



Number:

Title:

Title (EN):

Type:

Scope:

Area:

Country:

Previous Number:

Document Information

Revision:

Status:

Effective Date:

1 OBJECTIVE

The objective of this document is to describe the Process Validation as stage 2 of the product lifecycle approach according to the applicable Guidelines. This document is part of the Global Validation Master Plan framework and lays down the rules for Process Validation.

2 SCOPE

This document applies to all Grünenthal manufacturing sites involved in the initial validation of new processes, subsequent validation of modified processes or identified revalidation needs, and site transfers. The defined process in this document is focused on stage 2.2 of product lifecycle approach, see figure 1.

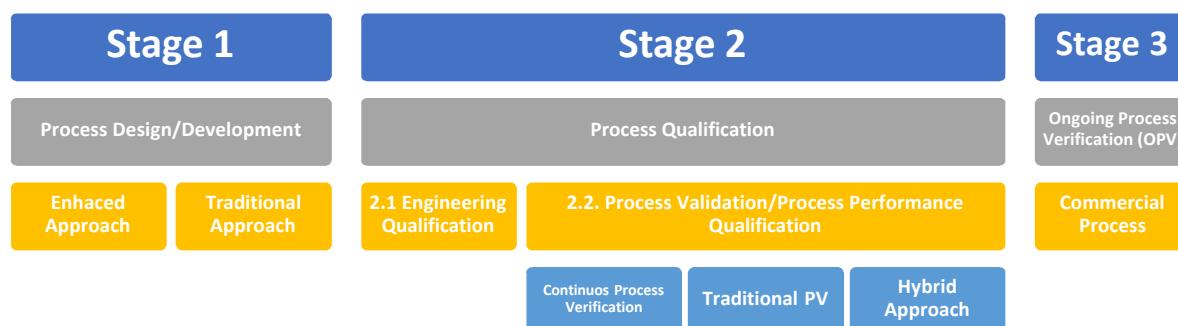


Figure 1. Product lifecycle Approach

This procedure is applicable to the manufacture and packaging of all commercial drug products including Investigation Medicinal Products (IMPs) and APIs including intermediates and/or active substances.

Out of Scope of this document are:

- The manufacturing of substances prior to the regulatory starting material.
- Stage 1: Process Design/Development
- Stages 2.1([PROC-004031](#)) and 3 ([PROC-007415](#))

3 RESPONSIBILITIES

The areas of Production, Quality Control and Quality Assurance have the shared or jointly exercised responsibilities relating to Process Validation. The process flowchart described in the chapter 5.11 includes a RACI matrix.

- Each involved department must be able to identify potential gaps to further define new validation needs
- The involvement of further departments (e.g. development departments as part of a validation team) must be defined individually, based on the scope of the validation

The responsibilities of roles listed in this document are as follows:

Function/Role	Responsibility
Internal Manufacturing Quality Assurance	<ul style="list-style-type: none"> • Implementing the process on a local level • Ensuring compliance with the Quality Management System and applicable local regulations • Ensuring training of this SOP • Reviewing and approving of Process Validation Protocols and Reports in compliance with the local signature procedure and in line with the Site Validation Master Plan and the Grünenthal Global Validation Master Plan strategy
Production or equivalent functions (Processes Owner)	<ul style="list-style-type: none"> • Ensure execution of the Process Validation program in the frame of the Validation Master Plan • Ensure that Process Validation Protocols and reports are reviewed and approved • Ensure that validation activities are performed by suitably trained employees following approved procedures
Quality Control or equivalent functions	<ul style="list-style-type: none"> • Ensures that testing of in-process controls (when applicable) and finished product is performed according to the Process Validation Protocol • Ensures that Process Validation Protocols and reports are reviewed and approved • Ensures that analytical procedures are validated and the employees trained
Subject Matter Expert (SME)	<p>SMEs have sufficient knowledge of the specific product, process, or system to ensure that validation strategies, execution, and outcomes are accurate, compliant, and aligned with regulatory expectations.</p> <p>SME may be Engineering, Automation, Validation, Research and Development, Quality Control, analytical development, Safety, or Manufacturing Technical Lead, etc.</p>
Contract giver (customer)	<ul style="list-style-type: none"> • To comment or finally agree to the proposed actions as defined in the QA agreement (when applicable)

4 TERMS AND DEFINITIONS

Term	Definition/Explanation
Bracketing approach	<p>A science and risk-based validation approach such that only batches on the extremes (e.g. lowest and highest dosage strengths) of certain predetermined and justified design factors, e.g. strength, batch size and/or pack size, are tested during Process Validation. The design assumes that validation of any intermediate levels is represented by validation of the extremes.</p>

