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 which includes process characterisation and process verification of biotechnology-derived active substances in the manufacture of medicinal products. This guideline addresses the data requirements for process characterisation and verification for submission of a marketing authorisation application or variation.

- Process characterisation can be based on a traditional or enhanced approach to process development. Traditional and enhanced approaches are not mutually exclusive.

- Process verification can be performed in a traditional way regardless of the approach to development taken. However, there is also the possibility to implement continuous process verification if an enhanced approach to development has been performed or where a substantial amount of product and process knowledge and understanding has been gained through historical data and manufacturing experience.

Current experience shows that a company can use a traditional 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 characterisation is the activity of defining the commercial manufacturing process that will be reflected in planned master production and control records. The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver an active substance that meets its quality attributes. Process characterisation includes process development and process evaluation. For the purpose of this guideline the following definitions apply:

- Process development includes studies to reach a potential design of a future manufacturing process;

- Process evaluation includes studies performed at small and/or commercial scale, to **provide evidence** that the complete manufacturing process and each step/operating unit have been appropriately designed to define the full operating ranges of the manufacturing process. The process is controlled to obtain an active substance of the intended quality for which, when challenging these ranges in univariate and multivariate studies, the quality will fulfil the pre-set acceptance criteria.

Process verification studies should **confirm** that the final manufacturing process as established based on the process evaluation studies performs effectively in routine manufacture and is able to produce an active substance or intermediate of the desired quality on an appropriate number of consecutive batches produced with the commercial process and scale.

Process validation should not be viewed as a one-time event. Process validation incorporates a lifecycle approach linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.

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Process characterisation and verification studies should normally be completed and included in the marketing authorisation application or a variation application as appropriate. 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. This document addresses the information, which normally includes process evaluation and verification studies, 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.

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.

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 recombinant polypeptides, their derivatives, and products of which they are components (e.g. conjugates).

The principles that are outlined in the document may also apply to other biological products such as vaccines or plasma-derived 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 characterisation

4.1. Process development

The goal of manufacturing process development of the active substance is to establish a commercial manufacturing process capable of consistently producing an active substance of the intended quality. Process development fulfils an essential role in defining the criteria and conditions to be addressed in further process evaluation and verification studies. For further information, please refer to the ICH Q11 guideline.

Manufacturing process development should identify which inputs (e.g. material attributes, process parameters) and outputs (e.g. quality attributes, performance indicators such as cell density, yield) for each process step/unit operation should be further evaluated during process evaluation and verification studies.

Documented prior knowledge and risk assessment are valuable tools to identify and justify the material attributes (e.g. of raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters which have the potential to affect the active substance critical quality attributes (CQAs) and/or process performance.

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

4.2. 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 generate a product of the intended quality. Successful process evaluation should thus demonstrate that the design of the manufacturing process, with the preliminary definition of operational ranges along with its control strategy is appropriate for commercial manufacturing.

The applicant should study selected inputs and outputs according to their potential criticality and justify their selection. For those which are not studied further it may be necessary to explain how it is ascertained that these are kept within the range that has been shown to have a non-critical impact.

These studies should include the evaluation of the ability of each step to generate an active substance or intermediate of desired quality at small and/or commercial scale as appropriate, when operating in accordance with the described process and process controls. Input data and results of 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 supports the proven acceptable ranges (PAR) that will be claimed. 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. Elements of the control strategy may be optimised following the outcome of the verification studies.

Prior knowledge (for example platform data) can be used as supportive information. 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.

Where appropriate, evaluation of selected step(s) operating in worst case and/or non-standard conditions (e.g. impurity spiking challenge) can be performed to support or demonstrate the robustness and the capability of the process to deliver product of the intended quality in these 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 justified, as an appropriate representation of the manufacturing 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 representative 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 managing 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 the control strategy).

In the light of the variability (e.g. intrinsic to the material, related to change in supplier) of certain raw materials and based on their potential influence on the quality of the product, the impact of these materials should be addressed. These studies should be conducted as early in the development process as possible, at small scale. 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).

5. Process verification

A prospective process validation, as defined in ICH Q7, is expected for biotechnology-derived active substances. 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 the 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 panel of controls used in process validation activities (e.g. quality attribute, performance indicator, process parameter and 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.

In the case of process changes, the modified process steps should be re-evaluated and/or re-validated, as appropriate. Typically, re-evaluation/re-validation activities for a simple change might be limited to the affected process step, if there is no evidence to indicate that there is an impact on the performance of subsequent (downstream) process steps, or on the quality of the intermediates resulting from the subsequent steps. When the change considered affects more than a single step, more extensive analysis of the change and resultant validation might be appropriate.

Considering that evaluation and verification activities are normally interlinked, it is not always necessary to make a difference between these activities as long as the evidence required for their demonstration is appropriately presented.

5.1. Approaches to process verification

Process verification studies should confirm that the final manufacturing process (i.e. commercial scale process) performs effectively and is able to produce an active substance or intermediate of desired quality. Such studies are generally performed in accordance with normal set points for operating conditions and process parameters.

