

# Hot Topics / RAQC Update

By: Karen Ginsbury

For: PDA Israel Chapter

Annual Meeting: Dec 10, 2008

# On the agenda

- FDA Draft Guidance for Industry Residual Solvents
- Phase I GMP Guidance and Final Rule
- US GMP revisions
- Draft Guidance for Industry Parametric Release
- Annex 13 – EU GMPs
- Annex 11 and Chapter 4 – EU GMPs
- Process Validation draft guidance
- Draft Guidance for Industry: Potency Determination Cellular and Gene Therapy Drug Products

# Residual Solvents - FDA Letter

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service



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**Food and Drug Administration  
Center for Drug Evaluation and Research  
Rockville, MD 20857**

To All Interested Parties:

As you are aware, there has been a proposed Chapter from the U.S. Pharmacopeia (USP) for control of residual solvents in drug products (See Attached Text). The effective date for this requirement has been postponed a number of times. However, beginning July 1, 2008, it will go into effect and all drug substances, excipients, and products are subject to relevant control of residual solvents, even when no test is specified in the individual USP monograph.

This Chapter, <467>, addresses levels of residual solvents acceptable for drug products official in the USP (i.e., drug products for which there is a USP monograph) to assure the safety of the drug products. The Chapter is derived from the International Conference on Harmonization (ICH) Q3C quality guidance.

With the Chapter becoming effective, it will be necessary for the Office of Generic Drugs to assure this safety information is addressed in abbreviated new drug applications

# Residual Solvents - FDA Letter

DAs). Therefore, starting July 1, 2008:

- any new ANDA must provide information and data as necessary to demonstrate control of residual solvents prior to approval (or tentative approval).
- ANDAs currently under review, but are not yet approved by July 1, 2008, must also contain this information and data as necessary.
- residual solvent information and data as necessary for approved products should be submitted in the next annual report for the ANDA.

specifications for residual solvents in ANDAs should:

Ensure that all drug substance and excipient components of the drug product, have residual solvent acceptance limits that fall within the ICH Q3C (option 1) limit<sup>1</sup>, or

Ensure that all drug substance and excipient components of the drug product, weighted by their amount in the drug product, results in a cumulative daily exposure for residual solvents that falls within the ICH Q3C (option 2) limit, or

# Residual Solvents - FDA Draft Guide

## August 2008

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# Guidance for Industry

## Residual Solvents in Drug Products Marketed in the United States

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft

# Federal Register, Vol 73, No. 136

## Tuesday, July 15, 2008

- Final rule
- The FDA is amending the CGMP regulations to exempt most phase 1 investigational drugs from complying with the regulatory CGMP requirements
- FDA will continue to exercise oversight under statutory CGMP authority and through review of the IND

# Final Rule continued

- FDA is taking the action to focus a manufacturer's effort on applying CGMP that is appropriate and meaningful for the manufacture of the earliest stage investigational drug products intended for use in phase I clinical trials while ensuring safety and quality. This action will also streamline and promote the drug development process.
- Rule effective September 12, 2008

# The Guidance

- “FDA’s guidance documents, do not establish legally enforceable responsibilities
- “...describe current thinking on a topic and should be viewed as recommendations, unless specific regulatory or statutory requirements are cited.”
- “ should = suggested or recommended but not required”

# Inspections?

- FDA reviews the submitted IND to determine if the drug is sufficiently safe to permit the trial to proceed
- FDA may also choose to conduct an inspection (if there is insufficient information to assess the risks to subjects)
- FDA could place a clinical hold...if there is evidence of inadequate QC procedures that would compromise the safety of an investigational product

# Revisions to US GMPs – now final

- Verification by Second Individual, the sections cited in the Final Rule do not adequately represent the intention of the statement "*Rather, in these situations, only one person is needed to verify that the automated equipment is functioning adequately. In cases where there is an operator for the automated equipment, the verifying individual may be, but is not required to be, the operator.*" FDA's proposed language does not seem to permit automated equipment operation where a check is performed by the operator of proper functioning of the equipment at the beginning of a shift, or acceptance of the validation of the calculation algorithm. Rather, it would seem that each component addition would need to be witnessed/verified, or that the calculation of the yield would need to be performed by hand following calculation by the system.

