CMC PLATFORM BEST PRACTICES

PART C

Process Validation for platform technologies:

Best Practices under accelerated scenarios

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1. Scope and guidance for process validation best practices under accelerated scenarios

This document provides a framework for accelerated execution of Process Validation (PV), as required in a public health emergency (PHE) situation e.g. in an epidemic, pandemic, or outbreak situation. It compiles PV best practices to consider under accelerated pathways by leveraging platform technologies and prior knowledge/data. It outlines how prior knowledge; risk assessment and risk mitigation can support those accelerated pathways towards requesting early regulatory authorisation for wide use of the vaccine product (emergency use; conditional marketing authorisation or emergency use listing, to only list a few examples). In the context of an early regulatory authorisation as supported by accelerated pathways, PV should no longer be regarded as a series of sequential stages (e.g. PV stage 1, 2, 3) but rather as a holistic exercise where the developer must assess the strong benefit-risk balance of the product for the patient. The thoughtful approach would be outlined in a clear plan to be shared with the relevant Health Authority (HA), which should describe e.g. how the data will be available to support reproducibility, how much data would be gathered and when. Consideration is to be given to the fact that data sets may vary and may originate from a wide range of sources, i.e. supportive data (e.g. non-PV batches from clinical or investigational); small scale supportive process evaluation; concurrent validation; data deferred to post-approval/authorisation; etc. All these possibilities will need to be documented in the validation strategy and, where required or beneficial, discussed and agreed in principle with the authority in advance (e.g. via scientific advice or rolling review). The developer will have to assess their specific situation (e.g. how much prior knowledge it owns and how robust its platform technology is) and justify the data to be presented to the HA, including the format and the estimated timelines for provision of such data (e.g. rolling submission).

Readers of this PV Best Practices document (called Part C) are advised to first consult the Overview of the CMC Platform Best Practices (called Part A) for an overall understanding of the framework and principles governing the Best Practices documents.

Regarding the structure applied to the PV Best Practices document, there are six distinct core sections (section 2 to 7) and an annex which should be read in the order provided:

- Section 2 deals with the clear expectation and the benefit to document the manufacturing process for internal use. Often in times, this will be the basis to build process descriptions intended for regulatory submissions.
- Section 3 describes the different steps to consider when performing a risk assessment.
- Section 4 deals with the design of the control strategy and what key elements shall be considered.
- Section 5 lists some tools that the developer may choose from (either isolated or in combination) when defining its PV strategy.
- Section 6 focuses on possibilities to defer certain activities and/or provision of PV-related data to the HA via post-approval commitments.
- Section 7 shows a real-life case study from the industry that exemplifies how some of the process validation strategies described in these Best Practices have been successfully applied.

- A template is included in the annex of this document as an example of a regulatory document to be shared with HAs. It details the company's PV strategy under an accelerated scenario.

Throughout the entire document and where suitable, information is provided in tabular format to guide developers with decision making and classification of actions, separating steps that can be accelerated by use of prior knowledge from those that should follow the standard pathway.

Sometimes terminology used in this document may not be accurate enough for all countries worldwide and therefore it will require readers to adapt wording and meaning in line with existing regulatory procedures that are equivalent to the ones being referred to. As an example, the term "emergency use batch(es)" refers to vaccine batches which are manufactured with the manufacturing process submitted as part of a regulatory dossier to request initial emergency use authorisation. In many countries an emergency use authorisation procedure is inexistent, or it may be designated differently. Therefore, readers will need to abstract the term and adapt to their circumstances. Once such authorisation is granted, produced batches could be called "commercial batches", thereby implying that those batches can be used in the context of broad immunisation outside of a clinical setting.

Lastly, it is generally understood that the availability of data depends upon the stage of development. As development progresses, the level of process knowledge increases. The developer is therefore encouraged to continually update internal documentation with the emerging knowledge and information, clearly identifying any changes, in preparation of regulatory engagement and submissions to the relevant HAs.

2. Process Description

Manufacturers will describe in their internal documentation the process overview in the form of a flow diagram of the manufacturing process along with the testing that should be done in each step. The process flow diagram should include every process step in a detailed description, listing relevant in-process controls and process parameters wherever applicable. For steps involving intermediates, the intended and maximum allowable hold-times and associated storage conditions (e.g. temperature, light protection, container/closure system) should also be specified, with cross-reference to supporting controls. Process flow should be clear on the chronology of the activities to be done in sequence vs. those running in parallel.

3. Risk based approach for PV Activities

3.1 Risk Assessment in an accelerated scenario

To establish a tailored process validation strategy under accelerated conditions, a key element—alongside leveraging existing knowledge from platforms—is conducting a detailed risk assessment focused on both product and process. Development reports should document assessed risks during development, which, together with prior knowledge, lay the groundwork for risk assessment preceding accelerated process validation. This approach ensures a direct path from the initial Quality Target Product Profile (QTPP) to lot acceptance and release criteria. The risk assessment process encompasses identification, analysis, and evaluation of risks. Outcomes of risk assessments should produce a list of

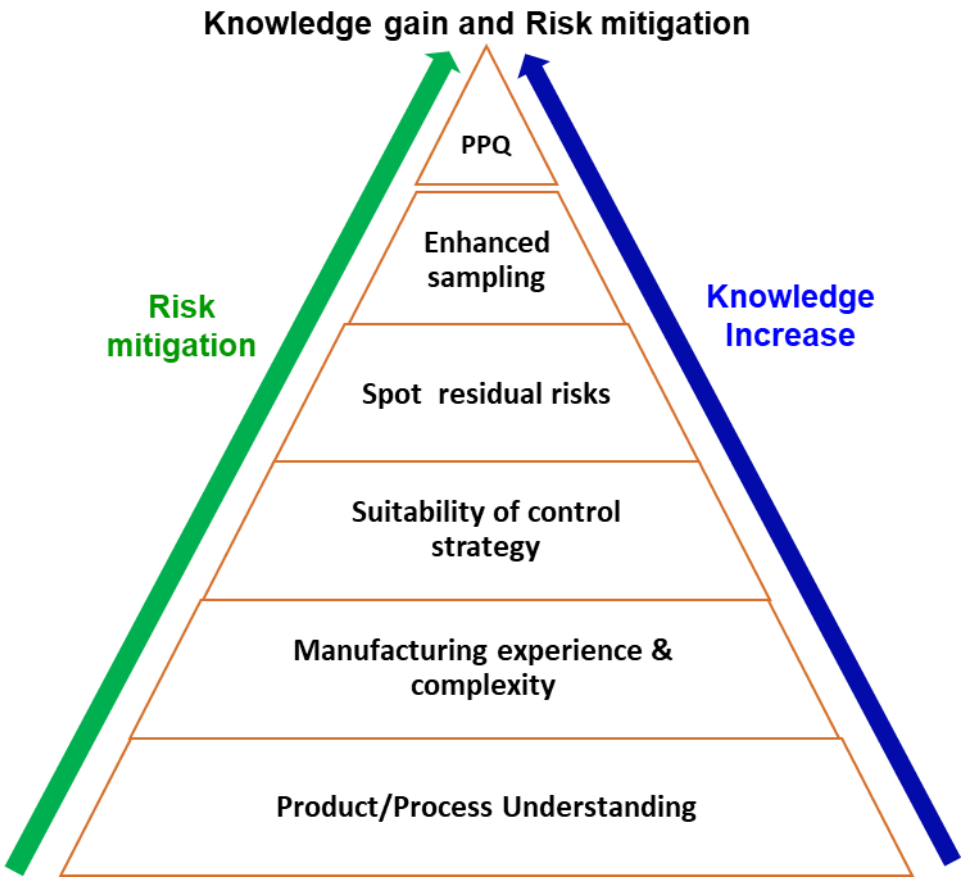
identified and prioritized risks, according to the company's procedures and risk scoring tools (e.g., FMEA or HACCP, at a minimum qualitatively, refer to risk factor tables). Risks deemed acceptable based on prior knowledge and scientific justification should be managed accordingly. The focus after risk assessment should shift to strategies aimed at reducing risk severity, decreasing likelihood, and enhancing detectability, thereby minimizing the risk of specific events. 3.2 Determine Residual Risk Level and Mitigation Strategies.

The level of residual and acceptable risk will depend on to what extent the following milestones can be met:

- There is enough prior knowledge and manufacturing experience to confirm that the relevant process parameters and ranges are robust to produce the desired product quality.
- The manufacturing process consistently produces a product that meets pre-determined specifications and is closely monitored.
- The variability of the manufacturing process is being assessed to determine its extent.
- The impact of various sources of variability on critical quality attributes (CQAs) is well understood.
- The risk associated with manufacturing is assessed and appropriate control strategy is adopted.

The residual risks should be defined using a rationale based on the flow illustrated in **Figure 1**:

Figure 1: Relationship between the level of knowledge and risk



3.2.1 Assess product knowledge (Step 1)

Product knowledge assessment has the objective of identifying product quality requirements. It is related to Critical Quality Attributes using at a minimum, severity and probability to each risk identified. The following key questions as listed in **Table 1** should be taken into consideration and a resulting overall risk score should be provided.

