



This update includes news of the restructuring of the EU GMP guide and revisions to Annex 1, an FDA presentation on foreign inspection results and the adoption of ICH Q8 (Pharmaceutical Development) and Q9 (Quality Risk Management).

N.B. If viewing this document electronically, with a suitable web browser, websites can be visited by clicking on the relevant link.

## **1. FDA News**

### **1.1 General**

#### **100 years of FDA**

This year marks the 100th anniversary of the FDA. To celebrate, they will be holding commemorative events throughout the year and have launched a special web page at:

<http://www.fda.gov/centennial>

Additionally, the January-February 2006 issue of *FDA Consumer*, will trace the agency's history over the last 100 years.

#### **Medical Device Safety**

The FDA have announced a 'Postmarket Transformation Initiative' which will help them to 'identify, analyze, and act more quickly on potential medical device problems' with the aim of strengthening medical device safety. It focuses on measures such as establishing an electronic reporting system for adverse events and improving device information in patients' records. The press release can be found here:

<http://www.fda.gov/bbs/topics/news/2006/NEW01300.html>

#### **Formal Dispute Resolution**

CDER and CBER have published the joint guidance document 'Guidance For Industry, Formal Dispute Resolution: Scientific and Technical Issues Related to Pharmaceutical CGMP'. This forms part of the Pharmaceutical CGMPs for the 21st Century initiative and outlines the process for addressing disagreements over 483s. The guidance can be viewed here:

<http://www.fda.gov/cber/gdlns/formaldis.pdf>

### **1.2 Centre for Drug Evaluation & Research**

CDER recently published a presentation detailing the 2004/2005 results for foreign inspections. The presentation, which also includes nearly thirty 483 examples, can be viewed here:

<http://www.fda.gov/cder/about/smallbiz/Presentations/6.ppt>

### **1.3 Centre for Biologics Evaluation & Research**

The FDA are amending the CGMP regulations for human drugs (including biologicals) to exempt most investigational 'Phase 1' drugs. They will instead

exercise 'oversight of production' under both their general statutory CGMP authority and IND authority. They have also simultaneously made available a guidance document setting forth recommendations on approaches to CGMP compliance for the exempted Phase 1 drugs. The final rule can be found here:

<http://www.fda.gov/cber/rules/gmpind.htm>

The guidance (INDs — Approaches to Complying with CGMP During Phase 1) can be found here:

<http://www.fda.gov/cber/gdlns/indcgmp.htm>

## **2. European Commission News**

### **New GMP Annex 19 for Reference and Retention Samples**

This new annex to the GMP Guide provides guidance on the taking and holding of reference samples of starting materials, packaging materials and finished products as well as for retention samples of finished products.

[http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005\\_12\\_14\\_annex19.pdf](http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005_12_14_annex19.pdf)

Updated guidance is also given on the size of reference samples and a consequential change was made to Chapter 6, section 14, of the GMP Guide to maintain consistency. Both the revised Chapter 6 and Annex 19 will come into operation on 01 June 2006.

### **Revised GMP Part I/ Chapter 8 on Complaints and Product Recall**

The revision was made to raise awareness of the possibility that a reported quality defect may be the result of counterfeiting activity and to clarify that the discovery of a counterfeit medicinal product should be reported to the competent authority. These changes are in line with WHO recommendations. The revised Chapter 8 came into operation on February 1st 2006.

[http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005\\_12\\_GMP\\_part1\\_chap8.pdf](http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005_12_GMP_part1_chap8.pdf)

### **EU (European Commission and EMEA) and FDA extend confidentiality arrangements for five more years**

The European Commission (EC), the EMEA and the FDA have extended their confidentiality arrangements related to medicinal products for human and veterinary use for five more years, following the positive experience

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gained since the initial arrangements were signed in September 2003. The arrangements allow the EC/EMEA and the FDA to exchange information (including legal and regulatory issues, scientific advice, orphan drug designation, inspection reports, marketing authorisation procedures and post-marketing surveillance) as part of their regulatory processes.

