

# ◆ BioQuality <sup>TM</sup> ◆

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## FEATURE ARTICLE

### 2011— The Year in Review

#### QBD, Comparability, FDA Priorities, Avastin and Biosimilars are among Hot Topics

2011 was a year in which industry, the FDA and other regulatory agencies continued to grow and change to meet the challenges of an increasingly-global regulatory landscape. In this regard, FDA released its five year plan outlining strategic priorities for the next half decade to address these and other challenges. Among the hottest of other hot topics were making changes and showing comparability, the seemingly-ubiquitous topic of Quality by Design (QbD), the increasingly-omnipresent topic of Biosimilars, compliance hotspots, FDA-EMA inspectional cooperation and mutual

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***“Preclinical to phase 1, and phase 2 to phase 3, are more qualitative comparisons, but when doing post-approval changes, we use all commercially available lots from all facilities to guard against drift and these are quantitative analysis.” --WCBP 2011 comparability workshop attendee from Genentech***

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recognition, and the "accelerated" disapproval of the accelerated approval of the monoclonal antibody Avastin for one of its indications by FDA, but not EMA. Follow along as we review that past year and see what lessons for the future it might hold.

#### **FDA, the Way Forward**

Government agencies and corporations love 5 year plans, and FDA re-

vealed the final version of its strategic priorities through 2015 during 2011--5 priorities for 5 years. These priorities are: 1) To advance regulatory science and innovation; 2) To strengthen the safety and integrity of the global supply chain; 3) To strengthen compliance and enforcement activities to support public health; 4) To address unmet public health needs of special populations; 5) To advance medical countermeasures and emergency preparedness. The document bears the title *Strategic Priorities 2011 – 2015: Responding to the Public Health Challenges of the 21st Century*, and links to the various sections of the document can be found at <http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm245959.htm>

Current FDA Commissioner Dr. Margaret Hamburg wrote an informa-

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***“We expect primary sequence to be the same. Although the guideline does not forbid changing expression system, we have language to encourage using the same expression system as the innovator. We would hesitate to approve a biosimilar in a novel expression system.”--Dr. Anthony Ridgeway, Health Canada***

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tive preface to the Strategic Priorities Document and following are quotes of some of her most revealing statements.

- “It’s no secret that the FDA’s responsibilities have increased sig-

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#### **BioQuality Goes Weekly!**

We are now sending you weekly BioQuality update editions three times each month, in addition to the monthly edition you are now receiving. There will be no additional charge for this enhanced service. We just want to be sure you get the knowledge you need in a timely fashion.

## 2011— The Year in Review

(Continued from page 1)

nificantly over the past several years. We must continue to build a stronger, more effective agency and, as this document outlines, do so in several specific ways.”

- “Today, it is clear that the FDA’s job is fundamentally different – and far more complex than it was even a few years ago. We will address these challenges and aim to

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***“I would argue that it is better to invest to assure quality rather than to pay the large penalties that we have seen being paid because of poorly-designed products.”-- Moheb***

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fulfill our mission by embracing innovation and actively pursuing partnerships with federal, state, and local agencies, international authorities, academia, non-government organizations, and the private sector.”

- “I would like to emphasize one priority in particular: Advancing Regulatory Science and Innovation. Science underlies everything we do at this agency and to serve the public health we must have the capacity to effectively oversee the translation of breakthrough discoveries in science into innovative, safe, and effective products and life-saving therapies for the people who need them most.”
- “We cannot achieve our vision and address the challenges of the 21st century by working alone. To make rapid and efficient improvements in public health and drive innovation, we must harness the best ideas from a broad range of stakeholders and leverage resources through collaboration with other federal, state, and local regulatory and public health agencies; nongovernment organizations; consumer and patient organizations; academic medical centers and research universities; the private sector; and the public.”

See BioQuality 16(5), April/May 2011 for more details on FDA’s 5 year vision.

On a similar theme, FDA’s former Director of Compliance and current New Jersey District Office Compliance Director Nanci Rolli provided insight into how the agency ranks the seriousness of deficiencies in order to set its enforcement priorities. See Table 2 for a checklist we prepared for you from this talk, and see BioQuality 16(10), October 2011 for a detailed discussion of this important topic.

### Going Through Those Changes

Kicking off the quality/regulatory year was the always-excellent WCBP meeting in January. Following the aforementioned theme of change, a major topic was the changes taking place in how changes are made and how, when necessary, comparability can be shown between drug substance and product before and after the change (see BioQuality 16(2), February, 2011). Evidence of the maturation of our industry could be seen in the shift of discussion away from comparability during clinical trials and towards comparability of commercial products pre- and post-manufacturing changes, where change must be tightly controlled, and the mandate is not to change the safety and efficacy profiles of the product. “Preclinical to phase 1, and phase 2 to phase 3, are more qualitative comparisons, but when doing post-approval changes, we use all commercially available lots from all facilities to guard against drift and these are quantitative analysis,” a workshop attendee from Genentech informed the audience. Expanding on the clinical/post commercialization comparison he continued, “The clinical comparability studies is more an analysis looking for the appearance of something new. It is more of a safety analysis. The comparability question you are asking is: “Is the material the same or different and if it

is different — what does this mean for the patient?” See Table 1 for a comparison of change procedures in Canada, the EU, and the US

### Biosimilars

Comparability was also on the minds of those developing biosimilars, aka follow-on biologics, follow-on protein products (fopps), and subsequent-entry biologics (see BioQuality 16(2), February, 2011). At WCBP, Dr. Martin Schiestl from Sandoz reminded attendees that for biosimilar products there are two comparability packages—a physicochemical characterization and a biological characterization. In fact, he went on, “These comparability studies are one of the major outputs of biosimilar product development.” On the subject of how comparable the biosimilar must be to the innovator product, Dr. Anthony Ridgeway, a regulator from Health Canada stated, “We expect primary sequence to be the same. Although the guideline does not forbid changing expression system, we have language to encourage using the same expression system as the innovator. We would hesitate to approve a biosimilar in a novel expression system.”

Biosimilars were also one of the dominant topics at the 2011 AAPS National Biotechnology Conference. Current opinion on biosimilars seems to be divided into two camps: 1) those with products to protect, who are all clamoring that biopharmaceuticals are too complex to be copied and 2) those with products to develop, who naturally espouse the opinion that biosimilars are badly needed and that the complexity can be dealt with successfully. Both camps are making not only self-serving statements, but also valid scientific and economic points, and you can read about this creative tension in BioQuality 16(7), July 2011 .

### Quality by Design (QbD): Invest now or pay later

QbD is one of FDA’s Quality Initiatives, the now almost 8 year old at-

## 2011— The Year in Review

tempt by the agency to encourage the early adoption of new technological advances by the pharmaceutical industry; facilitate industry application of modern quality management techniques, including implementation of quality systems approaches; encourage implementation of risk-based approaches; ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science, and enhance the consistency and coordination of FDA's drug quality regulatory programs. If you need a refresher on what QbD is, see the box on page 4. Moheb Nasr, Ph.D from CDER's Office of New Drug Quality Assessment summarized FDA's position on QbD saying "Some of you may argue at times, that it is costly to invest in good development and manufacturing, into Quality by Design and et cetera. I would argue that it is better to invest to assure quality rather than to pay the large penalties that we have seen being paid because of poorly-designed products. That's basically it--poorly designed products and lack of robust quality systems--these are the two main effects." See BioQuality 16(3) March 2011, for a detailed report on QbD.

### **Avastin There! (but not here)**

Around mid-year, FDA announced its intention to remove Genentech's monoclonal antibody Avastin's indication, in combination with paclitaxel, for metastatic breast cancer (MBC) not for safety concerns, but due to lack of efficacy. The MBC approval was an accelerated approval, and the disapproval happened with dispatch also. On November 18, the agency officially announced the revocation of approval. This however, was only one of the product's indications authorized for marketing in the US, and Avastin remains on the market for several other cancer indications. Interestingly, EMA did not follow FDA on this decision, but re-affirmed Avastin's marketing authorization for MBC. See BioQuality 16(6), June 2011 for and 16(11) No-

vember 2011 for details).

At the time, we expressed the following opinion on this decision by FDA and feel it still holds true.

Editorial Opinion: Kudos for Dr. Hamburg and FDA/CDER. So, what might be the broader implications of this decision? This author would like to aver that this landmark decision and the process leading to it are a positive thing for patients, the public health, and ultimately industry. Accelerated approvals are granted to treat life-threatening conditions lacking other therapies and when there are insufficient data to justify a regular approval, but enough evidence to provide a reasonable hope that, upon further testing, safety and efficacy will be confirmed. Implicit in this accelerated approval process is the certainty that some medicines will fulfill that hope and, more importantly, some will not.

Therefore, a timely, effective mechanism must exist to revoke the provisional approval of therapies which prove not to be effective. Otherwise, as Dr. Samuel Johnson might have put it, what we would have is "the triumph of hope over experience," and that ill serves the patients and the public health. These events are positive because they provide evidence that the process works and that FDA and the Commissioner are indeed able to make such difficult decisions by following this choreographed sequence of events.

But this revocation of approval is also a good thing for industry as well. The accelerated approval process is an important means by which companies can gain revenue on drugs which have only been partially tested. Most, if not all, FDA staff and especially reviewers, always have the patient and the public health foremost in their minds and thusly, these concerns inform their decisions. Now, the key question is: would FDA, and especially reviewers, readily, or ever, grant an accelerated approval if they feared that a drug which proved inefficacious upon further study could not be re-

moved from the market? Probably, not, in this writer's opinion, which would deprive industry of an important means for successfully bringing new medicines to market.

### **Other notable items from 2011**

Following are some other 2011 articles you might want to review. If you are a subscriber and are missing any issues, you can get them free from the subscriber area of our website [www.bioquality.biz](http://www.bioquality.biz). If you do not yet have a password, contact Cori at [bq\\_editor@surewest.net](mailto:bq_editor@surewest.net) and she will be happy to set up your access.

