Agenzia Italiana del Farmaco

AIFA

Investigational Medicinal Product GMP aspects (update ANNEX 13)

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Legal Basis: Applying GMP to IMPs

- The Principles of ICH GCP (CPMP/ICH/135/95)
  - 2.12. Investigational products should be manufactured, handled and stored in accordance with applicable GMP. They should be used in accordance with the approved protocol
- Directive 2001/20/EC (Clinical Trial Directive)
  - Whereas:
    - (12) The principles of good manufacturing practice should be applied to investigational medicinal products
    - (13) Special provisions should be laid down for the labelling of these products

Legal Basis: Applying GMP to IMPs

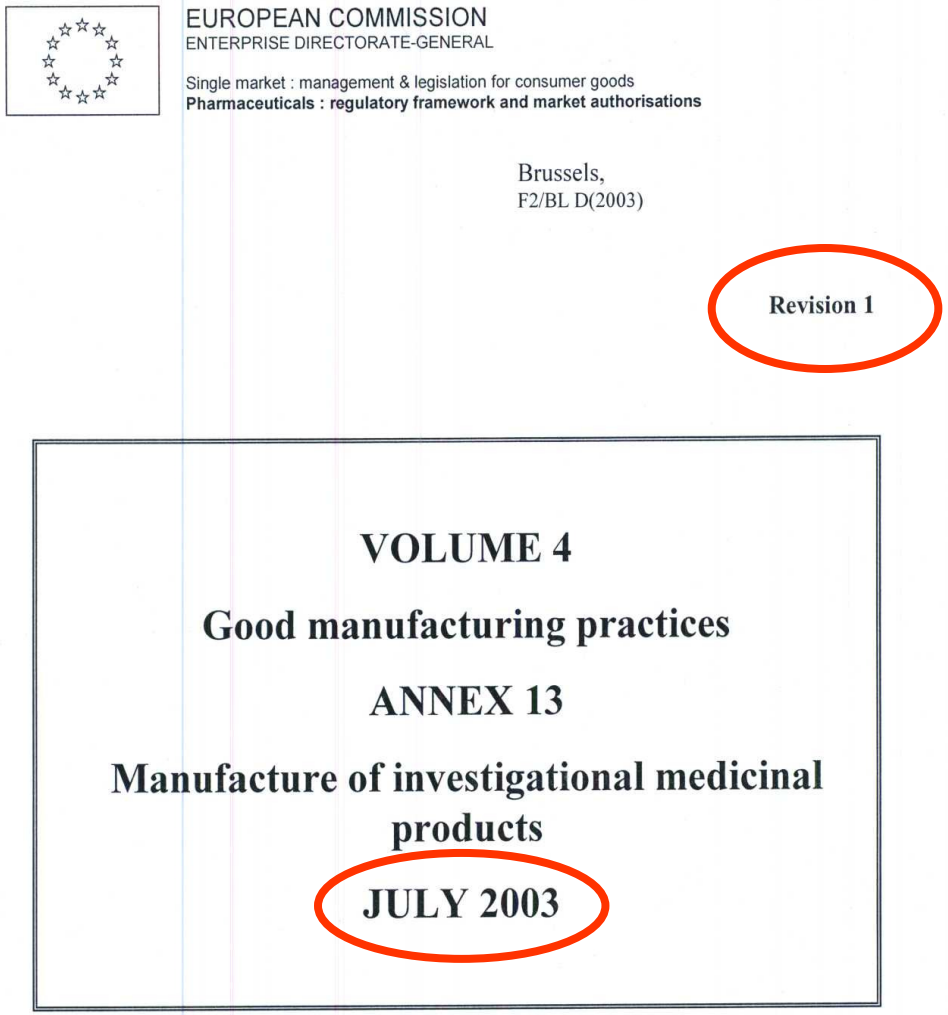
- Directive 2003/94/EC (GMP Directive)
  - "Laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use"

