointed out that the situation is different for small molecule products, most of which do not have a bonafide potency assay that is used for their release or characterization, because the molecule itself can be much more highly characterized.

Stressing the importance of understanding higher-order structure of protein molecules, the FDA biochemist noted the key questions that get raised in this context: "How do you know when you have the correct structure? How do you know when you have a structural variant present? How do you know if the structure has changed significantly, meaning that there would be a clinical difference? And consequently how do you know that change is important? And to what extent can we answer these questions using the various physicochemical tests that we have available?" One of the important tools in determining the correct structure for a protein is the bioassay, she emphasized.

While an important weapon in the arsenal, Shacter also pointed out that bioassays have their limitations.

"While important, bioassays do not reveal some very important aspects of clinical activity, like biodistribution. So when you are doing an *in vitro* assay for biological activity, that does not tell you anything about how much the protein is going to get around to where it is going to go or how long it is going to stay in the body, and consequently how long and where it will be active."

In addition, bioassays "do not reveal much" about the physiological modulators, whether there are low-level variants present, or the potential for immunogenicity.

"While tests for higher-order structure cannot replace bioassays, bioassays also cannot really fully replace higher-order structure [characterization] which is really what the body sees," Shacter pointed out, adding that both are needed "in order to reduce the risk that we have from a change in manufacture."

The challenges and advancing science around bioassays are drawing considerable attention at biotech-related forums, and conferences are being set up to focus on the issues involved.

The biotech analysis society CASSS put together a comprehensive bioassay conference held on the NIH campus in Bethesda, MD in November 2009. The meeting was designed to foster interactions between sponsors and regulators regarding expectations for these assays, and included presentations and workshops by key players in industry and FDA. The conference focused on bioassay: • scientific approaches & regulatory strategies • use throughout the product lifecycle • development and selection • post approval management • statistical analysis, and • validation and design for lot release and stability testing.

A second in what CASSS projects will be an annual meeting is scheduled for November 8-9.

The Biopharmaceutical Emerging Best Practices Association (BEBPA) will hold a conference in Barcelona, Spain on September 29 to October 1 also focused exclusively on bioassays. Included will be a pre-conference workshop on the USP chapter revisions.

Downloads from the story:

- USP <1032> Design and Development of Biological Assays
- USP <1033> Biological Assay Validation
- USP <1034> Analysis of Biological Assays
- CASSS 2009 Bioassay Conference Program
- BEPBA Bioassay Conference Agenda

FDA Tabling Public Biosimilar Discussions While Digesting Complexities of New Legislation

FDA speakers at recent conferences have been open about their inability to discuss biosimilar issues at this time, while they digest the implications of the recently-passed Patient Protection and Affordable Care Act (PPACA).

At the AAPS National Biotechnology Conference in San Francisco in May, CDER's Office of Biotechnology Products Laboratory of Biochemistry Chief Emily Shacter explained to the audience that the focus of her talk changed from biosimilars to the role of stability in comparability assessments to accommodate this hiatus.

The PPACA, which was signed into law on March 23, is the health care law in which was embedded a pathway for regulation and approval of biosimilars. "I have talked about biosimilars for years, but now that we actually have a law it is much more complicated," Shacter noted.

The FDA biotech official explained that biosimilarity involves comparing products from different processes made by different manufacturers, whereas comparability involves comparing a protein made by the same manufacturer after process or formulation changes to determine if the protein is comparable to the product manufactured before the change.

"When you think about it," she noted, "you can use your imaginations to extrapolate" the principles of comparability "to try to see what kinds of science and approaches will be used for biomilars. The science is not going to change, but the regulatory pathways and some fundamental differences will exist."

Under the recently enacted PPACA, FDA was given the authority and responsibility to regulate biosimilar products, which are now a newly-defined class of medical products. FDA is "carefully evaluating" the newly enacted biosimilars provisions that are in the health care law "in order to best determine how to implement" them, Shacter explained.

She told the audience that there is a cross-center working group that has the responsibility for establishing policies and procedures for implementation of the provisions "in the manner that works in the best service of the public health." This group is being led by CDER Director Janet Woodcock and the acting head of the Center for Biologics, Karen Midthun.

Shacter explained that FDA is in the process of developing their implementation policies, and while those are ongoing "the agency does not want to give any false messages, misleading messages, or wrong messages. Quite frankly we are just not talking right now, because we do not want to create any more confusion."

