Investigational Medicinal Products – Expectations and Effective Risk Mitigation

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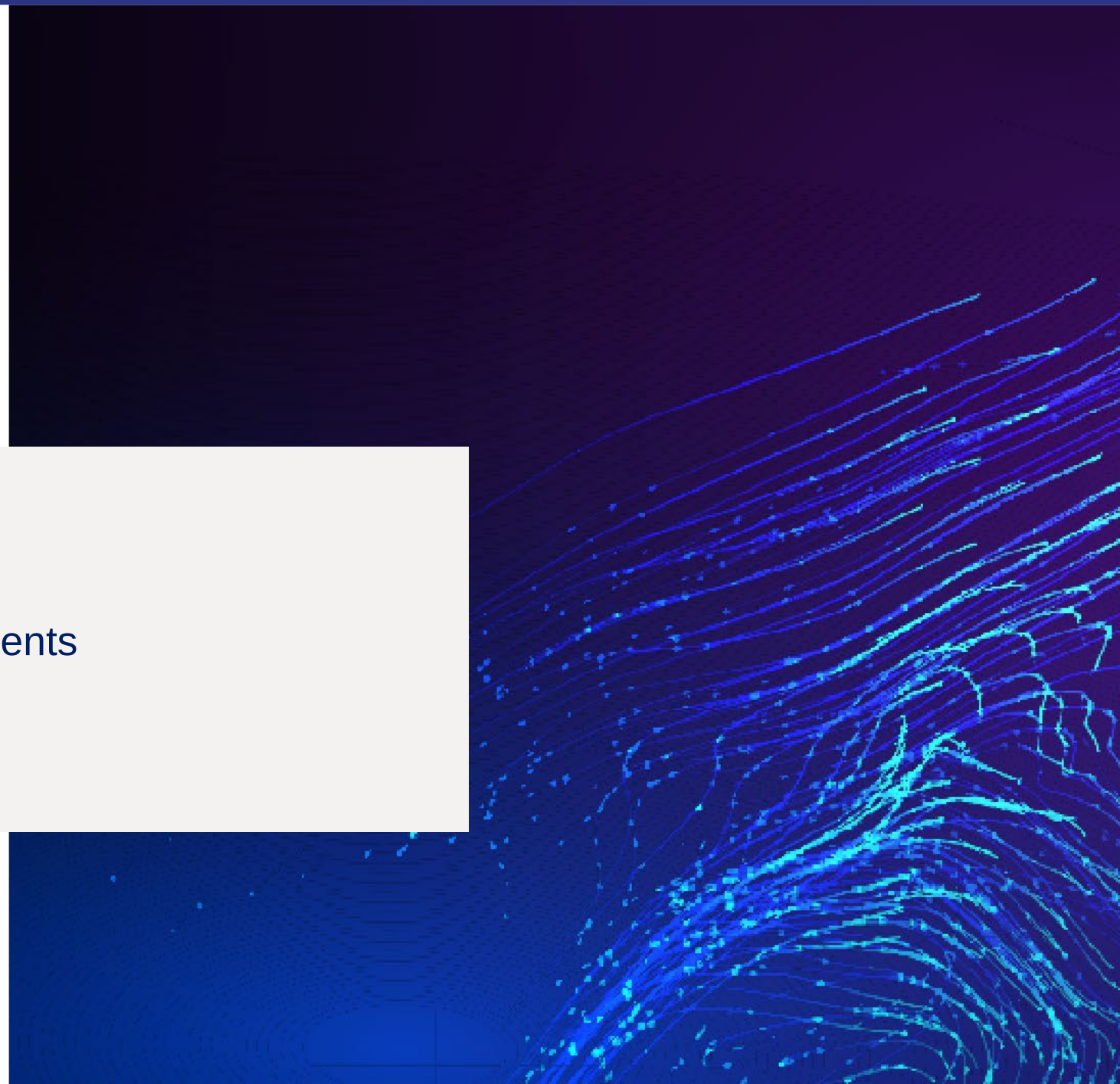
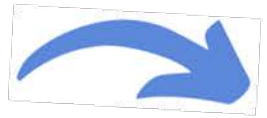
GMP FORUM 2024

