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European Federation of Pharmaceutical Industries and Associations

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Submission of EFPIA comments on GL on GMP for IMP

"Detailed Commission guidelines on good manufacturing practice for investigational medicinal products, pursuant to the second subparagraph of Article 63(1) of Regulation (EU) No 536/2014"

Author: EFPIA ✱ **Date:** 24 November 2015 ✱ **Version:** Final

1. General comments

1. EFPIA would like to express its strong concerns with regard to the potential duplication of GMP requirements in different sections or outside of EudraLex - Volume IV Good manufacturing practice (GMP) Guidelines. There is the need to maintain consistency across different parts of the guidance, which if not managed appropriately has the high potential to lead to divergences. EFPIA recommends that all GMP requirements for different kinds of products - IMPs, ATMPs and commercial medicinal products will be posted in Eudralex Volume 4. A core set of common GMP principles is proposed to be referred to in Part I. Rather than duplicating these core requirements in separate sections (e.g. in part III or Annexes) addressing, for example, IMPs or ATMPs, EFPIA recommends that only the differences in the GMP requirements for these kinds of products and their development phase should be described. Emphasising these core principles will facilitate the common application within the company's pharmaceutical quality system, and consistency in inspections across these different kinds of products by the different agencies of the member states.
2. The industry view expressed above is that, given the reliance on other sections of EudraLex Volume 4 for achieving appropriate GMP for IMPs, this document should be a revision of EudraLex Volume 4, Annex 13, not a new standalone guideline. **Please note** if Annex 13 is removed completely other guidance references will also change. In superseding the current version of Annex 13, allowance will need to be made of the fact that Clinical Trial Regulation 536/2014, Article 98, allows for a period of up to 3 years of transition during which supplies may be made in accordance with current requirements.
3. There is a change from NIMP to AMP within the CTR. There is currently a NIMP Guideline. We recommend that an AMP guidance and /or Q&A are produced.
4. The comments on the Delegated Act (DA) included comments on the QP (IMP) transitional status. i.e. The Clinical Trial Regulation art 61 2 (b) sets down the requirements for the Qualified Person. There are concerns that the current text does not appropriately cover persons who are qualified under the transitional arrangements of Article 13 (5) of Directive 2001/20/EC. It needs to be ensured that the repeal of Directive 2001/20/EC does not take this qualification away from anyone, thus impacting individuals' right to work and likely creating capacity issues in Member States where this clause was actively used. It is therefore suggested that the opportunity of this Delegated Act is taken to add wording that addresses this point. Recent information is that there are approximately 250 to 300 QPs for IMP in one Member State that would be impacted if this was not pragmatically addressed.

5. The comment below has been made assuming the question in the Delegated Act will lead to the acceptance of any ICH third country falling into section 2.9. ii

Section 2.9 was the subject of questions and comments in the consultation on the delegated act. A significant portion of commercial products that become IMPs come from Third Countries that are within the ICH environment (with or without MRA). This represents a significant proportion of studies.

The wording in section 2 below (Lines 441 to 453) has assumed ICH will be included in section 2.9 ii. If this is not the case there are concerns with section 2.9. ii around the omission of details from the current Annex 13 section 39 d and Table 2

6. The omission of text that is in the current Annex 13 section 43 on the initial shipment of IMP is understandable given the current status of the CTR implementation. This however has created concern in EFPIA members involved with IMP supply.

Although activities following shipment of IMPs might be regarded as being under the scope of Good Clinical Practice there are examples where coverage in this guidance from the GMP perspective would be helpful

a. What is the expectation of Part A and Part B approvals and how will that relate to GMP activities of the initial shipment to a clinical site.
b. A similar concern is the omission of guidance on Site to Site transfers. The current guidance assists by setting expectations at the GMP/GCP interface both in terms of rarity and the need to seek QP advice as part of the process.

7. Section 2.2 includes explanation of reconstitution. Many differences of interpretation between Member States and others involved at the interface of GMP and GCP exist over the process of Dispensing and where the division lies with the respect of IMP "Manufacture". It is recommended to add to the explanation that Dispensing is not in scope of these guidelines and to add a detailed definition of Dispensing in the glossary. See line 108 comment and Glossary definition of Dispensing

8. Line 375/376 has the text 'as authorised by the Member State' and Line 422 has the text 'accepted by the Member State'. It is suggested that these will require modification to reflect the new single submission process brought in by Regulation 536/2014.

