CEPI

CMC PLATFORM BEST PRACTICES

PART A

Overview

Vaccines Europe
An industry for healthy lives

CEPI

DCVMN INTERNATIONAL
Developing Countries Vaccine Manufacturers Network International

IFPMA International Federation of Pharmaceutical Manufacturers & Associations

KING'S College LONDON

IMPERIAL

October 2025

CEPI

TABLE OF CONTENTS

1 Problem statement 3

2 Scope and rationale 4

3 Guidance Note for the CMC Platform Best Practices 6

4 Description of the four vaccine platform types 8

4.1 mRNA 9

4.1.1 Description 9

4.2 Viral Vector 10

4.2.1 Description 10

4.3 Subunit Protein 11

4.3.1 Description 11

4.4 Inactivated virus 12

4.4.1 Description 12

5 QbD-driven product and process understanding in the context of accelerated scenarios 13

5.1 Quality by Digital Design 15

Computer-aided Design Space 16

6 Comparability and process validation: Interactions and Opportunities in accelerated scenarios 18

7 Glossary of terms 20

8 Acknowledgements 26

1 Problem statement

During the years 2020 to 2023 the world witnessed development and implementation of safe and effective COVID-19 vaccines and therapies in an expedited manner. This was possible, amongst others, by applying appropriate risk-based scientific tools to the areas of chemistry, manufacturing and controls (CMC), nonclinical and clinical as well as flexible regulatory mechanisms, without thereby compromising quality, safety and efficacy [1, 2, 3]. Across many different worldwide regions, regulatory authorities proved to be resilient and capable of streamlining activities and processes within established legislative frameworks to ensure rapid review and, if appropriate, approval/authorisation of novel vaccines and medicinal products against SARS-CoV-2. The level of effort, engagement and collaboration demonstrated by regulators across the world is with no doubt praiseworthy.

Based on the COVID-19 crisis, multiple reviews and lessons learned exercises have been executed to assess the potential for improvement, should a pandemic scenario arise again in the future. Out of those, it becomes apparent that developers are challenged in emergency situations by a multitude of constraints which have their origin in accelerated development timelines. Sometimes, this is inevitably carried over to later stages of the product life cycle, e.g., when facing disruptions in the supply chain due to global vaccine demand.

In this context, a collaborative group of CMC and regulatory experts from Vaccine Industry (most pertaining to Vaccines Europe, IFPMA and DCVMN) and Academia joined efforts under the leadership of CEPI to develop and document best practices and globally accepted tools that could be applied to expedite execution of comparability studies and manufacturing process validation. These two areas were identified out of a non-exclusive list of CMC elements that were observed to represent significant bottlenecks for accelerated access to vaccines [4, 5].

[1] Epidemic Preparedness Innovations: COVAX
[2] 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 I: Initial industry lessons learned and practical overarching proposals leveraging the COVID-19 situation. Vaccine. 2022;40(9):1215–1222
[3] 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
[4] The ICMRA-Industry Virtual Workshop Report on enabling Manufacturing Capacity in the COVID-19 Pandemic, July 2021.
[5] COVAX RAG recommendations as laid down in WHO Technical Brief: Regulation of COVID-19 vaccines, *April 2021*.

2 Scope and rationale

The vision to develop a vaccine in 100 days for deployment in case of emergency situations (e.g., pandemics and/or outbreaks) is one that automatically poses challenges to vaccine developers [6]. CEPI has assessed the overall vaccine development pathway to determine some principles and elements that could contribute to the decrease of development timelines from the 1-year period, as experienced during COVID-19, down to the 100-day aspiration [7]. The reduction of timelines requires, amongst others, the compression of the CMC activities. This, however, is a significant challenge since such activities would typically require months, if not years, to complete.

Multiple factors interplaying in a synergistic manner are likely to be considered to achieve such a milestone without compromising vaccine quality, safety and efficacy. One of those factors can be the use of prior knowledge by means of platform technologies. A platform technology is understood to be a technology or compilation of multiple technologies used in the manufacturing and/or quality control and/or testing of several and distinct pharmaceuticals, including vaccines. Because they pertain to the one and same platform technology, those pharmaceuticals share common underlying scientific principles that contribute to the building of prior knowledge inherent to that particular platform technology. It is noted that in this context, the term prior knowledge refers to EMA's understanding, as described in EMA Meeting Report on the Joint BWP/QWP Workshop with stakeholders in relation to prior knowledge and its use in regulatory applications [8].

Leveraging prior knowledge by utilizing platform technologies can reduce the risk associated with accelerated development [5, 9]. In addition, developing and documenting CMC best practices well ahead of an emergency can be a valuable tool in aligning regulatory bodies and developers in advance, i.e. prior to facing health emergency situations.

The set of documents built under this collaborative project (also called "CMC Platform Best Practices") provides a strategy-oriented CMC framework with approaches to efficiently assess comparability and to perform manufacturing process validation for newly developed vaccines which pertain to a platform technology. They are intended to assist in responding to public health emergencies such as pandemic and epidemic situations. It should be noted that these principles could also be applied to other situations, e.g. when addressing an unmet medical need by leveraging prior knowledge utilizing platform technologies as the quality, safety and efficacy of the product are not compromised. The Best Practices provide a series of

[6] 100 Days Mission to respond to future pandemics threats, June 2021.
[7] Saville M, Cramer J, Downham M, Hacker A, Lurie N, Van der Veken L, Whelan M, Hatchett R. Delivering pandemic vaccines in 100 days – what will it take?. N Engl J Med 2022; 387:e3
[8] Meeting Report: Joint BWP/QWP workshop with stakeholders in relation to prior knowledge and it use in regulatory applications, March 2018 (EMA/CHMP/BWP/187162/2018).
[9] Meeting Report: Workshop with stakeholders ion support to quality development in early access approaches (i.e. PRIME, Breakthrough Therapies), July 2019 2017 (EMA/CHMP/BWP/812924/2018).

options and tools that developers may choose to apply for developing CMC and regulatory strategies during vaccine development, emergency use authorisation (or equivalent regulatory mechanism) and subsequent registration and post-approval, as applicable.

