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SPOTLIGHT

COMMENTARY

Facilitating quality by design through patient-centric specifications

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Specifications are a part of an integrated vaccine control strategy. The current practice of setting acceptance criteria based on manufacturing variability has contributed to disparities in global specifications and thereby global quality. Instead, acceptance criteria should be based on assurance of patient requirements, both safety and efficacy, throughout a product's shelf life. Such limits might be viewed as the CMC definition of quality, and a necessary component in the implementation of quality by design. Test limits, or patient-centric specifications, can be derived from patient requirements and used to guide formulation, process and analytical development, and lifecycle management, using scientific and risk-based studies aimed at minimizing patient and manufacturing risks. Clinical studies using dose-ranging and with modified vaccines have been proposed to justify patient requirements, while preclinical and *in vitro* technologies can be used to further support these efforts. While patient-centric specifications are determined to manage quality, manufacturing consistency can be achieved without impacting quality to patients.

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INTRODUCTION

In many industries, specifications represent requirements which ensure that a product is fit for use. These conditions are on the product. This is distinguished from ICH Q6B which defines acceptance criteria as "ranges or other criteria for the tests" on the product [1].

The ICH definition can pose problems for risk-based development and lifecycle management (quality by design (QbD)). Aligning the requirement with a test result fails to

acknowledge other bases of product control. Because acceptance criteria usually relate to product release there is no easy way to extend the requirement to the end of shelf life or to post-licensure change control. This also limits vaccine control to testing rather than "building quality into the product" through material and process controls, analytical control, and strategic post-approval change management. The premise of this article is that a broader view of quality is required to develop robust manufacturing and analytical processes, and that specifications (acceptance criteria on test results) represent an integrated component of the vaccine control strategy.

This begins with the vaccine industry and regulatory authorities building consensus around the definition of product quality. This is implied in current guidelines [1,2]:

- ICH Q6B states that the specification "...establishes the criteria to which a...drug product...should conform to be considered acceptable for its intended use";
- ICH Q8A(R2) states that "a control strategy is designed to ensure that a product of required quality will be produced consistently";
- ICH Q8A(R2) further defines the quality target product profile (QTPP) as "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," and goes on to say that the QTPP should include "Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product".

From these criteria associated with "safety and efficacy", "required quality", and "desired quality", are expected of the product, and not test results.

This has been interpreted and implemented in different ways, but the viewpoint in this article is that patient requirements, limits on a CQA which ensure safety and efficacy, define quality. Patient requirements inform the target ranges for process, formulation, and analytical development, and are the basis for development of the integrated vaccine control strategy, including acceptance criteria on test results. This also provides opportunities for risk-based lifecycle management, including process and analytical maintenance and improvements.

If one agrees that specifications should be related to patient requirements, it is natural to question the custom of calculating acceptance criteria from manufacturing experience (e.g., a 3-sigma or tolerance intervals). This practice should be carefully evaluated, even in the case when the interval is calculated from data on clinical lots. Specification acceptance criteria and manufacturing limits address two different yet important aspects of product control: quality control, which relates to patient safety and efficacy, and manufacturing control, which relates to manufacturing consistency.

Related to this is the concept of patient-centric (or clinically relevant) specifications. While articles have addressed this for large and small molecule therapeutics [3,4] and recently vaccines [5], they do not address the interrelationship between specifications and other control features in an integrated control strategy. These include process and analytical method controls, continued performance verification, and change management procedures. Notably, statistical evaluation is restricted to setting limits, process capability analysis, and stability analyses, but not development and change management study design and analysis. Bayesian methods are reserved for the same and not as tools for continuous learning and knowledge improvement. A broader view of statistics fits into the paradigm of risk-based methods insofar as it acknowledges the concepts of uncertainty

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and decision risks in support of vaccine development and lifecycle management [25].

This article will review current practices in setting vaccine specifications (specifically acceptance criteria), and illustrate issues related to lack of harmonization of principles and practices of product quality and manufacturing consistency. The concept of patient requirements will be elaborated on and will be used as the CMC basis of quality. One derivative of patient requirements is patient-centric specifications (PCS), which will be coupled with concepts outlined in ICH Q1E [6] and the WHO Guidelines for Stability Evaluation of Vaccines [7]. This in turn will be extended to principles and tools presented in ICH Q5E, Q8(R2), Q9, Q10, and Q12 [2,8–11] for product development and lifecycle management, as well as USP General Chapter <1220> and ICH Q14 [12,13] for the analytical procedure lifecycle. The distinction between and co-management of quality control and manufacturing control will be described within the context of the integrated vaccine control strategy. The article will finish with some views regarding implementation and changes in regulatory standards that can facilitate the adoption of a harmonized vision of quality and PCS, and more broadly the vaccine control strategy.