9. Very strong comments have been made on the need to change Annex VI as soon as it is legally possible in the response to consultation on the Delegated Act.

Labelling of IMPs is not covered in this consultation as it is addressed by Annex VI of Clinical Trial Regulation 536/2014 itself.

EFPIA has previously communicated to the Commission, the changes made to this text compared with the current EU GMP Annex 13 will have significant impact and it is important for this to be amended as soon as legally possible and this remains the unanimous opinion of all the Industry subject matter experts involved with compiling these comments.

10. Glossary

The EFPIA recommendations strengthened some of the definitions. Two paths will be possible depending if this guidance remains part of volume 4. This glossary will need significant expansion if the document is not part of volume 4. If it remains part of volume 4 then only the limited number of definitions which are unique to IMP need to be included.

We believe it would be useful to retain definitions of 'Blinding' and 'Clinical Trial' in the Glossary of these guidelines." [Annex 13 currently has these; we are proposing adding 'Unblinding' and 'Dispensing' and amending 'Order']

11 The comments on the DA expressed concern over the Sponsor / Manufacturer. The comments were:
Where the manufacturer is not the sponsor of a trial a number of the responsibilities in this regulation that have been placed on the manufacturer will be divided between the manufacturer and the sponsor. This division will vary from one trial and / or manufacturing operation to another. An example of this is in ensuring the manufacture conforms with data submitted and reviewed by the Lead Reporting Member State. Throughout this regulation it should be made clear that the manufacturer responsibilities may be divided providing the responsibilities of the relevant parties are clear in the contractual agreements. This same division is also a key aspect in the inspection of a manufacturer by a member state where confidentiality requirements of inspection reports need to be assured if they undertake work for a number of sponsors.
The acknowledgement of Manufacture and Sponsor being separate needs to be covered either generically or considered separately for each reference to manufacturer

Consistency with the principles expressed above within this guidance document should be maintained

2. Specific comments on text

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they are highlighted using 'track changes')***
Line 69 to 71	Rational – The addition of the word undue is because the concept of zero risk in clinical trials is unattainable The application of GMP for the manufacture of investigational medicinal products is intended to ensure that subjects are not placed at undue risk, and that the results of clinical trials are unaffected by inadequate quality, safety or efficacy arising from unsatisfactory manufacture.
Line 107 to 108	An investigational medicinal product must exist before it can be dispensed or the ~~a~~ process can be defined as reconstitution, diluting or mixing as part of dispensing. Text without track change An investigational medicinal product must exist before it can be dispensed or the process can be defined as reconstitution, diluting or mixing as part of dispensing. Rational see comment 7
Line 109 to 111	The process of reconstitution has to be undertaken at a point in time as close to patient / subject ~~as possible to~~ administration as practical. If not immediately before administration the time period should be justified based on stability or in use data. ~~and~~ The process has to be defined in the clinical trial application/dossier and in the protocol, or related document, available at the clinical trial site. Rational – additional clarity around "as close as possible"
Lines 116 to 120	This section should be deleted or it should be made clear which issues concerning auxiliary medicinal products are addressed by these guidelines. Currently, the only other specific mention of them is in Line 346
Line 128 to 131	CAPA may not be required in every situation, so we propose adding 'as appropriate' to the end of this sentence: Deviations from any predefined specifications and instructions shall be investigated and corrective and preventive action (CAPA) measures

