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4 Guideline on process validation for the manufacture of 5 biotechnology-derived active substances and data to be 6 provided in the regulatory submission

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Guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission

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Executive summary

The guideline covers process validation of biotechnology-derived proteins used as active substance in the manufacture of medicinal products. This guideline addresses the data requirements for process validation for submission of a marketing authorisation application or variation. Process Validation can be based on a traditional or enhanced approach to process development. Traditional and enhanced approaches are not mutually exclusive. A company can use either a traditional approach or an enhanced approach to process validation, or a combination of both. Regardless of the approach followed, the validation data to be included in the regulatory submission should cover information relating to the evaluation and the verification of the manufacturing process.

1. Introduction

Process validation is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an active substance or intermediate meeting its predetermined specifications and quality attributes (ICH Q7).

Process validation studies should normally be completed and included in the marketing authorisation application or a variation application if relevant. It is acknowledged that process validation activities do not end at the time of the marketing authorisation, but continue through the lifecycle of the product and its process. This document addresses the information expected to be presented in a regulatory submission to demonstrate that the manufacturing process described in the Common Technical Document (CTD) section *S.2.2 Description of manufacturing process and process controls* consistently performs as intended. This information normally includes process evaluation and verification studies.

Process evaluation studies, performed at small and/or full scale, should **provide evidence** that the complete manufacturing process and each step/operating unit have been appropriately designed and are controlled to obtain a product of the intended quality.

Process verification studies should **confirm** that the final manufacturing process performs effectively and is able to produce an active substance or intermediate meeting its predetermined acceptance criteria, on an appropriate number of consecutive batches produced with the commercial process and scale.

Subsequent to successful process validation activities for regulatory submission, product quality and process performance must be maintained in a state of control throughout the commercial part of the product lifecycle. These activities have to be performed in compliance with EU Good Manufacturing Practices (GMP).

2. Scope

This document provides guidance on the data to be included in a regulatory submission to demonstrate that the active substance manufacturing process is in a validated state. The principles adopted and explained in this document apply to recombinant proteins and polypeptides, their derivatives, and products of which they are components (e.g. conjugates), as defined in ICH Q6B.

The principles that are outlined in the document may also apply to other biological products such as vaccines or blood products, as appropriate. To determine applicability, manufacturers should consult with the appropriate regulatory authorities.

For evaluation of viral safety, please refer to ICH Q5A.

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles (4) and Part II of Annex I to Directive 2001/83/EC as amended.

4. Process development

The goal of manufacturing process development for the active substance is to establish a commercial manufacturing process capable of consistently producing an active substance of the intended quality. Although not considered as part of process validation, process development comprises an essential role in defining the criteria and conditions to be addressed in process validation studies. For further information, please refer to ICH Q11 guideline.

Manufacturing process development should identify which inputs (e.g. material attributes, process parameters) and outputs (e.g. quality attributes, process indicators) for each process step/unit operation should be further evaluated during process validation studies.

Documented prior knowledge and risk assessment can help identify and justify the material attributes (e.g. of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters with the potential for having an effect on active substance critical quality attributes (CQAs) and/or process performance.

Process development information should usually be submitted in Section 3.2.S.2.6 of the CTD.

5. Process validation

A prospective process validation, as defined in ICH Q7, is expected for biotechnology-derived active substances. Process validation activities would normally include *i)* evaluation that process steps and the complete process are capable to perform as intended and *ii)* verification on commercial scale batches that the process does perform as intended. The contribution of data from small scale studies to the overall validation package will depend upon demonstration that the small scale model is an appropriate representation of the proposed commercial scale. Successful demonstration of the suitability of the small scale model could reduce data requirements for process verification (e.g. reduced number of batches) and/or impact on control strategy (e.g. alternative approach to end product testing, ongoing process verification) by evaluation and understanding of the sources of variability of CQAs. This is further discussed below.

