

# Regulatory Requirements & Recent Changes, including expectations for APIs & IMPs

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# Programme:

- Regulatory Requirements – Neil Raw
- Recent and upcoming changes to EU GMP – Neil Raw
- Regulatory requirements for APIs – Richard Andrews
- Regulatory requirements for IMPS – Neil Raw

# Relevant Legislation

- Amended EU medicines legislation effective 30 October 2005 – Directive 2004/27/EC (2001/83/EC as amended).
  - Articles 48-51
- Transposed into law in each member state (in UK as Statutory Instrument S.I. 2005/2789, October 2005).
- EU GMP Guide,
  - Chapter 1 – Quality Management
  - Chapter 2 – Personnel
  - Annex 16 – Certification by QP & Batch Release

# Requirements

- MIA Holders require QP at their disposal
- Qualification requirements
- Transitional QPs
- Batches must be manufactured according to EU GMP & MA
- Same for imported batches
- If not manufactured to MA – Batch specific variations
- No scope for QP discretion if product does not meet registered attributes

# Recent GMP changes

EU Guide to GMP – Introduction to the GMP Guide & Chapter 1 (Quality Management)

New Chapter Came into Operation – July 2008

- Introduction & Chapter 1 of the GMP Guide to be amended to reinforce references to quality risk management principles. The amendment is part of the EC implementation measures for the ICH Q9 guideline. The changes made are restricted to the principle and a new section.
- Doing quality risk management is mandatory.
- How you choose to do it is up to you, but reference is made to ICH/Annex 20

# Recent GMP changes

EU Guide to GMP – Annex 20 (Quality Risk Management)  
New annex came into operation – Mar 2008.

- Implementation of the ICH Q9 guideline on quality risk management without any changes.
- The ICH Q9 guideline on quality risk management defines quality risk management principles. It also describes processes and offers a selection of methods and tools when applying the quality risk management principles.
- Will be voluntary in nature i.e. Annex 20 will give you possible tools. How and whether you apply these tools or others is up to you. (NB. This is the only place ICH Q9 is published in the EU system, but it has a wider scope than just GMP, e.g. applications, variations).

# Upcoming GMP changes

EU Guide to GMP – Annex 1 (Manufacture of Sterile Medicinal Products)

Date of publication – December 2007

Date of implementation – March 2009

Date of implementation (capping of vials) March 2010

- To differentiate between room classification & monitoring.
- To align the classification table for the environmental cleanliness of clean rooms with ISO standards.
- Stated provisions for conditions under which capping of vials should be performed (effectively extension of UK expectations applied over the last 15 years).
- Alignment of media simulation acceptance criteria – makes it clear that the old concept of 1 contaminated unit in 1000 examined is not acceptable.

# Upcoming GMP changes

EU Guide to GMP – Annex 3 (Manufacture of RadioPharmaceuticals)

Date of publication – Aug 2008

Date of implementation – March 2009

- Annex 3 of the GMP Guide updated as a consequence of the restructuring of the GMP Guide. Includes reference to PET radio nuclides.
- Part II of the GMP Guide does not provide specific guidance on manufacturing/control aspects specific to radio nuclides, the active substances in the case of radiopharmaceuticals, and so annex 3 has been revised to modify the basic requirements laid down in Part II for application to radio nuclides, as well as update it to the current state of the art in all relevant aspects of GMP for radiopharmaceuticals.



# Upcoming GMP changes

EU Guide to GMP – Annex 6 (Manufacture of Medicinal Gases)

July 2007 – paper published for public consultation.

Now undergoing review of final text – expected in mid-2009

- Annex 6 of the GMP Guide is under revision as a consequence of the restructuring of the GMP Guide.
- Part II of the GMP Guide requires modification to make it applicable to medicinal gases. There is a need to define more clearly what should be considered as a starting material as opposed to a bulk pharmaceutical product. The existing annexe states that bulk gases could be regarded as an active substance used as starting materials or bulk medicinal products as decided by national competent authorities.
- Public comments are particularly invited on how Part II of the GMP Guide can be applied to medicinal air.

