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NOTE FOR GUIDANCE ON MANUFACTURE OF THE FINISHED DOSAGE FORM

Re-Issue *

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MANUFACTURE OF THE FINISHED DOSAGE FORM

Note for Guidance

Concerning the application of Part 2, section B of the Annex to Directive 75/318/EEC,
as amended by Directive 91/507/EEC,
with a view to the granting of a marketing authorisation.

[EMA status as of April 1996]

1. INTRODUCTION

According to Directive 65/65/EEC, an application for a marketing authorisation shall contain a brief description of the method of preparation.

This is described in more detail in the Annex, Part 2 of Directive 91/507/EEC, which states:

"The description of the method of preparation [...] shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.

For this purpose it shall include at least:

- Σ mention of the various stages of manufacture, so that an assessment can be made of whether the processes employed in producing the pharmaceutical form might have produced an adverse change in the constituents,
- Σ in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product,
- Σ the actual manufacturing formula, with the quantitative particulars of all the substances used, the quantities of the excipients, however, being given in approximate terms in so far as the pharmaceutical form makes this necessary; mention shall be made of any substances that may disappear in the course of manufacture; any overage shall be indicated and justified,
- Σ a statement of the stages of manufacture at which sampling is carried out for in-process control tests, where other data in the documents supporting the application show such tests to be necessary for the quality control of the finished medicinal product,
- Σ experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the product,
- Σ for sterile products, details of the sterilisation processes and/or aseptic procedures used."

This Note for Guidance provides guidance on the background and the interpretation of some aspects of the text of the Directive.

This Note for Guidance does not pertain to biological medicinal products such as vaccines, sera, toxins and allergens, products derived from human blood and plasma as well as medicinal products prepared biotechnologically.

2. THE APPLICATION FOR MARKETING AUTHORISATION AND GMP

Medicinal products on the market in the EC should be produced under the EC Rules for Good Manufacturing Practice (GMP), see Directive 91/356/EEC.

Many general elements of GMP and quality assurance do not need to be described in the application for marketing authorisation. Examples are qualifications of key personnel, cleaning procedures for the production equipment and production areas, final packaging and labeling procedures etc.

In general, the dossier for marketing authorisation should contain only those elements of the quality assurance which are specific for the medicinal product, whereas non product related elements of the quality assurance fall within the field of GMP, consequently, no description is necessary in the application for a marketing authorisation.

This Note for Guidance addresses the items that should be presented in the application for a marketing authorisation. For items not to be covered by the application for a marketing authorisation, the obligation for adherence to the EC GMP principles is implicit.

3. MANUFACTURING FORMULA

The intended batch size should be indicated.

An application for a variable and/or alternative batch size should be justified. Consistent conformity of the finished product to all the specifications should be made plausible.

The names and quantities of all ingredients used in the course of the manufacture should be stated. This includes ingredients which are removed from the product during the production process, such as solvents. Substances that may not always be used should also be mentioned, such as acids and alkalis for pH adjustment. Overages must be indicated in quantitative terms and justified in the section on Development Pharmaceuticals.

For each ingredient, the allowed upper and lower acceptance limits for the actual quantity of each ingredient from the nominal quantity of the batch manufacturing formula should be stated.

For active ingredients, these acceptance limits should be within 95 to 105% of the nominal quantity; for excipients, acceptance limits of 90 to 110% of the nominal quantity are acceptable without further justification.

Wider acceptance limits may be acceptable but should be justified by showing that batches with a composition close to the upper and lower proposed acceptance limits remain within the finished product specifications.

When that the quantity of an active ingredient to be used is calculated from the actual assay value of the batch of that active ingredient ("factorisation"), this has to be indicated. If another ingredient is used to keep the total mass per batch equal to the quantity provided for in the batch manufacturing formula, this should also be indicated.

4. DESCRIPTION OF THE MANUFACTURING PROCESS

A description of the manufacturing process should be given.

A proposal to allow alternative steps in the manufacturing process (for instance: two alternative sterilisation methods for the container) should be accompanied by evidence showing that all processes proposed will consistently produce a finished product in compliance with the specifications.

If relevant (see below), the apparatus to be used has to be described. The in-process controls and corresponding acceptance limits need to be described as well, when relevant (see below).

The various steps in the manufacturing process and corresponding in-process controls should also be shown in a flow-chart.