Table 1: Risk assessment based on product knowledge

Risk factor 1: Product knowledge	Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH	Example of a high-risk scenario that requires a mitigation strategy	Example of low-risk scenario which possibly supports acceleration	Risk score High Medium Low
	Is prior knowledge from within the sub-class vaccine (protein sub-unit, viral vector, mRNA, inactivated virus) available to confirm the completeness of attributes to be included in the release testing and characterization panel?	New product with new platform technology.	• Prior authorization of "prototype" strain. • Prior knowledge of a licensed product. • Prior knowledge from multiple development products, throughout different clinical phases, based on the same platform technology. • Specific tests for structural and antigenic differences of the molecule are available.	To be assigned

Risk factor 1: Product knowledge	Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH	Example of a high-risk scenario that requires a mitigation strategy	Example of low-risk scenario which possibly supports acceleration	Risk score High Medium Low
	Are all (p)CQAs for safety and efficacy identified by using a quality risk management approach? What is the level of understanding of the product attributes (i.e., how a particular attribute affects patient safety and efficacy)? Are the selected CQAs in the testing panel confirmed and supported by clinical data and relevance?	(p)CQAs are determined based on literature knowledge and compendial requirements. POC clinical batches have confirmed that batches are safe and immunogenic. Dose finding studies ongoing.	(p)CQAs and their acceptance criteria are all identified and justified in a QRA like document (e.g. QTPP) document and confirmed by clinical studies.	To be assigned
	Are suitable/justified analytical methods developed/validated and in place to measure specifically and with the adequate resolution any differences in the attribute's properties?	Non-compendial methods are used and are only qualified (not validated) for release and/or characterization testing.	Analytical methods are state of the art for the platform product or prototype strain and are at least qualified for characterization tests. Applying orthogonal tests for characterization is best practice. Most appropriate and justified release tests are validated for at least the safety tests.	To be assigned
	Have regulatory and pharmacopeial requirements been considered to establish the CQA list and the associated methods?	Compendial methods are not available or if available they are not adopted as first choice.	Regulatory advice has been sought and considered before finalizing the control strategy of the product.	To be assigned

Risk factor 1: Product knowledge	Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH	Example of a high-risk scenario that requires a mitigation strategy	Example of low-risk scenario which possibly supports acceleration	Risk score High Medium Low
	Sufficient DS and DP stability data available to justify the proposed shelf life	Stability data available from development studies/scale. or stability is predicted via modelling approaches(?)	Stability data from previously licensed vaccines using the same platform could be considered as supportive information. Or Sufficient and solid scientific justification is available to demonstrate low-risk and thus propose a shelf life that goes beyond real-time data (e.g. product is frozen storage below the endothermic transition temperature, which implies a low risk of degradation).	To be assigned
Residual risk level for product knowledge (factor 1): Take all assessment elements into account				High/medium/low

3.2.2 Assess Process understanding (Step 2)

Process development is an essential prerequisite for defining the criteria and conditions to be addressed in process validation studies. Process understanding gained during development aids in identifying which material attributes (e.g. raw materials, starting materials, reagents, solvents, process aids, intermediates) and process parameters should be further evaluated during process evaluation/validation studies, as per **Table 2**. Risk assessment may include documented prior knowledge from public or proprietary sources used to identify and justify material attributes and process parameters with the potential for affecting drug substance CQAs and process performance. An overall resulting risk score should be provided.

Table 2: Process risk assessment

Risk factor 2: Process understanding	Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH risk	Example of a high-risk scenario that requires a mitigation strategy	Example of low-risk scenario which possibly supports acceleration	Risk score High Medium Low
	Is the level of knowledge based on experimental design and studies that have been executed at small scale, pilot and/or commercial scale? Or is data leveraged from prior and platform knowledge? Is commercial experience available from a similar product(s)?	New product or new platform technology. CPP/CMA/CQA interaction is not fully understood, POC data is available with experimental data.	Similar Product with platform technology has been successfully validated.	To be assigned
	Are knowledge gaps adequately risk-assessed, scored/prioritized and mitigation actions planned during concurrent validation activities (more sample locations/frequency) or as part of later PV activities, e.g. during CPV?	Knowledge gaps are pertinent, experimental data show significant variability due to a lack of understanding of interaction effects of CPPs. Only high number of IPC/IPT mitigate a risk of failure.	No high knowledge gap has been indicated in QRM risk assessment. Routine sampling plan as for commercial manufacturing can be applied.	To be assigned

Risk factor 2: Process understanding	Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH risk	Example of a high-risk scenario that requires a mitigation strategy	Example of low-risk scenario which possibly supports acceleration	Risk score High Medium Low
	Are any validation studies already existing for similar products or unit operations that can be leveraged? (e.g. PQ, aseptic process simulation, homogeneity for filling lines and freeze-driers, viral inactivation, hold time, resin/membrane lifecycle etc.)	Any validation studies will be leveraged from prior knowledge or platform technology. Unit operations having an impact on safety are concurrently validated	All standalone validations are available or will be committed to be executed after PPQ as post approval commitments.	To be assigned
	Is the process based on unit operations that are fully qualified and confirmed to be robust in routine commercial production? Are facilities, equipment, and utilities reliable, automated and monitored/alarmed? Does the manufacturing facility comply with cGMPs?	Unit operations have not been fully designed (or will be) to the process needs but have been qualified to meet the process requirements.	GxP licensed facility is used for PPQ campaign. Facility and equipment are used for other commercial products based on similar technologies.	To be assigned
	Have qualification or engineering batches been executed at scale to gather further knowledge on robustness of equipment, production planning and to train operators, challenge, and check procedures during process execution (batch record and sampling)?	Limited number of representative qualification batches executed; those batches are trial/evaluation batches at scale or at pilot scale.	Commercial scale GxP like batches have been produced upfront to the PV campaign and data have been fully analysed and remaining risks are addressed. Those batches could fully support PV activities/conclusions.	To be assigned

Risk factor 2: Process understanding	Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH risk	Example of a high-risk scenario that requires a mitigation strategy	Example of low-risk scenario which possibly supports acceleration	Risk score High Medium Low
	Is a design space established for critical unit operations? Are CPPs and performance related parameters impacting CQAs, and process performance identified and assessed as part of a systematic QRM exercise using tools like FMEA or HACCP?	Ranges of CPPs/performance related parameters are not set experimentally or by modelling, literature data or prior knowledge of similar products is leveraged.	All ranges for CPPs and performance related parameters are confirmed, and adequate controls are in place.	To be assigned
	Are scale dependent parameters (SDP) identified and adequately addressed and resolved at pilot/commercial scale?	SDP are identified, but not experimentally confirmed.	Ranges of SDP are experimentally or by modelling confirmed, part of the platform technology can be leveraged from similar products.	To be assigned
	Are routinely compendial materials used or novel or non-compendial grade quality available?	Many materials are catalogue products, and preferred vendors are reliable and audited. Some exceptional materials are at least risk assessed.	Materials being used are well qualified and part of an existing platform technology.	To be assigned
	Are all input/starting materials (media, buffers, SUS, excipients, chemical& biological) and primary packing material GxP qualified and suitable to	Qualification of starting materials not completed in-house. Vendor specifications	Only catalogue materials are used, the variability impact has been understood during	To be assigned

Risk factor 2: Process understanding	Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH risk	Example of a high-risk scenario that requires a mitigation strategy	Example of low-risk scenario which possibly supports acceleration	Risk score High Medium Low
	maintain the product quality requirements? Are the CMAs identified that need to be controlled?	are in place, but unknown if they meet the process desires.	development for all identified critical materials.	
Residual risk level for the process understanding (factor 2): Take all assessment elements into account				High/medium/low

3.2.3 Assess the Complexity of the PV approach (e.g. Matrix and Bracketing) (Step 3)

Another factor that clearly influences the extent of the PV activities and therefore the number of validation runs is the scope or complexity of the manufacturing processes and the involved facility and equipment to be qualified or validated. Any sources of variability like multiple input/starting materials, scale-dependent parameters, multiple unit operations, operator interventions or organizational constraints (e.g. process duration, hold times, interruptions, shift changes etc.) might also need to be adequately addressed as part of validation studies, either prospectively, concurrently, or risk-based also retrospectively as detailed in **Table 3**. An overall resulting risk score should be provided.

In accelerated scenarios, not all validation activities can always be completed prior to initial distribution; therefore, validations directly linked to safety, sterility, identity and potency are expected before distribution, while other validation studies may be deferred where justified by risk assessment and managed via predefined protocols and enhanced controls.

Table 3: Assessment of Manufacturing Process Complexity and Variability Factors Affecting PV Activities

Risk factor 3: Manufacturing experience & Complexity including Matrix and Bracketing approach	**Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH risk**	**Example of a high-risk scenario that requires a mitigation strategy**	**Example of low-risk scenario which possibly supports acceleration**	**Risk score High Medium Low**
	Do the PV activities span the entire production process of DS/DP or is it only one unit operation, e.g. formulation or filling only?	For all process steps/unit operations PV data needs to be submitted as part of the initial submission.	Initial PV activities (i.e., - emergency use authorization (EUA) PV data submission) focus on covering high risk process steps driving the quality attributes of the DS or DP.	To be assigned

Risk factor 3: Manufacturing experience & Complexity including Matrix and Bracketing approach	Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH risk	Example of a high-risk scenario that requires a mitigation strategy	Example of low-risk scenario which possibly supports acceleration	Risk score High Medium Low
	Are more production lines or unit operations (fermentation trains, purification skids, formulation vessels, filling line, lyophilizers) in scope of the PV activities?	Data of multiple lines or facilities, including CMOs will be collected, assessed, and submitted.	Ideally for product launch a single production line will be used.	To be assigned
	Has the plant/equipment been used as part of other platform product/processes? Is the equipment considered as technically equivalent? Can equipment matrixing being applied to cover similar units?	Different equipment is used and is not fully designed for purpose.	The equipment is used for other platform products and unit operations are using technical equivalent equipment (PQ proven and applicable to new product).	To be assigned
	Has the equipment been used for other platform processes and can be considered as reliable/robust? Does the equipment capability meet the process capability?	Newly designed, qualified equipment for purpose.	The equipment is used for other platform products already commercialized. Equipment capability, reliability and robustness is demonstrated.	To be assigned
	Is the complexity of non-compendial materials to be used in the process high?	Material attributes especially in DS manufacturing have not	Good knowledge for CMAs of compendial materials.	To be assigned