During the content development of the CMC Platform Best Practices, focus has been kept on four particular platform technologies targeting viral infections: mRNA, viral vector, subunit protein, and inactivated virus. While the comparability documents provide illustrative examples for each of these four platforms, the process validation document does not. The latter has been conceived as a general best-practices guide that relies on the existence of prior-knowledge, with no need to include information specific to any of the four platform technologies under scope. On the contrary, for comparability, the inclusion of examples for each platform was deemed appropriate given the relatively less standardized expectations on comparability as compared to process validation, taking into account (i) the application of comparability principles both in development and during routine commercial manufacturing, and (ii) the nature of the vaccine platform technology, implying some diversity in use of prior knowledge/ product characterization opportunities.

3 Guidance Note for the CMC Platform Best Practices

The compiled CMC Platform Best Practices are structured in three parts containing a total of seven documents, as shown in **Figure 1** and listed here below:

- Part A consists of one single document that provides general background information common to both comparability and manufacturing process validation documents.
- Part B contains five documents intended for comparability assessments: one document with best practices for comparability under accelerated scenarios and a blank template; four illustrative comparability examples, each corresponding to one of the platform technologies under scope.
- Part C contains one document that collects best practices for process validation under accelerated scenarios, regardless of the vaccine platform technology. Often a comparison of practices applied under standard circumstances versus those suggested for accelerated situations is included in the document.

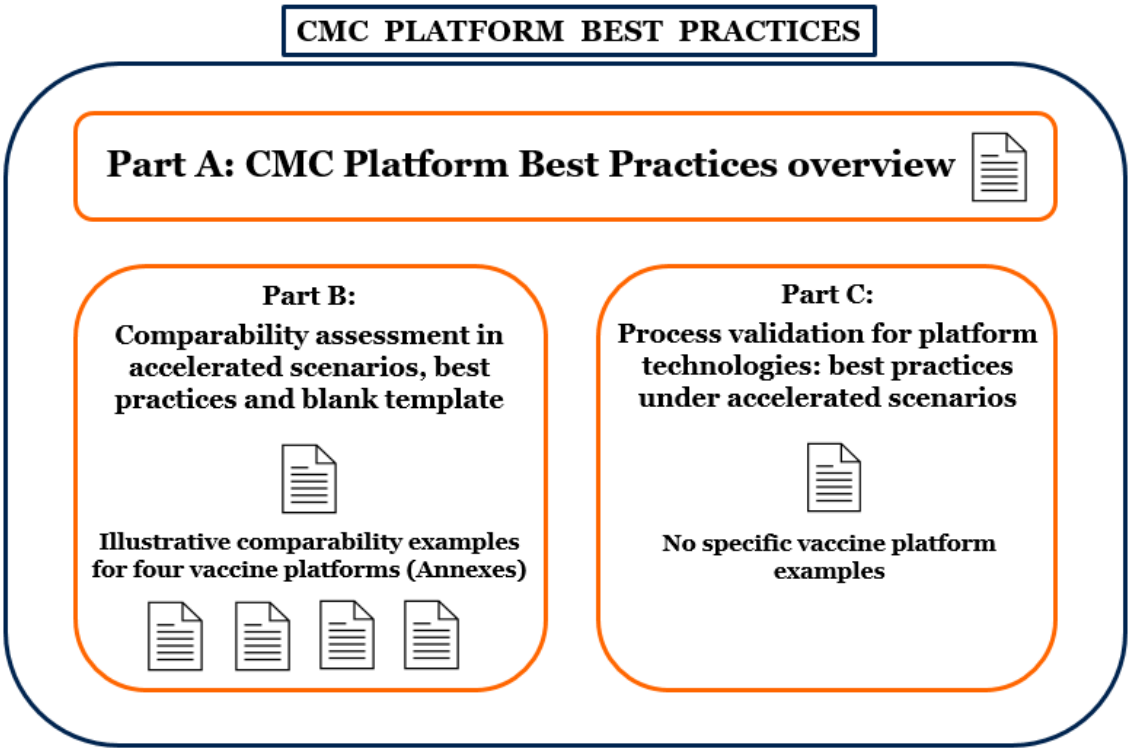


Figure 1 *Layout of CMC Platform Best Practices*

Readers and potential users of these CMC Platform Best Practices documents are kindly requested to note the following:

- The Best Practices documents are built to provide a strategy-oriented CMC framework with approaches to efficiently assess comparability and to perform manufacturing process validation for newly developed vaccines which pertain to a platform technology.
- These documents are intended to assist in responding to public health emergencies such as pandemic or epidemic situations; also when addressing an unmet medical need by leveraging prior knowledge utilizing platform technologies.
- They contain a non-exhaustive list of options and tools that developers may choose to apply for developing CMC and regulatory strategies during vaccine development, emergency use authorisation (or equivalent regulatory mechanism) and subsequent registration and post-approval, where applicable.
- The proposed options and tools do not necessarily need to be applied all in conjunction, i.e. every developer might assess which of those are applicable to their product/situation without necessarily having to use them all.
- The contents reflected in the Best Practices documents, including the illustrative examples, have been shared with a subset of regulatory agencies worldwide which have been engaged in the review process. While their input has been considered, no regulatory-binding status should be assigned to these documents.
- Users are strongly encouraged to discuss during development their specific comparability and process validation strategies with the relevant regulatory authority for concurrence prior to requesting emergency authorisation (or equivalent regulatory mechanism).