Noting that the law is complicated and "it needs to be gone through very carefully," Shacter emphasized that FDA's goal is to "come up with policies that actually work" and accomplish the bill's objectives.

FDA has been indicating that it prefers to delay meetings with potential biosimilar sponsors until completion of this legislative review phase.

New FDA Draft Guidance Reduces Reporting Burden for CMC Postapproval Changes

A new draft guidance from FDA specifies 40 types of low-risk manufacturing changes that will now qualify for annual report filing and represents a significant step in the agency's effort to reduce the number of supplements that have to funnel through the Center for Drug Evaluation and Research (CDER) clearance process.

Following a discussion of the agency's basic approach to regulating manufacturing changes and its goal to reduce the filing burden, the draft "guidance for industry" on "CMC Postapproval Manufacturing Changes Reportable in Annual Reports" provides the list of changes qualifying for annual reporting in an appendix.

The 40 types of changes are divided into six categories: • components and composition • manufacturing sites • manufacturing process • specifications • container/closure system, and • miscellaneous changes.

Examples from the list of qualifying changes include: a new supplier of inactive ingredients; addition of barriers in a filling or compounding area; certain minor manufacturing process changes made under conditions as prescribed; some changes to a drug substance or drug product to comply with the official compendia; some changes in container/closure systems for nonsterile drug substances; and reduction of expiration dating for a drug product for reasons other than stability failures.

The guidance is applicable to both new and abbreviated new drug applications (NDAs/ANDAs). A background section describes the categories of changes in FDA's three-tiered classification system (major, moderate, and minor) and the regulatory filing requirements for each.

A "discussion" section notes that the number of CMC manufacturing supplements for NDAs and ANDAs has continued to increase over the last several years. FDA explains that, in connection with its Pharmaceutical Product Quality Initiative and risk-based approach to CMC review, it has evaluated the types of changes that have been submitted as supplements and determined that many of these "present very low risk to the quality of the product and do not need to be submitted in supplements."

The guidance clarifies that the list of changes provided is to be used in the context of specific products and circumstances to determine whether the proposed change has the potential to adversely impact that product. Based on that analysis, the "NDA or ANDA holder may decide that a change described in Appendix A would more appropriately be submitted as a supplement rather than in an annual report. We, therefore, consider this guidance to provide recommendations" as opposed to requirements for annual reporting.

The guidance includes a description of the requirements for an annual report and the governing regulations.

FDA is asking that public comments and suggestions regarding its new draft guidance be submitted within 90 days of its June 25 publication date in the *Federal Register*. For questions regarding the document contact CDER Office of Pharmaceutical Sciences Associate Director for Policy Jon Clark at 301-796-2400.

Change Flexibility Also in Focus in EU

Reduction of the reporting burden for postapproval manufacturing changes has been a target for some time in both the US and the EU, with each moving in the same direction, but at different paces.

The effort is intimately linked to the fostering of the ICH's QbD/Q8-10 paradigm and the concerted push by regulators in the ICH regions to encourage the flow of changes that are needed throughout the product lifecycle to support a continuous improvement framework.

Industry and regulators have been debating how to reduce the constraints created by their marketing applications on the one side and the GMP process validation and change control requirements on the other as part of the effort to unleash the power of science and technology to improve products and processes ***(IPQ, May 2010, pp. 24-25)***.

Speaking at an IFPAC workshop in February, Center for Drug Evaluation and Research (CDER) Office of New Drug Quality Assessment (ONDQA) Director Moheb Nasr previewed the now-released guidance and shared his vision for the future.

Nasr suggested that "sometime in the future rather than having three categories of supplements, you may have only two – changes that are low risk that could be reported in annual reports and the high risk changes that will still need to be submitted to the agency for approval."

Manufacturers who have a good understanding of their products and processes and a robust quality system "may not need to have this CBE 0 category, and some of these changes would be moved to annual report," the ONDQA director said.

> **In Europe, the encumbrances of its multi-state system have resulted in its lagging behind the US in instituting more progressive policies. However, the EU has been actively working to update its rules and guidance in this area, and in January released a pair of guidances spelling out revised variation filing expectations and procedures.**

At the February IFPAC workshop, EMA Scientific Administrator Evdokia Korakianiti stressed the importance that the improved flexibility in the revisions provide. "Postapproval regulatory flexibility was not possible until the end of 2009," she stated. "We are quite happy to say that now this has been taken care of."