Risk factor 3: Manufacturing experience & Complexity including Matrix and Bracketing approach	Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH risk	Example of a high-risk scenario that requires a mitigation strategy	Example of low-risk scenario which possibly supports acceleration	Risk score High Medium Low
		understood variability and CQA impact.		
	How well characterized is the selection of materials to be used? Or are they used in similar products? Have established manufacturers' specifications been used?	Materials are new and they have never been used in GxP processes. They do not have established specifications.	Majority of materials are routinely used by other platform products and processes. GMP control and release process of materials according to the specifications is in place.	To be assigned
	Are additional sampling and monitoring for other standalone/concurrent validation studies (lifetime, hold time, cleaning, stability studies etc.) planned?	A series of stand-alone validations is planned concurrently to PV runs and their outcome also impacts the PV package.	Standalone validations have already been executed upfront or they will be generated as post approval commitments.	To be assigned
	Are all process and analytical validations completed or adequately planned before initial distribution under accelerated conditions?	Critical process or analytical validations (e.g. aseptic process simulation,	All critical process and analytical validations essential for batch release are completed	

Risk factor 3: Manufacturing experience & Complexity including Matrix and Bracketing approach	Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH risk	Example of a high-risk scenario that requires a mitigation strategy	Example of low-risk scenario which possibly supports acceleration	Risk score High Medium Low
		sterilizing filtration, or potency/identity assay validation) not completed prior to initial product distribution. Mitigation: implement enhanced interim controls such as increased in-process and release testing, use of qualified methods with robust change-control oversight, and submission of predefined post-approval validation protocols or a PACMP describing timelines for completion.	and supported by prior platform data; any remaining non-critical validations are covered by predefined post-approval protocols with agreed timelines.	
Residual risk level for process PV complexity (factor 3): Take all assessment elements into account				High/medium/low

Where any validation activities are deferred due to accelerated timelines, the associated protocols and completion plans should be clearly referenced in the validation strategy and under Post-approval commitments. This ensures transparency of the proposed deferral path and provides a defined mechanism for follow-up with the authority as additional data become available.

3.2.4 Assess Control Strategy risk (Step 4)

The process control strategy evolves through the development of process and product knowledge in stage 1 of the product lifecycle. Factors in the control strategy and their potential impact on product and process variability are especially important considerations in determining the appropriate number of Stage 2 PPQ batches. The Control strategy risk (suitability of the CS) is highly important to evaluate the impact of variability due to e.g. process input materials (how variability will be managed and controlled), environmental conditions, operational practice, equipment capability, process performance, experience with equipment, process technology and operators. Thus, engineering and qualification batches prior to commercial batches will highly contribute to reduce the risks.

There are other factors that can mitigate the risks. The variables inherent to each process and product should be considered and other elements can be chosen to support the risk assessment and define the residual risks as well as the mitigation actions to achieve process reproducibility with validation batches, as detailed in **Table 4**.

Table 4: Control Strategy Risk Assessment and Impact on Process Variability

Risk factor 4: Suitability of the control strategy	**Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH risk**	**Example of a high-risk scenario that requires a mitigation strategy**	**Example of low-risk scenario which possibly supports acceleration**	**Risk score High Medium Low**
	Have all relevant CPPs and CMAs impacting the CQAs been identified?	Limited control of CPPs/CMAs.	All CPPs and CMAs are defined, and controls are in place.	To be assigned
	Is the design space/proven acceptable range of those parameters defined and supported by prior	Operating Ranges partially or not in place or not	In case no product specific ranges are available, use platform ranges or	To be assigned

Risk factor 4: Suitability of the control strategy	Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH risk	Example of a high-risk scenario that requires a mitigation strategy	Example of low-risk scenario which possibly supports acceleration	Risk score High Medium Low
	knowledge, existing validations, or experimental studies (based on QbD principles)?	supported by prior knowledge, existing validations, or experimental studies.	control ranges by NORs (based on equipment capability).	
	Are CPPs and performance-related process parameters well controlled through the In-process-controls. Are In-process testing at critical intermediates available to assess if CPP/performance-related parameter controls are adequate?	No or limited detectability of CPPs/performance related parameters in place.	Controls to CPPs are in place and verified by the BR or measured as part of enhanced intermediate testing of the impacted CQAs.	To be assigned
	Are controls for operational parameters defined, built in by design for the used equipment, and translated into the batch record or by automation?	Controls are not systematically defined.	Parameters are monitored and alarmed by programmable Logic controller or, if manually, verified by second operator.	To be assigned
	Is platform or equipment specific experience available to ensure that controls are efficient, set at the right critical control point and robust (i.e., not causing recurrent deviations)?	Equipment and systems have been newly designed and never used as part of routine.	IPT and IPC strategy (sampling plan) is based on scientific sound risk assessment (e.g. FMEA).	To be assigned

Risk factor 4: Suitability of the control strategy	Assessment points of the risk level Please give rationales to the following key questions (if applicable) to assess if the risk factor is LOW/MEDIUM/HIGH risk	Example of a high-risk scenario that requires a mitigation strategy	Example of low-risk scenario which possibly supports acceleration	Risk score High Medium Low
	For lacking historical data to compare and estimate batch to batch variability, do you plan additional tests, non-routine monitoring or characterization tests during PV runs?	Only routine release testing performed with no provision for additional sampling or IPC.	Enhanced intra-batch sampling is applied at relevant intermediate processing steps (e.g. kinetics, homogeneity). High confidence that process capability is sufficient.	To be assigned
	Will the sampling frequency be increased for PV runs? Will more sampling locations be added for PV runs?	Limited sampling for release purposes only. Methods for IPT and characterization not reliable. Increased sampling causing a risk of OOS results.	See previous row above.	To be assigned
Residual risk level for control strategy (factor 3): Take all assessment elements into account				

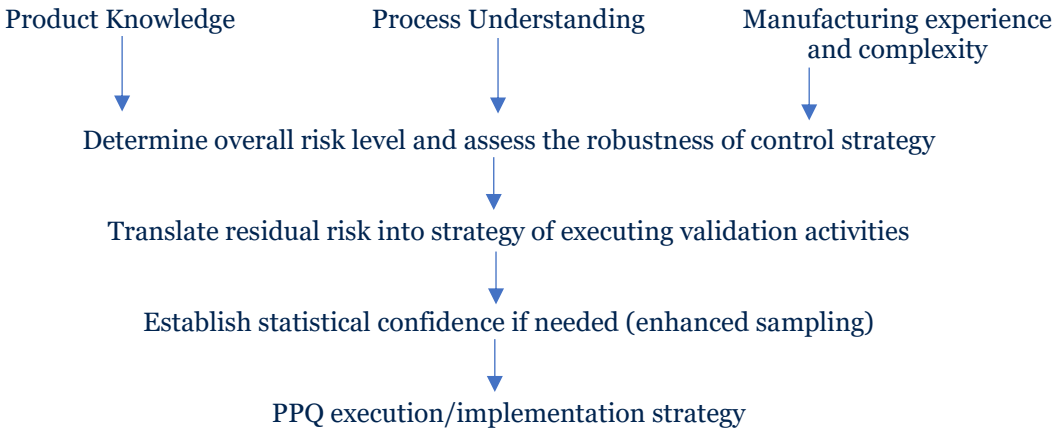
3.2.5 Determine residual risk level (Step 5)

The residual risk reflects the confidence in the performance of the commercial batches. If quality risk management was used in the development of the process to gain product knowledge and to build the control strategy, a lower residual risk should be achieved. The knowledge of residual risks (scores) can be used to streamline tailored approaches for PV activities, that will need to be discussed and agreed with Health Authorities as part of pre- or post-approval (e.g. application of PACMP protocols, deferral to post-approval space or other mechanisms) or even pre-authorisation measures (e.g. Emergency use authorization (EUA).

Identification of high residual risks indicate that there are significant gaps in knowledge and/or the control strategy. Additional efforts must be invested to improve knowledge and/or the control strategy before executing PV activities, in particular process qualification batches at scale. The residual risk level can span from Low (low risk level for all factors), over Low/Medium (medium risk levels for few/multiple factors) to High (where few factors have high risk ratings) or even Severe (where multiple factors have high ratings). The assessment of the factors in the tables above can facilitate the mapping of areas that must be prioritised for the implementation strategy of PV elements, or ultimately give rationales why these elements can also be provided as post approval commitments or covered by lifecycle management approaches (i.e. CPV),as detailed in **Figure 2: Assessment of residual risk assessment**.

Factors contributing to the overall residual risk level (see steps 1 to 4 above) should be adequately assessed (for all product CQAs or individually), summarized and justified.

Figure 2: Assessment of residual risk assessment



3.3 Rationale for Number of PPQ Runs

For PHE, and in case there is a clear expectation of HAs to submit formal validation data that support the consistency of the manufacturing process (i.e. Process Performance Qualification (PPQ) data), scientific and risk-based approaches could help in determining and justifying the number of PPQ batches. The overall residual risk level associated with manufacturing is determined based on product knowledge, process understanding and commercial/clinical manufacturing experience. Based on a reasonable approach (e.g., process impact score, risk priority number or by simple qualitative assessment based on the overall product, process understanding, manufacturing experience, process variability and control strategy as outlined in sections 3.2.1-3.2.4), the process risk (low, medium, or high) can be translated into the number of PPQ batches[1].

According to a traditional approach for PPQ, a minimum of three consecutive batches are executed. In any case, the number of PPQ runs should be defined as sufficient to demonstrate process consistency and to verify the effectiveness of the control strategy. The rationale for defining the number of PPQ runs for newly developed manufacturing and/or validating changes to existing processes should be based on science and risk.

During pandemic situations, in which an accelerated scenario aims at delivering a lifesaving vaccine as fast as possible, robust risk assessment is crucial for determining the number of PPQ runs and to define the residual risk and the mitigation actions to provide authorisation/registration and subsequent wide use of the product with a high level of confidence. The approach, the data used, the rationale, and the justification should be documented in the process validation master plan or a similar document. Fundamentally, a process with a higher residual risk may require more PPQ batches than a process with low residual risks.

To determine the number of PPQ batches, it is necessary to demonstrate a high degree of assurance, considering the variability between batches. This can be addressed with a rationale based on experience and residual risks and supplemented with statistical considerations, e.g. enhanced intra-batch sampling (e.g. monitoring and characterization). See section 3.2.4 on control strategy and risk assessment above.

