EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

N° d'enregistrement :
Ares(2013)3402121

Final, 31st October 2013

Submission of comments to Annex 16 'Certification by a Qualified Person and Batch Release'

Comments from:

Name of organisation or individual
EFPIA

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	EFPIA welcomes the revision of Annex 16 to the EU GMP Guide, which defines the specific responsibilities of the EU Qualified Person (QP). Industry acknowledges that with this revision, an effective QP role will be established, focusing on the specific core responsibilities and accountabilities of the QP, rather than tasks and duties that can be effectively managed within a Quality Management System (QMS). The revised draft reflects, inter alia, the realities of global supply chains, the existence of pharmaceutical quality systems, and new control strategies, e.g. Real Time Release Testing. It defines how the QP responsibilities can be fulfilled through reliance on effective site or global Quality Management Systems that may extend across third parties. EFPIA also appreciates the efforts towards harmonisation of the requirements and of their interpretation throughout the EU. Nevertheless, we also believe that actual harmonisation will require more attention, to avoid divergent interpretations between member states, and the addition of national or modified requirements. This is specifically relevant to duties that have to be performed by a Qualified Person (QP) and those that can be delegated. Also, allowing the QP to rely on the company or site-based pharmaceutical quality systems as given in ICH Q10 is a key aspect to ensure that requirements laid down in this annex are being fulfilled. EFPIA also has concerns with the practical implementation of some of the provisions; as currently written, these could lead to unnecessary challenges, while feasible alternatives are at hand. Detailed comments on the concerns are provided overleaf (page 3-5).	

	Scope (section 1.1), Investigational Medicinal Products (IMPs) The revised draft Annex should be made clearer with regard to its applicability to IMPs, and should be aligned with Annex 13. While we concur that the principles in Annex 16 apply to IMPs, certain specific aspects do not. Clarification is important, especially in the following sections: • 1.4 Investigational Medicinal Product Dossier (IMPD), • 3.4.5 Re-testing upon importation, • 3.5.9 QP declaration requirements and template and • 3.5.10 Excipient risk assessment.	
	Quality responsible persons outside the EEA - § 3.4.3 For manufacturing site(s) outside the EEA, item 3.4.3 states that the QP may share defined responsibilities with other QPs at sites in the EEA. We understand that this principle may equally be applied when the batch has been certified at manufacturing sites outside EEA by a **quality responsible person outside the EEA**, provided that it is clearly defined e.g. in written agreements. This approach prevents unnecessary duplication of work in case of e.g. batch documentation review, when the same activity has already been performed by the Quality Unit of the manufacturing site outside the EEA, and which is responsible for partial manufacture of the batch. The reliance on this approach is justified if there are equivalent GMPs in place and/or where the review has been performed by personnel at another manufacturing site operating under the same Quality System. Furthermore, we believe that this approach would be aligned with section 3.2, which allows QP certification when several sites are involved in the 'manufacture, importation testing and storage' of a batch, provided that 'all necessary steps have been completed through an agreed quality management system' – see also pages 10-11 for detailed comments and proposed changes.	

	Sampling requirements for import - § 3.4.6 and 3.4.7 Annex 16 requires for samples of batches manufactured outside the EEA to be taken after arrival in the EEA. We suggest that, alternatively, and with appropriate justification, it is acceptable to take samples in the third country. The prerequisite is that the sampling scheme is justified, and that the samples are representative of the batch so that subsequent steps, incl. transportation, do not negatively affect attributes of the representative sample. Such alternative will keep batch release cycle times at an acceptable level and facilitates timely availability of products to patients. It is recognised that additional measures aimed to enhance supply chain security are currently being put in place to assure the quality and integrity of products on receipt in the EEA (e.g. EU GMP Chapter 5, controls on supply chain traceability) – see page 12 for detailed comments and proposed changes.	
	Testing requirements for import - §3.4.8 Concerning the import testing of batches originating from the same bulk product batch, Annex 16 states that QC testing from another imported finished batch originating from the same bulk may be used for certification, provided that the ID and assay testing are conducted on each occasion within the EEA. We suggest deleting the requirement to repeatedly test ID and assay on each occasion. It should be substituted by risk-based approaches to determine the necessary tests - see page 13 for detailed comments and proposed changes.	
	Mutual Recognition Agreement (MRA) Annex 16 should make reference to MRA rules, which allow delegating more responsibilities, other than testing. A dedicated section could be introduced, to describe what is required when MRAs or other relevant arrangements like ACAA apply.	

