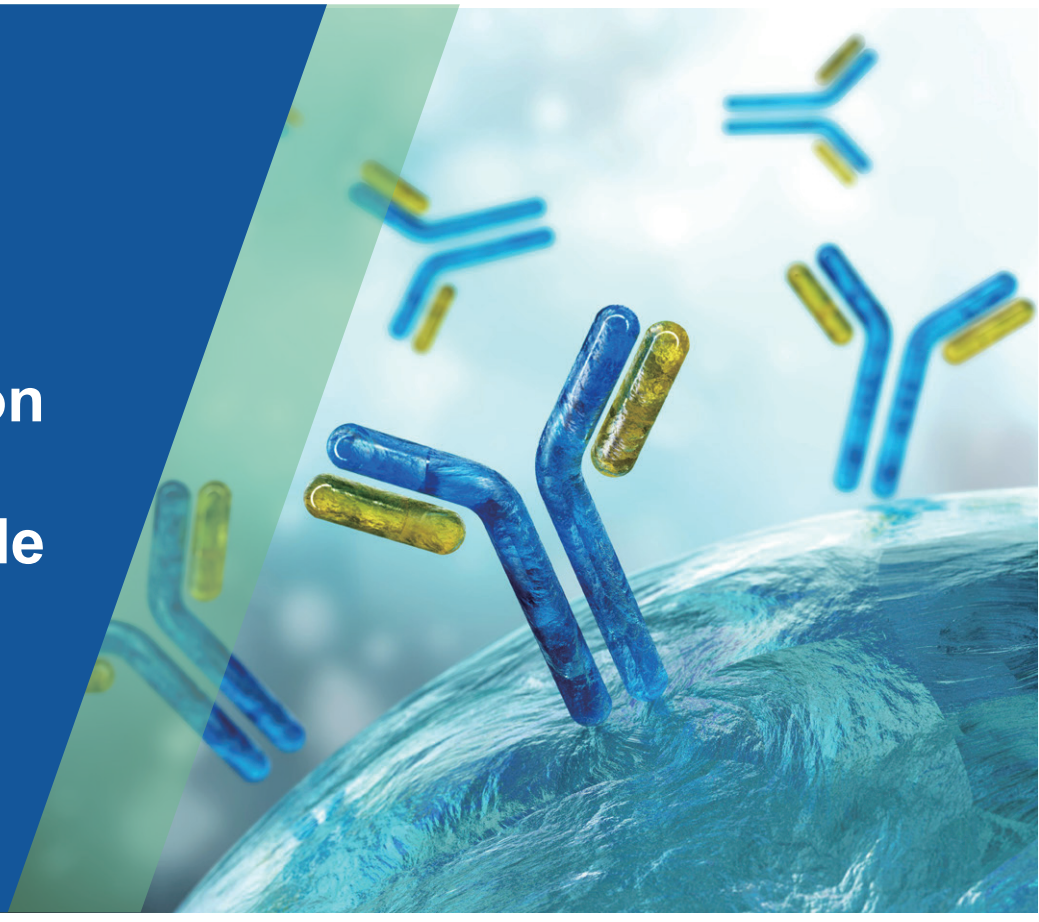
GenScript PROBIO

Process Characterization and Process Validation Guide



Inspiration, Acceleration & Co-Creation

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Concepts of Process Characterization and Process Validation

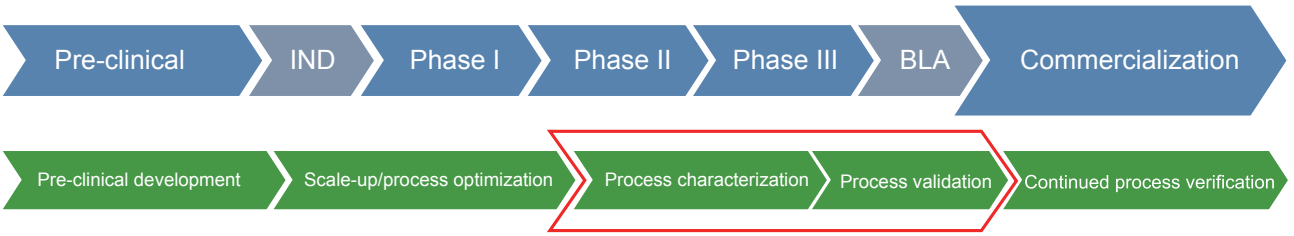


Fig 1: Process characterization & process validation in drug development process

Process Characterization (PC) is a set of experiments at small scale, in which operational parameters are purposely varied to determine their effects on product quality attributes and process performance.The results from PC are used to define the process performance qualification (PPQ) ranges and acceptance criteria, which is a control strategy. [1]

PC is based on risk assessment and is a part of quality risk management. During the initial stages of PC, potential critical process parameters (pCPPs) are defined of each operation unit. The acceptable ranges of all high–risk parameters must be defined in the subsequent PC studies and it must be confirmed that these ranges will not have bad effects on critical quality attribute (CQA).

Process Validation (PV) is the collection and evaluation of data from the process design stage through commercial manufacturing that establishes scientific evidence that a process is capable of consistently delivering quality product. [2]

PV is performed to prove that a process can be conducted as designed, and can get the products to meet quality standards consistently. Process validation should be performed before commercial manufacturing, which includes DQ/IQ/OQ of the facility and equipment, and process performance qualification which proves that process parameters are within control and products meet the desired quality standards.

