EMA /US FDA Workshop on
support to quality development in early access approaches

CMC information to support Vaccine Early Access designation- Composite Case Study from Vaccine Manufacturers
(*GSK, Janssen, MSD, Pfizer, Takeda*)

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Bio Biotechnology Innovation Organization

ebe european biopharmaceutical enterprises

efpia European Federation of Pharmaceutical Industries and Associations

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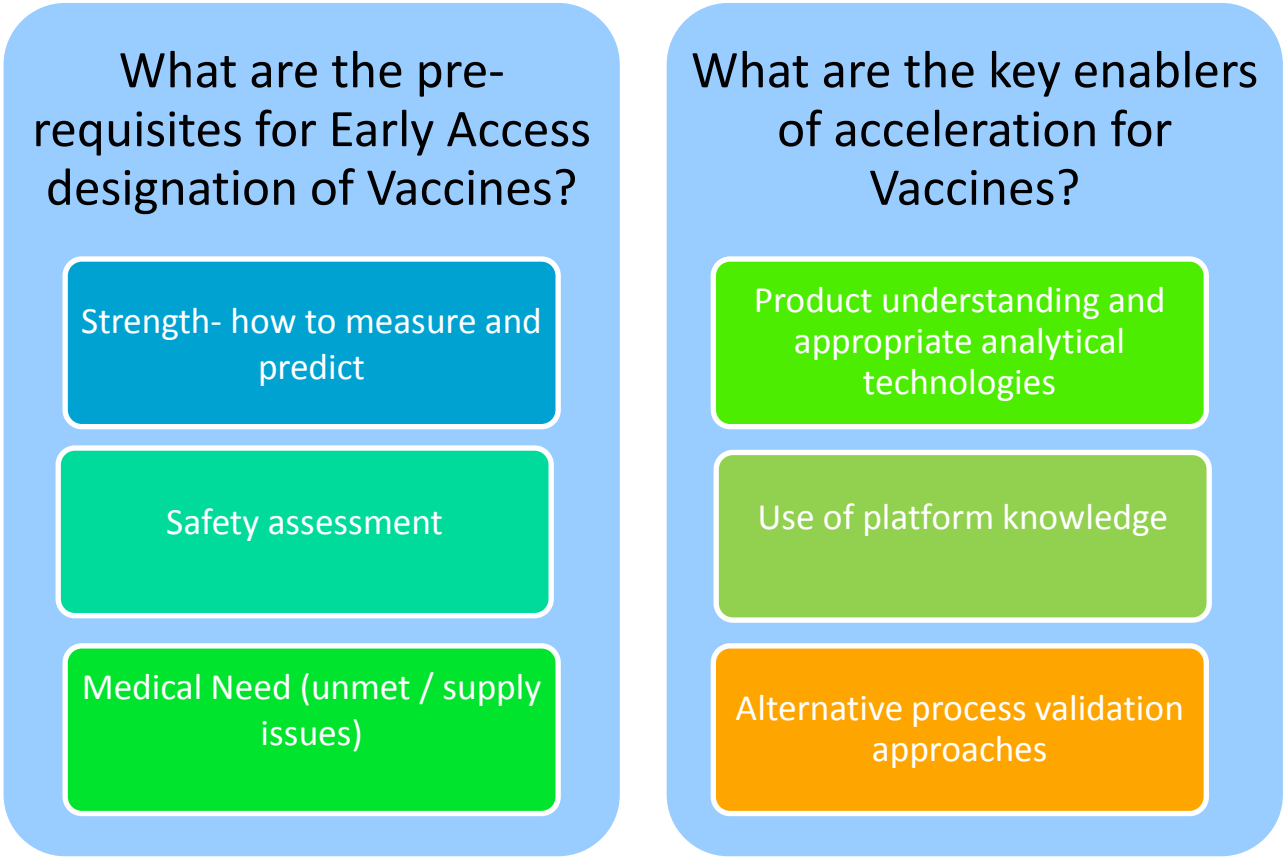
Vaccines Europe An industry for healthy lives

