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NOTE FOR GUIDANCE ON PARAMETRIC RELEASE

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1. INTRODUCTION

A medicinal product must comply with the requirements stated in the authorised specifications for release and shelf life. Nevertheless, this does not mean that all tests in the specifications have to be carried out on the finished product before release (1). The manufacturer may obtain assurance that the product is of stipulated quality - meets its specification - through a system called parametric release. Parametric release is based on evidence of successful validation of the manufacturing process and review of the documentation on process monitoring carried out during manufacturing to provide the desired assurance of the quality of the product.

The definition of parametric release used in this document is based on that proposed by the European Organisation for Quality, EOQ. Accordingly, parametric release is a system of release that gives assurance that the product is of the intended quality based on the information collected during the manufacturing process and on the compliance with specific GMP requirements related to parametric release.

Consequently, parametric release is used as an operational alternative to routine release testing of certain, specific parameters. The implementation of parametric release is in line with the text in the European Pharmacopoeia.

2. SCOPE

This document is intended to outline the requirements for applications that propose parametric release for finished products**.** The guideline highlights the different requirements that have to be fulfilled in the application and during the inspection, respectively, and has therefore been developed jointly by the CPMP/CVMP Quality Working Party and the Ad Hoc Group of Inspectors of the EMEA**.**

The principle of parametric release may be applied during the stages of manufacture of different products resulting in the elimination of certain, specific tests of the finished product. This document focuses on parametric release of products replacing the sterility test because more experience is at present available with such applications.

3. PARAMETRIC RELEASE

3.1 Parametric release and sterilisation

Parametric release is referred to in the monograph ”Methods of preparation of sterile products” in the European Pharmacopoeia (2). This states ”When a fully validated terminal sterilisation method by steam, dry heat or ionising radiation is used, parametric release, that is the release of a batch of sterilised items based on process data rather than on the basis of submitting a sample of the items to sterility testing, may be carried out, subject to the approval of the competent authority.”

Parametric release can only be applied to products terminally sterilised in their final containers. The statistical limitations of the sterility test in predicting sterility assurance are well known. Approval for parametric release eliminates the requirement for a finished product sterility test as a condition for batch release. The release of each batch is dependent on the successful demonstration that pre-determined, validated sterilising conditions have been achieved throughout the load. All relevant sterilisation parameters e.g. temperature, pressure and time, must be accurately controlled and measured.

3.2 Process monitoring

Process monitoring may be applied to other manufacturing processes, such as tabletting, on the basis of manufacturing history and appropriate testing at various stages in the process. Some parameters are usually checked routinely at defined intervals regardless of the design of the

manufacturing process of a tablet. Uniformity of mass, crushing strength and disintegration are such examples. The results of a comprehensive set of in-process tests and controls in these cases may constitute sufficient grounds for batch release and provide greater assurance of the finished tablet meeting certain criteria in the specification without the tests being repeated on a sample of the finished product.

Other examples are the use of process analytical chemistry test methods, such as vibrational spectroscopy techniques like near infrared spectroscopy (NIR) and Raman spectroscopy, usually used in combination with multivariate analysis. Spectral data monitored on-line controlling content of active substance, polymorphism, water content, blending homogeneity, particle/powder properties or film thickness could thereby replace end-product testing like e.g. uniformity of content, tablet strength and drug dissolution**.**

When parametric release is applied, the attribute that is indirectly controlled (e.g. sterility, uniformity of content) together with a reference to the associated test procedure, should still be included in the specifications. However, the relation between end-product testing and process monitoring, including acceptance criteria, should be justified.

4. ASSESSMENT OF APPLICATIONS

In general the documentation submitted for a new market authorisation or a variation should contain only those elements of the quality assurance that are specific for the medicinal product. The quality assurance of elements not specific to the product falls within the field of GMP.

It is likely that in most cases, parametric release will be introduced following a variation of an existing market authorisation when more experience has been gained with the manufacture of the product. However, parametric release may also be considered suitable where a new product is very similar to an existing product and test data for the closely related product are considered relevant.

The assessment of applications is made with close collaboration between assessors and inspectors as each has different tasks. The opinion of the inspector is obtained, which includes the evaluation of a risk analysis of the sterility assurance system, and included in the overall assessment of the application. Approval as well as withdrawal of parametric release is at the discretion of the Competent Authority**.** A withdrawal may be based on the results of an inspection or on the receipt of other information.

With the exception of sterility testing an approval may also be qualified by requiring a running in period of reduced confirmatory testing.

5. MANUFACTURING PROCESSES

5.1 General

For some dosage forms, the different stages of manufacturing process will be discrete, thus allowing sampling at critical parts of distinct stages of the process. For other dosage forms, the manufacturing process may be more or less continuous, necessitating a more integrated process monitoring. It is therefore not possible to specify in a guideline, specific details of how parametric release can be applied. This must be assessed in each individual case verifying that the requirements of appropriate Notes for Guidance are met.