# Validation of Depyrogenation

211.94(c)

- **Add:** new sentence at the end “Such depyrogenation processes shall be validated”
- **From:** Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use

# Bioburden

## 211.110(a)

- **Revised to:** include bioburden process control procedures and tests, where appropriate
- **From:** To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.

# Validation of Aseptic Processes

## 211.113(b)

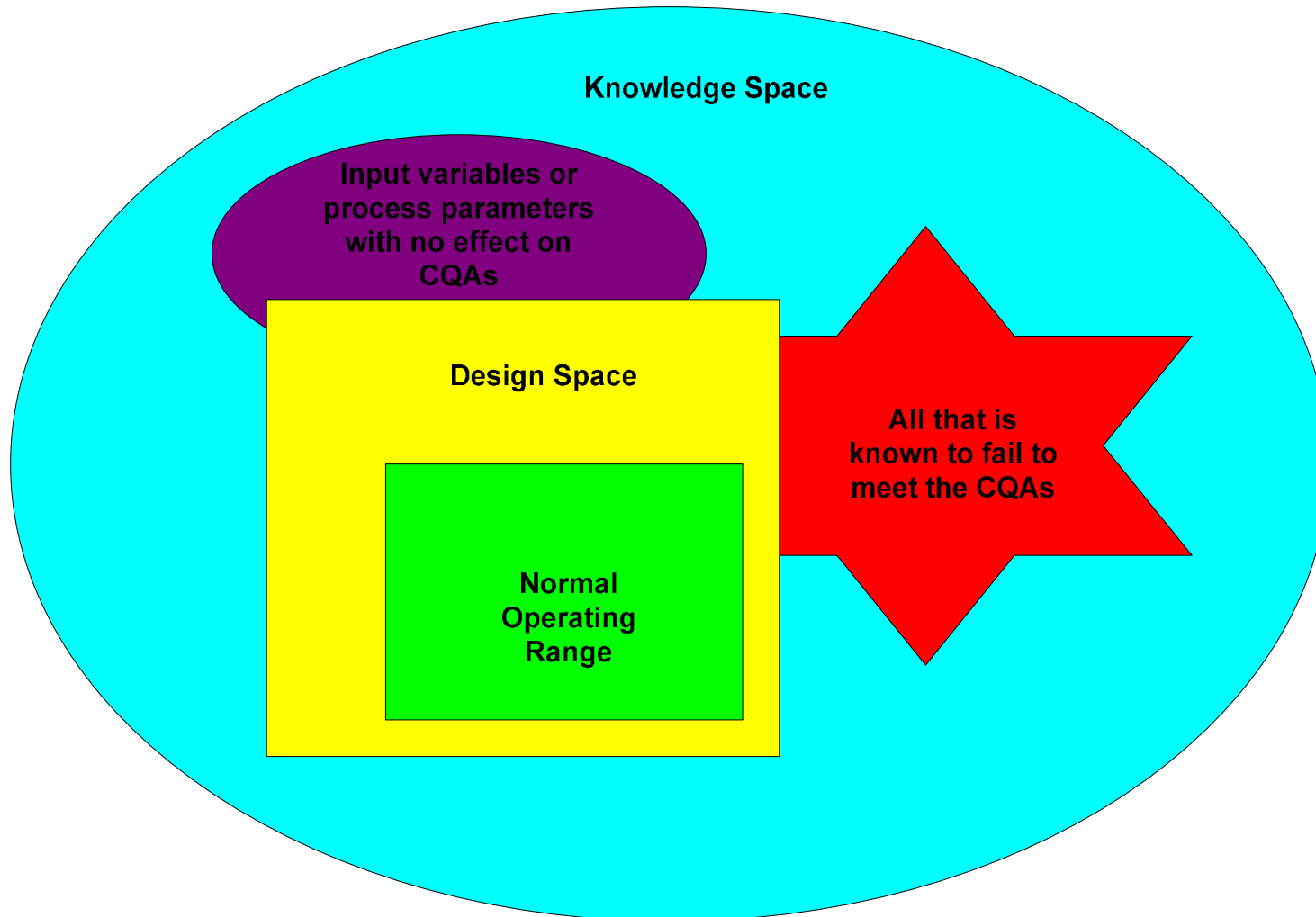
- **Revised to:** include validation of aseptic processes for drug products that are purported to be sterile
- **From:** Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process