Process verification data (including process step results and batch analyses) should normally be completed and presented in the regulatory submission using an appropriate number of consecutive batches produced with the commercial process and scale and taking into account the batch definition as detailed in the process description (see section 6 for details). Failure to present verification 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.

Continuous process verification in which manufacturing process performance is continuously monitored and evaluated is an alternative approach to traditional process verification. Making use of this approach could facilitate acceptance of fewer batches in the verification studies.

It is a science and risk-based real-time approach to verify and demonstrate that a process that operates within the predefined specified parameters consistently produces material which meets all its CQAs and control strategy requirements. In order to enable continuous process verification, companies should perform, as relevant, extensive in-line, on-line or at-line controls and monitor process performance and product quality on each batch. Relevant data on quality attributes of incoming materials or components, in-process material and finished products should be collected. This should include the verification of attributes, parameters and end points, and assessment of CQA and critical process parameter (CPP) trends. Process analytical technology (PAT) applications and Multivariate Statistical Process Control (MSPC) can be viewed as enablers for continuous process verification.

Sufficient knowledge and understanding of the process is required in order to support continuous process verification. However, the scope and extent of continuous process verification will be influenced by a number of factors including:

- Prior development and manufacturing knowledge from similar products and/or processes;

- The extent of process understanding gained from development studies and commercial manufacturing experience;

- The complexity of the product and/or manufacturing process;

- The level of process automation and analytical technologies used.

The description of the continuous process verification strategy should include a discussion on the appropriateness and feasibility of the strategy including the process parameters and material attributes that will be monitored, as well as the analytical methods that will be employed. The applicant should define the stage at which the process is considered to be under control and the basis on which that decision will be made.

In some exceptional circumstances and after consultation with regulatory authorities (e.g. urgent medical need), concurrent validation could be considered. In such case, evidence should be provided to demonstrate i) that studies performed for process evaluation are appropriate representations of the commercial process, and ii) that control strategy will properly verify that the process has performed as intended and that active substance and intermediates comply with pre-defined acceptance criteria.

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.

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

5.2. Ongoing process verification during lifecycle

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.

There may be cases where it will not be possible to present full validation data at the time of the regulatory submission and the process requires further verification. Examples include niche products that do not require large amounts of material for commercialisation and products under accelerated programs for unmet medical need. In these cases, the applicant may choose to present in the

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regulatory submission how the data generated through such verification activities will be managed to facilitate the acceptance of the claimed process step. This can be in the form of a protocol that indicates how process knowledge, control strategy and characterisation methods will be deployed to assess product quality throughout the lifecycle of the product. Such a protocol could include sets of tests and acceptance criteria that will be used to further demonstrate that the process remains in a validated state. In any case, the situations and conditions to be covered by such a protocol have to be clearly described and justified. This option should only be used when common validation studies are not possible and it is therefore expected to be a rare event. Acceptance of such a protocol should not be considered as a pre-approval of the overall ongoing process verification activities, as this rests within GMP.

6. Points to consider in process characterisation and verification

6.1. Upstream process

Process validation of the upstream process normally includes evaluation and verification that the cell culture steps, from the initiation of the manufacturing process (e.g. thaw of a vial of working cell bank (WCB)) up to the collection of the last harvest obtained at/or beyond the population doubling level (PDL) defined by termination criteria, are capable of performing as intended.

Considering the complex matrices during cell culture and harvest steps, the 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 initiation of the manufacturing process (e.g. thaw of a WCB vial) up to and/or beyond the PDL defined by termination criteria, are capable of consistently delivering inocula, harvest(s) and ultimately an active substance of appropriate quality after downstream processing. 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). Evaluation of any critical conditions for the control of expression of the desired product in the production bioreactor is crucial.

The conditions utilised to end fermentation/cell culture cycle and initiate harvest should be appropriately defined. Termination criteria should be defined and justified based on relevant information (e.g. yield, maximum generation number or population doubling level, consistency of cell growth, viability, duration and microbial purity and, ultimately, consistency of the quality of the active substance).

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 with normal set points. These studies should include all culture steps and cover the complete duration of the upstream process, using an appropriate number of consecutive runs.

6.1.3. General issues related to single use equipment

When single use equipment is used in evaluation studies, consideration should be given to leachables and extractables. Information should be provided on the nature and amount of potential leachables, and the removal of such impurities. Besides data, this normally includes a risk assessment. Data do not necessarily need to be generated under actual process conditions, for example supplier data or data generated under representative model conditions may be suitable. During process evaluation, small scale studies are acceptable to assess leachable profiles, leachable removal and the impact of such impurities on cell culture performance. For verification studies, commercial scale equipment should be used. Various batches of disposable components should be used, as appropriate, 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 (i.e. derived from initial harvest through to last harvest) and inter-batch (i.e. derived from different fermentation runs / cell culture cycles) consistency. 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 demonstrated 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 ageing cell population on the integrity of the product and to provide a scientific basis for the establishment of termination criteria.

