IMP Discussion Group
QP Forum 2026

Orla Campbell
Patryk Jegorow
Barry Heelan

Agenda

- Opening remarks – Introductions
- What is an IMP and what is a Clinical Trial?
- Phases of Clinical Trials
- Phase-appropriate QMS for IMPs
- Clinical Supplies
- Roles and Responsibilities of Clinical Quality
- Roles and Responsibilities of an IMP QP
- EU Regulations and Regulatory Requirements
- Regulations outside of the EU
- Batch confirmation, QP Certification and IMP Release
- Product Specification File (PSF)
- IMP related challenges and common deficiencies

What is an Investigational Medicinal Product?

- An investigational medicinal product is defined in Article 2(5) of Regulation (EU) No 14 536/2014 as a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
- Manufacturing is defined as total and partial manufacture, as well as the various processes of dividing up, packaging and labelling (including blinding) in Article 2(24) of that Regulation.
- Article 63(1) of Regulation (EU) No 536/2014 (previously Annex 13) provides that investigational medicinal products shall be manufactured by applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial.

What is a Clinical Trial

- A clinical trial is a research study conducted with human participants aimed at evaluating a medical, surgical, or behavioral intervention. It is used to gather information about new therapies, vaccines, or new ways of using known treatments.
- Clinical Trials are typically conducted in Phases:
  Phase I, II, III and Phase IV.

Phases of Clinical Trials

Tests the safety, dosage range, and side effects of a new intervention in a small group of people

Phase I

Phase II

Focuses on the efficacy of the intervention and further evaluates its safety in a larger group.

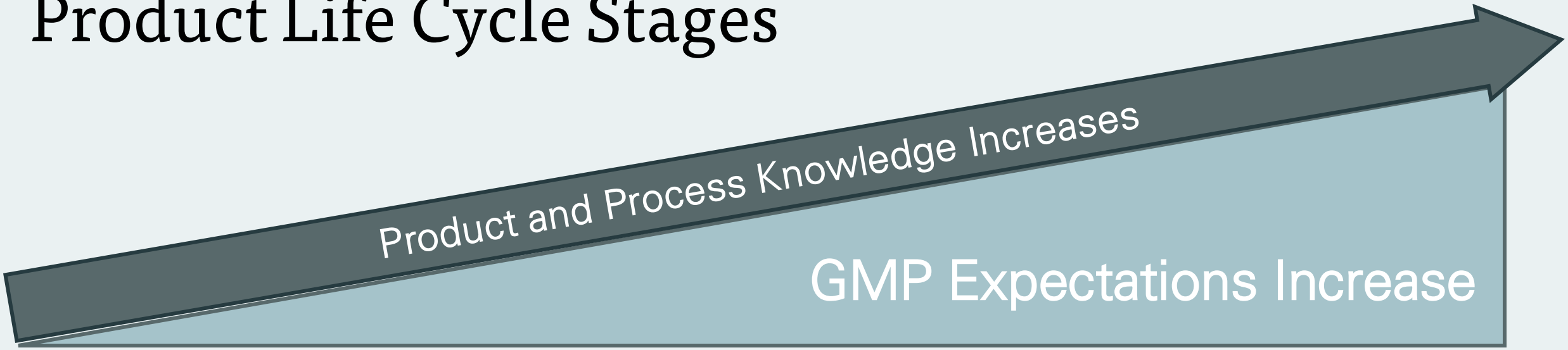
Confirms the intervention's effectiveness, monitors side effects, and compares it to commonly used treatments in large groups.

Phase III

Phase IV

Conducted after the intervention has been marketed to gather information on its effect in various populations and any long-term side effects.

