EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Guidance for the template for the qualified person's declaration concerning GMP compliance of active substance manufacture "The QP declaration template"

1. Introduction

The objective of this guidance and the Qualified Person (QP) declaration template is to emphasise the importance of providing a valid declaration, to harmonise the format for the declaration, to forestall questions during assessment, and to enhance the efficiency of the regulatory process, including the timely processing of relevant regulatory submissions.

Applicants are therefore strongly recommended to use the template to facilitate the validation of regulatory submissions and their review.

Guidance on the provision of the QP declaration is given in European Commission *Guidelines of 16.05.2013 on the details of the various categories of variations.*[1]

In summary, this states:

- Marketing authorisations require a QP declaration to confirm that the active substance has been manufactured in accordance with Good Manufacturing Practice (GMP) for medicinal products for human and veterinary use, Part II: Basic Requirements for Active Substances used as Starting Materials[2].
- Unless covered by an agreement as stated in the next bullet point, a QP declaration is required from each registered EEA manufacturer and Importer Authorisation Holder (MIAH) that uses the active substance as a starting material and/or is responsible for QP certification of the finished batch of a human or veterinary medicinal product.
- When more than one MIAH is involved, rather than provide multiple declarations it may be acceptable to provide a single declaration signed by one QP – if the declaration is clear that:
  - it is signed on behalf of all the involved QPs;
  - the arrangements are underpinned by a technical agreement;
  - 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).

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- That according to Article 46a (1) of Directive 2001/83/EC[3] and Article 50a (1) of Directive 2001/82/EC[4], manufacture includes complete or partial manufacture, import, dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or re-labelling as carried out by a distributor of a starting material (active substance).

MIAHs (using the active substance as a starting material and / or QP batch certification sites) should therefore act appropriately to:

- Verify the GMP compliance for each registered active substance manufacture, even if this site is not routinely used.
- Define and fully understand the supply chain and verify that active substances used in the manufacture of medicinal products have been sourced through this supply chain.
- Where the MIAH is not directly responsible for audit of the active substance manufacturing site(s), the QP of the MIAH should ensure that appropriate technical arrangements / agreements are in place with the companies responsible for such audits.

2. The basis of the QP declaration

Audit

For human and veterinary medicinal products, the QP declaration should be based upon an audit of the active substance manufacturers[5]. It is established good practice that the audit should be conducted at the manufacturing site i.e. an on-site audit[6].

Audits should be by or on behalf of the MIAH, by suitably trained and experienced person(s), who may be a third party contractor[7].

The audit cannot be replaced by GMP certificates from a relevant competent authority[8].

Scope

With respect to the application of GMP for products for human use, ICH Q11[9], states, *"Each branch of a convergent drug substance manufacturing process begins with one or more starting materials. The GMP provisions described in ICH Q7 apply to each branch beginning with the first use of a starting material. Performing manufacturing steps under GMP together with an appropriate control strategy provides assurance of quality of the drug substance."*

The GMP Basic Requirements for Active Substances used as Starting Materials[2] apply to each branch beginning with the first use of the starting material(s) (as designated in the quality module / section of the regulatory submission) at all active substance manufacturing sites, including intermediate sites.

For active substances for biological medicinal products, reference should be made to volume 4 GMP Guidelines including Annex 2 "Manufacture of biological active substances and medicinal products for human use" and Annex 5 "Manufacture of immunological veterinary medicinal products."

For chemically synthesised active substances, it is acknowledged that details of the suppliers of designated starting materials may be confidential. Their suitability should be assessed indirectly by audit of the active substance manufacturer's quality system for starting materials.

3. Application of the QP declaration

The QP declaration applies to all human and veterinary medicinal products.

A QP declaration is required to be submitted with all applications for new marketing authorisations, renewals and submissions of relevant quality variations, concerning changes (addition or replacement) to the manufacturer of a starting material and / or to the registered manufacturer(s) of the active substance, finished product or batch importation/certification sites[1]. This is irrespective of the means by which the data requirements for the active substance are met – by either EDQM Certificate of Suitability (CEP), Active Substance Master File (ASMF) or full details in the dossier.

If site changes are introduced during the regulatory review procedure, then a new declaration will need to be provided.

The QP declaration is not required:

- (a) for blood or blood components; these are not medicinal product and are subject to the requirements of Directive 2002/98/EC[10];
- (b) from MIAH sites that do not use the active substance as a starting material, e.g. packaging only sites, quality control testing sites.

4. Format of the QP declaration template

The attached QP declaration template provides a suitable means for documenting confirmation that the active substance manufacture complies with GMP requirements.