The traditional “rationale/experience-based” approach of executing three (3) PPQ batches to provide an acceptable degree of assurance to show reproducibility is only valid for products with low residual risks, meaning that knowledge (risk factors 1 and 2, see above) and control strategy (risk factor 4) are reliable and therefore scored as low.

Less than three batches should be used only for processes with minimal residual risks, such as a process with strong knowledge and a high degree of control. This is for example, a well-understood change to an existing process, a process and product using a control strategy that has succeeded for a similar product/process platform. For any situation with low, medium, high and severe residual risks, three or more consecutive batches should be considered as mitigation of the risks. This is to guarantee the product quality for the patient.

[1] Please also refer to methodology used in the ISPE discussion paper, PV Stage 2, Determining and Justifying the Number of Process Performance Qualification Batches (Version 2), ISPE discussion paper, 1 Jan 2016.

Another possibility to improve the degree of assurance is to define extensive sampling and testing as part of a limited number of PPQ batches but based on statistical tools and considerations and by this to provide enhanced data to conclude on the reproducibility of the process using within-batch process capability data. All above mentioned approaches can be complemented with ongoing sampling during further commercial batches that will be evaluated during phase 3 – Continued Process Validation (CPV).

4. Control Strategy (CQA, CPP & CMA)

An overall control strategy needs to be developed to ensure effective and reproducible manufacturing of a product meeting its quality requirements. Such a control strategy is designed through quality risk management principles in combination with process and product knowledge, understanding of sources of variability and controlling these (refer to ICH Q8 to –Q11 guidelines). As such, a control strategy includes many different elements of control; such as facility and utilities control, equipment operating conditions, operator qualification and facility management, control of parameters and attributes related to process intermediates, active pharmaceutical ingredient (API) and finished product; components including starting and raw materials (including process aids); in-process controls (including environmental monitoring and control); specifications and the associated test methods.

This section discusses the core of the control strategy for which typically and in standard circumstances data is collected throughout the manufacturing of formal qualification (PPQ) batches. Operational parameter control, IPCs and release data are collected to demonstrate the control of Critical Process Parameters (CPPs), Critical Material Attributes (CMAs) and Critical Quality attributes (CQAs), maintaining final product quality. However, this Best Practices document focuses on process validation applicable to accelerated scenarios and that may not necessarily rely on the knowledge acquired during PPQ manufacturing only. **Table 5** aims to provide guidance on how prior knowledge and models can help to build an adequate control strategy in such an accelerated case and to form an appropriate risk mitigation strategy. The use of prior product/platform knowledge allows a better assessment of the occurrence, frequency, and detection of the assessed risks and consequently prioritization of the most critical items. Known and already mitigated risks in the similar product/platform, reduce the risk for the product to be developed. Unknown risks can be prioritized and mitigated for emergency use batch production/PPQ.

Table 5: Assessment of Control Strategies under Standard and Emergency Use Authorization Conditions and risk mitigation

CONTROL OF CQA AND CPP/CMA	Standard circumstances	Accelerated path to emergency use authorization (or equivalent regulatory mechanism)	Risk mitigation
Control strategy	A fully integrated control strategy is in place before starting PPQ/commercial manufacturing. PPQ batches verify that the control strategy is adequate to ensure consistent product quality. Control elements are implemented at the earliest possible moment in the process. Residual risks are as low as reasonably possible.	When using a platform manufacturing process, the control strategy can, with justification, be leveraged from the platform. Potential knowledge gaps related to the product specific elements should be identified and need to be mitigated.	Risk resulting from temporary knowledge gaps could be mitigated by collecting process understanding by (temporary) additional process monitoring and characterization testing, until sufficient data is collected to close knowledge gaps.
CQA*	Criticality of Quality Attributes has been fully assessed prior to starting PPQ. CQA are controlled by an adequate combination of control elements which may include: -Release testing for the specific CQA -In process control testing related to the specific CQA	Criticality of Quality Attributes as identified for the platform will be leveraged. Platform CQA in combination with a Platform manufacturing process justifies a Platform Control strategy. This includes specifications ranges leveraged from platform and the associated control strategy as described for standard circumstances. Some Product specific Critical Quality Attributes may remain as “potential” (pCQA) at time of	pCQAs are treated as CQAs.

CONTROL OF CQA AND CPP/CMA	Standard circumstances	Accelerated path to emergency use authorization (or equivalent regulatory mechanism)	Risk mitigation
	-Control of CPP/CMA related to the specific CQA (see also below) Established CQA acceptance criteria are based on extensive knowledge of efficacy, safety and quality. Consistency limits can only be established when a significant number of representative batches has been manufactured and evaluated (Continued Process Verification).	starting emergency use batch production or PPQ. Although it is potential CQA, the attribute should still be monitored during production. Registration/authorization of wider preliminary specifications for those pCQAs based on experience (e.g. minimum is efficacy limit and maximum are safety limit) is deemed acceptable. Consistency limits can only be established when a sufficient number of representative batches has been manufactured and evaluated (as part of Continued Process Verification).	

CONTROL OF CQA AND CPP/CMA	Standard circumstances	Accelerated path to emergency use authorization (or equivalent regulatory mechanism)	Risk mitigation
	Small scale impurity clearance studies can be used to classify process-related impurities as critical or non-critical (based on their residual levels in the final DP in relation to the toxicological classification and acceptable levels). Critical impurities are carried as CQAs and subject to further confirmation of clearance on PPQ batches.	In case of extensive prior knowledge: impurity clearance data is leveraged from platform prior knowledge and used to assess impurity criticality. Product/matrix specific small studies are not conducted. In case of areas with limited prior knowledge: model-based estimation of clearance factor, informed model-based experimentation [combination of statistical methods and advanced modelling] can be used, in combination with measurements of impurities in emergency use/PPQ batches to demonstrate level is low.	Scientific justification of the applicability of platform prior knowledge to the new product. In case of limited prior knowledge: for impurities with limited clearance data control by release/characterization testing can be considered. Impurities carried forward to be checked at release testing may vary by platform.
Impurity	Impurity clearance confirmation on PPQ batches may be used to justify the removal of impurity testing for routine manufacture.	Impurity clearance confirmation on representative batches may be used to validate out testing of some critical impurities.	
Homogeneity	Homogeneity of the drug product is controlled by control of the relevant CPP – affecting the bulk homogeneity prior to fill – within their PAR as well as implementation of knowledge derived from filter (validation)	Platform mixing and product homogeneity knowledge can be leveraged, when justified to be applicable. In those cases, studies to verify homogeneity could be performed on emergency use/PPQ batches or deferred to post approval – as commitment – depending on the risk profile.	Scientific justification of the applicability of platform prior knowledge to the new product. Modelling of product homogeneity can potentially contribute to the risk reduction.

CONTROL OF CQA AND CPP/CMA	Standard circumstances	Accelerated path to emergency use authorization (or equivalent regulatory mechanism)	Risk mitigation
	studies. Typically, homogeneity of the product is demonstrated by studies pursued during the PPQ batches.		The extent of leveraging.
CPP*/CMA identification	CPP/CMAs are identified based on an extensive criticality assessment made on each raw material attribute and on each process parameter.	The design phase is typically shortened; however, a risk assessment on the impact of CPP/CMA on CQA is still performed: In case of prior knowledge established for the platform the CPP/CMA identification can be based on the criticality analysis that applies to the entire platform of the applicant. In cases where there are product specific knowledge gaps within the defined platform, those could be addressed by (temporary) enhanced process monitoring in the production of emergency use/PPQ batches to increase process knowledge and/or use of computer-based modelling.	In case of extensive prior knowledge: scientific justification of the applicability of platform prior knowledge to the new product. In case of areas with limited prior knowledge: Where accelerated experiments are not possible, longlist of (p)CPPs/CMAs and associated limits and controls are identified. For (p)CPPs with product-specific knowledge gaps, tight limits are put forward to reduce risk (see also control of CPP/CMA below). Post-approval performs product-specific small scale process characterization studies (which can be either based on lab experiments or based on digital twin simulations with limited lab experiment confirmations) and submit a final list of CPP/CMAs ranges.
Control of CPP/CMA	CPP/CMA are controlled within proven acceptable ranges (PAR) (which are the acceptance criteria for	In case of extensive prior knowledge: acceptance criteria for CPP/CMA are set based on platform prior-knowledge (i.e. proven acceptable	In case of extensive prior knowledge: scientific justification of the applicability of platform prior knowledge to the new product.

CONTROL OF CQA AND CPP/CMA	Standard circumstances	Accelerated path to emergency use authorization (or equivalent regulatory mechanism)	Risk mitigation
	PPQ). These PAR have been defined based on (small scale) process characterization studies (which can be either based on experimental studies or based on digital twin simulations with limited experimental confirmations).	ranges defined for the platform). In case of limited prior knowledge, e.g. product specific impact within the platform: acceptance criteria for CPP/CMA are then set based on tighter ranges based on primarily equipment control capability (Normal Operating Ranges, see also EMA Questions and Answers: Improving the understanding of NORs, PARs, DSp and normal variability of process parameters – EMA/CHMP/CVMP/QWP/354895/2017). For all scenarios above utilising computer-based modelling could be considered to fill knowledge gaps.	In case of areas with limited prior knowledge: For initial emergency use/PPQ manufacturing, control of those parameters in more narrow ranges and where desired post-approval submission of these product-specific PAR that will have been defined based on small scale process characterization studies.

* Lists of CQAs identified per platform are available in each of the Part B Comparability Annexes

** Performance-related parameters, for example impacting yield, could be defined and controlled and may be included when consistency will be evaluated.

5. Process Validation strategy

The Process Validation (PV) strategy for accelerated access is built and justified based on the outcome of the risk assessment performed, as described in **section 3** above.

The PV package at the time of submission of the initial (conditional) marketing authorisation/emergency use authorisation application (or equivalent regulatory path) is tailored e.g. considering the amount of prior knowledge available, the use of models, and the identified risks. The initially submitted PV data package is complemented with the submission of post-approval commitments and/or protocol(s) as the applicant sees the best fit (e.g., process validation scheme, CPV plan, PPQ protocol, post-approval change management protocol, etc.).

