CMC PLATFORM BEST PRACTICES

PART B

Comparability assessment in accelerated scenarios, best practices and blank template

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Principles and tools

1 Scope

According to the ICH Quality Guideline Q5E1, "the goal of the comparability exercise is to ensure that the quality, safety, and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes." In addition, the guideline mentions that "the demonstration of comparability does not necessarily mean that the quality attributes of the pre-change and post-change product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product."

Maintaining comparability line-of-sight from the preclinical toxicology study of an investigational product to the final commercial manufacture of the approved product is a key enabler of accelerated product development. When dealing with comparability assessment during development, ICH Q5E does not provide detailed information on data requirements, stating that "during early phases of nonclinical and clinical studies, comparability testing is generally not as extensive as for an approved product. As knowledge and information accumulate, and the analytical tools develop, the comparability exercise should utilize available information and will generally become more comprehensive." Also, the guideline mentions that "where process changes are introduced in late stages of development and no additional clinical studies are planned to support the marketing authorisation, the comparability exercise should be as comprehensive and thorough as one conducted for an approved product." This may imply extensive product and process knowledge, and may lead to the assumption that expected comparability criteria should be based on manufacturing consistency (statistical approach). Such expectations could not be applicable in accelerated or pandemic scenarios, when comparability is instrumental to manage the CMC challenges for the fast and equitable supply of vaccines, but there is typically a low number of lots manufactured in a short timeframe. Specific risk-based strategies for accelerated scenarios [1,2,3,4] are needed in these instances. Indeed, the past COVID-19 pandemic created urgent unmet medical needs, which, despite the significant challenge to manufacture and distribute vaccines at the required scale, led to the product and processes being developed and deployed very swiftly. In addition, making billions of doses post-launch supply requires the use of multiple manufacturing sites, their concurrent expansion, and the potential need for many manufacturing

1 ICH Q5E, Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process
2 COVAX CMC Comparability Workshop
https://media.tghn.org/medialibrary/2020/11/20200928_CMC_Comparability_Workshop_presentation.pdf ; January 27, 2021,
3 COVAX Best practices for tech transfer workshop
https://media.tghn.org/medialibrary/2021/02/012720_Tech_transfer_workshop.pdf
4 Quality by Design - An Indispensable Approach to Accelerate Biopharmaceutical Product Development, Eds M. A. Khan, C. Campa, PDA, 2021, Chapter 11, Comparability Assessment for Vaccines Development and Lifecycle

changes, demonstrating that post-change product is comparable to the pre-change product, with equivalent performance.

This document is intended to provide practical guidance and illustration of comparability assessment in accelerated scenarios (unmet medical needs, outbreaks or pandemics), covering different lifecycle stages and vaccine platforms. It describes the underlying logic and principles of a phase-appropriate, risk-based approach to support comparability for vaccine products during development and post- approval, with tailored implementation opportunities, depending on the level of prior knowledge and associated risks. This effort also supports the CEPI 100 days mission for equitable and rapid access to vaccines in case of new Public Health Emergencies[5].

Following the advice and strategies presented in this document does not constitute or guarantee any regulatory acceptance/approval; consultation of the relevant Regulatory Authorities on the adopted acceleration options is therefore strongly advised.

2 Recommendations/best practices

2.1 Background

During the COVID-19 crisis, some risk-based comparability approaches for vaccines were proposed by Industry associations (Vaccines Europe, VE & the International Federation of Pharmaceutical Manufacturers and Associations, IFPMA, and DCVMN) in the context of COVAX Manufacturing SWAT discussions. These approaches were published in the WHO Technical Brief and in other publications[6,7]

These options included, for instance:

Use of a risk-based analytical comparability assessment of manufacturing changes, such as:

- evaluation of Critical Quality Attributes (CQA's) related to the changes known to possibly impact safety and/or efficacy (examples of risk assessment for CQA identification are reported in literature [see for instance 4 and references therein] and is not part of this document)
- use of release data, degradation data (including accelerated stability and predictive modelling, as appropriate), and/or characterization data to demonstrate comparability.
- justification of comparability strategy and acceptance criteria with reliance on prior knowledge on similar products (e.g., within a given vaccine platform).

When prior knowledge is limited on process performance/ consistency, demonstration of preservation of CQA's based on analytical comparability should be taken into consideration. This is in line with ICH Q5E,

5 CEPI-100-Days-Report-Digital-Version_29-11-22.pdf
6 WHO 1st technical brief: regulation of COVID-19 vaccines synopsis from the August to October 2020 COVAX RAG meetings. April 2021. https://www.who.int/publications/m/item/annex-1st-technical-brief-regulation-of-covid-19-vaccines
7 McGoldrick M, Gastineau T, Wilkinson D, Campa C, De Clercq N, Mallia-Milanes A, et al. How to accelerate the supply of vaccines to all populations worldwide? Part II: Initial industry lessons learned and detailed technical reflections leveraging the COVID-19 situation. Vaccine. 2022;40(9):1223–1230

stating "the goal of the comparability exercise is to ascertain that pre- and post-change drug product is comparable in terms of quality, safety, and efficacy."

