AGENZIA ITALIANA DEL FARMACO

Tutela Ricerca e Sviluppo per la Salute

EC-DG SANTE/HMA-CTFG/EMA joint training on the Clinical Trials Regulation (EU) 536/2014

Manufacturing/importation and labelling (Chapter IX, X, Annex VI)

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Public Declaration of transparency/interests*

The view and opinions expressed are those of the individual presenter and should not be attributed to AIFA

Interests in pharmaceutical industry	NO	Current	From 0 to 3 previous years	Over 3 preavious years
DIRECT INTERESTS:				
1.1 Employment with a company: pharmaceutical company in an executive role	x	☐	☐	☐ mandatory
1.2 Employment with a company: in a lead role in the development of a medicinal product	x	☐	☐	☐ mandatory
1.3 Employment with a company: other activities	x	☐	☐	x optional
2. Consultancy for a company	x	☐	☐	☐ optional
3. Strategic advisory role for a company	x	☐	☐	☐ optional
4. Financial interests	x	☐	☐	☐ optional
5. Ownership of a patent	x	☐	☐	☐ optional
INDIRECT INTERESTS:				
6. Principal investigator	x	☐	☐	☐ optional
7. Investigator	x	☐	☐	☐ optional
8. Grant or other funding	x	☐	☐	☐ optional
9. Family members interests	x	☐	☐	☐ optional

*Giulia Praticò, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (25.03.2015) and published on the Official Journal of 15.05.2015 according to EMA policy /626261/2014 on the handling of the conflicts of interest for scientific committee members and experts.

N.B. < I am not receiving any compensation>

Clinical Trials Regulation (EU) 536/2014

CHAPTER IX MANUFACTURING AND IMPORT OF IMP AND AXMP	What's new:
Article 61 – Authorisation for Manufacture and Import	Different regulatory requirements for specific preparations which do not require manufacturing authorization (Article 61 (5));
Article 62 – Responsibilities of the Qualified Person (QP)	
Article 63 – Manufacturing and Import	Updated guidelines for Good Manufacturing Practice of Investigational Medicinal Products (IMPs) (article 63(1))
Article 64 – Modifications of authorised IMPs	
Article 65 – Manufacturing of AxMPs	Specific regulatory requirements for Auxiliary Medicinal Products (AxMPs) (Article 65)

CHAPTER X LABELLING REQUIREMENTS	What's new:
Article 66-70 Annex VI	Updated documentation for labelling of IMPs and AxMPs

CHAPTER IX - MANUFACTURING AND IMPORT OF IMP AND AxMP

Authorization of manufacturing and import (Article 61)

- The **manufacturing**[(1)] and **import** of investigational medicinal products in the Union shall be subject to the **holding of an authorisation**.

Manufacturing and Importation Authorisations (MIA)

Manufacturing and import – GMP (Article 63)

- IMPs should be manufactured[(1)] according to **Good Manufacturing Practice** in order to ensure subject safety and the reliability and robustness of data generated in a clinical trial (Article 63 (1) and Article 65).
- Equivalent quality standards should apply for imported IMP into EU (article 63(3)).

[(1)] Manufacturing is defined as total and partial manufacture, as well as the various processes of dividing up, packaging and labelling (including blinding) Article 2(24) of Regulation (EU) No 536/2014.

CHAPTER IX - MANUFACTURING AND IMPORT OF IMP AND AxMP

Responsibilities of the Qualified Person (Article 62)

- 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. (Article 62(1))

Inspections (Article 63(4))

- The Member States shall ensure compliance with the requirements of this Article by means of inspections.

Modification of authorised IMP (Article 64)

- Articles 61, 62 and 63 shall apply to authorised IMP only as regards any modification of such products not covered by a marketing authorisation.

CHAPTER IX - MANUFACTURING AND IMPORT OF IMP AND AxMP

NEW!