Legal Basis:
Manufacture an Importation of IMPs

- Directive 2001/20/EC (Clinical Trial Directive)
  - Art.13.1 – IMPs manufacturer and/or importer to hold an authorisation
  - Art.13.2 - Authorisation holder to have a QP (as set out in article 48 of Directive 2001/83/EC)
  - Art.13.3 – Duties of the QP
- Directive 2005/28/EC (GCP Directive)
  - Requirements for authorisation holder

By courtesy of Riccardo Luigetti

The ANNEX 13 in force



EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market : management & legislation for consumer goods
Pharmaceuticals : regulatory framework and market authorisations

Brussels,
F2/BL D(2003)

Revision 1

VOLUME 4

Good manufacturing practices

ANNEX 13

Manufacture of investigational medicinal products

JULY 2003

The revision of Annex 13

EUROPEAN COMMISSION
ENTERPRISE AND INDUSTRY DIRECTORATE-GENERAL

Consumer goods
Pharmaceuticals

Brussels, 02 July 2009
ENTR/F/2/SF D(2009)

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

Investigational Medicinal Products

Document History	
Revision to reinforce the principle of independence between production and quality control functions in cases where the number of personnel involved is small. Changes to sections 36 and 37 to supplement, for investigational medicinal products, the guidance for reference and retention samples given in Annex 19. An additional note has been introduced to clarify the meaning of "reconstitution" as referred to in article 9.2 of Directive 2005/28/EC. The content of the Batch Certificate referred to in Art. 13(3) of Directive 2001/20/EC, agreed following a separate public consultation, has been added as an attachment. A few editorial changes have been made to sections not consulted upon in the interests of updating references and consistency with terminology used throughout the GMP Guide.	February 2008
Public consultation	April 2008 until January 2009
Date of revised version coming into operation	Publication + 6

Commission Européenne, B-1049 Bruxelles / Europese Commissie, B-1049 Brussel – Belgium. Telephone: (32-2) 299 11 11

List of Changes

- Section 3 (Personnel): revision to reinforce the principle of independence between production and QC in cases where the number of personnel involved is small.
- Sections 36 and 37 (Quality Control): revision to supplement for IMP the guidance for reference and retention samples given in Annex 19.
- Sections 43 (Shipping): reworded to enhance understanding of the two-step release procedure for IMPs.

List of Changes

- The content of the Batch Certificate referred to in Art. 13(3) of Directive 2001/20/EC, agreed following a separate public consultation, has been added as an attachment.
- An additional note has been introduced to clarify the meaning of "reconstitution" as referred to in article 9.2 of Directive 2005/28/EC.

In this presentation…

- Section 3 (Personnel): revision to reinforce the principle of independence between production and QC in cases where the number of personnel involved is small.
- Sections 36 and 37 (Quality Control): revision to supplement for IMP the guidance for reference and retention samples given in Annex 19.
- Sections 43 (Shipping): reworded to enhance understanding of the two-step release procedure for IMPs.
- The content of the Batch Certificate referred to in Art. 13(3) of Directive 2001/20/EC, agreed following a separate public consultation, has been added as an attachment.
- An additional note has been introduced to clarify the meaning of "reconstitution" as referred to in article 9.2 of Directive 2005/28/EC.

2-step procedure for shipping Annex 13 – 44 (43)

Investigational medicinal products should remain under the control of the sponsor until after completion of a two-step release procedure: certification by the Qualified Person; and release by the sponsor for use in a clinical trial following fulfilment of the requirements of Article 9 (Commencement of a clinical trial) of Directive 2001/20/EC. Both steps should be recorded and retained in the relevant trial files held by or on behalf of the sponsor.