The set of controls used in process validation activities (e.g. quality attribute, process indicator, process parameter, controls implicit in the design of the process) are expected to go beyond the routine control system as described in S.2.2 and S.2.4.

Considering that evaluation and verification activities are often investigated in the same study, it is not always necessary to make a difference between these activities as long as the evidences required for their demonstration are appropriately presented.

Process validation information should usually be submitted in Section 3.2.S.2.5 of the CTD.

5.1. Process evaluation

Process evaluation studies should provide evidence that, when operating in accordance with the *Description of manufacturing process and process controls (CTD section S.2.2)*, the complete manufacturing process and each step/operating unit have been appropriately designed and controlled

to obtain a product of the intended quality. Successful process evaluation should thus demonstrate that the design of the manufacturing process and its control are appropriate for commercial manufacturing.

The applicant should base the inputs and outputs studied on their potential criticality and justify their selection. For those which are not studied further it may be needed to explain how it is ascertained that these are kept within the range that has been shown to be non-critical.

These studies should include the evaluation of the ability of each step to obtain a product or intermediate of desired quality at small and/or full scale as appropriate, when operating in accordance with the described process and process controls. The results of inputs and outputs should be presented for each step. These data should demonstrate that when operating within the proposed input ranges, the output meets relevant quality criteria (i.e. predefined acceptance criteria or internal limits), and thus support the proven acceptable ranges (PAR). The outcome of the evaluation studies serves as the main basis of defining the control strategy and also in setting the acceptance criteria for the verification studies.

Where appropriate, evaluation of selected step(s) operating in worst case and/or abnormal conditions (e.g. cumulative hold time, spiking challenge) could be performed to support or demonstrate the robustness and the capability of the process to deliver product of the intended quality in these conditions. In some cases, these activities could be built into process verification studies (e.g. lots produced with intermediates stored in worst case hold conditions).

Small scale models are important tools in the development and evaluation of biopharmaceutical manufacturing processes. During process evaluation, small scale models enable evaluation of input material and parameter variability to an extent that may not be feasible at manufacturing scale. A small scale model must be designed and executed, and ultimately demonstrated, as an appropriate representation of the manufacturing process.

It is acknowledged that small scale models are incomplete representations of commercial scale process. When used, small scale models should be described and their relevance for the commercial scale should be justified, in terms of objective, design, inputs and outputs. When validation studies are highly dependent on the small scale model studies (e.g. design space claimed), it may be necessary to demonstrate that when operating under the same conditions using the same input materials, the outputs resulting from the commercial scale process match those of the small scale model. Any difference in operating conditions, inputs or outputs should be appropriately justified. Depending on the differences observed and their understanding, approaches to manage these differences (e.g. use of correction factors in cases where Design of Experiments is used) could be acceptable if well documented and justified. The use of such an approach requires appropriate management of the risks linked to this uncertainty (e.g. managed through control strategy).

Where prior knowledge or platform manufacturing experience is utilised, the contribution of these data (e.g. to justify operating ranges, input set points) to the overall validation package will depend upon justification that the data is representative of the proposed commercial process. Usually, full scale validation studies should include data derived from the final manufacturing process and site(s) used to produce the product to be commercialised.

5.2. Process verification

Process verification studies should confirm that the final manufacturing process (i.e. full scale commercial process) performs effectively and is able to produce an active substance or intermediate

meeting its predetermined controls and acceptance criteria. Such studies are generally performed in accordance to the expected normal operating ranges (NORs).

Process verification data (including process step results, batch analyses) should normally be completed and presented in the regulatory submission on an appropriate number of consecutive batches produced with the commercial process and scale, taking into account the batch definition as detailed in the process description. Failure to present validation data on consecutive batches should be appropriately justified. The number of batches to be presented depends on several factors including but not limited to: (1) the complexity of the process being validated; (2) the level of process variability; (3) the amount of experimental data and/or process knowledge available on the process; and (4) the frequency and cause(s) of deviations and batch failure.