Documents for Good Manufacturing Practice (Article 63(1))

- **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
- **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
- Both Regulations and the guideline will become applicable at the same time as Regulation (EU) No 536/2014 and are available at https://ec.europa.eu/health/documents/eudralex/vol-10_en.
- Applicable document: EudraLex Vol 4, Annex 13: Good manufacturing practices for manufacture of investigational medicinal products

CHAPTER IX - MANUFACTURING AND IMPORT OF IMP AND AxMP

NEW!

Exceptions

Article 61(5): The requirement to hold an authorisation for manufacture or import of investigational medicinal products should not apply to:

- **re-labelling** or **re-packaging**;
- preparation of **radiopharmaceuticals** used as **diagnostic** investigational medicinal products;
- preparation of **magistral** and **officinal** formula;

where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member State concerned to carry out such processes, and if the investigational medicinal products are intended to be used exclusively in hospitals, health centres or clinics taking part in the same clinical trial in the same Member State .

The abovementioned processes **are not required to be performed under GMP,** according to Article 63(2).

Note: Reconstitution of investigational medicinal products is not considered manufacturing (Detailed Commission guidelines on GMP for IMPs for human use, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014).

CHAPTER IX - MANUFACTURING AND IMPORT OF IMP AND AxMP

NEW!

Exceptions

Article 61 (6)

Member States shall make the processes set out in paragraph 5 subject to appropriate and proportionate requirements to ensure subject safety and reliability and robustness of the data generated in the clinical trial. They shall subject the processes to regular inspections.

CHAPTER IX - MANUFACTURING AND IMPORT OF IMP AND AxMP

NEW!

Manufacturing of AxMP (Article 65)

The Regulation has introduced the term "**Auxiliary Medicinal Products**" (**AxMP**), which replaces the traditionally used term of Non-Investigational Medicinal Product (NIMP) and has implemented a new guideline, replacing the Guidance documents applying to clinical trials guidance on investigational medicinal products (IMPs) and 'non investigational medicinal products' (NIMPs):

Auxiliary Medicinal Products in Clinical Trials
Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use - 28 June 2017

NOTE: **IMPs** are medicinal products which are tested or used as a reference, including as placebo, in a clinical trial (Article 2(5)).
AxMPs are used in the context of a clinical trial as described in the protocol, but not as IMP (Article 2(8)). AxMP can be used for background treatments, as challenging agents, rescue medication or to assess the end-points.

CHAPTER IX - MANUFACTURING AND IMPORT OF IMP AND AxMP

NEW!

Manufacturing of AxMP (Article 65)

Only authorised AxMPs may be used in a clinical trial unless the use of unauthorized AxMPs is properly justified (e.g. authorised AxMP is not available in the Union or where the sponsor cannot reasonably be expected to use an authorised AxMP).

The general requirements for AxMPs are identical to those for IMPs (Article 65 and Annex I-H(55)), with respect to the manufacturing and import authorization, the requirement for GMP compliance and the QP certification process, as well as the requirements for the documentation in the product dossier. However, where the auxiliary medicinal product is authorised in the Member State concerned, no additional information apart from a valid SmPC is required.

ANNEX I- APPLICATION DOSSIER FOR THE INITIAL APPLICATION

Documentation Relating To Compliance With Good Manufacturing Practice (GMP) For IMP (F 31-35) and AxMP (H 55)

Type of IMP or AxMP	Documentation to be submitted
Authorised*, non-modified IMP or AxMP, whether or not it is manufactured in EU.	• No GMP documentation required
Non authorised IMP or AxMP, no marketing authorisation from a third country that is party to the ICH and not manufactured in EU.	• copy of MIA • certification by the QP in the EU that the manufacturing complies with GMP at least equivalent to the GMP in EU, unless there are specific arrangements provided for MRA between the EU and third countries.
All other cases	• copy of MIA.
IMPs or AxMPs manufactured according to Article 61(5), which are not subject to holding a MIA.	• documentation which demonstrates compliance with the requirements referred to in Article 61(6). !