DQ: design qualification; IQ: installation qualification; OQ: operation qualification

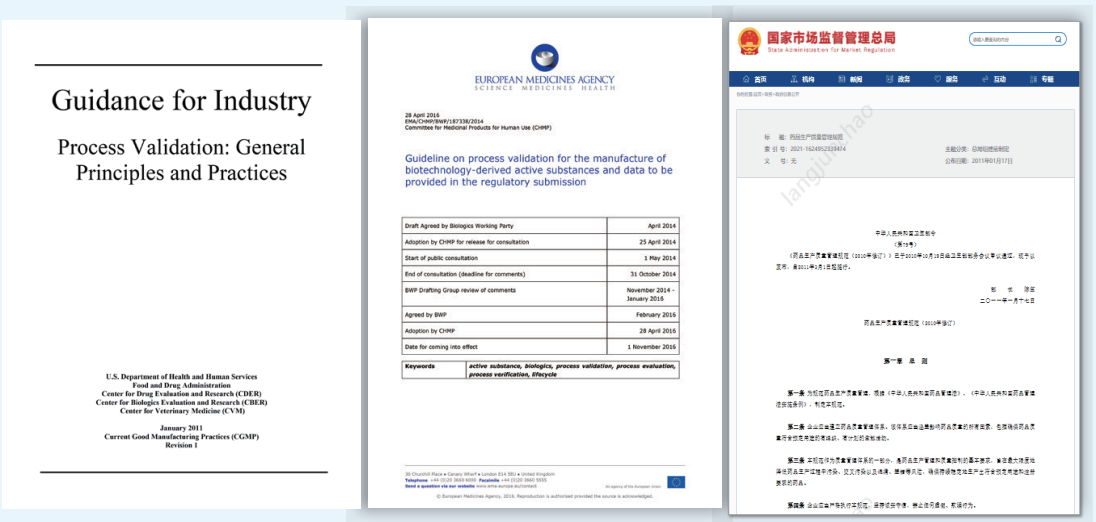


Fig 2: Requirements for PC/PV by global regulations

Related Definitions

Quality Target Product Profile (QTPP):

a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. [1]

Critical Quality Attribute (CQA):

is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality [2].

Critical Material Attribute (CMA):

is a physical, chemical, biological, or microbiological property of an input material that should be within appropriate ranges to ensure the desired product quality.

Critical Process Parameter (CPP):

an input process parameter that should be controlled within a meaningful operating range to ensure that the drug substance critical quality attributes meet their specifications. [3]

Scale-down Model (SDM):

small–scale models are built based on the manufacturing data from the commercial scale, to represent commercial manufacturing.

Design Space:

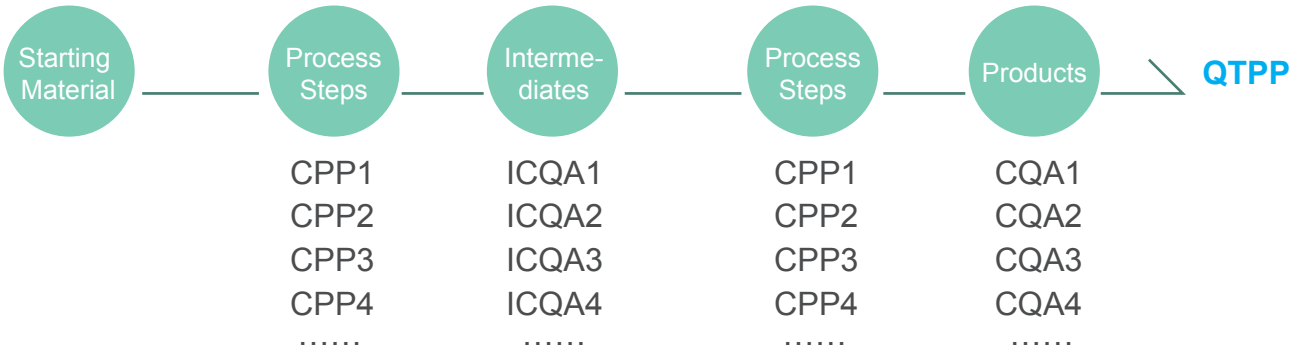
the multidimensional combination and interaction of input variables (e.g., material attributes and process parameters) that have been demonstrated to provide assurance of quality.

Control Strategy:

a planned set of controls, derived from current product and process understanding, which ensures process performance and product quality.

Process Performance Qualification (PPQ):

includes a combination of the actual facility, utilities, equipment, personnel trained in the commercial manufacturing process, control procedures, and components to produce commercial batches. A successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected.

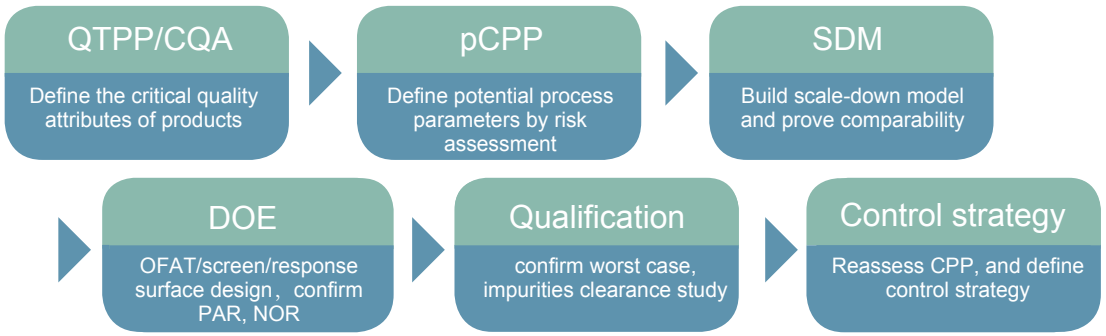


ICQA: intermediate critical quality attribute

Fig 3: Schematic diagram of process control

Process Characterization

Before drugs are launched, in addition to clinical data, process characterization data has also become the most concerned part of regulatory authorities because it serves as evidence to prove that the manufacturer can consistently deliver a quality product. The following parts play key roles and should be emphasized during process characterization.



IOFAT: one-fact-at-a-time; PAR: proven accept range; NOR: normal operation range

Fig 4: Key steps in PC

Risk Assessment

Define CQA of products by failure model effectiveness analysis (FEMA) or cause & effect matrix (C&E Matrix), and then evaluate the potential CPP in upstream, downstream, and formulation processes according to the CQA. Generally, based on experience and historical data (QTPP, CMC data, clinical data, and paper reports), only the parameters that will affect product qualities should be characterized and general process parameters can be ignored in process characterization.

Failure Model Effectiveness Analysis (FMEA)

A risk score can be calculated by taking into account each parameter's severity, possibility, and detectability. Then, using the risk ranking table, identify the priority of risk control, which is then used to evaluate the product's potential CQA as well as the CPP that may affect its quality.

Cause & Effect Matrix

Link key inputs (process parameters) to key outputs (quality attributes), and calculate the value by relevance and importance.