4 Description of the four vaccine platform types

The four selected vaccine platform technologies (mRNA, viral vector, subunit protein and inactivated virus) are representative of approved COVID-19 vaccines, with acceptable benefit/risk profile in case of a public health emergency, as reported in the literature [10, 11, 12]. All four vaccine platform types can stimulate an appropriate immune response and they are all considered safe since they cannot cause disease.

These platforms are a source of prior knowledge and successful examples of dialogue between developers and regulators. Nevertheless, the same principles described in these Best Practices documents could be used in future emergency preparedness scenarios for any other vaccine platform, depending on medical need.

In the following sub-sections, a general description of the four platforms is provided [13, 14], along with typical manufacturing process steps.

[10] Tregoning, J.S., Flight, K.E., Higham, S.L. et al. Progress of the COVID-19 vaccine effort: viruses, vaccines and variants versus efficacy, effectiveness and escape. Nat Rev Immunol 21 (2021) 626–636; Kudlay D, Svistunov A. COVID-19 Vaccines: An Overview of Different Platforms. Bioengineering. 9(2)2022; 72

[11] Acosta-Coley, I., Cervantes-Ceballos, L., Tejeda-Benítez, L. et al. Vaccines platforms and COVID-19: what you need to know. Trop Dis Travel Med Vaccines 8, 20 (2022)

[12] Szabó GT, Mahin AJy, Vlatkovic I, COVID-19 mRNA vaccines: Platforms and current developments, Molecular Therapy, 30 (5) (2022) 1850-1868

[13] Plotkin's Vaccines 8th Edition - December 21, 2022, Eds: Walter Orenstein, Paul Offit, Kathryn M. Edwards, Stanley Plotkin, ISBN: 9780323790598

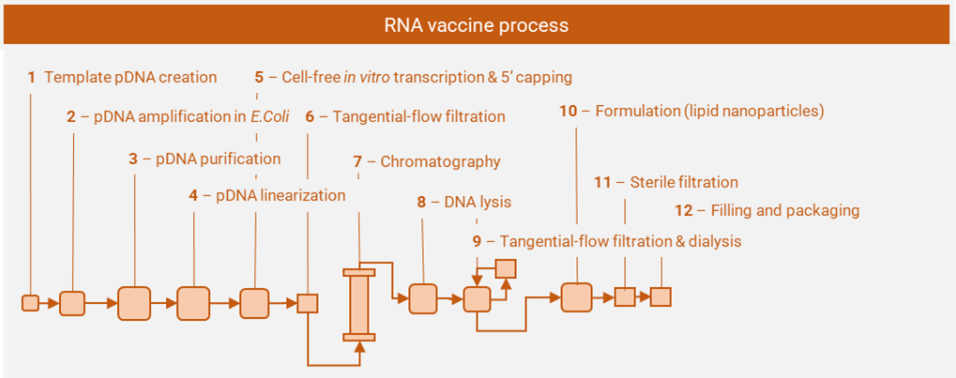
[14] What are nucleic acids and how could they be used against COVID-19?, GAVI, Dec. 2020.

4.1 mRNA

4.1.1 Description

Nucleic acid vaccines use genetic material from a disease-causing pathogen to stimulate an immune response against it. The mRNA provides the instructions for making a specific antigenic protein from the pathogen, which the immune system will recognize as an antigen. Once inserted into host cells, this genetic material is read by the cell's own protein-making machinery and used to manufacture antigens, which then trigger an immune response. mRNA vaccines encode the antigen of interest in messenger RNA (mRNA), encapsulated within nanoparticles.

High- level scheme for manufacturing process (cell- free enzymatic process)

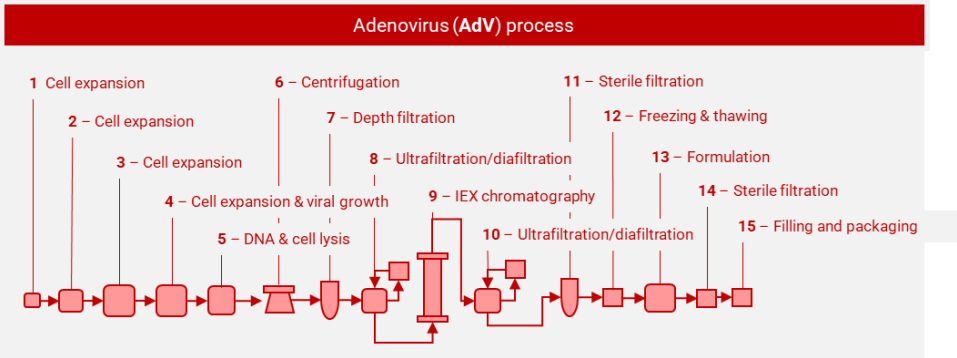


4.2 Viral Vector

4.2.1 Description

Viral vector-based vaccines use the body's own cells to produce antigens. They do this by using a modified virus (recombinant vector) to deliver genetic code for the antigen into human cells. By infecting cells and instructing them to make large amounts of antigen, they trigger a strong cellular immune response by T cells and also the production of antibodies by B cells. Drug substance containing the viral vector antigen is formulated with excipients to manufacture the drug product, which is sterile filtered and filled into final containers.