# Upcoming GMP changes

EU Guide to GMP – Annex 7 (Manufacture of Herbal Medicinal Products)

Date of publication – September 2008

Date of implementation – September 2009

- Revised to specify application of GMP provisions for active substances used as starting materials
- Additional changes related to new directive 2004/24/EC

# Upcoming GMP changes

Other parts currently under review

- Chapter 3 (Premises and Equipment)
  - Changes in relation to dedicated facilities
  - Text expected to be finalised by end 2008
  - Public consultation in 2009
- Chapter 5 (Production)
  - Changes in relation to dedicated facilities
  - Changes to reflect obligations to use APIs manufactured in accordance with GMP and C of As
  - Text agreed but on hold until EC publishes anti-counterfeiting legislation to ensure agreement

# Upcoming GMP changes

Other parts currently under review

- Annex 2 (Biological Products)
  - Public comments under consideration
  - There was a lack of comments on Advanced Therapy Medicinal Products
- Annex 11 (Computerised Systems) and consequential changes to Chapter 4 (Documentation)
  - Draft out for public consultation, comments by end of Oct 2008
- Annex 13 (Manufacture of Investigational Medicinal Products)
- Annex 14 (Manufacture of Products derived from Human Blood or Human Plasma)

# Upcoming GMP changes

- Annex 16 (Certification by a QP and Batch Release)
  - Considering the principle of “QP discretion”
  - Revised reflection paper on “QP discretion” (EMA/467989/2008)
    - “QP discretion” considering one-off type of deviations in the manufacturing process and/or analytical control methods.
    - Recurrent deviations and deviations from other aspects of the Marketing Authorisation dossier are outside the scope of the proposed solution.
    - Planned deviations are also outside the scope of this paper.
    - It does not allow acceptance of materials not meeting specification. The active substance and finished product specifications as described in the Marketing Authorisation must be complied with.
  - Delayed to come in line with new variation regulations and subsequent guidelines.

# Upcoming GMP changes

## Specific Conditions of the Application of the Principles and Guidelines of GMP for Certain Excipients.

- Output from online consultation with industry (excipient manufacturers and users) via questionnaire.
  - Six categories under discussion
  - Derived from TSE –relevant animal species
  - Derived from human/animal origin – potential viral contamination risk
  - Claimed to be sterile and used without further sterilisation
  - Present significant endotoxin/pyrogen contamination risk and used in products requiring endotoxin/pyrogen control such as parenteral
  - Propylene glycol
  - Glycerol

# GMP Compliance of Active Substances A Regulatory Perspective

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# Relevant Legislation

- Amended EU medicines legislation effective 30 October 2005 – Directive 2004/27/EC (2001/83/EC as amended).
- Transposed into law in each member state (in UK as Statutory Instrument S.I. 2005/2789, October 2005).



# Responsibilities of Manufacturing Authorisation Holders

- Article 46(f) of 2004/27/EC introduced an obligation (by law via S.I. 2005/2789 in UK) for *Manufacturing Authorisation* holders to use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for active substances.
- Marketing Authorisation Applications and variations to change the source of the active substances used as starting materials need to be supported by a declaration of GMP Compliance of the active substance manufacturer by a QP of the dosage form manufacturer.
- Such Manufacturing Authorisation holders may be EEA based manufacturers or importers of medicinal products from outside EEA.
- Compliance with these requirements are assessed during inspections of Manufacturing Authorisation holders.....

# Inspection Program for Manufacturing Authorisation Holders

- Inspections currently conducted on a two yearly cycle.
- Manufacturing Authorisation holders inspected for compliance with requirement to only use APIs, as starting materials, that have been manufactured in accordance with GMP.
- Any deficiencies are addressed via the inspection reporting system. Required action will vary between member states but could in certain circumstances involve:
  - Requirement to recall product.
  - Refusal to grant variation to Marketing Authorisation.
  - Removal of API site from Marketing Authorisation.
  - Suspension or removal of Manufacturing Authorisation.
  - Warning to a Qualified Person related to conduct/responsibilities or withdrawal of QP from a Manufacturing Authorisation.
  - Inspection of the API site by the Competent Authority.

# Expectations of Manufacturing Authorisation Holders

- MA holders must have a supplier evaluation and approval program covering APIs (this must be in place irrespective of whether a QP declaration has been required). This must accumulate a body of evidence which enables the status of each API supplier to be determined. The program must also consider periodic re-evaluation of each suppliers status.
- Approved manufacturers *and* supplier listings must be in place, be current, readily available and be supported by documented evidence gained through the above evaluation program.
- Procurement systems must only allow purchase or receipt of APIs that are approved or undergoing controlled assessment.

