BIOQUALITY

ISSUE NUMBER 18 (10)| OCTOBER | 2013

 ISSN: 1090-2759

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HCP Testing, Some Points to Consider

By Dr. Martin Vanderlaan,

In a recent article of BioQuality (July/August 18(7/8)), Dr. Laureen Little pointed out one controversial topic in the subject of host cell protein testing, namely, what sort of cell line should be used for the blank run to generate the anti-HCP antibody reagents. The issue is whether a "mock transfection" is needed, or whether the parental cell line without the expression vector is sufficient. Dr. Little cited a 2005 European Pharmacopea requirement for a mock transfection.

As with most things in host cell protein analysis, "it's a little more complicated" than might first appear. First, the choice of blank run cells might depend on whether one is discussing a mammalian or bacterial expression system. In the case of mammalian cells, the expression vector may only carry the selective marker (e.g. DHFR or Glutamine synthetase). In bacterial systems, the vector might also contain several chaperones in addition to the selective marker. Using a mock transfected cell line does, at least, potentially allow the assay originator to claim that these additional proteins were present in the immunogen whether or not they are immunogenic or result in antibodies to these proteins.

From the standpoint of the spectrum of anti-HCP antibodies that are produced, the question is whether the addition of one protein or a few proteins matters in the context of the thousands of proteins that are normally expressed by host cells. To some extent, the answer to that question may depend on how "overexpressed" the chaperones and selective proteins are. If chaperones are highly expressed (they can reach 5% of the total ECP proteins), they may be the immunodominant protein in the immunogen, eliciting many high affinity antibodies that participate in the sandwich immunoassay for HCPs to the detriment of antibodies to other HCPs (there is, after all, only a limited amount of surface area on microtiter plates). The sandwich immunoassay readout is "immunologically weighted", with highly immunogenic HCPs counting for more than weakly or non-immunogenic ones. In cases of chaperone overexpression, it may be a better strategy to make specific immunoassays for the over-expressed chaperones, and a general anti-HCP assay using the blank run of the parental cell line without the vector.

In the opposite case, where vector proteins are expressed at levels comparable to the many other proteins in the matrix, then they may or may not be immunogenic. In that case the question of parental vs. mock-transfected cell line becomes moot.

There are other issues that may also impact the immunochemical reagents beyond the choice of immunogen. For example, production culture conditions are optimized to produce high growth, high viability cultures for the particular clone that is selected for production. These conditions might not be equally optimal for the parental cell line (transfected or not). Optimal growth condi-

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HCP Testing Continued

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tions of a given clone may not translate into comparable growth of the host line, affecting viability of the blank run culture, which could affect the relative abundance of cytoplasmic proteins. It may be that cell viability trumps the choice of whether or not to use mock transfected cells in terms of the antibodies that result. But then, production runs also may differ in viability. So how can one or a few blank runs mimic the complete range one sees in production? Some companies pool the HCCF with cell lysate to include both secreted HCPs and intracellular soluble HCPs.

It is unlikely that any anti-HCP antibody prep can guarantee coverage of all possible HCPs, and using a mock transfected cell line does not change this. All this leads to a more fundamental question - what part of the control system is set up to guard against the possible presence of HCPs that are only weakly or non-immunogenic? Orthogonal methods that supplement the HCP ELISA may be employed to look for HCPs that the immunoassay misses. A variety of these orthogonal methods exist: SDS-PAGE gels stained with a high sensitivity total protein stain such as silver or fluorescent dyes, Western Blots of final product gels, and LC-MS/MS to identify peptides of HCP origin.

The CASSS (CASSS.org) will be hosting a workshop in January as part of the WCBP meeting in Washington DC to discuss methods of HCP detection. The workshop will be led by Ned Mozier of Pfizer and myself. In addition BEBPA (BEBPA.org) will host a meeting on HCP methods in Dubrovnik in May 2014. Both meetings are platforms to discuss how the HCP Immunoassay should be used in the context of a system of assays that seek to establish product purity by both immunological and non-immunological means.

Martin Vanderlaan, Ph.D., MBA, is Director of Analytical Operations at Genentech. This centralized testing laboratory is unique in the Roche network of sites, and provides analytical testing using such diverse analytical methods as PCR, ICP-MS, HPLC-MS, CE, FTIR, and ELISAs. Dr. Vanderlaan can be reached at: vanderlaan.martin@gene.com.

BEBPA Presents:

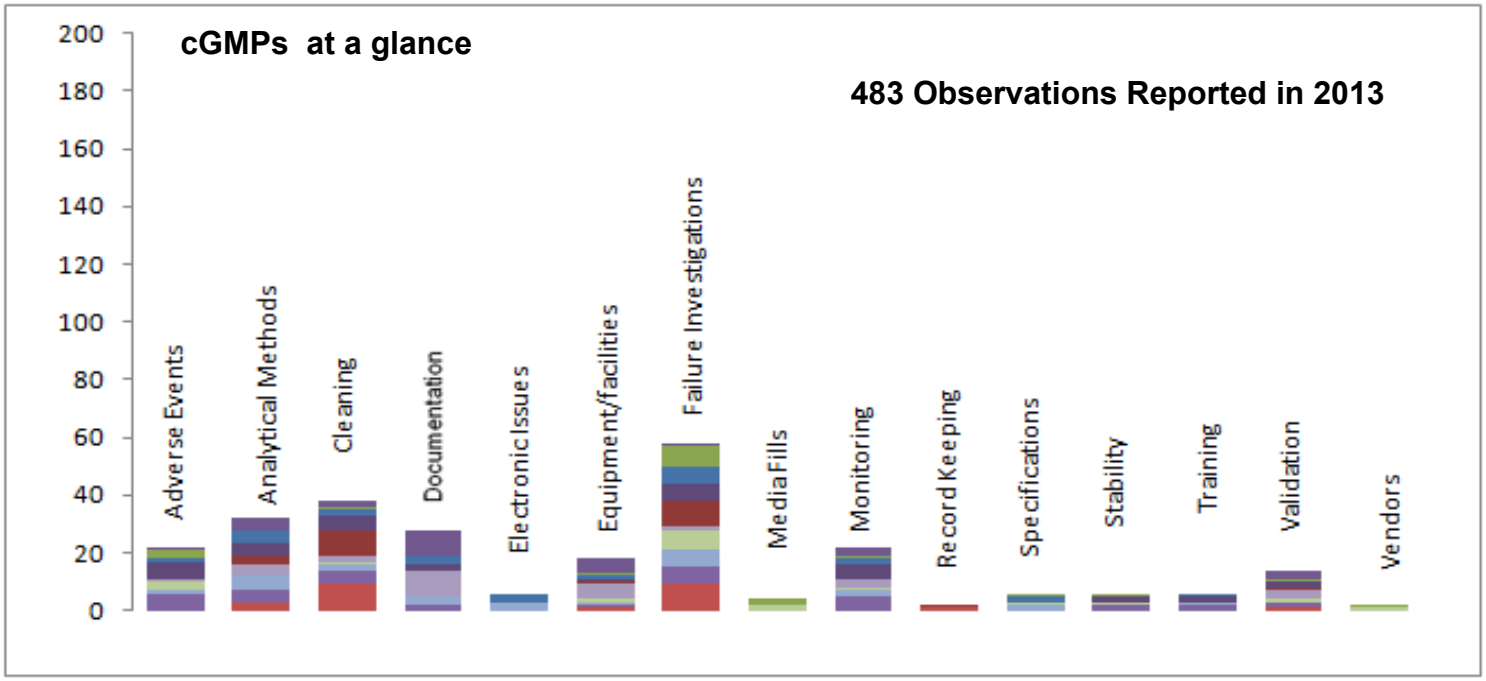
Host Cell Protein Methods Workshop

May 15-16, 2014~ Dubrovnik, Croatia

We are pleased to announce our first HCP Workshop to take place May 15-16, 2014 in Dubrovnik, Croatia. If you would like to present on any of the following topics or any other of your choosing, we'd like to hear from you:

- LC-MS/MS for identifying specific HCPs. What techniques, how applied?
- "High risk" HCPs. What properties of an HCP make it likely to co-purify with product. How can these high risk HCPs be identified?
- Demonstration of antibody coverage. Approaches to determining how broadly reactive are the antibodies raised. How does one maximize the response to weakly immunogenic proteins?
- Platform immunochemical reagents – What is the design-space of the assay platform? How much may the upstream cell culture conditions vary and still be suitable for the platform assay? What is needed to qualify a new process for the platform.
- HCP Immunoaffinity purification of anti-HCP antibodies – a requirement? Is there evidence that just using the IgG fraction of a well immunized animal is sufficient?
- What role do HCP assays play in the control system during product life-cycle? As CofA tests, or In-process tests, or can they be dropped once process validation of the commercial process demonstrates robust clearance?
- Orthogonal methods for demonstrating purity. What role do methods other than Sandwich immunoassay have? What is the role of 1D and 2D gels and Western Blots, CE-SDS and peptide maps?
- Validation of HCP immunoassays – the mathematics of LOQ, meaning of specificity and accuracy, dealing with dilution dependence and relative capture efficiency.
- Setting limits for HCP assays – Case studies in patient exposure; Safety vs. manufacturing capability. Targets, trends, and reject limits.
- International regulatory approaches to HCP data reporting, assays and standards. Meeting the expectations of the FDA, EMA, Japanese and Chinese HA.
- Biosimilars – matching the impurity profile of the innovator?
- Immunogenicity predictions. How good are models for predicting which impurities will be immunogenic in humans.
- Measuring the response of patients to impurities. Case studies in co-purifying host cell proteins and the clinical consequences.

Interested in presenting? Please fill out the abstract form Here or email: bebpa@surewest.net



GMP System: FE = Facilities and Equipment System**; L** = Laboratory Controls System**; M** = Materials System**; PL** = Packaging and Labeling System**; Pr** = Production System**; Q** = Quality System

Type of Establishment Inspected: BD = Biologic Device manufacturer**; CMO** = Contract Manufacturing Organization**; CTO** = Contract Testing Organization**; DS** = Drug Substance/API manufacturer**; FP** = Final Product manufacturer

Type of Product(s) Inspected: BD = biologic device; **CT** = cellular therapy product
GT = gene or other nucleic acid product (includes nucleic acid-based vaccines, coded GTv); **mAb** = monoclonal antibody product; **Pe** = peptide; **rDN**A = recombinant DNA product (includes vaccines produced by rDNA technology, coded rDNAv); **SP** = miscellaneous sterile biologic product; **TPh** = traditional (chemically-synthesized) pharmaceutical (these will only be included if the 483 is both important and cross-cutting); **tVac** = traditional vaccine (e.g. live-attenuate or whole-killed virus)

Location of Establishment Inspected: CA = Canada**; CH** = China**; EU** = Europe**; IN** = India**; LA** = Latin America**; US** = United States

Category	Cause for Recently Issued 483 Notices of Deficiency
Adverse Events, Complaints, & FDA Notification	(Q; FP; CT; US) Firm failed to establish and follow written procedures describing the handling of all written and oral complaints regarding a drug product ➢ Specifically, during the inspection firm could not provide evidence of the existence of written procedures describing the handling of written and oral complaints related to the AdMSC (adipose derived mesenchymal stem cells) product.
Analytical Methods, Sampling, In-process Controls	(L; FP; CT; US) Firm failed to maintain laboratory controls that include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to: ➢ Assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity ➢ Specifically, firm does not perform testing of the final AdMSC (adipose derived mesenchymal stem cells) product, including tests for identity, safety, purity and potency.