The authorisation of the parametric release programme will be granted on the basis of an assessment of how well the manufacturing process concerned is founded. The demonstration of the robustness through to the final validation of the manufacturing process will therefore be assessed. Monitoring of critical parameters must be capable of demonstrating that pre-determined validated conditions have been achieved throughout the batch. In addition, evaluators will assess the choice and limits of the critical parameters in relation to their effect on the

technical characteristics, stability and bioavailability of the product and its packaging. Methods of controlling critical parameters will also be assessed.

The application that proposes parametric release must be based on sufficient experience with the process, evaluation of the historical compliance to GMP as well as to current compliance. The general basis upon which an authorisation may be granted should include documentation that shows

- that the manufacturing process is validated adequately,
- that it is reliably controlled,
- relation between end-product testing and process monitoring, including justification of acceptance criteria
- that in process requirements chosen for approval/rejection are decided on the basis of the acceptance criteria defined in the validation records,
- that clear, specified procedures are in place describing the reporting and actions to be taken on approval/rejection
- historical batch data.

GMP compliance will be covered during inspections. Routine inspections are carried out in accordance with the general procedures of the Competent Authority concerned. The basic EU-GMP, annex 1 on manufacture of sterile products and other relevant annexes are used as the reference (3). In connection with evaluation of applications for parametric release pre-authorisation inspections should normally be carried out. Exceptions might be justified when the product applied for is similar to another product that is produced at the same manufacturing site and has approval for parametric release. If so the inspector will use the annex 17 on parametric release as reference (3) and focus the inspection on the accuracy of the process, the programmes for revalidation and change control. The in process controls and procedures are checked to be in accordance with the process described in the application and with the assessment report as a reference. As regards sterile products the inspector will on all inspections check that standard operating procedures for the various stages in the manufacturing process that are of significance for sterility are in place. In particular, the procedures for quality control of starting materials, packaging materials, process water and environmental monitoring are checked. Other aspects of importance are for example filtration procedures, equipment cleaning/sterilisation procedures, maximum holding times for bulk solutions and quality of the cooling medium.

5.2 Sterilisation processes

The sterilisation process in an application for parametric release of sterility must be in accordance with the requirements of the European Pharmacopoeia. Consequently, parametric release can only be applied to products sterilised in their final containers by moist heat, dry heat or radiation (2). The choice of a sterilisation process must be well founded considering both the knowledge of the stability of the product under relevant conditions and the data gained in development studies where critical process parameters are identified.

5.2.1 Sterilisation by heat

A sterilisation process shall be validated in accordance with GMP guidelines. Qualification of equipment and validation of the process which is applied at a particular time, including heat distribution and heat penetration studies with a given, established load pattern are thus carried out so that heat equivalents can be calculated. The technical validation of a heat sterilisation method shall be complemented by a biological validation. Consideration shall be given to the level and heat resistance of bioburden. When the sterilisation process has been defined, its reproducibility shall be demonstrated. Compliance with specific GMP requirements as described

in the annex 17 to the EU-GMP should also be demonstrated. An example of such a requirement is the segregation of non-sterile products from sterilised products.

An application for parametric release of sterility should be supported by

- a description of the sterilisation process including type of cycle, load pattern**,** specifications for cycle parameters **(**time, temperature, pressure**,** F_0-value**)** and chemical indicators (if applicable),
- specifications and methods/procedures applied for in-process controls e.g. pre-sterilisation bioburden, monitoring of cycle parameters and verification of load sterilisation,
- a process validation report comprising heat distribution and heat penetration studies for at least three runs, and a microbiological qualification showing sufficient efficacy (SAL) at the minimum level of the cycle including information on the biological indicators used (type, D-value, Z-value, stability), and bioburden characteristics (number, type, resistance) as applicable**,**
- package integrity data (if applicable).

In general**,** no new documentation is required regarding the sterilisation process. Reference could, where, applicable, be made to the previously submitted data.

Once parametric release has been granted, decisions for release or rejection of a batch must be based on the approved specification. Such a decision cannot be overruled by the use of sterility tests.

5.2.2 Sterilisation by radiation

Parametric release can also be applied in the case of sterilisation by radiation. The minimum absorbed dose should generally be 25 kGy. Lower doses can be acceptable if justified by low, routinely checked, bioburden levels and adequate validation data (ref. 4**,**5).

The same requirements regarding documentation as for sterilisation by heat must be met where applicable. The documentation shall comply with the guidelines defined by the EU in regard to ionising radiation.

6. REFERENCES

1. Ph Eur 3rd Ed., 1.2. (IV.2.) General Notices
2. Ph Eur 3rd Ed, 5.1.1, Methods of preparation of sterile products
3. The Rules governing Medicinal Products in the European Community, Volume 4 with annexes

4 NfG on The use of Ionisation Radiation in the Manufacture of Medicinal products (III/9109/90)

4. EN 552:1994, Sterilisation of medical devices – Validation and routine control of sterilisation by irradiation