Downloads from the story:

- CMC Postapproval Manufacturing Changes Reportable in Annual Reports
- EC Post-authorization Procedural Advice: Human Medicinal Products
- EC Q/A List for Submission of Variations

USP Seeks Help from Industry for its Monograph Modernization Effort

The US Pharmacopeia (USP) is seeking help from drug manufacturers in its effort to update monographs for small molecules and excipients that use outdated technology, have safety/environmental concerns, or are missing key aspects.

The focus for "modernization" of excipient monographs will be to replace relatively non-specific identification procedures with more specific tests such as infrared spectroscopy.

USP announced on May 28 that it is seeking proposals to replace or add procedures for the 200 small molecule monographs and 96 excipient monographs it has prioritized as most in need of updating.

USP emphasized that "in order to maintain consistency with FDA-approved control strategies, it prefers to receive submissions from manufacturers of FDA-approved prod-

ucts…or manufacturers intending to seek FDA approval." Submissions from other sources will be considered on a case-by-case basis and should follow ICH Q3 guidelines.

The announcement follows a resolution that was adopted at the 2010 USP convention in late April calling for the pharmacopeia to "strengthen its focus on core compendia activities," including updating monographs, during the next five year cycle.

USP CEO Roger Williams noted at the April meeting that "we have monograph backlogs in all our compendia including USP-NF – both missing monographs and monographs that need updating. USP is working diligently to solve this challenge."

Speaking at the same meeting, FDA Commissioner Margaret Hamburg underscored the importance of updating USP monographs, calling it "one of the most pressing tasks before us."

In an effort to focus the modernization effort, USP has developed a spreadsheet containing an initial list of the monographs for which it is seeking input, and intends to add more as the work progresses. The spreadsheet will be updated and posted on the USP website on the last Friday of each month.

Guidelines for submission of revisions and reference standard materials were included in the announcement.

Downloads from the story:

- May 28 USP press release
- Monograph modernization spreadsheet
- USP submission checklist
- USP guideline for suppliers of reference standard materials
- USP convention resolutions

Nanotechnology Under the Microscope at FDA

The rapidly expanding use of nanotechnology in therapeutic formulations is driving FDA to better define the regulatory and analytical framework needed to assess and address the potential concerns involved.

At the AAPS National Biotech meeting in San Francisco on May 19, FDA Center for Drug Evaluation and Research (CDER) research chemist Katherine Tyner elucidated some of the reasons for regulator caution regarding nanoparticles. "Nanoparticles have access to parts of the body other compounds do not," she emphasized. In addition, as particles get smaller their "surface properties dominate over bulk properties," and surface reactivity increases.

Addressing emerging regulatory considerations for nanoparticle-containing therapeutics at another recent conference, CDER Office of Pharmaceutical Science Research Policy Associate Director Nakissa Sadrieh pointed to the analytical uncertainties on the horizon. Sadrieh is chair of CDER's Nanotechnology Working Group that is exploring what further guidance and policy may be needed in the area.

"What I guess we don't know right now is for the type of nanoparticle that we may be looking at," for example, a dendrimer or nanotube, "what are going to be the important properties that we need to know [and] what is the best way for us to be able to evaluate those properties?" she said. "If somebody could actually generate a table with the particle, the property and the methods that one would use to actually evaluate or characterize, that would be a great help to be able to adequately review these products and to know whether there are issues that we need to look at or not."

Another area of concern, she added, is that the properties of nanoparticles may be "quite different from the normal properties that we look at right now for small molecules, [e.g.] electron microscopy methods. These are not methods that have been used in the past in manufacturing. So we need to find ways of being able to identify methods that are going to be adaptable to be able to actually develop drugs."

Sadrieh explained that there is an agency-wide guidance that is being developed to cover the use of nanoscale materials in FDA-regulated products.

[Editor's note: The opportunities and challenges around nanotechnology development and regulation, including Sadrieh's extended analysis, are explored in the May 2010 issue of IPQ as part of an in-depth report on the changing CMC landscape.]