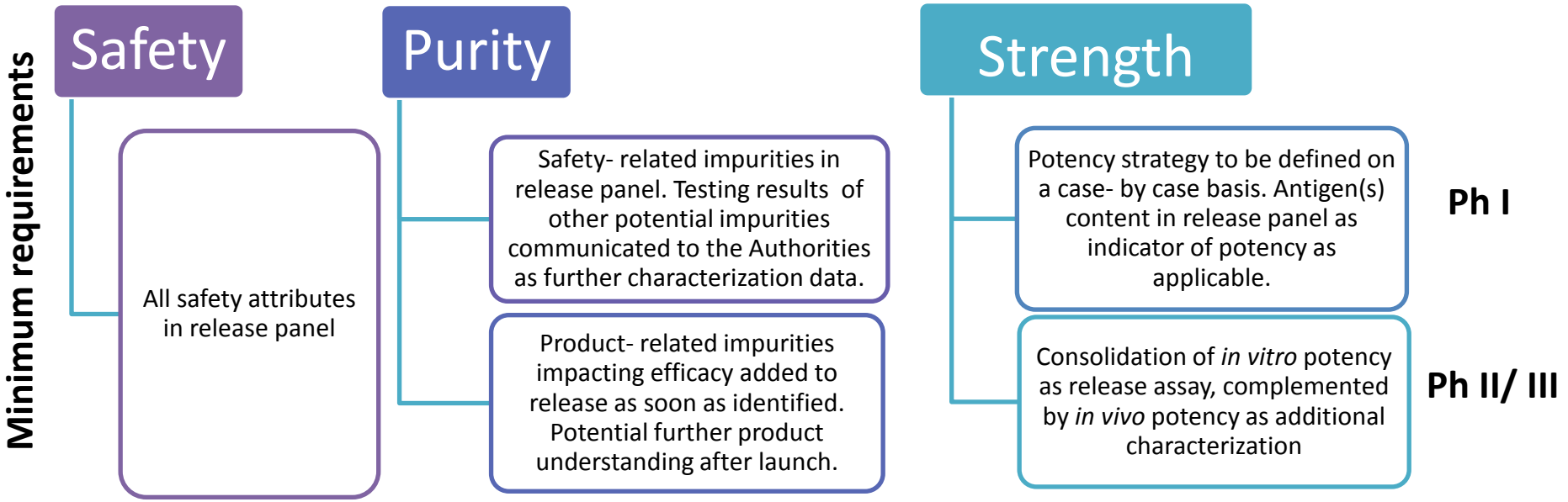
Outline



1. Building **information supporting early access designation- product quality requirements for Vaccines**: reflections on product understanding- specifications setting and related testing strategy
2. In an early access scenario, considerations on **risk- based activities prioritization**: considerations on process validation approach for vaccines

Specifications release panel can evolve during development

Product understanding sets the basis for product **safety and efficacy reliable monitoring in case of** changes/ optimization activities in accelerated scenarios like **delayed PV, product storage conditions updates, comparability need in case of facility changes/ process refinement.**



Note: scenarios / specific scope of clinical phases may be different from the illustrative picture shown above- the key concept of phase- appropriate specifications is applicable to these situations as well.

Key questions for Product understanding for early access designation

In order to support product understanding for early access designation, acceleration and lifecycle management:

- Is the introduction of new analytical technologies advantageous?

- What specific considerations are needed for efficacy prediction of vaccines?

- How can we make sure we smartly design and use clinical trials, given the complexity and continuously evolving knowledge on vaccines structure and stability?

Testing strategy- introduction of new analytical technologies in release

- Advances in analytics for vaccine products could be leveraged to improve knowledge of CQAs, thus allowing better control strategy development prior to process validation.

- What are the benefits and the barriers for introduction of new analytical strategies in accelerated scenarios?