High- level scheme for manufacturing process (adenovirus)



Cell expansion as described in the Figure is intended to be increasing in volume from pre-culture up to virus production.

4.3 Subunit Protein

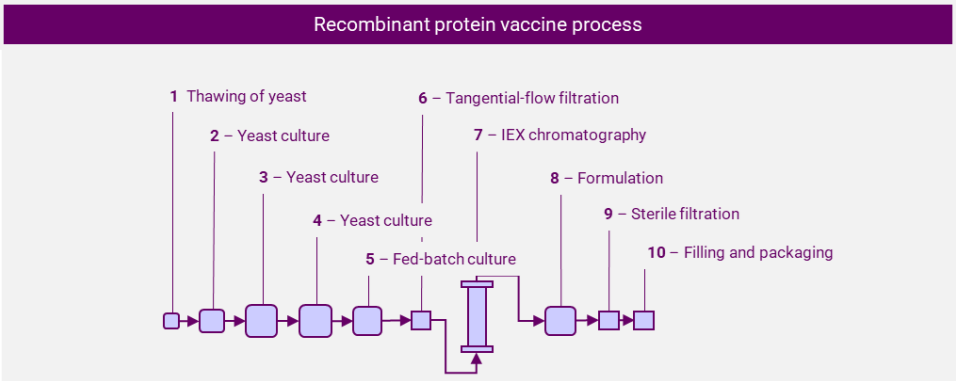
4.3.1 Description

Subunit vaccines contain purified pieces of a pathogen, which can stimulate appropriate immune response, and are considered safe since they cannot cause disease. Among the types of subunit vaccines, protein subunit vaccines contain specific isolated proteins from viral or bacterial pathogens.

To further stimulate immune systems, subunit vaccines are sometimes delivered with adjuvants (agents that stimulate the immune system) and may require boosting after primary immunization, like other platforms, also depending on the pathogen.

Depending on the medical need, subunit vaccines can include several antigens, which may be components of a liquid (adjuvanted) formulation or lyophilized and resuspended (with adjuvant, as needed) before administration.

High- level scheme for manufacturing process of a subunit protein (illustrative example, yeast- based)



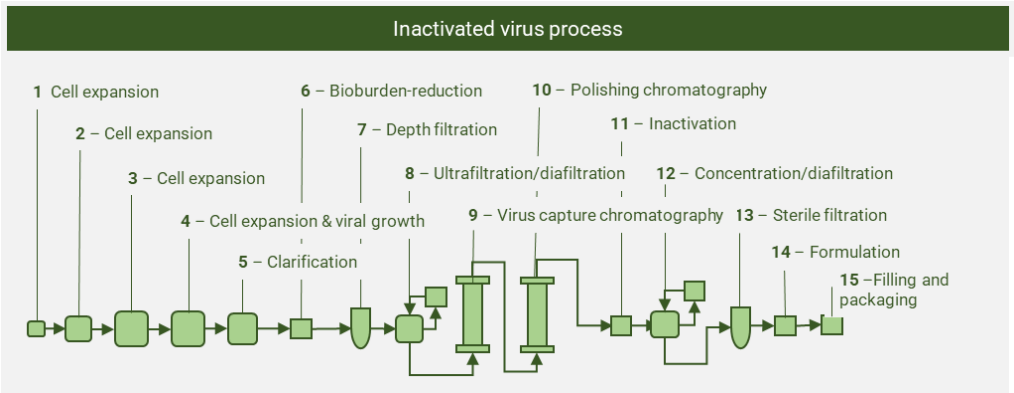
Yeast culture as described in the Figure is intended to be increasing in volume from pre-culture up to fermentation.

4.4 Inactivated virus

4.4.1 Description

Whole inactivated virus vaccines use an inactivated form of the pathogen that causes a disease to trigger protective immunity against the pathogen. In inactivated vaccines genetic material has been destroyed by physical or chemical methods so they cannot infect cells and replicate but can still trigger an immune response. Inactivated virus drug substance is formulated with or without adjuvants to thereafter be filled into final containers and packaged.

High- level scheme for manufacturing process*



* *Another option is to inactivate the virus prior to purification, which could be safer in case of a pandemic virus.*

Cell expansion as described in the Figure is intended to be increasing in volume from pre-culture up to virus production.

5 QbD-driven product and process understanding in the context of accelerated scenarios

Multiple strategies are available to develop a pharmaceutical product. Independently whether it is making use of an empirical approach, a more systematic approach (Quality by Design, QbD) or a combination of both, it is good practice at the starting point of such development to define a quality target product profile (QTPP).

Quality by Design (QbD) [ICH Q8(R2)] is defined as: "*A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management*".

Amongst others, the main objectives of a QbD approach, directly beneficial to an accelerated access, are that the product is designed to meet patient needs (safety and efficacy requirements) and that critical sources of variability are identified, understood, and well controlled through appropriate control strategies and quality risk management. In certain circumstances, QbD-enhanced approaches may be perceived as a risk-assessment toolbox for process robustness, like Six-Sigma approaches, multivariate studies for process design space, or similar approaches. The distinctive nature of QbD is, however, its focus on the quality expectations for the patient as prerequisites for process and analytical development [15].