Category	Cause for Recently Issued 483 Notices of Deficiency
Analytical Methods, Sampling, In-process Controls	(L; FP; CT; US) Firm failed to test the AdMSC (adipose derived mesenchymal stem cells) product, a [redacted by FDA] drug product, for the presence of [redacted by FDA] although: ➢ a reasonable possibility exists that the [redacted by FDA] drug product has been exposed to cross contamination with [redacted by FDA] ➢ The firm used [redacted by FDA] during culturing of the AdMSC product ➢ Specifically, [redacted by FDA] was used during manufacturing of [redacted by FDA] batches of your AdMSC product reviewed ➢ The [redacted by FDA] drug product must not be marketed if detectable levels of [redacted by FDA] are found (L; FP; CT; US) Firm failed to assure that each lot of components, drug product containers, and closures are withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit ➢ For example, the following components and containers are not tested or examined before release: ➢ The [redacted by FDA] used to rinse the cells and formulate the final drug product. More importantly, the Certificate of Analysis for the [redacted by FDA] states: "For in vitro diagnostic use. CAUTION: Not for human or animal therapeutic use. Uses other than the labeled intended use may be a violation of local law." ➢ The [redacted by FDA] that contain the final product. (L; FP; CT; US) There are no procedures for receipt, identification, storage, handling, sampling, testing, and approval or rejection of the following supplies and components used to culture and expand the AdMSC intermediates: ➢ The [redacted by FDA] used to prevent bacterial and fungal growth in the culture media. ➢ The [redacted by FDA] and [redacted by FDA] used for cell expansion ➢ The [redacted by FDA] used to harvest the AdMSC intermediates ➢ The [redacted by FDA] amd [redacted by FDA] conical [redacted by FDA] tubes ➢ The [redacted by FDA] and [redacted by FDA] serological pipettes ➢ The [redacted by FDA] added to the cells as a [redacted by FDA]
Cleaning & Cleanliness Issues	(FE; FP; CT; US) Firm failed to establish a written record of major equipment cleaning, maintenance and use to include in that record the date, time, product and lot number of each batch processed ➢ For example, there are no written records of cleaning, maintenance and use for the [redacted by FDA] and BSCs (biological safety cabinets) used for aseptic processing or the refrigerators and freezers used to store [redacted by FDA] and reagents used to manufacture the AdMSC (adipose derived mesenchymal stem cells) product (Pr; FP; CT; US) The [redacted by FDA] and [redacted by FDA] used in production are placed directly on the floor rather than elevated on tables. In addition, discarded [redacted by FDA] and media bottles were observed next to this equipment during use
Documentation, Recordkeeping, Change Control, and General Quality Issues	(Q; FP; CT; US) Firm failed to assure all drug product production and control records, including those for packaging and labeling, are reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before the batch is released or distributed ➢ There was no evidence of review and approval by the quality control unit prior to release of any of the [redacted by FDA] batches of your AdMSC (adipose derived mesenchymal stem cells) product.

Category	Cause for Recently Issued 483 Notices of Deficiency
Documentation, Recordkeeping, Change Control, and General Quality Issues	(Pr; FP; CT; US) Firm failed to assure batch production and control records are prepared for each batch of drug product produced and that each significant step is documented in the manufacture, processing, packing, or holding of the batch was accomplished ➢ For example: ➢ There is no documentation of the addition of [redacted by FDA] to your final AdMSC product. ➢ There is no documentation of the personnel involved in packaging of the final AdMSC product (Q; FP; CT; US) Firm failed to assure that distribution records contain the name and strength of the product and the description of the dosage form, and the name and address of the consignee ➢ Specifically, of the [redacted by FDA] batches reviewed, all were lacking a product name, dosage form, and the name and address of the consignee (Q; FP; CT; US) Firm failed to establish a quality control unit that: ➢ Has the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated ➢ Has the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the product ➢ Has the responsibilities and procedures applicable to the quality control unit in writing (Q; FP; CT; US) Firm failed to label each HCT/P in accordance with the requirements in 21 CFR 1271.370. For example: ➢ The following information does not appear on the AdMSC product label: a distinct identification number affixed to the HCT/P container, and assigned in accordance with 21 CFR 1271.290(c); a description of the type of HCT/P; an expiration date, if any ➢ The AdMSC product, which is for autologous use, was not prominently labeled as being “For autologous use only.” This warning is required under 21 CFR 1271.90(b). (Pr; FP; CT; US) Firm does not document the daily checks of the culture [redacted by FDA] for evidence of contamination (Pr; FP; CT; US) Firm does not document the temperature of your [redacted by FDA] used during the adipose tissue step for isolating stem cells ➢ The Batch Production Record specifies that the temperature of the [redacted by FDA] be [redacted by FDA] degrees Celsius for the [redacted by FDA] step (Pr; FP; CT; US) The components used in production were not always labeled correctly, which could result in mix-ups. For example: ➢ A bottle labeled [redacted by FDA] on one side was labeled [redacted by FDA] on the other ➢ A bottle containing the culture medium [redacted by FDA] (mesenchymal stem cell attachment culture medium supplemented with [redacted by FDA] was labeled [redacted by FDA] on the lid, but [redacted by FDA] on the side (Pr; FP; CT; US) Firm had no records of frozen vials of isolated AdMSCs, which had not been expanded in culture, which were received from the RNL locations in Germantown, MD, and Seoul, Korea for use in manufacturing