Assessment on inclusion of manufacturing variability in clinical trials and appropriate dose selection (higher than the minimum active, as per discussion at 2018 EMA/FDA early access workshop[8]) to support definition of such patient-driven acceptance criteria for product quality expectations and comparability.

For post-approval comparability, reliance on process understanding/process performance qualification (PPQ) data, analytical performance/validation knowledge, and clinical history, to de-risk comparability exercise.

Of note, some of the above- mentioned approaches are also reported in the 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[9].

Based on the above considerations, comparability demonstration is grounded on DS/DP quality assessment, considering expected efficacy and safety (specifications and additional characterization, as needed). If available and applicable, evaluation of comparability study results, with respect to manufacturing history, can be a supportive information aided by statistical approaches.

Table 1 reports a detailed comparison of standard vs. accelerated scenarios, including illustrative risk-based approaches of comparability during clinical phases and between Phase 3 and PPQ. Several of the risk-based strategies to support comparability in accelerated scenarios (including, for instance, reliance on analytical package as core expectation of comparability; robust reference standard strategy; or use of Analytical Target Profile for analytical strategy), are best practices equally recommended for comparability in non- accelerated scenarios, if well justified. The systematic implementation of such strategies becomes indispensable in case of accelerated development.

Despite some of the proposed risk-based strategies are not new, it is the combination of all risk-based approaches which is quite unique, knowing that standard practices typically consider only one or two aspects.

The subsequent sections provide more specific considerations for the establishment of a risk-based comparability strategy in accelerated scenarios.

8 EMA/ FDA Stakeholder workshop on support to quality development in early access approaches, such as PRIME and Breakthrough Therapies, 2018, https://www.ema.europa.eu/en/events/stakeholder-workshop-support-quality-development-early-access-approaches-such-prime-breakthrough#documents-section

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, 22 April 2022, EMA/CHMP/BWP/QWP/IWG/694114/2019, Committee for Human Medicinal Products (CHMP)

Table 1 Illustrative risk- based approaches to support comparability in accelerated scenarios

	Data package in standard scenario	**Data package in an accelerated path to emergency use authorization (or equivalent regulatory mechanism)**	**Illustrative risk- based approaches to support comparability in accelerated scenarios***
Phase 2/3 comparability	-Assessment of CQAs and potential CQAs. -Analytical package for routine and additional characterization, with phase-appropriate validation as applicable. -Process understanding supporting evaluation of process/ scale change impact on product quality. -Real time stability data available based on representative early development batches to support comparability.	-Ongoing assessment of CQAs and potential CQAs, also considering potential update of formulation/ presentation. - Ongoing consolidation of analytical strategy. -Ongoing process understanding, to assess process change impact on product quality. -Limited real-time stability information.	-Focus on CQAs impacted by the change, and on their analytical characterization. -Focus on analytical characterization of the product to justify comparability acceptance criteria while process knowledge evolves. - Minimal verification or validation to be performed. This means that only critical tests/CQAs with minimum parameters can be validated or verified. This may be decided on risk assessment basis. -In case of method change, analytical methods bridging strategy, grounded on pre-defined, technology independent analytical performance expectations (Analytical Target Profile). - Reliance on accelerated stability studies and predictive stability modelling to support comparability. -Use of prior knowledge to support product and process understanding/ definition of comparability criteria, as applicable.

	Data package in standard scenario	Data package in an accelerated path to emergency use authorization (or equivalent regulatory mechanism)	Illustrative risk- based approaches to support comparability in accelerated scenarios*
Phase 3/PPQ comparability	-Completed assessment of CQAs and potential CQAs. -Completed analytical method validation in preparation of the PPQ. -Process understanding completed to support PPQ campaign. -Real-time stability data available based on representative development batches to support comparability. - Often sufficient number of representative batches to define consistency- driven support for comparability, in addition to analytical package.	-Completed assessment of CQAs and potential CQAs, in the final formulation/ presentation - Ongoing consolidation of analytical strategy. -Ongoing process understanding, to assess process change impact on product quality. -Limited real- time stability information.	- Focus on CQAs impacted by the change -Focus on analytical characterization to justify comparability acceptance criteria in case of limited number of development lots - Minimal method verification or validation, with deferral of some activities as needed -In case of method change/ ongoing optimization, analytical methods bridging strategy, grounded on pre-defined, technology independent analytical performance expectations (Analytical Target Profile) -Reinforce implementation of Reference standard strategy reflecting use of Ph3 lots for PPQ and early commercial lots testing (e.g. potency). -Reliance on accelerated stability studies and predictive stability modelling to support comparability. -Use of prior knowledge to support product and process understanding/ comparability analysis results, and/ or definition of comparability criteria, as applicable.

