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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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Transmission of draft 4 to interested parties	December 1999
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Transmission of draft 6 to interested parties	January 2001
Comments expected	15 March 2001
Adoption at Pharmaceutical Committee	
PROPOSED DATE FOR COMING INTO OPERATION	

Rapporteur's Notes on draft 6:

1 Changes have been incorporated after formal consultation on draft 4 and consideration by the Drafting Group and the Commission's Working Party on Control of Manufacturer's and Inspections. The most significant change, and the reason for consulting again with interested parties, is the addition of a new Section 8 on the duties of a Qualified Person (Q.P).

2 It has been suggested that guidance should be added specifically on investigational medicinal products (IMPs) in view of the proposed Directive on regulation of clinical trials and its requirement for a Q.P. to certify batches of IMPs. Apart from a brief reference to IMPs under Scope (#1.1), this suggestion has not been accepted because it is felt that any issues which are peculiar to IMPs, either more or less than the guidance in this annex, should be put in annex 13 (IMPs) which is now being revised.

1. Scope

1.1 This annex to the Guide to Good Manufacturing Practice for Medicinal Products ("the Guide") gives guidance on the certification by a Qualified Person (Q.P) and batch release within the European Community (EC) or European Economic Area (EEA) of medicinal products holding a marketing authorisation or made for export. The relevant legislative requirements are contained in Article 22 of Council Directive 75/319/EEC or Article 30 of Council Directive 81/851/EEC.

1.2 The annex covers in particular those cases where a batch has had different stages of production or testing conducted at different locations or by different manufacturers, and where an intermediate or bulk production batch is divided into more than one finished product batch. It also covers 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. The guidance may also be applied to investigational medicinal products, subject to any difference in the legal provisions and more specific guidance in Annex 13 to the Guide.

1.3 This annex does not, of course, describe all possible arrangements which are legally acceptable. Neither does it 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.

1.4 Nothing in this annex should be taken as overriding arrangements for batch certification and release approved in a particular marketing authorisation.

2. Principle

2.1 Each batch of finished product must be certified by a Q.P. within the EC/EEA before being released for sale or supply in the EC/EEA or for export.

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

- to ensure that the batch has been manufactured and checked in accordance with the requirements of 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 Q.P. who certified the batch and the relevant records are readily identifiable.

3. Introduction

3.1 Manufacture, including quality control testing, of a batch of medicinal products takes place in stages which may be conducted at different sites and by different manufacturers. 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 Q.P. 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 Q.P. to be closely involved with every stage of manufacture. The Q.P. who certifies a finished product batch may need therefore to rely in part on the advice and decisions of others. Before doing so he should ensure that this reliance is well founded, either from personal knowledge or from the confirmation by other Q.Ps within a quality system which he has accepted.

3.3 When some stages of manufacture occur in a third country it is still a requirement that production and testing is in accordance with the marketing authorisation, that the manufacturer is authorised according to the laws of the country concerned and that manufacture follows good manufacturing practices at least equivalent to those of the EC.

3.4 Certain words used in this annex have particular meanings attributed to them, as defined in the glossary.

4. General

4.1 One batch of finished product may have different stages of manufacture, importation, testing and storage before release conducted at different sites. Each site should be approved under one or more manufacturing authorisations and should have at its disposal the services of at least one Q.P. However the correct manufacture of a particular batch of product, regardless of how many sites are involved, should be the overall concern of the Q.P. who certifies that finished product batch before release.

4.2 Different batches of a product may be manufactured or imported and released at different sites in the EC/EEA. For example a Community marketing authorisation may name batch release sites in more than one member sate, and a national authorisation may also name more than one release site. In this situation the holder of the marketing authorisation and each site authorised to release batches of the product should be able to identify the site at which any particular batch has been released and the Q.P. who was responsible for certifying that batch.