CURRENT PRACTICES RELATED TO VACCINE SPECIFICATIONS

In vaccines, a specification (acceptance criterion) is frequently viewed as limits on a CQA, which represent consistency of manufacturing. Surveys show [14] that limits are set which reflect previous manufacturing experience (sometimes default limits based on platform knowledge) over the course of clinical and CMC development, culminating in the calculation of commercial specifications from some selection of final process lots.

Putting the purpose of specifications aside, efforts to harmonize principles and practices of calculated limits are hampered by several factors [15]. One goes to the question of "which lots should be used in the calculation." Should these be phase 3 clinical lots, or can they extend to all clinical experience, or all lots manufactured using the process that generated clinical materials? A second question is "how many lots should be used to make the calculation?" Or maybe more aptly, "how much experience should there be with the final manufacturing process, including routine changes that are experienced over the product lifecycle?" Finally comes the question of "how should we calculate the limits?" Should the data be transformed before calculation (e.g., log transformation), and should these be 3-sigma limits or tolerance limits?

These and less obvious disparities (e.g., data evolution when filing in different regions; number of digits or decimal places in the specification) can result in significant delays in product reviews and differences in global specifications. These differences result in variation in product quality, and complex vaccine supply management.

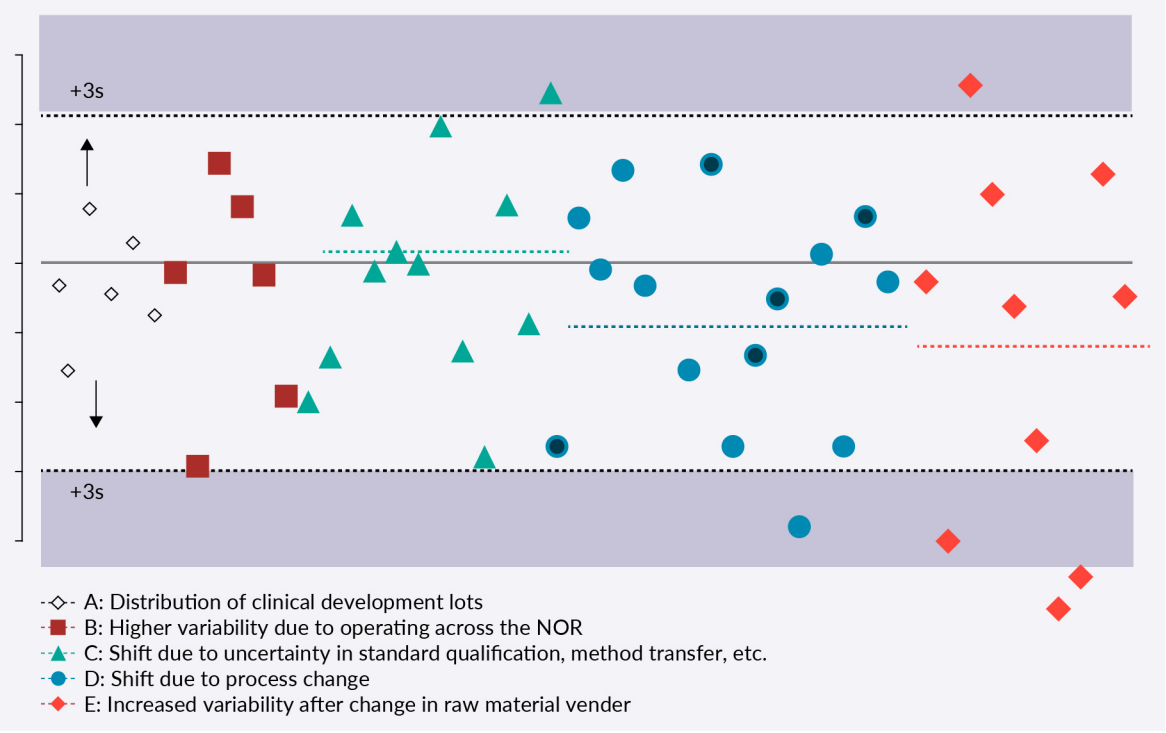
While not stated explicitly, manufacturers will "set limits which are as broad as possible" knowing that future measurements may be out of specification (OOS). Figure 1 illustrates several reasons for this.