**can be considered individually or in combination*

3 Inputs for Comparability criteria

3.1 Product understanding and analytical characterization

Building strong, quality risk-based comparability strategies is key to support fast access and sustainable lifecycle management. Product quality attributes are identified and scored based on the potential impact to safety and/or efficacy as well as the degree of uncertainty in the severity assessment (ICH Q8). This leads to non-critical Quality Attribute (QA), potentially critical (pCQA) and critical quality attributes (CQA). The list of pCQA can be modified as product knowledge and process understanding increase. If sufficient product knowledge has been accumulated, a (p)CQA could become a non-critical QA. Until then pCQA are treated as CQA. Furthermore, a change to the product and/or process may introduce a new product quality attribute (e.g., a newly introduced process impurity) which must be scored regarding its criticality; or a current non-critical QA, pCQA or CQA may have to be re-evaluated. These possible new pCQA and/or CQA must be taken along in the comparability assessment. The same principles apply to critical process parameters (CPP) and critical material attributes (CMA) assessment(s).

The ICH Q5E guideline states that "*predefined comparability criteria should allow an objective assessment of whether or not the pre- and post--change- product are comparable*". Quantitative comparative evaluation of quality attributes is an important aspect of determining comparability, also acknowledged by the various regulatory authorities (e.g., for drug development, see [10]).

Nevertheless, there are some specific challenges associated to defining the predefined comparability criteria in accelerated scenarios. As mentioned above, the limited number of clinical (and representative) batches available for use in comparability studies may result in a too limited historical dataset to establish relevant statistically based criteria.

Therefore, it is recommended to at least assess the results from the analytical test package (release, stability, additional product and process characterization data, when applicable) using specifications (where applicable), side-by-side comparison, based on method/product knowledge, and historical (min-max) ranges.

The emphasis on reliable analytical comparability in evolving process understanding and manufacturing facilities requires special attention to the analytical strategy. Comprehensive product characterization is critical for both purity and impurity for product understanding. Analytical method changes could take place either due to company needs (e.g., evolving knowledge, cross-testing site transfers/ changes) or considering transfer to National Control Laboratories (NCLs), which may also imply analytical changes to be managed even when a company has a standardized analytical platform approach. Addressing the risks associated with an evolving analytical strategy is key to define a robust reference standard strategy (i.e., with

10 Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (July 2021) by the European Medicines Agency (EMA) and adopted by the Committee for Medicinal Products for Human Use (CHMP) (EMA/CHMP/138502/2017

representative lot selection for comparability and for method bridging if needed, favoring clinically proven lots, extensive characterization and assessment of best storage conditions for reference standard). Also, definition of minimum set of tests (platform-specific) and analytical method purpose and performance expectations (product-specific) is of significant relevance[11]. This can be done upon definition of the Analytical Target Profile (ATP), "*a prospective summary of the performance characteristics describing the intended purpose and the anticipated performance criteria of an analytical measurement*"[12]. In this context, if evolving analytical procedures comply with pre-defined expectations of the ATP, these can be used as key criteria to support methods bridging.

3.2 Understanding of the impact of product/ process changes on CQAs

Identification of CPPs and CMAs is key to ensure an appropriate understanding of the impact of manufacturing changes on product quality, and to focus the comparability exercise on the specific steps impacting CQAs. Similar reasoning is applicable to formulation changes, where it is critical to understand the impact of formulation composition on CQAs and the related stability.

Statistical approaches

If sufficient pre-change data (clinical and representative batches) are available to set meaningful statistical predefined comparability criteria, this would additionally support comparability demonstration. This may be considered for post- launch comparability studies, while for comparability assessment during development the number of data and the nature of changes may not be compatible with statistical approaches.

After implementation of manufacturing changes, the post-change product does not need to be identical to the pre-change product, but they need to be highly similar[1]. As 'similarity' is context-dependent, not universally applicable/agreeable similarity conditions exist. Therefore, different similarity criteria can be computed based on different statistical approaches, when applicable. Additionally, as no criterion will lead to a correct decision in all situations, there are no similarity criteria that can be universally considered 'right' or 'wrong'. Some examples of statistical approaches to set up comparability evaluation criteria are:

1) Confidence intervals: based on a normal distribution characterized by 2 parameters (mean (μ) and standard deviation (SD; σ)).

2) Tolerance intervals: computed to estimate a data range by which a specified proportion p (e.g., the central 99%) of the units from the underlying population is assumed to be covered with a pre-specified degree of confidence c (e.g., 95%); this implies that a certain product quality would fall within the 99%/95% TI computed from the reference batches.

11 PDA Technical Report no. 89, Strategies for Vaccine Development and Lifecycle Management.

12 ICH Q14, Analytical procedure Development, November 2023

3) Prediction intervals: a data range covering data outcome of one or more future observations with a pre-specified degree of certainty (% PI, e.g., 95% PI, means that the future observation will have a 95% probability of falling within the PI).