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they are highlighted using 'track changes')***
	initiated **as appropriate**
Line 179 to 180	**Premises and equipment are expected to be ~~validated~~ qualified in accordance with EudraLex, Volume 4, Annex 15 in so far as appropriate, taking into account the stage of product development.** Rationale: Premises and equipment are generally deemed to be qualified rather than validated and there may be some differences in the approach taken depending on stage of product development.
Line 183 to 194	Specifications for starting materials, immediate packaging materials, intermediate products, bulk products and finished products, manufacturing formulae and processing and packing instructions should be as comprehensive as possible given the current state of knowledge. They should be ~~periodically~~ re-assessed during development and updated as necessary. Each new version should take into account the latest data, current technology used, regulatory and pharmacopoeial developments and should allow traceability to the previous document. Any changes should be carried out according to a written procedure which should address any implications for product quality ~~such as stability and bioequivalence~~. The approval process for instructions and changes thereof shall include appropriate ~~management~~ personnel at the manufacturing site. Rationale: The word 'periodically' suggests a set period for reassessment. In practice, the reassessment is likely to be driven by progression of product development, the pace of which will vary significantly from project to project Inclusion of the words 'such as stability and bioequivalence' does not usefully add to the requirement to 'address any implications for product quality' and could lead to an inappropriately limited focus. Approval of changes needs to be by appropriate personnel, but these do not need to be 'management'.
Line 200	The manufacturer should retain the order for investigational medicinal products. ~~The order should request the processing and/or packaging of a certain number of units and/or their distribution and be given by or on behalf of the sponsor to the manufacturer. It should be in writing, though it may be transmitted by electronic means, and be precise enough to avoid any ambiguity. It should be formally authorised by the sponsor or his representative and refer to the product specification file and the relevant clinical trial protocol as appropriate.~~ Deleted from here and placed in the Glossary

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they are highlighted using 'track changes')***
Line 207	Comments have been made on the virtual aspects of the Product Specification file for the Delegated act – This section should be consistent with those comments. We do not see the need to introduce a requirement for a Product Specification File into the Delegated Act; it is well enough covered by the Guideline. It should be noted that Product Specification Files typically exist, but that these are often in a virtual environment and different parts may be located across multiple locations, which may be in multiple companies. Often this is a table of contents that refers to the source of the information, which can change as knowledge develops. This practice has been accepted by inspectors and it would be beneficial for this to be reflected in the wording of this section.
Line 208 to 210	Applicable sections of the product specification file or equivalent information shall be available at the start of manufacturing of the first batch of investigational medicinal product for a clinical trial. Rationale as per the comment on Product Specification File above and the timing of the availability of information particularly in early stage development.
Line 219 to 220	v. Relevant CMC quality section of the clinical trial authorisations and amendments thereof, clinical trial protocol and randomisation codes, as appropriate;
Line 221	vi. Relevant contractual technical agreements with contract givers and acceptors, as appropriate; Rationale – Consistency with chapter 7 of Volume 4
Line 224	viii. Details of the plans and arrangements for Reference and retention samples ~~plans~~;
Line 231 to 235	Where different manufacturing steps are carried out at different locations under the responsibility of different qualified persons, it is acceptable to maintain separate files limited to information of relevance to the activities at the respective locations. The relevant sections ~~documentation~~ of the product specification file, including changes, shall be accessible at the manufacturing site**.**
Line 243 to 245	The relevant information in the product specification file should be used to ~~produce~~ capture the detailed written instructions on processing, packaging, quality control testing, storage, distribution conditions and storage conditions.
Line 268	EFPIA has made very strong comments on the retention of documents from the manufacturing process in the response to consultation on the DA. The practical needs are met by the recommendation of 15 years retention from Manufacture. i.e.

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	Much of the GMP activity may occur at a Contract Manufacturing Organisation (CMO) or even company facilities with little or no link to the Clinical trial and it is therefore not practical to tie the end of document retention to the Clinical Trial timelines - Typically manufacturer sets a simple measurable retention period of number of years from the date of the operation and we suggest that the new text aligns with this practice. A fixed time period of 15 years from date of manufacture is proposed with no perceived benefit in a longer retention period.
Line 288 to 290	EFPIA has made comments on this aspect in the in the response to consultation on the DA. This should be consistent with those comments. i.e. Manufacturing processes are not required to be validated, but shall be appropriately monitored and controlled, taking into account the stage of product development, in order to assure the quality required for the intended use. Track changes ~~The m~~ Manufacturing processes are ~~is~~ not required ~~expected~~ to be validated but shall be appropriately monitored and controlled, taking ~~to the extent necessary for routine production but shall be validated in its entirety in so far as appropriate, taking~~ into account the stage of product development, in order to assure the quality required for the intended use.
Line 291 to 292	Rationale Verification should not be mandatory - Assurance of cleaning should be appropriate for the operation being performed and may be assured by methods other than verification. For example, a cleaning validation matrix approach for a multi-product facility. To avoid cross-contamination, written cleaning procedures ~~and analytical methods to verify the cleaning process~~ shall be available. The effectiveness of sum of the control measures should be demonstrated.
Line 333 to 340	The expiry date stated for the comparator product in its original packaging might not be applicable to the product where it has been repackaged in a different container that may not offer equivalent protection. A suitable expiry date, taking into account the nature of the product, the characteristics of the container and the storage conditions to which the article may be subjected, should be determined by or on behalf of the sponsor. Such date should be justified and must not be later than the expiry date of the original package. ~~There should be comparability of expiry dating and clinical trial duration.~~ Rationale: The text proposed for deletion could be read as creating an expectation for the expiry date to cover the intended duration of the