The PV package will therefore be composed of:

- prospective effort (i.e. pre-approval PV data -platform process data and product-specific process data);
- concurrent effort (e.g. concurrent validation data, or PV data) and
- retrospective effort (e.g. life cycle CPV data).

Concurrent and retrospective efforts will constitute the post-approval commitments under the format of plans/protocols (see also section 6 of this document).

The deviations from expected conditions and handling of non-conforming data occurring during the PV data package generation shall be addressed. Data should not be excluded from further consideration in terms of process validation without a documented, science-based justification. The details of those deviations will be further justified in the report(s), where there is a clear impact on product safety and quality and validation conclusions. Depending on the prevailing QMS, a framework such as a decision tree could be used to analyze the nature and severity of the deviation and the implications for product quality, safety and efficacy and impact on process validation. Overall, handling of deviations is expected to follow the same procedure in the accelerated case as in the standard case.

In building the process validation strategy for accelerated access, synergies between PV and comparability are recommended to be considered. Data collected to support the comparability assessments can contribute to the assessment of manufacturing process consistency. In particular, collection of process intermediate analytical data can serve a dual purpose in demonstration of consistency of the commercial manufacturing process – for the individual and combined unit operations – as well as for demonstration of comparability. As outlined in Part A (section 6) of the Best Practices documents, the synergy between comparability and process validation may also facilitate the decoupling between DS and DP process validation (see also **section 5.1.7** of this document).

5.1 Available tools supporting an accelerated process validation strategy.

Opportunities to explore when building the tailored validation package in accelerated conditions are described in the ensuing sections below. Information has been sourced, amongst others, from publicly

available documents[2, 3, 4]. The choice of combination of these available tools is at the discretion of the developer, but the final approach for PV should be duly justified at the time of submission of the initial dossier requesting emergency use authorization (or equivalent regulatory mechanism). The chosen combination will define the type and number of batches entering the global PV strategy (e.g., other platform-based product batches, clinical batches, concurrent batches, PV batches, etc.).

5.1.1 Use of historical data from platform products and product-specific development data

As specified in the EMA guideline on process validation for finished products[5], where substantial product and process knowledge and understanding have been gained through historical data from similar products and/or processes and from development studies, it is possible to implement continuous process verification or to employ a combination of traditional process validation and continuous process verification. The FDA Guidance for Industry for the Development and Licensure of Vaccines to prevent COVID-19[6] supports the use of validation data from other platform-related products as useful supportive information, particularly in the identification of critical parameters. When available, names and marketing authorisation numbers of platform-based marketed products from which process validation data are used to support the new product-specific process validation package should be included by the applicant at the time of regulatory submission.

5.1.2 Use of concurrent validation

Concurrent validation is carried out in exceptional circumstances, where the validation protocol is executed concurrently with commercialisation of the validation batches.

Concurrent validation is already recognized by European guidelines (i.e. EMA Toolbox[3], EudraLex Annex 15[7],) and US FDA guidelines[8] as an appropriate tool where there is a strong benefit-risk ratio for the patient, or when there is limited demand and batches are manufactured infrequently. In any case, the acceptance of such approach requires a sound justification, and it is case-by-case driven, among others, depending on the amount of supportive data available.

The EMA Toolbox guideline[3] clarifies that:

"When concurrent validation is used, evidence should be provided to demonstrate i) that studies performed for process evaluation are appropriate representations of the commercial process, and ii) that the control strategy will properly assure that the process has performed as intended. It is recognised that in the case of accelerated development, the level of process understanding may still be

[2] EMA Workshop on support to quality development in early access approaches, EMA/CHMP/BWP/812924/2018, see presentation on "Process validation and accelerated access – challenges and solutions"
[3] EMA Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need (EMA/CHMP/BWP/IWG/694114/2019)
[4] WHO Technical Brief reporting on recommendations from the COVAX Regulatory Advisory Group, RAG
[5] Guideline on process validation for finished products -information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1)
[6] US FDA Guidance for Industry, Development and Licensure of Vaccines to prevent COVID-19 Vaccines
[7] EudraLex Volume 4, EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Annex 15: Qualification and Validation
[8] FDA Guidance for Industry - Process Validation: General Principles and Practices

evolving. Nonetheless, acceptance of a concurrent validation approach for active substances and/or finished products requires sufficient process evaluation data to justify that the parameters and acceptance criteria included in the protocol are suitable for concluding that the process is in a state of control and that the product is uniform."

Should concurrent validation be chosen as part of the developer's PV strategy intended for emergency use authorization (or equivalent regulatory mechanism), a decision shall be taken as to how many formal PV/PPQ batches will be submitted already with the initial authorization request. EMA has been explicit with regards to this and mentions in the Toolbox guideline[9] that at least one batch should be available prior to authorization. Prior to the COVID-19 crisis, this approach had already been envisaged in regulatory forums as a feasible concept[10]. However, in case of a PHE, availability of vaccine batches to the wide public and outside a clinical setting becomes an urgent need to meet. Therefore, release of batches to the market without having manufactured a PPQ campaign might well be justifiable, as EMA states in the Toolbox guideline[3].

"*It is generally expected that data from at least one formal process validation batch from the commercial manufacturing process will be available prior to approval. In exceptional cases, it may be acceptable not to have manufactured any process validation batches prior to approval. This will have to be supported by a comprehensive risk-based approach and will depend on the extent of prior knowledge which can be leveraged and other supporting validation data from non-PPQ batches or small-scale batches.*"

Considering this expedited approach, it is likely that even the PPQ protocol is lacking at the time of submission of the initial dossier to request regulatory emergency use authorization (or equivalent mechanism). While pending submission of the PPQ protocol within a timeframe previously agreed with the HA, vaccine release to the market could take place following *sensu stricto* the process applied to release clinical batches. Once the PPQ protocol would be in place, concurrent validation could be executed, as explained above. The developer will have to carefully assess and justify any difference arising from the PPQ and that would affect release of vaccine batches to the market as compared to the previous release process.

5.1.3 Deferral of certain validation activities

Deferral of certain validation activities to post-approval if driven by benefit/risk and scientifically justified may enable faster access to vaccines[9, 10]. This option should be considered in the whole PV strategy as one additional tool to accelerate vaccine deployment. The level of process validation and data to be submitted should be decided upon the risk associated with each manufacturing step, e.g. sterile filtration is considered a high-risk step and shall require validation prior to approval.

If pursued and sufficient information is available, this strategy could be supported with a process validation protocol based on prior knowledge of process. The protocol, which shall be submitted along

[9] EMA Toolbox guidance on scientific elements and regulatory tools to support quality data packages for PRIME and certain marketing authorisation applications targeting an unmet medical need (EMA/CHMP/BWP/IWG/694114/2019)

[10] EMA Workshop on support to quality development in early access approaches, EMA/CHMP/BWP/812924/2018, see presentation on "Process validation and accelerated access – challenges and solutions"

with the regulatory submission for authorisation/registration, should typically indicate how process knowledge, control strategy and characterisation methods will be deployed to assess product quality throughout the lifecycle of the product.

Sometimes conformity to validation protocols as included in the original application is acceptable by itself, with no further need to submit the generated results post-approval.

The framework and methodologies outlined in ICH Q12[11], such as employing post-approval change management protocols (PACMP) also offer a structured approach for deferring certain activities, though always bound to a post-approval submission.

In any case, whether using a PACMP or a validation protocol, it is advised to engage into dialogue with the corresponding HA to define the level of information that shall be provided prior and post authorization.

5.1.4 Use of Continuous Process Verification

As specified in the EMA Toolbox guideline[9], one possible tool to allow early access to medicines can be the use of continuous process verification. Indeed, where substantial product and process knowledge and understanding have been gained through historical data from similar products and/or processes and from development studies, it is possible to implement continuous process verification or to employ a combination of traditional process validation and continuous process verification. This approach is also described in EMA guideline on process validation for finished products[5]:

"*Continuous process verification is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8). Continuous process verification can be used in addition to, or instead of, traditional process validation. 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 critical quality attributes (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 such as NIR spectroscopy with or without feedback loop (e.g. end point determination of blend homogeneity, determination of granules surface area, determination of content uniformity with large sample size) and Multivariate Statistical Process Control (MSPC) can be viewed as enablers for continuous process verification.*"

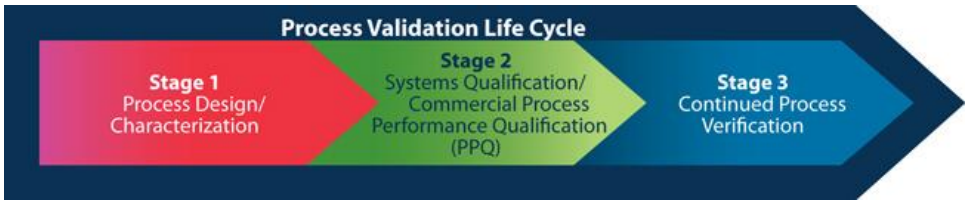
5.1.5 Use of enhanced Continued Process Verification (CPV)

A continued process verification (CPV) is the post-approval demonstration that process remains in a state of control during routine manufacture, with the use of trending and statistical tools. The launch of

[11] ICH Q12 Technical and regulatory considerations for Pharmaceutical Product Lifecycle management, Nov 2019

CPV typically starts after consistency demonstration with a PPQ campaign, therefore post-approval. However, in accelerated scenarios, PPQ execution may be split between pre- and post-authorisation stages, for example with the use of continuous process verification (see Section 5.1.4). Therefore, in those cases in which PPQ would be completed after authorization, CPV would be deferred further, i.e. post-completion of PPQ activities, post licensure/authorisation (refer to **Figure 3**).

Figure 3: Process validation stages[12]



The validation status should be ensured by a stage 3 of lifecycle of the product establishing a Monitoring Program of Continued Process Verification (CPV). The CPV has the objective of evaluating the state of control following the stage 2 and during commercial production. It is the longest segment of the process validation lifecycle.