Term	Definition/Explanation
Change Control	A formal process by which qualified representatives of appropriate disciplines evaluate any changes that might affect the qualification status of facilities, systems, equipment or utilities or the status of validated processes or analytical methods or computerized systems. The intent is to assess and determine the needed actions to ensure that the process/system/facility/equipment/utility or analytical methods are maintained in a qualified and/or validated status.
Concurrent Validation	Validation carried out in exceptional circumstances, justified on the basis of significant patient benefit, where the Validation Protocol is executed concurrently with commercialization of the validation batches.
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 drug substances and drug 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)
Deviation	Departure from an approved instruction, requirement or established standard.
Discrepancy	Departure of the defined range/acceptance criteria in the test protocol or validation/qualification plan. The discrepancy can be classified and managed as a Deviation in case of a potential impact on the current process and/or on the current operational status of the system.
FMEA (Failure Mode and Effect Analysis)	Risk analysis method. Within the validation process, this technique is based on the evaluation of potential non-compliances and their effects on the final quality and safety of the product.
IPC (In-Process-Control)	Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the product, intermediate or API conforms to its specifications.
Lifecycle	All phases in the life of a product, equipment or facility from initial development or use through to discontinuation of use.

Term	Definition/Explanation
Matrixing approach	Matrixing involves the assessment of the effect of more than one parameter or variable by using a multidimensional matrix to identify the "worst case" or "extreme" conditions for a combination of parameters or variables. These conditions are used during validation of the process, rather than validating all possible combinations.
Medicinal Products	Any substance or combination of substances presented for treating or preventing disease. Any substance or combination of substances which may be administered to human beings or animals with a view to making a medicinal diagnosis or to restoring, correcting or modifying physiological functions is likewise considered a medicinal product.
Ongoing Process Verification [OPV]	Documented evidence that the process remains in a state of control during commercial manufacture. OPV is also known as continued process verification.
Operating Characteristic Curve [OC]	Curve showing the relationship between probability of acceptance of product and the incoming quality level for a given acceptance sampling plan.
Process Analytical Technology [PAT]	Guidance to provide the framework for development and implementation of innovative pharmaceutical development, manufacturing, and quality assurance.
Process Validation [PV]	The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate, API, bulk or finished product meeting its predetermined specifications and quality attributes.
Process Validation Protocol	Document defines the critical systems, attributes and parameters and the associated acceptance criteria.
Process Validation Report	The review and conclusions of the validation must be reported and the results obtained summarized against the acceptance criteria.
Prospective Validation	Validation carried out before routine production of products intended for sale.
Quality by design (QbD)	A systematic approach that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.
Risk Analysis	The estimation of the risk associated with the identified hazards.
Traditional validation approach	A validation approach where a number of at least three subsequent batches of the finished product are manufactured under routine conditions to confirm reproducibility.

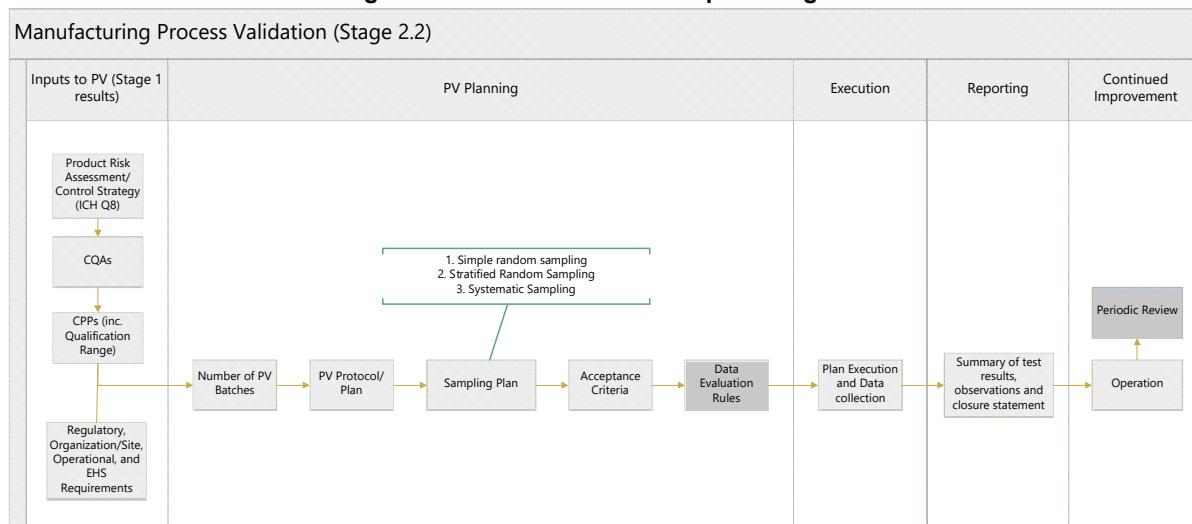
Term	Definition/Explanation
Validation	Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results.

5 PROCESS

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 (as reflected in figure 1).

The general overview of the process validation is reflected in figure 2.

Figure 2. Process Validation steps in stage 2.2



A control strategy must be designed to ensure that the product required will be produced consistently. The controls can include parameters and attributes related to drug substance or drug 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 related to each process step.

A control strategy is developed during stage 1 where the commercial process is defined considering science and risk-based approach.

