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Annex
to the Guide to Good Manufacturing Practice for medicinal products:

CERTIFICATION BY A QUALIFIED PERSON AND BATCH RELEASE

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Annex to
Guide to Good Manufacturing Practice for Medicinal Products:

Certification by a Qualified Person and Batch Release.

1. Scope

This annex gives guidance on the certification by a Qualified Person (QP) and batch release of medicinal products within the European Community (EC) or European Economic Area (EEA). It covers the situation where a batch has had different stages of manufacture or testing conducted by different manufacturers and where a bulk production batch is divided into more than one finished product batch. It also includes the release of batches which have been imported to the EC/EEA both when there is and is not a mutual recognition agreement between the Community and the third country.

This annex does not address the official control authority batch release which may be specified for certain blood and immunological products in accordance with Article 3 of Directives 89/342/EEC and 89/381/EEC and the general administrative procedure in relation to a particular marketing authorisation.

2. Principle

2.1 The legislative provisions for batch control, QP certification and batch release of medicinal products manufactured both within the Community and in third countries are contained in Article 22 of Council Directive 75/319/EEC or Article 30 of Council Directive 81/851/EEC. These require that each finished product batch of medicinal product sold or supplied in the EC/EEA undergoes batch release within the EC/EEA following certification by a QP within the EC/EEA.

2.2 The purpose of controlling batch release in this way is:

-to ensure that the batch has been manufactured and controlled in accordance with its marketing authorisation, the principles and guidelines of EC Good Manufacturing Practice or the good manufacturing practice of a third country recognised as equivalent under a mutual recognition agreement and any other relevant legal requirement before it is placed on the market,

-and, in the event that a defect needs to be investigated or a batch recalled, to ensure that the relevant QP and records are readily identifiable.

3. Introduction

3.1 Manufacture including quality control testing of a batch takes place in stages which may be conducted at different sites and by different manufacturers, including manufacturers in third countries. Each stage should be conducted in accordance with the relevant marketing authorisation, Good Manufacturing Practice and the laws of the Member State concerned and should be taken into account by the QP who certifies the finished product batch before release to the market.

3.2 However in an industrial situation it is usually not possible for a single QP to be involved with every aspect of manufacture and he may need to rely in part on advice and decisions of others. Before so doing, the QP who certifies the batch before release should ensure that this reliance is well founded. This may be achieved by personal knowledge of the facilities and procedures employed, the expertise of the persons concerned and of the quality system within which they operate. It may also be achieved when another QP has certified the correct performance of an intermediate stage of manufacture within a quality system approved by the QP who certifies the finished product batch.

4. General

4.1 Where reference is made in this annex to a written agreement, the agreement should be in general accordance with Chapter 7 of the Guide to GMP and the arrangements should be validated. Such an agreement might be made between different sites of the same company as part of a corporate quality system or between different organisations; in the latter case it should constitute a formal contract.

Such an agreement should include an obligation on the part of the provider of a bulk or intermediate product to notify the recipient(s) of any deviations, out-of-specification results, non-compliance with GMP, investigations, complaints or other matters which should be taken into account by the QP who is responsible for certifying the finished product batch.

4.2 The sites for manufacture or importation, testing and release of a product should be stated and approved in the marketing authorisation. These sites and those used for storage before release should be approved under a manufacturing authorisation and be under the procedural control of a QP.

4.3 Different batches of a centrally authorised product may be manufactured or imported and released at more than one site in the EC/EEA, for example in different member states, when justified to and authorised by the competent authority. In this case the marketing authorisation holder and each site authorised to release batches of the product should be able to identify from records the site at which any particular batch has been released and the QP who was responsible for certifying that batch.

4.4 When a computerised system is used for recording batch release, particular note should be taken of the guidance in paragraph 19 of Annex 11 to this Guide.

4.5 A batch certification and release by a QP in the EC/EEA should be recognised by other QPs and should not be repeated on the same batch provided the batch has remained within the EC/EEA.

4.6 More stringent requirements than are described in this annex may be imposed by the competent authority when considered necessary, for example when a particularly complex manufacturing process is involved

4.7 Whatever particular arrangements are made for certification and release of batches, it should always be possible to identify and recall without delay all products which may be affected by a batch failure which could render them hazardous..

5. Batch testing and release of products manufactured in EC/EEA

5.1 ***All manufacture occurs at a single authorised site.***

When all production and control stages are carried out at a single authorised site, the conduct of certain checks and controls may be delegated to others but the QP who certifies the finished product batch retains responsibility for these within a defined quality system.