3.3 Reference dataset

In order to apply one of the suggested statistical approaches, there needs to be a reference dataset of a certain minimal size. Various aspects can be used to assess if a batch is deemed representative. The most important, but not limited to these, are:

1) Meet the pre-change release acceptance criteria
2) Same manufacturing process as pre-change (can be GMP or non-GMP)
3) If a different manufacturing process but the material was used in a clinical study where potency was assessed and comparability to pre-change process has been demonstrated
4) Sufficient knowledge to determine platform expectations (i.e., prior knowledge)

The presence of outliers will affect both the mean (μ) and the standard deviation (σ) of a certain attribute. It is therefore imperative that reference datasets do not contain any outliers, unless validated clinically. These can be detected via various statistical tools and a proper assessment should be performed to confirm if these can be excluded rightfully so.

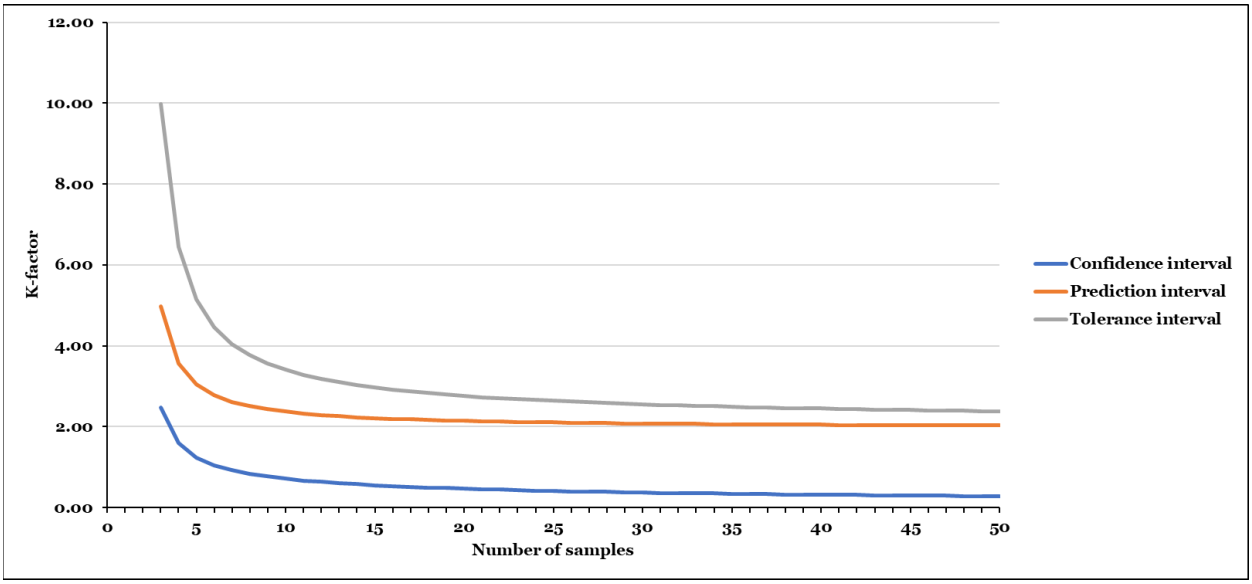
Furthermore, the size of the reference dataset (i.e., the number of batches) impacts the width of the interval depending on the selected statistical approach, e.g., confidence interval, prediction interval or tolerance interval as shown in **Table 2**. Of note, reaching a certain sample size, additional samples will have a limited impact on the width. On the other hand, a too low sample size usually implies that the reference dataset will provide higher uncertainties on the estimate of the true range (in other words, likely may not provide an adequate estimate of the true range). This is illustrated by **Figure 1** where for confidence, prediction and tolerance intervals there is a great reduction in uncertainty for every additional sample. This occurs until it starts to plateau, where for this case, depending on confidence, prediction and tolerance intervals, that is at least 10 samples. In other words, at a certain sample size there is barely any impact anymore.

To re-iterate, these more complex statistical approaches (e.g., confidence, tolerance and prediction intervals) may be used to additionally support comparability demonstration if sufficient pre-change data is available for an adequate estimate of the true range and one should debate if they should be applied or not when the reference dataset is limited. In this context, it is worth reminding that the core information to support comparability demonstration remains the assessment of product quality expectations before and after the change (i.e., statistical evaluation is one of the elements supporting the comparability strategy that we can use when appropriate).

Table 2: The impact of sample size on the broadness of the 95% confidence, 95% prediction and 99/95% tolerance intervals.

Sample size	95% Confidence Interval (K factor)	95% Prediction Interval (K factor)	99/95% Tolerance Interval (K factor)
3	2.48	4.97	9.98
5	1.24	3.04	5.14
6	1.05	2.78	4.46
7	0.92	2.62	4.05
8	0.84	2.51	3.77
9	0.77	2.43	3.56
10	0.72	2.37	3.41
11	0.67	2.33	3.28
12	0.64	2.29	3.18
13	0.60	2.26	3.10
14	0.58	2.24	3.03
15	0.55	2.22	2.97
16	0.53	2.20	2.92
17	0.51	2.18	2.87
18	0.50	2.17	2.83
19	0.48	2.16	2.80
20	0.47	2.14	2.76
25	0.41	2.10	2.64
30	0.37	2.08	2.56
35	0.34	2.06	2.50
40	0.32	2.05	2.45
45	0.30	2.04	2.41
50	0.28	2.03	2.38

Figure 1: The impact of sample size on the broadness of the 95% confidence, 95% prediction and 99/95% tolerance intervals.