- FDA and EMA are giving mutual recognition of each others' inspections another try, and this time it looks like they may succeed. See the Feature Article in our December, 2011 issue, Vol. 16(12).
- A study was released discussing the high failure rates of drugs during phases 2 and 3 in Europe. See BioQuality 16(12), December 2011, page 5 for details and a discussion.
- Brazil's Agência Nacional de Vigilância Sanitária (ANVISA) announced the establishment of a new office for biological medicines. See BioQuality 16(10), October 2011, page 5.
- Bioanalytical lab Cetero found itself in regulatory hot water. The FDA averred that Cetero engaged in pervasive and systemic violations that called into question data generated over a 5 year period, while Cetero thought the violations were isolated incidents that call only a small amount of data into question. See the Feature Article in our August/September, 2011 issue, Vol. 16(8/9).
- Australian flu vaccine manufacturer CSL, Ltd. also found itself in the soup, receiving an FDA Warning Letter signed by FDA Office of Compliance and Biologics Quality Director Mary A. Malarkey that stated, in part "The deficiencies described in the Form FDA 483

**WHAT IS QBD?**

A QUICK REFRESHER

From ICH Q8(R2)

- A systematic approach to development
- Begins with predefined objectives
- Emphasizes product and process understanding and process control
- Based on sound science and quality risk management

Why QbD?

- Higher level of assurance of product quality
- Efficiency for industry and regulators
- Minimize/eliminate potential compliance actions, costly penalties, and recalls
- Opportunities for continuous improvement
- Streamline post-approval manufacturing changes and regulatory processes
- More focused pre-approval (PAI) and post-approval cGMP inspections

and this letter are an indication of your Quality Control Unit not fulfilling its responsibility to assure the identity, strength, quality, and purity of your monovalent influenza bulks and final drug products.” See BioQuality 16(7), July 2011, page 3.

- Annex 11, the computerized systems annex to the European GMPs, took effect in mid-2011. See BioQuality 16(6), June 2011, pages 3-4 for a bullet-point summary.
- A CASSS WCBP Workshop provided valuable tips for product development from FDA and industry representatives, including a list--with examples, presented by Dr. Ruth Cordoba-Rodriguez from FDA's Office of Biotechnology Products, of what not to do during development. See BioQuality 16 (3), March 2011, page 4.

Table 1: Change Procedures in Canada, Europe and the US (adapted from BioQuality 16(2), February 2011)

Type of Change	Canadian Procedure (Health Canada)	European Procedure (EMA)	US Procedure (FDA)
Minor	<b>Called Level III (Annual Notification) :</b> Data not submitted to regulators, but is available within 30 days if requested, and <b>Level IV (Record of Change)</b> changes can be made without review by Health Canada but records of the change should be maintained by firm.	<b>Called Type 1A(anin) - annual notification and 1A(in) Immediate notification:</b> Variations which do not require immediate notification (1A(anin)) and those which do require immediate notification (1A(in)). This last is called a do and tell procedure, notification may be submitted by the marketing authorisation holder (MAH) within 12 months of implementation.	<b>Called Annual Report (AR):</b> The change is implemented, data is collected and put into an annual review.
Moderate	<b>Called Level II or Notifiable Change (NC):</b> Changes along with supporting data should be filed and changes cannot be implemented until a No Objection Letter (NOL) has been issued.	<b>Called Type 1B:</b> These changes can only be implemented after receiving a positive notification from the competent regulatory authority. Applicant must contact the Reference Member State at least 7 days prior to the submission to obtain current notification procedure number. 30 day clock for review.	<b>Called Change being effected (CBE) and CBE + 30:</b> Data is collected, submitted to the FDA. If it is a CBE the manufacturer does not wait but immediately implements the change. If it is a CBE+30 the change can be implemented after 30 days unless a negative opinion is sent by the agency.
Major	<b>Called Level 1 (Supplemental Changes)</b> Changes and supporting data should be submitted to HC as a Supplemental New Drug Submission (SNDS) or Supplemental Abbreviated New Drug Submission (SANDS). The change may not be implemented by the sponsor until a Notice of Compliance has been issued.	<b>Called Type II:</b> This is a supplement and usually has a 60 day review time, although the regulators can request a 90-day assessment time scale. If there is a safety issue involved the review time may be shortened to 30 days.	<b>Called a Pre-Approval Supplement:</b> The firm must put together the data to support the change and wait for FDA approval before implementing the change

**Table 2: A Checklist of Questions for Assessing a 483 Observation's Significance**

(from BioQuality 16(10), October 2011)

- To what type of product does the observation refer?
- What is the product used for?
- What degree of difficulty is associated with the manufacturing of the product?
- What is the targeted market?
- Is the product for pediatric use? Pediatric use generally makes an observation more significant.
- What is the magnitude of the failure? Is it just barely out or is it way out?
- What is the scope of the failure? Is it for a low or high percentage of lots?
- Does the observation represent a failure of one of the six inspection systems?
- Is the systems failure the type that would allow inferior product?
- Is the observation for a marketed product?
- Are there products in distribution that do not meet one or more specifications
- What factors are contributing to this observation?
- How does the observation impact other products?
- Does the observation reflect lack of documentation, inadequate documentation or failure to document at the time of occurrence?
- Does the observation involve: Out of Specification Results? Retesting? Re-sampling?
- Does the observation seem to involve testing into compliance?
- Does the observation involve qualification, cleaning, or maintenance of critical equipment?
- Is the equipment deficiency associated with another failure down the line?
- Does the observation involve packaging or labeling? Packaging observations tend to be more significant.
- Is the observation associated with or can it be tied back to one or more complaints or recalls?
- Does the observation involve a stability failure?
- Does the observation involve the firm not following its own Procedures or Protocols?
- Does the observation involve lack of notification of Production about QC Laboratory findings?
- Does the observation relate to Media Fills for an Aseptic Product?
- Does the observation reflect a pattern or a trend of deficiencies?
- Does the observation reflect a lack of Change Control?
- Does the observation involve deviations, discrepancies, investigations or retests associated with the validation batches?
- Does the observation involve changing specifications after failure to meet them?
- Does the observation involve failure to determine, or inadequate determination of, critical process parameters?
- Does the observation involve inadequate or deficient Media Fills for an aseptic product
- Does the observation involve personnel in an aseptic filling area who have not participated in a media fill?
- Does the observation involve inadequate Environmental Monitoring or Sampling for an aseptic product?
- Does the observation involve failure to perform or inadequate investigations?
- Does the observation relate to a process which appears to be out of control or drifting?
- Does the observation involve failure to perform or inadequate Annual Product Reviews?
- Does the observation involve failure to send or the untimely sending of Field Alerts (FAs) or Biological Product Deviation Reports (BPDRs)?
- Does the observation involve failure of the Quality Unit to perform its duties as specified by the CGMP Regulations?
- Does the observation relate to the firm not following its own official Policies and Procedures?
- Has this issue been seen before with this firm? Is/was there a promised remediation? Has the remediation/CAPA been: Implemented? Effective?

## EUROPEAN NEWS

**The International Pharmaceutical Excipients Council - Europe** (IPEC-Europe) has published a revised version of its 2008 Good Distribution Practice (GDP) Audit Guideline for Pharmaceutical Excipients. This guideline is intended to be used as the audit tool for evaluation of excipient distributors' compliance with GDPs, which are detailed in the IPEC GDP Guideline for Pharmaceutical Excipients (2006). To see the revised audit tool, which is designed in a questionnaire format to facilitate auditing, go to: [http://ipec-europe.org/UPLOADS/IPEC\\_Europe\\_GDP\\_Audit\\_Guide\\_-\\_Revision\\_2011\\_final.pdf](http://ipec-europe.org/UPLOADS/IPEC_Europe_GDP_Audit_Guide_-_Revision_2011_final.pdf)  
To see the 2006 GDP Guideline: [http://www.ipec-europe.org/UPLOADS/GDP\\_Guide\\_2006\(1\).pdf](http://www.ipec-europe.org/UPLOADS/GDP_Guide_2006(1).pdf).

### **Biosimilars**

The European Medicines Agency (EMA) has released, for public consultation, a guideline on testing of biosimilar medicines containing Interferon Beta, which are used to treat patients with multiple sclerosis (MS). Currently, there are three different medicinal products containing recombinant IFN- $\beta$  approved in the EU for the first-line treatment of MS, and they all differ with respect to their molecular structure, injection route, recommended posology (determination of appropriate dose), and MS indications.

The guideline, which was adopted by the Agency's Committee for Medicinal Products for Human Use (CHMP) in December 2011, covers the non-clinical and clinical requirements for interferon beta-containing medicines that claim to be similar to another interferon beta already on the market. The guideline is open for consultation (comment) until 31-May, 2012.