The CPV Program should be established during the commercial production and all commercial batches should be part of this evaluation. A CPV plan should include the responsibilities, sampling and testing strategy, data analysis methods (statistical tools), re-evaluation of original PPQ acceptance criteria, strategies on Out of Trend (OOT) and Out of Specification (OOS), strategies and criteria to come back to stage 1 or 2. The frequency for re-evaluation of the CPV plan may be triggered immediately by a process change, as part of the change control system. In addition, process parameters and some potential sources that are not part of process parameters (raw material quality, comparability of redundant equipment, personal impact on process) should be part of the CPV Plan too.

Regarding sampling plan during stage 3, the routine sampling is usually applied, but non-routine sampling can be considered. One example for such scenario is a stage 2 process without a high degree of confidence, as mentioned on section 3. Also, in the context described in these best practices document, i.e. in accelerated scenarios that require access to vaccine in expedited ways. In this case additional samples shall be collected. This has been called in this document “enhanced CPV” and could be one of the tools to apply in the PV strategy that is shared with regulatory agencies, since it will impact post-approval/authorization commitments (reference is made to section 6 of this document).

Some companies split stage 3 in several substages, i.e. 3a and 3b. In stage 3a, all parameters and attributes are evaluated for a period and/or until a number of batches (for low product demand) aiming at monitoring the variability of the process that may have seasonal influences of raw materials, personnel, environmental, equipment and utilities. Usually, companies define stage 3a as the first commercial production year or up to 30 batches for products with low demand. In those cases where the demand is very low, i.e. less than 30 commercial batches per year, the data from the batches

[12] Continued Process Verification: Reacting to Data Signals, Ajay Babu Pazhayattil, PDA Letter, 18 Nov. 2020

manufactured in the previous commercial production year could be considered. Stage 3b starts after the conclusion and evaluation of stage 3a. Some parameters that are considered controlled after stage 3a should be removed from the CPV program. It should be justified in the stage 3a CPV report.

Statistical tools should be used to define if each parameter and attribute is controlled. Process capability is very important on CPV plan. However, other statistical analyses are necessary to permit robust data analyses such as control charts, box plot, descriptive analyses, analysis of variance, tests for variance, hypothesis tests, pareto analysis, normal and non-parametric tolerance intervals.

5.1.7 Decoupling DS from DP

Considering the need for expedited release of Drug Product (DP), it may be acceptable to supply drug product process validation batches using Drug Substance (DS) produced prior to performing process validation, provided that the DS was manufactured and tested under GMP conditions. Reference hereto is made to the WHO Technical Brief from the COVAX RAG[4] that states the following:

"*The use of DS lots manufactured prior to validation of the DS process could be used to validate the DP process, provided analytical comparability is demonstrated between the pre-validation DS lots and the commercial lots".*

If the above approach is chosen, it should be demonstrated that such DS batches are representative of commercial manufacturing process and that will meet pre-determined specifications.

5.1.8 Bracketing and Matrixing

Bracketing and matrixing allow a 'most appropriate challenge' condition to be defined for a process or drug product family (e.g., the same drug product with different dosage strengths). This risk-based approach can allow the validation to focus on the most challenging circumstances, or "worst cases", with the significant benefit to reduce the overall validation effort. Bracketing or matrixing may be used for validation of DS, DP and packaging processes, when justified. These approaches are detailed in PDA's Technical Report on Strategies for Vaccine Development[13].

To obtain the maximum benefit with minimum risk from bracketing and matrixing, it is necessary to have a well-developed understanding of the impact of critical process parameters on critical quality attributes. There should be a documented and justified rationale that explains why one set of test conditions (e.g., manufacturing process, product presentation, etc.) is representative of one or more related test conditions.

Typically, the rationale is addressed by selecting parameters and/or products that represent the edges of a range or worst case of allowable conditions. The rationale and justification for the bracketing/matrixing strategy should be provided in the validation protocol.

Examples of variables that might be assessed by bracketing and matrixing include, but are not limited, to:

- Batch size

[13] Technical Report 89: Strategies for Vaccine Development, PDA, January 2023, PDA Item Number 43563

- DP dosage strength
- Identical equipment and facilities (e.g. where setup and operating conditions are the same)
- Product packaging, such as where only a minor adjustment in packaging parameters is required to accommodate different bottle heights or dosage counts.

5.1.8.1. Bracketing approach:

The bracketing approach should consider performing an efficient qualification at extremes of variables under the premise that the extremes are fully representative of intermediate levels. The bracketing approach is used when a single process element can be varied while the other process elements remain fixed. It is applied especially to products of different strengths with same qualitative and proportional quantitative composition, to different container sizes or different fill volumes in the same container closure system.

5.1.8.2 Matrixing approach:

The matrixing approach consists in performing an efficient qualification when configurations of the same process and product have more than one variable. The approach assumes that the batch configurations selected for inclusion in the Process Validation fully represent processes for all combinations. For example, the matrixing approach is applied to conduct process validation on different strengths of the same product (same formula) or on different vial sizes or fill volumes of the same drug product or different strains/types.

Matrixing approach can be applied also to distinct process steps used in the manufacture of several related products. It may also apply to groups of processes with identical process parameters without product impact (e.g. syringes filling with identical process parameters).

Rationale for selection of representative groups and number of batches should be scientifically justified and outlined in the Process Validation protocol.

5.2 Consecutiveness principle to conclude on process validation outcome

The PV should be viewed as a means to evaluate and confirm a sound process design, an effective control strategy, and operational proficiency at commercial scale. The number of batches in the PV study(ies) will be influenced by many factors such as

- The performance and acceptance criteria
- Testing to be performed and the type and amount of data necessary to perform those analyses
- The level of process knowledge and understanding gained from stage 1
- Type and complexity of manufacturing technology employed in the various unit operations
- The inherent/known variability of the process resulting from raw materials, excipients equipment design, operator training etc.

Using risk-based approaches allows a balance between the number of batches studied and the risk of the process as detailed in **Table 6**.

Table 6: Assessment of number of PV batches under Standard vs Accelerated scenario and risk mitigation

Standard case	Accelerated case examples	Risk Mitigation strategy
A minimum of three consecutive runs at scale shall be subjected as part the process validation study.	Number of batches considered for PV can be less than 3. The process risk (low, medium, or high) can be determined to be translated into the number of PV batches. Data from previous phases/development studies shall be used for supplementing the PV reports for submission.	In case of a PV campaign batch would be considered as "fail" or "invalid", a root-cause analysis (RCA) shall be performed for identifying the reason/s for failure. If the root cause is not intrinsic to the manufacturing process, a replacement batch shall be considered for process validation campaign. In such case, the consecutiveness expected within the process validation campaign is not considered invalidated. A replacement batch can allow continuation of the process validation campaign. The deviation shall be reported in the process validation report along with the RCA, impact assessment, risk to PV and recommended corrective and preventive actions followed batch disposition.

5.3 Pre-requisite for PPQ readiness versus deferred activities

Several studies are expected to be completed prior to the start of the PPQ batches campaign and shall contribute to establish design space and operating parameters during the routine operations. This may include worst-case scenario simulations, such as media and buffer hold times, buffer and in process materials mixing time and RPM, sterile hold time of components, vessels etc. The following non-exhaustive list are normally required before process validation, however in case of accelerated product development, some of these requirements could be deferred to post licensure/authorisation or justified with a risk assessment and supporting information such as prior knowledge, platform data etc. Details of the requirements that can be submitted post licensure/authorisation are captured in section 6 of this document on post approval commitments.

5.3.1 Product-specific activities to be addressed or evaluated

- Cleaning validation
  - Analytical method development specific to cleaning samples
  - Recovery studies for operator qualification for swab sampling

  - Cleaning validation execution, preferably using combination of direct (swab) and indirect sampling (rinse). Due consideration shall be given to simulate the worst case for clean and dirty equipment hold time during cleaning validation execution.
- Process intermediates hold-time.
- Filter validation
- Extractables and leachable risk assessment
- Media fill simulation
- Raw materials and consumables vendor qualification
- Test method validation.
- Product release testing specification
- Characterization protocol
- Sterilizing filtration step validation
- Comparability protocol

5.3.2. Product-independent activities

Facilities, utilities and equipment qualification, instrument calibration and personnel training have to be completed before starting process validation. If the facilities, utilities, and equipment are already qualified for a given platform technology, they do not need to be requalified for manufacturing of a new product that pertains to that platform technology. A checklist shall be generated and confirmed to ensure all necessary documentation are in place and any concerns/issues are discussed and resolved prior to manufacture of the process validation batches. The planned facility to be used for manufacturing activities shall have a valid GMP certificate from the corresponding NRA, this is of special relevance if the facility is not new and has been previously used for other licensed products.

The developer may consider deferring the supplier qualification activities to post licensure/authorisation stage. Alternatives to this approach may be i) to perform an online audit or 2) to leverage supplier qualification as performed by a third-party company, e.g. product independent evaluation such as BSE/TSE assessment. The developer shall consider utilizing the qualification of supplier performed by another company, e.g. if that company is willing to share it directly with the HA.

5.4 PPQ batches readiness based on Holistic Control Strategy

Whereas section 4 of this document aims to describe the product control strategy by defining all critical elements -CQA, CPP and CMA and their associated ranges- this section 5.4 describes the controls to be verified to support the execution of the PPQ exercise. It consists of all the elements that must be checked, as pre-requisites for the PPQ batches execution.