Comparability criteria application

For quality attributes of either a process intermediate, DS or DP for which there is a quantitative in-process control, release or stability specification criterion, it will be applied as main comparability criterion, in combination with additional characterization tests with orthogonal methods, as appropriate.

As mentioned above, statistical approaches may support the evaluation of comparability results with respect to historical pre-change data; it is worth noticing that, however the main decision driver for comparability is the DS/DP quality assessment.

If there is a too limited representative dataset, the results from the analytical test package (release, stability, product and process characterization data, when applicable) will be assessed based on both side-by-side comparison (considering the method criteria and method/product knowledge), and historical (min-max) ranges.

There are various additional comparability supportive information to be considered:

For product safety related quality attributes, a one-sided interval will be calculated whereas for all other quality attributes a two-sided interval will be calculated, unless properly justified.

For a quality attribute with intrinsically low or no variance (therefore standard deviation) no comparability evaluation criteria will be calculated, irrespectively of the reference dataset size. Otherwise, it would lead to extremely narrow, and potentially meaningless intervals.

In case of data censoring (e.g., <LOQ data), the mean μ and the standard deviation σ of the corresponding attribute will be estimated via an appropriate regression model (e.g., Tobit regression model).

Stability Trend Comparison

Stability assessment of the product after a product/ process change is an important component of comparability packages. As mentioned above, reliance on real time data might not be possible in accelerated scenarios, and alternative approaches may be needed. In particular, accelerated stability data allow comparative assessment of product behavior in case of exposure to different temperatures and may represent an important input for comparability, especially when combined to modelling strategies for long-term stability prediction[13,14].

Use of prior and platform knowledge

As mentioned in the report of the EMA Joint BWP/QWP workshop with stakeholders in relation to prior knowledge and its use in regulatory applications[15] *"prior knowledge, in the context of pharmaceutical development and regulatory applications can be:*

- internal knowledge from a company's proprietary development and manufacturing experience (e.g. historical experience based on similar compounds, products and processes, including data modelling, application of 'platform technologies', knowledge from previous filings),

- external knowledge such as reference to scientific and technical publications (including vendors data, literature and peer-reviewed publications). The application of established scientific principles (e.g. chemistry, physics and engineering principles and mechanistic understanding from studies evaluating structure-function relationships) is also considered to be prior knowledge."

In the context of risk- based comparability, prior and platform knowledge can be used to support all the above- mentioned approaches, including, for instance:

- Rapid identification of (p)CQAs based on knowledge available on similar products/ vaccine platform
- Rapid identification of (p)CPPs and (p)CMAs
- Rapid identification of a fit- for-purpose analytical strategy
- Stability assessment (e.g. trend prediction for similar products/ attributes)
- Comparability criteria (e.g., support statistical evaluation using data from similar products)

13 Campa, C.; Pronce, T.; Paludi, M.; Weusten, J.; Conway, L.; Savery, J.; Richards, C.; Clénet, D. Use of Stability Modeling to Support Accelerated Vaccine Development and Supply. Vaccines 2021, 9, 1114. https://doi.org/10.3390/vaccines9101114
14 COVAX CMC workshop on Storage temperature and shelf life media.tghn.org/medialibrary/2020/12/20201209_COVAX_Storage_temperature_and_shelf_life_workshop_presentation.pdf
15 EMA Joint BWP/QWP workshop with stakeholders in relation to prior knowledge and its use in regulatory applications, 2017, https://www.ema.europa.eu/en/documents/report/meeting-report-joint-biologics-working-party/quality-working-party-workshop-stakeholders-relation-prior-knowledge-its-use-regulatory-applications_en.pdf

The extent of prior/ platform knowledge use may depend, among others, on the manufacturer's experience, applicability of literature information, vaccine type, lifecycle stage of the product.

In order to cover different vaccine platforms and level of maturity of knowledge, the comparability best practices document provides also a comprehensive set of examples for mRNA, viral vectors, subunit proteins and inactivated virus vaccines. These comparability examples are illustrative, and they can be consulted respectively in the four separate annexes to this document. All of them follow the same comparability methodology as well as document structure (see details below, under section 3 of this document).

4 Real-life example from the industry

In this section, Johnson & Johnson Innovative Medicine kindly shares information on a product developed under accelerated conditions. Of note, comparability should be performed based on the related guidance. However, based on experience, a risk-based comparability 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, the company adopted the following approaches, taking into account the considerations/principles that are mentioned in the previous chapters, 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.