Product Life Cycle Stages



Non-human, Non-Regulatory

Laboratory setting

Compounds NOT dosed to humans

No regulatory submission

Discovery Research

Non-human, Regulatory

Compounds NOT dosed to humans

Regulatory dossier for a clinical trial

Preclinical Research

Early-Stage Clinical until Late-Stage Clinical and Pivotal

Human, Regulatory

Evaluated in humans

Phase 1-3

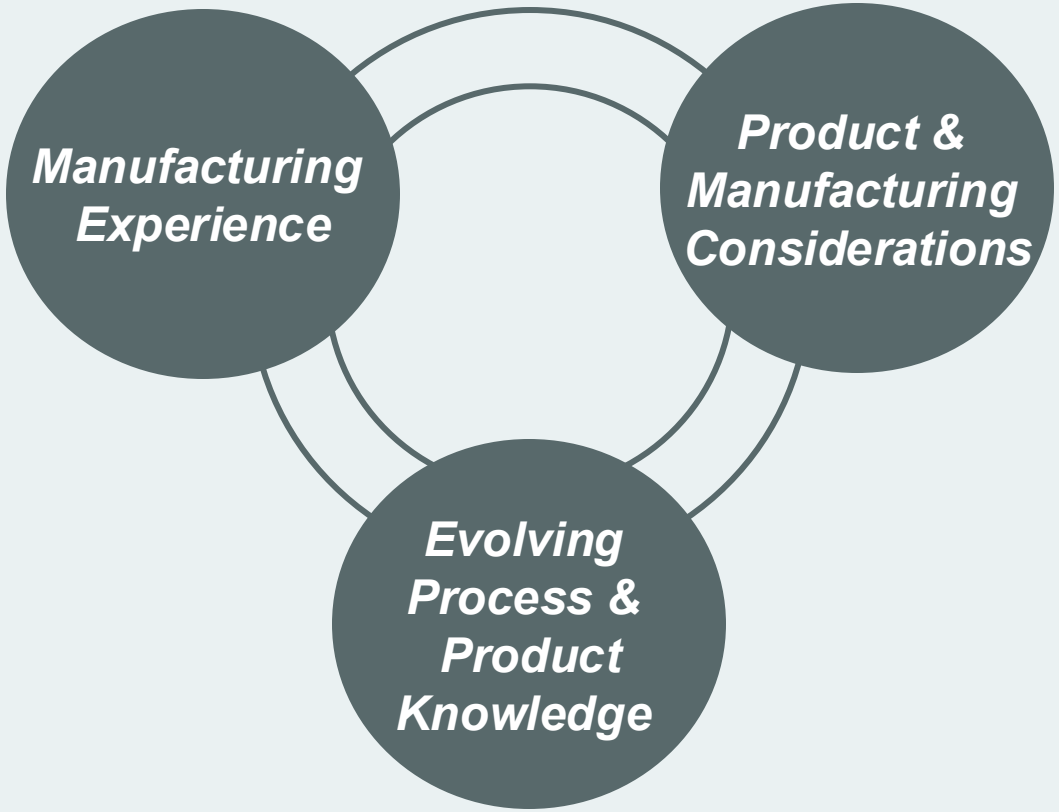
Human, Regulatory Commercial

Full GMP Requirements

Phase 4 & Commercial Product

Phase appropriate QMS designed with patient safety top of mind

Scientifically sound risk-based approach to compliance



Continous Review and Update of the Risk Profile

Quality Risk Management principles should be applied at each stage and identified risks should be addressed appropriately

Phase-Appropriate QMS

- Apply QMS requirements **phase appropriate based on the development of the product**
- Phase appropriateness should be **reflected within the QMS**
- Applying phase appropriate QMS oversight allows us to be **faster and more efficient**
    - **Ensure patient safety** during the entire product lifecycle
    - **Efficient supply** of clinical trial materials while also **maintaining compliance**

Imagine QMS as the music your Company is following. Along the product lifecycle, we modify the volume of the QMS, but even in the clinical phases the music is never turned off.

What are Clinical Supplies?

Clinical Supplies refer to products and/or materials that are required to conduct a Clinical Trial.

Such Supplies include:

IMPs	A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
Ancillary Supplies	Items used for the administration and delivery of IMPs e.g. syringes, needles, medical devices
Comparator Drugs	Standard treatment drug or placebos used for IMP comparison.
Packaging and labelling materials	Application of a Clinical Trial Label
Documentation	Informed Consent forms and Protocols
Monitoring and Diagnostic Tools	Blood Pressure Monitors, ECG machines, etc.