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	trial which is unrealistic. Shelf life extension or resupply plans may be valid and necessary as part of the trial management.
341 to 344	The packaging must ensure that the investigational medicinal product ~~remains in good condition~~ retains its integrity during transport and storage at intermediate destinations. Any opening or tampering of the outer packaging during transport should be readily discernible.
355 to 362	The current text is not clear regarding whether expiry extension labelling has to take place at an authorised manufacturing site or not. An additional sentence is proposed to address this: The re-labelling operation should be performed by appropriately trained staff in accordance with GMP principles and specific and standard operating procedures and should be checked by a second person. This additional labelling should be properly documented in the batch records. To avoid mix-up, the additional labelling activity should be carried out in an area which is partitioned or separated from other activities. A line clearance at the start and end of activity should be carried out and label reconciliation performed with 100 %. Any re-labelling limited to Expiry / Retest aspect does not require the site where it is undertaken to have a Manufacturing Authorisation e.g. it may be performed at a Clinical Site.
Line 382 to 384	Reference sample: a sample of a batch of starting material, packaging material, bulk formulated product, product contained in its primary packing or finished product which is stored for the purpose of being analysed should the need arise.
Line 411 to 419	It is proposed that the stipulation around the geographical location of the reference samples is removed and to simply state that these need to be stored in accordance with standards equivalent to EU GMP. The reason for this is that reference samples are those stored for the purpose of being analysed should the need arise. It therefore makes sense for them to be located at or near the site of testing, which for IMPs may be in a third country Reference samples ~~of finished product should be stored in the EU or in a third country where appropriate arrangements have been made by the Union with the exporting country to ensure that the manufacturer of the investigational medicinal product applies standards of good manufacturing practice at least equivalent to those laid down by the Union. In exceptional circumstances, the reference samples of the finished product may be stored by the manufacturer in another third country, in which case this should be justified and documented in a technical agreement between the sponsor, the importer in the EU and that manufacturer in the third country.~~ should be stored in

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	accordance with standards of good manufacturing practice at least equivalent to those laid down by the Union, so that in the event of analysis the results can be taken as being representative of the product in the supply chain.
Line 441 to 453	Propose amending this to cover marketed product from both the EU and ICH/MRA countries, thus providing a replacement for the current Annex 13, 39(d) text. As commented on in response to Delegated Act question 5, continued coverage of such comparator products is essential: ii. Marketed Product sourced from the open market within EU or ICH/MRA countries from authorised distributors can be accepted as having been manufactured in accordance with appropriate good manufacturing practice. ~~Article 80(b) of Directive 2001/83/EC and subject to a marketing authorisation granted by a competent authority in the EU, regardless of manufacturing origin: the duties are as described above. However, the scope of the certification can be limited to assuring that the products are in accordance with the~~ The qualified person can therefore certify the product on the basis of compliance with the authorisation of the clinical trial and any subsequent processing for the purpose of blinding, trial-specific packaging and labelling. **Please Note – This paragraph is another example of where the responsibilities of the Sponsor and Manufacture are potentially divided as per general comment 11**
Line 506 to 510	The current text may cause some confusion. The wording below is understood to represent current good practice and be clear to all parties. Procedures for retrieving investigational medicinal products and documenting this retrieval should be agreed by the sponsor in collaboration with the manufacturer, where different. The sponsor should ensure that any manufacturer, Sponsor representative (e.g. CRO) and Investigator Site understand their obligations under the retrieval procedure. The procedures for retrieval of investigational medicinal products should be in accordance with the principles detailed in EudraLex, Volume 4, Part I, Chapter 8. Procedures for retrieving investigational medicinal products and documenting this retrieval should be agreed by the sponsor in collaboration with the manufacturer, where different. The sponsor should ensure that any manufacturer, Sponsor representative (e.g.

