efpia
European Federation of Pharmaceutical Industries and Associations

Draft ☐ Final ✱

Submission of EFPIA comments on DA on GMP for IMP

"Commission Delegated Act on principles and guidelines on good manufacturing practice for investigational medicinal products and on inspection procedures, pursuant to the first 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 term Manufacturer line 52 and in many other places. 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.
3. Response to Question 1a and 1b 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.
4. Response to Question 2 a and 2 b 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.

5 Response to Question 3 - This would not be feasible In many cases a Certificate of Analysis does not exist at the time of import. For example if a drug product manufactured outside the EU having all its analytical release testing and stability performed in the EU. In other cases shipment under quarantine may be made in parallel with testing. The QP is responsible for ensuring that an imported investigational product has been fully tested before it is certified for supply; how they obtain documentation for this should remain flexible. In the case of commercial products a Certificate of Analysis may not be available at any point in time. (see response to question 5)
6.Response to Question 4 4a The fundamental requirement is adequately covered by the current wording. No additional text is needed in the Delegated Act to require retention samples or provide further details around reference samples. The detail is adequately covered by the Guideline. 4 b Investigational products are varied and complex - Photographs may be a useful aid to understanding what the pack looked like and should be an acceptable option for retention samples, but to mandate this in the vast majority of cases would add no value.
7.Response to Question 5a Comparators obtained via commercial channels are unlikely to have 'documentation certifying that each production batch has been manufactured in conditions at least equivalent to the standards of [EU good manufacturing practice]'. So, Article 13(3)(c) of Directive 2001/20/EC is actively used in conjunction with the guidance in CHMP/QWP/185401/2004 to approve these for use. Some companies could have up to 20% of studies impacted if this clause was removed
8.Response to Question 5b It is rare for comparator products not authorised in an ICH country to be used, but it has happened and the possibility for this to occur should remain
9. 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. 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.

11. Section 3 Inspections

EFPIA welcome the clarity that third country manufactures are enforced to follow EU GMP standards and might be subject to risk based inspections.
EFPIA consider that the definition of the role of the QP and the opportunity to issue a QP declaration should provide sufficient confidence to the authority that the third party IMP manufacturer successfully implemented GMP standards according to the EU regulations or apply similar standards.
Consequently, we propose that the final regulation enables flexibility that an inspection of a third country IMP manufacturer, if needed, would not normally cause a delay of a clinical study.

We understand that a full inspection coverage would represent a significant burden on MS depending on how the risk assessment is managed and applied consistently across the MS under the CTR. Given the QP oversight these resources might be better spend at higher risk areas.

Any actions taken as a consequence of any inspection should include consideration of patients that may have no other alternate therapy or source of IMP.

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 52	See the General comment 2 regarding use of the term 'manufacturer'.
Line 63	Not all countries have systems of "entitlement" to manufacture IMPs. Text proposed with track changes The importer of investigational medicinal products for human use shall ensure that the manufacturer located in a third country ~~is entitled to manufacture the relevant type of investigational medicinal product in that country~~ is notified and accepted as part of the information provided pursuant to Article 5 of Regulation (EU) No 536/2014. Full text proposed without track changes The importer of investigational medicinal products for human use shall ensure that the manufacturer located in a third country is notified and accepted as part of the information provided pursuant to Article 5 of Regulation (EU) No 536/2014.
Line 155	To better reflect actual expectations and practices. Text proposed with track changes ~~The~~ m Manufacturing processes ~~shall be validated in its entirety in so far as is appropriate,~~ 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. Full text proposed without track changes 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.
Line 163	Another example among many where General comment 2 applies – Some of the Quality control system will lie with the Sponsor and some