As a basic prerequisite, robust product development and product understanding support successful Process Validation. Hence, Process Validation is used to establish the link between product development, process development and commercial production. Finally, a robust and validated manufacturing process can be established for routine manufacturing of the product in question. Process Validation confirms that the control strategy adequately ensures the process performance and the product quality.

Process Validation is used to confirm:

- The suitability of the predetermined quality attributes and process parameters, that are considered important for the control of the manufacturing process,

- to ensure the specified product quality and
- to demonstrate that the predetermined quality attributes and process parameters can be consistently met by the process.

The scope of the validation shall cover all manufactured strengths, and all manufacturing sites used for production of the product.

For transfers of products, from one site to another site or within the same site, a bracketing or matrixing approach can be applied to reduce the number of validation batches. However, the existing product knowledge, including the outcome of the previous validation, must be considered for any validation activity.

For the site transfer of already established "legacy" products, the manufacturing process and controls must comply with the marketing authorization and meet the registered specifications and controls of the product in question.

However, irrespective of the validation approach, manufacturing processes must:

- be robust and
- ensure consistent product quality according to the specification before any product is released into the market.

Normally, the batch size used for Process Validation shall be the same size as intended for market supply. The use of any other batch sizes must be documented and justified before any validation starts.

5.1 Pre-requisites

Processes equipment, facilities, utilities and systems used for Process Validation and analytical equipment must be qualified.

Process design is assessed and found to be acceptable. In addition, process is characterized adequately and well understood. As consequence, Quality Target Product Profile, Control Strategy and Manufacturing process description are available.

Analytical test methods must be validated for their intended use before starting process Validation.

Personnel involved in the manufacturing of validation batches must be trained for the proposed task.

For Process Validation batches, production, development, or other site transfer personnel may be involved. Batches must only be manufactured by trained personnel in accordance with GMP using approved documentation (i.e., approved commercial batch records documentation). In the case of scale up, in addition to the production personnel involved in the manufacture of validation batches, development personnel can support the manufacturing to facilitate product understanding.

The suppliers of starting and packaging materials must be qualified prior to the manufacture of validation batches; otherwise, a justification based on the application of quality risk management principles must be documented.

It is especially important that the underlying process knowledge for the justification of the design space (if used) is supported e.g. by appropriate mathematical models to confirm a rational process control strategy.

5.2 Process Validation Planning

Process Validation must follow an approved protocol which describes the planning of the validation activities, which includes the validation strategy and the respective applied validation approach (see chapter 5.2.2).

For a successful PV, good planning is key and essential for activities such as:

- Determining the number of PV batches is necessary to demonstrate that acceptable control over the process has been achieved during the process validation studies. At least three consecutive batches per strength are used to validate a manufacturing process
- Giving instructions for the execution of PV in a protocol.
- Establishing the representative number of samples to assess process performance and to determine variability
- Developing clear specification of acceptance criteria and expectations for successful PV
- Evaluating data and test results obtained from PV (see chapter 5.3)
- Generating concise summary of test results, observations from PV batches, and a closure statement concluding the validation activity (see chapter 5.3)

5.2.1 Sampling Plan and Acceptance Criteria

The development of suitable sampling plans and associated acceptance criteria are essential to achieving the objectives of Process Validation. These activities are best addressed by incorporating the scientific knowledge of the product and process with statistical sampling methodology. It is important that science and statistics are leveraged so that the plans are rigorous and practical.

The acceptance criteria for each parameter must be justified in the PV Protocol if it is not part of development documentation, based on available Stage 1 data, prior knowledge, and/or equipment capabilities.

A sampling plan describes where (locations) and how the samples are taken from the batch, and the number of samples taken from each location. The sampling plan must ensure that the data collected is representative of the parameter to be measured and that the sample size is sufficient to support the conclusions needed for process validation.

The choice of acceptance criteria is part of generating a sampling plan. The sampling plan must be justified; Operating Characteristic (OC) curves are useful for this purpose.

In case of homogenous mixtures like in API and intermediate manufacturing, a detailed sampling plan or justification is optional.

There are three common sampling strategies, which are described as follows:

Type	Definition
1. Simple Random Sampling	"Simple random sampling gives each possible unit an equal probability of being chosen to be tested. A true random sample from a batch could theoretically be obtained by identifying each unit in the batch and then by a completely random process, pick 'n' units. To obtain a true simple random sample is nearly impossible or impractical for sampling a batch of units."

Type	Definition
2. Stratified Random Sampling	<p>It is possible with simple random sampling that, just by chance, the samples may not contain units from segments of the batch that are of interest. "For example, in process validation, the beginning and end of the batch may be of interest. So, although a simple random sample is statistically valid, one may not be satisfied with a sampling plan that does not include samples taken from the beginning or end of the batch."</p> <p>A stratified sampling strategy partitions the batch into "strata," or groups, where differences may exist between the strata. The combination of all strata must cover the entire batch. Then random sampling is performed within each stratum.</p>
3. Systematic Sampling	"A systematic sampling strategy is performed by taking a sample(s) at equal intervals throughout the batch, typically based on the total number of units or manufacturing time. The first sample location is determined at random and then the remaining samples are taken at equal intervals."