As an alternative approach, continuous process verification could facilitate acceptance of fewer batches in the verification studies. The success of such an approach will be highly dependent on the knowledge and understanding gained on the process and product, and the process analytical technologies deployed to control and monitor the process inputs and outputs in an uninterrupted manner.

In the case that a design space is claimed, it may be needed to include a protocol on how movement within the design space will be managed post approval to verify that the design space is still valid when run at commercial scale. Please refer to ICH Q11 for further details.

5.3. Ongoing process verification

Subsequent to successful process validation activities for regulatory submission, companies should monitor product quality and process performance to ensure that a state of control is maintained throughout the commercial part of the product lifecycle. These activities have to be performed in compliance with EU GMP, and should provide evidence of the continued capability of the process and controls to produce product that meets the desired quality through the lifecycle of the product.

6. Points to consider in process validation

6.1. Upstream process

Process validation of the upstream process normally includes evaluation and verification that the cell culture steps, from the introduction of the starting material in the manufacturing process (e.g. thaw of the working cell bank (WCB)) up to the collection of the last harvest obtained at/or beyond production level are capable to perform as intended.

Considering the complex matrices during cell culture and harvest steps, the evaluation/validation could, in part, rely on the analysis of active substance and/or intermediates obtained at a later stage of the process.

6.1.1. Evaluation of upstream process

Process evaluation activities should demonstrate that the cell culture steps, from the introduction of the starting material in the manufacturing process (e.g. thaw of the WCB) up to and/or beyond production level, are capable of consistently delivering inoculates, harvest(s), and ultimately an active substance of appropriate quality. Several aspects should be considered when validating cell culture. The level of detail provided should support the criticality assignment of process parameters.

These activities could include evaluation of specific cell traits or indices (e.g. morphological characteristics, growth characteristics (population doubling level), cell number, viability, biochemical

markers, immunological markers, productivity of the desired product, oxygen or glucose consumption rates, ammonia or lactate production rates), process parameters and operating conditions (e.g. time, temperatures, agitation rates, working volumes, media feed, induction of production).

The conditions utilised to end fermentation/cell culture cycle and initiate harvest should be appropriately defined and evaluated. Relevant information on the final culture steps (e.g. yield, maximum generation number or population doubling level, consistency of cell growth, viability, duration and microbial purity) should be presented.

Potential impact of raw materials (e.g. quality of media, supplements, treatment such as gamma irradiation of animal sera) should be evaluated, in the light of the variability of these materials (e.g. intrinsic to the material, related to change in supplier) and of their influence on the quality of the product. Where appropriate, a risk-based approach could be presented to illustrate how variability of these raw materials and their related risks are managed through the lifecycle of the product (e.g. included in ongoing process verification protocol).

6.1.2. Verification of upstream process

Process verification activities should focus on the confirmation of consistency of performance indicators and quality attributes when operating conditions and process parameters are in accordance to NORs. These studies should include all culture steps and cover the complete duration of the process, on an appropriate number of consecutive runs.

6.1.3. General issues related to single use equipment

When single use equipment is used, in development studies consideration should be given to leachables and extractables. Information should be provided on the nature and amount of potential leachables, their impact on the cell culture, and the removal of such impurities. Besides data this normally includes a risk assessment. For validation full scale equipment has to be used. Various batches of disposable systems should be used in the manufacturing of verification batches in order to assess their impact on the product quality.

6.1.4. General issues related to multiple harvests

Where multiple harvests from one cell culture run are collected, it should be demonstrated that the increasing cell age during the culture run does not have an impact on quality and intra-batch consistency (i.e. derived from initial harvest through to last harvest) and inter-batch (i.e. derived from different fermentation runs / cell culture cycles). Such evidence could be supported by appropriate analysis of performance indicators (e.g. yield, titre) and quality attributes (e.g. post-translational modifications, host cell proteins (HCP), DNA) which should be confirmed to be consistent throughout the harvesting steps, otherwise an approach to manage the variability of harvests (e.g. by suitable pooling strategy) should be proposed. As certain analyses of quality attributes (e.g. post-translational modifications) may be difficult in a crude matrix, there may be a need for a partial, small scale purification of single harvests representative of early, mid and late stages of the cell culture cycle, to assess the effect of an aging cell population on the integrity of the product and to provide a scientific basis for the establishment of termination criteria.