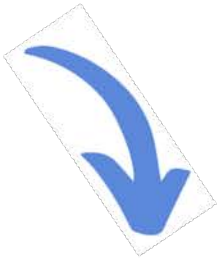
Overview

- Why GMP is important for IMPs
- PE009-16 and Annex 13 requirements
- Commonly observed deficiencies

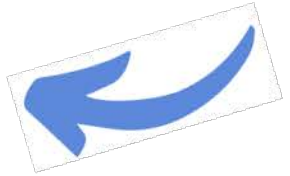


Journey of a Medicine





Testing for the medicine's safety and effectiveness

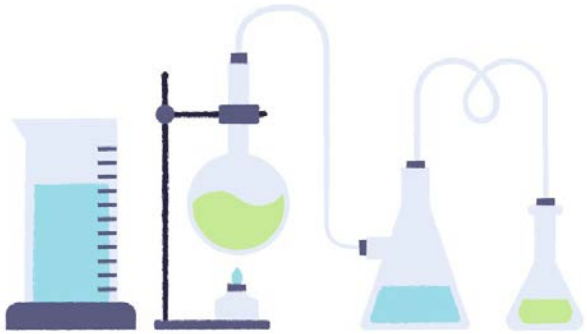


Clinical trials involving therapeutic goods are generally undertaken to ***assess the effects, efficacy, performance and/or safety of the product****. It is therefore, necessary that clinical trials are conducted using appropriate experimental designs* ***to obtain valid data without exposing participants to unnecessary risks****.*

Before starting a clinical trial, all parties should be satisfied that the rights, ***safety and well-being of trial participants will be protected and that clinical trial data generated will be reliable and robust****.*