5.2.2 Process Validation Approaches

Manufacturing processes can be validated by different approaches.

Process validation can be performed in a traditional way, regardless of the chosen development approach.

Manufacturing processes applying the traditional approach shall undergo a prospective validation program, prior to product approval.

However, as an alternative, continuous process verification can be applied for products that were developed by a QbD concept. As a prerequisite a substantial amount of product and process knowledge and understanding has been gained by e.g. Process Analytical Technology and statistical tools such as multivariate statistical process control.

A combination of traditional Process Validation and continuous process verification may be applied. The in-line, on-line or at-line monitoring that is often utilized for continuous process verification provides substantially information and knowledge about the process on going and might facilitate process improvements in a faster manner.

A Bracketing approach can be applied in the case of Process Validation referred to multiple strengths of identical or closely related formulations or different sites, if adequately justified.

Examples include but are not limited to:

- capsules of different strengths made with different fill plug sizes from the same powder blend,
- tablets of different strengths manufactured by compressing varying amounts of the same granules/powder blend,
- oral solutions of different strengths with formulations that differ only in minor excipients (e.g. colorants, flavorings) and
- site transfers.

Furthermore, bracketing can be applied to different container sizes or different fills in the same container closure system.

A Matrixing approach can be applied in the case of Process Validation when the target is to assess the effects of more than one parameter or variable. Matrixing approach foresees the usage of a multidimensional matrix to identify the "worst-case" or "extreme" conditions for a combination of parameters or variables. Examples include but are not limited to the same product manufactured by using alternative equipment, alternative raw material sources and alternative batch sizes. The rationale for using this strategy must be scientifically discussed and justified.

Validation trials using either bracketing or matrixing approaches must be described in detail and must be scientifically justified. A combination of both may be acceptable in complex cases where multiple variables must be considered (e.g. Process Validation Protocols where one or more changes must be applied to a product different dosage strengths, alternative equipment and/or alternative raw material source simultaneously).

5.2.2.1 Retrospective Process Validation

Retrospective validation is no longer an acceptable approach for finished product manufacturing.

For APIs a retrospective validation can be performed in case of well-established processes that are used without significant changes to API quality due to changes e.g. in raw materials, equipment, systems, facilities, or the production process. This is acceptable under the following conditions:

- Critical quality attributes and critical process parameters were identified in the past.
- Appropriate in-process acceptance criteria and controls were established,
- There have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability; and,
- The impurity profile has been established for the existing API.

Batches selected for retrospective validation must be representative of all batches made during the review period, including any batches that failed to meet specifications, and must be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process

5.2.2.2 Traditional Process Validation

Applying the traditional Process Validation approach, a certain, predefined number of batches of the finished product are manufactured according to the Validation Protocol to confirm reproducibility.

It is generally considered acceptable that a minimum of three consecutive batches per strengths are used to validate a manufacturing process. An alternative number of batches can be justified taking into account whether standard manufacturing methods are used and whether similar products or processes are already used at the site. An initial validation exercise with three consecutive batches may need to be supplemented with further data, obtained from subsequent batches as part of an on-going process verification exercise.

Traditional Process Validation is typically performed at the end of the pharmaceutical development and/or process development, normally after upscaling to full production scale and prior to marketing of the finished product.

As part of the Process Validation lifecycle, some Process Validation studies may be conducted on pilot scale batches if the process has not yet been scaled up to production scale (e.g. in case of variations). It is important to note that pilot batch sizes must be representative and 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 solid oral dosage forms this size must generally be 10% of the maximum production scale or 100,000 units whichever is the greater. Where the intended batch size is less than 100,000 units, the predictive value of the pilot batches may be limited. Those batches having a limited predictive value must be justified and followed by more predictive batches.

In the case of pilot batches of APIs or intermediates the pilot batch size must be representative compared to the industrial batch size. The batch scale must be justified with a science and risk-based approach.

Since it is not generally considered useful to conduct full validation studies on pilot scale batches, the Process Validation scheme must be completed for each product for subsequent execution on a production scale, if justified bracketing or matrixing can be applied.

5.2.2.3 Continuous process verification

Continuous process verification can be applied as an alternative to Traditional Process Validation. It may be applicable for the manufacturing of the finished product and API processes that were newly developed by a QbD approach, where it has been scientifically established during development that the applied control strategy provides a high degree of assurance of product quality.

The scope and extent of process verification will be influenced by a number of factors including:

- prior development and knowledge of the manufacturing of similar products and/or processes;
- the extent of process understanding gained during development;
- development studies and commercial manufacturing experience;
- the complexity of the product and/or manufacturing process;
- the level of process automation and analytical technologies used (e.g. Process Analytical Technology (PAT));
- for already established "legacy" products, the robustness of the process and the product understanding obtained during the product life-cycle;
- the manufacturing history since the point of commercialization, as appropriate.