# Second Signature

**211.101(c),211,101(d),211.103,211.182,211.188(b)(11)**

- **Revised to:** indicate that the use of automated equipment meeting the requirements of Sec. 211.68 and 21 CFR Part 11, may eliminate the need for verification by a second individual and that in those situations only one person is needed to verify that the automated equipment is functioning properly
- **From:** Requirement for second person review or check

# Ballot # 60 – Q8R1



# Ballot # 60 – Q8R1

## Some of PDA Comments

- The Annex provides clarification of key concepts outlined in the parent guideline (ICH Q8, Pharmaceutical Development). We believe that it may be clearer to users if the parent guideline was expanded to include most of the Annex, leaving only the actual case studies/examples as an Annex
- The Annex often suggests that development is either univariate or multivariate. In actual practice, most development activities occur over a continuum, not as an “either/or” approach
- The general principles described in the Annex apply to biologics and sterile drug products as well as solid dosage forms. However, few examples are provided for these types of products. It would be useful to include illustrative examples for sterile dosage forms

# Ballot #61 – Parametric Release Guidance for Industry

## Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Marla Stevens-Riley (CDER) at 240-276-

# Annex 13 – Could be Ballot #62!



EUROPEAN COMMISSION  
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods  
Pharmaceuticals

Brussels, 11 April 2008

**EudraLex**  
**The Rules Governing Medicinal Products in the European Union**

**Volume 4**  
**EU Guidelines to**  
**Good Manufacturing Practice**  
**Medicinal Products for Human and Veterinary Use**

**Draft Annex 13**  
**Manufacture of Investigational Medicinal Products**

Draft agreed by GMP/GDP and GCP Inspectors Working Groups	February 2008
Release for public consultation	April 2008
Deadline for comments <a href="mailto:entr-gmp@ec.europa.eu">entr-gmp@ec.europa.eu</a> and <a href="mailto:GMP@emea.europa.eu">GMP@emea.europa.eu</a>	31 October 2008
Final text agreed by GMP/GDP Inspectors Working Group	

# Annex 13

- Changes of relatively minor nature

- Under Personnel

In cases where the number of staff involved is small, there should be, for each batch, separate people responsible for production and quality control

# Annex 13

- 37. The storage location of Reference and Retention samples should be defined in a Technical Agreement between the sponsor and manufacturer and should allow timely access by the competent authorities.
- Reference samples of finished product should normally be stored within the EEA or in a third country where appropriate arrangements have been made by the Community with the exporting country to ensure that the manufacturer of the investigational medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Community. In exceptional circumstances the reference samples of the finished product may be stored by the manufacturer in another third country, in which case this should be justified, and documented in a technical agreement between the sponsor, importer in the EEA and that third country manufacturer.

# Ballot #63

## Annex 11 – From 3 – 9 Pages!!

Click to increase the magnification of the entire page

Brussels, 08 April 2008

**EudraLex**  
**The Rules Governing Medicinal Products in the European Union**

**Volume 4**  
**EU Guidelines to**  
**Good Manufacturing Practice**  
**Medicinal Products for Human and Veterinary Use**

**Draft Annex 11**  
**Computerised Systems**

Draft agreed by GMP/GDP Inspectors Working Group	February 2008
Release for public consultation	April 2008
Deadline for comments to <a href="mailto:entr-gmp@ec.europa.eu">entr-gmp@ec.europa.eu</a> and <a href="mailto:GMP@emea.europa.eu">GMP@emea.europa.eu</a>	31 October 2008
Final text agreed by GMP/GDP Inspectors Working Group	
Adopted by European Commission	
Deadline for coming into operation	

# What has changed?

- Principle expanded to all computerized systems
- Risk Management
- Greatly expanded section on validation
- User testing and fitness for purpose
- Security
- Accuracy checks
- Audit trails
- Signatures
- Back up, changes, recovery and disaster plans

# Some PDA comments on Annex 11

- suggest adding an opening paragraph “level of detail for requirements outlined in the annex be based on a documented analysis of how the system is used, the level of complexity and risk assessment
- The manufacturing authorization holder’s ... together with up to date listings of systems and their GxP functionality be changed to read:  
“with up to date listings of systems and their intended use”
- On line archiving of data where applicable. Add sentence:  
“The archive process should be verified as allowing retrieval of data without any effect on data integrity.”