CQA Evaluation

Based on the understanding of your products and historical data, define the CQA of products through risk assessment. This is the starting point of process characterization.
CQAs are mainly derived from QTPP, and determined by safety and efficacy of the product. CQA evaluation mainly considers the effects on patients, not process capability or historical data.

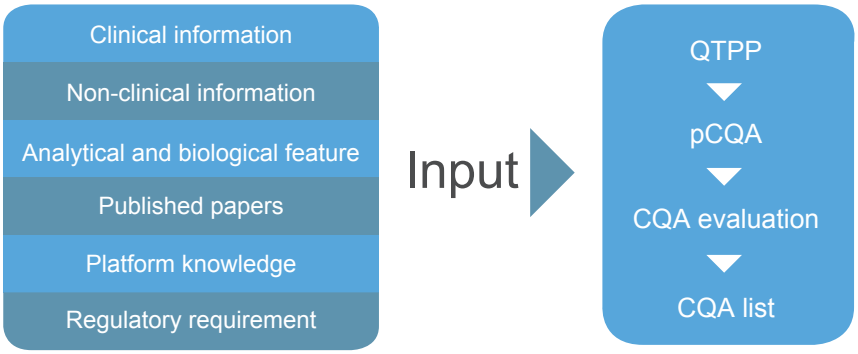


Fig 5: CQA evaluation process

CPP Evaluation

Based on the CQA list, use risk assessment tools (such as FMEA, C&E Matrix, fishbone diagram) to eliminate non–critical process parameters from a large number of process parameters and select all potential critical process parameters (pCPP) that will be studied to create a robust control strategy.

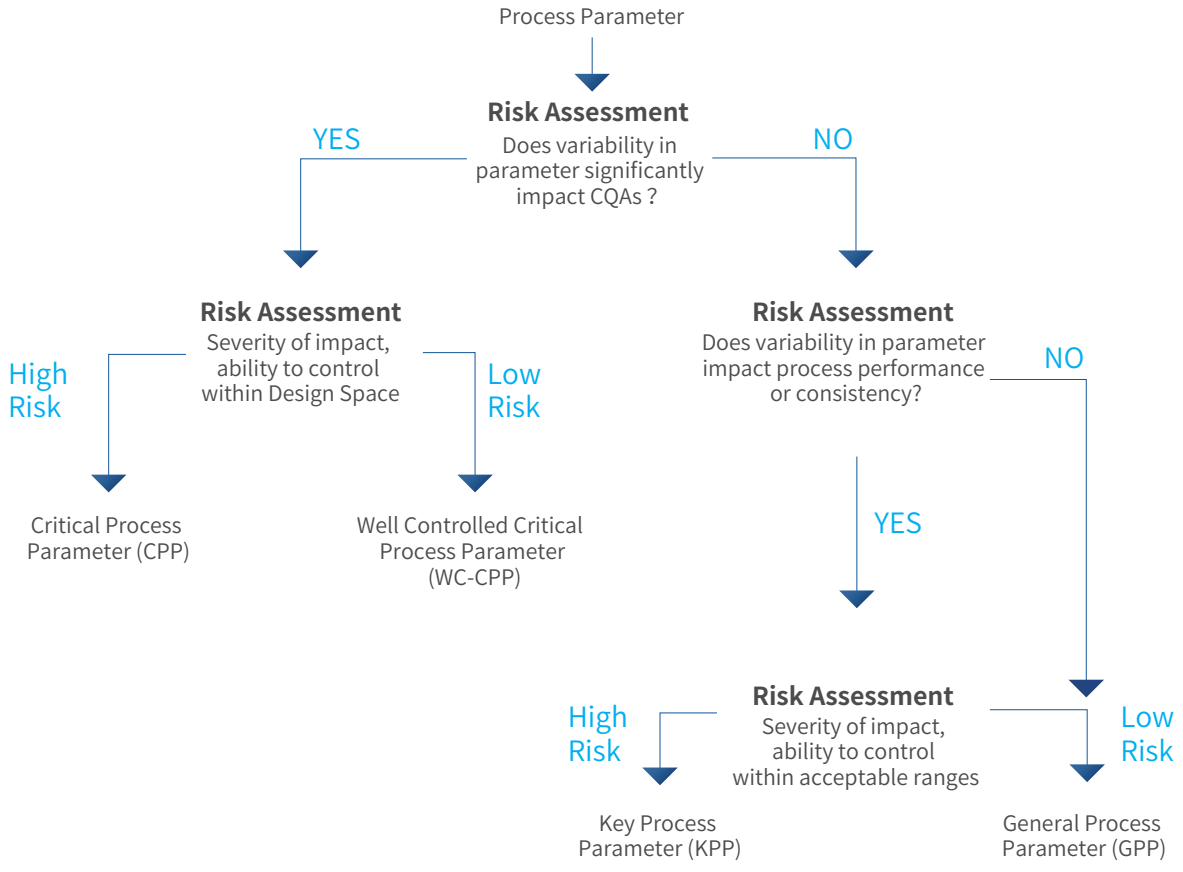


Fig 6: CPP evaluation process

Scale-Down Model

Build scale–down models (SDMs) that can represent commercial manufacturing, and use them to study all CPPs so that a large number of experiments can be conducted at a low cost. A good SDM can represent commercial process, and it can be regarded as a small–scale commercial manufacturing. Therefore, key process performance must be similar between the commercial scale and the small–scale under the defined process. To a certain degree, the larger the factor of scale–down, the lower the experimental cost.

Cell Culture Scale-Down Model

When building a cell culture scale–down model, parameters independent of the scale should be kept consistent with manufacturing process, such as pH, temperature, and feeding strategy. For parameters dependent on scale, it is common to use constant P/V or constant tip speed to ensure consistent mixing effect; or to maintain the k_La of O_2 and CO_2 consistent with manufacturing process to ensure consistent oxygen mass transfer and CO_2 removal efficiency.