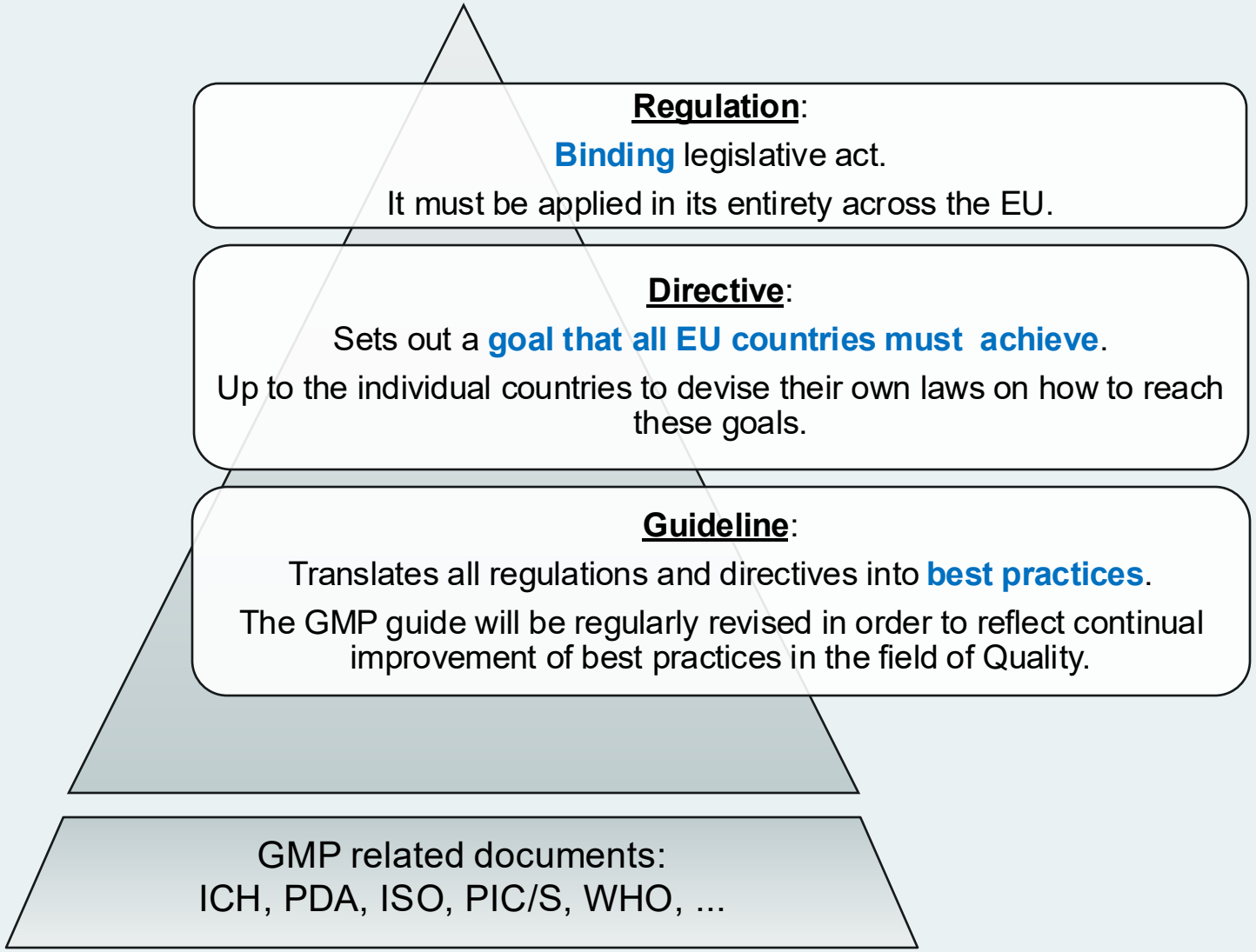
Clinical Quality Responsibilities

Project/Product	Quality Agreements	Quality Reporting	Self Inspection Program	Audits	Regulatory	QP Certification
• MBR Pre Approval • PSF Creation and Maintenance • QP Declaration	• Client Q Agreement • QP to QP Agreement	• Quality Events/Actions • Temperature Excursions • Trending	• Facility & Process audits	• DS/DP Manufacturing • QC Test Labs • Primary/ Secondary Packaging Facilities	• Regulatory Inspection Management • Recall and Complaints • HPRA License variations	• DS/DP Batch record review • Secondary P&L batch record review

Roles and Responsibility of the IMP QP

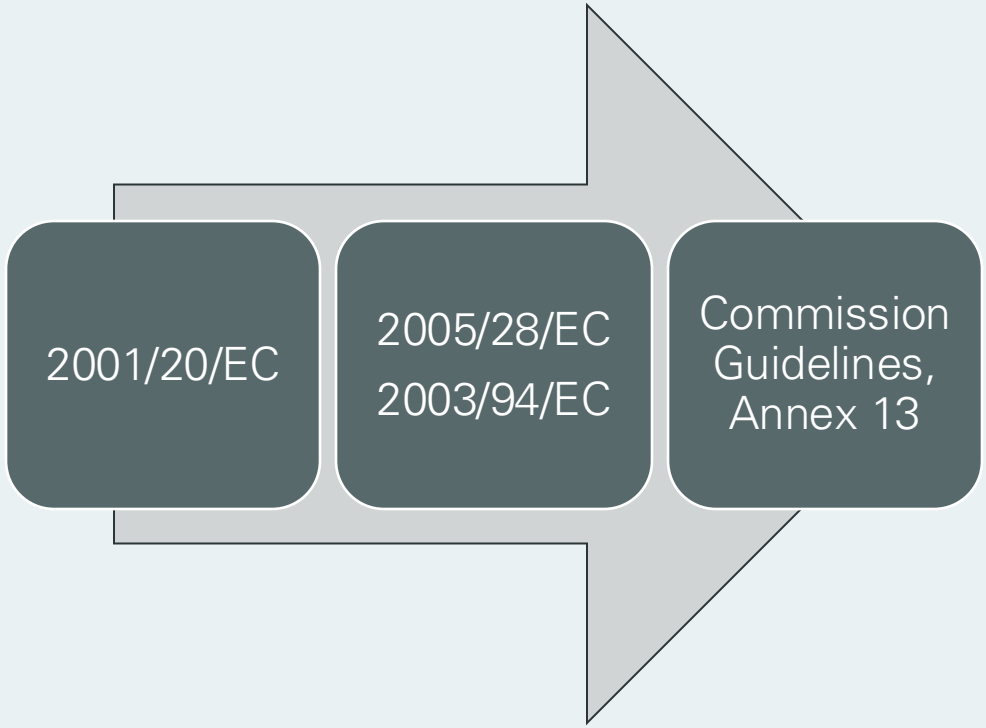
- Certify and release each batch of Investigational Medicinal Product (IMP) as compliant to EU GMP standards before it is released to clinical trial site.
- Overview of supply chain (Annex 16):
  - Ensure adequate audits of Drug Substance and Drug Product manufacturing facilities to support QP Declaration required for Clinical trial submission
  - Ensure adequate audits of Laboratories
- Adherence to Annex 21- Importation of Medicinal Products:
  - Ensures that Third-Country Manufacturer complies with GMP standards equivalent to EU GMP
  - QP Certification or confirmation, as appropriate, of a batch of a medicinal product takes place only after physical importation and custom clearance
- Ensure Clinical Trial document in place:
  - Clinical Supplies Project Plan
  - Relevant Quality Agreement(s)
  - QP to QP Agreement(s)
  - Temperature Excursion Plan
  - Implementation of a Product Specification File