According to ICH Q8, there are elements that would need to be identified at a minimum for a QbD strategy in accelerated scenarios, namely the:

- Quality target product profile (QTPP)
- Critical quality attributes (CQAs)
- Critical process parameters (CPPs)

Further to that, consideration should also be given to the identification of critical material attributes (CMAs) and the assessment on how those would be impacting CQAs if modified. Also, considering the recent publication of ICH Q14, a QbD-driven approach for analytical development requires the establishment of the Analytical Target Profile, allowing pre-defined expectations for analytical procedure performance and driving right-first-time selection of fit-for-purpose analytical technologies.

Identification of CQAs represents the first fundamental step for patient-driven pharmaceutical development, in accordance with the QTPP expectations. In accelerated scenarios in which a platform technology exists and can be utilized, prior knowledge from the CQAs already identified for that platform will serve as a strong starting point, provided appropriate risk assessments are in place to recognise potential differences between the product to be developed and the platform elements. For product quality

[15] Quality by Design - An Indispensable Approach to Accelerate Biopharmaceutical Product Development, Eds M. A. Khan, C. Campa, PDA, 2021

assurance, CQA acceptance criteria need to be embedded in the design of the development process, as a key output of manufacturing performance. In that, analytical strategy can greatly assist in monitoring process conditions and final product quality. Several examples have been published showing approaches for identification of CQAs, CPPs and fit- for-purpose analytical strategies for vaccines [14, 16, 17].

An emphasis placed on the CQA understanding for vaccines is key to define priorities during accelerated development, because it allows the developer to focus only on the attributes that are critical for safety and efficacy, and to tailor process and analytical understanding to this scope. On the contrary, traditional approaches based on the notion of "*process is product*" lead to non-essential activities without necessarily understanding the relevant attributes for product quality.

In this context, comparability evaluation can be successfully executed in accelerated scenarios focusing on the comparison of CQAs for the DS or DP before and after a given CMC change is implemented, provided that a strong analytical package is in place supporting CQA designation and testing. Understanding the relationship between process variables and product quality can help to identify which CQAs are impacted by the changes and ensure tailored analytical evaluation [18]. Equally, understanding of the critical process parameters and impact of incoming materials would be typically confirmed by successful Process Performance Qualification (PPQ) data package. In case of critical manufacturing changes after product launch, new PPQ campaigns may be needed, further supported by commercial manufacturing history and comparability assessment on the relevant CQAs.

In addition, computer-based models can be embedded in a QbD approach, to enhance product (e.g., formulation development, stability predictions- not discussed in detail in this document but reported in the literature, e.g. [3, 14]), and process knowledge designing tailored experiments on the CQAs and CPPs of high interest (see section 5.1). This translates into further accelerating process development and supporting quality versus risk-based decisions on experimental activities that need to be prioritised. Such models can be used to quantitatively analyse measurement data and as cost-efficient experimental platforms for computational experiments. In the context of accelerated vaccine development, the latter refers primarily to swift computational experiments to assist the identification of CQA-CPP relationships that are critical for the design of the manufacturing process. It is important to highlight that under an accelerated scenario, platform knowledge can be leveraged using mathematical models that have been validated on previous products using the same platform for manufacturing.

[16] A-VAX: Applying Quality by Design to Vaccines, CMC-Vaccines Working Group, May 2012
[17] Daniel S, Kis Z, Kontoravdi C, Shah N, 2022, Quality by Design for enabling RNA platform production processes. Trends in Biotechnology, Volume 40, Issue 10, Pages 1213-1228
[18] Papathanasiou, M.M. and Kontoravdi, C., 2020. Engineering challenges in therapeutic protein product and process design. Current Opinion in Chemical Engineering, 27, pp.81-88

5.1 Quality by Digital Design

Quality by Digital Design (QbDD) refers to the application of Quality by Design (QbD) principles in combination with computer modelling tools to expedite the end-to-end workflow [19, 20]. Computer-based models can be embedded in a QbD approach to enhance and quantify product and process knowledge and interactions. Such models comprise mathematical expressions and can be either data-driven, mechanistic or a combination of both (hybrid). Data-driven models are typically statistical formulas that are agnostic to the process dynamics and are highly dependent on the existence of experimental data. On the other hand, mechanistic models comprise mathematical expressions that describe the biological, physical, and chemical interactions of the system components. It is important to note that all models are valid for certain process conditions and need to be validated by wet-lab experiments prior to being used for any purpose. Approaches adopted to validate these models may differ from company to company upon the level of knowledge already acquired with a particular platform.

Regulatory product and process authorisation/approval require manufacturers to demonstrate in-depth knowledge of the production setup and product formulation as well as control over possible in-process deviations [21]. To this end, mathematical models can be used in at least three contexts:

1. To design tailored experiments for the identification of CPPs;
2. To perform data analysis and quantify CPP-CQA correlations;
3. To identify suitable operating conditions and associated control strategy.

The first two cases require data from offline experiments that provide reasonable coverage of process parameters. To enable this, suitable analytical technologies must be in place to demonstrate that manufacturers can guarantee control over their process during online operation. In the third case, the models can act as a dry-lab, generating new data points within the operating conditions under which they were developed and validated. In this context, mathematical models offer a lower-cost experimentation platform that can assist both the design of targeted experiments and process monitoring, leading to knowledge-rich submissions.

Under accelerated scenarios, when time is pressing, existing models that have been validated leveraging platform knowledge from previous products can be used as a standalone or in combination with a reduced number of experiments. In the context of accelerated vaccine access, models can allow for swift computational experiments to assist the identification of CQA-CPP relationships that are critical for the design of the manufacturing process.