4.3 The Q.P. who certifies a finished product batch before release may do so based on his personal knowledge of all the facilities and procedures employed, the expertise of the persons concerned and of the quality system within which they operate. Alternatively he may rely on the confirmation by one or more other Q.Ps of the compliance of intermediate stages of manufacture within a quality system which he has accepted. This confirmation by other Q.Ps should be documented and should identify clearly the matters which have been confirmed. The systematic arrangements to achieve this should be defined in a written agreement.

4.4 The agreement mentioned above is required whenever a Q.P. wishes to rely on the confirmation by another Q.P. The agreement should be in general accordance with Chapter 7 of the Guide. The Q.P. who certifies the finished product batch should ensure the arrangements in the agreement are verified. 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 even if within the same group.

4.5 The 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 Q.P. who is responsible for certifying the finished product batch.

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

4.7 Certification of a finished product batch against a relevant marketing authorisation by a Q.P. in the EC/EEA need not be repeated on the same batch provided the batch has remained within the EC/EEA.

4.8 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 could be rendered hazardous by a quality defect in the batch.

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

5.1 *When all manufacture occurs at a single authorised site*

When all production and control stages are carried out at a single site, the conduct of certain checks and controls may be delegated to others but the Q.P. at this site who certifies the finished product batch normally retains personal responsibility for these within a defined quality system. However he may, alternatively, take account of the confirmation of the intermediate stages by other Q.Ps on the site who are responsible for those stages.

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

When different stages of the manufacture of a batch are carried out at different sites within the same company (which may or may not be covered by the same manufacturing authorisation) a Q.P. should be responsible for each stage. Certification of the finished product batch should be performed by a Q.P. of the manufacturing authorisation holder responsible for releasing the batch to the market, who may take personal responsibility for all stages or may take account of the confirmation of the earlier stages by the relevant Q.Ps responsible for those stages.

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

One or more intermediate production and control stages may be contracted to a holder of a manufacturing authorisation in another company. A Q.P. of the contract giver may take account of the confirmation of the relevant stage by a Q.P. 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 Q.P. 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 several finished product batches which are released under a single marketing authorisation.This could occur, for example, under a national marketing authorisation when the assembly sites are all within one member state or under a Community marketing authorisation when the sites are in more than one member state.*

5.4.1 One alternative is for a Q.P. of the manufacturing authorisation holder making the bulk production batch to certify all the finished product batches before release to the market. In doing so he may either take personal responsibility for all manufacturing stages or take account of the confirmation of assembly by the Q.Ps of the assembly sites.

5.4.2 Another alternative is for the certification of each finished product batch before release to the market to be performed by a Q.P of the manufacturer who has conducted the final assembly operation. In doing so he may either take personal responsibility for all manufacturing stages or take account of the confirmation of the bulk production batch by a Q.P. of the manufacturer of the bulk batch. The arrangements should be defined in written agreements.

5.4.3 In all cases of assembly at different sites under a single marketing authorisation, there should be one person, normally a Q.P. of the manufacturer of the bulk production batch, who has an overall responsibility for all released finished product batches which are derived from one bulk production batch. The duty of this person is to be aware of any quality problems reported on any of the finished product batches and to co-ordinate any necessary action arising from a problem with the bulk batch. The arrangements to achieve this should be defined in written agreements.

While the batch numbers of the bulk and finished product batches are not necessarily the same, there should be a documented link between the two numbers so that an audit trail can be established

5.5 *A bulk production batch is assembled at different sites into several finished product batches which are released under different marketing authorisations. This could occur, for example, when a multi-national organisation holds national marketing authorisations for a product in several member states or when a generic manufacturer purchases bulk products and assembles and releases them for sale under his own marketing authorisation.*

5.5.1 A Q.P. of the manufacturer doing the assembly who certifies the finished product batch may either take personal responsibility for all manufacturing stages or may take account of the confirmation of the bulk production batch by a Q.P. of the bulk product manufacturer.