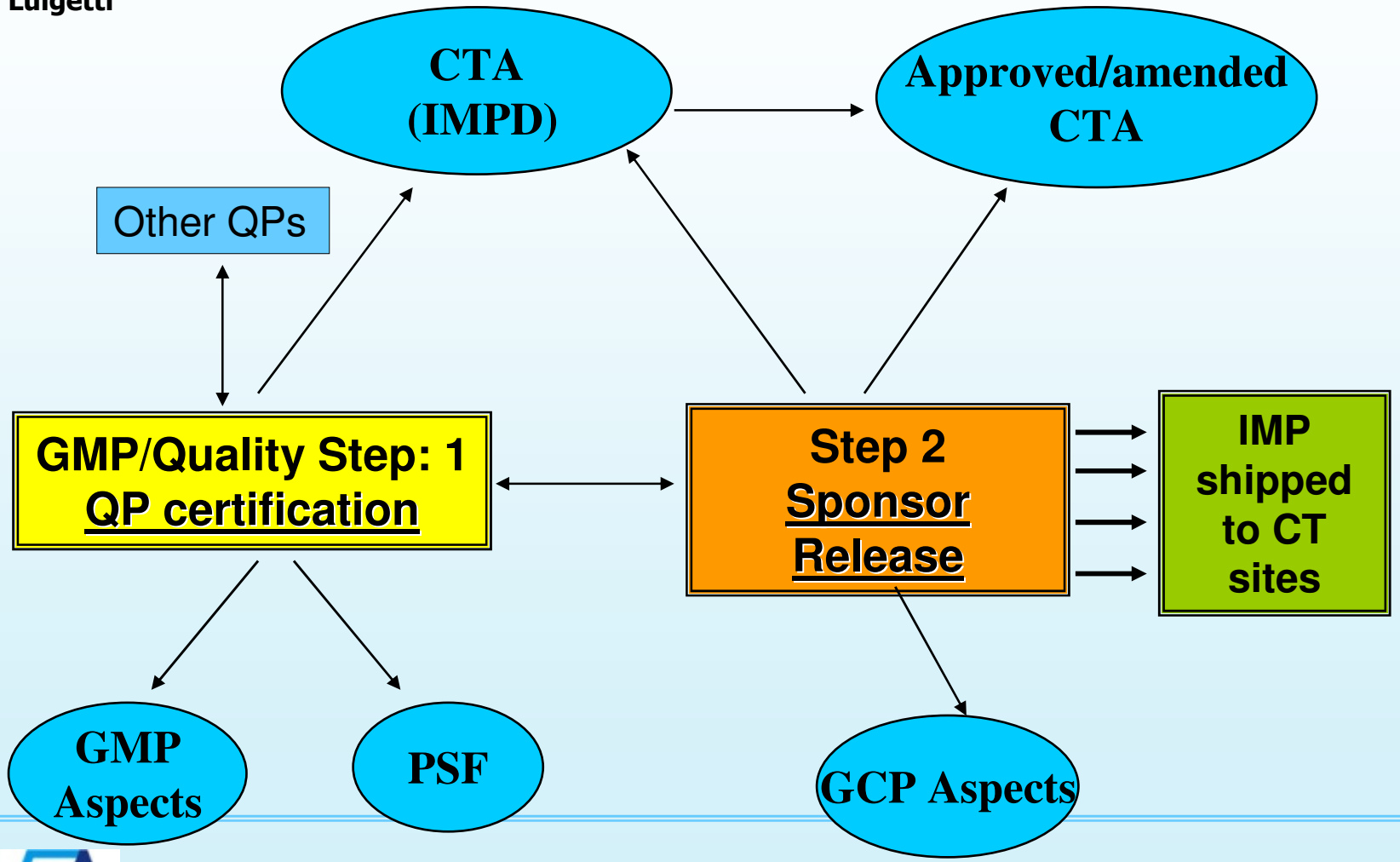
2-step procedure for shipping Annex 13 – 44 (43)

The Sponsor should ensure that the details set out in the clinical trial application and considered by the Qualified Person are consistent with what is finally accepted by the Competent Authorities.

Suitable arrangements to meet this requirement should be established. In practical terms, this can best be achieved through a change control process for the Product Specification File and defined in a Technical Agreement between the QP and the Sponsor.