Australian clinical trial handbook v.2.4, Aug 2021

IMP may pose increased risk to patients

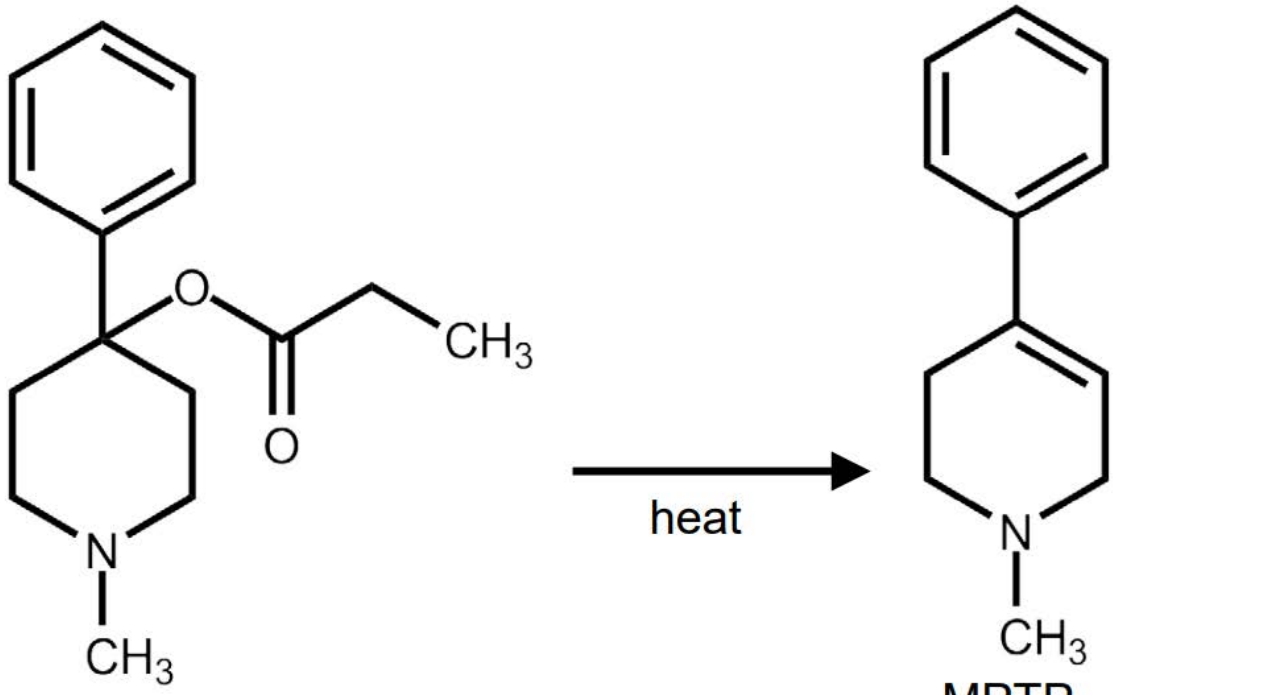


Incomplete knowledge of potency and toxicity	→	↑ risk of contamination
Lack of full process validation	→	↑ inter- and intra- batch variations
Added complexity due to CT design and consequential packaging design	→	↑ risk of mix-up

*There are many different types of **poor-quality drugs** that could mistakenly be included in clinical trials, including those with no, too little, or too much active pharmaceutical ingredient, those with the wrong active pharmaceutical ingredient, those with inadequate bioavailability, and those that degrade with toxic products or contaminants.*

BMJ 2015; 350 doi: https://doi.org/10.1136/bmj.h602
(Published 25 February 2015)

Poor quality medicines due to impurities



Desmethylprodine
an opioid analgesic

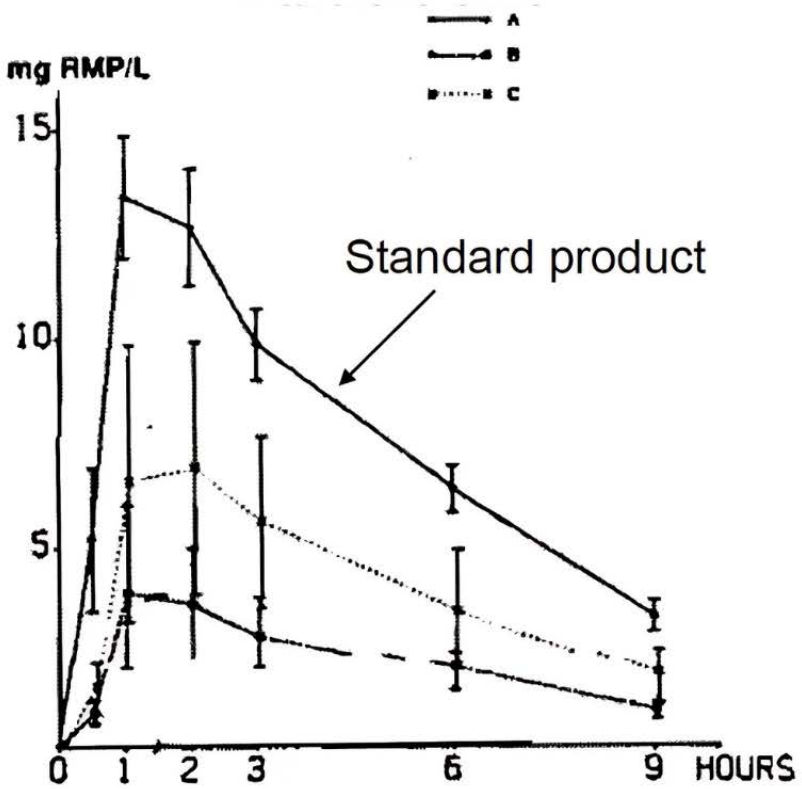
MPTP
causes chronic irreversible
Parkinsonian symptoms

