HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

IMP Manufacturing & Labelling

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CTR Webinar - 25th November 2021

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Legislation – Some Key Points

- Directive 2001/20/EC replaced by Regulation 536/2014
- "GMP Directive" 2003/94/EC will be replaced by:
  - Commission Directive (EU) 2017/1572 – applicable to medicinal products for human use
  - Commission Delegated Regulation (EU) 2017/1569 for IMPs
- Consequential changes to National Legislation

Legislation – Some Key Points

- Article 17 - Commission Delegated Regulation 2017 / 1569
  - Requirement for inspection of third country IMP manufacturers
  - Risk based inspection
  - Discussions at EU level on framework for implementing a system of risk based inspections
  - Sites of batch release in Ireland required to list contract manufacturers in Annex 3 of the MIA Format
  - Cooperation and coordination of inspections (ref Art. 18) will be important

Legislation – Some Key Points

- Brexit has resulted in significant increase in the number of **sites of batch certification** in Ireland.
- A number are office based operations where no manufacturing or product storage activities take place.
- These sites must comply with the following requirements:
  - Must be a permanent physical site in Ireland at which announced and unannounced inspections can be performed.
  - Must have the equipment and facilities to enable QP certification in accordance with legislation and GMP Guidance.
  - HPRA inspectors must have access to the site and documentation at all times. (Delegated Regulation 2017 / 1569, Art. 24)

Legislation – Some Key Points

Batch Certification

- QP certification at site designated for this purpose in the clinical trial application

- Duties of the QP described in Article 12 of Delegated Regulation 2017 / 1569

- Template for Batch Certificate for IMPs – in Part III of EU GMP Guide
  - Batch Certificated must be available at sponsor site – (CTR Article 62(2))

Legislation – Some Key Points

Importation of IMPs

- Importation by an authorised IMP manufacturer
  - Site of QP Certification / Site of Physical Importation
- No legal requirement for importation testing, regardless of MRA status of third country (no change)
- Third country manufacturer must operate to a standard equivalent to Commission Guidelines on GMP for IMPs.

Exemption from Requirement for Manufacturer's Authorisation

Article 61(5) – Exemptions from requirement for a MIA

a) **Re-labelling or re-packaging** of the product

b) **Preparation of radiopharmaceuticals** used as diagnostic IMPs

c) Preparation of **IMP in accordance with a doctor's prescription** or in accordance with a **pharmacopoeial monograph.**

Exemption from Requirement for Manufacturer's Authorisation

CTR Article 61(5) – Exemptions from requirement for a MIA

- Manufacture under exemption to take place in hospitals, health centres or clinics participating in the clinical trial
- No export of IMP manufactured under Art 61(5)
- Compliance with IMP GMP Guidance not required (ref Art. 63 does not apply)
- Appropriate and Proportionate Requirements to apply
- Inspection to ensure compliance with requirements (Art. 61(6))

Exemption from Requirement for Manufacturer's Authorisation

Registration Process

- HPRA will implement a registration process for sites intending to operate under exemptions provided in Art 61 (5) after 31st January 2022
- Registration document will be issued to the site
- Registration should be completed in advance of submission of the clinical trial application.
- Details of how to register, application forms to be used and supporting information to be provided will be published on the HPRA website.
- National legislation to make provision for inspections by the HPRA.
- HRPA will carry out risk based inspections of registered sites.

Exemption from Requirement for Manufacturer's Authorisation

Appropriate & Proportionate requirements

For Example – Relabelling & Repackaging activity

- Approved procedures for the activity
- Training of personnel in the procedures
- Documented in batch records
- Independent second person check
- Line clearance at start & end
- Documented reconciliation of materials
- Documented investigation of discrepancies
- Final approval by a responsible person

Changes in GMP Guidance

- **New Commission Guidelines on GMP for IMPs published on EudraLex**
  - Replaces Annex 13 of the GMP Guide
  - Extensive cross references to Part I of the GMP Guide, including Annex 16
  - Several references to requirement for written agreement between manufacturer and sponsor
  - Two step release process in Annex 13 (QP Certification followed by Sponsor Release) not described except where the sponsor has delegated regulatory release to the manufacturer.
  - Transfer of IMPs between clinical trial sites not described (post QP certification activity)

GDP For IMPs

- No requirement under CTR for sites holding / distributing IMPs to have a Wholesale Distribution Authorisation
- Sponsor must make arrangements to ensure that IMPs are handled under appropriate conditions after certification / release by manufacturer
- Wholesaler may supply an authorised IMP (e.g. comparator) or auxiliary medicine to:
  - Authorised manufacturer e.g. for blinding / packaging / labelling
  - Pharmacy
  - Medical Practitioner

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Labelling

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Definitions

Introduction of "Auxiliary Medicinal Product" (AxMP) to replace the term "non-Investigational Medicinal Product" (NIMP).

- AxMP defined as a product used within the clinical trial and described in the protocol, but is not an IMP itself. Examples include rescue medication and challenge reagents.
- Authorised AxMP in the EU to be used unless justified (justification to be included in the protocol).
- Unauthorised AxMP to be manufactured to a GMP or equivalent standard and labelled per Article 66 and Annex VI of Reg 536/2014.
- New Guidance: Auxiliary medicinal products in clinical trials (rev. 2, June 2017), available at: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/2017_06_28_recommendation_on_axmps.pdf

Authorised and unauthorised IMP/AxMP

- Authorised in a MS within the EU line with Directive 2001/83/EC and Regulation (EC) No 726/2004 (i.e. nationally or centrally authorised product)

Labelling under the CTR – main changes (1)

Guidance for labelling has been moved from GMP (Annex 13) to the CTR including Annex VI

Labels assessed as part of CT application

- Strict timelines for assessment
- Important to ensure labels comply with requirements at submission

Use period required on both the immediate and outer packaging

Labelling under the CTR – main changes (2)

Amendment of the ability to use a centralised electronic information system (IxRS) to replace information on product labels

- Justification in the protocol required
- Only certain aspects may be omitted (see Annex VI, D of Regulation 536/2014)
  - Include: name, address and telephone no. of main contact, CT reference code, name of PI and directions for use
- Should only be omitted **where considered safety of subject and reliability of trial not impacted**

The address and telephone number of the main contact may be omitted if subject provided with a card with those details and told to keep on their person

Unauthorised IMP and AxMPs (Article 66)

The following information shall appear on both the outer and immediate packaging

- contact persons or persons involved in the clinical trial,
- identity of the clinical trial,
- the medicinal product,
- directions for use of the medicinal product,
- period of use.

A full list of information which is to appear on the outer packaging and immediate packaging is set out in Annex VI

Authorised IMPs and AxMPs (Article 67)

In accordance with article 66 (1) – the same as unauthorised IMP and AxMP,

OR

In accordance with Title V of Directive 2001/83/EC – the same as authorised products

- Where the specific circumstances of a clinical trial require additional labelling to ensure the safety of the subject or the reliability and robustness of data generated, additional particulars should be included;
  - Name of main contact
  - CT reference code
  - 'For clinical trial use only' or similar

Radiopharmaceuticals as IMPs or AxMPs

Articles 66 and 67 shall not apply to radiopharmaceuticals used as diagnostic IMPs or AxMPs.

Should be labelled appropriately in order to ensure the safety of the subject and the reliability and robustness of data generated in the clinical trial.

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Thank you