A web page with a download link for the guideline and for the form for submission of comments can be found by pointing your browser to: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2012/01/news\\_detail\\_001423.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/01/news_detail_001423.jsp&mid=WC0b01ac058004d5c1)

### **Gene Therapy**

EMA has released the "Work plan for

the Gene Therapy Working Party 2012," which was adopted in December, 2011. Planned activities include the following:

- Finalization and release for public consultation of the parent gene therapy guideline, "Note for Guidance on Quality, Preclinical, and Clinical Aspects of Gene Transfer Medicinal Products" (CPMP/BWP/3088/99)
- Public consultation and revision of the draft "Guideline on the risk-based approach according to annex I, part IV of directive 2001/83/EC applied to advanced therapy medicinal products"
- Finalization of the Guideline on quality, non clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CHMP/GTWP/671639/2008)
- Concept Papers, or consideration of the need for a Concept Paper on:
  - ⇒ The quality requirements for investigational gene therapy medicinal products before first clinical use
  - ⇒ Insertional mutagenesis issues DNA vaccines
- Initiation of a navigating map on EMA website to facilitate the search for Gene Therapy Working Party (GTWP) applicable guidelines
- Preparation of scientific reports to address the following topics:
  - ⇒ Consequences of pre-existing immunity of vectors
  - ⇒ Role and need of immunosuppression in conjunction with gene therapy
  - ⇒ Genetic technology methods to produce induced pluripotent stem cells (virtual expert meeting)
  - ⇒ Technology/methods for integration site directed gene therapy
  - ⇒ Technology/methods for sequencing

To see the GTWP Work Plan: [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Work\\_programme/2010/01/WC500059113.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2010/01/WC500059113.pdf)

### **Cell-based Products**

EMA has also released the 2012 Work

Plan for the Cell-based products working party. Also adopted in December, 2011, the Work Plan includes:

- Public consultation and revision, jointly with the GTWP, of the draft "Guideline on the risk-based approach according to annex I, part IV of directive 2001/83/EC applied to advanced therapy medicinal products"
- Release for consultation, revision, and finalization of a Reflection Paper on clinical aspects specific to tissue engineered products
- Development of a draft Reflection Paper on comparability of cell-based medicinal products covering issues during development, the pre-authorization phase, and variations during the post-authorization phase
- A Concept Paper/Reflection Paper on the need to develop guidance for cell-based investigational medicinal products
- Development of a flowchart of existing guidelines for cell-based medicinal products
- Preparation of Scientific Reports on standardization of raw materials for production of cell-based medicinal products
- Collection of information on hot topics in the cell-based area (e.g. mesenchymal stem cells and tumorigenicity, immunotherapeutic products)

### **COMING SOON...**

- Analysis of product approvals for 2011
- More about Biosimilar
- 483 year in review
- Analysis of USP Bioassay Chapters
- Breaking News and Hot Topics
- And much more
- Stay ahead of the curve with BioQuality

## FDA NEWS

**The FDA homepage** ([www.fda.gov](http://www.fda.gov)) has a new look (yes, again...). It has a nice clean look, but don't worry, if it is not to your taste, there will probably be a re-vamp again soon. And the good news is that this time all your old bookmarks to your favorite places inside should still work.

### " I'd like to introduce you to FDA

**Voice** – FDA's newest communications vehicle designed to give you information from behind the scenes here at FDA, and in our own words," wrote FDA commissioner Margaret Hamburg, M.D. in the December 23rd first post on the agency's new blog. She went on to write about the blog, which seems thus far to be aimed mainly at consumers, "FDA Voice is a new forum for us. Although I am writing the first blog post, in the future you will see posts from a wide range of FDA officials and staff, including scientists and public health professionals, employed at headquarters here in the Washington DC area, across the United States, and in posts abroad in countries as far away as China and India." To see the blog: <https://blogs.fda.gov/fdavoic/>

**FDA has released the final version** of its Current Good Tissue Practice Guidance, which was released in draft form in January, 2009. We will be bringing you a summary of this document in the January monthly issue of BioQuality. To see the new final guidance: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM285223.pdf>

CBER has released a list of Draft Guidelines it plans to publish during calendar year 2012. The list of 6 documents contains the following three Guidelines that may be of interest to BioQuality Readers:

⇒ Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture

- ⇒ Preclinical Safety Assessment of Investigational Cellular and Gene Therapy Products
- ⇒ Early Clinical Trials With Live Biotherapeutic Products: Chemistry, Manufacturing, and Control Information

See the complete list at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/UCM269057.pdf>

### More On FDA's New Website

**In a January post to his Eye on FDA blog**, Mark Senak discusses the new look of FDA's website and FDA's new blog (see FDA News, above). Here are some quotes from the post (which can be seen in full at <http://www.eyeonfda.com/>):

- " The old version was kind of like your grandma's attic – there was a lot of stuff there and you couldn't see anything because you had to see everything. It looked old. It was like being in a bargain store where there are too many bargains."
- "The new version is very nice and neat. It isn't like someone came into the attic and cleaned it up and put things where they belong, it is like they pulled a dumpster up to the house, emptied it all in there, and then went to IKEA and filled with all nice, new neat stuff. The most compelling feature is that the landing page is CLEAN and follows a logic. Tabs are nicely displayed at the top to feature each area in which the FDA operates and there are some nifty icons to the right that direct distinct stakeholders – consumers and patients, health professionals, scientists and researchers and finally industry, though not one for media which might have been a good idea. The information is grouped and organized and the space is not crowded."

### Biotech CEOs Sound Off on FDA

**On his Pharmalot blog** (<http://www.pharmalot.com/>), Ed Silverman discusses biotech CEOs' opinion of FDA regulations, writing that "As they say, money isn't everything. And while CEOs

at some biotechs as well as small drug and device makers, lament the lack of funding for their projects, an overwhelming majority also blame the FDA for slowing the growth of their companies. At least that is what a new survey of approximately 100 such companies has found." "Roughly 80 percent of the CEOs surveyed," he goes on to write, "agreed or strongly agreed that the the current FDA approval process has slowed growth. A similar percentage do not believe the FDA has the best regulatory approval process in the world. The survey of approximately 100 CEOs was conducted by BayBio, the California Health Institute and PriceWaterhouse Coopers consulting."

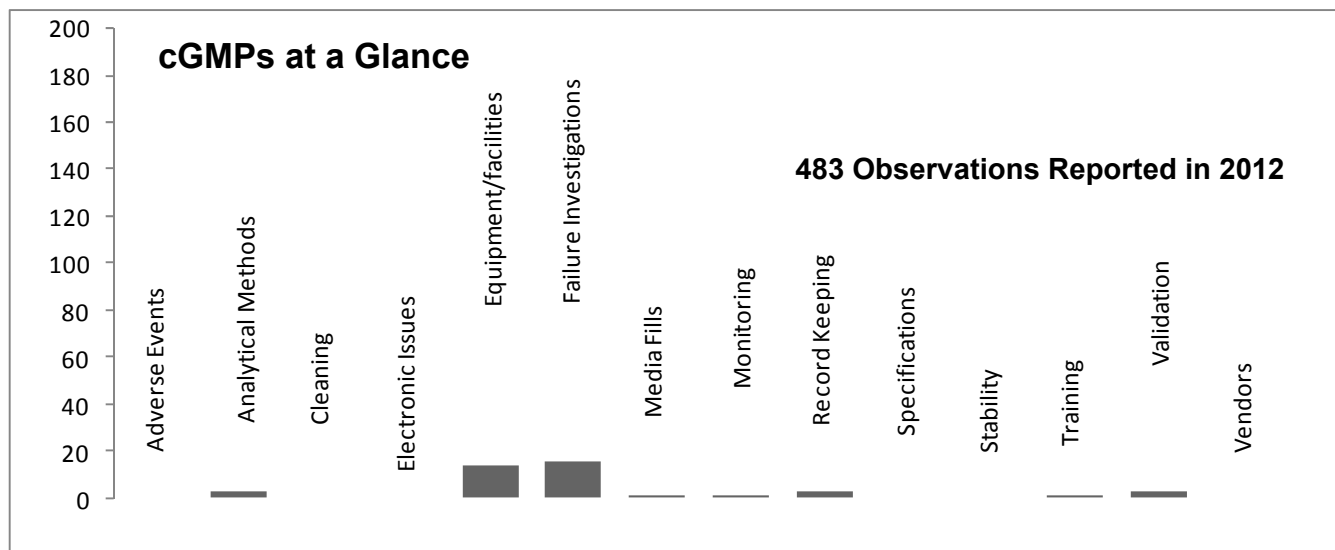
### Heads up! PDUFA V recommendations include a new program for Biosimilars, including those under development.

An abbreviated pathway was established for biological products shown to be biosimilar to or interchangeable with an FDA-licensed biological product by a subtitle of the Affordable Care Act of 2010 called the Biologics Price Competition and Innovation Act (BPCI) of 2009. This proposed new Biosimilar and Interchangeable Products User Fee program is intended for products approved under the new abbreviated pathway.

The recommended user fee program for biosimilars includes fees for products in development to generate revenue in the near-term and to provide FDA with the resources needed to support development-phase meetings with sponsors of biosimilar biological product candidates.

In addition, the recommendations HHS Secretary Kathleen Sebelius transmitted to Congress on behalf of FDA (ahead of the agency's mid-January deadline) contain a new User Fee program for generic drugs and, of course, for products seeking NDA approval or BLA licensing. FDA Commissioner Margaret A. Hamburg, M.D. said that these programs will "help speed safe and effective drugs and lower-cost generic drug and biosimilar biological products to patients."

To see a blog post on this subject by the FDA Commissioner: <https://blogs.fda.gov/fdavoic/?p=234>



**Note for This Month's 483s:**

The letter(s) in brackets preceding each observation represent the system category of the deficiency. Q = Quality System; FE = Facilities and Equipment System; M = Materials System; Pr = Production System; PL = Packaging and Labeling System; L = Laboratory Controls System

Category	Cause for Recently Issued 483 Notice of Deficiency Note: The letter(s) in brackets preceding each observation represents the system category of the deficiency. Q = Quality System; FE = Facilities and Equipment System; M = Materials System; Pr = Production System; PL = Packaging and Labeling System; L = Laboratory Controls System
<b>Analytical Methods, Sampling, In-process Controls</b>	(L) SOP for final product inspection and re-inspection is inadequate in that: <ul style="list-style-type: none"> <li>• It does not define or provided instructions for the re-inspection process</li> <li>• It does not address in what situations re-inspections are appropriate or how this determination can be made</li> <li>• It does not specify the number of re-inspections that may be performed</li> </ul> Firm did not notify FDA of significant complaint in a timely fashion  The firm conducts meetings to discuss open Complaint Reports, but these meetings are not a part of any approved procedure and not records of the meetings are maintained
<b>Equipment/Facilities/Operations</b>	(Q) Firm lacks adequate oversight by the Quality Unit to: <ul style="list-style-type: none"> <li>• approve or reject the products manufactured and processed,</li> <li>• as well as, to approve or reject the established procedures or specifications impacting the quality of the drug product</li> </ul> (Q) The quality control unit lacks responsibility to approve and reject all procedures or specifications impacting on the identity, strength, quality, and purity of drug products.  (Q) Firm's Quality Unit does not review or approve maintenance procedures and records  (FE) Not all manufacturing fill equipment used for media fills has met the periodic requalification requirements  (Q) GMP equipment is not always qualified within SOP-required time frames