# Some PDA comments on Annex 11

- Add: “Spreadsheets should be saved within a system that provides audit trails and version control ”  
Agree with requirement to control changes and versions of validated spreadsheets. Since spreadsheets do not provide an audit trail to capture an accidental change on a formula, add sentence indicated
- Quality system and audit information relating to suppliers ... change to: “Quality system and evidence of performance of audits and close out of CAPA items relating to suppliers ...”  
so that the audits themselves continue to be frank and open

# Ballot #64 – EU GMP Chapter 4



EUROPEAN COMMISSION  
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods  
Pharmaceuticals

Brussels, 08 April 2008

**EudraLex**  
**The Rules Governing Medicinal Products in the European Union**

**Volume 4**  
**EU Guidelines to**  
**Good Manufacturing Practice**  
**Medicinal Products for Human and Veterinary Use**

**Draft Chapter 4**  
**Documentation**

Draft agreed by GMP/GDP Inspectors Working Group	February 2008
Release for public consultation	April 2008
Deadline for comments to <a href="mailto:entr-gmp@ec.europa.eu">entr-gmp@ec.europa.eu</a> and <a href="mailto:GMP@emea.europa.eu">GMP@emea.europa.eu</a>	31 October 2008
Final text agreed by GMP/GDP Inspectors Working Group	
Adopted by European Commission	

# Ballot #64 – EU GMP Chapter 4

- Changes made to electronic records should be visible both on-screen and on printouts  
Delete the sentence beginning with “Changes made to ,” and replace with “It should be possible to view changes as an attached history record or in a detail panel on screen or in the printed record”
- Records should be retained for at least one year after the expiry date of the finished product  
Not all “records” are directly associated with product. The last sentence should be rewritten to read “Allow for an appropriate retention period based on the business activity the record supports.”
- For any critical documentation elements ...a record of changes and deletions (even at System Administrator level),  
Delete the phrase “...(even at System Administrator level)...”  
[Otherwise most systems do not comply]

# Ballot #65– USP on Bovine Serum

**⟨1024⟩ Bovine Serum.** Because there is no information in the *USP* on this subject, it is proposed to add this general information chapter that discusses considerations in the manufacture of bovine serum and how the attributes of the different types of bovine serum are characterized.

(BB CGT: F. Atouf)      RTS—C49113

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***Add the following:***

## ■ ⟨1024⟩ BOVINE SERUM

### INTRODUCTION

# Ballot #65– USP on Bovine Serum

- We understand the purpose of the chapter is an overall review on bovine serum products used as raw materials...
- We are concerned that, as currently written, there is an over emphasis on the risks and mitigation of viruses and BSE
- the amount of information and the manner in which it is presented has the effect of overstating the risks and implying that the product is more dangerous than has been proven in scientific studies and over many years of experience as an ingredient of products for human use

# Process Validation – Ballot still out

KSG comments:

- FDA is redefining process validation
- Lifecycle approach is in
- Three batches is OUT

# Process Validation – Ballot still out

FDA proposed definition:

- ***process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products***
  - What about protocols ?
  - What about optimization first ?
  - What about repeatability ?

# Process Validation – Ballot still out

KSG proposed definition

Process validation is the provision of scientific evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined critical quality attributes and performance characteristics. Process validation is a lifecycle activity

# Process Validation – Ballot still out

## Stage 1 – Process Design:

*The commercial process is defined during this stage based on knowledge gained through development and scale-up activities*

KSG: this is a pre-requisite for process validation but it is NOT part of the validation process

# Process Validation – Ballot still out

Some KSG comments on draft:

- Each step of a manufacturing process is controlled....all design characteristics and quality attributes including specifications

Change to: Each step of a manufacturing process is controlled to assure that the finished product meets its Critical Quality Attributes and Performance characteristics as defined in the Target Product Profile

- Change in line with ICH Q8 definitions whereas “design characteristics” is not defined anywhere

# Draft Guidance: Potency Testing of Cellular and Gene Therapy Based Drugs

- Overall a helpful guidance
- Potency assays are complex
- Often need more than one type of assay
- Definitions in CFR differ from those developed by ICH particularly wrt validation of analytical methods

# Other Business

- Ongoing participation / meetings with regulators
- WHO Good Distribution Practice update
- WHO Good Development Practice update
- ICH Q11 concept paper
- EU Interested parties meetings – presentations from PDA on supply chain issues (after FDA supply chain conference)
- PDA continues to be one of the leading professional organizations in the field of pharmaceutical science...watch this space!