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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

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NOTE FOR GUIDANCE ON PROCESS VALIDATION

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NOTE FOR GUIDANCE ON PROCESS VALIDATION

1. INTRODUCTION

Validation is the act of demonstrating and documenting that a procedure operates effectively. Process validation is the means of ensuring and providing documentary evidence that processes (within their specified design parameters) are capable of consistently producing a finished product of the required quality. In terms of pharmaceutical process validation it is intended that the combination of the guidance provided in the *Note for guidance on Development Pharmaceutics* with this guidance should cover all the critical elements in a manufacturing process for a pharmaceutical product, from development of the process through to final validation at the production scale. While it is recognised that the term validation is intended to apply to the final verification at the production scale (typically 3 production batches), the guidance presented here is intended to encompass the information that should routinely be included in the marketing authorisation application.

Since it is essential that only valid manufacturing processes be used, it is increasingly expected that data should be submitted in the application for marketing authorisation demonstrating the validity of a given process. In this regard it is clear that compliance with the finished product specification alone may be insufficient to demonstrate to the reviewer of the dossier that the processes are valid and that the manufacturer has full control over the manufacturing process. Thus in addition to batch analysis it may well be necessary to conduct further testing depending upon the complexity of the product and of the manufacturing process.

This note for guidance is intended to demonstrate and standardise the data that should be routinely included in the marketing authorisation dossier describing the evaluation or validation of the manufacturing process and distinguish them from those validation data which more properly fall under the remit of GMP Inspection. Scientific evaluation of the data on the manufacturing process and the control procedures described in the dossier is routinely carried out by the assessor prior to granting of the marketing authorisation.

It is recognised that at the time of submission of a marketing authorisation dossier manufacturers may not have completed formal validation studies on production scale batches. However the guideline will attempt to link the development and evaluation studies conducted on laboratory and pilot scale batches, process development and optimisation together with the production scale data (if available) or consideration of an appropriate process validation scheme to be applied to production scale batches of the product.

This scheme will form part of the application for marketing authorisation and should outline the formal studies planned for the production scale batches (normally three) before the product is placed on the market. The results of these studies should be available for verification by the supervisory authority according to national procedure.

Thus the progress from pre-formulation → formulation → pilot manufacture → industrial scale manufacture should be shown in the Marketing Authorisation Application dossier to be logical, reasoned and continuous.

2. SCOPE

This Note for Guidance is intended to give advice to the applicant for marketing authorisation in relation to studies to evaluate the manufacturing process and/or data which need to be generated to validate the processes used for the manufacture of the finished product.

In this regard, it is intended to supplement information requested and thereby provide a formal link between the related guidelines on development pharmaceutics, manufacture of the finished

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dose form and specification and control tests on the finished product.

The note for guidance is intended to apply to data generated to evaluate or validate the manufacturing process of the intended commercial dosage form only - it is not directly relevant to the manufacture of the active substance or other starting materials, although it may contain information useful for such activities. It is not intended to apply to products of biotechnological or biological origin including products extracted from human or animal tissues or fluids since these processes are themselves very complex in nature and have an inherent variability which generally require the submission of more extensive validation data. Nevertheless, the principles and practices outlined in this guideline may well also be useful in such more complex operations.

The note for guidance also applies to products manufactured outside the European Union to help to provide the reassurance necessary to demonstrate the suitability of the quality of the product for marketing within the E.U.

The guideline will also address issues such as additional data required on change of manufacturing site or change of process once marketing has been approved.

3. RELATIONSHIPS BETWEEN PRODUCT DEVELOPMENT, MANUFACTURING PROCESSES, PRODUCT SPECIFICATIONS AND VALIDATION

3.1 Relationship between development studies and process validation data

It is expected that during the development stage, the manufacturer of the product should gain sufficient information about the behaviour and the physical and chemical properties of the drug substance, the composition of the product in terms of active ingredient(s) and key excipients and the manufacturing process to clearly define the critical steps in the manufacturing process. Critical parameters of the product should be identified at an early stage; for example the dissolution rate of an active substance and the effect of the presence, type and amount of lubricant.