Category	Cause for Recently Issued 483 Notices of Deficiency
Equipment/Facilities/Operations	(Pr; FP; CT; US) Firm failed to establish and follow written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures ➢ Specifically, there are no written procedures in place for the supplies and reagents used to manufacture the AdMSC (adipose derived mesenchymal stem cells) product (FE; FP; CT; US) Firm failed to assure that automatic, mechanical and electronic equipment used in the manufacture, processing, packing and holding of a drug product is routinely calibrated, inspected or checked according to a written program designed to assure proper performance, and that written records of those calibration checks and inspections are maintained ➢ Specifically, there is no evidence that operational or performance qualification has been performed for the BSCs (biological safety cabinets) to assure their proper function. (Pr; FP; CT; US) Firm failed to assure an adequate control system for temperature and humidity is in place to prevent contamination during aseptic processing ➢ Specifically, there is no system for the monitoring of temperature or humidity of the processing rooms at the facility, where the AdMSC product is manufactured. ➢ The manufacturer's manual for your [redacted by FDA] BSCs states that they should be operated in environmental conditions of a maximum relative humidity of (b)(4) (FE; FP; CT; US) Firm has not qualified any of the equipment used in manufacture, processing, packaging and holding of your AdMSC (adipose derived mesenchymal stem cells) intermediates (FE; FP; CT; US) There are no procedures designed to assure proper performance of equipment used in the culture/expansion of AdMSC intermediates. For example: ➢ No calibration was performed [redacted by FDA] for temperature and [redacted by FDA] to assure that their displays are accurate. Your manufacturing record specifies that culture is to be performed [redacted by FDA] degrees Celsius and [redacted by FDA] ➢ There is no indication that the temperature of the refrigerators and freezers used to store culture media, [redacted by FDA], and reagents used to manufacture the AdMSC product is consistently monitored.
Investigations, Deviations, Change Control Tracking, Trending, and Corrective and Preventive Actions (CAPA)	(Q; FP; CT; US) Firm failed to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed ➢ For example, there were no investigations performed for the following: ➢ There were numerous in-process sterility failures for AdMSC (adipose derived mesenchymal stem cells) batches ➢ Bacterial and fungal limits have been exceeded for the Biological Safety Cabinets (BSCs) used in manufacturing, and in the gowning and general areas.
Monitoring and Contamination Issues	(FE; FP; CT; US) Firm failed to assure an air supply filtered through high-efficiency particulate air filters under positive pressure for aseptic processing operations is in place to prevent contamination during aseptic processing ➢ Specifically, the facility does not filter the air supply through high-efficiency particulate air filters under positive pressure between the clean rooms and the exterior rooms to assure that non-controlled air does not flow into the clean rooms (Pr; FP; CT; US) Routine personnel monitoring is not performed

Category	Cause for Recently Issued 483 Notices of Deficiency
Monitoring and Contamination Issues	(L; FP; CT; US) Firm failed to assure a system for monitoring environmental conditions is in place to prevent contamination during aseptic processing ➢ Specifically, facility does not have an established environmental monitoring program.
Validation	(Pr; FP; CT; US) Firm has failed to establish and follow written procedures designed to prevent microbiological contamination of drug products purporting to be sterile. ➢ Specifically, all aseptic and sterilization processes have not been validated. For example: o The aseptic manufacturing process at one facility has not been validated. o Firm has not validated aseptic gowning process o Firm has not validated autoclave sterilization cycle for an autoclave which is used to sterilize equipment used in aseptic processing (Pr; FP; CT; US) Firm failed to establish and follow written production and process control procedures designed to: ➢ assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess ➢ assure such procedures are drafted, reviewed and approved by the appropriate organizational units ➢ For example, firm failed to validate the manufacturing process one of its facilities (Pr; FP; CT; US) Firm has not validated the cell culture process and the aseptic processing involved in culturing of the cells ➢ There were numerous in-process sterility failures for AdMSC (adipose derived mesenchymal stem cells) batches indicating a lack of control of the aseptic process.

In the Federal Register

Guidance Documents

Draft Guidance for Industry on Bioanalytical Method Validation; Availability

Reference and FR Link: Federal Register Volume 78, Number 178 (Friday, September 13, 2013), Pages 56718-56719; http://www.gpo.gov/fdsys/pkg/FR-2013-09-13/pdf/2013-22309.pdf

FDA Docket Number: FDA-2013-D-1020

Summary: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled ``Bioanalytical Method Validation.'' The draft guidance is intended to provide recommendations regarding analytical method development and validation for the measurement of drugs and/or metabolites, therapeutic biologics, and biomarkers for sponsors of investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics license applications (BLAs) for therapeutic biologics regulated by the Center for Drug Evaluation and Research. This draft guidance may apply to some studies related to the veterinary drug approval process (Investigational New Animal Drugs (INADs), New Animal Drug Applications (NADAs), and Abbreviated New Animal Drug Applications (ANADAs)) regulated by the Center for Veterinary Medicine. This guidance was originally issued in 2001. FDA is revising the guidance to reflect advancements in the science and technology of bioanalytical method validation.

Effective Date or Comment Date: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by December 12, 2013.

Addresses: Submit written requests for single copies of the revised draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 2201, Silver Spring, MD 20993-0002, or
Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Pl., Rockville, MD 20855. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

In the Federal Register

Submit electronic comments on the draft guidance to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Contact for More Information: Brian Booth, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 2186, Silver Spring, MD 20993-0002, 301-796-1508; or John Kadavil, Center for Veterinary Medicine (HFV-151), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 240-276-9589.