Pros

Typically ensuring high- performance methods for reliable quality monitoring while process controls are under definition

Possibility to improve throughput and ensure fast release, potentially with multi-attribute methods

Reduce animal use (as applicable)

Minimize the risk of method replacement in later stages, ensuring sustainable lifecycle and supporting comparability studies

Support product understanding and building of new platform knowlege which may be helpful to accelerate other product development (especially for non product-specific attributes)

Cons

Justification of changes to authorities is perceived as potential time loss in case of pushback

Missing or misaligned pharmacopoeias related to new technologies

May require investment with high business risk (especially first time)

Specific considerations for efficacy prediction of vaccines

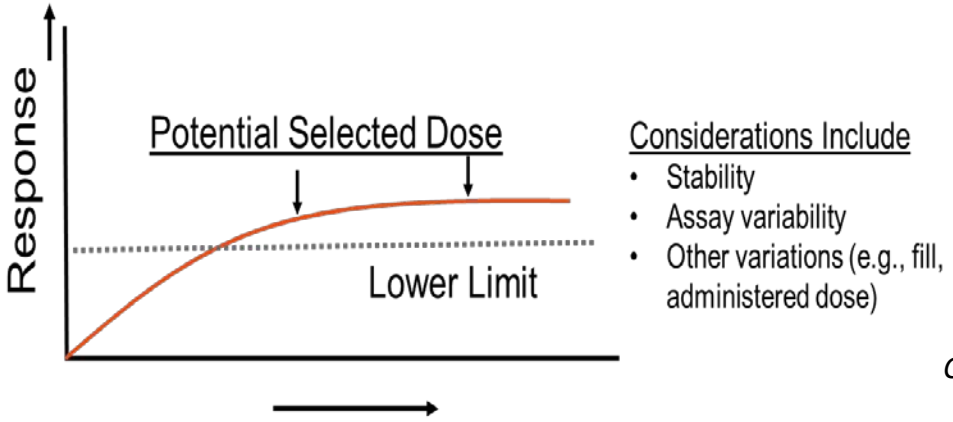
- For antigens with well- understood activity/ preclinical models (eg glycoconjugate vaccines, some subunits, adjuvants selection), safety demonstration combined with physicochemical characterization/ *in vitro* potency testing could be the supportive information for early access

- How to deal with vaccines with limited or no knowledge on mechanism of action & structure- function relationship? Strategies could include use of animal surrogate models or human challenge studies, to support efficacy prediction. In addition, clinical & dose selection strategy is a possible pathway to support evolving product understanding in accelerated scenarios (see next slide).

Clinical studies design is critical for rapid access to patients: how to manage the «unknown» with smart dose finding and selection

- In the course of development, **the target antigen amount in the final product should be higher than the minimum active dose** based on the clinical trials of the antigen under study.