The format of the QP declaration template is in five parts (Parts A to E).

PART A: Concerned active substance manufacturing sites

The name of the active substance should be stated.

The name and address of each manufacturing site to be registered that is involved in the manufacture of the active substance should be stated, beginning from the first use of the designated starting material.

All sites should be stated, including intermediate sites.

For EDQM CEPs, the MIAH should confirm with the active substance manufacturer, the names and addresses of all sites involved, including any intermediate manufacturing sites in case these are not openly declared on the CEP.

The manufacturing operation / activity of each site should be stated e.g. complete synthesis, intermediate synthesis, micronisation.

The site address should be provided in detail to ensure that the site is accurate, e.g. where appropriate building numbers should be included in the address.

In the case of an intermediate, which is itself an active substance and is supported by either an independent ASMF or CEP, the sites of manufacture for this intermediate should also be registered in the marketing authorisation and be the subject of a QP declaration.

PART B: Manufacturing / Importer Authorisation Holder(s) (MIAHs) to which this QP declaration applies

As stated in the introduction, declarations are required from the QP of each registered EEA MIAH (using the active substance as a starting material and / or QP batch certification). When more than one MIAH is involved, rather than provide multiple declarations, it may be acceptable to provide a single declaration signed by one QP.

In this section, the relevant MIAHs for which the QP declaration is applicable should be listed.

The registered MIAH site, number and manufacturing activity should be provided.

PART C: Basis of the declaration

An on-site audit is expected and this should be confirmed by completion of the section (i) tick box.

Where the auditor's on-site access is unreasonably restricted or not permitted by the active substance manufacturer, then alternative sources should be sought on public health grounds.

Exceptional circumstances, when an on-site audit is not practical (e.g. atypical actives[11]), are out of scope of the declaration template.

An off-site, remote or "paper-based" audit may be justifiable in terms of benefit risk, but this can only be considered on a case-by-case basis.

In these cases, a suitable quality system is expected to be applied by the active substance and finished product manufacturers. As a principle, such controls must provide confidence that the active substance is fit for purpose and will not negatively affect the safety and efficacy of the medicinal product. The QP is expected to justify the controls in place on a scientific basis and record a risk assessment on a product specific basis[6].

Specific guidance addresses the case of non-traditional (or atypical) active substances[11] and veterinary ectoparasiticides[12].

In these exceptional circumstances, the QP declaration should be supported by:

- (a) the justification for assessment of GMP compliance in lieu of on-site audit;
- (b) a listing of the documents forming the basis of the off-site audit, for example - questionnaires, review of documents, ISO 9000 certification, results of analytical testing and historical experience with the supplier, and risk analysis.

Section (ii) sites audited, auditors and date of audit

The audit of the active substance manufactured at the site(s)s listed in PART A may be completed either by MIAH(s) or by a third party body(ies) i.e. contract acceptor(s) on behalf of the MIAHs i.e. contract giver(s).

The table should be completed with the relevant MIAH(s) as contract givers and auditing body(ies) as contract acceptors. If the audit is undertaken by the MIAH (or corporate representative, within the same group of companies) then the auditing body column should be left blank.

The site that has been audited and the date of audit should be stated.

Audits of each site for GMP compliance should be undertaken at regular intervals, normally within three years. Justification should be provided if the date since the last audit exceeds this period.

Section (iii) supplementary information

Section (iii) refers to supplementary information that may be attached to the QP declaration to support a risk-based approach by the manufacturer in establishing priorities for its own audit programme[8].

For example, results of inspection report(s) or GMP certificate(s) issued by EEA, Mutual Recognition Agreement (MRA) partners or other recognised authority together with other supporting information may be submitted[13].

With respect to human medicines, this may also include the written confirmation of GMP compliance from the competent authority of the exporting third country, according to Article 46b(2)(b) of Directive 2001/83/EC.

A listing of relevant attachments should be given in the table provided.

PART D: QP declaration

This section consists of a list of statements that form the QP declaration.

The QP in signing the QP declaration is confirming that these statements are correct and are the basis by which the regulatory submission may be approved.

The statements relate to the following components:

QP responsibility

The signatory confirms that he or she is the authorised QP with specific responsibility for GMP compliance of the active substance manufacture and that audit reports and all other documentation relating to the QP declaration will be made available for inspection by competent authorities, if requested.

GMP compliance

The signatory confirms that the manufacture of the active substance complies with GMP, that this is based on an audit and that the audit outcome confirms compliance with GMP.

Audit

The signatory confirms, in the case of third part audit(s), that each contract acceptor has been evaluated and technical agreements are in place.