Several sources of information regarding manufacturing variability are under-utilized or unrealized at the time of setting specifications, such as using 3-sigma limits on data from clinical or early manufactured lots (Figure 1a). In fact, the problem begins earlier during development insofar as clinical materials are usually manufactured at or near the set-points (critical process parameter (CPP) targets) of process parameters. Additionally, a higher risk of OOS could have been anticipated during process characterization (Figure 1b) when predictions can be made of the variability when controlling across the normal operating range (NOR) of the process [16].

Changes over the product lifecycle should also be anticipated and addressed during

FIGURE 1

Long term variability induced by routine and unplanned changes in manufacturing and analytical methods.



development. Shifts will arise after assay changes such as method transfers, bridging to new technologies, and standard qualifications (Figure 1c), and due to process corrections and improvements (Figure 1d). Unanticipated factors such as a change in a raw material vendor can either shift the manufacturing distribution or cause an unexpected increase in manufacturing variability (Figure 1e). Efforts to manage the consequences of normal lifecycle changes and unexpected factors are disruptive to supply and burdensome for both industry and regulators. Anticipation of a region depicted in grey in Figure 1 is useful in the development of specifications and represents a basis of "limits which are as broad as possible" which may be sought by a company at the time of licensure.

Likewise, quality at release does not assure quality at the end of vaccine shelf life. All biological products degrade, some more so than others. ICH Q6B hints at another consideration for assuring quality in stating: "The concept of release limits vs. shelf-life limits may be applied where justified." This is also a choice presented in the WHO Guidelines for Stability Evaluation of Vaccines, which may or may not be heeded by a manufacturer or required by some regulatory authorities.

Thus, the current practice of basing vaccine specifications on calculations from the distribution of release measurements on manufactured lots is subject to numerous choices, lack of foresight regarding routine changes and improvements over the vaccine lifecycle, potential instability of a vaccine, and just as many opinions and beliefs. Finally, and most importantly it places limited emphasis on the principle that specifications should be related to patient outcomes, reflecting fitness for use of a vaccine and not the ability to manufacture to some historical level of consistency; controlling product to "what is needed" rather than "what is seen."

From here I turn to the concept of patient requirements and illustrate how these drive the development of the integrated vaccine control strategy.

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PATIENT REQUIREMENTS: A BASIS OF QUALITY

The introduction of QbD, while laudable, was left incomplete without agreement on the definition of quality. This was less an issue in small molecule pharmaceuticals, where quality is often defined in compendia or as permitted daily exposure levels; but is more an issue with vaccines, which have fewer and sometimes disparate requirements. Some compendial vaccine requirements are viewed as too broad to be a meaningful basis of "product control" (e.g., endotoxin limits) but this interpretation confuses product quality with manufacturing consistency.

Limits on attributes that are predicted to impact vaccine efficacy, however, must be considered and controlled on a product-by-product basis due to the variety of infectious diseases, vaccine motifs, and levels of product characterization. Historically, potency has been treated as an attribute (or test) related to vaccine efficacy. This is usually assessed using a bioassay (or appropriate surrogate such as a binding assay) but does not preclude control of attributes that are related to potency when an association has been established, and the tests of those attributes are more sensitive than a typical vaccine potency assay. Here, the aspects of a specification related to the attribute and the test of the attribute can be important components of the justification of a specification.

Nevertheless, potency will be used to illustrate the concepts of patient requirements and their utility to the application of QbD. This begins with a framework for the analytical control of potency. Figure 2 shows a three-tier system of analytical limits, which is the basis for control rules and decisions.

Patient requirements are first-tier limits, which can be justified as predicting the safety and efficacy of a vaccine [17,18]. These are the interface between product quality and patient outcomes and should be viewed as fixed requirements against which elements of the integrated control strategy are derived.