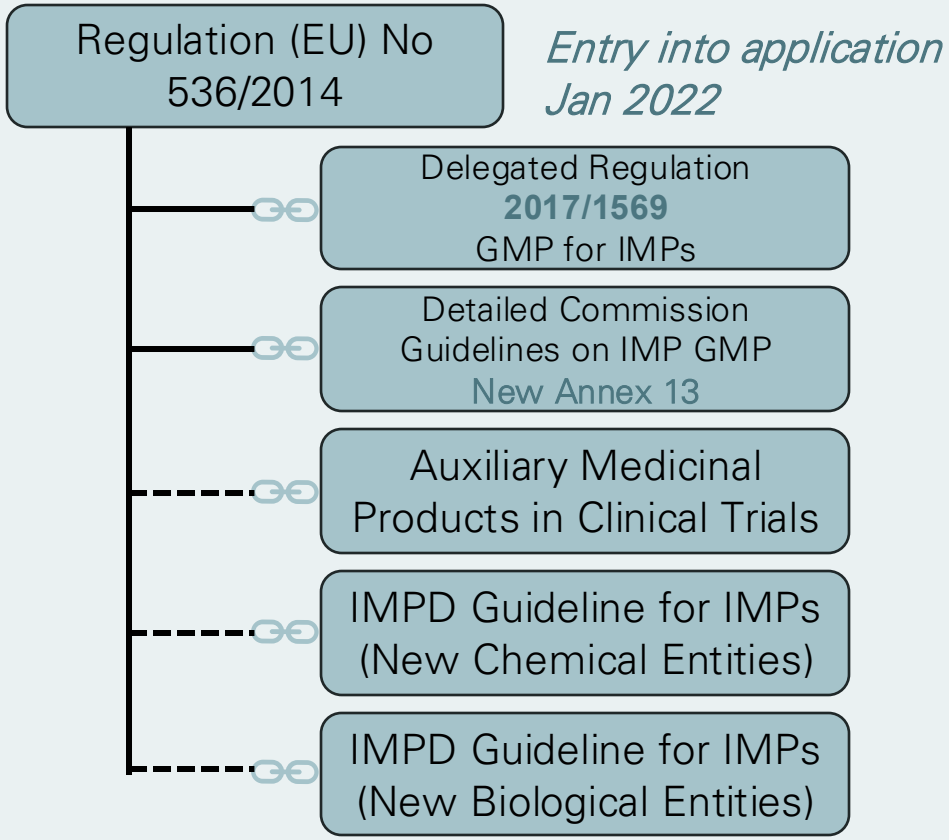
EU Regulations and Regulatory Requirements



EU Regulations and Regulatory Requirements

- REGULATION (EU) No 536/2014 OF EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 April 2014
  on clinical trials on medicinal products for human use – repealed Directive 2001/20/EC





EU Regulations and Regulatory Requirements

EU Guidelines

- Translates all regulations and directives into best practices.
- The GMP guidelines are periodically revised in order to reflect continuous improvement of best practices in the field of Quality.
  - **EudraLex – Volume 4** – Good Manufacturing Practice (GMP) guidelines and its Annexes, incl. EU GMP Guidelines Part II, Ch19 > Active Substances for Clinical Trials
  - **EudraLex – Volume 10** – Set of documents applicable to clinical trials authorised under CTR (EU) 536/2014

Regulations outside of the EU

IMP GMP beyond the EU

- PIC/S (Annex 13 and Annex 16)
- China (Chinese GMP for IMPs, Appendix 43-2022)
- MHRA (The Medicines for Human Use (Clinical Trials) Regulations 2004 [SI 2004/1031], The Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025 [SI 2025/538]
- WHO (e.g.: TRS 1044 - Annex 7, TRS 1044 - Annex 3)
- US FDA: 21 CFR Part 210/211 (cGMPs) and Part 312 (Investigational New Drug Application)

Product Specification File (PSF)

PSF- Applicable Guidelines

COMMISSION DELEGATED REGULATION (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014 of the European Parliament and of the Council by specifying principles of and guidelines for good manufacturing practice for investigational medicinal products for human use and arrangements for inspections

