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Q&A – QP Declaration

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1. Why can an audit performed by a European National Health Authority not be used in order to support a QP Declaration? / Why is an on-site audit performed by the QP of the European manufacturing / batch release site now mandatory even if the site has been recently audited by a European National Health Authority and there is a European GMP Certificate available?

Answer (Human & Veterinary):

Please refer to the EMA's Q&A on Inspections/GMP: EU GMP guide part II: Basic requirements for active substances used as starting materials: GMP compliance for active substances, Question 2

2. Regarding the manufacturing chain of active substances, must the QP declaration consider only the final active substance manufacturer site and its intermediate, or does it need to consider the manufacturing sites of the raw-materials used for the first synthesis step (in case those sites are mentioned only on the restricted part of the drug master file, not being indicated in the applicant's part)?

Answer (Human & Veterinary):

The QP declaration should cover all sites involved in the manufacture of the active substance and its intermediates starting from the 1st use of the designated API starting material. All these manufacturing sites should be declared in the Applicant's Part of the ASMF. There is no need to declare the GMP compliance for the manufacturing sites of the starting materials; these sites are only provided in the Restricted Part of the ASMF.

3. When the only change in an updated CEP is the name of the HOLDER (the manufacturing site remains the same) what is the rationale for requiring a new QP Declaration?

Answer (Human & Veterinary):

Please refer to the Commission guideline on Variations:

- the relevant category, conditions and documentation highlighted here:

B.III CEP / TSE / MONOGRAPHS

B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: **For an active substance** **For a starting material / reagent / intermediate used in the manufacturing process of the active substance**	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph			

1. New certificate from an already approved manufacturer	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IAIN**
2. Updated certificate from an already approved	**1, 2, 3, 4, 8**	**1, 2, 3, 4, 5**	**IA**

(….)

Conditions	
1.	The finished product release and end of shelf life specifications remain the same.
2.	Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3.	The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4.	For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier.
5.	The active substance/starting material/reagent/intermediate/excipient is not sterile.
6.	The substance is not included in a veterinary medicinal product for use in animal species susceptible to TSE.
7.	For veterinary medicinal products: there has been no change in the source of material.
8.	For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.
9.	If Gelatine manufactured from bones is to be used in a medicinal product for parenteral use, it should **only** be manufactured in compliance with the relevant country requirements.
10.	At least one manufacturer for the same substance remains in the dossier.
11.	If the active substance is a not a sterile substance but is to be used in a sterile medicinal product then ccording to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.

Documentation	
1.	Copy of the current (updated) Ph. Eur. Certificate of Suitability.
2.	In case of an addition of a manufacturing site, the variation application form should clearly outline the “present” and “proposed” manufacturers as listed in section 2.5 of the application form.
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format.
4.	Where applicable, a document providing information of any materials falling within the scope of the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* including those which are used in the manufacture of the active substance/ excipient. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. For the Centralised Procedure, this information should be included in an updated TSE

Documentation	
	table A (and B, if relevant).
5.	Where applicable, for active substance, a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the QP of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances - see the note under variation no. B.II.b.1. The manufacture of intermediates also require a QP declaration, while as far as any updates to certificates for active substances and intermediates are concerned, a QP declaration is only required if, compared to the previously registered version of the certificate, there is a change to the actual listed manufacturing sites.
6.	Suitable evidence to confirm compliance of the water used in the final steps of the synthesis of the active substance with the corresponding requirements on quality of water for pharmaceutical use.

Comment: Under "Documentation" p 5, it is stated:

"… as far as any updates to certificates for active substances and intermediates are concerned, a QP declaration is only required if, compared to the previously registered version of the certificate, there is a change to the actual listed manufacturing sites."

4. When a new API manufacturing site is added in an updated CEP, is it necessary to present a QP Declaration for the already approved API manufacturers?

Answer (Human & Veterinary):

It is stated in document 5 applicable to submission in category B.III.1.a.2: *"The manufacture of intermediates also require a QP declaration, while as far as any updates to certificates for active substances and intermediates are concerned, a QP declaration is only required if, compared to the previously registered version of the certificate, there is a change to the actual listed manufacturing sites"*. This means that it is acceptable to submit a QP declaration mentioning only the new manufacturer(s). A new QP declaration is not required if the update only concerns a change in the name and/or address while the actual site(s), including plots/buildings, remain the same.

5. A CEP has 2 manufacturing sites A and B (both sites perform complete manufacture of the API). The MAH wishes to approve only manufacturing site A. It this acceptable to register only manufacturing site A and therefore submit a QP declaration only for site A?