#### **Draft Amendment to Annex 1 of the GMP guide for public consultation (corrected version)**

Following the May 2003 revision of Annex 1 (on the manufacture of sterile medicinal products), the need for an ongoing discussion on the table providing environmental cleanliness and a number of other aspects to the annex were identified. The results of this discussion are reflected in a draft amendment of the guide.

[http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/11\\_05/Annex 1 amended 09-2005.pdf](http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/11_05/Annex 1 amended 09-2005.pdf)

An outline of the proposed changes is as follows:

- Clarification of the text associated with the environmental classification table (harmonising further with ISO 14644 Parts 1 & 2)
- Guidance on the frequency of pre-sterilisation bioburden monitoring
- Harmonisation of the media simulation acceptance criteria with the requirements of the FDA's 'Sterile Products Produced by Aseptic Processing' guidance

Public comments are invited on the proposal and should be sent to Sabine.Atzor@cec.eu.int and David.Cockburn@emea.eu.int before 30 April 2006.

#### **New GMP Provisions for Product Quality Review and On-going Stability Programme: (Revision of GMP Guidelines, Part I Revision of Chapter 1 and Chapter 6)**

Chapter 1 on Quality Management has been revised to include new requirements on Product Quality Review and came into force in January 2006.

[http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005\\_10\\_gmp\\_part1\\_chap1.pdf](http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005_10_gmp_part1_chap1.pdf)

Chapter 6 on Quality Control includes new provisions for an On-going Stability Programme and an update for reference samples (see info on Annex 19 above) and will come into operation on 01 June 2006.

[http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005\\_10\\_Chapter 206.pdf](http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005_10_Chapter 206.pdf)

#### **Restructuring of GMP guide - Revised basic requirements for active substances used as starting materials now public as GMP Part II**

The Commission has published the basic requirements for the manufacture of active substances used as starting materials as GMP Part II. This replaces the former GMP Annex 18. The guide is applicable for active substances used in the manufacture of human and veterinary medicinal products. The technical requirements remain unchanged compared to the former Annex 18.

[http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005\\_10\\_03\\_gmp-partII-activesubstance.pdf](http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005_10_03_gmp-partII-activesubstance.pdf)

The creation of GMP part II has led to restructuring of the GMP Guide. The existing basic requirements have now become Part I and the existing annexes remain, except for Annex 18, which has now been withdrawn. For additional information see the revised introduction to the GMP guide here:

[http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005\\_10\\_introduction.pdf](http://pharmacos.eudra.org/F2/eudralex/vol-4/pdfs-en/2005_10_introduction.pdf)

### **3. MHRA News**

The MHRA will be hosting a one-day GMP Symposium on 7th March 2006 which will cover various topics relating to GMP including up-to-date knowledge on legislative changes, the MHRA Inspectorate, expectations, GMP deficiencies and future issues. The symposium will be held at the Moathouse Hotel in York. For further information see:

[http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&us eSecondary=true&ssDocName=CON2022644&ssTargetNodeId=314](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&us eSecondary=true&ssDocName=CON2022644&ssTargetNodeId=314)

The MHRA have also published the latest edition of Mail, which includes news on the EC's proposals for a regulation on advanced therapies/tissue engineering as well as news on the 'Better Regulation of Over-the-counter Medicines Initiative'. It can be viewed here:

[http://www.mhra.gov.uk/home/idcplg?IdcService=GET\\_FILE&dDocName=CON2023141&RevisionSelectionMethod=LatestReleased](http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023141&RevisionSelectionMethod=LatestReleased)

### **4. Pharmacopoeial News**

#### **4.1. United States Pharmacopeia**

USP have published the latest edition of USP Press which can be found here:

<http://www.usp.org/pdf/EN/aboutUSP/uspPress2006Jan.pdf>

Its highlights include:

- Details of USP's first European Stakeholder Forum on Wednesday, December 14th 2005, in Basel, Switzerland.