(8) requirement of a PSF for IMPs
Article 2, (3) Definitions
Article 8, (1) & (3) Documentation (all specific documents with IMPs should be consistent with PSF, retention 5 years after completion / discontinuation of clinical trial)

Product Specification File (PSF)

PSF- Applicable Guidelines

- 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 (EudraLex-Volume 4-Good Manufacturing Practice (GMP) guidelines)

- 2.1 Product Specification File (definition, content)
- 5. Documentation (documentation shall be consisted with PSF, retention period-at least 5 years)
  - 5.2 Order (order should refer to PSF)
  - 5.3 Manufacturing formulae and processing instructions (PSF is basis for manufacturing instructions)
  - 8. Release of batches (PSF is basis for certification by QP, QP needs access to PSF, documentation is in compliance with PSF, delegation of regulatory release to manufacturer-clinical trial authorization and amendment information should be in the PSF)

Product Specification File (PSF)

PSF- Definition & Purpose

COMMISSION DELEGATED REGULATION (EU) 2017/1569 of 23 May 2017 supplementing Regulation (EU) No 536/2014	,….means a reference file containing, or referring to files containing, all the information necessary to draft detailed written instructions on processing, packaging, quality control, testing and batch release of an investigational medicinal product and to perform batch certification.
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	,…..brings together and contains all of the essential reference documents to ensure that investigational medicinal products are manufactured according to good manufacturing practice for investigational medicinal products and the clinical trial authorization.

Information in the PSF should form the basis for assessment of the suitability for certification and release of a particular batch by the Qualified Person and should therefore be accessible to the IMP QP.

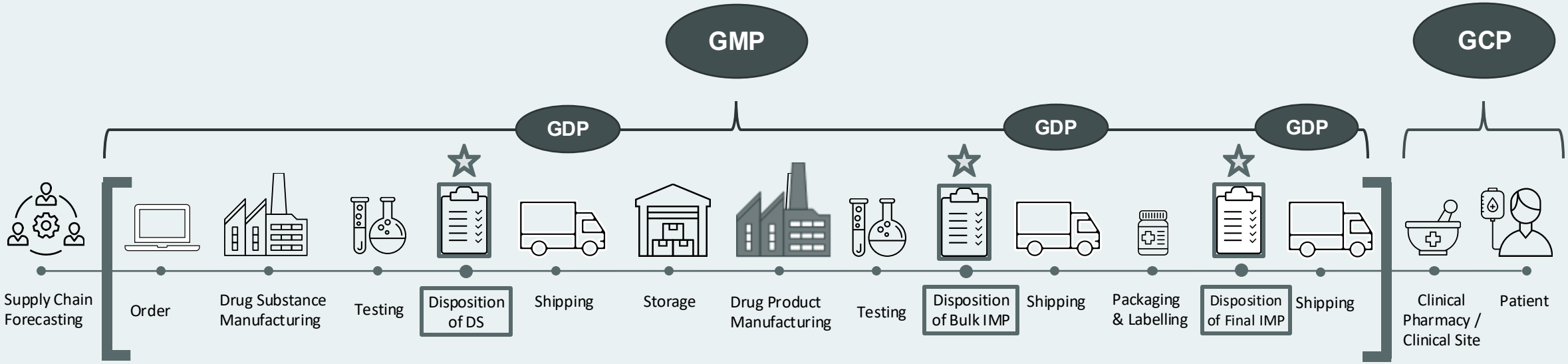
Product Specification File (PSF)

- It should include or refer to at least the following documents:

  i. Specifications and analytical methods for:
     -starting materials
     -packaging materials
     -intermediate product
     -bulk product
     -finished product
  ii. Manufacturing methods
  iii. In-process testing and methods
  iv. Approved label copy
  v. Relevant clinical trial authorizations and amendments thereof, clinical trial protocol and randomization codes, as appropriate
  vi. Relevant technical agreements with contract givers and acceptors, as appropriate
  vii. Stability plan and reports
  viii. Details of plans and arrangements for reference and retention samples
  ix. Storage and transport conditions
  x. Details of the supply chain including manufacturing, packaging, labelling and testing sites for the investigational medicinal products, preferably in the format of a comprehensive diagram

This list of documents is neither exhaustive nor exclusive. The contents of the product specification file will vary depending on the product and the stage of development. It is acceptable to maintain separate files, if different manufacturing steps are carried out at different locations under the responsibility of different IMP QPs.