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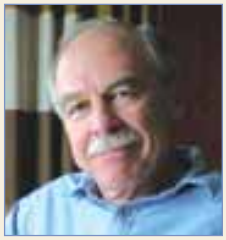

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Particulates in Biotech Products: Standard Setting Effort Gaining Traction

The development of measurement standards for visible and sub-visible particles in parenteral products is drawing attention from regulators and industry at biotech conferences.

At the AAPS National Biotech meeting in San Francisco on May 18, FDA Office of Biological Products Division of Therapeutic Proteins Deputy Director Barry Cherney underscored the need for particle standards.

Noting the lack of standards for protein particles, Cherney pointed out that an effort is taking shape in which FDA, The National Institute of Standards and Technology (NIST), and industry will partner to develop these much-needed standards. A proposal by NIST to assist on this front drew discussion at CASSS' annual WCBP conference in January.

At the AAPS San Francisco meeting, FDA Center for Drug Evaluation and Research (CDER) Principal Investigator and Senior Regulatory Research Officer, Jack Ragheb, commented on why FDA is concerned about particles. He cited the potential for immunogenicity, and added that the level of particles in an injectable product also serves as "a sentinel of product quality."

[Editor's note: The opportunities and challenges around standards development for biotech product particulates and NIST's potential role are explored in the May 2010 issue of IPQ as part of its analysis of the changing CMC landscape.]

FDA Wants to See More Transparency Between Drug Companies and Contractors on Sponsor's Application and Contractor's GMP Status

FDA investigators will be looking for more transparency between a sponsor and its contract sites regarding the sponsor's drug application commitments and the contractor's plant-wide GMP status, FDA Cincinnati District Investigator and Preapproval Manager Kathleen Culver emphasized at a Global Outsourcing Conference at Xavier University on June 14.

Drug firms that outsource manufacturing and testing activities should share the appropriate sections of their drug applications with the contract firms to avoid misunderstandings, facilitate site compliance with the commitments in the application and aid review and pre-approval inspections, Culver emphasized. "I am looking for this when I do the pre-approval inspection to assure there are no misunderstandings and that we will not end up with adulterated or misbranded drug product," she explained.

In turn, where the contract firm manufactures for multiple clients, it is important that the sponsor have access to other client's audit findings and records that shed light on the contractor's overall quality system, Culver stressed.

"How can you really thoroughly audit a GMP system when you cannot review all the deviations, investigations or data generated in that system?" the FDA investigator asked. She stressed the importance of performing thorough audits of the quality systems during the contract manufacturer selection process.

Application Commitments Should be Shared with Contractors

"Transparency between the sponsor and the contract site regarding drug application commitments is crucial," Culver emphasized. She pointed out that "sometimes this transparency about these commitments in the drug application is missing. I think this really needs to change if the contracting industry is going to thrive and continue."

The field official called on industry to "reconsider the current practice of not providing copies of the drug application to your contract site, or at least the sections of the drug application that apply to what that contract site will be doing for you." She reminded the attendees that the commitments in the drug application are legally binding and must be met once the application is approved.

Culver pointed to the FDA investigator concern when inspecting a contract site with the finding that the contractor had not been supplied with the CMC section of the application, or at least the parts applicable to the work being done at the site.

"This lack of full disclosure between the sponsor and the contract site can impede my pre-approval inspection because from the get-go I do not have that assurance that this contract site knows what the commitments are in the drug application," she explained. "I have to figure that out before I can start evaluating GMPs."

"It is becoming a big red flag for me," Culver said. "How can the contract site assure they are meeting the drug application commitments if they do not have a copy of these commitments? What if the NDA/ANDA sponsor fails to disclose critical drug application information to the contract site? We see this happen."

Culver pointed out that the only party ever likely to discover that the sponsor has omitted critical information to the contract site is an FDA investigator when auditing against the application.

When a contract site does not have a copy of the drug application commitments applicable to their contracted responsibilities, FDA must conduct the GMP audit and also audit the integrity of the information transfer process between the sponsor and the contract site. "Is it really FDA's job to manage the disclosure process of critical information to your contract site?" she asked, replying "I do not think it is."

Culver stressed that transparency over the application commitments is important to the compliance status of both the sponsors and the contract sites.

"I would like to suggest to you all today that it is time to re-examine this business practice that some of you might have of not providing the drug application information directly to the contract site in light of your collective responsibility to assure that the commitments in that drug application are met," she proposed. "The transparency it adds to the drug approval inspection and review process for contract sites and for FDA is tremendous when all parties are working from that same document, that key legally-binding document, the filed drug application."