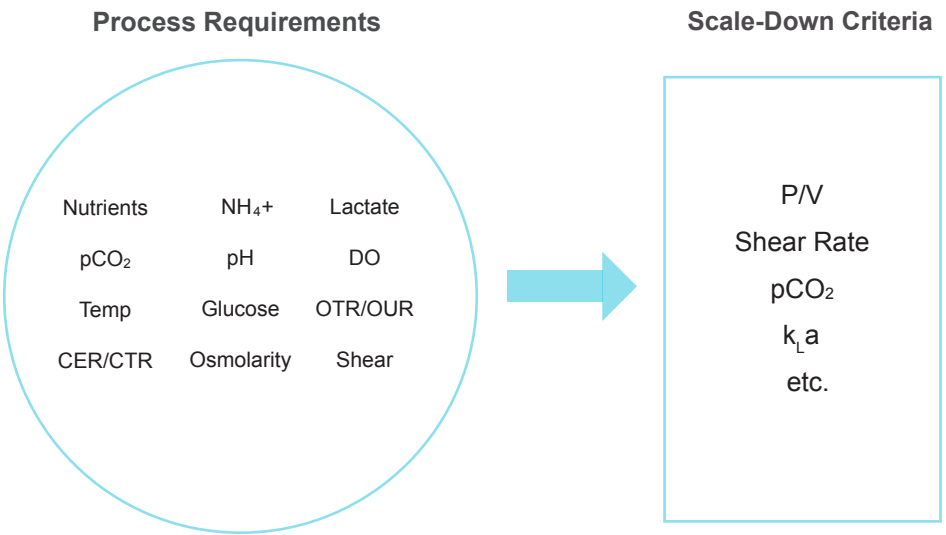
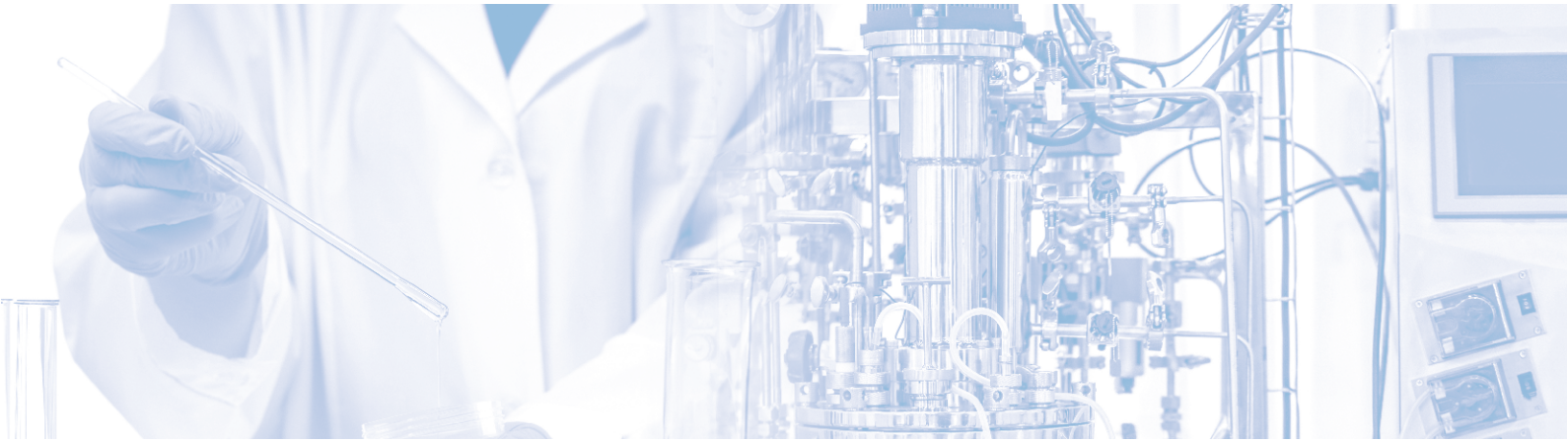


Fig 7: Parameters design of cell culture scale–down model

temp: temperature; DO: dissolved oxygen; CER: carbon dioxide evolution rate; k_La: volumetric mass transfer coefficient
CTR: carbon dioxide transfer rate; OTR: oxygen transfer rate; OUR: oxygen uptake rate; P/V: power input/volume ratio



Purification Scale-Down Model

In chromatography steps, usually keep the retention time and column height the same with manufacturing process, and linearly scale down the parameters dependent on the scale.
In the mixing step, linearly scale down the parameters dependent on the scale, and apply measures such as consistent P/V to ensure the mixing effect.
In the filtration step, linearly scale down the parameters dependent on the scale, and keep the loading capability, flow flux, or pressure consistent with manufacturing process.

Fig 8：Figure of building purification scale-down model

Comparability Study

The scale-down models need to undergo comparability studies with manufacturing process in terms of metabolism, product quality, etc., to ensure that the scale-down models can represent the manufacturing scale.
Usually, comparability criteria are set as 3 standard deviations (dash line in Fig 9) or 95% confidence interval (spherical region in Fig 10) according to manufacturing data. If metabolism data, production quality, and intermediates quality fall within the acceptable range, the scale-down models can be regarded to represent the commercial scale and can be used in the process characterization study.

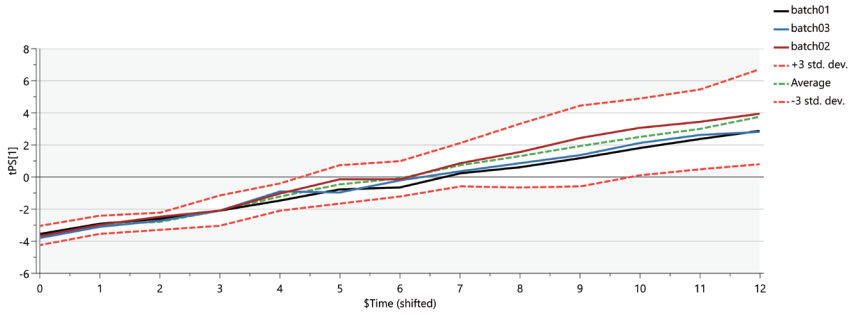


Fig 9: Score figure of cell metabolism on different days (Simca)

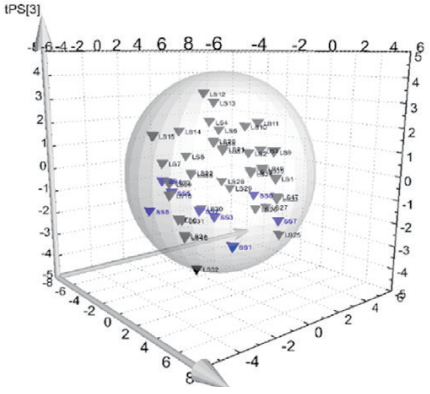


Fig 10: Score figure of product quality (Simca)

Simca: a statistical software can build PCA/PLS models based on commercial production data

Experimental Design

Design of experiments (DOE) is a structured, systematic, and efficient method that enables scientists to study the relationship between multiple input variables and key output variables. During the process characterization study, CPPs should be characterized by a reasonable DOE design and the control range of CPP should be defined. This is done to confirm the accepted ranges of parameters in commercial manufacturing and define the control strategy.