A generic approach was applied for the introduction of all the DS manufacturing processes/sites resulting in one post approval management protocol (PACMP), and the same regulatory strategy was deployed for the introduction of all the DP manufacturing processes/sites. This led to a swift and consistent implementation of new DS/DP manufacturing processes/sites. Nevertheless, there was one additional PACMP for a specific DS manufacturing process as the generic approach was not fully applicable.

A two-tiered approach was used to determine comparability for both DS and DP versus Phase 3 batches data. The Tier 1 analytical tool packages were determined based on a comprehensive risk-based assessment leveraging product and process platform knowledge. The Tier 1 package primarily consisted of release methods for DS and solely of release testing for DP of the first 3 post-change batches. If the comparability criteria were met for Tier 1 (primarily release specification), the batches would be released to the market. Tier 2 consisted of (additional) characterization data of the first 3 post-change batches which were compared to the pre-change batches in order to gain more understanding of product and process variability and further confirm the initial comparability assessment. If data of other commercial manufacturing processes/sites (i.e., of other previously introduced sites post approval where comparability was demonstrated) were available, the first 3 batches were also compared to those data. No forced degradation or stability data were required to demonstrate comparability. Of course, stability studies were still

performed for each manufacturing process/site to confirm the shelf-life, which was modelled based on platform knowledge.

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

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.

Platform knowledge was applied to specifications for various platform-related methods, e.g., the process-related impurity 'residual host cell protein'.

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 comparability strategy with accelerated pathways without thereby compromising product quality, safety and efficacy.

5 Comparability methodology for the template

The structure of the comparability template is underpinned by the methodology shown in Figure below. The overall strategy assumes that there is sufficient product understanding as described by a comprehensive set of CQAs (appropriate to the specific vaccine platform) and is broadly defined by the five key elements below:

- Describe changes that are implemented to manufacturing processes impacting CPP, CMAs, specifications, overall control strategy and analytical methods.
- Assess impact of the changes on CQAs, applying a risk-based approach.
- Develop comparability strategy, including the analytical strategy employed and the comparability criteria to be applied.
- Analyze the analytical results and describe the impact of the changes quantitatively.
- Draw conclusions, which summarize the outcomes of the study.

The methodology in Figure 2 has been developed to support two scenarios, (1) accelerated development in emergency scenarios and (2) post-approval changes.

As part of pandemic preparedness, it is encouraged to develop a vaccine platform suitable for rapid response. Prior knowledge from products and manufacturing processes could be acquired through development of vaccine platforms, which ultimately lead to a thorough understanding of CQAs per vaccine type and their linkage to CMAs and CPPs. Each annex describes an illustrative example for each of the four selected vaccine types: mRNA, protein subunit, viral vector and inactivated virus. The elements proposed for those four examples can be applied to other vaccine types or to adjuvants.

As mentioned above, prior and platform knowledge would contribute significantly to a proper risk assessment by quicker determination of which manufacturing changes potentially impact CQAs. Prioritization of comparability testing for the impacted CQAs could be a strategy pre-aligned with regulators to enable rapid supply while keeping sufficient confidence that the vaccines are equally safe and efficacious despite the changes.

Various risk assessment tools are available for use to assist comparability prioritization. An example of risk assessment is presented in the mRNA annex. A risk of CQA impacted by changes is determined by compounding together the severity, probability and detectability of the impact. Subsequently, CQAs of high impacts are subjected to analytical testing at suitable process steps, such as in-process, release and/or characterization for the assessment.

It is important that each developer chooses a tool appropriate to rank the criticality of the changes, as needed.