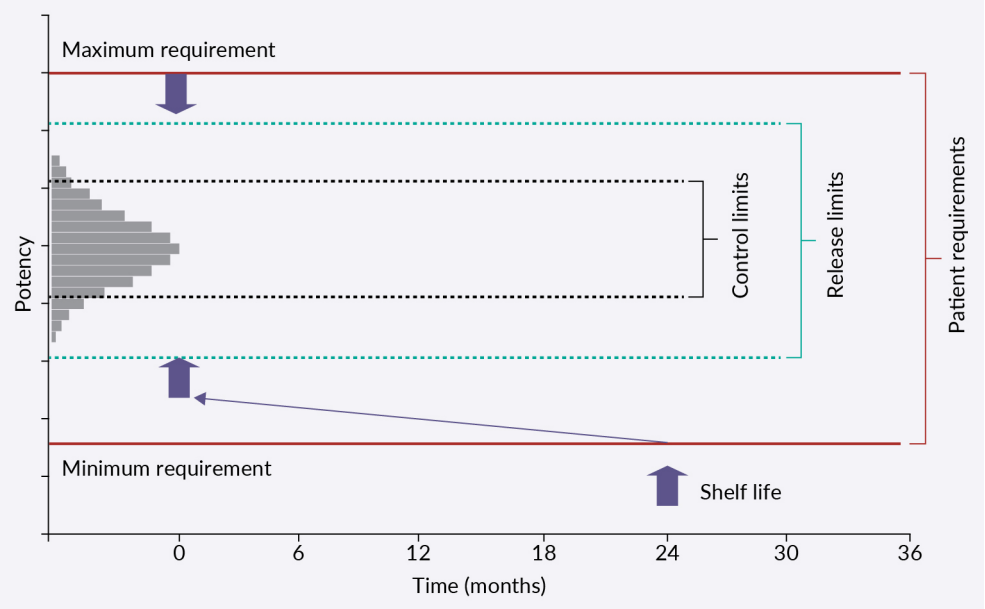
Release limits are calculated to ensure that each manufactured lot satisfies its patient requirements (with 95% confidence or 5% patient risk) at the time of release and throughout shelf life (shown here as 24 months). Stability estimates of the losses from vaccine release to the time of vaccine administration (shown as the sloped line) are used along with release assay and stability estimate(s) uncertainties (shown as vertical arrows at time 0) to calculate the release limits [19]. Design of the release assay (e.g., through replication) [20] and stability studies (e.g., through statistical optimization of stability time points and testing) [19] can be used to minimize these uncertainties and thereby relax the release limit range. Because release limits calculated in this way are linked to patient requirements and are applied to test results, these are viewed as PCS to be consistent with the definition of acceptance criteria in ICH Q6B; such as 'ranges for a test result.' Unlike patient requirements, which directly interface patient safety and efficacy (or a clinical assay endpoint), these are a second-tier interface to testing.

Finally, control limits (third tier) can be calculated from a selection of potencies on manufactured lots to monitor consistency and detect shifts or trends in manufacturing over the vaccine lifecycle. It is important to note that consistency defined in this way is dependent upon manufacturing and analytical conditions accumulated up to the time of calculation. As described previously, this will change over the vaccine product lifecycle, and thus control limits should be flexible to support process and analytical changes and improvements, and avoid unnecessary interruptions in the supply of quality vaccine (i.e., vaccine that falls within PCS).

Figure 2 is illustrated with two-sided limits, owing in part to the confusion that specifications represent control on the variability of manufactured lots. I will return to this when discussing some practices that might be allowed when quality limits have been appropriately distinguished from manufacturing limits.

FIGURE 2

Three-tier limits with patient requirements, release limits, and control limits.



Continuing this viewpoint, the control limits form the basis of manufacturing control and are subject to the manufacturer's risk (viz., evaluated as process capability analysis) while the release limits (or PCS) represent quality control and are established to manage patient risk.

PCS AS A BASIS FOR "BUILDING QUALITY INTO A VACCINE"

With this framework in mind, a company can proceed down a development pathway (with line-of-sight to lifecycle management), which ensures the quality and supply of commercial vaccines. This is illustrated as budgets in Figure 3, which derives from Figure 2.

Here the total of the analytical, process, lifecycle management, and shelf-life budgets must fit within the maximum and minimum patient requirements (the overall budget).

Using the parlance of QbD, formulation development is tasked with building shelf life into the vaccine, and performing studies designed to yield reliable (low uncertainty associated with low risk) predictions of loss of potency over shelf life. A practical start is to define a shelf-life target using early predictions of process and product hold times, times for regulatory release and exportation delays, and desired time in inventory as its basis. This drives optimization of these factors rather than reacting to insufficiently robust shelf life at the end of development. Simply put, shelf life should be forecast from commercial considerations and proactively built into stability factors, rather than calculated from 'what was seen' at the end of development.

At the same time process characterization is performed to identify CPPs and determine a design space that is predicted to assure adequate capability (i.e., low percentage of out-of-specification lots), while analytical development formulates an analytical target profile, specifying performance requirements that drive method design and development, and a replication strategy that manages the impact of procedure uncertainty on release decisions (as well as decisions from other uses of the method) [21].