[19] Daniel et al., Vaccine Insights (2022)1(4), 219–233
[20] Daniel et al., Trends in Biotechnology (2022) 40(10), 1213-1228
[21] Antonakoudis et al. (2020) Accelerating product and process development through a model centric approach, In: Quality by Design—An Indispensable Approach to Accelerate Biopharmaceutical Product Development, Editors: Cristiana Campa, Amin Khan, Parenteral Drug Association, ISBN Number: 9781945584220

While the application of computer modelling tools is well recognised and widely used for monoclonal antibodies, little progress has been achieved when it comes to accepting the use of those models with vaccine products. A context of unmet medical need such as the one originating in a pandemic situation is worthwhile considering the benefits these tools could offer.

Computer-aided Design Space

Mathematical models can assist with the identification of the Design Space (DSp) as defined by EMA [22]. The use of such models under an accelerated scenario can help with the identification of acceptable ranges that can guarantee product quality and efficacy. **Figure 2** provides an illustrative, simplified example of a generic design space as mapped for two possible CPPs. It should be highlighted that the DSp can be of various shapes and the square used in this example is only for illustration purposes. There are several scientific contributions in the open literature that have developed computer-aided methodologies for the identification of the DSp and its boundaries [23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35].

An important consideration is that validated mathematical models enable high throughput scanning of the DSp without the requirement for wet-lab experimentation for each single point. In this case, the grey points can be identified through computer modelling simulations. Once completed, sponsors can perform tailored, wet-lab experiments at the CPP boundaries (solid green lines) for validation. Mathematical models can also be used to assist the identification of the DSp, which can be then validated through experiments.

[22] Questions and Answers: Improving the understanding of NORs, PARs, DSp and normal variability of process parameters (EMA/CHMP/CVMP/QWP/354895/2017)
[23] Kusumo et al., Ind. Eng. Chem. Res., vol. 59 (6) (2019), pp. 2396-2408
[24] Close et al., Computer Aided Chemical Engineering (2013), pp. 115-120
[25] Close et al., Chem. Eng. Sci., vol. 116 (2014), pp. 284-295
[26] Rogers and Ierapetritou, Chem. Eng. Sci., vol. 137 (2015), pp. 986-1004
[27] Zhao et al., AIChE J., vol. 68 (5) (2022)
[28] Nie et al., AAPS PharmSciTech, vol. 20 (6) (2019), p. 246
[29] Vogg et al., J. Chromatogr. A, vol. 1619 (2020)
[30] Rogers and Ierapetritou, Chem. Eng. Sci., vol. 137 (2015), pp. 1005-1013
[31] Metta et al., AIChE J., vol. 67 (2) (2020)
[32] Ding and Ierapetritou, Int J. Pharm., vol. 609 (2021), Article 121161
[33] Yang and Ierapetritou, Processes, vol. 9 (2) (2021), 10.3390/pr9020324
[34] Zhao et al., Comput. Chem. Eng., vol. 166 (2022), 10.1016/j.compchemeng.2022.107969
[35] Bano et al., Comput. Chem. Eng., vol. 127 (2019), pp. 254-271

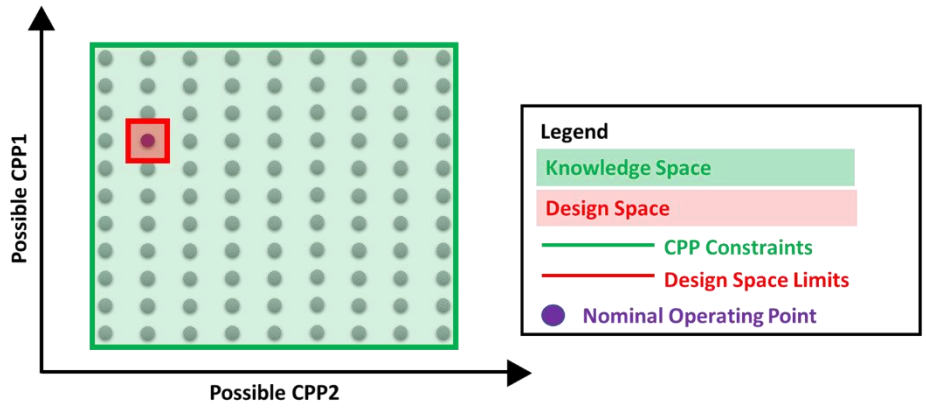


Figure 2 *Graphical visualization of the design space (DSp) as can be generated with the assistance of mathematical modelling. The green-shaded area illustrates the knowledge space which is a collection of points satisfying performance constraints imposed on the Key Performance Indicators (KPIs). The red-shaded areas depict the DSp surrounding a nominal operating point (NOP) (purple point) of interest. The boundaries (red lines) depict the acceptable variation range of an input for which operation is guaranteed to remain within spec (DSp limits)*

6 Comparability and process validation: Interactions and Opportunities in accelerated scenarios

Synergies between Process Validation and Comparability have been commented by the COVAX Regulatory Advisory Group (RAG) in the WHO Technical Brief: Regulation of COVID-19 Vaccines [5]. This document reports some reflections on CMC acceleration strategies addressing the past COVID emergency. Regarding risk-based approaches for Process Validation, it reports:

"*The RAG considered that, in principle, the tools outlined in ICH Q9 could be applied. [….] Where multiple site manufacture and scale up was necessary to ensure sufficient vaccine would be available for global markets, the RAG stressed that demonstration of comparability during development would help inform on the validation approach taken.*"

RAG also adds, with respect to the possibility to decouple DS and DP validation, 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. [….]. Overall, the RAG agreed that the issues of comparability of the same vaccine produced at different manufacturing sites, as well as scale up, were particularly challenging in the light of the Covid 19 pandemic and the urgent need for vaccine availability*".