# Expectations of Manufacturing Authorisation Holders

- The entire supply chain for a supplied API must be defined and approved by the Manufacturing Authorisation holder.
- It is expected that in order to approve an API source an audit(s) will have been conducted on or on behalf of the Manufacturing Authorisation holder.
- All steps in the supply chain of the active substances in use by a Manufacturing Authorisation holder will have been audited, including those in third countries, by or on behalf of the Manufacturing Authorisation holder.
- Audits of API sites must be conducted against the requirements of the EU GMP Guide Part II (ICH Q7) by auditors with suitable experience/knowledge in API manufacture.

# Expectations of Manufacturing Authorisation Holders

- Any deficiencies identified through the audit(s) must be risk assessed and appropriate action taken.
- Any deficiencies identified must be managed to conclusion.
- The audit report (or suitable audit summary) should be available for inspection. The report and/or the summary should confirm the following information:
  - Dates performed
  - Auditors (their qualifications should be available separately for inspection)
  - The scope of the inspection

# Expectations of Manufacturing Authorisation Holders

- The outcome i.e. number and category of deficiencies. Any deficiencies that could threaten patient safety must be declared.
- Current status of deficiencies / CAPA.
- Period of validity of the audit (depends on circumstances, three years appears to be the industry consensus.)
- Conclusion / recommendations for supplier approval.
- A Technical Agreement (TA) must be in place with the API manufacturer/supplier.
- Inform MA holder if different from MIA holder.

# Expectations of Manufacturing Authorisation Holders

- Contents of the TA should be compliant with Chapter 7 of the EU GMP Guide and specifically include:
  - Change control and agreement that the API site will notify the Manufacturing Authorisation holder of any changes that could impact the quality of the API or alter the typical profile.
  - Requirement to notify the Marketing Authorisation holder of any changes submitted to the Drug Master File.
  - Agreement to allow access to audit the API site.
  - Document the agreed specification.
  - Agreement that sub contracting will not be allowed without Manufacturing Authorisation holders consent.

# Expectations of Manufacturing Authorisation Holders

- An incoming goods inspection program must be in place that documents:
  - Requirement for confirmation checks on source of API (manufacturer and supplier) and a visual inspection of goods.
  - Sampling plans.
  - Testing arrangements / Certificate of Analysis requirements
  - Non conforming goods process.
  - Requirement to fully investigate any anomalies e.g. atypical test data, unusual C of As, different packaging.



# Expectations of Manufacturing Authorisation Holders

- Qualified auditors must be used:
  - Trained in techniques of auditing.
  - Have sufficient training or experience in API manufacture to support capability to audit effectively.
  - Have specific knowledge of requirements of EU GMP guide Part II.

# Expectations of Manufacturing Authorisation Holders

- API audits by 3<sup>rd</sup> Party Auditors are regarded as suitable by MHRA on the following basis:
  - The scope of the audit must be clearly defined and must include appropriate/defined elements of the supply chain.
  - Auditors must be appropriately qualified.
  - A 3<sup>rd</sup> party auditor may provide audit reports to multiple Manufacturing Authorisation holders. Manufacturing Authorisation holders may make use of such a report as far as the scope is fully pertinent to the APIs in question.

# Expectations of Manufacturing Authorisation Holders

- If auditing as a 3<sup>rd</sup> party have a technical agreement with the contract giver complying with chapter 7 of the EU GMP Guide and have no vested interests in the outcome.
- Competent Authority inspections may be used as *supporting information* in the risk assessment of API suppliers.

# Expectations of Manufacturing Authorisation Holders

- Action expected in the event of non compliant API manufacturer:
  - Should an API supplier be identified by audit or other means as not fully GMP compliant a risk assessment must be performed and appropriate action must be taken by the Manufacturing Authorisation holder, for example:
    - Consideration of product recall and notification of same to local Competent Authority.
    - Suspension of approved status and discontinue further use.
    - Restricted approval and increased surveillance e.g. additional testing of API.
  - Where the MIA holder is not the MA holder the latter must be fully involved and agree with the course of action.

# Expectations of Manufacturing Authorisation Holders

- Repeat audit or coaching of API supplier.
- Consideration of notification to Competent Authority of API site details (to allow assessment against other licenses or as preventive information for new submissions and may trigger inspection of API manufacturer).