Individual budgets should be dynamic, with increases or decreases among components depending upon the playoff between development restrictions and costs,

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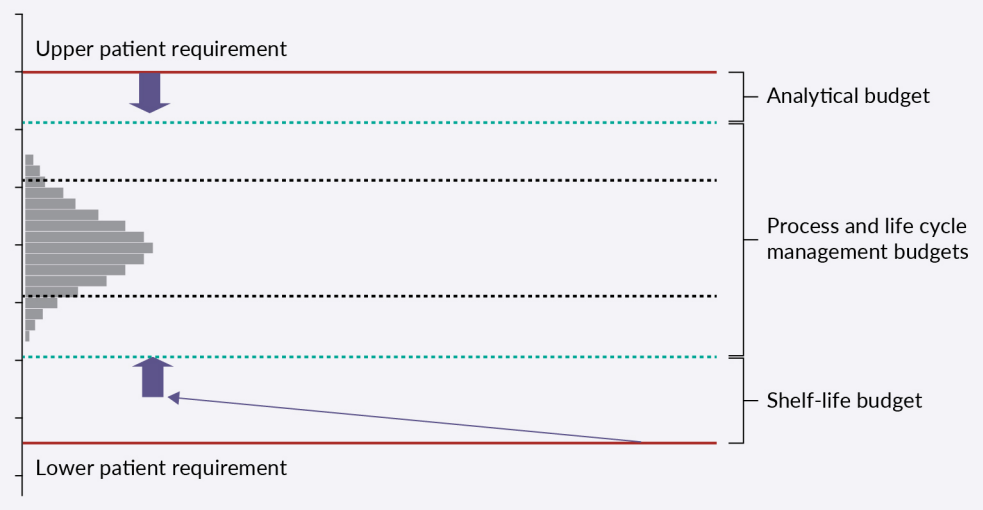
FIGURE 3

Analytical, process and lifecycle management, and shelf life budgets.



and costs of manufacturing failures and resulting regulatory interactions. Those costs should account not only for typical CMC investments, but also investments in defining patient requirements using clinical, preclinical, and *in vitro* studies, or prior knowledge.

While commercial specifications are often established late in product development, driven by the perceived need to manufacture enough lots, patient requirement targets should be resolved earlier and in concert with preclinical and clinical development. One basis for early action can be the strategic use of prior knowledge from platform experience with an antigen type and its formulation, associated test procedures, and other long-term sources of variability to predict the range of patient exposure to commercial potencies (at release and throughout shelf life). This can be used to drive laboratory or clinical studies that support the determination of patient requirements.

AN EXAMPLE OF BUDGET-DRIVEN PROCESS CHARACTERIZATION

Process characterization is a term used in most companies to represent the stage of vaccine development during which CPPs are identified and a process (or unit operation) design space is established. Here, design space represents "process knowledge" and is not meant to be associated with "regulatory relief." As such the design space evolves as information accrues during late development and into commercial manufacture. That information may be useful for investigations, process improvements, or as prior knowledge to support a platform process.

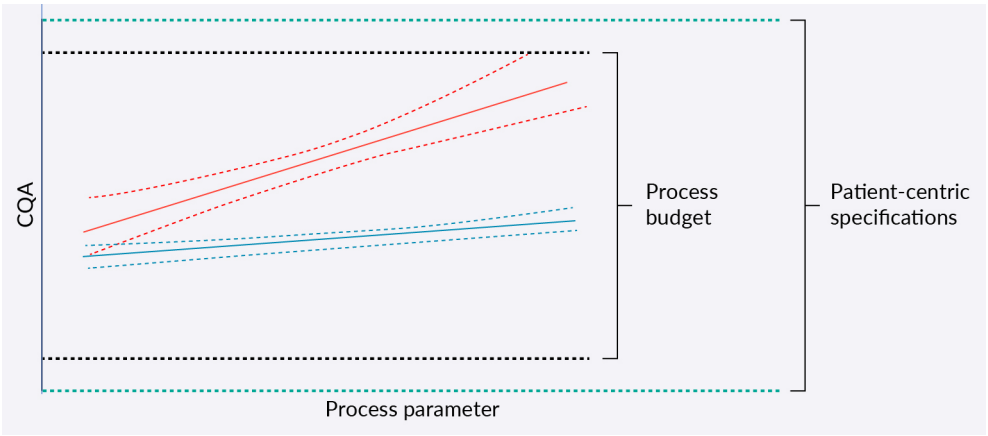
This is carried out through a series of multifactor designed experiments, first to screen process parameters for their impacts on one or several CQAs, followed by studies to develop mathematical models (response surfaces) relating CPPs to CQAs. Both stages require a process budget to make informed decisions. Results from a screening study are illustrated in Figure 4, showing a process budget along with PCS (which are broader, anticipating lifecycle management).

Two potential outcomes are depicted in Figure 4 [22]:

- 1. a case where the predicted impact on the CQA over some predefined process parameter range falls outside the process budget; and
- 2. a case where there is a minor change falling well within the budget.

