

EU Changes

Changes to EU **Legislation** and **Guidelines**



Peter H Gough, QP Symposium, 7 Nov 2006

EU Changes

Legislation



Recently Revised/Implemented EU Directives

- **Human Medicines Directive 2004/27/EC**
- **Veterinary Medicines Directive 2004/28/EC**
- **Herbal Medicinal Products Directive 2004/24/EC**
- **GCP Directive 2005/28/EC**
- **Blood Directive 2002/98/EC**
- **Tissue and Cells Directive 2004/23/EC**
- **Proposed legislation for Paediatric Medicines**



EU Directive 2004/27/EC

- **Amends Directive 2001/83/EC (HUMAN MEDICINES)**
- **Effective 30 October 2005**
- **Includes/updates laws, for example:**
 - ★ ***Refers to European Medicines Agency (EMA)***
 - ★ ***To include CT manufacture***
 - ★ ***Updates MAA application procedures***
 - **Decentralised process**



EU Directive 2004/27/EC

- **Revised definitions ...**

- ★ ***Proprietary Medicinal Product – term is deleted***

- ★ ***Medicinal Product:***

- a) **Any substance or combination of substances *presented as having properties* for treating or preventing disease in human beings; or**

- b) **Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by *exerting a pharmacological, immunological or metabolic action*, or to making a medical diagnosis.**



EU Directive 2004/27/EC

- **APIs must be made in accordance with GMP (ICH Q7a, Part 2 of EU GMP guide)**
- **QPs will have to declare APIs have been made in compliance with GMP**
 - ★ ***When MA application or Variation is submitted***
 - ★ ***De facto when releasing finished products***



EU Inspection of API Manufacturers

EMEA Guidance:

- **“Guidance on the occasions when it is appropriate for Competent Authorities to conduct inspections at the premises of Manufacturers of Active Substances used as starting materials”**
 - ★ *First published in March '05*
 - ★ *Now part of “Compilation of Procedures on Inspections and Exchange of Information”*



Inspection of API Manufacturers

- **Regulatory Authority inspection of API Manufacturers may be required when:**
 - ★ *A new MAA application is being assessed*
 - ★ *Requested by the EDQM*
 - ★ *Requested by a Member State Authority, the European Commission or the EMEA*
 - ★ *There are grounds for suspecting serious non-compliance with GMP*
 - ★ *Requested by a manufacturer*
 - **e.g. in order to obtain a GMP Certificate**



API Manufacture and GMP

- **Inspectors will examine MA holders audit programmes for API suppliers**
 - ★ ***Including reviewing Audit Reports***
- **Cannot rely solely on Regulatory audits of API producers**
- **Expectation is that industry will conduct regular audits of API suppliers**
 - ★ ***Using appropriately qualified auditors***
 - ★ ***Every 2 to 3 years***



EU Directive 2004/27/EC

- **Surveillance of API manufacture for CT use**
 - ★ ***Directive 2004/27 provisions for API GMP compliance do not apply to IMPs***
 - ★ ***Yet?***



EU Directive 2004/27/EC

- API and “**certain excipients**” must be made in accordance with GMP
- List of ‘certain’ excipients to be published in a separate Directive
 - ★ *EFPIA, IPEC, PDA, AESGP & the UK IQA PQG produce joint Position Paper recommending that no excipients be listed*
 - EC lawyers rejected



GMP for Excipients

- **EU has no adopted GMP for excipients**
 - ★ *Commission initially proposed using EU GMP Part 2 (GMP for APIs) for excipients*
 - ★ *Industry view is you need separate GMP for excipients*
- **UK IQA PQG, IPEC Europe and IPEC Americas have written GMP Guide for Excipients**
 - ★ *Launched January 2006*
 - ★ *May be used as basis for EU GMP Part 3 ?*



GMP for Excipients

- **EMA & Commission are now aware of difficulties in implementing this requirement.**
- **May come to accept that implementation is impossible**
- **Requirement to be removed in future amendment ?**