**cGMPs at a Glance...continued**

Category	Cause for Recently Issued 483 Notice of Deficiency
<b>Equipment/Facilities/ Operations continued</b>	<p>(FE) Vial washer failed to meet re-qualification specifications for the particulate challenge test, but continued to be used for GMP production activities</p> <p>(FE) No scientific rationale for event driven equipment re-qualification system:</p> <ul style="list-style-type: none"> <li>• Equipment included in this re-qualification system includes: <ul style="list-style-type: none"> <li>• Portable Laminar Flow (HEPA) carts, clean steam system, distillation system, vial fillers, and headspace analyzer</li> </ul> </li> <li>• This equipment is only re-qualified on an event driven basis, whereby: <ul style="list-style-type: none"> <li>• the piece of equipment must undergo a change or atypical event before the need to re-qualify is assessed</li> </ul> </li> </ul> <p>(FE) Periodic review to assess need for re-qualification, which is required by firm's SOP is either:</p> <ul style="list-style-type: none"> <li>• past due by approximately 1 year or</li> <li>• has not been performed for equipment such as <ul style="list-style-type: none"> <li>• Phase IV clean steam system, Phase IV and South vial fillers, various distillation systems, portable headspace analyzer units</li> </ul> </li> </ul> <p>(FE) Personnel did not follow firm's SOP which requires that equipment undergoing re-qualification be "tagged out" with a visual notification to production employees that:</p> <ul style="list-style-type: none"> <li>• a piece of equipment is out-of-service until returned to service by the quality unit</li> </ul> <p>(FE) Qualification study to determine the location of thermocouples used to monitor incubator rooms used to incubate media filled vials is deficient</p> <ul style="list-style-type: none"> <li>• The purpose of the thermocouples is to detect the highest and lowest temperatures in the rooms, but</li> <li>• The locations were determined by taking the highest and lowest temperatures observed during the study, which did not determine: <ul style="list-style-type: none"> <li>• the locations in which the highest and lowest room temperatures occurred</li> </ul> </li> </ul> <p>(FE) Routine preventative maintenance activities for GMP equipment are not performed at their scheduled intervals</p> <ul style="list-style-type: none"> <li>• More than 100 preventative maintenance activities were more than 30 days past the scheduled due date</li> </ul> <p>(Q) The firm lacks adequate oversight by the Quality Unit to approve or reject the products manufactured and processed, as well as, approve or reject:</p> <ul style="list-style-type: none"> <li>• the established procedures or specifications impacting the quality of the drug product</li> </ul> <p>(Q) The Quality Unit does not review or approve maintenance procedures or records</p> <p>(Q) Preventative maintenance schedules for GMP equipment were changed without involvement of the Quality Unit</p>
<b>Investigations, Tracking, Trending, and Corrective and Preventive Actions (CAPA)</b>	<p>(Q) Firm does not regularly perform the following actions which are required by their Quality Manual</p> <ul style="list-style-type: none"> <li>• Trending of the types of rejects found during production</li> <li>• Executing regular historical checks and analyzing data required to evaluate whether each of the defect causes is a root cause or probably cause</li> <li>• Recommending adequate CAPAs as necessary</li> </ul> <p>(Q) Firm conducts meetings to discuss open complaint reports and deviation reports, but these meetings are not part of any approved procedures and no records are maintained</p> <p>(Q) Firm's procedures allow retesting without involvement of the Quality Unit</p>

**cGMPs at a Glance...continued**

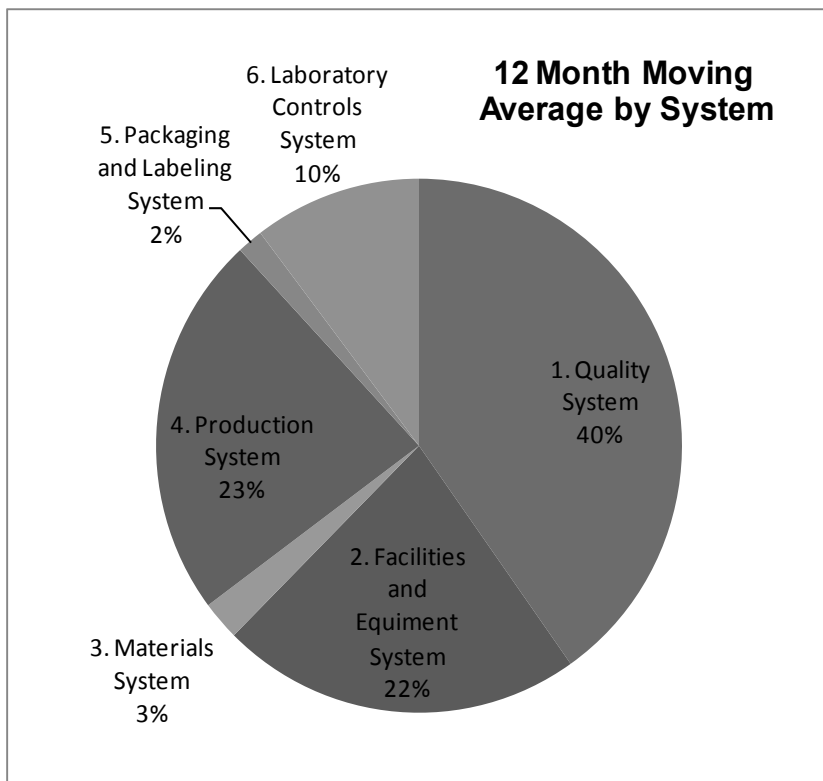
Category	Cause for Recently Issued 483 Notice of Deficiency
<b>Investigations, Tracking, Trending, and Corrective and Preventive Actions (CAPA)</b>	<p>(Q) Environmental Monitoring assessments fail to identify the source and root cause of contaminations</p> <p>(Q) Investigation into missing Qualification Report incident which was not discovered by firm for nearly 10 months after the Qualification took place is insufficient:</p> <ul style="list-style-type: none"> <li>• The investigation concluded that human error was the root cause, however:</li> <li>• The investigation failed to examine other possible causes such as lack of an oversight system to alert the Validation Group that equipment qualifications were past due</li> </ul> <p>(Q) The Quality Unit discovered a missing Equipment Qualification Report, but investigation into this incident was not opened until almost one month later</p> <p>(Q) The Quality Unit failed to follow firm's SOP which requires:</p> <ul style="list-style-type: none"> <li>• Immediately reporting "Critical" findings to the Vice President of Quality Operations and the Vice President of Operations</li> </ul> <p>(Q) A deviation which was rated as "critical" when it was opened was downgraded to "major" without the approval or knowledge of senior management, which is required by firm's SOP</p> <ul style="list-style-type: none"> <li>• Furthermore, the firm did not provide any justification for this downgrade</li> </ul> <p>More than 400 Investigation Reports for deviations, complaints, change controls, CAPAs, and quality protocols are past their due dates and remain in open status, however:</p> <ul style="list-style-type: none"> <li>• The significance of these open reports has not been fully evaluated by the quality unit with respect to: <ul style="list-style-type: none"> <li>• the potential impact to the manufacturing processes and quality control testing in support of the finished drug products</li> </ul> </li> </ul> <p>Complaint investigations are inadequate and fail to follow established procedures</p> <p>(Q) Firm failed to retain a written record of employee interviews during investigation of complaint regarding metal particles in the drug product</p> <p>(Q) Firm did not provide justification of sample size for equipment wipe samples taken as part of complaint investigations:</p> <ul style="list-style-type: none"> <li>• The sample sizes were not reviewed by an appropriate person knowledgeable in statistics to ensure statistical significance</li> </ul> <p>(Q) Investigation is incomplete in that it does not include an impact assessment of other products manufactured in the facility</p> <p>(Q) The firm's investigators failed to follow SOPs in that they did not perform a detailed risk analysis when complaints remained open for more than 30 days</p> <p>(Q) The criteria for inspecting retain samples as part of investigations is inconsistent and not in writing</p> <p>(Q) The firm does not track or trend the types of rejects that are observed during production, in violation of the firm's SOPs</p>
<b>Media Fills</b>	<p>(Pr) Firm's media fills are deficient and do not follow the firm's SOPs for media fills:</p> <ul style="list-style-type: none"> <li>• Not all the manufacturing operators perform the SOP-specified interventions as required by the procedure</li> <li>• Media filled vials in the area of the interventions are not incubated, and: <ul style="list-style-type: none"> <li>• Discarding these vials precludes the Quality Unit from adequately assessing and assuring that the manual interventions do not create or provide: <ul style="list-style-type: none"> <li>• adverse conditions that can result in having microbial and /or non-viable contamination</li> </ul> </li> </ul> </li> <li>• The firm does not a scientific rationale to support discarding and not incubating the vials from the intervention zone</li> <li>• The firm's media fill SOP does not permit or discuss discarding of intervention zone vials</li> <li>• Multiple interventions occur simultaneously during routine aseptic filling, but multiple simultaneous interventions are not included in the media fill process simulations</li> </ul>

**cGMPs at a Glance...continued**

Category	Cause for Recently Issued 483 Notice of Deficiency
<b>Monitoring and Contamination Issues</b>	(FE) The firm's documentation requires an Environmental Monitoring Performance Qualification (EMPQ) which is "a comprehensive environmental monitoring performance qualification" <ul style="list-style-type: none"> <li>• However, an EMPQ has not been performed for all sterile manufacturing facilities</li> </ul>
<b>Record Keeping and Documentation</b>	(Pr) The firm's Media Fill Validation Master Plan and Media Fill SOP are not in concert with each other  (Q) The Report for the qualification of a vial washer was not reviewed by the Validation staff or other Quality Unit personnel <ul style="list-style-type: none"> <li>• The Report was misplaced and this error was not discovered until almost 10 months after completion of the qualification</li> </ul> (Q) The Quality Unit uses an uncontrolled Batch Summary Sheet to make batch release decisions <ul style="list-style-type: none"> <li>• For example:                             <ul style="list-style-type: none"> <li>• Changes are effected to Preventive Maintenance schedules and procedures without the approval of the Quality Unit</li> </ul> </li> </ul>
<b>Training</b>	There is no oversight ensuring validation group employees complete required training. <ul style="list-style-type: none"> <li>• For example, one validation manager is overdue for process validation safety training by more than 168 days</li> </ul>
<b>Validation</b>	(FE) Air flow pattern validation has not been performed for all Class 100 and Class 10,000 areas as required by the firm's SOP  (L) Air flow pattern testing to validate unidirectional air flow in aseptic processing areas is not performed under dynamic conditions  (Q) The Validation Group lacks appropriate oversight and technical expertise to perform their duties <ul style="list-style-type: none"> <li>• The Group frequently fails to perform periodic reviews and qualification/re-qualification of equipment within required time frames</li> </ul>

A New BioQuality Feature--12 Month Moving Average of 483s Categorized by System 12-month moving averages of systems deficiencies, a new BioQuality feature to help you spot and track enforcement trends and focus your compliance resources. One of the best ways in which to spot and track trends is the use of a moving average (MA), and this new feature does exactly that. Each month a table and chart like the ones below will show which systems are generating the most Notices of Deficiency (483s).