FIGURE 4

Illustration of two potential impacts of a process parameter on a CQA.



The first case would result in a parameter being designated a CPP and taken into a second-stage response surface experiment, while the latter is not critical to the management of quality (viz., patient safety and efficacy). Three points can be made:

1. Without the process budget, a risk-based interpretation of the impact of a process parameter on a CQA is difficult to address;
2. The approach of fitting the confidence interval into the process budget is called equivalence testing, using a two one-sided test (TOST) [25]; and
3. This concept translates to multiple unit operations where the process budget is shared or divided among steps.

Alternatively, each unit operation may impose a budget (intermediate acceptance criterion) on the previous step, until the cumulative steps fulfill their combined restriction [23]. The relationship to the process budget constitutes a proactive effort to identify CPPs and thereby take steps towards ensuring "satisfactory process capability."

Figure 5 shows the determination of a design space from a response surface study on two CPPs that have been identified during screening (shown as time and temperature).

The experimental ranges on the CPPs are shown as the square area at the bottom of panel A, while the modeled responses (of the CQA) are the hatched surface above. The process budget (between 1.2 and 1.6) is the amount that the CQA can vary yet have negligible impact on process capability. Contour plots derived from the intersections of the lower budget limit with the hatched (response) surface (panel B), and together with the upper budget limit (panel C) yield a region in time and temperature (yellow shaded area) that ensures that the CQA will remain within the process budget. The design space is usually determined by inscription of a rectangle into this region. In principle, the design space is the whole of the acceptable region. However, for operational and regulatory reasons, this is usually expressed as a set of limits. Note that these steps might be combined to both identify CPPs and define a design space. This is particularly true when performed to verify ranges using a platform process.

In summary, CPP identification and design space development are driven by PCS, and from this a process (or unit operation) budget. In this way, the vaccine manufacturer can manage their risks (ensure satisfactory process capability) by operating within the design space, while patient risk is managed by the PCS.

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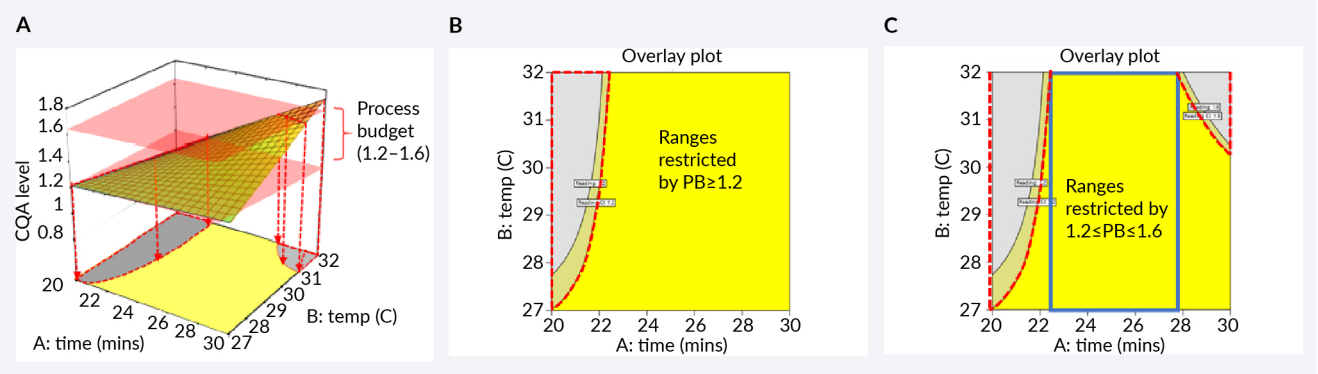
FIGURE 5

Design space determination from a response surface relating a CQA to two CCPs and using a process budget.



COLLAPSE OF THE DESIGN SPACE WHEN SPECIFICATIONS ARE CALCULATED FROM MANUFACTURING DATA

The previous illustration can be used to show issues related to using manufacturing data (e.g., 3-sigma limits) as the basis for specifications (Figure 6).

Figure 6a shows the predicted range of responses when operating within the NOR of the two CPPs. Here, the resulting range becomes the basis of control limits for the CQA. This range is narrower (1.3–1.4) than the budget obtained from PCS (1.2–1.6) and is consistent with the preferred separation between control and release limits shown in Figure 2.

If the control limits are subsequently used as the specification, and thus the process budget, the NOR becomes the de facto design space (Figure 6b). The design space is restricted to previous experience and limits opportunities to absorb the impacts of future manufacturing variability, as well as changes and improvements.