The verification of inter batch consistency based on several fermentation runs/ cell culture cycles could necessitate the production of a large number of batches spanning a long production period. In such a situation, an applicant may propose a protocol to verify batch consistency through ongoing process verification and limit the number of batches included at the time of the application.

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 aimed at modifying the intermediate (for example conjugation to other proteins, carbohydrates or chemicals, e.g. pegylation) are included.

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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 and reagents used in the modification of the protein) to acceptable levels should be thoroughly evaluated. This generally includes establishment of adequate analytical methods required for respective impurity 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 purification steps for which high impurity clearance are claimed, operating in worst case and/or non-standard conditions (e.g. process hold times, spiking challenge) could be performed to document the robustness of the process. For some components (e.g. low-molecular weight media components), a risk-based approach is acceptable showing that no safety concerns like immunogenicity or toxicity are present.

Evaluation of steps where viral clearance is claimed should be performed as described, according to ICH Q5A (R1).

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

Columns should also be evaluated throughout the expected lifetime of the column regarding purification ability (e.g. clearance, peak resolution in separation of isoforms), 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, 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 the regulatory submission, provided that commercial scale verification is performed on an ongoing basis to confirm the column performance and integrity, in accordance with a protocol approved at the time of marketing authorisation application.

6.2.2. Verification of downstream process

Verification activities should confirm the intended performance of the entire downstream process (e.g. regarding purity, impurity clearance, correct refolding and formation of intended modifications) to consistently generate the targeted quality of process intermediates and active substance (i.e. appropriate purity/impurity profile for the given stage). This should be supported by in-process testing results of process parameters and process outputs.

6.2.3. Reprocessing

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

This demonstration can be done at commercial scale or with appropriate small scale models. In the latter case these small scale studies may be accompanied by a verification protocol, to be applied in case of the need for reprocessing at large scale.

6.2.4. Hold time, storage and transportation

Where process intermediates are held or stored, the impact of the hold times and conditions on the product quality from a structural and microbial point of view should be appropriately evaluated. The evaluation should be conducted as real-time, real-condition studies, usually on commercial scale material. However, scale-down studies could alternatively be considered for assessment of structural stability. 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 the maximum hold time claimed.

Studies conducted under worst case conditions and/or non-standard 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 cumulative hold time should be discussed by the applicant. Provided the intermediate is stable and allows meaningful analyses, independent studies of individual steps are likely to be sufficient and cumulative studies are not considered necessary.

Shipping and transportation of intermediates and the active substance should be verified according to EU GMP. Such a study should include demonstration that the quality of the intermediate or active substance is maintained 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.

In addition to the successful demonstration of comparability of products manufactured at the different sites, it must be demonstrated that the process at the new site has reached a validated state as further described below. 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. maximum PDL, clearance of impurities). Nevertheless, process verification studies should be part of the submission. In case the differences between the sites are not major and it can be demonstrated that the previous validation studies are a suitable representation of the new site, the ongoing process verification could reduce the amount of process verification data to be submitted. Similar principles apply for new manufacturing trains added to the same facility.

Optimisation 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) is considered to constitute an alternate process and is not allowed within the same marketing authorisation. Site-specific technical adaptation of the process per se is allowed if appropriately justified by the sponsor and approved by authorities. If more than one production site is used, it needs to be ensured that processes between sites remain harmonised, e.g. to avoid two

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different processes running in parallel. In case there is doubt as to whether the changes result in an alternate process, it is recommended to seek advice from the authorities.

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).

Concurrent validation

Validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the validation protocol is executed concurrently with commercialisation of the validation batches (GMP Annex 15).

Enhanced approach to process development

In an enhanced approach, risk management and scientific knowledge are used more extensively to identify and understand process parameters and unit operations that impact critical quality attributes (CQAs) and develop appropriate control strategies applicable over the lifecycle of the active substance which may include the establishment of design space(s) (ICH Q11).

Hold time

Time limits for holding specified materials at different stages of production. Hold time studies are performed to assure that the quality of the product does not deteriorate during the hold time.

Ongoing process verification (also known as continued process verification)

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

Performance indicator

Measurable values used to quantify quality objectives to reflect the performance of an organisation, process or system (ICH Q10).

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 evaluation

Studies, performed at small and/or commercial 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 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 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.

Proven Acceptable Range (PAR)

A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria (ICH Q8).

Small scale

Small scale batches are any scale smaller than full scale commercial batch size e.g. pilot scale, or lab scale.

References

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

Guideline on process validation for finished products – information and data to be provided in the regulatory submission (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1)

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 Q8 (R2) Guideline on Pharmaceutical development (CHMP/ICH/167068/2004)

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)

EU Guidelines for Good Manufacturing Practice for medicinal products for human and veterinary use – Eudralex Volume 4, Annex 15: Qualification and validation