Common types of experimental designs:

Fractional Factorial Design:

this design can screen out the main effects with fewer experimental runs, but cannot identify interaction effects and quadratic effects.

Full Factorial Design:

a simple systematic design style that allows for estimation of main effects and interactions. This design is very useful, but requires a large number of tests, and quadratic effects may be ignored.

Response Surface Methodology:

this method adds more points on the basis of factorial design. It can identify main effects, interaction effects and quadratic effects. But the number of experiments that are run is so large that it is only suitable for analyzing 3–4 factors.

Definitive Screening Design:

this design requires only a small number of runs, uses three levels of continuous factors, and allows for the estimation of main effects as well as some interactions and quadratic terms.

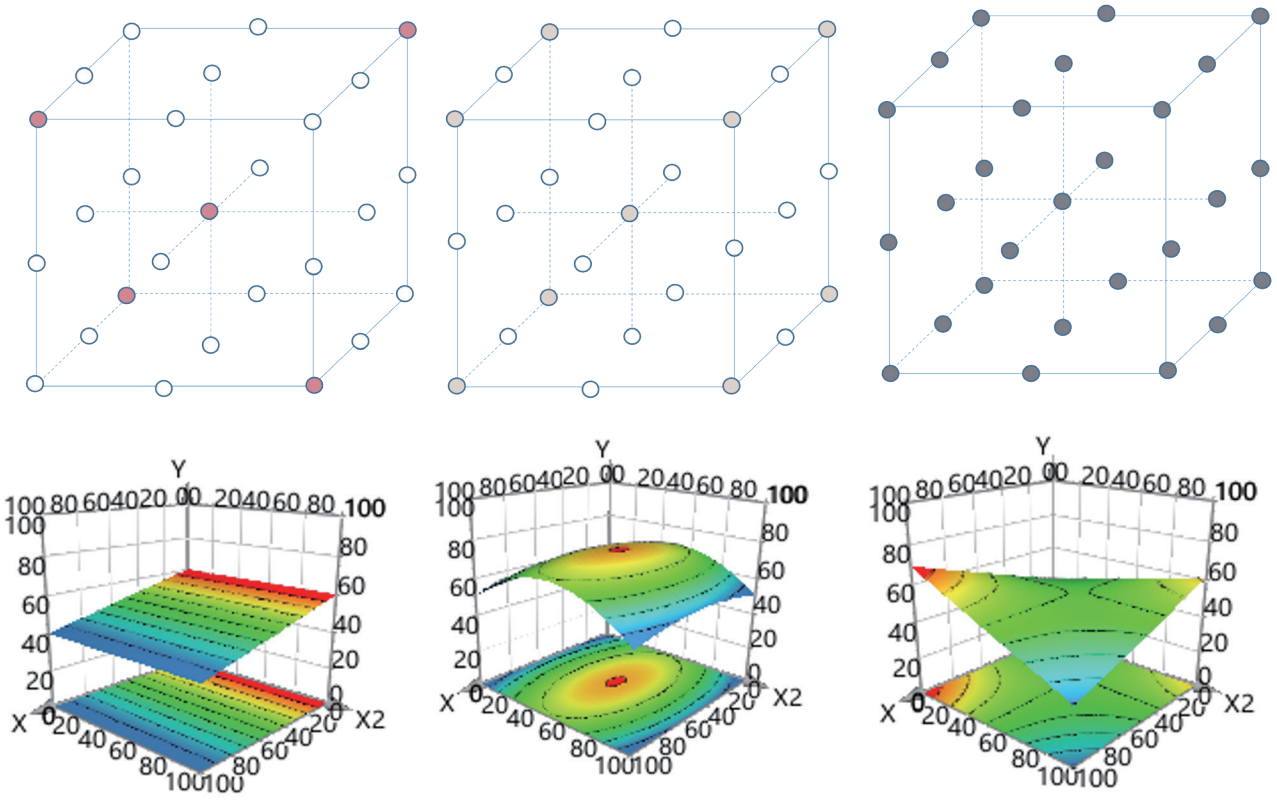


Fig 11: Diagram of different DOE design principles (MODDE)