OPPORTUNITIES FOR LIFECYCLE MANAGEMENT WITH PCS

Manufacturing monitoring is useful but sometimes reactive. Process monitoring (or continued process verification) can be made more proactive by using results coupled with manufacturing inputs to improve process knowledge. This is particularly true in

FIGURE 6

Collapse of the design space when specifications have been determined using a manufacturing process operating within its NOR.

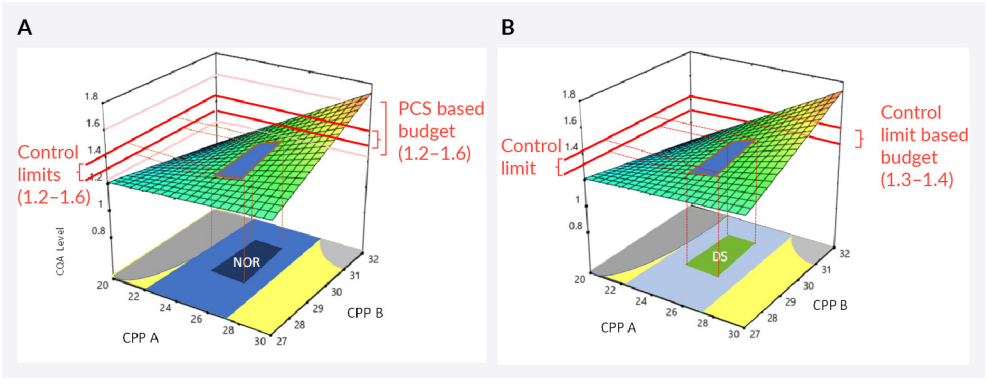
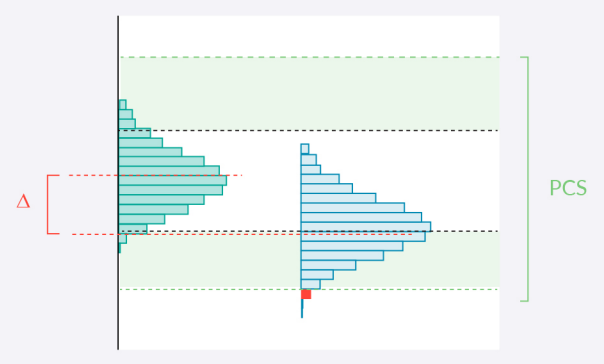


FIGURE 7

Operating within the lifecycle management budget (shaded green).



building a platform where long-term manufacturing experience with several vaccines can be used to inform future development and as a means of acceleration.

Since change is inevitable, it is advantageous for a company to develop a control strategy that can absorb the consequences of routine changes or improvements in the process or analytical methods. If limits are adequately broad (broader than routine manufacturing variability, as with PCS), change management can be based on the preservation of satisfactory process capability (and thereby vaccine supply). Take the example illustrated in Figure 7, in which a lifecycle management budget (the area between control limits and PCS) has been accounted for during development (Figure 7).

In this depiction, the manufacturing distribution can shift by an amount symbolized by Δ (delta) and still preserve satisfactory process capability (i.e., only a small proportion of lots are predicted to fall below the lower PCS; depicted in red). This forms a basis for designing an equivalence procedure using TOST. A study is designed (using pairing, sample size, and other variance reduction tools) aimed at minimizing the risk of failing the procedure when the shift in results is not meaningful (i.e., within ±Δ). The basis of design is the width of a confidence interval on the difference in mean results for the pre- and post-change conditions and confirming its inclusion within the ±Δ range. Potential outcomes from this procedure are illustrated in Figure 8.

When the confidence interval (upper limits shown as brackets) falls completely within the ±Δ region the conclusion is that the two conditions (different laboratories, new and old standards, etc.) are 'equivalent' – the shift is less than would compromise satisfactory process capability. If the interval falls outside the ±Δ region the study is unable to confirm equivalence. This might be due to there being a meaningful difference between conditions (i.e., a difference truly outside of ±Δ) or that the study was poorly designed, resulting in an unacceptably wide confidence interval.

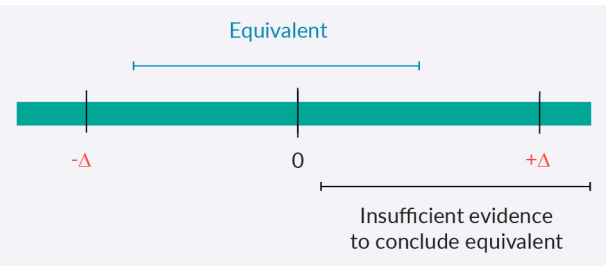
Key to the implementation of this approach is the foresight during development for the need to evaluate post-licensure changes against limits derived from patient requirements, and designing a process that delivers well within those limits. If specifications are set based on manufacturing data, then the process is fixed to the conditions used to generate those data, and there is little opportunity to apply risk-based approaches to manage process capability and supply.