To download the Guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf

International Conference on Harmonisation; Draft Guidance on Elemental Impurities; Availability

Reference and FR Link: Federal Register Volume 78, Number 205 (Wednesday, October 23, 2013), Pages 63219-63220; http://www.gpo.gov/fdsys/pkg/FR-2013-10-23/pdf/2013-24786.pdf

FDA Docket Number: FDA-2013-D-1156

Summary: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance entitled ``Elemental Impurities.'' Prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), this guidance is intended to develop a harmonized approach for the control of elemental impurities that helps industry avoid the uncertainty and duplication of work resulting from differing requirements across ICH regions. It includes the specific elements to be limited and the appropriate limits for impurities, and emphasizes control of supply chains and risk assessments. It is expected to provide appropriate safety-based limits for the control of elemental impurities, consistent expectations for test requirements and regulatory filings, and a global policy for limiting elemental impurities, both qualitatively and quantitatively, in drug products and ingredients.

Effective Date or Comment Date: Although you can comment on any guidance at any time (see 21 CFR 10.115 (g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by December 23, 2013.

Addresses: Submit written requests for single copies of the draft guidance to the Division of Drug Information, Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002, or the Office of Communication, Outreach and Development (HFM-40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist the office in processing your requests. The draft guidance may also be obtained by mail by calling CBER at 1-800-835-4709 or 301-827-1800. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

Submit electronic comments on the draft guidance to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Contact for More Information: Regarding the guidance: John Kauffman, CDER, Food and Drug Administration, 1114 Market St., DPA Facility, suite 1002, St. Louis, MO 63101, 314-539-2135. Regarding the ICH: Michelle Limoli, International Programs, CDER, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 3342, Silver Spring, MD 20993-0002, 301-796-8377.

To download the Guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM371025.pdf

International Conference on Harmonisation; Guidance on Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the International Conference on Harmonisation Regions; Annex 14 on Bacterial Endotoxins Test General Chapter; Availability

Reference and FR Link: Federal Register Volume 78, Number 205 (Wednesday, October 23, 2013), Pages 63221-63222; http://www.gpo.gov/fdsys/pkg/FR-2013-10-23/pdf/2013-24784.pdf

FDA Docket Number: FDA-2010-D-0343

Summary: The Food and Drug Administration (FDA) is announcing the availability of a guidance entitled ``Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the International Conference on Harmonisation Regions; Annex 14: Bacterial Endotoxins Test General Chapter.'' The guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guidance provides the results of the ICH Q4B evaluation of the Bacterial Endotoxins Test General Chapter harmonized text from each of the three pharmacopoeias (United States, European, and Japanese) represented by the Pharmacopoeial Discussion Group (PDG). The guidance conveys recognition of the three pharmacopoeial methods by the three ICH regulatory regions and provides specific information regarding the recognition. The guidance is intended to recognize the interchangeability between the local regional pharmacopoeias, thus avoiding redundant testing in favor of a common testing strategy in each regulatory region. The guidance is in the form of an annex to the core guidance on the Q4B process entitled ``Q4B Evaluation and Recommendation of Pharmacopoeial Texts for Use in the ICH Regions (core ICH Q4B guidance).

Effective Date or Comment Date: Submit either electronic or written comments on Agency guidances at any time.

Addresses: Submit written requests for single copies of the guidance to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research (CDER), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002, or the Office of

In the Federal Register Continued…

Communication, Outreach and Development (HFM-40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist the office in processing your requests. The guidance may also be obtained by mail by calling CBER at 1-800-835-4709 or 301-827-1800. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

Submit electronic comments on the guidance to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Contact for More Information: Regarding the guidance: Robert King, Sr., Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 4166, Silver Spring, MD 20993-0002, 301-796-1242; or Stephen Ripley, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike,
suite 200N, Rockville, MD 20852-1448, 301-827-6210.

Regarding the ICH: Michelle Limoli, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 3342, Silver Spring, MD 20993-0002, 301-796-8377.

To Download the Guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM219167.pdf

Draft Guidance for Industry: Use of Nucleic Acid Tests To Reduce the Risk of Transmission of West Nile Virus From Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products; Availability

Reference and FR Link: Federal Register Volume 78, Number 206 (Thursday, October 24, 2013), Pages 63476-63477; http://www.gpo.gov/fdsys/pkg/FR-2013-10-24/pdf/2013-24940.pdf

FDA Docket Number: FDA-2013-D-1143

Summary: The Food and Drug Administration (FDA) is announcing the availability of a draft document entitled ``Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus From Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps),'' dated October 2013. The draft guidance document provides establishments that make donor eligibility determinations for donors of HCT/Ps, with recommendations for donor testing for West Nile Virus (WNV) using an FDA-licensed donor screening test. The guidance recommends the use of an FDA-licensed nucleic acid test (NAT) for testing donors of HCT/Ps for infection with WNV. The draft guidance replaces the draft guidance entitled ``Guidance for Industry: Use of Nucleic Acid Tests to Reduce the Risk of Transmission of West Nile Virus From Donors of Whole Blood and Blood Components Intended for Transfusion and Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)'' dated April 2008, with respect to HCT/Ps. The testing recommendations in the guidance, when finalized, will supplement the donor screening recommendations for WNV (which will remain in place) that were made in the guidance entitled ``Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)'' dated August 2007 (2007 Donor Eligibility Guidance).

Effective Date or Comment Date: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit either electronic or written comments on the draft guidance by January 22, 2014.

Addresses: Submit written requests for single copies of the draft guidance to the Office of Communication, Outreach and Development (HFM-40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist the office in processing your requests. The draft guidance may also be obtained by mail by calling CBER at 1-800-835-4709 or 301-827-1800. See the SUPPLEMENTARY INFORMATION section for electronic access to the draft guidance document.