Batch confirmation, QP Certification and IMP Release



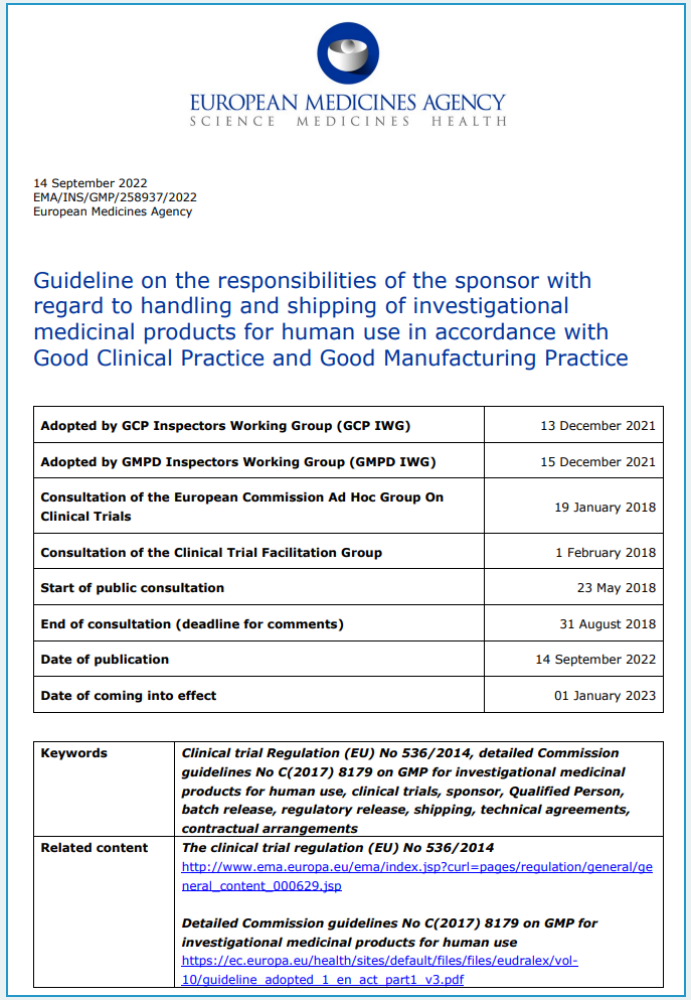
1 Oversight

MIA IMP licensee must be able to demonstrate oversight of the manufacturing, testing, shipping, and release of a medicine

2 Compliance

All of the regulations pertaining to GMP manufacture, storage and shipping of IMPs must be adhered to

Batch confirmation, QP Certification and IMP Release



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 September 2022
EMA/INS/GMP/258937/2022
European Medicines Agency

Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with Good Clinical Practice and Good Manufacturing Practice

Adopted by GCP Inspectors Working Group (GCP IWG)	13 December 2021
Adopted by GMPD Inspectors Working Group (GMPD IWG)	15 December 2021
Consultation of the European Commission Ad Hoc Group On Clinical Trials	19 January 2018
Consultation of the Clinical Trial Facilitation Group	1 February 2018
Start of public consultation	23 May 2018
End of consultation (deadline for comments)	31 August 2018
Date of publication	14 September 2022
Date of coming into effect	01 January 2023

Keywords	***Clinical trial Regulation (EU) No 536/2014, detailed Commission guidelines No C(2017) 8179 on GMP for investigational medicinal products for human use, clinical trials, sponsor, Qualified Person, batch release, regulatory release, shipping, technical agreements, contractual arrangements***
Related content	***The clinical trial regulation (EU) No 536/2014*** http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000629.jsp ***Detailed Commission guidelines No C(2017) 8179 on GMP for investigational medicinal products for human use*** https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/guideline_adopted_1_en_act_part1_v3.pdf

Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with GCP and GMP (01 Jan 2023)

- IMP release procedure
- Shipping
- Contractual arrangements or Technical agreements

Batch confirmation, QP Certification and IMP Release

A clinical trial in the EU can only start after a clinical trial authorisation has been granted by the EU member states concerned, following fulfilment of the requirements of Chapter II (Authorisation procedure for a clinical trial) of Regulation (EU) No 536/2014. This involves the assessment of the site suitability adapted to the nature and use of the investigational medicinal product. The necessary documentation that needs to be submitted with the initial application or an application for a substantial modification to approve a new site is described in Annex I.N.67 of Regulation (EU) No 536/2014. An EU harmonised template for site suitability and the declaration of site suitability is published on Eudralex-10[1]. According to Article 15 of Regulation (EU) No 536/2014, the addition of a new site is always a substantial modification to the trial and therefore requires assessment and regulatory approval.

The release process consists of the batch certification by the Qualified Person (QP) followed by the regulatory release of the IMP by the sponsor to the sites for use in a clinical trial. These steps should be recorded and retained in the clinical trial master file. Investigational medicinal products should remain under the control of the sponsor until the release process is complete.

The certification of each batch by the QP ensures, in line with Article 62(1) of Regulation (EU) No 536/2014, that the provisions of 63(1) and 63(3) of Regulation (EU) No 536/2014 and those set out in Article 12 of the Commission Delegated Regulation (EU) No 2017/1569, have been complied with and documented.

The regulatory release is the verification of completion of batch certification by the QP and that the necessary authorisations are in place for the clinical trial, before supply of IMP to the clinical trial site.