EU Directive 2004/27/EC

- **EMEA will issue GMP certificates and keep a database, EudraGMP, of approved and non-approved manufacturers**
 - ★ ***Applies to all GMP inspections***
 - **including finished product inspections**
 - ★ ***Certificate issue and database entry to be within 90 days of inspection***
 - ★ ***Database should be operational by mid-2006***
 - ★ ***Unsure if database will be 'public'***



EU Directive 2004/27/EC

- **Braille for package label and leaflet**
 - ★ *The **name** of the medicinal product **must also be expressed in Braille** format on the packaging*
 - ★ *MA holder shall ensure that the package information leaflet is made available **on request** from patients organisations **in formats appropriate for the blind and partially-sighted.***

- **INN on package label**
 - ★ *Where the product contains up to three active substances, the **international non-proprietary name (INN)** shall be included*



EU Directive 2004/27/EC

- **Braille and INN on packaging**
 - ★ ***Will apply to new MA applications after 30 October 2005***
 - ★ ***5 year transition period for existing products***
 - ★ ***EMA guidance published in April 2005***
 - ★ ***UK Q&A document published in October 2005***



UK Braille Q&A document

- **What packs must include Braille?**
 - ★ ***Medicines that are directly handled by patients***
 - ★ ***Medicines that are only administered by health professionals (e.g. anaesthetics, radiopharmaceuticals and infusions) need **not** have Braille applied***



EU Directive 2004/28/EC

- **Amends Directive 2001/82/EC
VETERINARY MEDICINES**
- **Similar updates to laws as per
2004/27/EC but does not include CT/GCP
elements**
- **Clarifies residues in food controls and
allows Veterinary Surgeons to use Human
Medicines for 'careful' treatment if no
veterinary remedy is available**



EU Directive 2004/24/EC

- **Amends Directive 2001/83/EC for TRADITIONAL HERBAL MEDICINES**
- **Traditional Herbal Medicines:**
 - ★ *Where there is well established, long term medicinal use, with recognised efficacy*
 - ★ *Long term = used for 30 years, of which 15 years experience within the EC*



EU Directive 2004/24/EC

- **Traditional Herbal Medicines must**
 - ★ *Be oral, external and/or inhalation dosage forms*
 - ★ *Have qualitative/quantitative composition*
 - ★ *Have no harmful effect under normal use*
 - ★ *Sufficient data on Pharmacological effect*
- **A committee for Herbal Medicinal Products will advise (part of EMEA) the HMPC started end 2004**



EU Directive 2004/24/EC

- **A reduced 'dossier'/simplified registration is to be used**
 - ★ ***Safety assurance from historical experience***
 - ★ ***Do **not** have to prove efficacy***
- **Marketing Authorisations will be National licences**
 - ★ ***No centralised application process***
 - ★ ***No 'mutual recognition' provisions***



EU Directive 2004/24/EC

- Draft revision of EU GMP Guide, **Annex 7, Manufacture of Herbal Products**, issued.
- New EU Herbal Medicines guidelines adopted March 2006:
 - ★ *Quality of Herbal Medicinal Products / Traditional Herbal Medicinal Products*
 - ★ *Specifications: Test procedures and Acceptance Criteria for Herbal Substances, Herbal Preparations and Herbal Medicinal Products*



EU Directive 2002/98/EC

- **Effective November 2005**
- **BLOOD, PLASMA & DERIVATIVES.**
**Collection, testing, processing, storage
and distribution**
- **Some licensed medicinal products are
derived from blood and plasma**



EU Directive 2002/98/EC

- **Two further technical Directives adopted September 2005 and should be effective by 31 August 2006.**
 - ★ ***Directive 2005/61/EC – Traceability requirements and notification of serious adverse reactions and events***
 - ★ ***Directive 2005/62/EC – Standards and specifications relating to a quality system for blood establishments***



EU Directive 2004/23/EC

- **TISSUES AND CELLS** including amongst other cells, haematopoietic progenitor stem cells and embryonic stem cells
- **Effective 7 April 2006**
- **Only applies to T & Cs used in humans**
- **Stem cells currently being used in medical research**



EU Directive 2005/28/EC

- **GCP Directive**
- **Implementation date 29 January 2006**
- **GCP Guidelines to be applied to trials**
- **The rights, safety and well being of trial subjects shall prevail over the interests of science and society**
- **Ethics Committee responsibilities**