The process validation readiness could be established according to the Holistic Control Strategy (HCS). This would be developed for a new product to support and justify all the means to control the product quality as defined in the control strategy through site controls, material controls, contamination controls, analytical controls, process controls, and digital controls. A brief description of each of these controls is provided here below:

- **Site controls** include the quality systems and procedural, environmental and engineering controls that provide assurance that:
  - Personnel are qualified and trained.
  - Facility and equipment are fit for use.
  - Controls to minimize deviations are in place.
  - Activities based on change controls are documented.
- **Material controls** provide assurance that raw materials (purchased or manufactured) are fit for use (including hold times for process intermediates and manufactured raw materials), and that intermediates can be forward processed to make product of desired quality.
- **Contamination controls** assure that the risks of viral, mycoplasma, microbial, pyrogen (including endotoxins and non-endotoxin pyrogens), chemical, cross contamination and particulate contamination are mitigated to protect product quality and patient safety.
- **Analytical controls** assure that fit-for-purpose analytical methods (for both in-process controls (including Process Analytical Technology (PAT)), release and stability) are used to confirm product and raw materials of desired quality.
- **Process controls** provide assurance that product quality and process performance are robust to normal variability in operating conditions and materials. The process control part defines where the manufacturing process impacts CQAs and CPPs, also how well and by what means these can be measured and controlled over the different process steps.
- **Digital controls** act as an enabler ensuring that all controls (material, analytical, site, process, and contamination) are digitally interfaced with each other under cybersecurity and data integrity assurance.

The ***Table 7*** presents examples of practices adopted under standard or accelerated conditions for all types of controls described above, together with the mitigation strategy for each type of control and potential risk originating from acceleration. It is noted that this table should be seen as a non-exhaustive source of examples (classified according to the HCS approach), to identify opportunities for accelerating PV/PPQ execution.

Table 7 Types of Control in Standard vs Accelerated scenario with Corresponding Risk Mitigation Strategies

Type of control	Standard case examples	Accelerated cases examples	Risk Mitigation strategy
Site controls	Site controls shall be available prior to PPQ: - Personnel training - Site procedures (procedural controls)	Manufacturer may start PQ with: - Prior experience on the process/platform technology shall be considered to leverage some of the PPQ Parameters, such as	Procedural controls shall be finalized based on the knowledge gained during process development, equipment qualifications and engineering batches.

Type of control	Standard case examples	Accelerated cases examples	Risk Mitigation strategy
	- Equipment parameter controls	Training, standard Operating procedures, Batch Records, equipment parameters (scale independent). - Facility/Utility Qualifications in parallel to PPQ. - Equipment basic functionality verification can be performed during commissioning phase and proceed with PPQ	
Material controls	Material controls shall be available prior to PPQ: Raw materials (RM) and critical process consumables (CPC) Controls in place	Manufacturer may use RM - CPC without vendor qualification. Manufacturer COAs shall be considered for release of material for PPQ. Raw and Packing Materials of not critical category can be used directly in PPQ without suitability/machinability trials. Manufacturer may start PPQ with an extractable and leachable risk assessment on-going.	- Online audit can be performed to qualify suppliers. - Evaluation of RM and CPC with the similar existing approved RM and CPC. - Evaluation of BSE (Bovine Spongiform Encephalopathy) and TSE (Transmissible spongiform encephalopathies). - Risk assessment based on the extractable's data from vendor and prior knowledge of the manufacturer could be used as supportive information.

Type of control	Standard case examples	Accelerated cases examples	Risk Mitigation strategy
			- Specific samples shall be collected on the PPQ batches to demonstrate the absence of any leachable or extractable outside the acceptable range.
Contamination controls	Contamination Control Strategy (CCS) shall be available prior to PV	Manufacturer may start PV with a CCS based on the knowledge gained from process development stage with appropriate scientific rationale. Manufacturer may start PV with a concurrent cleaning validation procedure with enhanced sampling plan for product contact equipment.	Define acceptance limits as per previous process knowledge.
Analytical controls	Testing and Sampling strategy shall be available prior to PV for the following: - In-Process - Batch Release - Stability - PPQ samples (additional samples for characterization) Stringent Product Release Specifications approved and available. Analytical Method Validation should be	Analytical Method Verification can be performed in parallel to PPQ batches followed by method validation post PPQ	Sampling plans need to be established which should facilitate following studies: - Process characterization - In process controls - Batch release - Cleaning validation - Analytical Method Validation - Leachable and extractable studies - Stability studies Some of the studies listed above may be deferred to post-

Type of control	Standard case examples	Accelerated cases examples	Risk Mitigation strategy
	completed for all CQAs. Sampling plan is available with proper rationale derived from the control strategy.		approval if appropriately justified.
Process controls	PARs for CPPs shall be available prior to PPQ.	Manufacturer may start PPQ without process characterization completed, with the available data derived from process development stage. Manufacturer may start PPQ with scale-down studies supporting process solution and intermediate mixing steps.	Process characterization: - Assess process development data and define acceptance criteria for scale independent parameters. - Pursue and perform process characterization studies on the PPQ batches with appropriate risk mitigation, to support PARs. - PC samples shall be collected from PPQ batches to perform studies. Process solution and intermediate mixing steps: - Process hold time samples shall be collected at manufacturing scale by extending the left-over volumes up

Type of control	Standard case examples	Accelerated cases examples	Risk Mitigation strategy
			to predefined time which facilitates at scale process hold time establishment.
Digital controls	Digital controls are interfaced and shall be available prior to PPQ.	Manufacturer may start PPQ with all the controls defined in the PPQ protocol.	Supportive documentation must be defined based on a risk-assessment.

6 Post-approval commitments

Recognizing that under accelerated conditions not all necessary activities preceding process performance qualification (PPQ) can be finalized by the time emergency use authorization is requested, certain process validation tasks will occur at commercial scale post-PPQ, thus post authorization. These include, for instance, lifetime studies of reused membranes and resins, long-term stability studies for Drug Substance (DS) and Drug Product (DP) from PPQ batches, extended leachable studies, and validation of transportation processes, to list a few examples. To address these, post-approval commitments can be made, promising to submit relevant data to regulatory bodies post product approval or emergency use authorization, using risk-based methodologies.

A specific statement outlining these post-approval commitments should be prepared, detailing the activities to be deferred, their descriptions and justifications, connections to specific study protocols, and projected timelines, among other details. This comprehensive statement must be submitted for regulatory approval during the product registration/authorization process.

Manufacturers are expected to fulfill these post-approval commitments, which may include but are not limited to, one or multiple activities specified in section 6.1 to section 6.10.

The framework and methodologies outlined in ICH Q12[9], such as employing post-approval change management protocols (PACMP) also offer a structured approach for deferring certain activities. Alternatively, validation protocols can be included in the original application, sometimes with no need to submit the generated results post-approval as far as they conform to the submitted protocol. In any case, whether using a PACMP or a validation protocol, it is advised to engage into dialogue with the corresponding HA to define the level of information that shall be provided prior and post authorization.

6.1 Deferral of PPQ batches and/or certain validation activities to post-authorisation

As mentioned earlier in this document, vaccine developers may opt for example to conduct concurrent validation with or without PPQ batches submitted in the initial application, or to risk assess which validation activities need to be prioritized pre-approval (see sections 5.1.2 and 5.1.3 in this document).

As a result, post-authorisation measures will need to be defined in line with those strategies. Typically, validation protocols and/or PACMPs shall be submitted with the original application to define how validation data will be complemented and submitted once in the post-approval space to confirm the expected ability of the manufacturing process to consistently deliver a product of quality.

6.2 Lifetime studies of membranes and chromatography resins at scale

Manufactures perform small scale re-use studies for UF membranes and chromatography resins as part of the initial submission while committing to providing additional data for commercial scale post approval/authorisation.

Prior knowledge of the similar processes and products based on the same platform technology can be used to support such claim of re-use.

6.3 Long term stability of DS and DP

Stability data from early clinical material and phase 3 clinical lots together with prior knowledge of similar products with same formulation can be used to support shelf-life settings for both DS and DP. Stability data from elevated temperatures studies can also be supportive. Equally, stability modelling/extrapolation could represent a viable strategy to determine the long-term stability profile and the associated shelf-life of a product[4], e.g. for variants/strains. Manufactures should submit stability protocols for PPQ lots at time of submission and commit to continuing to update stability data from PPQ lots.

In line with practices applied under standard circumstances, some commercial lots shall be put on stability as post-approval commitment and CPV.

6.4 Extractables and long-term leachable studies for DS and DP

If disposable containers (bags, bottles etc.) or processing materials (e.g., filters, resins etc.) are used for DS and/or DP, companies are expected to submit risk assessments and supporting preliminary data on extractables and leachable available from the vendors at the time of submission. Developers may perform an extractables and leachable risk assessment. If risk assessments have been performed as part of same platform or other similar products, they could be used to justify the decision to delay these kinds of studies to post licensure/authorisation.

6.5 Filtration validation studies

Critical filtration process steps (e.g. DS final filtration and DP filtration) are validated and submitted for product registration/authorisation. Other less critical filtration steps, including earlier steps in DS manufacturing processes and re-filtration (re-process in case of filter integrity test failure), can be validated and submitted as a part of post-approval commitments.

6.6 Cell bank stability

For products like protein subunit vaccines, where cell bank stability is relevant, existing stability data from the same cell bank used in other vaccine productions within the company can support regulatory submissions. However, for pandemic vaccines developed from new cell banks, the stability data

available at the time of product registration or authorization should be submitted, even if limited. Additionally, a commitment to provide ongoing stability data for these new cell banks is essential.

6.7 Media simulation on all aseptic process steps

Media simulations on critical aseptic process steps (e.g., DS dispensing, DP formulation and filling) should be validated and submitted as part of product registration/authorisation, while committing to providing media simulation data on other aseptic process steps based on the risk assessment.

6.8 Full validations of analytical methods

Under standard conditions, all release tests are expected to be validated at time of submission for product registration. In case of accelerated scenarios due to a PHE, some validation elements could be deferred to post-approval after appropriate alignment with the relevant authority. Methods used for in-process control and cleaning validation can be qualified for intended use and validated and submitted later as post-approval commitments.

6.9 Transportation validations

Transportation data from clinical lots and prior knowledge with a similar packaging format may be used to support initial distribution. Transportation qualification/validation protocols (DS and DP) should be submitted at the time of authorization/registration and, where required, reviewed/approved in advance. Full lane/seasonal performance data may be submitted post-authorization, provided that qualified shippers, pre-defined acceptance criteria, calibrated data loggers and real-time monitoring are in place, and any excursions are managed per the approved protocol. Changes to packaging, lanes or conditions shall follow change control and be notified or agreed as applicable.