Markey SP, Schmuff NR, Med Res Rev. 1986, 6(4):389-429

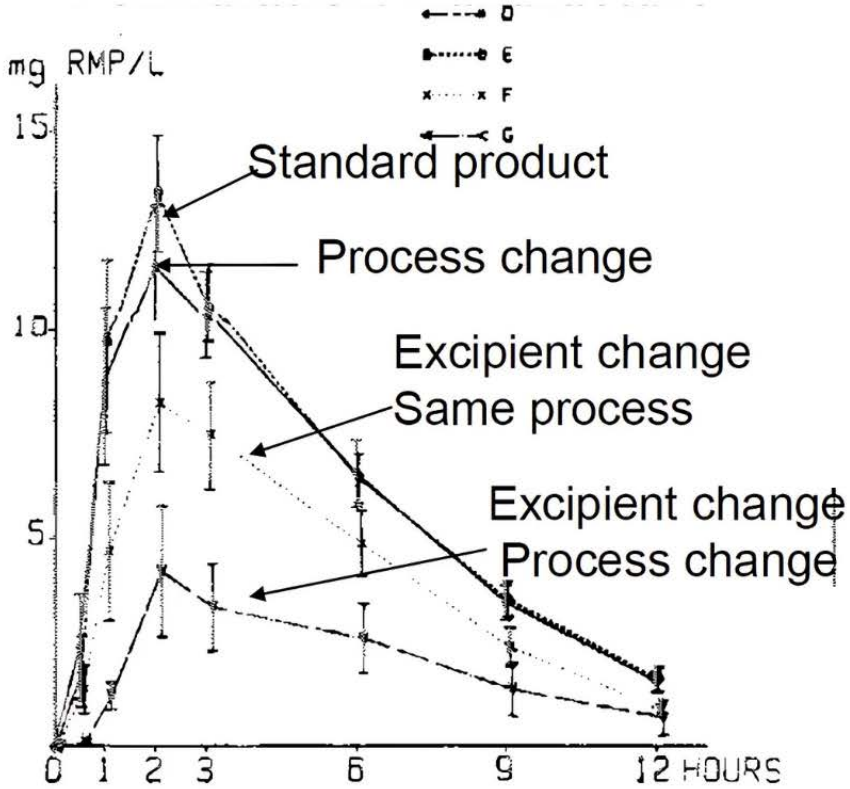
Poor quality medicines due to different bioavailability