Information generated during the development stage should thus be used to identify and evaluate the critical pharmaceutical process parameters which may need to be examined and possibly controlled in order to ensure batch to batch reproducibility. In order to define these critical parameters it may be necessary to challenge the process by making deliberate changes to demonstrate the robustness of the process and define the limits of tolerance. Such parameters will vary depending upon the nature of the product, the composition and the proposed method of manufacture, as highlighted in the note for guidance "Development Pharmaceutics". The choice of the method of manufacture should be properly justified in the context of the development data obtained.

3.2 Relationship between method of manufacture and process validation data

Having defined and justified a particular method of manufacture based on a consideration of the physical and chemical properties of the active ingredient, the key excipients, the choice of formulation and the impact of processing on the product quality and stability, the applicant should progress to fully describe the manufacturing process (see *Note for guidance on Manufacture of the finished dosage form*).

Such a description should address also the need and value of in-process controls and the manufacturer's approach to process optimisation. The evaluation of the process should provide adequate proof of the feasibility of the process at the production scale thereby ensuring the consistent quality of the product in line with the approved specification.

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3.3 Relationship between Process Validation and the Specification of the Finished Product

The ICH guideline Q6A *Specifications for new drug substances and products* permits skip lot testing, i.e. replacement of routine verification of certain tests on a batch by batch basis.

In addition, data generated through process evaluation or validation can be used to justify why certain test need not be conducted routinely on the finished product at release. In such cases the applicant must explain and justify such an approach in Part IIE of the dossier and in the expert report and should cross-refer to this approach in Part IIB3.

The appropriate veterinary guidance on Specifications should also be consulted.

4. DATA SUBMISSION

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. Nevertheless it is essential that valid manufacturing processes are always utilised. Validation data should be held at the manufacturing location and made available for verification by the supervisory authority according to national procedure.

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. These data should be submitted from all sites where production is intended to take place.

The amount of data submitted in the dossier will depend to a certain extent on the nature and complexity of the product and the active ingredient, and the complexity, type and stage of development of the manufacturing process.

Data will be generated on different scales as the manufacturing process is developed.

4.1 Laboratory Scale Batches

These are produced at the research and early development laboratory stage; they may be of very small size (e.g. 100-1000x less than production scale). These batches may find many uses, for example to support formulation and packaging development, clinical and/or pre-clinical studies.

The data derived from these batches assist in the evaluation and definition of critical product performance characteristics and thereby enables the choice of the appropriate manufacturing process. Such experiments should be described in the section 'Development Pharmaceutics'. (Part IIA.4)

4.2 Pilot Batches

These may be used in the process development or optimisation stage, may be used to support formal stability studies and also to support pre-clinical and clinical evaluation. Pilot batch size should correspond to at least 10% of the production scale batch, i.e. such that the multiplication factor for the scale-up does not exceed 10.

For oral solid dosage forms this size should generally be 10% of production scale or 100,000 units whichever is the greater[1].

The role of pilot scale batches is to provide data predictive of the production scale product. It may be necessary to further develop and optimise the manufacturing process using pilot scale

[1] In the case of veterinary medicinal products, the minimum pilot batch size may be smaller than 100,000 units where justified.

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batches. The pilot batch therefore provides the link between process development and industrial production of the product.

The purpose of the pilot batch is to challenge the method proposed for routine production, i.e. to analyse and evaluate:

- the difficulties and critical points of the manufacturing process
- the apparatus and methods most appropriate to large-scale production.

To summarise, the production of pilot batches should provide a high level of assurance that the product and process will be feasible on an industrial scale.

4.3 Production-scale Batches

These batches are of the size which will be produced during the routine marketing of the product. Data on production scale batches may not always be available prior to granting marketing authorisation.

Where production scale data are not available or presented at the time of submission, the two stage approach outlined below should be followed.

First a thorough evaluation and characterisation of the critical process parameters at laboratory or pilot scale, followed by a formal validation programme on production scale batches for which the validation scheme (as outlined in Annex I) has been described to the regulatory authorities in the dossier (MAA) and for which the results can be subsequently verified by the supervising authority according to national procedure.

4.4 Data requirements

Since it is not generally considered useful to conduct full validation studies on pilot scale batches, the validation scheme outlined in Annex I should be completed for each product for subsequent verification at the production scale.