The verification of the consistency of batches based on several fermentations runs/ cell culture cycles could lead to the necessity of producing a large number of batches spanning a long production period. In such situation, an applicant may propose a protocol to verify the consistency of these batches through ongoing process verification.

6.2. Downstream process

Downstream processing starts with the first step after final harvest and leads to a product of the desired quality: it may include steps required for cell disruption, concentration of drug intermediates and impurity clearance, polishing procedures but also protein refolding or potential modifications for the protein of interest. Most frequently various chromatographic and filtration methods are applied. In certain cases, specific steps aiming at a modification of the intermediate (e.g. conjugation to other proteins, carbohydrates or chemicals, e.g. pegylation) are included.

6.2.1. Evaluation of downstream process

The capacity of the proposed purification procedures to deliver the desired product and to remove product and process-related impurities (e.g. unwanted variants, HCPs, nucleic acids, media components, viruses, reagents used in modification of the protein) to acceptable levels should be thoroughly evaluated. This generally includes establishment of adequate analytical methods required for their detection and an estimation of the concentrating or removing capacity for each unit operation followed by the determination of appropriate acceptance criteria. For certain process-related impurities (e.g. HCP, DNA, antibiotics) scale-down spiking experiments may be required to determine the removal capacity of the individual purification steps. Evaluation of selected purification step(s) (e.g. steps for which high impurity or viral clearance are claimed) operating in worst case and/or abnormal conditions (e.g. cumulated hold times, spiking challenge) could be performed to document the robustness of the process.

Process conditions (e.g. column loading capacity, flow rate, length, elution/washing conditions conditions) and performance parameters/indicators (e.g. yield, chromatographic profiles) should be appropriately evaluated.

In the case where feed forward and/or feedback loop systems are used to accommodate the conditions of process steps, all claimed conditions should be appropriately evaluated regarding their impact on output material(s), according to an appropriate design of experiments, and verified according to an approved protocol.

Columns should also be evaluated throughout the expected lifetime of the column regarding purification ability (e.g. clearance, collection of intended variants), leaching of ligands (e.g. dye, affinity ligand) and/or chromatographic material (e.g. resin). Absence of specific leaching studies may be acceptable for some resins with small molecule functional group, but requires appropriate justification. Considering the number of purification cycles required for this evaluation, small scale studies are considered appropriate to estimate and set the maximum number of cycles at the time of regulatory submission, provided that full scale verification is performed on an ongoing basis, to confirm the column performance and integrity, in accordance with an approved protocol.

6.2.2. Verification of downstream process

Verification activities should confirm the clearance capability of the entire downstream process, showing that process parameters and performance indicators - in accordance to normal acceptable ranges - are able to consistently generate the targeted quality of process intermediates and active substance (i.e. appropriate purity/impurity profile for the given stage).

6.2.3. Reprocessing

Reprocessing, as defined in ICH Q7, could be considered in exceptional circumstances. For biological products, these situations are usually restricted to some refiltration or re-concentration steps upon technical failure of equipment. These steps should be appropriately described and validated in the regulatory submission. Such documentation should include the demonstration that the reprocessing step(s) do(es) not impact the quality of the active substance and the description of conditions for which reprocessing could be applied (e.g. equipment failure). An essential prerequisite for the acceptance of a reprocessing step is the clearly identified root cause.

6.2.4. Hold time, storage and transportation

Where hold times or storage are applied to process intermediates, the impact of the hold times and conditions on the product quality should be appropriately evaluated. The evaluation should be conducted as real-time, real-conditions studies, usually on commercial scale material. However, lab-scale studies could additionally be considered if appropriately justified. A selection of stability indicating assays and parameters addressing for example the biological activity, protein aggregation and degradation, pH and bioburden should be applied in order to justify a maximum hold time for each process step.