	Alignment with Annex 11 With regard to the different certification and release activities, Annex 16 should be aligned with Annex 11 'Computorised systems'.	
	Terminology We recommend that the following terms be defined: • MIA (Manufacturing/Importation Authorisation), and its differences with Marketing Authorisation; • Equivalence with EC GMP, for which we propose: "**Any standard recognised by health authorities and inspectorates where a Mutual Recognition Agreement (MRA) is in place, or where the inspectorate is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) can be considered as 'EU GMP equivalent'** '' – see sections 2.2 and 2.4.2; to also be added to 2.4.3; Furthermore, consistent wording should be used throughout the document, e.g.: • 'Finished product batch' (vs. other forms used as 'Finished medicinal production batch', 'Finished product', or 'Medicinal product'); • 'Parallel importation' and 'Parallel Distribution'.	
	QP Discretion We acknowledge section 5., which clarifies the 'handling of unplanned deviations'. EFPIA believes that this is consistent with previous proposals to include minor deviations, which are deemed to have no impact on the safety, efficacy or quality of the product.	

2. Specific comments to the text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Section 2. General Principles			
2.2, page 2		Comment: for a global acting company, medicinal products are delivered worldwide. Due to the lack of harmonisation of international regulations, it is very unrealistic that the Qualified Person can certify that the batch has been manufactured in compliance with laws of the destination country of the medicinal product. However, the QP certifies compliance with the European legislation, which ensures acceptable standards. Proposed change: to delete "and of the destination country of the medicinal product" as follows: "*However, the responsibility for ensuring that a particular batch has been manufactured in accordance with its marketing authorisation, with EU Good Manufacturing Practice (GMP), or equivalent, and that it is in compliance with the laws in force in the Member State where certification takes place* ~~***and of the destination country of the medicinal product***~~*, lies with the QP certifying that batch as being suitable for release*."	
2.2, page 2 2.3.2 / 2.4.2		Comment: the concept of compliance with EU GMP "or equivalent" is mentioned, also in 2.4.2, as a basis for certifying batches. The concept of standards considered to be "equivalent" to EU GMP should be defined in the Glossary and used consistently throughout the document, e.g. it should also be referred to in 2.3.2.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change: add a definition for 'Equivalence with EU GMP' as follows: "**Any standard recognised by health authorities and inspectorates where a Mutual Recognition Agreement (MRA) is in place, or where the inspectorate is a member of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) can be considered as 'EU GMP equivalent'**."	
2.3.3, page 2		Proposed change: replace "SOP" with "procedure" to align with wording in 3.3. ii).	
2.4.3, page 3		Comment: for export countries non-members of the EU/EEA, it may sometimes be difficult to comprehensively know local legal requirements. In addition, a local release usually follows after import to that destination country member of EU/EEA. This Annex should be limited to EU/EEA and MRA/ACAA countries, where applicable. Proposed change: to modify the text as follows: "*any other relevant legal requirements, e.g. of the destination* ***country within the EEA****, are taken into account*."	
Section 3. The process of certification			
3.2, page 3		Comment: the first § reads that the QP 'should be able to demonstrate knowledge of the product', which we believe can be achieved through written agreements (as per 3.3.i)), between QPs for which areas of responsibility and expertise are defined. Thus, not all QPs involved in batch manufacturing shall demonstrate knowledge of all the processes and changes at all the facilities.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		Proposed change: to delete the sentence: "~~*Any QP involved in the certification, or confirmation, of a batch must have detailed knowledge of the steps for which they are taking responsibility*~~."	
3.3 Manufacturing performed at sites in the EEA			
3.3 i), page 4		Comment: the responsibilities of the QPs operating at different manufacturing holders should be described in a written agreement. Such a written agreement can be a (standard operating) procedure within a company or a contract between different companies (see current Annex 16). Proposed change: 3.3 i): "*In a written agreement between manufacturing authorisation holders if the QPs are located at different* ***sites*** ~~***manufacturing authorisation holders***~~. ***The form of such an agreement should be appropriate to the relationship between the parties; for example a standard operating procedure within a company or a formal contract between different companies***."	
3.3 – last sentence		Comment: the last sentence refers to a specific template (as attachment). We believe that companies should be able to adapt the template, if necessary. Proposed change: "***An example of*** *template for the confirmation is presented as an Attachment*."	