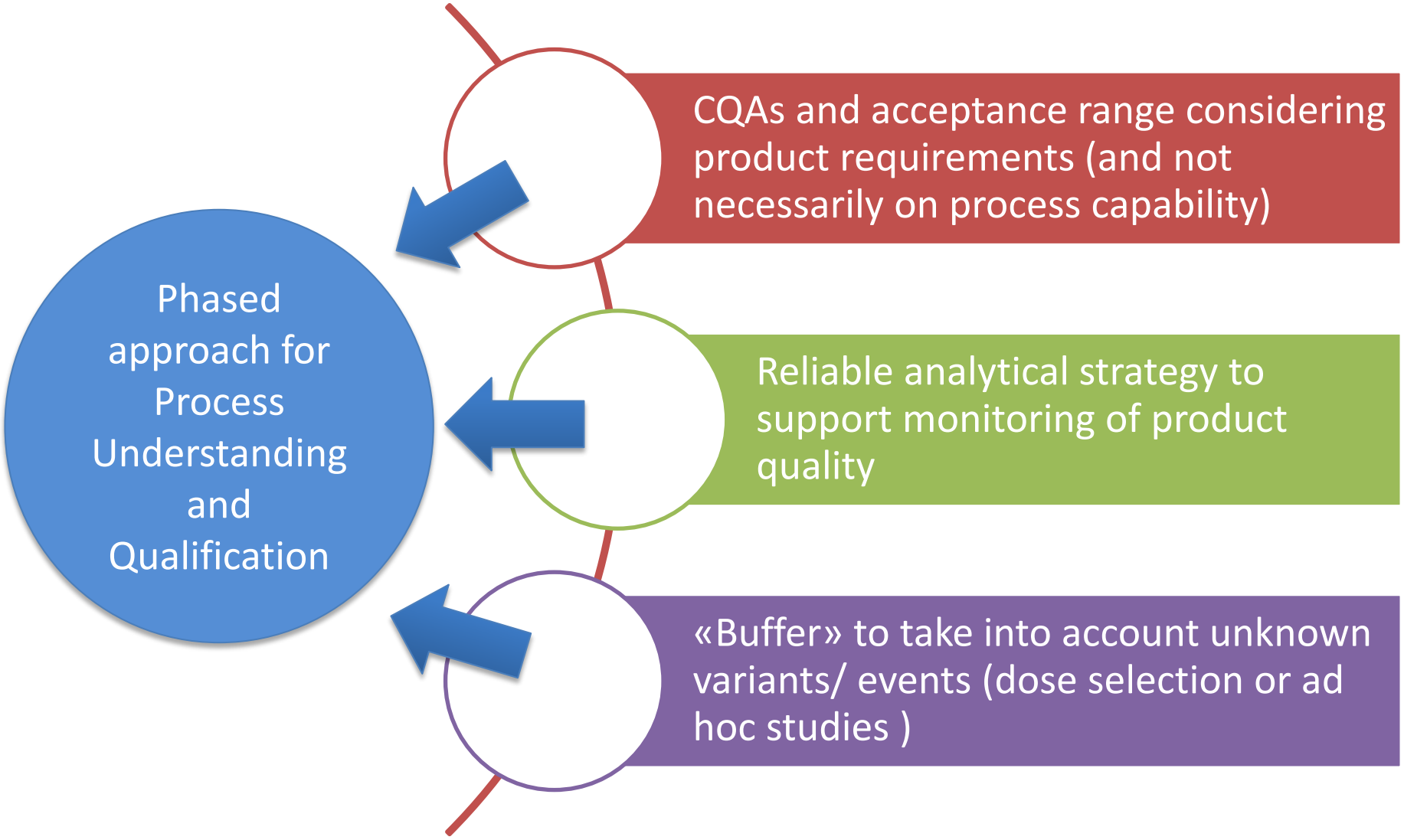
- In this scenario, if the real antigen amount, in the presence of variant(s) impacting efficacy, is lower than the target but still higher than the minimum active dose, the product will be still effective. Of course, we should demonstrate control over the variants to appropriate levels (including stability considerations, as applicable)



Courtesy of Bill Egan, GSK Vaccines

Although dose ranging studies may often be helpful in setting product specifications to encompass product changes that may occur over the course of the product's shelf life, other changes may occur that require additional clinical *ad hoc* studies, e.g., foreseen structural changes which might not be described as a dose reduction

Robust strategy for Product Understanding supports smart planning of process understanding