* "a medicinal product authorised in accordance with Regulation (EC) No 726/2004 or in any MS concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product. " (Article 2 (9))

CHAPTER X- LABELLING

Updated documentation

Labelling of IMP and AxMP

DIRECTIVE 2001/20/EC	REGULATION (EU) No 536/2014
Article 14	Article 66-70
Currently the particulars which should appear on the outer packaging of investigational medicinal products or, where there is no outer packaging, on the immediate packaging, are reported in **EU GMP Annex 13: Investigational Medicinal Products**	With the new Regulation, a list of information which is to appear on the outer packaging and immediate packaging of both IMP and AxMP is set out in **Annex VI of REGULATION (EU) No 536/2014: LABELLING OF IMPs AND AxMPs**

CHAPTER X- LABELLING

Labelling of Unathorized IMPs and AxMPs (Article 66)

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

(a) information to identify contact persons or persons involved in the clinical trial;

(b) information to identify the clinical trial;

(c) information to identify the medicinal product;

(d) information related to the use of the medicinal product.

The full list of information is available in Annex VI.

ANNEX VI - A. Labelling details of unauthorised IMPs

- Very similar information already reported in EU GMP Annex 13
- Period of use information will be compulsory for all immediate packaging types, including small packing units

NEW!

ANNEX VI - B. Labelling details of unauthorised AxMPs

- Specific labelling information is specified for unauthorized AxMPs (similar to the general rules for unauthorized IMPs)

CHAPTER X- LABELLING

Labelling of Unathorized IMPs and AxMPs (Article 66)

ANNEX VI - D. Replacing of Information

- Annex VI (D) allows for some particulars to be omitted from the label in case they are made available by other means, for example by use of a centralised electronic randomisation system, use of a centralised information system, provided that the safety of the subject and the reliability and robustness of data are not compromised.
- The Annex lists the particulars which **cannot** be omitted from the label on both the immediate and the outer packaging, such as

  - information to identify the medicinal product;
  - the batch or code number;
  - the subject identification number;
  - period of use.

! **Mandatory information**

CHAPTER X- LABELLING

Labelling of Authorised IMPs and AxMPs (Article 67)

Authorised IMPs and authorised AxMPs shall be labelled:

(a)in accordance with Article 66(1); → **Same as unauthorised IMP and AxMP**

or

(b) in accordance with Title V of Directive 2001/83/EC. → **Same as authorised products**

(b.1) Where specific circumstances of a clinical trial require additional labelling to ensure the safety of the subject or the reliability and robustness of data generated in a clinical trial, additional particulars relating to the identification of the clinical trial and of the contact person shall appear on the outer packaging and the immediate packaging of authorised IMP.

ANNEX VI - C. Additional labelling for authorised IMP

7. In accordance with Article 67(2), the following particulars shall appear on the immediate and the outer packaging:
(a) name of the main contact;
(b) clinical trial reference code allowing identification of the clinical trial site, investigator, sponsor and subject;
(c) 'For clinical trial use only' or similar wording.

CHAPTER X- LABELLING

NEW!

Labelling of radiopharmaceuticals used as diagnostic (Article 68)

- For specific products, such as **radiopharmaceuticals used as diagnostic investigational or auxiliary medicinal product**, the general rules on labelling are inappropriate in view of the very controlled setting of their use in clinical trials. Anyway, these products 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.

Language (Article 69)

- The **language** should be determined by the Member State concerned. The medicinal product may be labelled in several languages.

Other relevant documentation on Quality
EudraLex - Volume 10 - Clinical trials guidelines

Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (revision 1 – October 2017)
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-chemical-pharmaceutical-quality-documentation-concerning-investigational_en.pdf

Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (Revision 1 - Oct 2017)
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-quality-documentation-concerning-biological-investigational-medicinal_en-0.pdf

Thank you

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BACKUP SLIDES