3.4 Manufacturing site(s) outside the EEA			
3.4		Comment: section 3.4 implies that importation is a manufacturing step in itself. This is inconsistent with the definition of the term 'manufacture' in the glossary to the GMP-Guide; also this could have significant implications for distribution sites in the EU functioning as an importer/intermediate hub for fully released finished products imported as such from outside the EEA, and solely intended for further shipping / distribution to other destination countries outside the EEA. Such batches would then require EU importation testing/QP certification even if not required by the relevant marketing authorisation in the destination country. Thus, this section should be amended to clarify that importation as such is not a manufacturing step. Proposed change: to delete 'physical importation' as follows: '*For medicinal products manufactured outside the EEA,* ***~~physical importation~~*** *certification and batch release are the final stages of manufacturing.*'	
3.4.2		Comment: if Quality Agreements are in place, not all activities (e.g. sampling) have to be done in the EEA. In terms of a simple supply chain or of representative samples, some activities can be assured outside the EEA, where supported by a QMS. Proposed change: "*Importation activities including* ***~~at least~~*** *receiving, sampling, storage of the un-released and un-certified batch, quality control testing, certification and release should be conducted by authorised sites in the EEA according to Directive 2001/83/EC, Directive 2001/82/EC and Directive 2001/20/EC.* ***Some activities can be carried out outside the EEA, provided they are described in the quality agreement*****."**	

3.4.3		Comment: this section states that the QP is allowed to share defined responsibilities with other QPs. It should further provide for QPs in the EEA to ensure batch release, when the batch has been certified at manufacturing sites outside the EEA, and provided it is clearly defined, e.g. in written agreements. This will prevent unnecessary duplication of work for e.g. review of batch documentation when this has already been performed by the Quality Unit of the manufacturing site outside EEA responsible for partial manufacture of the batch. Circumstances where this may be appropriate would be where there is equivalent GMP in place and/or where the review has been performed by personnel at another manufacturing site operating under the same Quality System. This approach would be in line with section 3.2. (the process of certification) which allows QPs to certify finished product when several sites are involved in the 'manufacture, importation testing and storage' of a batch, and through an agreed quality management system. Proposed change: "*In accordance with the principles described in section 3.3 of this Annex, the QP certifying the finished medicinal product batch may take account of the confirmation by, and share defined responsibilities with, other QPs* ***in the EEA, or quality responsible persons outside EEA*** *in relation to any manufacturing or importation operations taking place at sites in the EEA where this other manufacturing authorisation holder is defined in the relevant marketing authorisation*."	
3.4.4		Comment: this section on storage and transport does not appear under 3.3; also it is covered already by 3.5.21, which reads: "The appropriate arrangements for distribution and shipment are in place.'' Proposed change: to delete 3.4.4.	