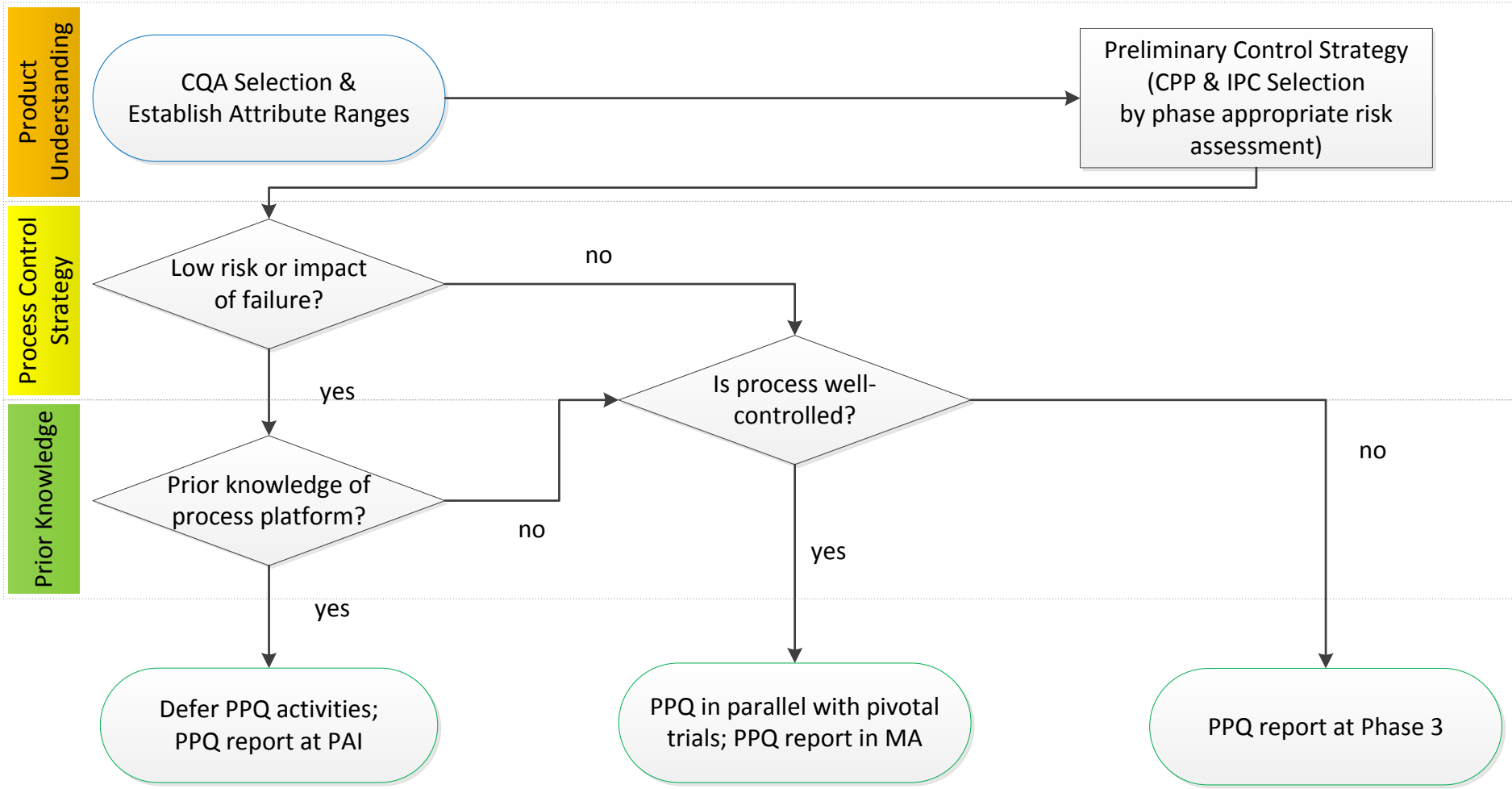
PPQ strategy proposal

- For DS manufacturing, the complexity of the process and level of prior knowledge should drive the decision on validation state for pivotal trials
  - For complex, novel vaccine products with limited process understanding in accelerated scenarios, PPQ should be performed on DS to supply material for pivotal trials, in order to support product consistency as in commercial manufacturing
  - For products with an established manufacturing platform/well-understood mechanism of action, PPQ could be deferred until after pivotal trials