Submit electronic comments on the draft guidance to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

Contact for More Information: Benjamin A. 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.

Information Collection Activities

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Requirements for Submission of Labeling for Human Prescription Drugs and Biologics in Electronic Format

Reference and FR Link: Federal Register Volume 78, Number 178 (Friday, September 13, 2013), Pages 56715-56717; http://www.gpo.gov/fdsys/pkg/FR-2013-09-13/pdf/2013-22312.pdf

FDA Docket Number: FDA-2013-N-0577

Summary: The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

Contact for More Information: FDA PRA Staff, Office of Operations, Food and Drug Administration, 1350 Piccard Dr., PI50-400B, Rockville, MD 20850, PRAStaff@fda.hhs.gov.

Meetings

Complex Issues in Developing Drug and Biological Products for Rare Diseases; Public Workshop; Request for Comments

In the Federal Register Continued…

Reference and FR Link: Federal Register Volume 78, Number 184 (Monday, September 23, 2013), Pages 58311-58313; http://www.gpo.gov/fdsys/pkg/FR-2013-09-23/pdf/2013-22959.pdf
FDA Docket Number: FDA-2013-N-0985
Meeting Date(s) and Time: The public workshop will be held on January 6, 2014, from 8 a.m. to 5 p.m. and on January 7, 2014, from 8 a.m. to 4:45 p.m.
Meeting Location: The public workshop will be held at FDA's White Oak Campus, 10903 New Hampshire Ave., Building 31 Conference Center, the Great Room (Rm. 1503), Silver Spring, MD 20993-0002. Entrance for the public meeting participants (non-FDA employees) is through Building 1 where routine security check procedures will be performed.
About the Meeting: The Food and Drug Administration (FDA) is announcing the following public workshop entitled ``Complex Issues in Developing Drug and Biological Products for Rare Diseases.'' The purpose of the public workshop is two-fold: To discuss complex issues in clinical trials for developing drug and biological products (``drugs'') for rare diseases, including endpoint development and selection, use of surrogate endpoints and the accelerated approval pathway, clinical trial design, conduct and analysis, safety considerations, and dose selection; and to discuss ways to encourage and accelerate the development of new therapies for pediatric rare diseases. FDA is seeking input on these topics from academic, clinical, and treating communities; patients and advocacy groups; industry; and governmental agencies. Input from this public workshop will help develop a strategic plan to encourage and accelerate the development of new therapies for rare diseases.
More Information and To Register: To register for the public workshop, please visit FDA's Drugs News & Events--Meetings, Conferences & Workshops calendar at http://www.fda.gov/Drugs/NewsEvents/ucm132703.htm. (Select this public workshop from the posted events list.) Please provide complete contact information for each attendee, including name, title, affiliation, address, email, and telephone number. Those without Internet access should contact Tomeka Arnett to register (see Contact Person). Registrants will receive confirmation after they have been accepted. You will be notified if you are on a waiting list.

Streaming Webcast of the Public Workshop: This public workshop will also be Webcast. Persons interested in viewing the Webcast may visit FDA's Drugs News & Events--Meetings, Conferences & Workshops calendar at http://www.fda.gov/Drugs/NewsEvents/ucm132703.htm. (Select this public workshop from the posted events list.) Select https://collaboration.fda.gov/drugbiord/ to view the Webcast. If you have never attended a Connect Pro event before, test your connection at https://collaboration.fda.gov/common/help/en/support/meeting_test.htm. (FDA has verified the Web site addresses in this document, but FDA is not responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

In The Calendar

2013 Annual AAPS Meeting & Exhibition
Henry B. Gonzales Convention Center~ San Antonio, TX
November 10-14, 2013
For more information and registration: AAPS.org

Antibody Engineering & Therapeutics
Hyatt Regency Huntington Beach Resort & Spa
December 8-12, 2013
For more information and registration: Ibclifesciences.org

Biopharmaceutical Development & Production Week
Hilton San Diego Bay Front Hotel
March 24-27, 2014
For more information and registration: Ibclifesciences.org

2014 PDA Annual Meeting
JW Marriott San Antonio Hill Country
April 7-9, 2014
For more information and registration: PDA.org

Host Cell Protein Workshop
Valamar Lacroma~ Dubrovnik, Croatia
May 15-16, 2014
For more information and registration: BEBPA.org

2014 AAPS National Biotechnology Conference
Sheraton San Diego Hotel and Marina
May 19-21, 2014
For more information and registration: AAPS.org

BEBPA's 7th Annual Bioassay Conference
Hotel Avenida Palace~ Barcelona, Spain
September 24-26, 2014
For more information and registration: BEBPA.org

In the Literature

ADME/DMPK [absorption, distribution, metabolism, and elimination/ drug metabolism and pharmacokinetics]: Technical Articles

Analytical Method Development for Characterization and Control: Technical Articles; Technical Reviews

Anti-drug Antibodies and Unwanted Immunogenicity: Technical Articles; Technical Reviews

Basic Science Relevant to Biopharma and Biologics Quality: Technical Articles; Technical Reviews

Bioanalytical Methods and Issues: Technical Articles; Technical Reviews

Biomarkers: Technical Reviews

Biosimilars, Follow-on Biologics, FOPPs, Biobetters, etc.: Technical Articles; Regulatory Reviews; Articles by Regulators

Business Articles and Reviews

Carbohydrate/Glycan/Oligosaccharide/Polysaccharide Characterization and Analysis: Technical Articles

Cellular Therapies, Tissue-based products, and Regenerative Medicine: Technical Articles; Technical Reviews; Regulatory Reviews