Confidentiality Agreements Can Create GMP Blind Spots

Culver noted that sponsors performing audits at contract manufacturing or testing sites are at a disadvantage when they cannot review all the records because of confidentiality agreements with other clients.

The FDA field preapproval manager is "starting to be concerned there is a huge blind spot possibly being created…. What if there is evidence of a serious GMP system failure in client A's records, but client B cannot review those records?"

Culver cited an example of a recent inspection of the raw materials system at a contract manufacturing site in which she found a deviation regarding the use of an excipient from an unapproved supplier. Although the deviation was approved and the product released, no root cause was identified.

The question became, she noted, "are the raw material controls in the SOPs inadequate to prevent this from happening again? Or are the raw material controls written in the SOPs really adequate but people are not actually following them?"

Culver's investigation revealed that the excipient was not available from the approved supplier, so the contactor sourced it from an unapproved supplier to allow manufacturing to continue in violation of the firm's SOPs. "If you just sat down and read all the SOPs that said anything about a raw material control, you would be misled into believing everything was fine," the investigator pointed out.

She noted that the major incident involving melamine in pet food a few years ago was analogous, also stemming from the use of an unapproved supplier.

In the end, she told the drug sponsors in the audience, "it is your product. Your name is on the label. You are liable. You are responsible. You have to make sure your audits of these contract firms are robust enough and rigorous enough to find these serious system deficiencies if they exist despite all the confidentiality agreements."

Selecting Contract Sites on Cost Could be Costly

Culver shared her concern about the practice of selecting contract sites on the basis of cost alone, emphasizing the importance of rigorous GMP system inspections in the contract site selection process.

"Some sponsors I hear select their contract sites based on unit dose cost alone. I do not think that this is a good idea." She provided a mock example to illustrate the point.

In setting up the example, the FDA inspector explained that the agency's Compliance Policy Guide on drug manufacturing inspections (CPG 7356.002) lays out the FDA roadmap for conducting routine GMP inspections of drug firms, and also prescribes how to classify the inspection after it is completed. According to the CPG, when performing a systems inspection, if one system is found to be out of control, the facility as a whole is deemed to be out of control.

Culver then walked the audience through the example involving a routine inspection at the "Lowest-Cost Tablet Manufacturer" (LCTM) in Cincinnati, Ohio. "We go out and do this inspection, we cover the quality system and at least one other system, and we find serious deficiencies in the quality system, and a 483 is issued."

The investigations branch classifies this routine inspection as Official Action Indicated (OAI), and a warning letter is recommended. In FDA's Field Accomplishment and Compliance Tracking System (FACTS) on the company's profile screen, "everything is unacceptable because we did a system inspection," Culver explained. Next the supervisor confirms on that screen in FACTS that those profiles are unacceptable.

A compliance officer then reviews the report and all the records and drafts the warning letter and forwards this case to CDER's Office of Compliance in Washington for final review and approval. That compliance officer also goes into that profile screen for this company in the FACTS system and again confirms all product lines are unacceptable.

The warning letter is then approved and issued. The profiles remain unacceptable until corrections are made and verified by FDA.

"Meanwhile," Culver explained, "up in CDER, a drug application is being reviewed for a tablet. The sponsor of the drug application contracted out the manufacturing to LCTM. The sponsor selected [this manufacturer] about two years ago based on unit dose cost alone. Of course it takes some time to negotiate the contract, make the submission lots, do the stability testing, assemble the application and send it in. Months or maybe a couple of years have gone by since they selected them," she said.

As CDER begins to process this ANDA or NDA, one of the things they have to do is look at the GMP status of every company that is associated with making or testing the product, Culver explained. For this application, there is a GMP status enquiry for LCTM which goes to the CDER Office of Compliance. OC forwards it to the Cincinnati district office, which recommends withholding approval for this drug application and for any new products at this facility until the corrections are made and the profiles are acceptable.

"What is the cost impact of selecting LCTM to make your drug product now?" Culver queried. "What does a one month, two month, six month, twelve month or eighteen month delay in approval of your application cost?"

She acknowledged that cost is always a factor in any business dealing, but "if it is the only thing you are looking at, you are going to get burned by the systems inspection eventually if that contract site goes out of compliance."