5.2 ***Different stages of manufacture are conducted at different sites within the same company.***

Then different stages of manufacture are carried out at different authorised sites within the same company (which may or may not have the same manufacturing authorisation) each stage should be under the responsibility of a QP. The certification of the finished product batch should be performed by a QP of the manufacturing authorisation holder responsible for releasing the batch to the market, who may take account of the certification of the earlier stages by the relevant QPs responsible for those stages in accordance with a written agreement between them.

5.3 ***Certain intermediate stages of manufacture are contracted to a different company.***

One or more intermediate production or control stages may be contracted to a holder of a manufacturing authorisation in another company**.** A QP of the contract giver may take account of the certification of the relevant stage by a QP of the contract acceptor but is responsible for ensuring that this work is conducted within the terms of a written agreement. The certification of the finished product batch should be done by a QP of the manufacturing authorisation holder responsible for releasing the batch to the market.

5.4 ***A bulk production batch is assembled at different sites into finished product batches and released under a single marketing authorisation.***

5.4.1 This may occur, for example, when a bulk production batch is divided and assembled into different language packs in different member states all under the same marketing authorisation.

5.4.2 A QP of the manufacturing authorisation holder making the bulk production batch may certify all the finished product batches before release to the market. In doing so he may take account of the certification of assembly from the QPs of the assembly sites. The arrangements should be defined in written agreements.

5.4.3 Alternatively the certification of each finished product batch before release to the market may be performed by a QP of the manufacturer who has conducted the final assembly operation. In doing so he may take account of the certification of the bulk production batch by a QP of the manufacturer of the bulk batch. The arrangements should be defined in written agreements.

5.4.4 In all cases there should be one QP who has overall responsibility for all finished product batches which are derived from one bulk production batch and are released to the market. The duty of this person, who should normally be a QP of the manufacturer of the bulk production batch, is to be aware of any quality problems reported on any of the finished product batches and to co-ordinate any necessary action. The arrangements to achieve this should be defined in written agreements.

5.5 ***A bulk production batch is assembled at different sites into several finished product batches and released under different marketing authorisations***.

5.5.1 This may occur, for example, when a multi-national organisation holds national marketing authorisations for different member states or when a generic manufacturer purchases bulk products and assembles them for sale under his own marketing authorisation.

5.5.2 A QP of the assembler who certifies the finished product batch may take account of the certification of the bulk production batch by a QP of the bulk product manufacturer.

5.5.3 Any problem identified in any of the finished product batches which may have arisen in the bulk production batch should be communicated to the QP responsible for certifying the bulk production batch, who should then take any necessary action in respect of <u>all</u> finished product batches produced from the suspected bulk production batch.

5.5.4 The arrangements should be defined in a written agreement.

5.6 ***A finished product batch is purchased and released to the market by a manufacturing authorisation holder in accordance with his own marketing authorisation.***

5.6.1 This may occur, for example, when a generic company holds a marketing authorisation for products made by another company, purchases finished products and releases them under its own manufacturing authorisation in accordance with its own marketing authorisation.

5.6.2 A QP of the purchaser must certify the finished product batch before release. In doing so he may take account of the certification of the batch by the QP of the vendor manufacturer in accordance with a written agreement between them.

5.7 ***Testing is done in a laboratory authorised under a different manufacturing authorisation***.

A QP certifying a finished product batch may take account of testing and results certified by another QP as complying with the relevant parts of the marketing authorisation and GMP. The other laboratory and QP do not need to be in the same member state as the manufacturing authorisation holder releasing the batch but there should be a written agreement between them. In the absence of such certification the QP should himself have personal knowledge of the laboratory as described in Section 3.2.

6. Batch testing and release of products imported from a third country.

6.1 *General*.

6.1.1 Importation of finished products should be conducted by an importer as defined in Section 8.

6.1.2 Each batch of imported finished product should be certified by a QP acting for the importer before release for sale in the EC/EEA.

6.1.3 Unless a mutual recognition agreement has been concluded between the Community and the third country, samples from each batch should be tested in the EC/EEA before certification of the finished product batch by a QP. Testing and importation need not necessarily be performed in the same member state.

6.1.4 The guidance in this section should also be applied where appropriate to the importation of partially manufactured products.

6.2 *A complete batch of medicinal product is imported.*

The batch should be certified by a QP of the importer before release. This QP may take account of the certification of the checking, sampling or testing of the imported batch by a QP of another manufacturing or importation authorisation holder in accordance with a written agreement.