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')***
	will be with the Manufacturer
Line 184	The current text stipulates that it is the manufacturer who retains these samples, whereas in practice this could be the sponsor. The change below ensures delivery of the requirement for samples to be retained whilst providing flexibility regarding who actually holds the samples. In addition, a generic sample keeping period from the date of manufacture is proposed rather than one that is tied with trial endpoints. Seven years is proposed as this will be at least 2 years after the expiry date of the product and stability considerations are likely to eliminate value in longer retention. **Proposed text final text:** Sufficient samples of each batch of bulk formulated product and of key packaging components used for each finished investigational medicinal product batch shall be retained for seven years from the date of manufacture. Where the manufacturer is not the sponsor, the responsibility for sample retention shall be defined in written agreement.
Line 194	To remove variation between requirements of Member States. ~~Unless a longer period is required under the law of the Member State of the manufacture, t~~ The manufacturer shall retain samples of starting materials, other than solvents, gases or water, used in the manufacturing process for at least two years after the release of the product.
Line 227 to 235	See General comment 4 - 15 years from manufacture would be simpler and much more appropriate than a retention period tied with the trial endpoint.
Line 287 and 288	This has been modified so that the aspect of third country inspection in the comment below can be separated By means of repeated inspections the Member States shall ensure that manufacturers and Importers that they have authorized comply with the principles of good manufacturing practice laid down by Union law.
Line 289 to 295	See General Comment 11

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')***
	Text proposed with track changes Member States shall carry out ~~inspections of manufacturers located in third countries to ensure that investigational medicinal products imported into the Union are manufactured by applying quality standards at least equivalent to those laid down in Union law. The frequency of such inspections shall be based on an assessment of risk, but shall in any case take place if the Member States have grounds for suspecting that the quality standards are lower than those laid down in Union law.~~ risk assessments of IMP manufacturers located in third countries. This assessment should include the oversight provided by the Qualified Person (QP) and decide whether or not on-site inspections are required to verify if the IMPs are manufactured by applying quality standards at least equivalent to those laid down in Union law. A QP declaration provides a major component of the risk assessment. The need for an inspection, its timing, level of detail and frequency of re-inspection shall also be based on the assessment of risk. Any regulatory actions taken as a result of an inspection should include an assessment of patients undergoing treatment Full text proposed without track changes Member States shall carry out risk assessments of IMP manufacturers located in third countries. This assessment should include the oversight provided by the Qualified Person (QP) and decide whether or not on-site inspections are required to verify if the IMPs are manufactured by applying quality standards at least equivalent to those laid down in Union law. A QP declaration provides a major component of the risk assessment. The need for an inspection, its timing, level of detail and frequency of re-inspection shall also be based on the assessment of risk. Any regulatory actions taken as a result of an inspection should include an impact assessment for patients undergoing treatment.
Line 298 to 300	Manufacturers and Sponsor situations are very different here. There is a concern around confidentiality issues which have been addressed in the Sponsor / Manufacture comment in the General comment 2 above. An example may be a manufacturer acting for more than one company. In these circumstance good judgement is needed of what details are company confidential.
Line 323	(3) The ability to apply the principles of quality risk management as per ICH Q9;
Line 325	Delete this line; it is redundant – This is covered in the previous line '(4) Knowledge of current technology relevant for inspections'

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 326	There is a concern with the current wording that inspectors will not be required to maintain confidentiality unless they are specifically made aware that information is confidential. All information should be treated as confidential and we therefore propose that: The inspectors shall ~~be made aware of and~~ maintain confidentiality whenever they gain access to confidential information as a result of their inspections in accordance with applicable Union legislation, national legislation or international agreements.

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 53	The manufacturer shall ensure that the manufacturing or import operations for investigational medicinal products for human use ~~sue~~ are carried out in accordance with good manufacturing practice for investigational medicinal products laid down in the Commission Delegated Regulation on good manufacturing practice for investigational medicinal products, with Regulation (EU) No 536/2014 and with the authorisation referred to in Article 61(1) of Regulation (EU) No 536/2014.
Line 91	The personnel shall receive initial ~~internal~~ and on-going training,
Line 251	The manufacturer shall, in cooperation with the sponsor, implement a system for recording and reviewing complaints together with an effective system for recalling promptly and at any time investigational medicinal products which have already entered the distribution
Line 308	(1) Inspect the manufacturing or commercial establishments of manufacturers of investigational medicinal products for human use, and ~~lay~~ laboratories employed by manufacturer to carry out quality control;
Line 310	(2) Take samples including with a ~~view~~ potential to perform independent tests being carried out by an Official Medicines Control Laboratory or a laboratory designated for that purpose in a Member State;
Line 314	(4) ~~Inspection~~ Inspect the premises, records and documentation of the manufacturer