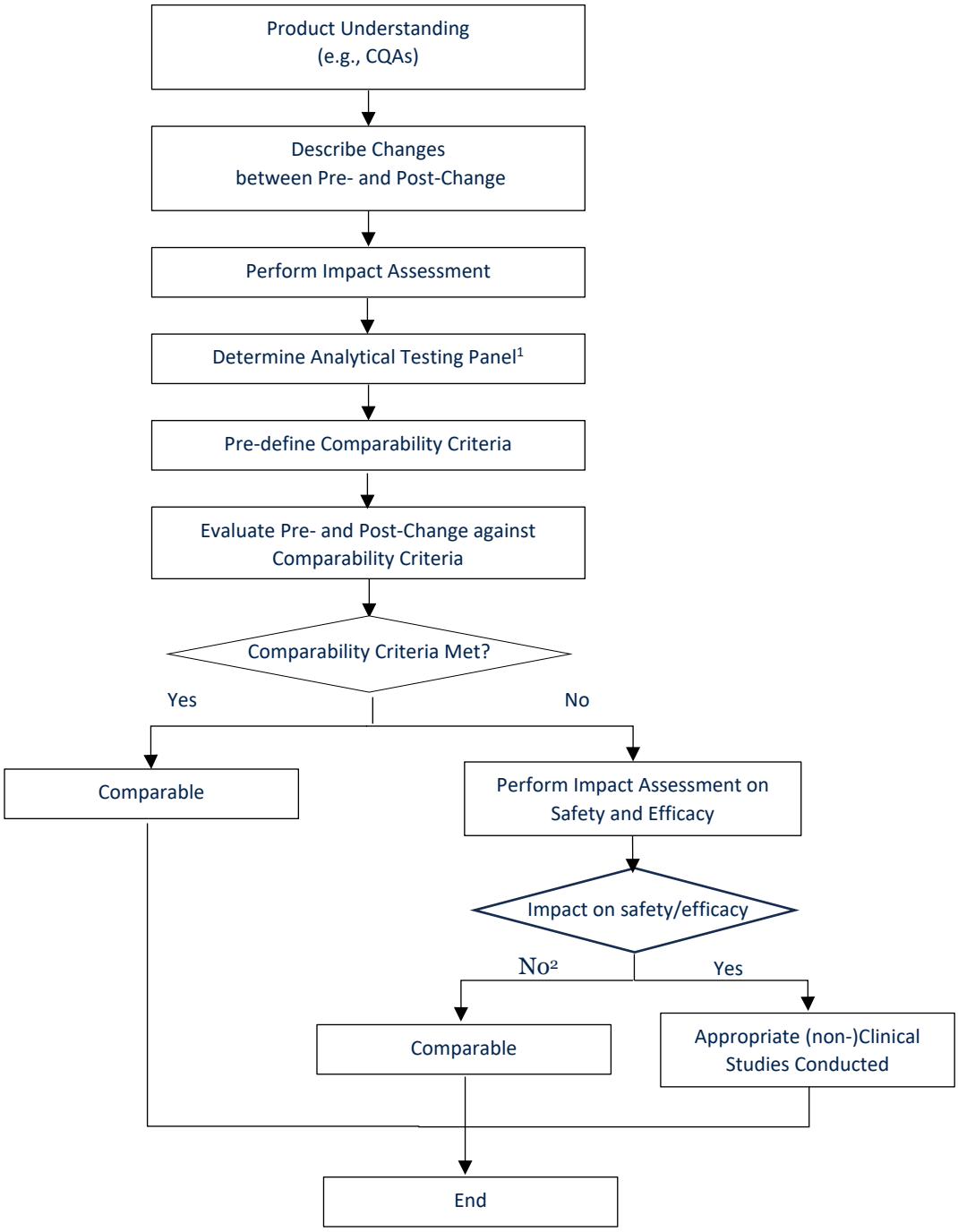


Figure 2: Comparability strategy employed by this template.

[Footnote 1. Which CQAs will be tested at which manufacturing process step(s) by which method(s).; and 2. Proper scientific justification should be provided].

1 Introduction

1.1 Product information/problem statement

[Insert a narrative part describing product and platform information. As appropriate, add a justification on how the product fits into the platform]

1.2 Critical Quality Attributes & Related Analytical Strategy

[Product quality attributes are identified and scored based on the potential impact to safety and/or efficacy as well as the degree of uncertainty in the severity assessment (ICH Q8). This leads to non-critical , potentially critical (pCQA) and critical quality attributes (CQA). The list of pCQA can be modified as product knowledge and process understanding increase. Until then, pCQA will be treated as CQA. Furthermore, a change to the product and/or process may introduce a new product quality attribute (e.g., a newly introduced process impurity) which has to be scored regarding its criticality; or a current non critical attributes, pCQA or CQA may have to be re-evaluated. These possible new pCQA and/or CQA have to be taken along in the comparability assessment.]

Table 1 summarizes a guideline of (p)CQA(s), as well as the rationale for the criticality assignment. If sufficient product knowledge has been accumulated, a (p)CQA in this list could become a non critical quality attribute.

Table 1 (p)CQAs for <Name of Product>

Quality Attributes	**Criticality Assignment**	**DS/DP**	**Rationale**
General physicochemical characteristics *Determination of the physicochemical properties of the product*			
Excipients			

Quality Attributes	Criticality Assignment	DS/DP	Rationale
A constituent other than the active substance, added in the formulation for a specific purpose.			
Content *A measure of the amount of product required to determine the dose*			
Potency *A measure of the biological activity based on the attribute(s) of the product which is linked to the relevant biological properties*			
Identity			
Product Related Substances and Impurities *Certain product variants, such as aggregates and viral protein degradation products, may have an impact on safety and efficacy*			
Process-related Impurities			
Contaminants			

Table 2 Analytical Testing Control Strategy**

Category	**CQA**	**Analytical Method**	**Drug Substance**	**Drug Product**
General physicochemical characteristics	Attribute 1	Method ID	Release/stability/IP*/characterization	Release/stability/IP*/ characterization
Excipients				
Content				
Potency				
Identity				
Product-related substances and impurities				
Process-related impurities				
Contaminants				

**IP: meaning both In Process Controls or In Process Monitoring tests*

***Not exhausted list of attributes, all the mandatory tests should be performed as per regional requirements (eg. Sterility, CCIT, Microbial tests)*

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2 Description of the Changes & Justification

[Insert narrative describing the change as the following examples:

A narrative section outlining the changes and the reasons/rationale for the changes:

- Description of changes explains which parameters are changed in manufacturers, manufacturing scales and processes, raw materials or other deemed important areas related to drug substances and drug products. Changes can be grouped under categories defined by sponsors.
- Pre-change column describes the conditions of the parameters before the change is made.
- Post-change column describes the conditions of the parameters after the change is made.
- Justification column describes reasons of the changes made and any references if available.]