In line with the detailed Commission guidelines No C(2017) 8179 on good manufacturing practice for investigational medicinal products for human use, where the manufacturer is delegated by the sponsor to perform the regulatory release of the IMP to the trial sites in addition to certification by the QP, the arrangements should be defined in an agreement between the sponsor and the manufacturer. The sponsor should provide all the necessary information to the manufacturer to allow the delegated regulatory release. The manufacturer should verify that the necessary clinical trial authorisations are in place prior to shipping the medicinal product for use in the trial (e.g. by consulting the Clinical Trials Information System (CTIS) referred to in Articles 80 and 81 of Regulation (EU) No 536/2014).

Guideline on the responsibilities of the sponsor with regard to handling and shipping of investigational medicinal products for human use in accordance with GCP and GMP
(01 Jan 2023)

Article 62

Responsibilities of the qualified person

1. The qualified person shall ensure that each batch of investigational medicinal products manufactured in or imported into the Union complies with the requirements set out in Article 63 and shall certify that those requirements are fulfilled.

2. The certification referred to in paragraph 1 shall be made available by the sponsor at the request of the Member State concerned.

Article 63

Manufacturing and import

1. Investigational medicinal products shall be manufactured by applying manufacturing practice which ensures the quality of such medicinal products in order to safeguard the safety of the subject and the reliability and robustness of clinical data generated in the clinical trial ('good manufacturing practice'). The Commission shall be empowered to adopt delegated acts in accordance with Article 89 in order to specify the principles and guidelines of good manufacturing practice and the detailed arrangements for inspection for ensuring the quality of investigational medicinal products, taking account of subject safety or data reliability and robustness, technical progress and global regulatory developments in which the Union or the Member States are involved.

In addition, the Commission shall also adopt and publish detailed guidelines in line with those principles of good manufacturing practice and revise them when necessary in order to take account of technical and scientific progress.

3. Investigational medicinal products imported into the Union shall be manufactured by applying quality standards at least equivalent to those laid down pursuant to paragraph 1.