System	12 Month MA%
<b>1. Quality System</b>	<b>40%</b>
<b>2. Facilities &amp; Equipment Systems</b>	<b>22%</b>
<b>3. Materials System</b>	<b>3%</b>
<b>4. Production System</b>	<b>23%</b>
<b>5. Packaging &amp; Labeling System</b>	<b>2%</b>
<b>6. Laboratory Controls Systems</b>	<b>10%</b>
<b>Total</b>	<b>100.0%</b>



## In the Federal Register

### **Final Rules**

**Title:** Revisions to Labeling Requirements for Blood and Blood

Components, Including Source Plasma

**Docket Number:** FDA-2003-N-0097

**Effective Date:** July 2, 2012

**Reference and FR Link:** Federal Register Volume 77, Number 1 (Tuesday, January 3, 2012); <http://www.gpo.gov/fdsys/pkg/FR-2012-01-03/pdf/2011-33554.pdf>

**Summary:** The Food and Drug Administration (FDA) is revising the labeling requirements for blood and blood components intended for use in transfusion or for further manufacture by combining, simplifying, and updating specific regulations applicable to labeling and circulars of information. These requirements will facilitate the use of a labeling system using machine

readable information that would be acceptable as a replacement for the "ABC Codabar" system for the labeling of blood and blood components. FDA is taking this action as a part of its efforts to comprehensively review and, as necessary, revise its regulations, policies, guidances, and procedures related to the regulation of blood and blood components. This final rule is intended to help ensure the continued safety of the blood supply and facilitate consistency in labeling.

**Contact for More Information:** Benjamin Chacko, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852 1448, (301) 827-6210.

### **Meetings**

**Meeting Name:** Vaccines and Related Biological Products Advisory Committee

**Docket Number:** FDA-2012-N-0001

**Meeting Date(s) and Time:** The meeting will be held on February 28, 2012, from approximately 8 a.m. to 4 p.m. and February 29, 2012, from approximately 8 a.m. to 1 p.m.

**Meeting Location:** FDA White Oak Campus, 10903 New Hampshire Ave., Bldg. 31 Conference Center, the Great Room (rm. 1503), Silver Spring MD 20993-0002 For those unable to attend in person, the meeting will also be web-

cast. The link for the webcast is available at: <https://collaboration.fda.gov/cberac>.

**Reference and FR Link:** Federal Register Volume 77, Number 16 (Wednesday, January 25, 2012); <http://www.gpo.gov/fdsys/pkg/FR-2012-01-25/pdf/2012-1456.pdf>

**About the Meeting:** On February 28, 2012, the committee will meet in open session to hear an overview of the research program in the Laboratory of Mycobacterial Diseases and Cellular Immunology, Division of Bacterial, Parasitic and Allergenic Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, FDA. The committee will then discuss and make recommendations on the selection of strains to be included in the influenza virus vaccine for the 2012 to 2013 influenza season. On February 29, 2012, the committee will discuss licensure pathways for pandemic influenza vaccines. Background material is available at <http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>. Scroll down to the appropriate advisory committee link

**To Register:** Contact Person: Donald W. Jehn or Denise Royster, Center for Biologics Evaluation and Research (HFM-71), Food and Drug Administration, 1401 Rockville Pike Rockville, MD 20852, (301) 827-0314, or FDA Advisory Committee Information Line, 1-(800) 741-8138

(301) 443-0572 in the Washington, DC area), and follow the prompts to the desired center or product area. Please call the Information Line for up-to-date information on this meeting. A notice in the Federal Register about last minute modifications that impact a previously announced advisory committee meeting cannot always be published quickly enough to provide timely notice. Therefore, you should always check the Agency's Web site and call the appropriate advisory committee hot line/phone line to learn about possible modifications before coming to the meeting.

**Other Deadlines:** Those individuals interested in making formal oral presentations should notify the contact person and submit a brief statement of the gen-

eral nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an indication of the approximate time requested to make their presentation on or before February 13, 2012.

**Meeting Name:** Blood Products Advisory Committee

**Docket Number:** Docket No. FDA-2012-N-0001

**Meeting Date(s) and Time:** The meeting will be held on February 29, 2012, from 8:30 a.m. to 4 p.m.

**Meeting Location:** Washington DC North/Gaithersburg, 620 Perry Pkwy., Gaithersburg, MD 20877, (301) 977-8900 The Blood Products Advisory Committee Web cast will be available at <http://fda.yorkcast.com/webcast/Viewer/?peid=11253ea88a9041e5a91883236f342bfc1d>

**Reference and FR Link:** Federal Register Volume 77, Number 19 (Monday, January 30, 2012); <http://www.gpo.gov/fdsys/pkg/FR-2012-01-30/pdf/2012-1888.pdf>

**About the Meeting:** On February 29, 2012, the committee will discuss the evaluation of possible new plasma products manufactured following storage at room temperature for up to 24 hours, namely, plasma for transfusion prepared from whole blood held at room temperature for up to 24 hours prior to separation and freezing, or from apheresis plasma held at room temperature for up to 24 hours before freezing. In the afternoon, the committee will hear the following updates: Report from the Health and Human Services Advisory Committee on Blood Safety and Availability and summary of the December 5-6, 2011, meeting; update on HHS activities related to the evaluation of the donor deferral policy for men who have had sex with other men; summary of the November 8-9, 2011, public workshop on hemoglobin standard and maintaining an adequate blood supply; summary of the November 29, 2011, public workshop on data and data needs to advance risk assessment for emerging infectious diseases for blood and blood products; and an update on thrombotic adverse events and

**In the Federal Register Continued**

immune globulin products. FDA intends to make background material available to the public no later than 2 business days before the meeting. If FDA is unable to post the background material on its Web site prior to the meeting, the background material will be made publicly available at the location of the advisory committee meeting, and the background material will be posted on FDA's Web site after the meeting. Background material is available at <http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>. Scroll down to the appropriate advisory committee link.

**To Register:** Contact Person: Bryan Emery or Pearl Muckelvene, Center for Biologics Evaluation and Research (HFM-71), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, (301) 827-1281, or FDA Advisory Committee Information Line, 1-(800) 741-8138, (301) 443-0572 in the Washington, DC area), and follow the prompts to the desired center or product area. Please call the Information Line for up-to-date information on this meeting. A notice in the Federal Register about last minute modifications that impact a previously announced advisory committee meeting cannot always be published quickly enough to provide timely notice. Therefore, you should always check the Agency's Web site and call the appropriate advisory committee hot line/phone line to learn about possible modifications before coming to the meeting.

**Other Deadlines:** Those individuals interested in making formal oral presentations should notify the contact person and submit a brief statement of the general nature of the evidence or arguments they wish to present, the names and addresses of proposed participants, and an

indication of the approximate time requested to make their presentation on or before February 13, 2012.

**General and Misc. Notices**

**Title:** Privacy Act of 1974; Report of an Altered System of Records, Including Addition of Routine Uses to an Existing System of Records; Bioresearch Monitoring Information System

**Docket Number:** FDA-2011-N-0454

**Effective Date and Comment Date:**

This notice will be effective without further notice on February 8, 2012 unless modified by a subsequent notice making changes in response to public comments. FDA invites comments on all parts of the systems notice. Comments must be received on or before February 8, 2012.

**Reference and FR Link:** Federal Register Volume 77, Number 5 (Monday, January 9, 2012); <http://www.gpo.gov/fdsys/pkg/FR-2012-01-09/pdf/2012-114.pdf>

**Summary:** The Food and Drug Administration (FDA) is announcing an alteration to an existing System of Records (System) titled "Bioresearch Monitoring Information System, HHS/FDA" (System No. 09-10-0010). Among other updates, this alteration adds new routine uses for disclosures of certain relevant information to Agencies, authorities, and organizations with responsibilities related to clinical investigations and/or clinical investigators; persons who require access to records to perform services for FDA; and individual research subjects.

**Contact for More Information:** Kathleen E. Pfaender, Office of Good Clinical Practice, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, Rm. 5129, Silver Spring, MD 20993-

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

**FDA NEWS**


**FDA Biosimilar Guidance**  
**Where is the FDA biosimilar guidance?** It has left the FDA according to Emily Schacter, CDER, FDA at the CASSS CMC forum yesterday. "We are waiting along with you for its appearance." She further stated that unfortunately, until it is published the agency is "hamstrung about what we can say". However, the lack of the guidance has not stopped the industry from Biosimilar product development, To date there have been 34 pre-ind meeting requests for proposed biosimilar products for 11 different reference products. Twenty-one pre-IND sponsor meetings have been held and 9 INDs have been submitted.

**Development User Fees for Biosimilars**  
**Why the development user fee?** According to FDA Office of Biotechnology Products Director Steve Kozlowski, M.D. at the WCBP meeting in San Francisco today, it stems from the fact that significant CMC review resources are required to review the development data because of the large amount of characterization data included in the early development submissions. This is contrast with the innovative products which have less CMC data early on.