3.4.5		Comment: testing for products imported from third countries should not be required in all circumstances. Section 3.4.5 should be revised to allow a risk based approach to determining which additional tests other than a quantitative analysis of the active substance are necessary to assure quality. The risk assessment would be available for inspection. Proposed change: "*The QP certifying the finished product is responsible for ensuring that each finished medicinal production batch has been manufactured in accordance with GMP and the MA. Also, unless an MRA or similar agreement is in place between the EEA and the exporting country,* ***the QP certifies that a full qualitative analysis and a quantitative analysis of the active substances have been carried out in a member state. The QP confirms that the need for other tests has been evaluated in a risk assessment, or that the quality of the product is ensured with an approved Real Time Release Testing programme***. ~~***that it has undergone in a Member State a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or checks necessary, or in accordance with an approved Real Time Release Testing programme to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation***~~*."*	
3.4.6 3.4.7		Comment: the requirement to sample imported products after arrival in the EEA is excessive, and inappropriate for certain products (e.g frozen or cold stored products). It also contradicts long-standing practices for products where the use of pre-delivery samples has been justified and validated, and is not aligned with the concept of a science and risk-based quality management system. The current wording implies that sampling after arrival in the EU would be fully representative of the batch, however this would not be the case for bulk batches. Furthermore, allowing testing to occur in parallel with the transport of the batch keeps batch release cycle times to a minimum and	

		facilitates market availability of products for patients. In terms of preventing entry in the EU market of falsified medicinal products, additional measures are currently being put in place to assure the quality and integrity of products on receipt in EEA e.g. EU GMP Chapter 5 – controls on supply chain traceability – section 5. Proposed change: to combine 3.4.6 and 3.4.7 and build in a science and risk based approach as follows: "***Sampling of imported product should be fully representative of the batch. Samples may either be taken after arrival in the EEA, or be taken during processing in the third country by a technically justified approach and documented within the company quality system. The samples taken outside the EEA should be shipped under the equivalent transport conditions as the batch that they represent; if sent separately, it should be demonstrated that the samples are still representative of the imported batch. This can be applied to all samples, including samples for sterility tests.***"	
3.4.8		Comment: the requirement to test ID and assay on each occasion is an additional requirement, which is not always feasible (e.g. Narcotics – multiple shipments), which may delay availability for patients, and unlikely to increase protection of public health. Testing of batches originating from the same bulk should be defined if needed by the QP according to a risk analysis. We also believe ID test should be sufficient (including for anti-counterfeit assurance), but no assay should be required, and recommend this is harmonized practice throughout the EU. Furthermore, additional measures are currently being put in place to assure the quality and integrity of products on receipt in EEA e.g. EU GMP Chapter 5 – controls on supply chain traceability – section 5. So, we question what is the added value of this requirement if representative sampling is performed and shipment is controlled/conditioned? Finally, the reference to "secured documented evidence" and the choice of the word "secured" are not clear.	

		Proposed change: to replace the first paragraph with: "***When different finished product batches originating from the same bulk product batch are imported, the QPs certifying the different finished product batches may base their decision on the quality control testing of another imported finished batch originating from the same bulk product batch based on an risk analysis, and there is documented evidence that ID testing are conducted on each occasion within the EEA…"***	
3.4.8		Comment: the consequence of implementing the requirements of chapter 3.4.8 would in some cases preclude the possibility of having packaging operations of a bulk batch outside EEA. Proposed change: to revise this chapter to allow sampling for ID and assay testing from the bulk batch outside the EEA and analysis in the EEA provided the transport conditions are similar to those for the imported finished goods batches).	
Section 3.5			
3.5.3		Comment: in practise, such a register is seldom used for what was its original purpose. The requirement should be rephrased in such a way, that appropriate tools should be in place, that immediate investigation is possible, which product was placed on which market (member state), and at what time. The register is nowadays more data based or paper based list to support such a requirement, and not to support the QP in his responsibility to maintain and provide transparency. Proposed change: "*Certification* ***of a medicinal product*** *is recorded* ***by the qualified person*** *in a register* ***(including validated electronic registers)*** *or equivalent document..."*	