The key elements that need to be scientifically considered in the continuous process verification are:

- required attributes for incoming materials;
- critical quality attributes of the product;

- critical process parameters;

The following elements must be defined:

- the type of testing or monitoring to be performed;
- the acceptance criteria to be applied;
- Data evaluation

Any statistical models or tools must be described. A regular periodical assessment of the control strategy throughout the product life cycle must be described. Enhanced sampling and monitoring can be applied (e.g. after change control, after detection of trend etc.) in order to confirm the validity of the process. Periods of enhanced sampling and monitoring may help to increase process understanding (continuous improvement) and can be part of a further process monitoring program (i.e. predefined investigation program/CAPA). Process trends, such as the quality of incoming materials or components, in-process and finished product results and non-conformances must be assessed.

It is necessary to use tools like Process Analytical Technology or multivariate statistical process control to confirm the process robustness.

The general principles laid down in the previous chapters 5.1 General Considerations and 5.2 Prerequisites still apply.

5.2.2.4 Hybrid approach

A hybrid of the traditional approach and continuous process verification can be applied where there is a substantial amount of product and process knowledge and understanding which has been gained from manufacturing experience and historical batch data.

This approach can be also used for any validation activities after changes or during ongoing process verification even though the product was initially validated using a traditional approach.

5.2.2.5 Prospective Validation vs. Concurrent validation

Process Validation activities must be complete before the release of the batches on the market (Prospective Validation). In fact, processes must be shown to be robust and ensure consistent product quality before any product is released to the market.

In exceptional circumstances, where there is a strong benefit-risk ratio for the patient e.g., for rare diseases or limited availability of medicines, it may be acceptable not to complete a validation program before routine production starts (concurrent validation). However, if the company intends to apply in exceptional cases the Concurrent Validation this decision must be justified and documented in the VMP as well as in the Validation Protocol approved by Qualified Person (QP or function with equivalent responsibilities) using a risk-based approach.

Where a concurrent validation approach is adopted, sufficient data must be presented to support a conclusion that any given batch of products meets the predefined acceptance criteria. The results and the conclusion must be formally documented and available to the Qualified Person or person responsible for batch release prior to certification of the batch.

5.3 Process Validation Execution and Reporting

After the process validation execution is completed, graphical tools like run charts, individual value plots, and (in some cases) box plots can be used to confirm that the process performance is like that expected based on stage 1 data, when available. Statistical tools (e.g., Minitab) can be used to perform the defined statistical evaluations.

Data must be collected and reviewed against predetermined acceptance criteria of the Validation Protocol and fully documented in Process Validation reports. The report must reflect the Validation Protocol.

The validation report ([SUP-012078](#)) includes an assessment of all executed validation activities.

Any change or departure to the approved protocol during execution (e.g. acceptance criteria, operating parameters etc.) must be scientifically assessed on the impact of the finished product and must be documented as a discrepancy ([SUP-012243](#)) and/or event/deviation ([PROC-005388](#)).

Results which fail to meet the pre-defined acceptance criteria must be recorded as a deviation/OOS and be fully investigated according to global procedures ([PROC-004019](#)). Any implications for the validation must be discussed in the validation report.

Moreover, a suitable conclusion (i.e. CAPA) to correct any deficiency must be included.

Finally, the completion of the PV triggers the initiation of the Ongoing Process Verification ([PROC-007415](#)).

5.4 Risk Assessment

The decision on the scope and extent of validation must be based on a justified using a risk-based approach of the manufacturing process.

The basis by which process parameters and quality attributes are identified as being critical or non-critical must be clearly documented and justified, considering the results of any risk assessment activities. The CPPs and CQAs are defined in the respective control strategy, which is established during stage 1 of the product lifecycle. The methodology for the definition of the CPPs and CQAs is described in the [TMAT-002332](#).

The potential risk identified during risk analysis for any new processes/changes, introduced in existing processes, is mitigated by the development of an adequate risk mitigation plan. The detectability of possible failures during Process Validation is supported by a suitable testing and sampling plan.

Based on the outcome of Process Validation, the risks associated with routine production must be re-assessed, and the results must ensure the control of the whole production process.

5.5 Validation of Packaging

Process Validation may also cover primary and secondary packaging operations. Process Qualification of packaging equipment (primary and secondary) can be combined with Process Validation. Minimum and maximum operating ranges defined for the critical process parameters such as temperature, machine speed and sealing pressure or for any other critical factors must be tested within lifecycle approach.

In the case of well-established packaging processes, a scientific evaluation associated to a Matrixing, Bracketing or worst-case approaches can be applied to define the extension of the revalidation for e.g. changes affecting the primary and secondary packaging steps.

Exchanges of the packaging equipment and consequential changes of the processing parameters during primary packaging may have a significant impact on the integrity and correct functioning of the pack, e.g. blister strips, sachets and sterile components. As prerequisite, the packaging equipment must be qualified.

5.6 Validation documents

Validations documents, including at least protocols and reports, must be created to support and to provide documented evidence about Process Validation Activities.

Where Validation Protocols and other documentation are supplied by a third-party providing validation services, the validation responsible team at the manufacturing site must confirm suitability and compliance with internal procedures and regulations before approval. Vendor protocols may be supplemented by additional documentation/test protocols by the manufacturer before use.