Release of IMPs: a 2-step process

By courtesy of
Riccardo Luigetti



QP Certification

- batch records, including control reports, in-process test reports and release reports demonstrating compliance with the product specification file, the order, protocol and randomisation code. These records should include all deviations or planned changes, and any consequent additional checks or tests, and should be completed and endorsed by the staff authorised to do so according to the quality system;
- production conditions;
- the validation status of facilities, processes and methods;
- examination of finished packs;
- where relevant, the results of any analyses or tests performed after importation;
- stability reports;
- the source and verification of conditions of storage and shipment;
- audit reports concerning the quality system of the manufacturer;
- documents certifying that the manufacturer is authorised to manufacture investigational medicinal products or comparators for export by the appropriate authorities in the country of export;
- where relevant, regulatory requirements for marketing authorisation, GMP standards applicable and any official verification of GMP compliance;
- all other factors of which the QP is aware that are relevant to the quality of the batch.

The Batch Release Certificate

ATTACHMENT 3

[LETTERHEAD OF MANUFACTURER]

Content of the Batch Certificate

Referred to in Art. 13.3 Directive 2001/20/EC

(1) Name(s) of product(s)/product identifier(s) as referred to in the clinical trial application, where applicable.

(2) EudraCT No(s) and sponsor protocol code number, when available.

(3) Strength

Identity (name) and amount per unit dose for all active substance(s) for each IMP (including placebo). The manner in which this information is provided should not unblind the study.

(4) Dosage form (pharmaceutical form)

(5) Package size (contents of container) and type (e.g. vials, bottles, blisters).

(6) Lot/batch number

(7) Expiry/retest/use by date

(8) Name and address of manufacturer where the Qualified Person issuing the certificate is located.

(9) Manufacturing Authorisation number for the site listed under item 8.

(10) Comments/remarks

(11) Any additional information considered relevant by the QP.

(12) Certification statement.

(13) "I hereby certify that this batch complies with the requirements of Article 13.3 of Directive 2001/20/EC "

(14) Name of the QP signing the certificate

(15) Signature

(16) Date of signature

The Batch Release Certificate (BRC)

- Art. 13.3 of Directive 2001/20/EC requires a batch release certificate signed by the QP to allow free movement of IMPs within the EEA
- The content of BRC was agreed following a separate public consultation
- The GCP-IWG proposed to have it in the Eudralex Volume 10, as in cases changes are needed its revision would be much easier
- In the EEA these will be interpreted as the "certificates of analysis" referred to in ICH GCP 8.2.16 and 8.3.9

Manufacturing authorisation and reconstitution

Both the total and partial manufacture of investigational medicinal products, as well as the various processes of dividing up, packaging or presentation, is subject to the authorisation referred to in Article 13(1) Directive 2001/20/EC, cf. Article 9(1) Directive 2005/28/EC.

This authorisation, however, shall not be required for reconstitution under the conditions set out in Article 9(2) Directive 2005/28/EC. For the purpose of this provision, reconstitution shall be understood as a simple process of:

Manufacturing authorisation and reconstitution (cont.)

For the purpose of this provision, reconstitution shall be understood as a simple process of:

- dissolving or dispersing the investigational medicinal product for administration of the product to a trial subject,
- or, diluting or mixing the investigational medicinal product(s) with some other substance(s) used as a vehicle for the purposes of administering it.

Manufacturing authorisation and reconstitution (cont.)

Reconstitution is not mixing several ingredients, including the active substance, together to produce the investigational medicinal product.

An investigational medicinal product must exist before a process can be defined as reconstitution.

The process of reconstitution has to be undertaken as soon as practicable before administration.

This process has to be defined in the clinical trial application / IMP dossier and clinical trial protocol, or related document, available at the site.

Some Additional Issues

- Clarification about destruction of IMP to avoid the destruction of expensive marketed IMPs
- Clarification about labelling (26): information that could be excluded on the label if justified (e.g. use of a centralised electronic randomisation system)
- For Bioequivalence Trials: need to stress issues about traceability


THANK YOU
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