5.5.2 Any problem identified in any of the finished product batches which may have arisen in the bulk production batch should be communicated to the Q.P. responsible for confirming the bulk production batch, who should then take any necessary action in respect of all finished product batches produced from the suspected

bulk production batch. This arrangement 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. This could occur, for example, when a company supplying generic products holds a marketing authorisation for products made by another company, purchases finished products which have not been certified against his marketing authorisation and releases them under his own manufacturing authorisation in accordance with his own marketing authorisation.*

In this situation a Q.P. of the purchaser should certify the finished product batch before release. In doing so he may either take personal responsibility for all manufacturing stages or may take account of the confirmation of the batch by a Q.P. of the vendor manufacturer.

5.7 *The quality control laboratory and the production site are authorised under different manufacturing authorisations.*

A Q.P. certifying a finished product batch may either take personal responsibility for the laboratory testing or may take account of the confirmation by another Q.P. of the testing and results. The other laboratory and Q.P. need not be in the same member state as the manufacturing authorisation holder releasing the batch. In the absence of such confirmation the Q.P. should himself have personal knowledge of the laboratory and its procedures relevant to the finished product to be certified.

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 the glossary to this annex.

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

6.1.3 Unless a mutual recognition agreement is in operation between the Community and the third country (see Section 7), samples from each batch should be tested in the EC/EEA before certification of the finished product batch by a Q.P. Importation and testing need not necessarily be performed in the same member state.

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

6.2 *A complete batch or the first part of a batch of a medicinal product is imported*

The batch or part batch should be certified by a Q.P of the importer before release. This Q.P. may take account of the confirmation of the checking, sampling or testing of the imported batch by a Q.P. of another manufacturing authorisation holder.

6.3 *Part of a finished product batch is imported after another part of the same batch has previously been imported to the same or a different site.*

6.3.1 A Q.P. of the importer receiving a subsequent part of the batch may take account of the testing and certification by a Q.P. of the first part of the batch. If this is done, the Q.P. 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.

6.3.2 When different parts of the batch are released under the same marketing authorisation, one person, normally a Q.P. of the importer of the first part of a batch, should take overall responsibility for ensuring that records are kept of the importation of all parts of the batch and that the distribution of all parts of the batch is traceable within the EC/EEA. He should be made aware of any quality problems reported on any part of the batch and should co-ordinate any necessary action. This should be ensured by a written agreement between all the importers concerned.

6.3.3 The conditions in paragraphs 6.3.1 and 6.3.2 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 Q.P. cannot ensure that the conditions in paragraphs 6.3.1 and 6.3.2 are met, each part of the batch should be treated as a separate batch.

6.4 *Location of sampling for testing in EC/EEA*

6.4.1 Samples should be representative of the batch and be tested in the EC/EEA. In order to represent the batch it may be preferable to take some samples during processing in the third country. For example, samples for sterility testing may best be taken throughout the filling operation. However in order to represent the batch after storage and transportation some samples should also be taken after receipt of the batch in the EC/EEA.

6.4.2 When any samples are taken in a third country, they 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. When the Q.P. wishes to rely on testing of samples taken in a third country, this should be justified on technical grounds and described in the application for the marketing authorisation.

[*NOTE*: the above section only refers to the taking of samples for the purpose of quality control 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 (MRA).

7.1 Unless otherwise specified in the agreement, an MRA does not remove the requirement for a Q.P. within the EC/EEA to certify a batch before it is released for sale or supply within the EC/EEA. However, subject to details of the particular agreement, the Q.P. of the importer may rely on the manufacturer's confirmation that the batch has been made and tested in accordance with its marketing authorisation and the GMP of the third country. and need not repeat the full testing. The Q.P. may certify the batch for release when he is satisfied with this confirmation 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 procedures**,** including those for receipt and certification of part batches at different times and/or at different sites, should be the same as in Section 6.