Rifampicin Bioavailability

Particle size

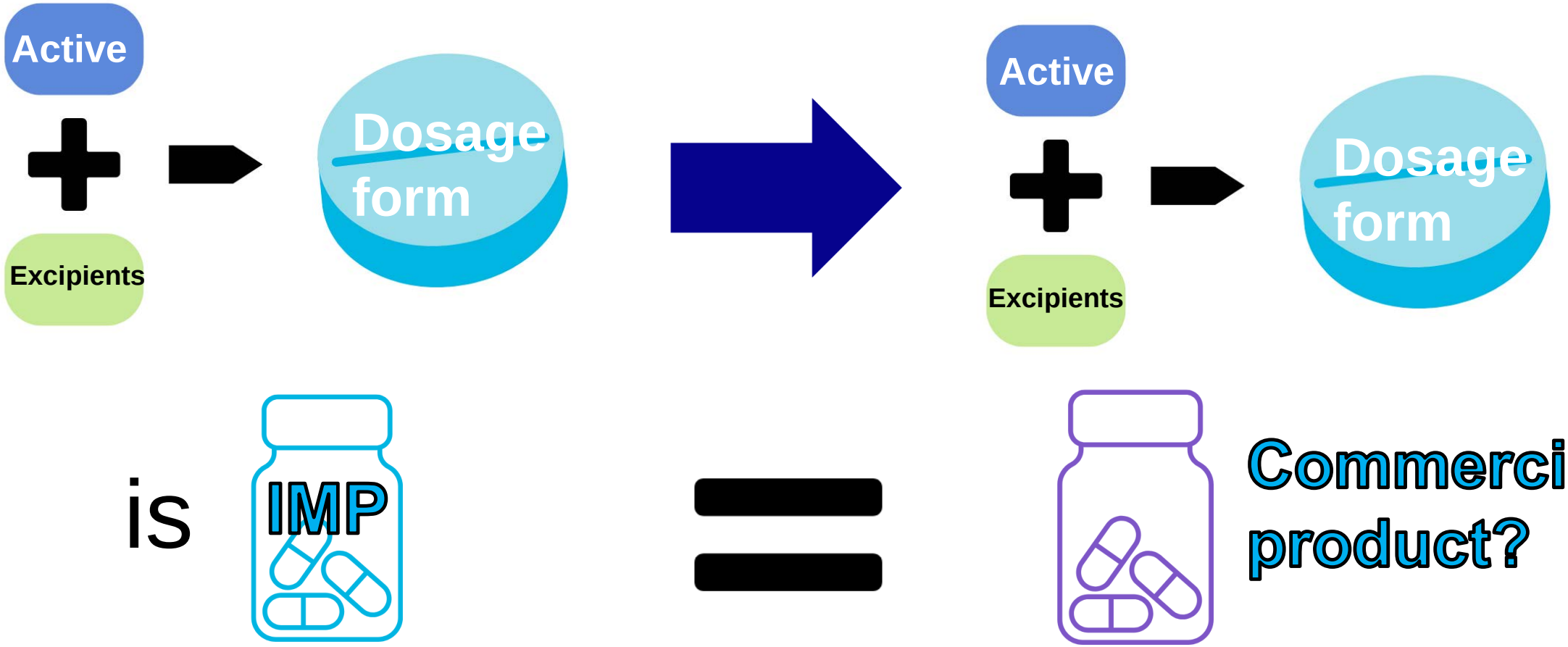


Formulation / manufacture

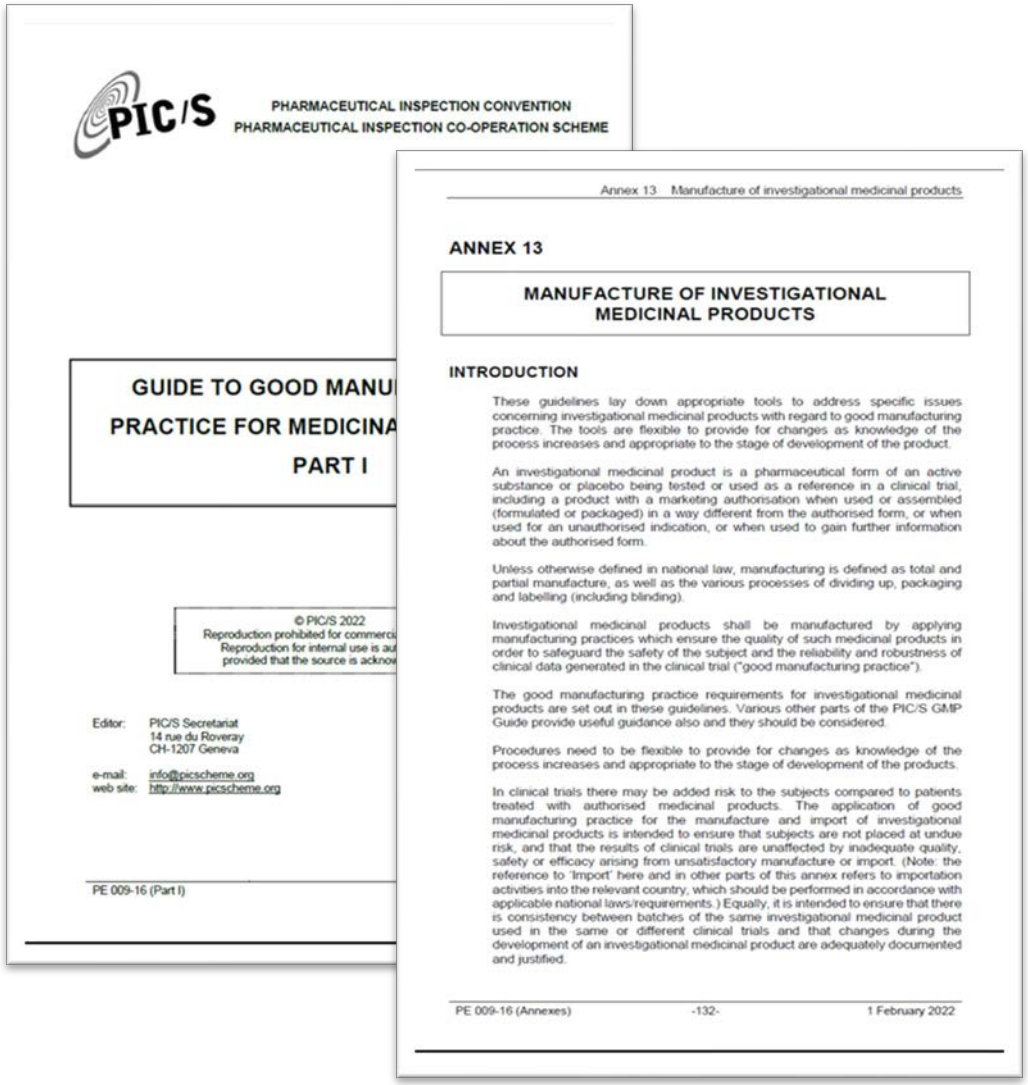


R. Cavenaghi, Bull Int Union Tuberc Lung Dis 1989 Mar; 64(1):26-7

Equivalency of IMP batch and commercial batch



PIC/S Guide to Good Manufacturing Practice PE009-16



Principles in PE009 Part I applies to IMPs. Annex 13 addresses specific issue relating to IMPs.

PE009-16 Annex 13 is applicable to investigational medicinal products that are a ***pharmaceutical form of an active substance or placebo…***

PE009-16 Annex 13 describes requirements to ensure that:

- subjects/patients are not placed at undue risk,
- results of clinical trials are reliable
- consistency between batches of the same IMP used in the same or different CT,
- any changes are adequately documented and justified.

PE009-16 Annex 13 – Section 2 Pharmaceutical Quality System

Expectation that material suppliers are assessed, qualified/approved and supply chain integrity assured

Examples of non-conformances observed:

- Suppliers not assessed
- Suppliers not adequately assessed
- Supply chain not checked or not adequately checked

The principles of Annex 16 apply to the release for supply of IMPs

PE009-16 Annex 13 – Section 2.1 Product Specification File and Section 5.2 Order

Expectation that there is a Product Specification File (PSF) containing all information/documents relevant to the manufacturing and quality of the IMP.

Examples of non-conformances observed:

- PSF not established or complete
- Documents forming the PSF not authorised and/or controlled
- No ‘order’ or order not appropriately authorised

PE009-16 Annex 13 – Section 4 – Premises and Equipment

Expectation that facilities, utilities and equipment are fully qualified and there is a robust cross contamination control in place including cleaning verification