# GMP Compliance of Investigational Medicinal Products A Regulatory Perspective

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# Historical background

- EC Directive 2001/20
- Implemented in the UK as SI 2004/1031
- Effective as of 1 May 2004

# Statutory Instrument 2004:1031

## Regulation 13

### **Supply of investigational medicinal products for the purposes of clinical trials**

**13.** No person shall sell or supply any investigational medicinal product for the purpose of administering that product in a clinical trial unless:

- the licensing authority has authorised the clinical trial.
- the product has been manufactured, assembled or imported in accordance with appropriate authorisations.
- the batch of IMP has been checked and certified by a Qualified Person (Article 13 of Directive 2001/20/EC).



# Statutory Instrument 2004:1031

## Regulation 36

### **Manufacture and Importation of Investigational Medicinal Products**

**36.** No person shall manufacture, assemble or import any investigational medicinal product except in accordance with an authorisation granted by the licensing authority (“a manufacturing authorisation”).

This restriction does not apply to licensed products where the manufacture or assembly of a medicinal product is in accordance with the terms and conditions of a marketing authorisation relating to that product.

# Statutory Instrument 2004:1031

## Regulation 37

### Exemption for hospitals and health centres

- 37.** The need for a manufacturing authorisation (Regulation 36) shall not apply to the assembly of an investigational medicinal product where:
- The assembly is carried out in a hospital or health care centre, and by a doctor, a pharmacist or person acting under the supervision of a pharmacist.
  - The investigational medicinal products are assembled exclusively for use in that hospital or health centre, or any other hospital or health centre which is a trial site for the clinical trial in which the product is to be used.

# Statutory Instrument 2004:1031

## Regulation 46

### Labelling of Investigational Medicinal Products

- 46.** An IMP shall be labelled in accordance with Article 15 of Commission Directive 2003/94/EC (a) unless the IMP is:
- for use in a clinical trial with the characteristics specified in the second paragraph of Article 14 of the Directive.
  - dispensed to a subject in accordance with a prescription given by an authorised health care professional.
  - labelled in accordance with the requirements of Schedule 5 to the Medicines for Human Use (Marketing Authorisation etc) Regulation 1994 (b) that apply in relation to dispensed relevant medicinal product.

# Annex 13 Considerations

## Annex 13 Principle

Trial sponsors undertake the ultimate responsibility for all aspects of the clinical trial *including the quality of the IMPs*.

## Annex 13 Paragraph 44

IMPs should remain under the control of the Sponsor until after completion of a two step procedure: certification by the QP; and release following fulfilment of the requirements of Article 9. ...Both releases should be recorded and retained in the relevant trial files held by or on behalf of the sponsor.

# Impact On IMP Supply - (1)

## **Product licensed in the UK or another EEA country**

- From external wholesaler in the UK or EEA
  - Bona fide checks i.e. evidence of licence
  - Goods receipt note – maybe without batch number

NB - Arrangements must be in place to ensure that any recall of the product would be notified

# Impact On IMP Supply – (2)

## Product manufactured outside the EEA

- If it is not licensed in the UK or the EEA then it will need to be imported into the UK via the holder of a MIA IMP and be certified by a QP.
- A QP declaration providing assurance of the compliance of the product with EU GMP will need to have been submitted with the Clinical Trial application.

# Impact On IMP Supply - (3)

## IMP & Matching Placebo manufactured in EU/EEA

- Annex 13 – Paragraphs 8,9,38,39,40 apply
- Formal order – against
  - PSF – Product Specification File
  - CTA – Clinical Trial Authorisation
  - IMPD – Investigational Medicinal Product Dossier
- Authorised manufacturer/importer – evidence
- QP certification – GMP compliance/ PSF etc
- Batch specific documentation including C of A

NB – it is the duty of the sponsor to ensure that information used by the QP to certify a batch is consistent with the CTA/IMPD i.e. he/she is made aware of any changes and any conditions imposed by the MHRA.

# Impact On IMP Supply - (4)

## **IMP & Matching Placebo manufactured in 3<sup>rd</sup> country**

- QP (importer) declaration submitted with CTA
- QP certification of each batch

NB – In the case of a non-MRA country it would be expected that the QP would have audited the manufacturing facility or made arrangements for it to have been audited on his/her behalf by an appropriately trained auditor. (Annex 13: 39(b))



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# **Good Manufacturing Practice (GMP) Symposium**

## **Best practice guidance for Qualified Persons**

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