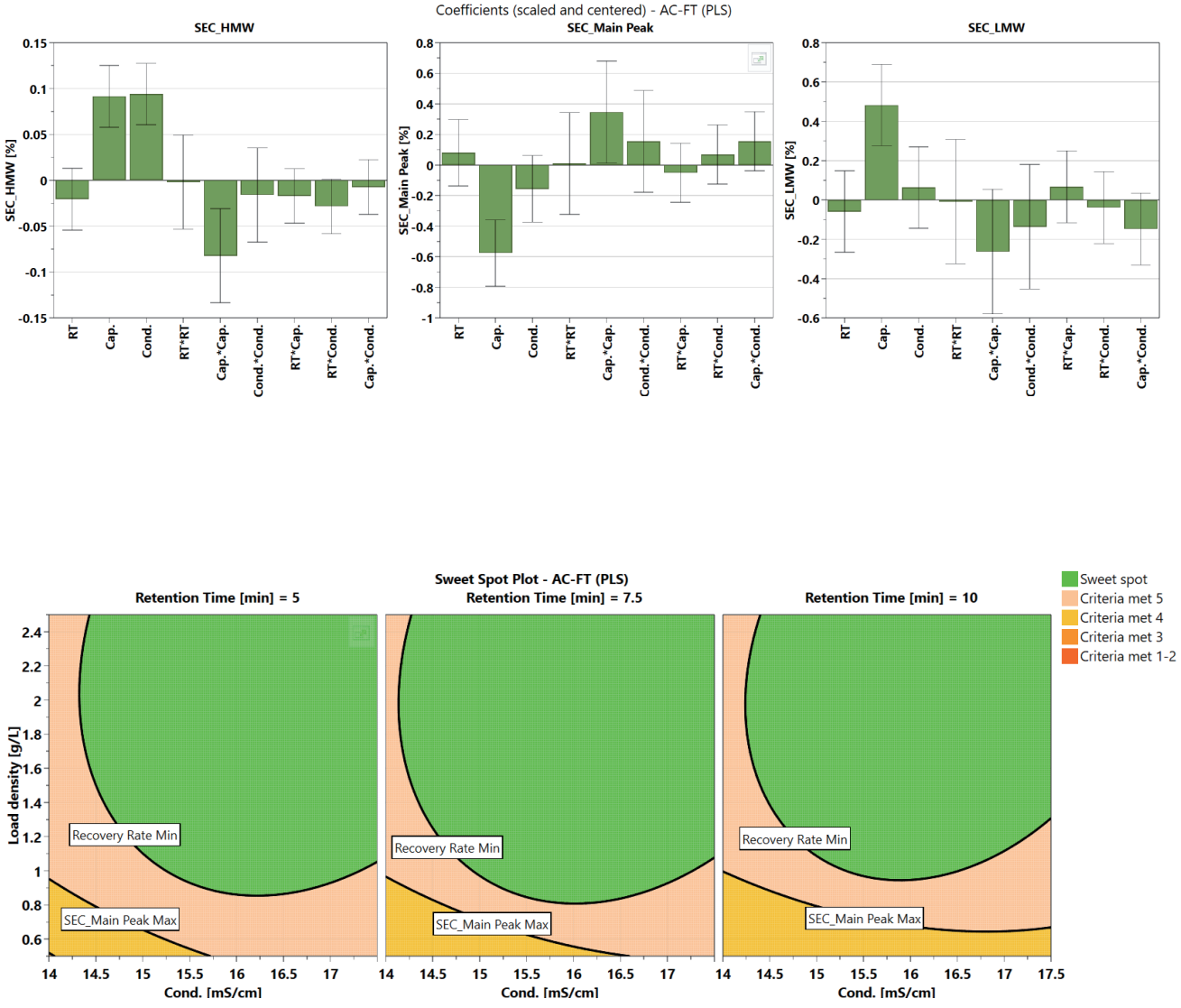


Fig 12: Diagram of design space (MODDE)

According to the results of the screening study, confirm the parameters with main effects, and if the interaction effects or quadratic effects are significant, then response surface studies are needed. Lastly, define the design space based on the experimental data.

Control Strategy

Based on the results of the DOE and worst–case studies, the design space can be defined.

The validated Proven Acceptable Range (PAR) of parameters can be defined according to the design space, and keeping other parame–ters constant, the parameter varied within PAR produce quality products.

Normal Operation Range (NOR) can be refined within the confines of PAR by comprehensive consideration of the set point, equipment and process variability.

During commercial manufacturing, once a parameter exceeds PAR/NOR, it indicates the batch failure. Variations within the design space will not be regarded as change and manufacturers need not submit supplementary applications to their regulatory agency.

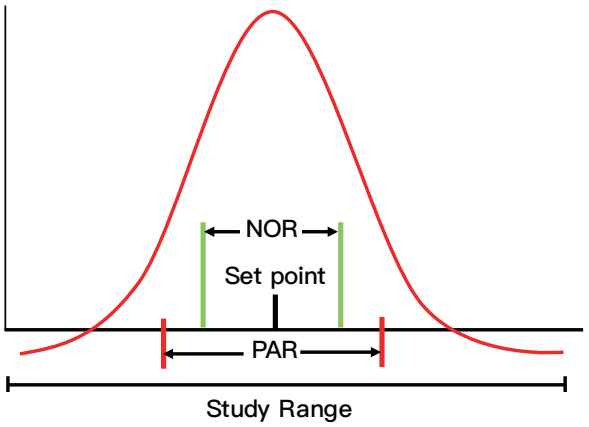


Fig 13: Diagram of control strategy

The main purpose of process characterization is to establish a suitable and efficient **control strategy**.
As the knowledge of product increases during process characterization, a robust control strategy should include all elements of each operation unit. If the process inputs are under control, stable process performance and quality products can be obtained.
After the control strategy is validated in process validation, this strategy is used in the commercial manufacturing that follows.