8. Routine duties of a Qualified Person

8.1 Before certifying a batch prior to release the Q.P. doing so should ensure, with reference to the guidance above, that at least the following requirements have been met:

a) the batch and its manufacture comply with the provisions of the marketing authorisation (including the authorisation required for importation where relevant);

b) manufacture has been carried out in accordance with Good Manufacturing Practice or, in the case of a batch imported from a third country, in accordance with good manufacturing practice standards at least equivalent to EC GMP;

c) the principal manufacturing and testing processes have been validated; account has been taken of the actual production conditions and manufacturing records;

d) any deviations or planned changes in production or quality control have been authorised by the persons responsible in accordance with a defined system. Any changes requiring variation to the marketing or manufacturing authorisation have been notified to and authorised by the relevant authority;

e) all the necessary checks and tests have been performed, including any additional sampling, inspection, tests or checks initiated because of deviations or planned changes;

f) all necessary production and quality control documentation has been completed and endorsed by the staff authorised to do so;

g) all audits and inspections have been carried out as required by the quality assurance system;

h) all relevant factors have been considered including any not specifically associated with the batch to be certified.

A Q.P. may have additional duties in accordance with national legislation or administrative procedures.

8.2 A Q.P. who confirms the compliance of an intermediate stage of manufacture, as described in paragraph 4.3, has the same obligations as above in relation to that stage unless specified otherwise in the agreement between the Q.Ps.

8.3 A Q.P. should maintain his knowledge and experience up to date in the light of technical and scientific progress and changes in quality management relevant to the products which he is required to certify.

8.4 If a Q.P. is called upon to certify a batch of a product type with which he is unfamiliar, for example because the manufacturer for whom he works introduces a new product range or because he starts to work for a different manufacturer, he should first ensure that he has gained the relevant knowledge and experience necessary to fulfil this duty.

In accordance with national requirements the Q.P. may be required to notify the authorities of such a change and may be subject to renewed authorisation.

9 Glossary

Certain words and phrases in this annex are used with the particular meanings defined below. Reference should also be made to the Glossary in the main part of the Guide.

Bulk production batch*:* a batch of product, of a size described in the application for a marketing authorisation, either ready for assembly into final containers or in 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 of filled ampoules).

Certification of the finished product batch: the certification in a register or equivalent document by a Q.P., 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.

Confirmation*:* a signed statement that a process or test has been conducted in accordance with GMP and the relevant marketing authorisation, as agreed in writing with the Q.P. responsible for certifying the finished product batch before release. *Confirm* and *confirmed* have equivalent meanings.

Finished product batch: with reference to the control of the finished product, a finished product batch 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.

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 for importing medicinal products from third countries.

Mutual Recognition Agreement (MRA): the 'appropriate arrangement' between the Community and an exporting third country mentioned in Article 22.1 of Directive 75/319/EEC and Article 30 of Directive 81/851/EEC.

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

Revision History

Draft	Description	Date
Draft 1	Based on EMEA Policy paper for centrally authorised products dated 17/2/99, Commission's Concept paper dated 9/4/99 and a meeting Between the Commission, the drafting group and representatives of trade associations on 4/6/99	23/6/99
Draft 2	Includes amendments introduced at drafting group meeting on 14/7/99	14/7/99
Draft 3	Includes amendments introduced following discussion at ad hoc meeting of inspectors on 15 July 1999	28/7/99
Draft 3.1	Includes amendments introduced in the light of comments following Informal consultation with industry representatives and at ad hoc meeting of inspectors on 16/9/99; adopted, subject to minor changes, by the pharmaceutical committee for formal consultation	22/9/99
Draft 3.2	Includes minor amendments introduced in the light of comments from the drafting group	18/11/99
Draft 4	Includes further minor amendments introduced in the light of comments at ad hoc meeting of inspectors on 25/11/99 prior to distribution for formal consultation	28/11/99
Draft 4	With addition of proposed changes and comments added for consideration by the drafting group and then the Commission's Expert Working Party on Inspections	26/06/00
Draft 5.0	Incorporating the agreed changes	05/11/00
Draft 5.1	Spelling and editorial corrections	10/11/00
Draft 6	Minor amendments from Inspections meeting Dec. 2000 and some rearrangement of text	06/01/01