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








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## In the Literature

### QuickScan of Sub-Topics Covered by This In The Literature Search

- **Bioanalytical Methods and Issues**
- **Biological Potency and other Biological Assays**
- **Biomarkers**
- **Biosimilars, Follow-on Biologics, FOPPs, Biobetters, etc.**
- **Container/Closure Issues**
- **Formulation and Delivery**
- **Manufacturing and Production Issues**
- **Microbial Analysis and Control**
- **Preclinical Issues**
- **Protein, Glycoprotein, Peptide, and Other Bio-molecule Structure/Function**
- **Proteins, Peptides and Other Bio-molecules: Characterization, Analysis, and Control**
- **Regulatory Submissions, Review, Reporting, etc.**
- **Safety and Efficacy Issues**
- **Stability Issues**
- **Unwanted Immunogenicity**

### Articles by FDA and Other Regulatory Bodies

#### Unwanted Immunogenicity

**Plasma derivatives: New products and new approaches.** Sauna ZE, et al. *Biologicals*. 2012 Jan 10. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22239993>

#### Technical Articles

#### Bioanalytical Methods and Issues

**A novel microfluidic immunoassay system based on electrochemical immunosensors: An application for the detection of NT-proBNP in whole blood.** Liang W, et al. *Biosens Bioelectron*. 2012 Jan 15;31(1):480-5. Epub 2011 Nov 20. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22169814>

#### Biomarkers

**Quantum-dot-based biosensor for simultaneous detection of biomarker**

**and therapeutic drug: first steps toward an assay for quantitative pharmacology.** Yang C, et al. *Analyst*. 2012 Jan 16. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22245799>

**Protein biomarkers for multiple sclerosis: semi-quantitative analysis of cerebrospinal fluid candidate protein biomarkers in different forms of multiple sclerosis.** Avsar T, et al. *Mult Scler*. 2012 Jan 17. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22252467>

#### Formulation and Delivery

**Efficient siRNA delivery using novel siRNA-loaded Bubble liposomes and ultrasound.** Endo-Takahashi Y, et al. *Int J Pharm*. 2012 Jan 17;422(1-2):504-9. Epub 2011 Nov 22. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22119963>

**Erythropoietin-Coated ZP-Microneedle Transdermal System: Preclinical Formulation, Stability, and Delivery.** Peters EE, et al. *Pharm Res*. 2012 Jan 19. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22258935>

#### Manufacturing and Production Issues

**Use of High-Gradient Magnetic Fishing for Reducing Proteolysis During Fermentation.** Maury TL, et al. *Biotechnol J*. 2012 Jan 18. doi: 10.1002/biot.201100376. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22252924>

#### Proteins, Peptides and Other Bio-molecules: Characterization, Analysis, and Control

**Development and qualification of the parallel line model for the estimation of human influenza haemagglutinin content using the single radial immunodiffusion assay.** van Kessel G, et al.

*Vaccine*. 2012 Jan 5;30(2):201-9. Epub 2011 Nov 19. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22107849>

**Development and qualification of an antibody rapid deglycosylation method.** Cook KS, et al. *Biologicals*. 2012 Jan 16. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22257749>

**Evaluation of Electrospray Ionization Mass Spectrometry as a Tool for Characterization of Small Soluble Protein Aggregates.** Wang G, et al. *Anal Chem*. 2012 Jan 12. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22240037>

**A MALDI-TOF MS method for the simultaneous and quantitative analysis of neutral and sialylated glycans of CHO-expressed glycoproteins.** Tep S, et al. *Carbohydr Res*. 2012 Jan 10;347(1):121-9. Epub 2011 Oct 20. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22138464>

**Using Hydrogen/Deuterium Exchange Mass Spectrometry to Study Conformational Changes in Granulocyte Colony Stimulating Factor upon PEGylation.** Wei H, et al. *J Am Soc Mass Spectrom*. 2012 Jan 7. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22227798>

**Analytical measurement of PEGylated molecules.** Cheng TL, et al. *Bioconjug Chem*. 2012 Jan 15. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22242549>

**Microchip capillary electrophoresis-electrospray ionization-mass spectrometry of intact proteins using uncoated Ormocomp microchips.** Sikanen T, et al. *Anal Chim Acta*. 2012 Jan 20;711:69-76. Epub 2011 Nov 9. **To**

## In the Literature Continued

see the **Abstract**, and a link to purchase this paper: <http://www.ncbi.nlm.nih.gov/pubmed/22152798>

[www.ncbi.nlm.nih.gov/pubmed/22152798](http://www.ncbi.nlm.nih.gov/pubmed/22152798)

### **Biological Potency and other Biological Assays**

**Phaedra, a Protocol-Driven System for Analysis and Validation of High-Content Imaging and Flow Cytometry.**

Cornelissen F, et al. *J Biomol Screen*. 2012 Jan 10. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22233649>

**Reproducibility of serology assays for pandemic influenza H1N1: Collaborative study to evaluate a candidate WHO International Standard.**

Wood JM, et al. *Vaccine*. 2012 Jan 5;30(2):210-7. Epub 2011 Nov 17. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22100887>

### **Container/Closure Issues**

**Nondestructive detection of glass vial inner surface morphology with differential interference contrast microscopy.** Wen ZQ, et al. *J Pharm Sci*. 2012 Jan 10. doi: 10.1002/jps.23048. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22234873>

### **Protein, Glycoprotein, Peptide, and Other Bio-molecule Structure/Function**

**Perfluoroalkyl chains direct novel self-assembly of insulin.** Malik L, et al. *Langmuir*. 2012 Jan 10;28(1):593-603. Epub 2011 Dec 22. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22129241>

### **Safety and Efficacy Issues**

**A need for careful evaluation of endotoxin contents in acellular pertussis-based combination vaccines.**

Kataoka M, et al. *Biologicals*. 2012 Jan 10. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22239994>

### **Stability Issues**

**Effects of pH on Proteins: Predictions for Ensemble and Single-Molecule Pulling Experiments.** O'Brien EP, et al. *J Am Chem Soc*. 2012 Jan 18;134(2):979-87. Epub 2011 Dec 27. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22148729>

**Protein hot spots: the islands of stability.** Kuttner YY, Engel S. *J Mol Biol*. 2012 Jan 13;415(2):419-28. Epub 2011 Nov 12. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22100447>

**A mass spectrometry-assisted study reveals that lysine residues 1967 and 1968 have an opposite contribution to the stability of activated factor VIII.** Bloem E, et al. *J Biol Chem*. 2012 Jan 3. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22215677>

**The role of entropy in initializing the aggregation of peptides: a first principle study on oligopeptide oligomerization.** Pohl G, et al. *Phys Chem Chem Phys*. 2012 Jan 4;14(4):1507-16. Epub 2011 Dec 12. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22159787>

**Salting Effects on Protein Components in Aqueous NaCl and Urea Solutions: Towards Understanding of Urea Induced Protein Denaturation.** Li W, et al. *J Phys Chem B*. 2012 Jan 4. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22216970>

### **Formulation and Delivery**

**Oral vaccination with inactivated influenza vaccine induces cross-protective immunity.** Quan FS, et al. *Vaccine*. 2012 Jan 5;30(2):180-8. Epub 2011 Nov 19. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22107852>

**Vaccine vectors derived from a large collection of simian adenoviruses induce potent cellular immunity across multiple species.** Colloca S, et al. *Sci Transl Med*. 2012 Jan 4;4(115):115ra2. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22218691>

**Aggregation factor analysis for protein formulation by a systematic approach using FTIR, SEC and design of experiments techniques.** Feng YW, et al. *J Pharm Biomed Anal*. 2012 Jan 5;57:143-52. Epub 2011 Aug 31. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/21920692>

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**Process optimization and scale-up for production of rabies vaccine live adenovirus vector (AdRG1.3).** Shen CF, et al. *Vaccine*. 2012 Jan 5;30(2):300-6. Epub 2011 Nov 8. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22079076>

### **Regulatory Reviews**

#### **Regulatory Submissions, Review, Reporting, etc.**

**Compliance with mandatory reporting of clinical trial results on ClinicalTrials.gov: cross sectional study.** Prayle AP, et al. *BMJ*. 2012 Jan 3;344:d7373. doi: 10.1136/bmj.d7373. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22214756>

#### **Bioanalytical Methods and Issues**

**Model-based strategy for bioanalytical method comparison: measurement of a soluble ligand as a biomarker.** Thway TM, et al. *J Pharm Biomed Anal*. 2012 Jan 25;58:65-70. Epub 2011 Sep 10. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22005590>

#### **Biological Potency and other Biological Assays**

**Development and validation of an egg-based potency assay for a triva-**

## In the Literature Continued

### **lent live attenuated influenza vaccine.**

Yeolekar LR, Dhare RM. *Biologicals*. 2012 Jan 21. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22269606>

### **Biosimilars, Follow-on Biologics, FOPPs, Biobetters, etc.**

#### **A Comparison of the Pharmacodynamic Behavior of Branded and Biosimilar Enoxaparin in Primates.**

Jeske W, et al. *Clin Appl Thromb Hemost*. 2012 Jan 23. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22275388>

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**Graphene multilayers as gates for multi-week sequential release of proteins from surfaces.** Hong J, et al. *ACS Nano*. 2012 Jan 24;6(1):81-8. Epub 2011 Dec 29. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22176729>

#### **Protein-loaded PLGA-PEG-PLGA microspheres: A tool for cell therapy.**

Tran VT, et al. *Eur J Pharm Sci*. 2012 Jan 23;45(1-2):128-37. Epub 2011 Nov 9. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22085679>

**Magnetized Aerosols Comprising Superparamagnetic Iron Oxide Nanoparticles Improve Targeted Drug and Gene Delivery to the Lung.** Hasenpusch G, et al. *Pharm Res*. 2012 Jan 21. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22271050>

### **Microbial Analysis and Control**

#### **One Test Microbial Diagnostic Microarray for Identification of Mycoplasma mycoides subsp. mycoides and Other Mycoplasma Species.**