EU Directive 2005/28/EC

- **Sponsor's responsibilities**
- **Manufacturing Authorisation required for manufacture and importation of IMPs**
- **GMP to be applied to manufacture and importation of IMPs (including placebos and comparators)**
- **Purpose of the Trial Master File**
- **Qualifications and training requirements for GCP Inspectors**
- **Inspection Procedures**



Future EU Regulation - Paediatrics

PAEDIATRIC MEDICINES

- **New Regulations expected to be published soon and come into force in January 2007**
 - ★ *Proposals issued by Commission in Sep 2004*
- **About 50% of medicines used in children are not authorised for such use**
- **A Paediatric Committee (PDCO) will advise EMEA**
- **PUMA (Paediatric Use Marketing Authorisation) will be required**



EU Changes

GMP Guidelines



Changes to EU GMP Guide

New structure:

- **Part 1: Medicinal Products**
 - ★ *The current Chapters 1 to 9*
- **Part 2: Active Pharmaceutical Ingredients**
 - ★ *ICH Q7A; formerly Annex 18*
- **Annexes**
 - ★ *Annex 18 will not be re-used*



EU GMP Guide - Revised Chapter 1

- Adds requirement to perform periodic **Product Quality Reviews**
 - ★ *Effective 1 January 2006*
- Review should:
 - ★ *Verify the consistency of the existing process*
 - ★ *Verify appropriateness of current specifications for both starting materials and finished product*
 - ★ *Highlight any trends*
 - ★ *Identify product and process improvements*
- Reviews should normally be conducted and documented annually



EU GMP Guide - Revised Chapter 1

- **The manufacturer and MAA holder, where different, should evaluate the results of this review:**
 - ★ ***Assess whether corrective and preventative action or any revalidation should be undertaken***
 - ★ ***Actions should be completed in a timely and effective manner***
 - ★ ***Management procedures for ongoing management and review of actions***



EU GMP Guide - Revised Chapter 1

- Where MAA holder is not the manufacturer, there should be a **technical agreement** in place between the various parties
- The **Qualified Person** responsible for final batch certification together with the MAA holder should ensure that the quality review is performed in a timely manner and is accurate.



Implementation of EU GMP Guide - Revised Chapter 1

EMEA:

“Companies performing their first Product Quality Review in 2006 should cover a period of at least 6 months. Subsequent reports should cover a full 12 months' period.”



EU GMP Guide - Revised Chapter 6

- **Adds requirement to conduct ongoing stability studies**
 - ★ *Effective 1 June 2006*
- **The stability of the medicinal product should be monitored according to a continuous appropriate programme that will permit the detection of any stability issue**



EU GMP Guide - Revised Chapter 6

- **The purpose is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labelled storage conditions.**
- **Results of ongoing stability studies should be made available to key personnel and, in particular, to the QP(s).**



EU GMP Guide - Revised Chapter 6

- **The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis.**
- **Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type.**
- **The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.**



EU GMP Guide - Revised Chapter 8

- **Changes agreed in December 2005 which became effective on 1 February 2006**
- **Main change to add:**
“Special attention should be given to establishing whether a complaint was caused because of counterfeiting”
- **Minor change:**
“The effectiveness of the arrangements for recalls should be evaluated **regularly**”



EU GMP Guide – Annex 1 Sterile Products

- **New draft was published for comment
23 November 2005**
 - ★ *Comments were due by 30 April 2006*
 - ★ *Further draft expected by end 2006*
- **Main changes proposed are:**
 - ★ *A clearer text associated with the
environmental classification table in
section 3 and 4.*



EU GMP Guide – Annex 1 Sterile Products

- **Main proposed changes continued :**
 - ★ ***Media simulation acceptance criteria to be harmonised with the requirements of the FDA***
 - ★ ***Guidance on the frequency of pre-sterilisation bioburden monitoring***
 - ★ ***Additional guidance on the appropriate environmental conditions for the handling of freeze-dried vials between partial stoppering and final sealing***