5.6.1 Process Validation Protocol

Validation of process must be conducted according to the approved written Process Validation Protocol ([SUP-012077](#)). The protocol must be reviewed by Quality Assurance and at least by Production, QC or equivalent functions.

The Process Validation Protocol must be approved at least by the process owner and QA/QP.

Each protocol must be properly identified including edition.

If there is the need to revise a protocol after it was signed and approved, it is possible to issue an updated edition that replaces the previous one. The Validation Protocol must include a dedicated table (history) where all editions are properly listed, with the description of the reasons for the updating.

Process Validation Protocol must include or refer at least to the following elements:

1. Review and approval of the protocol by appropriate departments and the QA;
2. Involved product description (Dosage form and Dosage Strength, APIs);
3. Process Validation Scope (including reference to change control);
4. Functions and responsibilities;
5. Involved Personnel Training;
6. Reference to Previous Validation(s) (if applicable);
7. Validation Strategy (including suitable justifications):
 - Validation Approach (Traditional, Continuous process verification, Hybrid Approach);
 - The number of batches for which additional monitoring is proposed;
 - Process for release and certification of batches, if applicable (Prospective Validation, Concurrent Validation);

8. Process flow sheet;
9. List of the equipment/facilities to be used (including measuring / monitoring / recording equipment) together with the qualification/calibration status;
10. Control strategy which includes:
 - a. Summary of Critical Process Parameters and Critical Quality Attributes with their associated limits/specifications.
 - b. The type of testing in place during the standard routine (in-process, release characterization) and acceptance criteria for each significant processing step;
 - c. Additional testing to be carried out with acceptance criteria;
11. The manufacturing conditions including operating parameters, processing limits and component (raw material) inputs;
12. Summary of other (non-critical) attributes and parameters (including yield) which will be investigated or monitored during the validation activity and the reasons for their inclusion;
13. List of analytical methods and method validation status, as appropriate;
14. Risk Analysis and relevant outcome or a reference to (when it is part of another document);
15. Sampling plan and the rationale behind it: who, where, when, how, how many and how much (sample size);
16. Methods for recording and evaluating results;
17. Change History.

5.7 Validation of Clinical Trials Batches

Process Validation for the production of APIs and Investigational Medicinal Products for use in clinical trials is normally inappropriate where a single batch is produced but the extension of Process Validation must be scientifically sound and reflect the stage of the development process.

The combination of controls, calibration and equipment qualifications assures quality during this development phase and guarantees GMP compliance.

Production steps such as e.g. the sterilization process for Investigational Medicinal Products must be completely validated.

5.8 Change Management

Changes to validated processes must follow the change control procedure and must be formally authorized before execution, where also the impact to the registered product dossier must be assessed.

All planned actions to process equipment, process environment (or site), method of production or testing or any other change that may affect the product quality or reproducibility of the process must be documented and executed as defined in the corresponding plan.

The likely impact of the changes of facilities, systems and equipment on the product must be evaluated, including risk analysis. The need for, and the extent of, revalidation must be determined.

The Change Control procedure ensures that sufficient supporting data are generated to demonstrate that the revised process is maintained in a validated status.

See also the global SOP for "Global Process for Change Management" ([PROC-007059](#)).