Table 3 Changes to Drug Substance

Change ID	**Description of changes**	**Pre-Change** (Toxicology/Early phase or Late phase clinical trial)	**Post-Change** (Commercial/Launch)	**Justification of the change**
DS1	Site of manufacture	Pilot plant	Large scale facility	
DS2				
DS3				

Table 4 Changes to Drug Product

Change ID	**Description of changes**	**Pre-Change** (Toxicology/Early phase or Late phase clinical trial)	**Post-Change** (Commercial/Launch)	**Justification of the Change**
DP1	*Site of Manufacture*	*Pilot Plant*	*Large scale facility*	

Change ID	Description of changes	Pre-Change (Toxicology/Early phase or Late phase clinical trial)	Post-Change (Commercial/Launch)	Justification of the Change
DP2	*Scale*			
DP3	*Batch Numbers/ CT Phase*			
DP4	*Antigen*			
DP5	*Excipients*			
DP6	*Adjuvant*			
DP7	*Primary packaging components*			
DP8	*Container closure system*			
DP9	*Formulation process*			
DP10	*Filter utilization*			
DP11	*Sterility*			
DP12	*Filling Line*			
DP13	*Storage conditions*			
DP14	*Product labelling*			
DP15	*Transport validation*			

3 Change Impact Assessment

[Describe the impact of each individual change on the quality of the product, for example, on CMAs of raw/starting materials, CPPs of the corresponding process step and/or CQAs of the product. A justification of this impact is given and the potential impact on safety and efficacy is described.

- "Change ID" refers to the change numbers. This column is to help reviewers to cross-reference between changes and the associated impacts.

- "CQAs and Attributes impacted" list potential impacts on the product quality or process performance caused by the associated changes. DS and DP stabilities are captured as product attributes as a consequence of proposed changes.

- "Risk Score on safety and efficacy" is dedicated for risk assessment.

Risk assessment needs to be performed based on developer's risk assessment framework

- The "Justification" column explains the outcome of the risk assessment and the criticality of the changes, which explains why the CQA has been included in the comparability assessment.

- Provide a summary paragraph concluding the overall criticality level to identify the comparability strategy.]

Various risk assessment tools are available for use to assist comparability prioritization. It is important that each developer chooses a tool, appropriate to rank criticality of the changes. One example of a risk assessment tool can be found in the mRNA annex.

Table 5 Drug Substance - Change Impact Assessment on CQA

Change ID	**CQA / Attributes impacted**	**Risk Score on safety and efficacy***				**Justification**
		Proba-bility	**Impact**	**Detec-tability**	**Risk Score**	
DS1						

Change ID	CQA / Attributes impacted	Risk Score on safety and efficacy*				Justification
		Proba-bility	Impact	Detec-tability	Risk Score	
DS 2						

*if available

Table 6 Drug Product - Change Impact Assessment on CQAs

Change ID	CQA / Attributes impacted	Risk Score on safety and efficacy*				Justification
		Probability	Impact	Detectability	Risk Score	
DP1						
DP2						
DP3						
….						

*if available

4 Comparability Strategy

[Refer to Figure 1 in the General Part B which shows a flowchart depicting how to derive the comparability strategy.

Comparability could include raw materials, process intermediates, drug substance drug product and non-clinical/toxicology/clinical lots.]

Table 7 Comparability strategy*

Change ID	Affected Step	Affected Attributes	Analytical Method	Comparability Acceptance Criteria	Justification
RAW1/DS1/DP1					

*[*this table can be used multiple times and subdivided into CPPs and CMAs depending on the manufacturing step impacted (for example, raw materials, in-process intermediates, DS and DP)]*

5 Results and Analysis

[Present results and analysis of the comparability exercise in this section]

5.1 In process controls

Table 8 In process results and comparability Analysis

Change ID	Samples from Unit Operations	Tested Attributes	Pre-Change*	Post-Change*	Comments
			Batch #	Batch #	
DS1					

*Number of batches depend on a case-by-case basis.

5.2 Drug Substance

Table 9 Release and extended characterization

Quality Attributes	Pre-Change	Post-Change	Analysis	Comments
	Batch #	Batch#		

5.3 Drug Product

Table 10 Release and Extended Characterization

Quality Attributes	Pre-Change	Post-Change	Analysis	Comments
	Batch #	Batch#		

6 Conclusion

[Provide a general conclusion of your comparability exercise]

7 References

8 Annexes