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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

COMMITTEE FOR MEDICINAL PRODUCTS FOR VETERINARY USE (CVMP)

ANNEX II TO NOTE FOR GUIDANCE ON PROCESS VALIDATION CHMP/QWP/848/99 AND EMEA/CVMP/598/99 NON STANDARD PROCESSES

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Process Validation Guideline

ANNEX II – Non Standard Processes

Introduction

The Note for Guidance (ref CPMP/QWP/848/96) and (EMEA/CVMP/598/99) sets out the data to be included in a marketing authorisation application (MAA) in terms of validation of the manufacture of the medicinal product as described in Part 3.2.2 of Annex I to Directive 2003/63/EC and part 2.B of Directive 2001/82/EC. The Directive and the NfG specifically refer to "a non-standard method of manufacture". This Annex aims to set out what is understood by a "non-standard" manufacturing process and thereby to assist in the interpretation of the NfG.

The NfG on process validation (ref.CPMP/QWP/848/96) and (EMEA/CVMP/598/99) contains the following statements:

- Validation data should be generated for all products to demonstrate the adequacy of the manufacturing process. It is recognised that, at the time of submission, process validation data may not always be available.
- Where the manufacturing process utilises a non-standard method of manufacture, data demonstrating the validity of that method should be submitted in the marketing authorisation dossier.
- In certain cases, however it is considered necessary to provide production scale validation data in the MA dossier, e.g. in those circumstances where the applicant is proposing a non-standard method of manufacture is being used, where pilot-scale data may not be predictive of production scale or for specialised products such as certain modified release preparations.

Definition of Non-standard Processes

For the purposes of this NfG the designation of a process as non-standard is determined by a combination of the nature of the drug substance, the nature of the product, the actual process itself and the production experience of the manufacturer.

The following categories are examples of processes which could be considered as non-standard, and for which production scale validation data might need to be provided in the MAA dossier, unless otherwise justified.

1. The manufacture of specialised pharmaceutical dose forms
2. The incorporation of some new technology into a conventional process
3. (Highly) Specialised processes involving new technologies or an established process known, or likely, to be complex and therefore to require particular care
4. Non-standard methods of sterilisation

In addition a manufacturing process type not previously approved for pharmaceutical products within the EU is usually considered a non standard process. However it should be noted that a manufacturers own experience in the manufacture of specialised products or use of processes which might otherwise be considered "non standard", might exempt them from the need to provide production scale process validation data at the time of submission provided sufficient supporting data are provided. This needs to be justified on a "case-by-case" basis, on the basis of appropriate pharmaceutical development data or by reference to similar products.

The applicant should clearly state (in section 3.2.P3.5 of the dossier for human medicines, in section 2.B of the dossier for veterinary products) whether they consider the manufacturing process to be standard or non-standard and the justification for their decision should be presented.

1. Specialised Pharmaceutical Dose forms

A non exhaustive list of types of products which might be considered as "specialised", is provided below for illustrative purposes.

- Preparations for metered dose inhalation in the lungs e.g. pressurised metered dose inhaler (MDI's) and dry powder inhalers (DPI's)
- Suspension, emulsions or other liquid dispersed forms
- Prolonged release preparations
- Unit dose products containing drugs in low content (≤2% of composition)
- Other specialised dose forms eg parenteral depot preparations based on biodegradable polymers; liposomal preparations; micellar preparations.

2. Conventional pharmaceutical processes incorporating new technologies

A conventional process is well established and approved and for example could include such activities as tabletting using wet granulation. However the introduction of a new technology into such a conventional process eg a new drying technology not usually used by the pharmaceutical industry might result in the need for full-scale validation data based on a case by case consideration of the product and process development studies.

3. Specialised processes or established processes known to be complex

- Processes with critical steps such as lyophilisation, microencapsulation
- Processes where the physicochemical properties of the active substance or a key excipient (eg lubricant, coating agent) may give rise to processing or scale up difficulties, or stability problems during manufacture at larger scale for related products.

4. Non-standard methods of sterilisation

- Terminal sterilisation by moist heat using non-pharmacopoeial conditions
- Terminal sterilisation by irradiation using less than 25 KGy
- Aseptic processing unless otherwise justified
- Standard methods of sterilisation with related application for parametric release c/f Note for Guidance on Parametric Release.