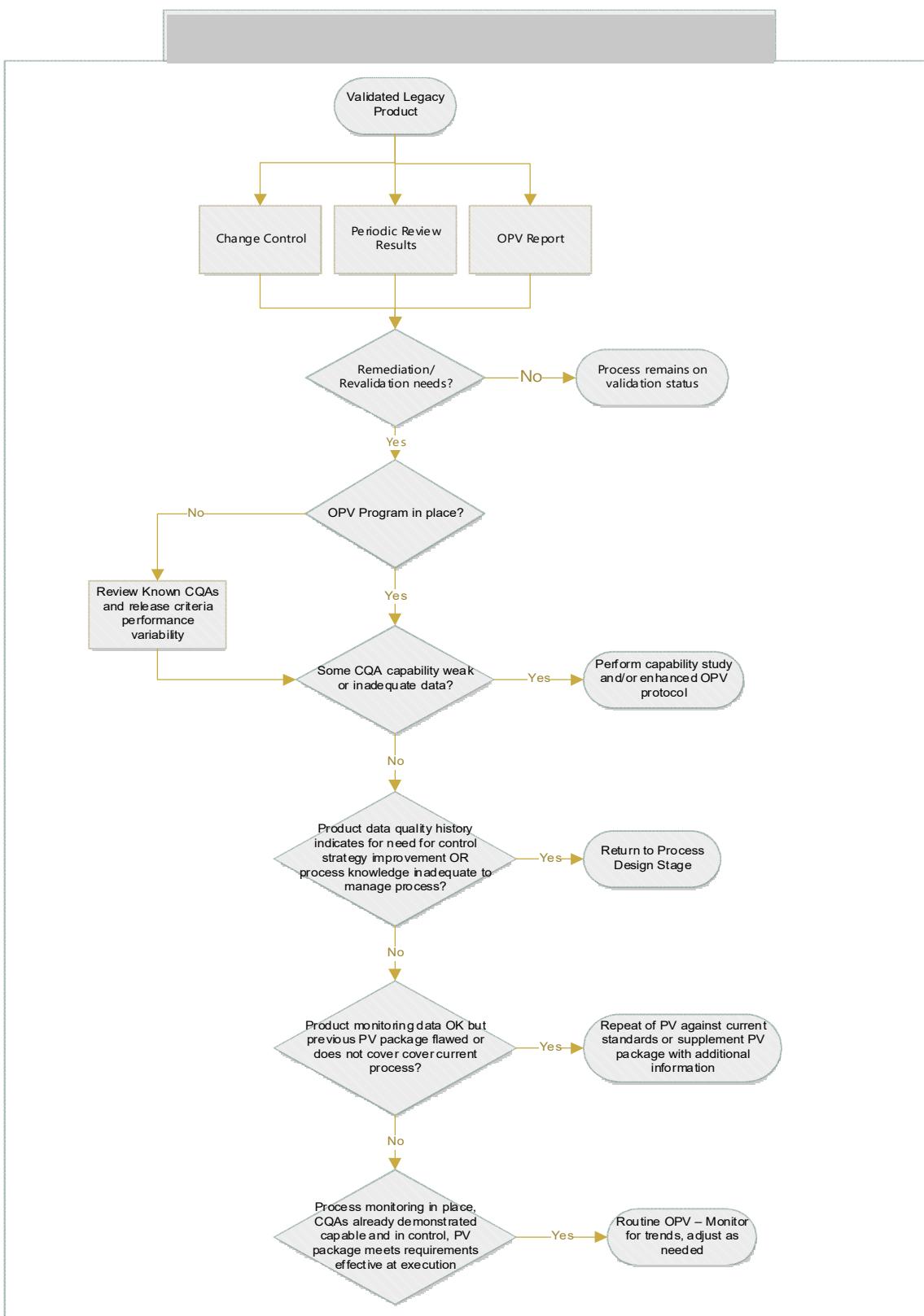
5.9 Legacy Products Implementation

The implementation of the product lifecycle approach for legacy products can be determined by the following scenarios:

- Expectations for revalidation activities due to changes in the current process
- Evaluation of OPV results indicates the need for control strategy improvement, where the stage 1 application is required.
- Previous PV package flawed or does not cover current process according to the Periodic Review results.

Where an evaluation is required to identify which stage of the product lifecycle must be started to ensure product and process robustness.

Figure 3 reflects the decision tree for legacy products and must be used to determine the respective stage of the product lifecycle according to the assessment:



5.10 Periodic Review and Revalidation

The process shall be reviewed and evaluated in a defined period to determine if a revalidation is required. Moreover, frequency of revalidation depends on the rigor of the OPV program ([PROC-007415](#)), including the frequency and thoroughness of within and between batch variability evaluation.

The elements to be reviewed are the following but not limited to:

- Trends of Critical Quality Attributes and Critical Process Parameters or outcome of ongoing process verification (OPV) report.
- Trends in quality indicators (e.g., CAPA, deviation, change requests, complaint, etc.)
- Quality Management Review outcome
- Change(s) to the actual process
- Transfer of product to another facility
- Findings (from Audit or Self-Inspection)