6.3 *A part of a finished product batch is imported.*

The part batch should be certified by the QP of the importer before release.

6.4 *A further part of a finished product batch is imported to the same or a different site.*

6.4.1 A QP of the importer receiving a subsequent part of the batch may take account of the testing and certification by a QP of the first part of the batch. If this is done, the QP should ensure, based on evidence, that the two parts do indeed come from the same batch, that the subsequent part has been transported under the same conditions as the first part and that the samples that were tested are representative of the whole batch.

6.4.2 One QP, normally the QP of the importer of the first part of a batch, should take overall responsibility for recording the importation and subsequent traceability of all parts of the batch within the EC/EEA. He should be made aware of any quality problems reported on any of the parts of the batch and should co-ordinate any necessary action. This should be ensured by a written agreement between all the importers of parts of the batch.

6.4.3 The conditions in paragraphs 6.4.1 and 6.4.2 are most likely to be met when the manufacturer in the third country and the importer(s) in the EC/EEA belong to the same organisation operating under a corporate system of quality assurance.

If the QP cannot ensure that the above conditions are met, each part of the batch should be treated as a separate batch.

6.5 ***Location of sampling for testing in EC/EEA***.

Samples should be representative of the batch. In order to achieve this it may be necessary to take some samples during processing, necessarily in a third country when products are imported. However to represent conditions of the batch after storage and transportation and to ensure sampling is supervised by the QP other samples should be taken after receipt of the batch in the EC/EEA.

Any samples taken in a third country should either be shipped with and under the same conditions as the batch which they represent, or if sent separately it should be demonstrated that the samples are still representative of the batch, for example by defining and monitoring the conditions of storage and shipment. The taking of samples in the third country and their shipment to EC/EEA for testing should be justified on technical grounds and described in the application for the marketing authorisation

[NOTE: this section only refers to the taking of samples for testing before batch release. Other samples are required for retention and reference.]

7. Batch testing and release of products imported from a third country with which the EC has a mutual recognition agreement.

7.1 Unless otherwise specified, an MRA does not remove the requirement for a QP within the EC/EEA to certify a batch before it is released for sale or supply within the EC/EEA. However in accordance with the particular agreement concerned and in place of further testing, the QP of the importer may rely on the manufacturer's statement that the batch has been made in accordance with the GMP of the third country and has been tested and complies with its marketing authorisation. The QP may certify the batch for release when he is satisfied with this statement and that the batch has been transported under the required conditions and has been received and stored in the EC/EEA by an importer as defined in section 8.

7.2 Other requirements, including those for receipt and certification of part batches at different times and/or at different sites, are the same as in section 6.

8. Glossary

Definitions given below apply to words used in this annex. They may have different meanings in other contexts. relevant to this annex

Batch: [DRAFTING NOTE: For convenience of readers the definition in the glossary to the Guide to GMP is repeated here. It will be removed from the annex when published].
A defined quantity of … product processed in one process or series of processes so that it could be expected to be homogeneous.

Bulk production batch: the batch of product, of a size described in the application for a marketing authorisation, completed to the stage either of product ready for assembly into final containers or individual containers ready for assembly to final packs. (A bulk production batch may, for example, consist of a bulk of liquid, a bulk of tablets, or filled ampoules).

Finished product batch: for the control of the finished product, a batch of finished product is defined in Part 2 section E 1 of the annexes to Directives 75/318/EEC and 81/852/EEC. In the context of this annex the term in particular denotes the batch of product in its final pack for release to the market.

Finished product batch number: a unique reference (either letters or numbers or a combination of both) which identifies a particular batch of a finished product. While the batch numbers of the bulk and finished product batches are not necessarily the same, there should be a link between the two numbers so that an audit trail can be established.

Bulk production batch number: a unique reference which identifies a particular batch of bulk product.

Certification of the finished product batch: the certification in a register or equivalent document by a QP, as defined in Article 22 of Directive 75/319/EEC and Article 30 of Directive 81/851/EEC, before a batch is released for sale or distribution.

Importer: the holder of the authorisation required by Article 16.3 of Directive 75/319/EEC or Article 24.3 of Directive 81/851/EEC required for imports coming from third countries.

Mutual Recognition Agreement (MRA): An MRA, according to its particular nature, may constitute the 'appropriate arrangement' between the Community and an exporting country mentioned in Article 22.1 of Directive 75/319/EEC and Article 30 of Directive 81/851/EEC.

Qualified Person (QP): the person defined in Article 21 of Directive 75/319/EEC or Article 29 of Directive 81/851/EEC.

Revision history.

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