3.5.4		Comment: equivalence to EU GMP should be allowed (e.g. PIC/S GMP) to be consistent with section 2.2. Proposed change: "*All activities associated with manufacture and testing of the medicinal product have been conducted in accordance with the principles and guidelines of EU GMP,* ***or equivalent (e.g. PIC/S GMP)***."	
3.5.5		Comment: as long as the document describing the entire supply chain of the medicinal product is comprehensive and effective in providing the appropriate level of visibility and understanding to the QP, the format of such a document does not need to be defined in this Annex. Proposed change: to delete the last sentence: '*~~The document should preferably be in the format of a comprehensive diagram, where each party, including sub-contractors of critical steps such as e.g. the sterilisation of components and equipment for aseptic processing are included~~*''.	
3.5.9		Comment: the GDP reference in this paragraph relates to active substances; this should be clarified. Proposed change: *"… in accordance with Good Distribution Practices (GDP)* ***for active substances***".	
3.5.17		Comment: the term 'adverse trend' is not used in GMP Guidelines, and should be replaced with 'out of trend'. Proposed change: *"All investigations pertaining to the batch being certified (including out of specification and ~~adverse~~* ***out of*** *trend investigations) have been completed to a sufficient level to support certification*."	

3.5.18		Comment: it is written as a statement that any on-going complaints do not negate certification, whereas the opposite is intended, i.e. they may well impact the certification decision. Proposed change: *"~~Any~~ **No** on-going complaints, investigations or recalls ~~do not negate~~ **should prevent** the conditions for certification being met for the batch in question."*	
3.7.4		Comment: it should be clarified that this sentence refers to the sourced product. Proposed change: to amend the text as follows: "*The re-packager must ensure authenticity by verifying safety features **of the sourced product**, where applicable*."	
3.8.1		Comment: as per 3.5.3, the certification step should also make reference to the use of electronic registers. Proposed change: "*The certification of a medicinal product is recorded by the qualified person in a register **(including validated electronic registers)** or equivalent document..."*	
Section 4. Relying on GMP assessments by third parties, e.g. audits			
4, page 7/10		Comment: it should be clarified that in a global company, self-inspections may also include site and global auditors. Third party audits occur when an outside contractor is hired for specific audits (e.g. suppliers). Proposed change: to revise the Title as follows: "*Relying on GMP assessments **via self inspections, internal audits and 3rd party audits***. And to add: ***In a global company, self-inspections may include site and global auditors***."	

4.2, page 7/10		Comment: approval of audit reports should be under the QMS managed by the audit department. QPs should have transparency to the audit process. Proposed change: approval of audit reports should be covered under the QMS.	
Section 5. Handling of unplanned deviations			
5.2.2, page 8/10		Comment: 'Adverse effect' is a concept associated to safety. As quality and efficacy should be also be evaluated, negative impact is more clarifying and avoid different interpretations in different EU countries. Proposed change: replace 'adverse effect' by 'negative effect'	
5.2.4, page 8/10		Comment: this step is redundant with 5.2.2 and should be deleted. Proposal: to delete 5.2.4.	
5.3, page 8/10		Comment: by definition, every deviation has a potential impact on compliance with GMP. Proposed change: *"The QP performing certification should be aware and take into consideration any deviations which have potential impact ~~for compliance with GMP~~* ***on the product quality*** *or the Marketing Authorisation."*	
Section 6. The release of a batch			
6.1		Comment: a batch cannot be sold until it is released, but it should be possible to move it under the quarantine system of the company. Proposed change: Until a batch is released it should remain at the site of manufacturing or be shipped under the quarantine system of the company.	

Content of the confirmation			
		Comment: the QP confirms that the manufacturing stage has been carried out in full compliance with terms of the Technical Quality Agreement under point 5. Therefore, an additional reference to the Technical Quality Agreement under point 4 is superfluous. Proposed change: remove point 4.	