Changes to EU GMP Guide Annexes 2 and 3

- Annex 2, **Biological Products**, to clarify the boundary between the requirements for APIs in Directives 2004/23/EC and 2004/27/EC
- Annex 3, **Radiopharmaceuticals**, to modify the basic requirements for APIs for radionuclides and to cover GMP for short-lived PET radiopharmaceuticals
- Draft revisions not yet issued for comment



Changes to EU GMP Guide Annex 6

- **Annex 6, Medicinal Gases**, to clarify requirements for whether medicinal gases are APIs or bulk pharmaceutical products. Other changes will cover:
 - ★ *Storage of empty cylinders*
 - ★ *Maintenance of valves*
 - ★ *Filling of mobile vessels used by hospitals*
 - ★ *Reference will be made to the Ph.Eur.*
- **Draft revision not yet issued for comment**
 - ★ *Revised PIC/S Aide-Memoire on “Inspection of Medicinal Gases” published Aug. 2006*
 - ★ *Likely to be basis for revised Annex 6*



Changes to EU GMP Guide Annex 7

- **Annex 7, Herbal Medicinal Products,** revised to incorporate the requirements for APIs in Directive 2004/27/EC and for herbal medicines in Directive 2004/24/EC
- **Draft revision for comment, dated March 2006, was issued in May**
 - ★ ***Comments due by 31 July 2006***
 - ★ ***Final version by end 2006 ?***



EU GMP Guide - New Annex 19

"Reference and Retained Samples"

- Final version , dated 14 December 2005, was published on the web in February 2006
- It became effective from **1 June 2006**

NOTE:

**Only applies to marketed products.
Requirements for IMPs in Annex 13.**



New Annex 19

- **'Reference' samples**
 - ★ *Stored for purpose of analysis*
 - ★ *Need to store samples of “critical intermediate stages” and “intermediates that are transported outside of the manufacturer’s control”.*
 - **Critical = “those requiring analytical testing and release”**
 - ★ *Each packaging site should keep reference samples of each batch of primary and printed packaging materials*



New Annex 19

- **'Retained' samples**
 - ★ *Stored for identification purposes*
 - ★ *Must always be stored licensed premises within EEA, preferably at site where QP certifying batch is located*
- **Reference and Retained samples may be presented identically, i.e. as fully packaged units.**



New Annex 19

- **Duration of storage**
 - ★ ***Finished product; 1 year past expiry date***
 - ★ ***Starting materials; 2 years after release of product (shorter if unstable)***
 - **unless a longer period is required by Member State law**
 - ★ ***Packaging materials should be retained for the duration of the shelf life of the finished product***



New Annex 19

- **Written agreements**
 - ★ *Need to define responsibilities for sample retention in Technical Agreement*
 - ★ *The QP releasing batch must ensure samples are accessible at all times*



Additional GMP changes ?

Dedicated facilities

- **Revision of Chapters 3 and 5 being considered**
 - ★ *To better define when dedicated facilities are required when handling high potency products*
 - ★ *Concept Paper on 'Dedicated manufacturing facilities in the manufacture of products using high-risk substances' published February 2005*
 - ★ *Draft revisions to sections 3.6, 5.18 and 5.19 of the EU GMP Guide expected*



ICH Q9 – EU Implementation

- **EMEA stated on website in January 2006:**
 - ★ ***“ ..the principles of quality risk management can be applied not only in the manufacturing environment but also in connection with pharmaceutical development ...
In addition the guideline applies also to the regulatory authorities in the fields of pharmaceutical assessment of the quality part of the marketing authorisation dossier, GMP inspections and the handling of suspected quality defects.”***



Q9 – Implementation in EU

- **EMEA Q9 Implementation Group consisting of inspectors and regulatory assessors**
- **EU adoption expected be as follows:**
 - ★ ***Added as Annex 20 of GMP Guide (with clear note that it is optional)***
 - ★ ***Changes to Introduction and Chapter 1 of EU GMP Guide***
 - ★ ***Revisions to some CHMP NfGs***



Conclusion

- **The rules keep changing!**
- **The rate of change is currently at an unprecedented level**
- **QPs, in particular, must keep up with these changes**
 - ★ ***Take the time***
 - ★ ***It is a GMP expectation (Annex 16, 8.3)***





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