Batch confirmation, QP Certification and IMP Release

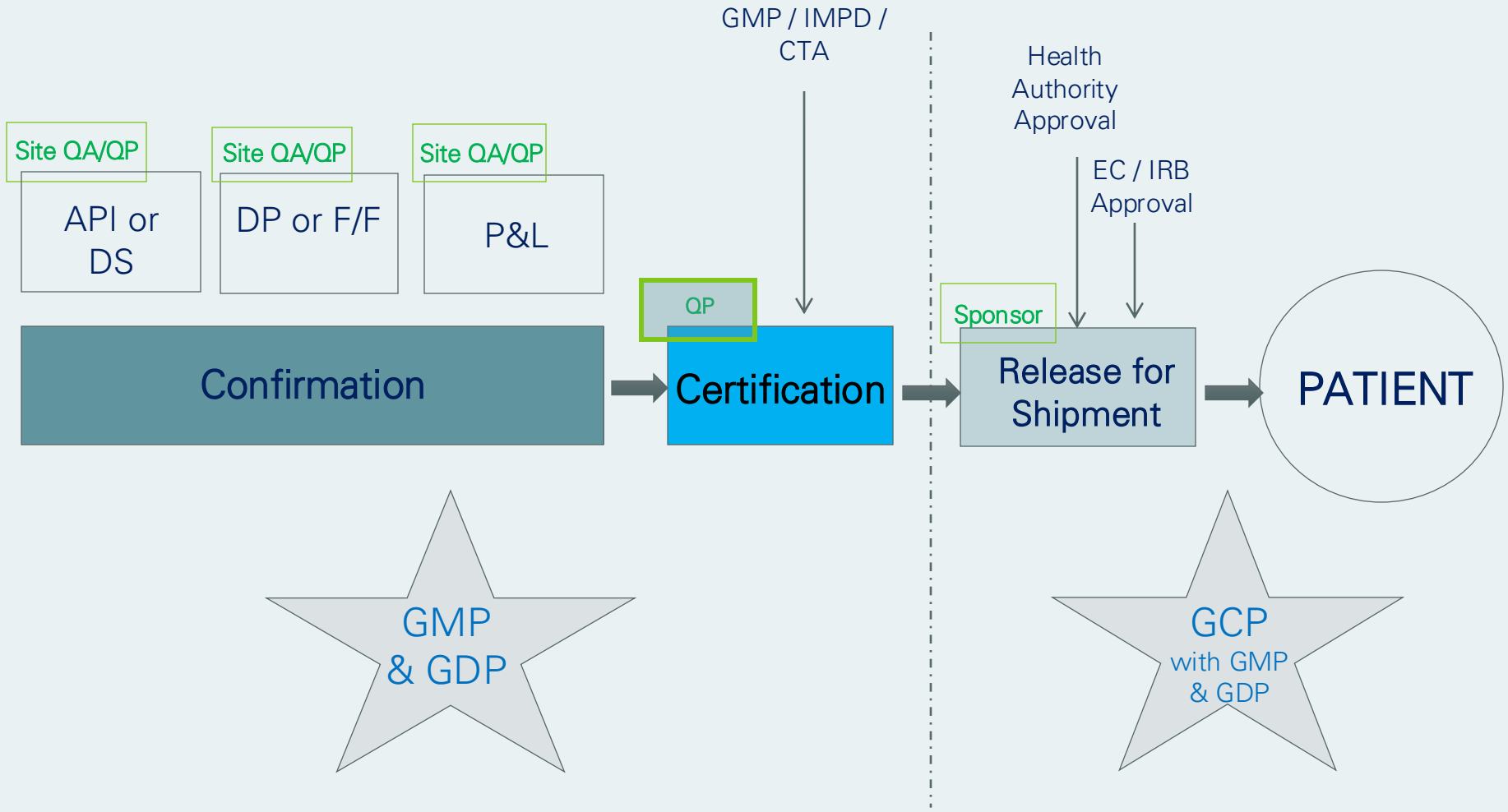
IMP release procedure

- IMP should stay under control of the Sponsor until two-step release process is completed. The release process consists of:
    - Batch Certification by the Qualified Person (IMP QP)

      (Batch Certificate for IMP / QP Register or equivalent document)
    - Regulatory release of IMP by the Sponsor for use in a clinical trial

      (Final batch release cert if completed by IMP QP on behalf of a Sponsor / or a dedicated Form confirming the status of CTA and EC/IRB approvals if completed by e.g. Clinical Operations on behalf of a Sponsor)
- Steps should be recorded and retained in the clinical trial master file
- Sponsor is accountable for ensuring information is available and correct

Batch confirmation, QP Certification and IMP Release



IMP Deficiencies in HPRA Inspections

- IMP Manufacture- Cleaning:
  - *The company had not re-assessed the suitability of the existing validated cleaning processes as part of the introduction of IMP XXXX to the commercial equipment train. In this regard:*
    - *The reliance on the pre-established validated cleaning processes to ensure that the equipment was appropriately cleaned was not appropriately assessed or justified.*
    - *The company had not demonstrated that the new IMP product was visually detectable at its cleaning acceptable residue limit. As such the reliance on visual inspection only to demonstrate that IMP XXX was removed to a suitable level following cleaning was not well founded.*

IMP Deficiencies in HPRA Inspections

- Product Specification File Management & Batch Certification- Company A
  - *During the review of the certification of IMP for batch XXXXXX and associated PSF the following non-compliances were identified:*
    - *The PSF had been created at the time of QP certification only.*
    - *In relation to the contents of the PSF:*
      - *Executed batch manufacture and analytical records had been included in the PSF instead of reference documents describing manufacturing methods, analytical methods and associated specifications*
      - *The certification site and associated QPs did not have access to the associated clinical trial authorisation, and it could not be demonstrated how it was ensured that the executed records were aligned with the CTA at the time of release.*
      - *Based on this it was not clear how the QP ensured that the batch had been certified inline with the requirements of the clinical trial authorisation (CTA), since it could not be demonstrated that the PSF contents were aligned with the CTA content.*

IMP Deficiencies in HPRA Inspections

- Product Specification File Management & Batch Certification – Company B
  - *During review of records relating to the QP certification of IMP lot XXXXXXX it was noted that the bulk product certificate of conformance (CoC) was dated July 2020 and certification for release of finished product was not completed until August 2022. The bulk product CoC was issued when IMP dossier version 2 was effective, but at the time of QP batch certification for release, IMP dossier version 10 was the effective version.*
    - *No assessment between version 2 and version 10 of the IMPD had been performed to ensure that bulk product was suitable for release in line with version 10.*
    - *Based on this, at the time of the inspection, it was not clear if the bulk product had been manufactured in compliance with the details within the CTA that was effective at the time of release of the finished product.*

IMP Deficiencies in HPRA Inspections

- IMP Manufacture (Outsourced Activities) – Company C
  - *The management of outsourced manufacturing of clinical medicinal products, certified for release by the company, was deficient as follows:*
    - *The certification site stated that the Sponsor was responsible for the management of outsourced GMP activities. However the certification site and QP had no knowledge of the sponsor's processes which were utilised to manage the outsourced manufacturing supply chain. For example, an overview of the processes for the monitoring of the performance of Contract Manufacturing Organisations (CMOs) to ensure ongoing GMP compliance could not be provided during the inspection.*
    - *The company had not ensured that audits of CMO sites located within the EU had been performed. In this regard, the company (or a contracted third party) or the sponsor had not performed audits of CMO sites located within the EU.*

IMP Deficiencies in HPRA Inspections

- Regulatory Release of clinical batches
  - *An agreement between the certification site and the sponsor clearly defining processes and responsibilities for regulatory release of products was not available. In this regard:*
    - *It was noted that following QP certification that QPs at the company also performed a release disposition on the inventory management system, which permitted shipment of IMP batches to clinical sites.*
      - *The company stated that it did not perform regulatory release of IMP batches but it was not clear and not defined in the companies quality system how the QP release process differed from regulatory release performed by the sponsor.*
      - *The process for regulatory release following QP certification was not defined in an agreement (or equivalent document) between the certification site and sponsor entity.*
      - *The company could not provide details of the controls that were in place that ensured that QP released product was restricted from use until regulatory release was completed.*

Thank you