Tonelli A, et al. *Mol Biotechnol*. 2012 Jan 24. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22271459>

### **Safety and Efficacy Issues**

#### **Pharmaceutical industry perspective on risk evaluation and mitigation strategies: manufacturer take heed.**

Nicholson S, et al. *Expert Opin Drug Saf*. 2012 Jan 10. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22233294>

### **Technical Reviews**

#### **Stability Issues**

**How ionic liquids can help to stabilize native proteins.** Weingärtner H, et al. *Phys Chem Chem Phys*. 2012 Jan 14;14(2):415-26. Epub 2011 Nov 16. **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22089969>

### **Manufacturing and Production Issues**

**Industrial production of recombinant therapeutics in Escherichia coli and its recent advancements.** Huang CJ, et al. *J Ind Microbiol Biotechnol*. 2012 Jan 18. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22252444>

### **Preclinical Issues**

**Monoclonal antibodies: what are the pharmacokinetic and pharmacodynamic considerations for drug development?** Deng R, et al. *Expert Opin Drug Metab Toxicol*. 2012 Jan 17. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22248267>

**Standardization of pluripotent stem cell cultures for toxicity testing.** Pistolato F, et al. *Expert Opin Drug Metab Toxicol*. 2012 Jan 17. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22248265>

### **Unwanted Immunogenicity**

**Development of resistance to biologic therapies with reference to IFN- $\beta$ : Understanding drug resistance to biological therapy.** Farrell RA, et al. *Rheumatology (Oxford)*. 2012 Jan 18. [Epub

ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22258390>

### **Business Articles and Reviews**

#### **Biosimilars, Follow-on Biologics, FOPPs, Biobetters, etc.**

**The economic pressures for biosimilar drug use in cancer medicine.** Cornes P. *Target Oncol*. 2012 Jan 17. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22249658>

#### **Colony stimulating factors (CSF) biosimilars. Progress?**

Scotté F, et al. *Target Oncol*. 2012 Jan 17. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22249656>

**Biosimilars and market access: a question of comparability and costs?** Simoens S, et al. *Target Oncol*. 2012 Jan 17. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22249657>

**Presently available biosimilars in hematology-oncology: G-CSF.** Gascon P. *Target Oncol*. 2012 Jan 19. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22258705>

**Erythropoietin biosimilars currently available in hematology-oncology.** Kamioner D. *Target Oncol*. 2012 Jan 18. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22252675>

**What do prescribers think of biosimilars?** Aapro MS. *Target Oncol*. 2012 Jan 19. [Epub ahead of print] **To see the Abstract, and a link to purchase this paper:** <http://www.ncbi.nlm.nih.gov/pubmed/22258706>

## NEWS YOU CAN USE


**The European Compliance Academy (ECA) has a GMP Discussion Forum** where you can post your questions and/or respond to the questions of others. While not exclusively for biopharmaceuticals and biologics, it is worth a regular visit. Recent topics of discussion include: Particulates, Cleaning Validation, Risk Assessment, Proper QA Staffing Levels, Batch Records, Equipment Validation, and Failure Investigations. Find the Forum here: [http://www.gmp-compliance.org/eca\\_forum\\_eca.html](http://www.gmp-compliance.org/eca_forum_eca.html)

The ECA also has a well-organized archive of FDA Warning Letters, from 2002 through the present, they call the "FDA Warning Letter Tree." See it here: [http://www.gmp-compliance.org/eca\\_wl\\_tree.html](http://www.gmp-compliance.org/eca_wl_tree.html)

EMA has published its latest Organization Chart. See it here: [http://www.ema.europa.eu/ema/pages/includes/document/open\\_document.jsp?webContentId=WC500017948](http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500017948)

**You have questions, they have answers.** EMA, the US FDA, and Health Canada all maintain a FAQ section on their websites. You may want to bookmark these links for future reference.

- The EMA Q&A page can be found here: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q\\_and\\_a/q\\_and\\_a\\_detail\\_000027.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800296ca&jsenabled=true](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800296ca&jsenabled=true)
- For the FDA Q&A page point your browser to: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124740.htm>
- The Health Canada (HC) Q&A page can be found at: <http://hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/question/gmp-bpf-eng.php>

Agency	Question Followed by Agency Answer
FDA	<p><b>Q. Do the CGMP regulations permit the destruction of an internal quality assurance audit report once the corrective action has been completed?</b></p> <p><b>A. The CGMP regulations (21 CFR 210 and 211) for finished pharmaceutical manufacturing do not specifically address the requirement to conduct, or to keep records of, internal quality assurance audits. If the report in question were from a routine audit to verify that the firm's quality system is operating as intended, then it would be acceptable if the firm elected to discard the report once all corrections have been verified.</b></p> <p><b>However, any documentation of corrective action as a result of such an audit would have to be retained (see 211.180 and 211.188). For example, if a routine internal audit finds a problem with a mixing step and the outcome is a change in mixing time, all affected procedures, including the master production record, are to reflect the necessary changes, and such records are subject to FDA inspection as usual. Any investigation into the impact this problem had on related batches is to be retained and also made available for inspection by FDA (see 211.192).</b></p> <p><b>In addition, any reports of investigations or evaluations prepared in response to, for example, a product complaint (211.198), vendor qualification (211.84), periodic review of records and data (211.180(e)), and a failure investigation (211.192) are not internal audits as discussed above. Such records are subject to FDA inspection and must be retained for at least the time specified in the CGMP regulations (see 211.180).</b></p>
EMA	<p><b>Q. Is an audit performed by a third party [to Qualify a supplier] acceptable?</b></p> <p><b>An audit conducted by the manufacturing authorisation holder itself should be integral to the manufacturer's quality assurance system and subject to the basic GMP requirements i.e. conducted by properly qualified and trained staff, in accordance with approved procedures, should be properly documented and these aspects can be inspected as necessary by the Competent Authorities. If a third party is involved then the arrangements should be subject to Chapter 7 of the <u>GMP Guide</u>  and there should be evidence that the contract giver has evaluated the contract acceptor with respect to the aspects described above. All parties involved should be aware that audit reports and other documentation relating to the audit will be made available for inspection by the competent authorities if requested. This should normally provide sufficient assurance that the results of an audit carried by the third party are credible thus waiving the need for an audit conducted by the manufacturing authorisation holder itself. However, it must also be satisfactorily demonstrated that there is no conflict of interest. Conflicts of interest could arise for example from:</b></p>

## Agency Q&A Continued

Agency	Question Followed by Agency Answer
EMA (Continued)	<ul style="list-style-type: none"> <li>• <b>A commercial relationship between the organisation performing the audit and the organisation being audited.</b></li> <li>• <b>A personal conflict on the part of the auditor where he/she has been employed by the organisation being audited in the recent past (i.e. within the last 3 years) or has a financial interest in it.</b></li> </ul> <p><b>This topic should also be addressed in the technical contractual arrangements and any measures taken by the contract giver should be documented e.g. signed undertakings by the auditors. Similarly, the principles outlined above could be used to allow sharing of audit reports between different manufacturing authorisation holders using the same active substance supplier, provided the scope of the audits can be shown to be applicable to the active substances of mutual interest.</b></p>
HC	<p><b>Q. What are the requirements applicable to Quality Control (QC) and engineering personnel who travel many times daily between self-contained facilities and the regular facilities?</b></p> <p><b>A. Movement of personnel between self-contained and other facilities must be subject to procedures that will prevent cross-contamination. This may include but is not limited to decontamination procedures such as showering and change of clothes.</b></p>

## COMPLIANCE AND ENFORCEMENT NEWS

**As the globalization of Active Pharmaceutical Ingredient (API), also known as Bulk Drug Substance (BDS), manufacturing continues, some compliance trends for several regions are emerging. The following Table, from an analysis of FDA Inspections, lists compliance hot spots for several important regions.**

Region	Frequently Observed Compliance Problems of API/BDS Manufacturers
USA	<ul style="list-style-type: none"> <li>• Failure to perform or deficient investigations of Out Of Specification (OOS) results and complaints</li> <li>• Inadequate training of personnel</li> <li>• Incomplete documentation of GMP analytical methods</li> <li>• No or inadequate Qualification of suppliers and contract labs</li> <li>• Failure to perform or inadequate analytical methods validation</li> <li>• Failure to qualify all analytical instruments/equipment</li> <li>• Failure to calibrate analytical balances and other equipment</li> <li>• Missing or deficient cleaning protocols</li> </ul>
Canada	<ul style="list-style-type: none"> <li>• Inappropriate facilities design to prevent contamination and cross-contamination</li> <li>• Failure of the Quality Unit to perform its required functions</li> <li>• Failure to perform or inadequate Process Validation</li> <li>• Cleaning validations not done or incomplete</li> <li>• Missing or deficient SOP(s) for: <ul style="list-style-type: none"> <li>- Preventing contamination and cross-contamination</li> <li>- Change Control</li> <li>- OOS investigations</li> <li>- Handling and management of deviations</li> <li>- Handling and management of complaints</li> <li>- Conducting Annual Product Reviews</li> </ul> </li> <li>• Failure to perform or deficient investigations of Out Of Specification (OOS) results</li> <li>• Missing raw data from QC analyses</li> <li>• Failure to record all information in Batch Records at time of occurrence</li> </ul>
China	<ul style="list-style-type: none"> <li>• Missing or inadequate procedures to prevent cross-contamination</li> <li>• Inadequate analytical procedures for Quality and Process control</li> <li>• Failure to perform or inadequate analytical methods validation</li> <li>• Failure to confirm ability of stability methods to be stability indicating</li> <li>• Failure to perform special stability studies after API re-processing</li> <li>• Deficient complaint investigations</li> <li>• Inadequate calibration program for QC lab equipment</li> <li>• Failure to perform or inadequate Performance Qualification (PQ) of QC lab equipment</li> </ul>

## COMPLIANCE AND ENFORCEMENT NEWS

**Continuing its saga of regulatory problems**, the American Red Cross (ARC), which has been operating under an Amended Consent Decree of Permanent Injunction issued 15-April, 2003, has received an Adverse Determination Letter from FDA. In the Letter, FDA referred to inspections of 16 ARC Blood Services facilities which occurred during 2010.