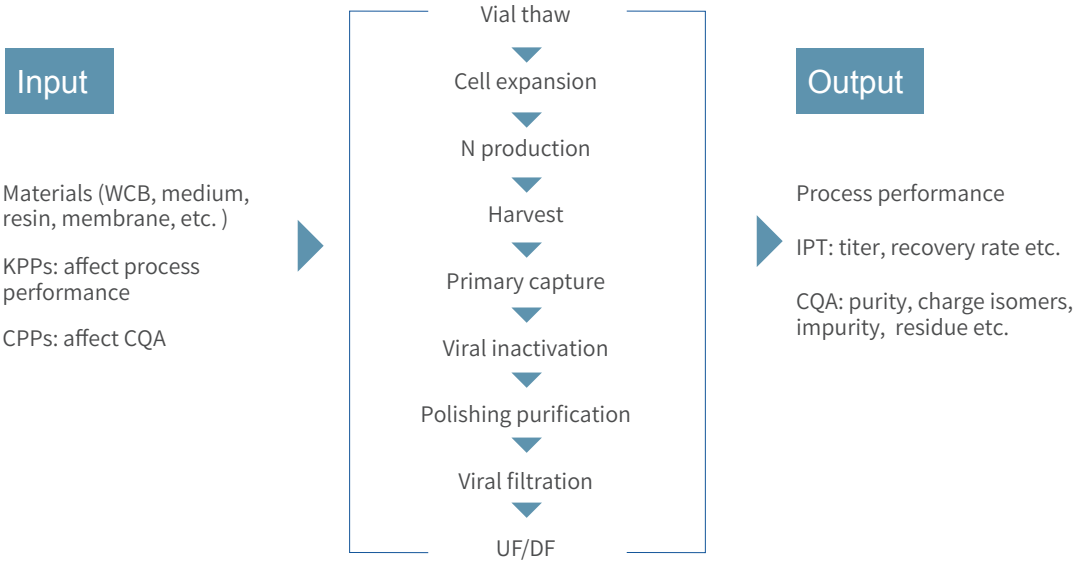


Fig 14: Diagram of control strategy in each operation unit

WCB: working cell bank; UF/DF: ultrafiltration/diafiltration

Process Validation

Design and control of the manufacturing process are required by cGMP regulations to ensure intermediates and drug products consistently meet quality standards. Process validation is to demonstrate that products produced according to the strategy determined in process characterization can continuously meet the quality standards. Process validation should be carried out before releasing the commercial manufacturing batches. Validation of facility, equipment, utilities, and process should be included in PV. The general and specific terms of CGMP also stipulate that process validation is compulsory. [4]

Validation Master Plan

The Validation Master Plan (VMP) should be completed before conducting process validation. It describes the validation scope, basic principles, and establishes the validation targets. This plan requires that all validation documents are controlled according to the planned workflow. All staff responsibilities should also be defined in this plan.

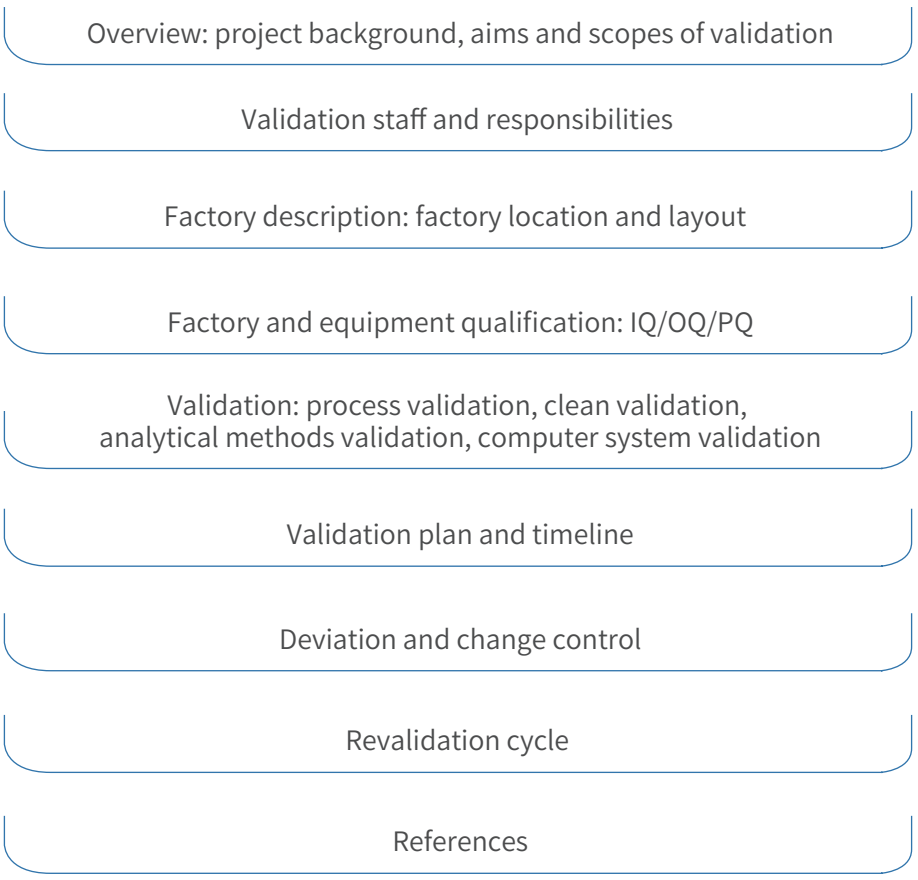


Fig 15: Main contents of the Validation Master Plan

PQ: performance qualification

Process Validation Preparation

Upon formulation of the validation master plan, and before proceeding to the next step PPQ (process performance qualification), a readiness assessment should be conducted to ensure that there are appropriate facilities, equipment, and trained personnel to successfully carry out the practice.

Equipment	IQ/OQ/PQ validation, clean validation, calibration of instruments, computer system validation.
Factory	Environment validation, human flow and material flow control, factory disinfection procedures.
Analytical methods	Confirm that the analytical methods used for PPQ are validated.
Materials	Release the relevant raw materials and excipients according to the related pharmacopeia standards and confirm the CMA.
Quality system	Close all deviation and change control and complete staff training.

Fig 16: Preparation work for process validation

Process Performance Qualification

Process Performance Qualification (PPQ) is the main work of process validation. It proves process consistency and determines impurity removal efficiency. PPQ is performed to prove that all CPPs, intermediates, process performances, and CQAs are within their acceptable ranges.

PPQ related validation:

Table 1: The scope of PPQ

Validation items	Validation contents
3 batches PPQ (including DS/DP production/release)	Conduct 3 batches of commercial scale production at the control strategy defined by PC to validate qualified products can be produced continuously
DS/DP stability	Use products from PPQ to validate DS/DP stability (including long-term stability, accelerated stability, and stability in stressed conditions)
Intermediates holding time	Confirm the holding time of intermediates in PPQ
Mixing validation	Validate the mixing efficiency of tween, sucrose or protein
Characterization of products from PPQ	Validate structure or translational modification of products from PPQ
DS/DP shipping validation	Validate stability after shipping the DS/DP obtained from PPQ
EOPC testing (1 batch)	Test UPB and EOPC from PPQ to control the potential viral contamination
UPB testing (3 batch)	
Viral clearance validation (1 batch)	Validate the clearance or inactivation efficiency of possible endogenous virus and exogenous virus
Impurities study	Confirm the impurities clearance efficiency by small-scale studies and PPQ