Cleaning and Sanitization Issues: Technical Articles

Comparability Studies: Technical Articles

Congress, Forum, and Meeting Reviews

Development Issues, Concerns, Strategies, etc.: Technical Articles

Formulation/Pre-formulation and Delivery: Technical Articles; Technical Reviews

Gene and other Nucleic Acid Therapies and Vaccines: Technical Articles; Technical Reviews

Manufacturing and Production Issues: Technical Articles; Technical Reviews;

Preclinical and Animal Toxicology Study Issues: Technical Articles

Process Monitoring, and Control, Process Analytical Technology (PAT): Technical Articles

Process Development: Technical Articles

Protein--including Antibody, Glycoprotein, Peptide--and Other Bio-molecule Structure/Function: Technical Articles

Proteins--including Glycoproteins, Antibodies, Peptides--and Other Biomolecules: Characterization, Analysis, and Control: Technical Articles

Quality by Design (QbD): Technical Articles; Articles by Regulators

Regulatory Submissions, Review, Reporting, etc.: Regulatory Reviews

Safety and Efficacy Issues and Studies: Technical Reviews

Stability, Aggregation, Degradation and Shelf Life Issues: Technical Articles; Technical Reviews

Vaccine Development, Testing, Production, Delivery, Stability, and other issues: Technical Articles

Articles by Regulatory Authorities

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

Pani L, Montilla S, Pimpinella G, Bertini Malgarini R. **Biosimilars: the paradox of sharing the same pharmacological action without full chemical identity.** Expert Opin Biol Ther. 2013 Oct;13(10):1343-6. doi: 10.1517/14712598.2013.815722. Epub 2013 Jun 28. **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/23805906

QbD and PAT

Kimchi-Sarfaty C, Schiller T, Hamasaki-Katagiri N, Khan MA, Yanover C, SaunaZE. Laboratory of Hemostasis, Divi-

sion of Hematology, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD 20892, USA. **Building better drugs: developing and regulating engineered therapeutic proteins.** Trends Pharmacol Sci. 2013 Oct;34(10):534-48. doi: 10.1016/j.tips.2013.08.005. Epub 2013 Sep 20 **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/24060103

Rahman Z, Siddiqui A, Khan MA. Division of Product Quality and Research, Center of Drug Evaluation and Research, Food and Drug Administration, Maryland. **Characterization of a Non-ribosomal Peptide Antibiotic Solid Dispersion Formulation by Process Analytical Technologies Sensors.** J Pharm Sci. 2013 Oct 1. doi: 10.1002/jps.23740. [Epub ahead of print] **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/

Return to QuickScan List

Technical Articles

ADME/DMPK

Cao Y, Balthasar JP, Jusko WJ. **Second-generation minimal physiologically-based pharmacokinetic model for monoclonal antibodies.** J Pharmacokinet Pharmacodyn. 2013 Oct;40(5):597-607. doi: 10.1007/s10928-013-9332-2. Epub 2013 Aug 31 **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/23996115

Chen X, Hickling T, Kraynov E, Kuang B, Parng C, Vicini P. **A mathematical model of the effect of immunogenicity on therapeutic protein pharmacokinetics.** AAPS J. 2013 Oct;15(4):1141-54. doi: 10.1208/s12248-013-9517-z. Epub 2013 Aug 30. **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/23990500

Diao L, Meibohm B. **Pharmacokinetics and pharmacokinetic-pharmacodynamic correlations of therapeutic peptides.** Clin Pharmacokinet. 2013 Oct;52(10):855-68. doi: 10.1007/s40262-013-0079-0. **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/23719681

Golor G, Bensen-Kennedy D, Haffner S, Easton R, Jung K, Moises T, Lawo JP, Joch C, Veldman A. **Safety and Pharmacokinetics of a Recombinant Fusion Protein Linking Coagulation Factor VIIa with Albumin (rVIIa-FP) in Healthy Volunteers.** J Thromb Haemost. 2013 Sep 20. doi: 10.1111/jth.12409. [Epub ahead of print **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/24112951

Analytical Method Development for Characterization and Control

Debaene F, Wagner-Rousset E, Colas O, Ayoub D, Corvaïa N, Van Dorsselaer A, Beck A, Cianférani S. **Time Resolved Native Ion-Mobility Mass Spectrometry to Monitor Dynamics of IgG4 Fab Arm Exchange and "Bispecific" Monoclonal Antibody Formation.** Anal Chem. 2013 Oct 15;85(20):9785-92. doi: 10.1021/ac402237v. Epub 2013 Sep 26. **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/24007193

Goyder MS, Rebeaud F, Pfeifer ME, Kálmán F. **Strategies in mass spectrometry for the assignment of Cys-Cys disulfide connectivities in proteins. Expert Rev Proteomics.** 2013 Oct;10(5):489-501. Doi: 10.1586/14789450.2013.837663. Epub 2013 Oct 3 **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/24087910

Kinoshita M, Nakatsuji Y, Suzuki S, Hayakawa T, Kakehi K. **Quality assurance of monoclonal antibody pharmaceuticals based on their charge variants using microchip isoelectric focusing method.** J Chromatogr A. 2013 Sep 27;1309:76-83. doi: 10.1016/j.chroma.2013.08.021. Epub 2013 Aug 13. **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/23958695

Lévêque C, Ferracci G, Maulet Y, Grand-Masson C, Blanchard MP, Seagar M, El Far O. **A substrate sensor chip to assay the enzymatic activity of Botulinum neurotoxin A.** Biosens Bioelectron. 2013 Nov 15;49:276-81. Doi: 10.1016/j.bios.2013.05.032. Epub 2013 May 29. **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/23787358 http://www.ncbi.nlm.nih.gov/pubmed/23787358