In this context, process understanding and control strategy, defined as part of the process validation strategy, may in turn support comparability assessment through understanding of the potential impact of manufacturing changes on product quality. This knowledge is key to streamline comparability activities, allowing focus on relevant steps and impacted Critical Quality Attributes (CQAs) [36].

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

Figure 3 below shows a synergistic relationship between comparability and process validation.

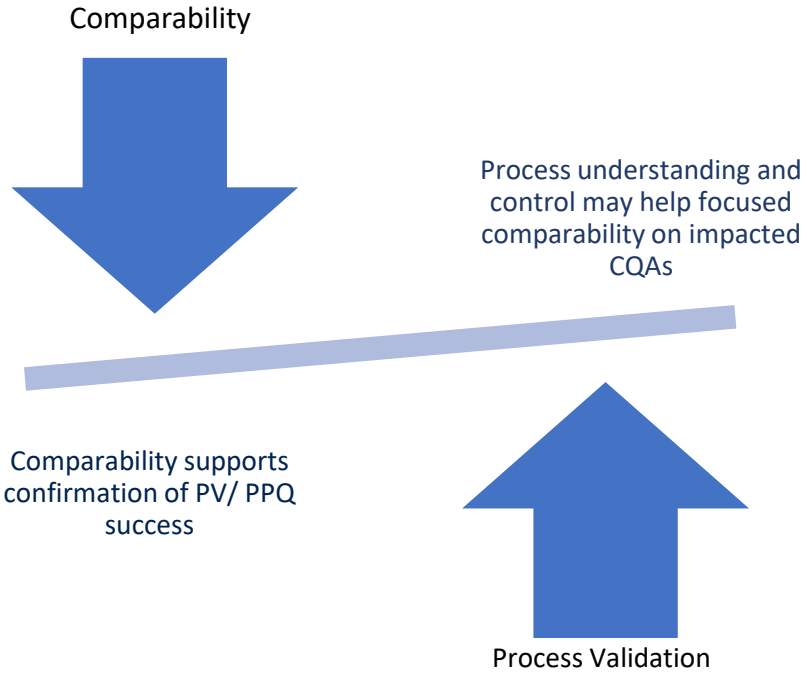


Figure 3: *Synergies between Comparability assessment and Process Validation*

The above-mentioned interplay represents a key driver for combining process validation and comparability best practices as part of the same package reported in Parts B and C. Of note, comparability considerations and examples reported in Part B will focus on both late development/ lifecycle (with synergy with Process Validation/Process Performance Qualification efforts) and early development (to support bridging among preclinical/ clinical phases or among different clinical phases).

7 Glossary of terms

API:	Active Pharmaceutical Ingredient
ATP:	Analytical Target Profile
AEX:	Anion Exchange
BLA:	Biologic License Application
BR:	Batch Record
BSE:	Bovine Spongiform Encephalopathy
BWP:	Biologics Working Party
CCIT:	Container Closure System
CCS:	Contamination Control Strategy
CD:	Consolidated-Drained (Triaxial Compression)
CEPI:	Coalition for Epidemic Preparedness Innovations
cGE:	Capillary gel electrophoresis
CMA:	Critical Material Attribute
CMO:	Contract Manufacturing Organisation
CPC:	Critical Process Consumables
CPP:	Critical Process Parameter
CPV:	Continued process verification
CQA:	Critical Quality Attribute. A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.
CoGs:	Cost of Goods

CS:	Control Strategy
CT:	Clinical Trial
DCVMN:	Developing Countries Vaccine Manufacturers Network
DLS:	Dynamic Light Scattering
DP:	Drug Product
DS:	Drug Substance
DSp:	Design Space
dsRNA:	Double stranded RiboNucleic Acid
ELISA:	Enzyme-Linked Immunosorbent Assay
EMA:	European Medicines Agency
EUA:	Emergency Use Authorization
EP:	European Pharmacopoeia
FMEA:	Failure Mode Effects Analysis. FMEA provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures and the likely effects of these failures.
FDA:	Food and Drug Administration
FFF-MALS:	Field-Flow Fractionation with Multi-Angle Light Scattering
GMP:	Good Manufacturing Practice
HA:	Health Authority

HACCP:	Hazard Analysis and Critical Control Points (HACCP): is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety. It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.
HCP:	Host Cell Protein
HCS:	Holistic Control Strategy
HPLC:	High-performance liquid chromatography
HPLC-CAD:	High-Performance Liquid Chromatography with Charged Aerosol Detection
HPLC-ELSD:	High-Performance Liquid Chromatography with Evaporative Light Scattering Detection
ICP-MS:	(Inductively Coupled Plasma-Mass Spectrometry
IND:	Investigational New Drug (application)
IMPD:	Investigational Medicinal Product Dossier
IPC:	In-Process Control. Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or Active Pharmaceutical Ingredient (API) conforms to its specifications.
IP-RP-HPLC:	Ion-Pair Reversed-Phase High-Performance Liquid Chromatography
IPT:	In-Process Test
IVT:	In-Vitro Transcription
IVR:	Inverted Terminal Repeat
IVRP:	In Vitro Relative Potency
LAL:	Limulus Amebocyte Lysate
LC-MS:	Liquid Chromatography-Mass Spectrometry
LNP:	Lipid Nano-Particles