6.10 GMP certificate

- If the manufacturing site already holds a valid GMP certificate for the same or a closely related manufacturing scope, a copy should accompany the application.
- If certification is still in progress at the time of the marketing-authorisation application, the dossier will confirm that an inspection (on-site or remote) has been scheduled and will include a binding commitment to provide the certificate before any commercial supply.
- When a certificate is not yet available, a comprehensive risk assessment will be submitted. The assessment will consider:
    - whether the facility is new or previously licensed;
    - the status and expiry of any existing certificates; and
    - the need for, and preferred format of, an inspection (in-person or virtual).

  Where appropriate, GMP inspection and certification may run in parallel with PPQ batches, and the newly issued certificate will be added to the dossier immediately on receipt.

7 Real-life example from the industry

In Section 5 of this Best Practices document, multiple tools have been described to build a tailored validation package in accelerated circumstances. It is reiterated that, the choice of combination of these available tools remains at the discretion of the developer. The final approach for PV should be duly justified at the time of dossier submission for initial regulatory approval dossier requesting emergency use authorization (or equivalent regulatory mechanism).

In this section, Johnson & Johnson Innovative Medicine kindly shares information on a product developed under accelerated conditions. Of note, process validation should be performed based on the related guidance and regulation. However, based on experience, a risk-based process validation strategy determined from scientific product and platform experience as proposed in this document can be successfully implemented in real-life without thereby compromising product quality, safety and efficacy.

Based on scientific product and platform experience, taking into account the considerations/principles that are mentioned in the previous chapters, the company adopted the following approaches towards regulatory approval: The DS and DP manufacturing processes for the product were based on extensive platform technology experience (platform technology, manufacturing process and analytical knowledge):

- Prior knowledge was leveraged to establish CQAs, preliminary CPPs and preliminary CMAs, as well as an initial control strategy.
- Where applicable, manufacturing operating ranges based on platform knowledge and equipment control capability were applied as PV acceptance criteria for preliminary CPPs.
- The acceptance criteria for preliminary CMAs were determined based on experience with product-specific process development and clinical batch manufacturing as well as experience with other platform-based products.

Confirmation of final CPP, final CMA and final integrated control strategy was a post-approval commitment.

Process validation and comparability of the DS and DP manufacturing processes of different manufacturing sites were decoupled, permitting interchangeability of DS source and thus a greater flexibility in the manufacturing network when supplying DP sites with DS. This was supported by successful comparability between DS manufacturing processes/sites.

Validation of analytical procedures for release tests was ensured with a hybrid approach combining product-specific validation activities with prior knowledge. Specifically, robustness was leveraged from previous products manufactured within the platform.

A generic approach was applied for the introduction of all the DS manufacturing processes/sites resulting in one PACMP, and the same regulatory strategy was deployed for the introduction of all the DP manufacturing processes/sites. Nevertheless, there was one additional PACMP for a specific DS manufacturing process as the generic approach was not fully applicable.

The above Industry example should be regarded as one of the many possible ways on how to leverage prior knowledge and platform experience to define a PV strategy with accelerated pathways without thereby compromising product quality, safety and efficacy.

8 Glossary

Please refer to the glossary included in the Overview of the CMC Platform Best Practices document (also named Part A).

Annex: Template Example

This Template represents an example of a Process Validation Strategy document that could be submitted for regulatory purposes at different moments of a product lifecycle, e.g., when seeking Scientific Advice; when applying for Emergency Use Authorisation (Listing), for conditional Marketing Authorisation or while in the Post Approval phase. It is intended to provide a clear outline of the company's overall approach for process validation in public health emergency situations, thus likely requiring alternative mechanisms to the known routine Process Performance Qualification (PPQ), among others. In return, such mechanisms would enable earlier access to vaccines for unmet medical needs.

It is to be recognised that whatever the strategy might look like, the core element of the defined plan will remain anchored in scientific risk-based methodologies, as appropriately justified. Therefore, it is important to also include and detail how the company plans to decrease the level of residual risk associated to process validation, eventually with a list of commitments for subsequent stages (please refer to section 6 of this Template Example on post-approval commitment).

Guidance for use of the Template:

- *Guidance text* is written in italics to indicate the type of content that could be provided.
- Example texts and/or Tables are in regular text, preceded by the wording "Example".

1. Introduction

This section is intended to provide a very first notion of the process validation approach the company is proposing. Elements to consider:

- *the need to have a vaccine authorised based on a risk approach given the pandemic/outbreak situation.*
- *statement that there is currently not formally completed PPQ for <vaccine X>*

Example text:

Due to the current emergent viral concern, an acceleration of vaccine manufacturing is needed to swiftly respond. To shorten the time for vaccine access, prior knowledge, platform technology, and targeted qualification/validation [*add additional high-level summary of information used as needed*] of the manufacturing process will be used. At this point, a traditional PPQ has not been performed. However, the information provided below will support the use of the manufacturing process and provide a commitment to provide additional data for further confirmation that the process is under control.

2. Manufacturing Process Description

If this document is submitted within a CTA/IND or within a cMAA/EUA/EUL, provide a cross-reference to 3.2.S.2.2 and/or to 3.2.P.3.3 CTDs. Consider if the level of detail is sufficient, especially in case of a CTA/IND.

Should the level of detail in the cross-referenced CTDs not be sufficient, provide a brief process description.

Manufacturers shall describe the process overview in the form of a flow diagram of the manufacturing process along with the testing that should be done in each step. The process flow diagram should include every process step, listing relevant in-process controls and process parameters wherever applicable. Process flow should be clear on the chronology of the activities to be done in sequence vs. those running in parallel.

The author of this document should be mindful of keeping a similar level of detail as applied in the authoring of additional documents that are being submitted concomitantly.

Figure 4: Example of process flow diagram template for a vaccine

Environment (room, classification), Equipment	Materials/ Reagents	Process Steps	Process Parameters (CPP, performance-related parameters)	Process Controls/ In-process testing Process Monitoring, IPC with defined limit/criteria *, In-process release tests**
Pre-culture room LAF (BSC II class) Water Bath Pipet aid	WCB #xxx Thawing solution/ medium (pre-warmed at 37°C)	***Step 1*** WCB vial thawing & dilution	Temperature (Thawing): 35-38°C Thawing time: < 3 min Ratio thawing solution/cell suspension: 9/1	
Centrifuge Automated cell counter	Washing solution/ medium (pre-warmed at 37°C)	***Step 2*** Washing of cells	Temperature (centrifuge) : RT (20-25°C) Duration (centrifuge) : 10 min Speed (centrifuge) : 2-8°C	Cell viability*: > 80% Viable cell count*: > QTY of cells required to respect cell density. Total cell count (monitoring) Viable cell recovery rate*: > 70%
Shaking CO_2 Incubator	Shake Flash 125 mL	***Step 3*** Cell seeding and expansion in SF 125	Incubation parameters (T°, CO_2, Humidity): 37 ± 1 °C, 5 ± 1 % CO_2, 80%± 10% RH Orbital shaker parameters (RPM, orbit diam): 120 RPM, 50 mm Viable cell density for seeding: 0.5 x 10^6 cells /mL Culture medium volume/ area: xx	
		Step 4		

3. Process Validation Strategy proposed by the Company

Include a clear description of the PV Strategy the Company has chosen to apply. Reference is made to Section 5 on "Process Validation Strategy" of the Best Practices document.

4. Summary of Data that support the proposed Process Validation Strategy

Include a summary of datasets that can be found in module 3 of cMAA/EUA/EUL. Also reference the sections where the detailed data reside in Module 3.

Process validation prior knowledge should be available from the platform technology and can be summarised here. Also reference the sections where the detailed data reside in Module 3.

Should there be possibilities to cross-refer to platform technology master files which contain process validation information, consider cross-refencing to that master file.

5. Justification for the proposed Process Validation Strategy

1. *Provide the rationale on why the process is fit for purpose even if full validation has not been completed. Make use of the risk assessment conducted according to Section 3 on "Risk-based approach for Process Validation" of the Best Practices document.*
2. *Describe any additional controls that will be put in place to assure process control in the absence of full validation, if needed (e.g., IPCs, hold times, etc.).*
3. *Explain how the follow-up activities will support the initial assumption that the process is under control and leads to the expected product quality, that is, justify the proposal for the data you will commit to in Section 6 of this Template.*

6. Post-approval Commitment

Summarize how the Company will approach PV after emergency use authorisation (or equivalent regulatory mechanism) taking into account the points listed in the previous section of this Template (i.e. Section 5, "Justification for the proposed PV strategy").

Provide a statement of commitment for the following activities to be performed and submitted to the Health Authority. If you know approximately when this data should be available, provide a tentative date (only if you are reasonably confident).

Include a table with proposed activities that will be performed and how each of them will contribute to minimise/mitigate known risks, as identified in the risk assessment included in Section 5 of this Template, "Justification for the proposed PV strategy".

Table 8: Example of a table with Post approval commitment and its justification/assessment

No.	***Post approval commitment Activities***	***Descriptions***	***Justifications/Assessments***	***Relevant Protocols***	***Tentative data available date***
1	*Stability study for DS PPQ batches*	*The accelerated stability studies for DS PPQ batches have been initiated at XXX °C for XX months. The long-term studies have been initiated at XXX°C for XXX months. Detail of the stability study refer to Doc No. XXX*	*Stability data from earlier clinical and phase 3 clinical lots are available, and could be used to support DS shelf-life settings*	*Stability study protocol for DS PPQ batches Doc no. XXX*	*YYYY/MM*
2					

This should be detailed enough to provide information that an agency can assess that the data to be provided is appropriate for validation.

Provide specifications where appropriate or what studies will be performed to set those specifications.

Provide the number of lots to be used in the validation process.