Studies conducted under worst case conditions and/or abnormal conditions (e.g. higher temperature, longer time) could be used to further support the suitability of the claimed conditions.

The suitability of the studies to support the claimed cumulative hold time should be discussed by the applicant. Provided the intermediate is stable and allows meaningful analyses, studies of separate steps are likely to be sufficient.

Shipping and transportation of intermediates and active substance should be validated. Such study should include demonstration that the quality of the intermediate or active substance will not be altered if transported according to the defined conditions. A short summary of the study should be provided in the dossier.

6.3. Multifacility production

During the lifecycle of biotechnological medicinal products, authorisation of additional manufacturing sites may be required to meet market demand. The process established at the new site generally requires technical adaptations of the approved process (e.g. scale up, different filters) in order to accommodate the equipment and provisions of the additional site. The adapted process should be capable of achieving comparable outputs when operating within the same input ranges.

In addition to the successful demonstration of comparability of products manufactured from the different sites, it must be demonstrated that the subsequent site has reached a validated state.

The relevance of previous validation studies should be discussed. Where appropriate, it may be necessary to re-demonstrate that models perform as expected. There is normally no expectation to re-evaluate the complete process (e.g. clearance of impurities). Nevertheless, process verification studies should be part of the submission. Depending on the differences between the sites and the demonstration that previous validation studies are suitable representation of the new site, the ongoing process verification could reduce the amount of process verification data to be submitted.

Optimisations of the production by using new processes (e.g. addition of new purification steps, replacement of one step with another (such as size-exclusion chromatography with ion exchange

chromatography), different conditions in buffers) is considered to constitute an alternate process and is not allowed within the same marketing authorisation.

Definitions

Continuous process verification

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8).

Control strategy

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to active substance and finished product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (ICH Q10).

Feedback

The modification or control of a process or a system based on its results and effects.

Feed forward

The modification or control of a process or a system using its anticipated results or effects.

Feed forward and/or feedback loop

Adjustments to the process based on feed forward or feedback information.

High-impact model

A model can be considered high-impact if prediction from the model is a significant indicator of quality of the product.

Normal operating range (NOR)

The NOR describes a region around the target operating conditions that contains typical operational variability and is within the claimed acceptable ranges. As such NORs themselves are not expected to be submitted in the dossier for a biological product.

Ongoing process verification

Documented evidence that the process remains in a state of control during commercial manufacture.

Platform manufacturing

The approach of developing a production strategy for a new drug starting from manufacturing processes similar to those used by the same applicant to manufacture other drugs of the same type (e.g. as in the production of monoclonal antibodies using predefined host cell, cell culture, and purification processes, for which there already exists considerable experience).

Process validation

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

Process evaluation

Studies, performed at small and/or full scale, should **provide evidence** that the complete manufacturing process and each step/operating unit have been appropriately designed and are controlled to obtain a product of the intended quality.

Process verification

Studies which should **confirm** that the final manufacturing process performs effectively and is able to produce an active substance or intermediate meeting its predetermined acceptance criteria, on an appropriate number of consecutive batches produced with the commercial process and scale.

References

ICH Q5A (R1) Guideline on quality of biotechnological products: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin (CPMP/ICH/295/95)

ICH Q6B Guideline on specifications: test procedures and acceptance criteria for biotechnological /biological products (CPMP/ICH/365/96)

ICH Q7 Guideline on good manufacturing practice for active pharmaceutical ingredients (CPMP/ICH/4106/00)

ICH Q10 Guideline on Pharmaceutical quality system (EMA/INS/GMP/79818/2011)

ICH Q11 Guideline on development and manufacture of drug substances (chemical entities and biotechnological/biological entities) (EMA/CHMP/ICH/425213/2011)