LOQ:	Limit of Quantification
NTA:	Nanoparticle tracking analysis
KPP:	Key Process Parameter - Non-CPPs that do not affect product quality, but may affect process performance such as yield, are classified as key process parameters.
nCQA:	Non Critical Quality Attribute
NCLs:	National Control Laboratories
NDA:	New Drug Application
NGS	Next Generation Sequencing
NOR:	Normal Operating Range describes a region around the target operating conditions that contain common operational variability.
NRA:	National Regulatory Authority
MCW:	Master Cell Bank
MVS:	Master Virus Bank
WCB:	Working Cell Bank
WVB:	Working Virus Bank
OOS:	Out of Specification
OOT:	Out of Trend
PCR:	Polymerase Chain Reaction
pDNA:	Plasmid DeoxyriboNucleic Acid
PACMP:	Post-approval Change Management Protocol
pCQA:	Potentially Critical Quality Attribute
PHE:	Public health emergency

PI:	Prediction interval
POC:	Proof of concept
PQ:	Performance Qualification
PPQ:	Process Performance Qualification
PAT:	Process analytical technology. A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.
PAR:	Proven Acceptable Range. A characterised range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria
Platform technology:	A collection of technologies used in the manufacturing process and/or the quality control of one or more medicinal products or their components that rely on shared prior knowledge and are established under the same underlying scientific principles. Platform technologies can encompass a variety of activities, including without being limited to similar formulations, manufacturing steps and analytical testing.
PLC:	Programmable Logic Controllers
PV:	Process Validation
QbD:	Quality by Design
QMS:	Quality Management System
QRA:	Quantitative Risk Analysis
QRM:	Quality Risk Management. A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.
QTPP:	Quality Target Product Profile. A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product.
QWP:	Quality Working Party
qPCR:	Quantitative Polymerase Chain Reaction

RCA:	Root Cause Analysis
RM:	Raw materials
RPM:	revolutions per minute
RP-HPLC:	Reversed-Phase High-Performance Liquid Chromatography
RT-PCR:	Reverse Transcription Polymerase Chain Reaction
SD:	Standard deviation
SDP:	Scale-dependent parameter
SDS-PAGE:	Sodium Dodecyl Sulphate - PolyAcrylamide Gel Electrophoresis
SE-HPLC:	Size exclusion-high-performance liquid chromatography
SE-HPLC-MALS:	Size-Exclusion Chromatography with Multi-Angle Light Scattering
SUS:	Single-use systems
TI:	Tolerance intervals
TSE:	Transmissible Spongiform Encephalopathy
USP:	United States Pharmacopeia
UV:	Ultra Violet (radiation)
UPLC:	Ultra Performance Liquid Chromatography

8 Acknowledgements

The set of documents (also generally called “CMC Platform Best Practices”) built under this collaborative project represents the view of the two working groups formed with representation from the Vaccine Industry (including Trade Associations: Vaccines Europe/EFPIA, IFPMA, DCVMN), Academia and CEPI.

The contribution of the following project members is acknowledged:

Acep Riza W.	Bio Farma
Adrian Azhari	Bio Farma
Adriana Miranda	Instituto Butantan
Andreas Dautel	CureVac
Antonio Guzzi	CEPI
Awa Ly	Institut Pasteur Dakar
Benedicte Mouterde	Sanofi
Calvin Cooke	Astra Zeneca
Carla Cristina Vellasco	Bio-Manguinhos, Fiocruz
Caroline Caudal	Sanofi
Celine Tellier	Exothera
Cleo Kontoravdi	Imperial College London
Cristiana Campa	GSK
Diane Wilkinson	Astra Zeneca
Georg Sambeth	CureVac
Geraldine Seveste	Sanofi

Harris Makatsoris	King's College London
Hassan Askary	CEPI
Holger Luebben	GSK
Homero Seiiti Nagano	Instituto Butantan
Joanke Graveland-Bikker	Janssen, Johnson & Johnson
Jennifer Eck	Astra Zeneca
June Kim	CEPI
Kristof Vandekerckhove	Quantoom
Lais Amaral	Instituto Butantan
Lokender Kaushik	Walvax
Made Amrita Adihutama	Bio Farma
Malika Mohseni	Merck & Co. Inc.
Maria Papathanasiou	Imperial College London
Melisa Di Corrado	Sinergium Biotech
Mic McGoldrick	Merck & Co. Inc.
Monique Collaço	Bio-Manguinhos, Fiocruz
Muharrem Seleci	CureVac
Murtuza Ali	CEPI
Nilay Shah	Imperial College London
Olga Rovira	CEPI (Consultant)
Patricia Neves	Bio-Manguinhos, Fiocruz

Pepijn Burgers	Janssen, Johnson & Johnson
Raghu Veerapaneni	BioVac
Sarah Touw-Mercier	Janssen, Johnson & Johnson
Satish Muchakayala	Touchlight
Sebastian Comellas	Sinergium Biotech
Shirley Loos	Merck & Co. Inc.
Simon Agwale	Innovative Biotech Nigeria
Sudhir Uppala	Biological E
Vikram Paradkar	Biological E
Vishal Sonje	CEPI
Vincent Loh	Former CEPI
Xiaoyu Chen	Astra Zeneca
Xicheng Jiang	CanSino Bio