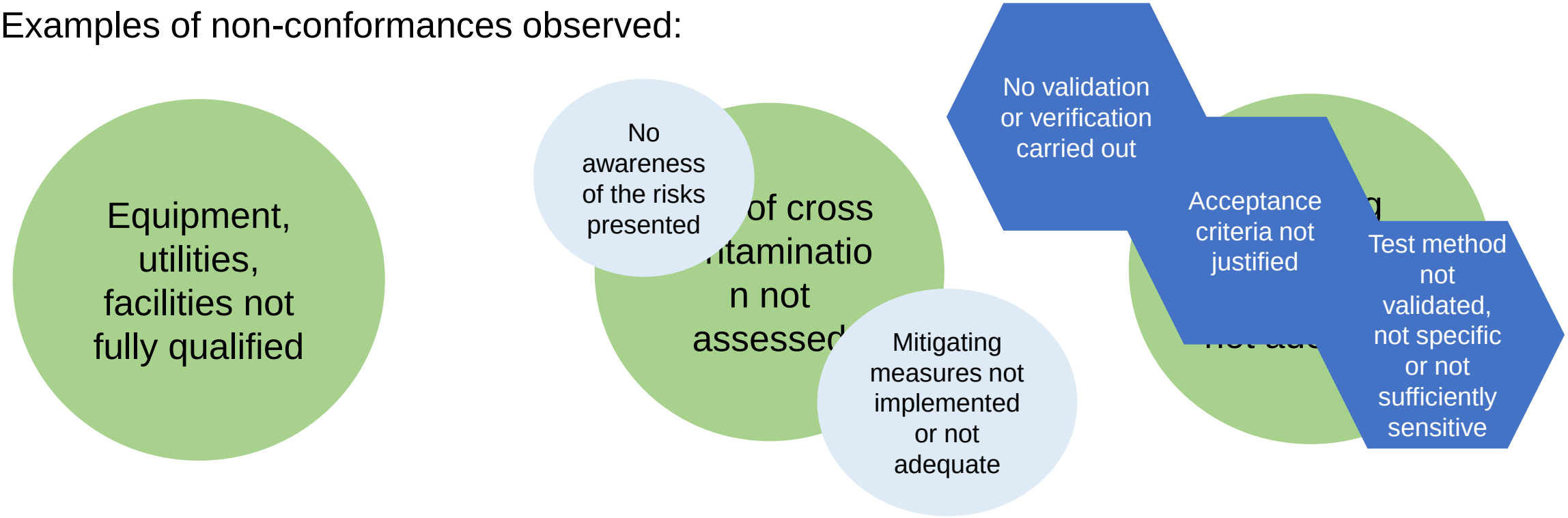
Examples of non-conformances observed:

- Equipment, utilities, facilities not fully qualified
- Risk of cross contamination not assessed
- Cleaning validation/ verification not adequate

PE009-16 Annex 13 – Section 4 – Premises and Equipment

Expectation that facilities, utilities and equipment are fully qualified and there is a robust cross contamination control in place including cleaning verification

Examples of non-conformances observed:



PE009-16 Annex 13 – Section 5 – Production

Expectation that manufacturing and packing processes are controlled

Examples of non-conformances observed:

- Process not adequately controlled
- No data to justified expiry/retest date assigned to the product
- Labelling not in accordance with the requirements
- Risk of mix-up not assessed, and no mitigating actions implemented

PE009-16 Annex 13 – Section 5 – Production

Expectation that manufacturing and packing processes are controlled

Examples of non-conformances observed:

For sterile products, validation of controls and processes related to sterility should be the same standards as for authorised medicines

No data justifie piry/rete date signed to the product

Expiry date provided by sponsor

No data for comparator product in different 1° pack

Labelling not in accordance with the requirements

Risk of mix-up

High risk particularly for packing of blind trials.

actions implemented

PE009-16 Annex 13 – Section 6.6 – Labelling

Expectation that IMP labels meet Clause 6.6.1 requirements.

Annex 13 Clause 6.6.1 lists label requirements

Reduced labelling requirements (as per PE009-15 Annex 13) continued to be permitted if criteria are met. (TGA Interpretive Guide, expected to be released 1Q2025)

PE009-16 Annex 13 – Section 8 – Release of batches

Annex 13 and Annex 16

New in Annex 13

- Verification of the supply chain (manufacturing, packaging and testing)
- If multiple entities are involved, responsibilities of all AP's mut be in a document agreed by all parties

Annex 16

- Batch '**confirmation**' requirement if there are multiple entities in the supply chain of the finished IMP.
- Audits of suppliers and manufacturers and testing labs carried out and Audit reports are available to the AP **certifying** the batch

Manufacturing of IMPs has added complexity

Trial participants should not be exposed to unnecessary risks

Trail results are not affected due to poor GMP

In conclusion

- These challenges require personnel with a thorough understanding of and training in the application on GMP to IMPs, and
- The manufacturing operations require highly effective quality system.

Questions?

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