Answer (Human & Veterinary):

This situation is considered acceptable as long as it is clearly stated in relevant parts of the dossier in order to accept omission of QP declaration from site B.

Relevant parts of the dossier also include module 1 (human) or part I (veterinary): QP declaration, application form.

If, in this scenario, manufacturing site B is ever added to the authorization, a valid QP declaration needs to be provided for both sites (A and B).

6. How should the information on change in Qualified Person be notified to the National Competent Authorities?

Answer (Human & Veterinary):

A change in Qualified Person is not classified as a variation with respect to marketing authorisations and as such does not need to be notified to the National Competent Authorities in this context. However such changes may need to be notified in the context of the relevant manufacturing authorisation.

7. Which Qualified Person declaration(s) are required in support of individual types of changes to a Marketing Authorisation, to confirm that the active substance is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union?

Answer (Human & Veterinary):

Active substance manufacturer:

In case of addition of a new active substance manufacturer or updating of information about an already approved API manufacturer which involves a new site, supported by a CEP (B.III.1 - all relevant sub-categories, including z), ASMF and Module 3 data (human) or part II (veterinary) (B.I.a.1 – all relevant sub-categories, including z), QP declarations should be provided from each of the registered finished product manufacturing and batch release sites located in the EU/EEA. The declarations should cover all new intermediate and API manufacturers, as reported in the 3.2.S section of the dossier (human) or in the section 2.C (veterinary).

Finished product manufacturer:

In case of addition of a new finished product manufacturer (B.II.b.1.c, B.II.b.1.d, B.II.b.1.e, B.II.b.1.f or B.II.b.1.z), as a minimum QP declarations should be provided from the proposed new finished product manufacturer (if located within EU/EEA), as well as at least one of the registered EU/EEA batch release sites. In fact, as reported in the note of the classification guideline to variations under category B.II.b.1, as the QP responsible for batch certification takes overall responsibility for each batch, a further declaration from the QP responsible for batch certification is expected when the batch release site is a different site from the site which is added with the proposed variation. The declarations should cover all registered drug substance manufacturing sites (main and intermediate manufacturing sites).

In case of addition of a new finished product manufacturer which is also responsible for batch release or simultaneous addition of a new finished product manufacturer and a new batch release site (grouping of variations including at least one variation under both categories B.II.b.1 and B.II.b.2.c), as a minimum QP declarations should be provided from the new batch release site, as well as the proposed new finished product manufacturer (when located within EU/EEA, if different from the former).

It should be noted that, regardless of what is presented in terms of QP declarations in relation to the specific variations for the introduction of a new finished product manufacturer in the above scenarios, the absence of QP declaration(s) from any other relevant responsible registered manufacturer (product

and batch release) does not imply any restrictions in terms of the full registered supply chain arrangements nor limit any site from its ongoing responsibilities. Site audits are expected to be carried out on a regular basis of each registered drug substance manufacturer (main and intermediate) by each relevant registered EU/EEA based manufacturer (product and batch release), unless underpinned by a technical agreement, and the outcome notified to regulatory authorities to reflect satisfactory ongoing GMP compliance.

Batch release site:

In case of addition of a new batch release site (B.II.b.2.c.1, B.II.b.2.c.2, B.II.b.2.c.3 or B.II.b.1.z), a QP declaration should be provided from the proposed new batch release site, covering all registered drug substance manufacturing sites (main and intermediate manufacturing sites).

In each of the three cases described above, when more than one EU/EEA based manufacturing authorisation holder, i.e. finished product manufacturer(s) which potentially use the active substance as starting material and/or batch release site(s), are involved, rather than provide multiple declarations, it may be acceptable to provide a single declaration signed by one QP. This will be accepted provided that: the declaration makes it clear that it is signed on behalf of all the involved QPs. The arrangements are underpinned by a technical agreement as described in Chapter 7 of the GMP Guide and the QP providing the declaration is the one identified in the agreement as taking specific responsibility for the GMP compliance of the active substance manufacturer(s).

In addition, it should be noted that in accordance with the requirements of change code A.8 and CMDh's and CMDv's published Q&As on variations (specifically 2.12a and 2.12b), it is also possible, as a means of "otherwise transmitted", to include any new QP declaration(s), which reflect the positive outcomes of any new site audits as part of any one of these Type IB and II, B-category variations and this approach is encouraged. In these cases, no separate variation application for the change in the audit date has to be submitted. However, the change has to be clearly mentioned in the scope of the application form as well as under "present/proposed".