"Some people might say that FDA is being unreasonable to automatically recommend withhold for this application just because that contract site messed up on somebody else's products," Culver noted. However, using a systems inspection approach, "what we know is that it does not make any sense to give approval for another application at this contract manufacturing site that is out of control."

"They have shown us that their systems are out of control and potentially or definitely are producing adulterated or misbranded drug products. Our thinking is that if we add another new product into that mix and they go through that dysfunctional system, we are going to get adulterated or misbranded drug product…. They need to fix their systems first and then they can add new products into that system once it is under control."

The field official offered a list of questions for sponsor firms to consider when selecting a contract site:

- "Does this site have a really good GMP track record for consecutive inspections? Do they stay in compliance? If they stay in compliance that means they must have good systems that are under control.
- If they have those robust GMP systems, those six systems, do they have good quality assurance oversight of the operations and the products?
- Do they have a well-controlled raw materials system?
- Do they have a production system that is under tight control?
- Is the facility and the equipment well-maintained?
- Is the lab capable of generating scientific and sound test data?
- Are the packaging and labeling systems well-defined and controlled?"

Culver commented that "once you know the answers to those questions and you have answers you are comfortable

with – that these systems meet GMPs – then cost is obviously a factor." However, she cautioned, "it is important that you evaluate GMP systems and not just cost when you are selecting your contract sites."

Sponsors and Contract Firms Share in Results

Noting the intimate relationship between sponsors and contract sites, Culver cautioned that under FDA's enhanced enforcement approach, contractor compliance problems may lead to investigations of sponsors.

"Many times there are very good partnerships between sponsors and contract sites and they make very high quality drug products. Of course that is what we all want," Culver affirmed.

However, she commented, "I do have to start wondering how FDA is going to manage this or react when we have a commercial drug product produced at a contract firm under the sponsor's oversight and it is found to be non-compliant – it is adulterated or misbranded. Aren't both parties really responsible?"

Pointing to the joint responsibility the two parties have for assuring the drug product meets the filed specifications, Culver said she is starting to wonder "if the contract site gets a warning letter because the drug product that they made for that sponsor is adulterated or misbranded, then maybe shouldn't we also go after the sponsor?"

On the clinical side this focus of attention on the sponsor is already taking place. A recent FDA Bioresearch Monitoring Program inspection resulted in a warning letter issued to Pfizer in April for "failure to ensure proper monitoring of the investigation" at a contract clinical investigation site. Johnson and Johnson Pharmaceutical Research and Development received a similar letter as a study sponsor in August of last year.

Culver noted that the FDA deputy chief counsel for litigation has been warning industry about increasing misdemeanor prosecutions against responsible corporate executives under the FD&C Act.

"I do not think they have him out here giving those speeches for no good reason, folks," she emphasized. "That is what I am assimilating down here on the front lines – that I need to pay more attention to who is making the decisions at the contract sites, and possibly at the sponsor. Don't you think responsible executives could be found both at the sponsor and the contract site? I am starting to think yes."

Downloads from the story:

- Kathleen Culver's presentation at Xavier University
- Pfizer April 2010 BIMO warning letter
- J&J August 2009 BIMO Warning letter

FDA Shares Concerns, Expectations Regarding Pharma Cargo Thefts

FDA sent a letter to medical companies expressing concern about the increase in cargo thefts of FDA-regulated drug products and clarifying its expectations from companies and the agency's role when thefts occur.

In the letter, Acting Assistant Commissioner for Regulatory Affairs Michael Chappell urged stakeholders to "immediately" review security throughout their supply chains from manufacturing through distribution to the point of sale, stating they should be "one step ahead of thieves" in securing warehouses and transportation.

Chappell emphasized that drug manufacturers and others in the pharmaceutical supply chain "have a fundamental responsibility to continuously review their warehouse physical security and security practices and procedures for transporting products to ensure that measures are in place to minimize the risk of warehouse and cargo theft."

The letter directs firms to contact FDA's Office of Criminal Investigation when a theft occurs, and provides contact information and a list of questions an FDA district office may ask about the incident. It notes that prompt public notification of a theft is a critical step in protecting public health, and strongly encourages companies to issue press releases as soon as possible after such an incident.

Download from the story:

- FDA Letter regarding cargo thefts