MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD

agencia española de
medicamentos y
productos sanitarios

DIRECCIÓN DE LA
AGENCIA ESPAÑOLA
DE MEDICAMENTOS Y
PRODUCTOS SANITARIOS

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.

Comments from the Spanish Agency of Medicines and Medical Devices (AEMPS)

Nº of the comment	Num (line).	ACTUAL TEXT	PROPOSED TEXT	REASON FOR THE PROPOSED CHANGE
1	92	These guidelines apply to manufacture of investigational medicinal products for human use. An investigational medicinal product is defined in Article 2(5) of Regulation (EU) No 536/2014 as a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial, and 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 said Regulation.	These guidelines apply to manufacture of investigational medicinal products for human use. An investigational medicinal product is defined in Article 2(5) of Regulation (EU) No 536/2014 as a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial. **This includes products with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form**. 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 said Regulation.	Clarification to the definition. Proposed additional text is already included in Annex 13.

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2	122	The pharmaceutical quality system required of the manufacturer according to the	The pharmaceutical quality system required of the manufacturer **or importer** according to the	Article 63 of Regulation (EU) 536/2014 refers to Manufacturing **and import**
3	125	manufacturer should also be described in…	manufacturer **or importer** should also be described in…	See comment 2.
4	125	…written procedures taking into account	…written procedures **available to the sponsor** taking into account	Clarification to this responsibility of the manufacturer/importer
5	150	The responsibilities of the qualified person are set out in Article 62 of Regulation (EU) No 536/2014 and …	The responsibilities of the qualified person are set out in **Article 51 of Directive 2001/83/EC** and Article 62 of Regulation (EU) No 536/2014 and …	Cross reference to Directive 2001/83/EC is needed.
6	151	(EU) No 536/2015…	(EU) No 536/**2014…**	Typing mistake
7	183	Specifications for starting materials, immediate packaging materials,	Specifications for starting materials, **primary** packaging materials,	The correct term, already used in other GMP texts, must be included.
8	179	Premises and equipment are expected to be validated in accordance with EudraLex, Volume 4, Annex 15.	Premises and equipment are expected to be **subjected to appropriate qualification and validation** in accordance with EudraLex,	Both appropriate qualification and validation apply.

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			Volume 4, Annex 15.	
9	194	site.	site **and the sponsor.**	To reflect the shared responsibility between the manufacturing site and the sponsor.
10	296	…Likewise, when required, virus inactivation/removal and removal of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived products by following the scientific principles and techniques defined in the available guidance in this area.	…Likewise, when required, virus inactivation/removal and removal of other impurities of biological origin should be demonstrated, to assure the safety of biotechnologically derived products by following the **principles for the manufacture of biological active substances and medicinal products for human** **Use detailed EudraLex, Volume 4, Annex 2 and other** scientific principles and techniques defined in the available guidance in this area.	Cross reference to Annex 2 is needed.
11	337	container and the storage conditions to which the article may be subjected	container and the storage conditions to which the **product** may be subjected	Correct term
12	340	There should be comparability of expiry dating and clinical trial duration	There should be **compatibility** of expiry dating and clinical trial duration	Correct term

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13	349	labelling is set out in Annex IV to said Regulation	labelling is set out in Annex **VI** to said Regulation	Correct number of the Annex
14	365	**2.8. Quality control**	Include the following paragraph: **Reference and retention samples of investigational medicinal product should be retain by the manufacturer for the periods specified in the Delegated Act on GMP for investigational medicinal products pursuant to the first paragraph of Article 63(1) of Regulation (EU) No 536/2014.**	No mention of retention time of reference and retention samples is made. Cross reference to the Delegated Act is needed.
15	454		Include the following subsection: **iiii) For imported investigational medicinal products used as reference, where adequate assurance cannot be obtained, in order to certify that each batch has been manufactured to equivalent standards of Good Manufacturing Practice, the duty of the qualified person is defined in Article 62 of Regulation (EU) 536/2014.**	Subsection included in Annex 13. Despite the fact this situation is not frequent, it should be defined.

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16	473	the country of export	the **third** country	Correct term
17	481	the phase of development of the product.	the phase of development of the product. **The sponsor should ensure that the elements taken into account by the qualified person when certifying the batch are consistent with the information notified pursuant to Article 63 of Regulation (EU) 536/2014.**	Relevant responsibility not mentioned.
18	486	out pursuant to Article 61(5)(a) of Regulation (EU) No 536/2014.	out pursuant to Article 61(5)(a) of Regulation (EU) No 536/2014. **Nevertheless, the sponsor is responsible for ensuring that the activity is adequately documented and carried out in accordance with the principles of GMP and should seek the advice of the qualified person in this regard.**	Relevant responsibility not mentioned.
19			Include the following new section: **<u>Shipping</u>** **Investigational medicinal products should remain under the control of the sponsor until after completion of a two-step procedure: certification by the qualified person; and**	This section already included in Annex 13 must be included. The terms shipping /distribution and

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Nº of the comment	Num (line).	ACTUAL TEXT	PROPOSED TEXT	REASON FOR THE PROPOSED CHANGE
			release by the sponsor for use in a clinical trial. **Relevant sections of the EC guidelines on Good Distribution Practice of Medicinal Products for Human Use should be taken into account when distributing investigational medicinal products in order to ensure that the products delivered maintain its quality and integrity during the storage and transportation.**	transportation are already defined in the glossary section. Reference to GDP should be done, in consistency with EC GDP guidelines introduction: *'Relevant sections of these Guidelines should also be adhered to by other actors involved in the distribution of medicinal products'.*
20	500	The conclusions of the investigation should be discussed between the manufacturer	The conclusions of the investigation should be discussed between the manufacturer **or importer**	See comment 2
21	508	manufacturer, where different.	manufacturer **or importer**, where different.	See comment 2
22	505	*2.12.1. Recalls*	Include the following paragraph: **The sponsor should ensure that the supplier of**	Relevant responsibility

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			any investigational medicinal product or other auxiliary medicinal product to be used in a clinical trial has a system for communicating to the sponsor the need to recall any product supplied.	regarding recall procedures not mentioned.
23	513	*2.12.2. Returns*	Include the following paragraph: **Investigational medicinal products should be returned on agreed conditions defined by the sponsor, specified in approved written procedures.**	Relevant information about returning conditions not mentioned.
24	517	*2.12.3. Destruction*	Include the following paragraph: **The sponsor is responsible for the destruction of unused and/or returned investigational medicinal products.**	Relevant responsibility not mentioned.
25	525	that all operations may be accounted for.	that all operations may be accounted for. **The records should be kept by the sponsor.**	Relevant responsibility not mentioned.
26	531		Include the following new section after 2.12. Recalls and returns: **2.13. <u>Self-inspections</u>** **The manufacturer should perform periodic**	In consistency with Delegated Act, this section must be included

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			self-inspections in accordance to principles detailed in EudraLex, Volume 4, Part I, Chapter 9.	with a cross reference to EudraLex, Volume 4, Part I, Chapter 9.
27	532	**2.13. Glossary of terms** Manufacturer	Manufacturer**/Importer**	See comment 2.

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