Other Validations

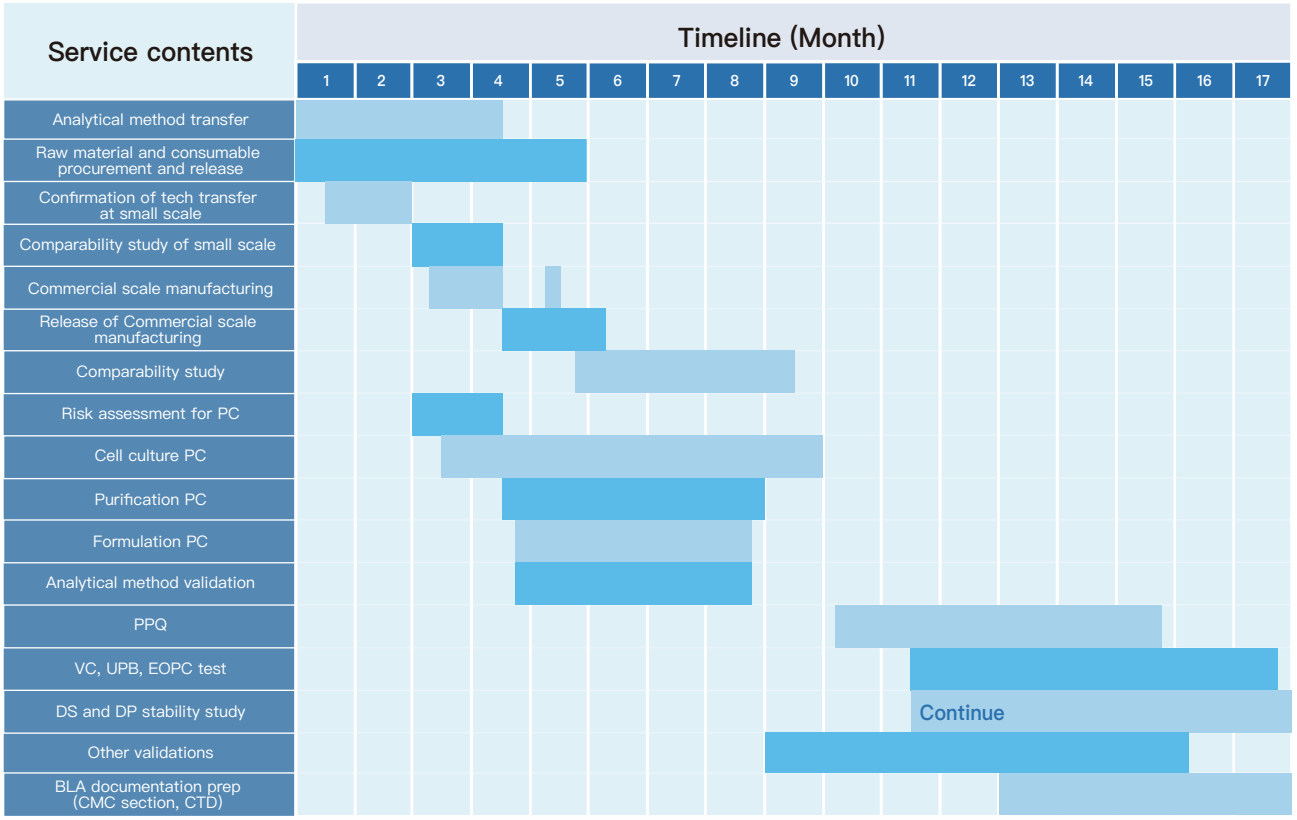
Table 2: Other validation works in PV

Validation items	Validation contents
Clean Validation (equipment, chromatography)	Validate the clean efficiency
Medium holding time validation	Validate the storage time of culture mediums
Buffer holding time validation	Validate the storage time of buffer
Resin lifetime validation	Conduct the lifetime studies of resin on scale down model, and confirm it on commercial scale
UF membrane lifetime validation	Conduct the lifetime studies of UF membranes on scale–down model, and confirm it on commercial scale
Sterilization validation and depyrogenation validation of equipment that directly contacts with sterile materials and products	Validate the sterilization, depyrogenation and asepsis period of key equipment in sterilization Process
E&L study of single use materials	Conduct risk assessment on single use materials and conduct extractable or leachable study on key materials
Filters validation	Bioburden retention study/safety assessment and absorption assessment
Seal integrity validation of container closure	Choose vacuum decay, microbial immersion or aerosol challenge to test container seal integrity
Cell bank validation	Monoclonal verification and cell stability validation/LIVCA study
Cell bank storage validation	Validate the stability of the cell bank in the determined storage condition

Timeline

GenScript ProBio's standard process characterization protocol typically takes 7 months. It takes 17 months from the initial technology transfer to the completion of process validation, including pivotal clinical sample preparation and process characterization.

We also offer an expedited process characterization solution, Fast PC, which can advance your project to the PPQ stage in 4 months. It only takes 14 months from technology transfer to the completion of process validation. Fast PC is appropriate for products with accelerated approval pathways or monoclonal/symmetrical bispecific antibodies in liquid formulation.



GenScript ProBio, a subsidiary of GenScript Biotech Corporation, is a global player dedicated to providing premium end–to–end service from discovery to commercialization with professional solutions and efficient processes to accelerate drug development for customers. GenScript ProBio has established companies in the United States, the Netherlands, South Korea, and China (Hong Kong, Shanghai, and Nanjing) and other regions to serve global customers, and has helped customers in the United States, Europe, Asia Pacific and other regions obtain more than 70 IND approvals since October 2017.

GenScript ProBio's total CGT solution covers CMC of plasmid, virus, mRNA vaccine and nucleic acid drugs for IND filing as well as clinical manufacturing and commercial manufacturing. GenScript ProBio's innovative solutions for biologics discovery and development include therapeutic antibody discovery, antibody engineering and antibody characterization. In the biologics CDMO service, GenScript ProBio has built a DNA to GMP material platform, including stable cell line development, host cell commercial license, process development, analytical development to clinical and commercial manufacturing, and offer fed–batch and perfusion processes to meet the growing needs for antibody and protein drugs. GenScript ProBio has established GMP capacity that meets regulatory requirements of the US Food and Drug Administration (FDA), European Medicines Agency (EMA) and National Medical Products Administration (NMPA).

References

[1] PDA TR60-3

[2] FDA Guidance for Industry: Process Validation: General Principles and Practices

[3] ICH Q8

[4] FDA cGMP 21CFR part 210-211

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