The presented data on the manufacturing process, apparatus and in-process controls are binding for the future manufacturing of the medicinal product, unless authorisation for changes is given by the Competent Authority.

It is in the interest of both the applicant and the regulatory authorities to avoid unnecessary applications for variations. Very detailed descriptions of the manufacturing process, apparatus and in-process controls should therefore be avoided.

In selecting the necessary level of detail the following should be considered:

- Σ the testing at release of the finished product,
- Σ the description of the manufacturing process and apparatus,
- Σ the in-process controls and validated acceptance limits.

Together these should provide a high degree of probability that each unit of every batch of the finished product, will be in conformity with the specifications.

So, if the consistent quality of a medicinal product can be fully safeguarded by the "implicit" production under GMP and testing of the finished product at release, the description of the manufacturing process need not be comprehensive, and apparatus and in-process controls need not to be described.

However, many quality parameters that are tested at release do not provide sufficient certainty of the quality of the whole batch from a statistical point of view, because the quality parameter may not necessarily be homogeneous within the batch.

An example is the homogeneous distribution of the active ingredient in solid and semi-solid dosage forms, i.e. content uniformity. Testing at release alone does not provide sufficient certainty for the content uniformity of the whole batch from a statistical point of view.

So, the apparatus to be used and the appropriate in-process controls (i.e. mixing time, mixing speed etc.) and the validated acceptance limits for these in-process controls (see below) must be proposed in the application file.

Another example is sterilisation. For all sterilisation processes, appropriate in-process controls and their acceptance limits are to be described in the application file, see below.

5. DESCRIPTION OF THE MANUFACTURING CHAIN

An account shall be given of the sites at which each stage of the manufacturing and assembly operations takes place. Different manufacturing sites belonging to the same company shall be

mentioned as separate units. The company responsible for the final approval of the release of the product onto the market shall be specified.

6. VALIDATION DATA OF THE MANUFACTURING PROCESS

Validation studies that are used to identify critical steps in non-standard manufacturing processes are part of the Development Pharmaceuticals, and should be described in Part IIA of the application file.

Examples are: new dosage forms, the manufacturing of liposomes, etc.

Irrespective of these Development Pharmaceutical process validations, process Validation results of the actual production process must be described in Part IIB if conformity to the finished product specifications cannot be guaranteed to an acceptable degree of statistical certainty by testing the finished product at release. This holds also for standard manufacturing processes.

Examples are mixing, granulation and emulsifying processes of solid and semi-solid dosage forms and non-pharmacopoeial sterilisation procedures, see below.

Process validation data obtained with closely related medicine products may be acceptable.

Please note that notwithstanding a successful process validation, the quality parameters related to the validated process should be specified under the release specifications and end-of-shelf-life specifications. For instance, sterility should always be specified at release and end-of-shelf-life, notwithstanding a successful validation of the sterilisation process. Also, the content uniformity of solid and semi-solid dosage forms should be specified in the release and end-of-shelf life specifications, notwithstanding a successful process validation with respect to homogeneity.

It may be acceptable to refrain from the routine testing at release of such a specification ("parametric release"), see the Note for Guidance "Specifications and Control Tests on the Finished Product". With respect to parametric release in relation to sterilisation, the text of the Ph. Eur. "Methods of preparation of sterile products" is to be observed.

7. SPECIAL ITEMS

7.1 Method of sterilisation

The choice of the method of sterilisation should be justified under Development Pharmaceuticals, Part IIA.

According to the text of the Ph. Eur.: "Methods of preparation of sterile products", terminal sterilisation in the final container is to be preferred. Refraining from terminal sterilisation in the final container should be justified in the application file.

In Part IIB the actual sterilisation process to be applied should be described.

All sterilisation processes should be carried out according to the instructions of the Ph. Eur. In the application file, an explicit statement should be made that the instructions of the Ph. Eur. are followed.

According to the Ph. Eur., all sterilisation procedures should be validated and be carried out under the EC GMP-rules. However, in the application file for marketing authorisation for

some sterilisation procedures no, or only limited validation data and data on the bioburden of the product prior to the sterilisation need to be presented, see below.

In the case of terminal sterilisation in the final container by heat using a reference condition of the Ph. Eur., only the time and temperature of the cycle and the acceptance limits of the corresponding in-process controls need to be provided in the application file.