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	CRO) and Investigator Site understand ~~investigator~~ ~~and the sponsor's representative need to understand~~ their obligations under the retrieval procedure. The procedures for retrieval of investigational medicinal products should be in accordance with the principles detailed in EudraLex, Volume 4, Part I, Chapter 8.
Glossary	Please note comment 10 has made some general recommendations.
Glossary – Blinding	The full formal definition should be obtained from ICH E6 **1.10 Blinding/Masking** A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s). Within the Manufacturing process this can be supplemented with In relation to an investigational medicinal product, blinding shall mean the deliberate disguising of the identity of the product in accordance with the instructions of the sponsor
Glossary – Unbinding	We believe it would be helpful to add the definition of unblinding below This is the intended or unintended disclosure of the identity of blinded products.
Glossary – Clinical Trial	The full formal definition should be obtained from ICH E6 Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of one or more investigational medicinal product(s) with the object of ascertaining its/their safety and/or efficacy.
Glossary – Preparation	Delete this Term it is not used in the Guidance

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Glossary - Dispensing	This is a proposed new definition that has been introduced at line 108 as well as being part of general comment 7 Within the scope of this Guideline Dispensing of an IMP can only take place after an IMP exists. Dispensing is the action of giving the IMP to the patient /subject and /or where appropriate preparing it for administration, which may include reconstitution and or dilution. It should not include adding any dispensing label that repeats or replaces any items covered by Annex VI of the CTR. (the exception would be the addition of information into pre prepared spaces on the IMP label e.g. Dispensing Date or Investigator name). Dispensing may include adding a label with information such as facility address where these are applied to take home medication as part of an institution /site dispensing practices. Where IMP is reconstituted and or diluted for the administration to a single subject / patient, then the dispensing can include applying a label with sufficient details to the reconstituted medication that are needed to ensure the safe administration of the treatment to the subject / patient.
Glossary -Order	We consider that this text taken from Lines 200 – 206 is definition and therefore best placed in the Glossary. The order should request the processing and/or packaging of a certain number of units and/or their distribution and be given by or on behalf of the sponsor to the manufacturer. It should be in writing, though it may be transmitted by electronic means, and be precise enough to avoid any ambiguity. It should be formally authorised by the sponsor or his representative and refer to the product specification file and / or the relevant clinical trial protocol as appropriate.

3. Typographical errors and grammatical suggestions

Line number(s) of the relevant text ***(e.g. Lines 20-23)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they are highlighted using 'track changes')***
Line 151	(EU) No 536/~~2015~~ 2014 and (anticipated) further elaborated in the Delegated Act on
Line 226	The list of documents is neither exhaustive, nor exclusive.
Line 349	labelling is set out in Annex ~~IV~~ VI to said Regulation.
Line 366 to 369	According to the Delegated Act on GMP for investigational medicinal products pursuant to Article 63(1) of Regulation (EU) No 536/2014 the manufacturer is required to establish and maintain a quality control system placed under the authority of a person who has the requisite qualifications and is independent of production
378 to 381	Proposed additional clarity regarding 'finished product' and grammatical change: Samples are retained to fulfil two purposes: firstly, to provide a sample for future analytical testing, and secondly, to provide a specimen of the finished product (IMP) ~~and~~ which may be used in the investigation of a product quality defect. Samples may therefore fall into two categories:
Line 463	Cleaning records to be replaced by cleaning evidence (cleaning records are not part of the batch records itself) iii Cleaning ~~Records~~ evidence
Line 500 to 503	The conclusions of the investigation should be discussed between the manufacturer and the sponsor, if different, in a timely manner. This should involve the qualified person and those responsible for the relevant clinical trial in order to assess any potential impact on the trial, product development and on subjects