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- Work plans for 2005 –2010
- USP & PDG convening to discuss the future of harmonization and to approve new monographs and general chapters
- Pharmaceutical Ingredient Verification Programs build on USP 's dietary supplement verification program (DSVP) new program will focus on pharmaceutical drug substances and excipients. The programs will include both a verification component, which would be for suppliers of drug substances and excipients to drug product manufacturers, and a qualification component, which would be for the manufacturers themselves as they qualify raw material supplies under GMPs.

The new edition of the United States Pharmacopeia and National Formulary (USP –NF ) is now official, effective January 1st 2006.

#### **4.2. European Pharmacopoeia**

The EDQM has launched a new question and support service called Helpdesk. Helpdesk allows one to view FAQs covering all aspects of the EQDMs activities as well as sending questions or contacting them. The topics include:

- Technical questions on Monographs and General Chapters
- Electronic Publications
- Reference Standards - Purpose and Use
- Conferences, Events, Public Relations
- EDQM Mission and Role
- Quality Assurance
- HelpDesk Functionalities and Use

The new 'Helpdesk' homepage can be found here:

[http://www.pheur.org/site/page\\_521.php](http://www.pheur.org/site/page_521.php)

### **5. Miscellaneous News**

#### **5.1 ICH**

The ICH Steering Committee and expert working groups met in Chicago in November 2005 for a meeting entitled 'A modern harmonised approach to Pharmaceutical Quality and Manufacturing'.

The Steering Committee approved a new topic, "Quality Systems" (Q10) that 'will augment existing Good Manufacturing Practices (GMPs) with modern quality systems elements.' They also adopted two related guidelines as final:

- **ICH Q8 (Pharmaceutical Development)**, detailing what should be submitted to a regulatory authority in the relevant section of the Common Technical Document

[http://www.ich.org/MediaServer.jsr?@\\_ID=1707&@\\_MODE=GLB](http://www.ich.org/MediaServer.jsr?@_ID=1707&@_MODE=GLB)

- **ICH Q9 (Quality Risk Management)**, providing principles and examples of quality risk management from development through to manufacturing and inspections

[http://www.ich.org/MediaServer.jsr?@\\_ID=1957&@\\_MODE=GLB](http://www.ich.org/MediaServer.jsr?@_ID=1957&@_MODE=GLB)

The aim for these guidelines is to form the foundation for a modern risk-based approach to pharmaceutical quality and manufacturing.

Additionally, several meetings were held to discuss potential future ICH topics in Biotechnology, Pharmacogenomics, and Pharmacovigilance. The full press release can be viewed here:

[http://www.ich.org/MediaServer.jsr?@\\_ID=2566&@\\_MODE=GLB](http://www.ich.org/MediaServer.jsr?@_ID=2566&@_MODE=GLB)

#### **5.2 EMEA**

##### **ICH Q9**

Following the adoption at step 4 of ICH Q9 on Quality Risk Management the next stage is formal adoption in the EU. Work is currently underway to determine the most appropriate way to adopt ICH Q9 into the European regulatory system.

##### **Process Analytical Technology**

An addition has been made to the PAT Questions and Answers section of EMEA's website giving answers to questions regarding with PAT, Design Space and process validation.

The process validation answer suggests that the traditional 3 PQ batches may not be necessary in cases where a product is subject to enhanced process understanding and monitoring i.e. continuous validation. For further information see:

<http://www.emea.eu.int/Inspections/PATQaA.html>

#### **5.3 EFPIA**

The European Federation of Pharmaceutical Industries and Associations have published their bimonthly newsletter Ephi@News which can be viewed here:

<http://www.efpia.org/efpianews38.pdf>

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#### **5.4 ISPE**

ISPE have published the February 2006 edition of Regulatory Review. Pharmaceutical Regulatory and GMP Structure in Russia, by Mike Bennoson, provides a brief overview of the pharmaceutical regulatory structure and GMP organization in Russia and can be found here:

<https://www.ispe.org/Template.cfm?Section=Regulations&CONTENTID=19933&TEMPLATE=/ContentManagement/ContentDisplay.cfm>

Also, the January edition of ISPE's European Informer is available on the ISPE website at:

<http://www.ispe.org/EUinformer>

It includes details of the new GAMP Good Practice Guide for Testing of GxP Systems. This guide provides a review of all aspects of the testing of GxP systems and current good practice and is available for free download for ISPE members.