Lund H, Paus E, Berger P, Stenman UH, Torcellini T, Halvorsen TG, Reubsaet L. **Epitope analysis and detection of human chorionic gonadotropin (hCG) variants by monoclonal antibodies and mass spectrometry.** Tumour Biol. 2013 Sep 7. [Epub ahead of print] **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/24014048

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Ni MW, Ye WJ, Cong WT, Hong GY, Zhu ZX, Duan YM, Zhou X, Jin LT. **Fluorescent staining of protein in sodium dodecyl sulfate polyacryl-**

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Anti-drug Antibodies and Unwanted Immunogenicity

Barbosa MD, Gokemeijer J, Martin AD, Bush A. **Altering drug tolerance of surface plasmon resonance assays for the detection of anti-drug antibodies.** Anal Biochem. 2013 Oct 15;441(2):174-9. doi: 10.1016/j.ab.2013.07.019. Epub 2013 Jul 22. PubMed **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/23886888

Bautista AC, Zhou L, Jawa V. **Universal immunogenicity validation and assessment during early biotherapeutic development to support a green laboratory**. Bioanalysis. 2013 Oct;5(20):2495-507. doi: 10.4155/bio.13.216. **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/24138623

Bi V, Jawa V, Joubert MK, Kaliyaperumal A, Eakin C, Richmond K, Pan O, Sun J, Hokom M, Goletz TJ, Wypych J, Zhou L, Kerwin BA, Narhi LO, Arora T. **Development of a human antibody tolerant mouse model to assess the immunogenicity risk due to aggregated biotherapeutics.** J Pharm Sci. 2013 Oct;102(10):3545-55. Doi: 10.1002/jps.23663. Epub 2013 Aug 7. **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/23925953

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Driscoll RO, Zhou L, Moxness M, Mytych D, Chirmule N, Jawa V. **Statistical and bioanalytical considerations for establishing a depletion criterion for specificity testing during immunogenicity assessment of a biotherapeutic.** AAPS J. 2013 Oct;15(4):1160-7. doi: 10.1208/s12248-013-9523-1. Epub 2013 Aug 30. **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/23990502

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Repessé Y, Peyron I, Dimitrov JD, Dasgupta S, Moshai EF, Costa C, Borel-Derlon A, Guillet B, D'Oiron R, Aouba A, Rothschild C, Oldenburg J, Pavlova A, Kaveri SV, Lacroix-Desmazes S; ABIRISK consortium. **Development of inhibitory antibodies to therapeutic factor VIII in severe hemophilia A is associated with microsatellite polymorphisms in the HMOX1 promoter.** Haematologica. 2013 Oct;98(10):1650-5. doi: 10.3324/haematol.2013.084665. Epub 2013 May 28. **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/23716558

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Basic Science Relevant to Biopharma and Biologics Quality

Blumlein A, McManus JJ. **Reversible and non-reversible thermal denaturation of lysozyme with varying pH at low ionic strength.** Biochim Biophys Acta. 2013 Oct;1834(10):2064-70. doi: 10.1016/j.bbapap.2013.06.001. Epub 2013 Jun 15 **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/23774197

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Bioanalytical Methods and Issues

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Kragstrup TW, Vorup-Jensen T, Deleuran B, Hvid M. **A simple set of validation steps identifies and removes false results in a sandwich enzyme-linked immunosorbent assay caused by anti-animal IgG antibodies in plasma from arthritis patients. Springerplus.** 2013 Jun 15;2(1):263. Print 2013 Dec. **To see the Abstract, and a link to obtain this paper:** http://www.ncbi.nlm.nih.gov/pubmed/23875127

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Biological Potency, Activity, and other Biological Assays

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

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Particulate Matters

Particles have been on the mind of many of late, from the Higgs boson, which gives mass to other particles, to particulate matter which gives more weight to Deficiency Notices given during biopharmaceutical inspections. All kidding aside, however, FDA estimates that almost 25% of injectable drug recalls during the past 5 years were triggered by particulate issues. Regarding inspecitons, FDA has been increasingly expecting to see companies performing supplemental inspection(s) of products for which 100% visual inspection is not possible (for example, light-sensitive products in opaque containers). In the US, companies and the FDA often turn to the USP for particle testing methods and acceptable limits. An historic problem has been the imprecise specification in USP <1> that every lot of an injectable be “essentially free from visible particles.” However, the new draft chapter <790>, expected to become effective in mid-2014 will provide clarity by quantifying “essentially free” (see Table below). One expects that other Pharmacopeias will follow suit. Here is a summary of notable USP chapters, present and anticipated, dealing with particle testing for injectable products.

Name & Number	Status	Details & Notes
Injections <1>	In effect. Revisions discussed in Pharmacopeial Forum (PF) 39(5)	Revisions include removal of labeling, packaging, container and storage sections
Particulate Matter in Injections <788>	In effect	<788> will remain after <787> and <790> become effective
Methods for the Determination of Particulate Matter in Injections <1788>	In effect	Informational chapter for light obscuration and membrane microscopy methods
Subvisible Particulates Matter in Therapeutic Protein Injections <787>	Draft (see PF39(2)); planned publication in USP 37 supplement	Provides improvements to the historical <788> light obscuration method for protein products
Visible Particles in Injections <790>	Draft; planned publication in USP 37, May, 2014	Gives requirements for illumination during visual inspection; the term "essentially free of particles" will be defined as meeting an AQL of 0.65% or tighter.
Visual Inspection of injectable products <1790>	Unpublished and currently in Expert Panel deliberations	Will provide general information and guidance for best practices in the area of particulate and container/closure defect monitoring and control

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