Under the aforementioned Consent Decree, ARC is required to "establish and properly implement appropriate quality assurance (QA) and quality control (QC) measures." Further, "Proper QA and QC programs by blood establishments include measures to prevent, detect, investigate, evaluate, and correct errors."

Decree Violations cited by FDA in Adverse Determination Letter include the following:

1. Failure to establish, implement and continuously maintain managerial control over QA in all regions and laboratories
2. Inadequate QA
3. Failure to comply with reporting requirements
4. Inadequate National Donor Deferral Register
5. Inadequate problem management
6. Failure to promptly, thoroughly, and adequately investigate and correct problems
7. Failure to follow Standard Operating Procedures
8. Inadequate system for distribution or receipt of blood products
9. Failure to ensure that supplies are used in a manner consistent with the manufacturer's instructions
10. Failure to establish, maintain and follow written procedures that include all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components for transfusion and further manufacturing purposes
11. Inadequate training and staffing levels
12. Inadequate recordkeeping

In addition, the Letter lists 17 specific actions which FDA is ordering ARC to complete, mostly providing information such as Status Updates, and states that fines totaling almost \$9.6 million are being assessed. A new feature is that fines are now being charged on a per diem basis for each violation, rather than a flat \$10,000 per day as before.

To see the 32 page Adverse Determination Letter, which includes details and breakdowns of the items summarized above, point your browser to: <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAElectronicReadingRoom/UCM287834.pdf>

The main FDA web page regarding the ARC's regulatory problems can be found here: <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORAElectronicReadingRoom/ucm183503.htm>

### INSPECTION NEWS

**Joint inspections and sharing of inspectional information** among regulatory agencies are on the rise and are expected to continue to increase throughout 2012 (see BioQuality December, 2011 16(12) for a related story). Sterile manufacturing/aseptic processors seem to be, as would be expected in the present risk-driven regulatory climate, a strong initial focus of the initiatives behind these increased "multi-agency" inspections.

Ben Venue Laboratories has been a recent recipient of such an inspection, and although not a biopharmaceutical manufacturer, Ben Venue is a sterile products manufacturer and so reviewing this inspection should be informative for the biopharmaceutical, biologics world.

Here is EMA's summary of a joint inspection, involving the FDA and two European inspectorates of a Ben Venue site in Ohio: "A joint GMP inspection of the site, where a number of sterile medicines are manufactured, by the United Kingdom and French medicines regulatory agencies together with the United States Food and Drug Administration (FDA) on 7-11 November 2011 highlighted several shortcomings in the quality-management system, particularly in relation to the aseptic filling process in the North complex of the Ben Venue facility. During the inspection, Ben Venue decided to cease all manufacture and distribution of medicines from its site, which has been the object of increased GMP surveillance, and to investigate the GMP issues identified". To read the EMA Press Release: [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news\\_and\\_events/news/2011/11/news\\_detail\\_001392.jsp&mid=WC0b01ac058004d5c1](http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/11/news_detail_001392.jsp&mid=WC0b01ac058004d5c1)

Oddly, FDA's announcement about this matter does not mention the joint inspection all, but states that "On November 19, 2011, Ben Venue Laboratories, Inc. ("BVL") announced the voluntary shutdown of manufacturing and distribution at its site in Bedford, Ohio due to significant manufacturing and quality concerns. BVL's decision to shut down is a result of their own findings." To see the FDA announcement: <http://www.fda.gov/Drugs/DrugSafety/ucm281782.htm>

Ceasing all manufacture and distribution of medicines? Ouch! If history is any indication, the early stages of these joint inspection may, as did early Team Biologics inspections, involve some degree of "one-upmanship" to demonstrate how rigorously each agency enforces its regulations. So, get you plants and labs ready, because you are quite likely to be on the receiving end of one of these inspections sooner rather than later.

## Blog Buzz

### House Bill Would Improve Access to Investigational Medicines for Rare Diseases

In a January article in **The FDA Law Blog** ([http://www.fdalawblog.net/fda\\_law\\_blog\\_hyman\\_phelps/](http://www.fdalawblog.net/fda_law_blog_hyman_phelps/)), Kurt R. Karst discusses H.R. 3737, the Unlocking Lifesaving Treatments for Rare-Diseases Act (ULTRA). Mr. Karst, quoting one of the bill's sponsors, writes that "The bill would amend the FDC Act to 'improve access to the existing accelerated approval pathway for patients with life threatening ultra-rare genetic diseases with the added attribute of promoting private investment in new biotechnology companies and job growth in the United States.'"

### Setting Your Records Straight

A recent GMP News post by the European Compliance Academy (ECA) provides a reminder of the importance of properly archiving complete paper and electronic GMP records. The unnamed author writes " Demonstrating the integrity and security of laboratory data, records, results and information is paramount for a successful audit or inspection for any GMP regulated quality control laboratory."

The informative post goes on to give several examples from FDA Warning Letters issued in 2009 and 2010:

#### **This company did not keep track of its chromatograms**

- The gas chromatographic analysis performed and the data provided to the application sponsor is not traceable to raw data. The original chromatograms could not be located during the inspection. (FDA Warning Letter, September 2010)

#### **This company was found to have falsified data, thus calling into suspicion all data from the lab**

- An analyst substituted IR spectra from a passing batch: This practice is unacceptable and raises serious concerns regarding the integrity and reliability of the laboratory analyses conducted by your firm. (FDA Warning Letter, January 2010).

#### **This company sent FDA incomplete lab notebooks in their response to a Warning Letter**

- Note that the copies of analytical notebooks submitted in your response remain incomplete in that they lacked: laboratory equipment/instrument information; standards and reagents information; filter information; dates and signatures of the persons who performed each test and reviewed the data; reference to the test method, version number, and effective date; and statement of how the test results compare with acceptance criteria. (FDA Warning Letter, August 2009).

To see the entire post: [http://www.gmp-compliance.org/eca\\_news\\_2915\\_7306@@menuopt@@.html](http://www.gmp-compliance.org/eca_news_2915_7306@@menuopt@@.html)

### eStability Reporting: the once and future topic

According to a recent post by George Miller on FiercePharma Manufacturing (<http://www.fiercepharmamanufacturing.com/>), FDA is again showing interest in its Electronic Stability Reporting Initiative, which the agency started back in 1999. Miller writes "Watch for eStability reporting to become mandatory in the 'next few years,' said Catherine Hosage Norman, an expert in stability submissions and enthusiastic supporter of the FDA's eStability effort. Speaking at last night's PDA New England chapter meeting in Woburn, MA, she said the agency wants to improve stability data exchange." However, "To some observers," Miller adds, "'next few years' is a phrase that sometimes lacks meaning in regulatory initiatives, especially those in process for more than a decade."

### Firm Cited for "Cover-up" at Meeting Booth

This is not a biopharma or biological product, but the same thing could happen to any firm regulated by FDA. Ed Silverman, in his *Pharmalot* Blog (<http://www.pharmalot.com/>) reports that NeurogesX got an Untitled Letter from FDA for obscuring risk information at the bottom of a panel in their booth at the American Academy of Nurse Practitioners meeting in Las Vegas. Writes Silverman:

"To be specific, the risk info was noted at the bottom of the display panels, but this was apparently obscured by bags, boxes and other stuff. This meant the safety info was inaccessible to those who stopped or walked by. As a result, the FDA deemed the entire booth to be false or misleading for presenting efficacy claims, but not risk info, according to an untitled letter written on December 13."

"How did the FDA know? Well, the obscured panel was seen by three different personnel from the FDA Office of Prescription Drug Promotion, each of whom viewed the booth separately at three separate times. In other words, there was ample opportunity for NeurogesX employees to move the stuff, but they apparently never bothered."

To see the offending panel: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM283646.pdf>

To see the Untitled Letter: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM283644.pdf>

**ICH News**

**After more than 5 years in development**, ICH Q11, *Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)*, should complete Step 4 soon, at which point it will be adopted as official guidance in the ICH region (Europe, Japan, US) and beyond.

After reviewing and evaluating over 1,300 total and around 200 unique comments during Step 3 Review, the EWG (Expert Working Group) made significant changes to the Step 2 document, which was released on 19 May, 2011. The revised document is now undergoing review by ICH regulatory agencies. Here are some highlights of what to expect in the Final Guidance when it is released:

- The definition in Q11 for critical quality attributes (CQAs), and general statements about those attributes will remain the same as that found in Q8R
- Continuation of the concept that CQAs are for the drug substance, but not for raw materials, starting materials or intermediates.
  - ⇒ “Q11 does not specifically say that only the drug substance itself has CQAs, although there is a strong hint of that,” said Q11 rapporteur Brian Withers, from Abbott UK, at a recent meeting in Europe.
- Addition of a section on the inherent limitations in detecting a CQA in the drug substance itself
  - ⇒ For example, in some instances a CQA such as virus testing may need to be performed downstream for the drug substance
- Changes in the following sections
  - ⇒ Manufacturing process development
    - ◆ for example, a toning down of expectations for providing information on the reasons changes were made during development and the impact of those changes on quality
  - ⇒ Design Space
    - ◆ for example, a paragraph was added for biotech products that includes comments on movement within the design space and the management of residual risk, ie how movements within the design space will be managed post approval
  - ⇒ Manufacturing process description
  - ⇒ Starting materials definition
  - ⇒ Use of commercially-available chemicals
  - ⇒ Control strategies
  - ⇒ Process validation
  - ⇒ CTD (Common Technical Document) submission
  - ⇒ Product lifecycle management

BioQuality will be bringing you a bullet-point summary of Q11 as soon as a Notice of Availability--indicating FDA adoption--appears in the Federal Register.

To see the current Step 2 version of Q11: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Quality/Q11/Step\\_2/Q11\\_Step\\_2.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q11/Step_2/Q11_Step_2.pdf)

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or Mail: PO Box 7087, Citrus Heights, CA 95621

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