The signatory also confirms, in all cases, that the audits were conducted by suitably qualified and trained staff.

Responsibilities in the case of multiple MIAH(s):

The signatory confirms that the declaration is made on behalf of all the involved QPs named on the relevant MIAH(s) specified in Part B and that a documented procedure defining GMP responsibilities is in place and that technical agreements exist between the named companies concerning management of GMP responsibilities.

Part E: Name and signature of QP responsible for this declaration

The declaration is signed and the relevant details of the QP are provided (name, status, and MIAH name and number). The QP details should be consistent with those named within the relevant regulatory submission application form and/or the Manufacturing Authorisation (if applicable).

The QP template allows the entry of an optional reference number.

Applicants are reminded that, according to Art. 41 of Directive 2001/83/EC and Article 45 of Directive 2001/82/EC, Manufacturing Authorisation holders shall have at their disposal at least one Qualified Person located in the EEA. Therefore declarations from persons employed by manufacturers in third countries, including those located within MRA partner countries, are not acceptable. The latter may, however be used to provide supportive information for the QP declaration – see PART C (iii).

References

1. Guidelines of 16.05.2013 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.
http://ec.europa.eu/health/files/eudralex/vol-2/2013_05_16_c2804_en.pdf

2 ENTR/F/2/AM/an D(2010) 3374, The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Part II: Basic Requirements for Active Substances used as Starting Materials.
http://ec.europa.eu/health/files/eudralex/vol-4/2007_09_gmp_part2_en.pdf

3 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version: 21/07/2011). http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83/2001_83_ec_en.pdf

4 Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products (Official Journal L 311, 28/11/2001 p. 1 - 66). (consolidated version : 18/7/2009). http://ec.europa.eu/health/files/eudralex/vol-5/dir_2001_82_cons2009/dir_2001_82_cons2009_en.pdf

5 European Medicines Agency: Inspections: Q&A: Good Manufacturing Practice (GMP)

EU GMP guide part II Basic requirements for active substances used as starting materials: GMP compliance for active substances

Q1: How can GMP compliance for active substance manufacturers be demonstrated?

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800296ca&jsenabled=true

6 European Medicines Agency: Inspections: Q&A: Good Manufacturing Practice (GMP)

EU GMP guide part II Basic requirements for active substances used as starting materials: GMP compliance for active substances

Q3 Is it acceptable to perform a remote assessment based on, for example, questionnaires, review of documents, ISO 9000 certification, results of analytical testing and historical experience with the supplier? - H+V July 2006

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&mid=WC0b01ac05800296ca#section2

7 European Medicines Agency: Inspections: Q&A: Good Manufacturing Practice (GMP)

EU GMP guide part I Basic requirements for medicinal products: Chapter 5 Qualification of suppliers. Q1 Is an audit performed by a third party acceptable?
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800296ca&jsenabled=true#section10

8 European Medicines Agency: Inspections: Q&A: Good Manufacturing Practice (GMP)

EU GMP guide part II Basic requirements for active substances used as starting materials: GMP compliance for active substances

Q2: Do I need to perform an audit of an active substance supplier if it has been inspected by an inspectorate from an EEA member state and a valid GMP certificate is available? http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800296ca&jsenabled=true

9 CHMP/ICH/425213/2011, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use guideline Q11 on development and manufacture of drug substances (chemical entities and biotechnological / biological entities). http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/06/WC500107636.pdf

10 Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (Official Journal L 33, 8/2/2003 p. 30 - 40). http://ec.europa.eu/health/files/eudralex/vol-1/dir_2002_98/dir_2002_98_en.pdf

11 European Medicines Agency: Inspections: Q&A: Good Manufacturing Practice (GMP)

EU GMP guide part II Basic requirements for active substances used as starting materials: GMP compliance for active substances

Q6: The Notice to Applicants requires the submission of a declaration signed by the Qualified Person that the active substance used is manufactured in accordance with GMP.

The active substance in my product is widely used, but not normally as a pharmaceutical active substance, and I am having some difficulty in confirming compliance.

What should I do to furnish the required declaration?

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000027.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac05800296ca&jsenabled=true

12 ENTR/F/2/AM/an D(2010) 3374, The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Part II: Basic Requirements for Active Substances used as Starting Materials, Chapter 1.2, page 5. http://ec.europa.eu/health/files/eudralex/vol-4/2007_09_gmp_part2_en.pdf

13 European Medicines Agency: Inspections: Mutual Recognition Agreements

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000248.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058005f8ac

All sites accessed 1 May 2014.