- Typically, DP manufacturing is less complex than DS manufacturing for vaccines, and a risk-based approach could be followed
  - Control strategy for formulation of DP is straightforward (dose targeting and maintenance of potency), and experience with performance of operations is common to multiple vaccines (lyophilization, filling, other standard operations)
  - DP process characterization will be completed prior to pivotal studies, along with CPP selection and IPC established as control strategy, facility & equipment qualification, aseptic process validation
  - Defer DP Stage 2 PPQ in parallel to MAA review, PPQ protocol to be included in MAA, PPQ report to be available for PAI

- Such approach could be discussed as part of scientific advice/Type C/early interaction meetings (PRIME/Breakthrough) during development. Examples could include
  - Well-defined filling model for predicting potency of a labile live virus vaccine over shelf-life
  - Simple dilute & fill process for alum-absorbed bulk, a well-controlled and low risk process
  - Vaccines with broad clinical experience ranges of attributes
  - Vaccines developed based on platform technology

Decision Tree – Deferral of PPQ



* Well controlled process defined as fully characterized with appropriate parameter-level controls and in-process controls

Conclusions

- Dedicated reflection is needed for efficacy prediction of Vaccines to support early access designation. Early Focus on product understanding is critical, with phase- appropriate expectations for specifications
- The use of innovative analytical approaches for characterization is of outstanding importance in accelerated scenarios
- Clinical studies design may help rapid access to patients, upon smart dose selection
- Process understanding focused on product quality expectations, and risk- based assessment (including platform knowledge), are critical to support new approaches for process validation

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Backups

Background

- Today, close to 30 diseases are preventable by vaccination but there remain many unmet medical needs, including antimicrobial resistance and healthy ageing. Enhanced interaction and early dialogue between developers and regulators could help to speed up evaluation so these vaccines can reach patients earlier.

- Early Access regulatory designations require early demonstration of evidence that a product has the **potential** to fulfil an unmet medical need.

- Vaccines are very complex and diverse products, requiring continued product and process understanding throughout development and lifecycle, and, as a consequence the generation of such evidence is particularly demanding.

- In addition, efficacy prediction during early development of vaccines is challenging. Therefore, risk- based product understanding strategies utilizing innovative technologies are needed to assess potential for prevention of the targeted disease, and, ultimately, support Early Access designation.

- In this presentation, **several vaccine manufacturers jointly share some reflections and CMC strategy proposals**, in the attempt to promote rapid and broad access to new vaccines and how accelerated approval strategies can enable early Health Agency interactions, including GMP aspects.

Comparison of Pharmaceutical Modalities – PPQ Timing

- PPQ is not required for standard dosage forms of small molecules
  - Validation reports are reviewed on inspection
  - High level of understanding of mechanism of action and molecular structure, therefore the manufacturing process is not as important as the molecular understanding

- Biological products (e.g. mAbs) require PPQ reports at the time of BLA/MAA submission
  - The molecular structure is well understood and can be linked to the mechanism of action (binding/affinity/effector function)
  - The consistency of the manufacturing process can impact the molecular structure in ways that may/may not be able to be detected through comparability

- Vaccines products have been traditionally expected to demonstrate efficacy using the final commercial process (PPQ) in Phase 3 pivotal studies
  - The molecular structure and structure/function relationships are not able to be understood as there is no discreet target of the molecule
  - Complexity in DS process, source of structural variation in antigen and impurities in vaccine composition
  - Comparability can be difficult; requires process definition at pivotal trials

PPQ Expectations for Vaccines in Pivotal Trials

- Molecular complexity and lack of established mechanism of action drive process validation requirements earlier (pivotal trials) for vaccine products
  - The molecular structure and structure/function relationships may not be fully understood
  - Process validation activities prior to pivotal trials cause significant impediment to acceleration approaches, and changing this expectation enables early access

- Advances in analytics for vaccine products could be leveraged to improve knowledge of CQAs, thus allowing better control strategy development prior to process validation

- Propose a risk-based approach accounting for:
  - Product understanding
  - Process control strategy
  - Prior process knowledge
  - Medical necessity