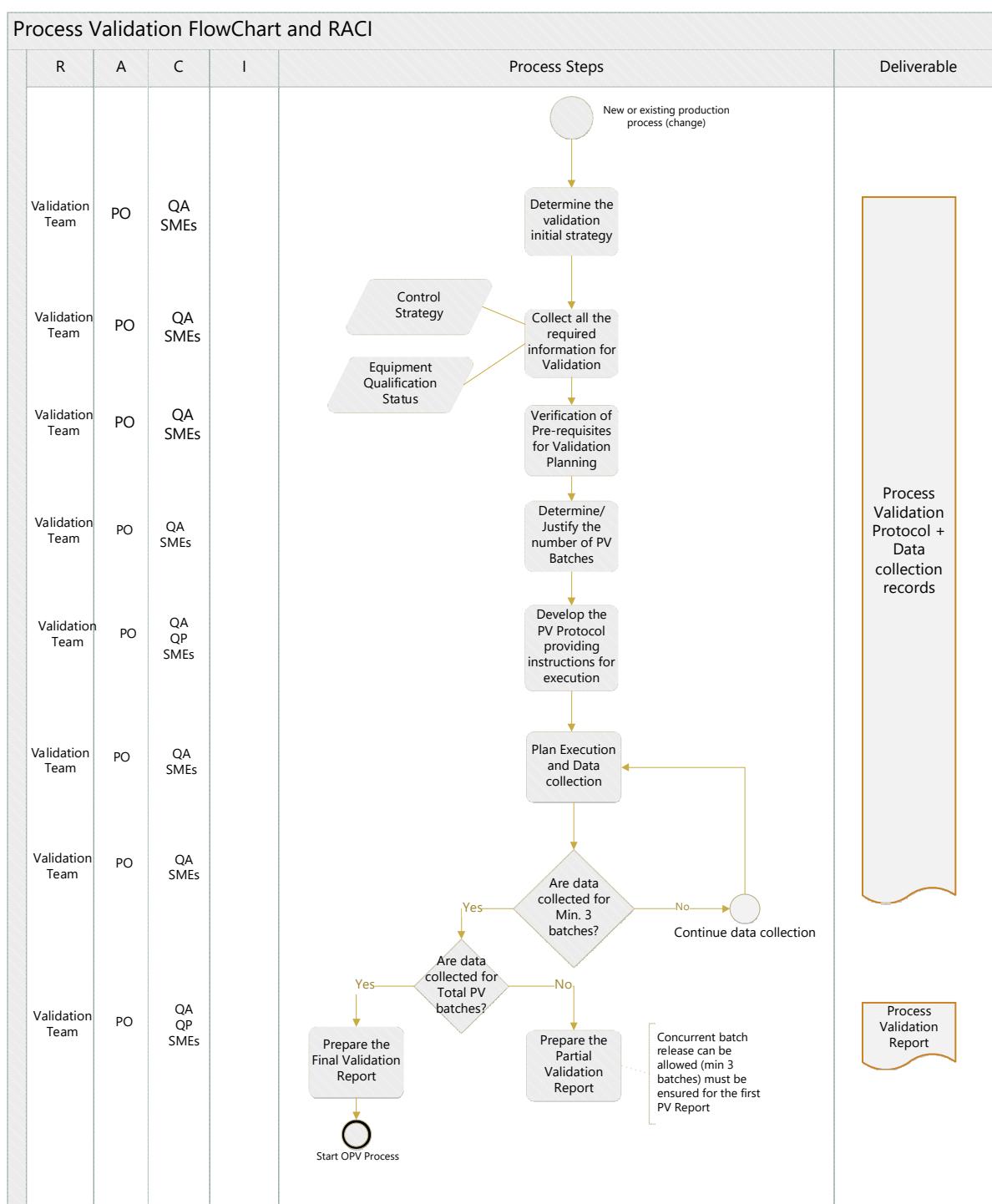
The periodic review of the validation status can be done by:

- leveraging OPV data analysis and,
- trending for the process performance which is evaluated within Product Quality Review.

OPV is implemented using the risk-based approach defined in the [PROC-007415](#). Therefore, if the OPV is not established for a particular product, a revalidation must be performed in a maximum period of 5 years.

Finally, the conclusion of validation status must be included within the PQR report, including the revalidation needs.

5.11 Process flowchart



SMEs: Subject Matter Experts

6 REFERENCES

6.1 Guidelines

- EU Directive 2003/94/EC
- EU Guidelines for GMP, Part I 1.2, 2.5, 2.6, 2.7, 5.23-5.26

- EU Guidelines for GMP, Part II 2.2, 8.45, 12, 19.6
- EU Guidelines for GMP, Annex 15, Annex 13
- EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev.1, Corr. 1 (EMA guideline on Process Validation)
- FDA Guidance for Industry - Process Validation: General Principles and Practices
- ISPE Practical Implementation of the Lifecycle Approach for Process Validation, 2019
- WHO Technical Report Series 992, 2015, Annex 3, Appendix 7
- WHO Technical Report Series 937, 2006, Annex 4
- 21 CFR §211.68, 21 CFR820
- ICHQ2, ICHQ7A, ICHQ8, ICHQ9, ICHQ10
- PIC PE-009, Annex 15
- PE-009-12 Part I, Part II

6.2 Standard Procedural Documents

PROC-004019	Global Process for Deviation Management
PROC-004031	Commissioning and Qualification (C&Q) of Equipment
PROC-005388	Global Process for Quality Event Management
PROC-007059	Global Process for Change Management
PROC-007415	OPV-Ongoing Process Verification
SUP-012077	PV Template: Process Validation Protocol
SUP-012078	PV Template: Process Validation Report
SUP-012243	C&Q/PV Discrepancy Form
TMAT-002332	Application of QRM to Qualification and Process Validation

7 HISTORICAL INDEX

Revision no.	Description of changes
01	Initial document migrated to MasterControl
02	Adaptations due to periodic review as following: Section 3: Function/role name were modified to stay more general without describing department or position. Section 4: Some abbreviations were removed and some definition introduced or updated like: Discrepancy, Deviation and OPV. Section 5: Following changes included: <ul style="list-style-type: none"> • It was replaced deviation by the wording “discrepancy”.

Revision no.	Description of changes
	<ul style="list-style-type: none">Section 5.4. It was reworded one of the sentences to provide examples how the trends of CQA and CPP can be periodically evaluated.Section 5.10. is a new section to provide the frame for the periodic revalidation <p>In addition, it was replaced the wording "should" by "must", "shall" or "can".</p>
03	The content of the process was adapted to introduce the product lifecycle approach where the three stages are differentiated. The RA approach was clarified to include as part of the Product Development/Design phase and OPV section was removed due to a dedicated procedure is in place.