EU Regulation/Guidelines IMPs

Overview

Clinical Trial Regulation

Delegated Regulation GMP for IMPs

Commission Guideline GMP for IMPs

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Overview IMP Regulations/Guidelines

Current	**New**	
Clinical Trial Directive 2011/20/EC	**Clinical Trial Regulation 536/2014**	Transition period until mid 2019
Commission Directive 2003/94/EC GMP for Medicinal products and IMP	**Delegated Regulation 2017/1569 GMP for IMP**	Applied together with 536/2014.
Annex 13 of Vol 4 EU GMP for IMP	**Detailed Commission Guideline GMP for IMPs for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014**	Will replace Annex 13 with 536/2014 and 2017/1569
ATMP Regulation 1394/2007		Effective

EU Regulation/Guidelines IMPs

EU Delegated Regulation

- Special category of law in addition to EU Directives and Regulations-

is directly implemented, has **superiority over national laws**

Regulation: Binding legislative act

Directive: Sets a goal all EU countries must achieve

Guideline: Translates all Regulations and Directives in best practices, Guidance for Interpretation of Directives/Regulations

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Delegated Regulation 2017/1569 GMP for IMP

In accordance with No 536/2014 the Commission published now **Delegated Regulation 2017/1569** laying down **principles GMP for investigational medicinal products for human use and arrangements for inspection (effective October 06, 2017)**

and Directive 2017/1572 GMP for medicinal products for human use (national laws to be adapted till March 31, 2018)

Adobe Acrobat Document

Delegated Regulation 2017/1569 GMP for IMP

Delegated Regulation 2017/1569 GMP for IMP cover GMP related activities and Inspections

Chapter 1 General Provisions**, Chapter 2** Conformity with GMP, Compliance with Clinical Trial Authorization, Pharmaceutical Q- System, Personnel, Premises and Equipment, Documentation, Production, Quality Control, Retention of Samples, Responsibilities of QPs, Outsourced operations, Complaints/recall/emergency unblinding, Self inspections, Advanced Therapy (refers to regulation ATMP)

Chapter 3 Inspections

- Supervision by inspection
- Cooperation and coordination of inspection
- Recognition of insp. Conclusion
- Empowerment of the inspectors
- Competence and obligations of the inspectors
- Quality system for inspectors
- Impartiality of inspectors
- Access to premises by inspectors
- Suspension of Authorization

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Commission Guidelines GMP for IMPs

Published in **December 2017:**
Detailed Commission guidelines on good manufacturing practice for investigational medicinal products for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014

Article 63(1) of Clinical Trial Regulation states that **IMPs shall be manufactured under GMP** to ensure that clinical data are reliable and robust

Existing Annex 13 – Manufacture of IMPs- still applicable and mostly comparable to (see attachment)

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Microsoft Word Document

Commission Guidelines GMP for IMPs

The guideline address specific issues concerning investigational medicinal products with regard GMP, appropriate to the stage of development of the product.

In clinical trials there may be **added risk** to the subjects compared to **patients** treated with authorized medicinal products

The application of GMP for the manufacture and import of investigational medicinal products shall ensure that

- No patient risk due to quality, safety and efficacy of product manufactured/imported
- Consistency between batches
- Changes are adequately documented and justified

Commission Guidelines GMP for IMPs

Production of **IMP**- versus authorized medicinal products

Added complexity - lack of fixed routine
- variety of clinical trial and packaging designs
- randomization/blinding (cross contamination risk)
- incomplete process/product knowledge; lack of full process validation)
- repackaging /relabeling operations

These **challenges require**
- good trained personnel
- highly effective quality systems

Commission Guidelines GMP for IMPs

- **1. SCOPE** These guidelines apply to manufacture or import of investigational medicinal products for human use.

- **2. PHARMACEUTICAL QUALITY SYSTEM**
- **2.1** Product specification file -applicable sections to be ready at start of manufacturing/Reference and Retention samples included

- **3. PERSONELL**
  responsibilities of QP acc. current guidelines and 536/2014 (article 62- QP releases batches manufactured/imported under GMP), now **final** certifying QP has to have knowledge…
- **4. PREMISES EQUIPMENT**
- Design/methods/cleaning should reflect nature of risks – acc Qriskmgt. Chapter 3 and 5 (Eurdalex Vol4), consideration to campaign, cross contamination risks to be evaluated, validation acc. Annex 15

Commission Guidelines GMP for IMPs

- **5. DOCUMENTATION**

- **5.1** Specification and instructions- Approval process for instructions should include management of manufacturing site
- **5.2** Order
  Manufacturer shall retain the order for manufacturing request
- **5.3** Manufacturing Formulae and processing instructions
  Instructions acc. to PSF and specific clinical study information
- **5.4** Packaging instructions

- **5.6** Batch Records
  Document deviations from predefined criteria
  Retention of Clinical Trial master file (sponsor resp.) 25 years after end of trial

Commission Guidelines GMP for IMPs

- **6. PRODUCTION**
- **6.1** Packaging Materials
- **6.2** Manufacturing Operations

  process to validated so far as appropriate/stage of development, cleaning procedures and analytical methods to verify cleaning process to be available.
  for sterile products Annex 1 applicable
- **6.3** Modifications of Comparator products
- **6.4** Blinding Operations
- Expiration date to the shortest dated to be assured
- **6.5** Packaging

  Documentation must show segregation within packaging to avoid mix up
- **6.6** Labelling
- Requirements now defined in 536/2014 Article 66 and 67
- Re-labelling done separated from other activities/outsourcing with written contract
- **7. QUALITY CONTROL**

  The person who has authority for QC has to be independent of production
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Commission Guideline GMP for IMPs

- **8. RELEASE OF BATCHES**
- QP release according Article 63 of regulation 536/2014
  Annex 16 applies for manufacturing at different sites (nor recommended)

- **9. OUTSOURCED OPERATIONS**
- Chapter 7 of Eudralex Vol 4 Part I applies

- **10. COMPLAINTS**
  Chapter 8 of Eudralex Vol 4 Part I applies

- **11.RECALLS AND RETURNS**
  11.1 Recall
  in accordance with Chapter 8 of Eudralex Vol 4 Part I
- **11.2** Return
- **11.3** Destruction

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Questions?