In certain cases however, it is considered necessary to provide production scale validation data in the marketing authorisation dossier, e.g. in those circumstances where the applicant is proposing a non-standard method of manufacture, where pilot scale data may not be predictive of production scale or for specialised products such as certain modified release preparations (for medicinal products for human use, see *Note for guidance on Modified release products*).

Non standard methods of manufacture would include non-standard methods of sterilisation and, aseptic processing. In some cases lyophilisation, micro-encapsulation, certain mixing and coating processes and other specialised processes may also be considered non-standard. Where non-standard sterilisation methods or aseptic processing are employed, data should be provided on three consecutive batches at production scale prior to approval. For other specialised non-standard processes, data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches, and by a history of consistent manufacture of products by essentially equivalent processes.

The studies should address those phases of manufacture, in particular the critical phases which would not necessarily be adequately addressed by application of the finished product specification alone, by conducting additional testing as necessary. A justification for the chosen process validation scheme and the verification strategy should be presented in the pharmaceutical expert report.

5. SCALE-UP

In order to avoid the repetition of lengthy and costly tests, it is necessary to gather information during properly designed development and process optimisation studies, when scaling up from

laboratory through pilot to production scale. Such information provides the basis for justification that scale-up can be achieved without a consequent loss in quality. Those parts of the process likely to be critical in scale-up should be identified in Part IIA of the dossier.

Where ranges of batch sizes are proposed, it should be shown that variations in batch size would not adversely alter the characteristics of the finished product. It is envisaged that those parameters listed in the Validation scheme (Annex I) will need to be re-validated once further scale-up is proposed post-authorisation.

6. CHANGE CONTROL

Clearly defined procedures are needed to control changes proposed in production processes. Such procedures should tightly control planned changes, ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specification and ensure that all aspects are thoroughly documented and approved. Such procedures are fundamentally part of GMP but may result in the need for variation in the marketing authorisation dossier requiring regulatory authority approval before implementation.

Minor changes in SOP's, equipment, environment etc. which can be shown not to have an impact on the quality of the final product are unlikely to need regulatory approval.

However, significant changes to processes (e.g. mixing times, drying temperatures), new equipment involving different design and operating parameters, which are likely to impact on product quality are likely to need prior regulatory authority approval, and the appropriate supporting data should be submitted by way of a variation to the marketing authorisation. In general terms very detailed description of processing instructions and equipment design need not be included in the dossier, otherwise prior approval by variation will be necessary before they can be altered.

The strategy proposed in Section 4.4 above should be followed in order to support such changes and the applicant should conduct full scale validation studies or provide pilot scale data together with the validation scheme outlined in Annex I, depending upon the nature of the product and process, in order to obtain regulatory approval.

Refer to guidance on Type I and Type II variations and regulations 541/95/EC and 542/95/EC as amended for further details.

ANNEX I

PROCESS VALIDATION SCHEME

Where validation data on production scale batches are not provided with the application, the validation scheme described below should be submitted by the applicant. This should outline the formal process validation studies to be conducted on production scale batches (usually 3 consecutive batches). The information from these studies will be available for verification post authorisation by the supervisory authority according to national procedure. The scheme should be submitted in the marketing authorisation dossier and should include the following information as a minimum:

- Short description of the process with a summary of the critical processing steps or critical parameters to be monitored during validation
- Finished Product Specification (release)
- Details of Analytical Methods (References to the dossier)
- In Process Controls proposed with Acceptance Criteria
- Additional testing intended to be carried out (e.g. with proposed acceptance criteria and analytical validation as appropriate)
- Sampling plan - where, when and how the samples are taken
- Details of methods for recording and evaluation of results
- Proposed Timeframe

Following completion of the scheme, a report containing the following information and signed by the appropriate authorised person should be generated for examination by the supervisory authority according to national procedure:

- Batch Analytical Data
- Certificates of Analysis
- Batch Production Records
- Report on unusual findings, modifications or changes found necessary with appropriate rationale
- Conclusions

Where the results obtained show significant deviations from those expected, the regulatory authorities need to be informed immediately. In such cases corrective actions should be proposed and any changes proposed in the manufacturing process should receive prior regulatory approval by way of variation.