#### **5.5 European Compliance Academy**

The ECA have reported on a new ISO standard being created for lubricants used in situations where product contact cannot be avoided.

ISO 21469 "Lubricants with Incidental Product Contact" will be published in spring 2006 (the target is 15th March).

According to ECA, this standard will state that in addition to the substances listed in 21 CFR § 178.3570 (Lubricants with incidental food contact), further substances can be used on the condition that they have an official authorisation as food ingredients.

See here for further details:

<http://www.gmp-compliance.org/pa2.cgi?ecanews=665>

#### **5.6 PIC/S**

On 1 January 2006, the PIC/S Aide-Memoire PI 023-1 'Inspection of Pharmaceutical Quality Control Laboratories' came into force.

This useful document consists of an audit checklist with general questions and also specific checklists for physical/chemical laboratories and microbiological laboratories. It is intended for use when training GMP inspectors and also for inspection preparation for QC labs and can be downloaded from the PIC/S website here:

<http://www.picscheme.org/indexnoflash.php?p=recommandations>

Another aide-memoire recently published by PIC/S is PI 024-1 'Inspection of Biotechnology Manufacturers' which can be found here:

<http://www.picscheme.org/indexnoflash.php?p=recommandations>

Lastly, Chapter 1 of the PIC/S GMP Guide has been revised in parallel with the EU GMP Guide to include a new section on product quality review. The revised PIC/S GMP Guide entered force on 1 January 2006 and can be viewed here:

<http://www.picscheme.org/publis/news/PE%20009-3%20GMP%20Guide%20January%202006.pdf>

#### **5.7 PQRI**

The Biologics Inspection work group of the PQRI has initiated an on-line survey project regarding FDA inspections of the biological products industry.

The working group, comprised of both industry and FDA representatives, has developed a survey questionnaire to assess the impact of recent Team Biologics inspections over the past 36 months.

Specific firms have been selected to participate. These firms will receive a letter requesting the company complete and respond to the survey questionnaire.

[http://www.pqri.org/pdfs/survey\\_questionnaire.pdf](http://www.pqri.org/pdfs/survey_questionnaire.pdf)

#### **5.8 Parenteral Society**

The Parenteral Society have announced that they will be changing their name to The Pharmaceutical and Healthcare Sciences Society. The new name will come into effect on 1st March 2006.

#### **5.9 PDA**

The PDA have reported on the FDA issuing proposed regulations on CGMPs for Positron Emission Tomography drug products.

They state that the rule will apply to approved PET drug products. For investigational and research PET drugs, the proposed rule states that the requirement to follow CGMP may be met by producing PET drugs in accordance with the USP general chapter on compounding PET radiopharmaceuticals.

The FDA also published a companion draft guidance entitled "PET Drug Products- Current Good Manufacturing Practice (CGMP)."

<http://www.fda.gov/OHRMS/DOCKETS/98fr/98d-0266-gdl0002.pdf>

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## **5.10 Pharmaceutical Technology**

The current issue of Pharmaceutical Technology includes the article 'Enhancing Drug Development by Applying LC-MS-MS for Cleaning Validation in Manufacturing Equipment' by Kevin J. Kolodsick.

This explores the use of liquid chromatography-mass spectrometry to achieve the sensitivity and selectivity necessary for the determination of low-level drug residues in performing cleaning verification analyses and can be viewed here:

<http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=301459>

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