So, this holds for sterilisation by saturated steam at a minimum of 121 °C for 15 min. and by dry heat at a minimum of 160 °C for at least 2 hours.

In accordance with the Ph. Eur., these conditions should be met within all units. However, the validation data showing that all units are subjected to these conditions are normally not required in the application file. They may be requested by the competent authorities in certain circumstances.

For terminal sterilisation cycles in the final container by heat with a time and/or temperature below the values of the reference conditions of the Ph. Eur., not only the acceptance limits for the in-process controls for time and temperature should be stated, but also the maximum acceptable bioburden before sterilisation.

The results of the validation of the sterilisation cycle with regard to the effectiveness in terms of the Sterility Assurance Level (SAL) obtained should be presented in the application file.

For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be stated in the application. In most situations NMT 10 CFU's/100 ml will be acceptable, depending on the volume to be filtered in relation to the diameter of the filter. If this requirement is not met, it is necessary to use a pre-filtration through a bacteria-retaining filter to obtain a sufficiently low bioburden.

The type of bacteria-retentive filter, and its pore size should also be described in the application. Pore sizes of 0.22 µm or less are acceptable without further justification, in accordance with the Ph. Eur. A proposal to use a larger pore size in combination with an additional sterilisation step has to be validated and justified in the application file.

Results of media filling fall within the field of GMP and need not be presented routinely in the application for marketing authorisation but may be requested by the competent authorities in certain circumstances.

For sterilisation by gamma and electron radiation, see the Note for Guidance "The Use of Ionization Radiation in the Manufacture of Medicinal Products".

For sterilisation by ethylene oxide, the provisions laid down in the Note for Guidance "Limitations to the use of Ethylene Oxide in the manufacture of medicinal products" should be followed, i.e. its use as a sterilisation method is only acceptable if no other method of sterilisation is available.

The application for marketing authorisation should contain a description of the apparatus, quantitative data on the mixture of gases to be used, data on the bioburden prior to sterilisation, the time of exposure of the gas, the temperature and humidity prior to and during the sterilisation cycle, and the conditions for the removal of ethylene oxide. All these conditions should be monitored by suitable in-process controls that are to be described together with the acceptance limits for these in-process controls.

Results of the process validation should be presented to justify these acceptance limits for the in-process controls. The results should demonstrate both an acceptable assurance, of sterility and removal of ethylene oxide to an acceptable level.

Limits of NMT 1 ppm of ethylene oxide (if applicable, measured by means of a simulated use extraction method) and NMT 50 ppm of ethylene chlorhydrin (or any other halogenated ethylenehydrin) are acceptable without further justification, once sterilisation by ethylene oxide has been justified.

Notwithstanding successful process validation, a limit for residual ethylene oxide, and the corresponding validated analytical method, should be included in the product release- and end-of-shelf-life specifications.

7.2 Re-processing of residual product

Procedures for the re-processing of residual product of non-biological medicinal products fall within the field of GMP and need not to be described in the marketing authorisation dossier.

7.3 Removal of solvents or gases

If toxic gases or solvents are used in the manufacture of the finished product, release and end-of-shelf-life specifications for maximum acceptable residues of these solvents or gases should be proposed for the product. A justification for the proposed limits can be presented if required in Part IIA, Part IIB or IIE of the file. Both toxicological and technological aspects should be discussed in this justification.

Stages of the manufacturing process which affect the levels of such materials in the product should be controlled by in-process controls and the acceptance limits for these in-process controls should be validated. The results of these process validations should be presented in the application for marketing authorisation; see the paragraph in 7.1 above on ethylene oxide sterilisation.

7.4 Cleaning of primary packaging material

Washing procedures of the primary containers and closures normally fall within the field of GMP and are not needed routinely in the application for marketing authorisation but may, in certain circumstances, be requested by the Competent Authority.

7.5 Sterilisation of primary packaging material

Where applicable, the sterilisation procedure of the primary containers and closures should be described, and, when necessary, validated according to the paragraph on sterilisation.

7.6 Production areas

Details on the production area, i.e. specifications for the microbiological quality of the areas and freedom from particles in the air normally fall within in the field of GMP and are not needed routinely in the application for marketing authorisation but may, in certain circumstances, be requested by the Competent Authority.