DISCUSSION

This article introduces the concept of patient requirements and PCS as principles to resolve issues related to current practices and as a pathway to global harmonization of vaccine quality. This viewpoint provides a

FIGURE 8

Illustration of the implementation of TOST, showing both success and failure in concluding equivalence.



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rational basis for process, shelf life, and analytical development together with lifecycle management, yielding elements that can be built into an integrated vaccine control strategy to ensure quality to patients, and an agile and robust manufacturing process. While not described in the article, this points to pathways for the development of in-process controls, real-time release testing, and continuous manufacturing, which can be similarly developed and managed against patient requirements.

Agreement on this principle does not ensure ease of practice. Some clinical tactics to define patient requirements have been proposed, such as dose-ranging, deliberate manufacture or alteration of clinical lots, and clinical stability to predict what subjects received over the course of a clinical trial. Important questions remain related to the size of studies and the phase of conduct in a clinical program. Advanced technologies should be embraced, including 'hardware' like organ-on-a-chip as well as 'software' such as Bayesian analysis. Technology platforms together with advanced information management are additional enablers.

Patient requirements need not represent 'the edge of failure' (e.g., a boundary between 'good' and 'bad' potency). In fact, potency and other attributes follow a kinetics (sigmoid) model over the breadth of clinical outcomes (e.g., biomarker response), allowing exploration of a broad region of patient responses. Patient requirements can be determined to predict a specified level of efficacy when there is a correlate of protection (i.e., a level in the biomarker used to predict protection versus non-protection) or as a difference in average biomarker response as used to assess noninferiority and consistency among clinical groups.

The reader should have grasped the value of patient requirements and PCS insofar as it helps to bridge concepts in ICH Q6B with ICH Q1E, Q5E, Q8–Q12, and Q14. Implementation of scientific, risk-based approaches to vaccine development and life cycle management begins with patient needs and a paradigm that rewards scientific and risk-based development. Those rewards can be shared by manufacturers, regulators, and patients alike in the form of robust manufacture (i.e., free of deviations and the inherent burden of investigations and regulatory interactions), more predictable supply, and global assurance of quality to the patient.

Patient requirements and PCS, which are broader than manufacturing variability, together with relaxed expectations for regulatory oversight of manufacturing control, facilitate the introduction of new technologies and innovative practices. Here again, vaccine manufacturers and technology vendors are rewarded for innovation, and not penalized with prolonged global regulatory reviews and approvals and shunning of technology improvements.

To a statistician like me, the 'reward' comes from supporting development and lifecycle management study designs and analyses [24–26]. When patient requirements, and thereby development and lifecycle management budgets, are based on scientifically meaningful acceptance criteria, statisticians partner with clinical, preclinical, and *in vitro* laboratories, as well as with process, formulation, and analytical development to design studies that manage uncertainty and its impact on product quality. With appropriate design and analysis comes the reward of a higher likelihood of confirming quality, meeting study objectives, and avoiding future failures.

While the acquisition of 'the right data' (i.e., data obtained from well-designed studies) enables the implementation of these approaches, expectations on individual measurements from those designs (e.g., OOS of individual measurements) should be relaxed to facilitate the use of replication [27,28]. This includes resolution of the disconnect between shelf life (and release) guidance and stability OOS. Both expectations address the wrong quality questions, which should relate to batch analysis at release and product kinetics (the decay model or degradation rate), respectively.

A more subtle consequence of the adoption of patient requirements and PCS is the opportunity to control product quality against scientifically rational expectations. Thus, if potency has no impact on product safety, it makes no sense to establish an upper safety requirement. This practice is a reflection of using specifications for manufacturing control. Clinical studies should be dedicated to establishing the 'end-of-shelf-life' potency of a vaccine, while manufacturing is controlled within upper as well as lower control limits. Here, quality is not constrained between limits, and the reward for tightening the process and running well-designed studies is less vaccine overfill to offset the impacts of potency losses and study uncertainties. Less overfill translates into improved production capacity and thereby greater vaccine supply. Here, as before, the product is appropriately controlled without risk to the patient.

One reason for requests to tighten specifications by regulators is the lack of visibility into a company's quality management system (QMS). A healthy QMS should be comprised of a sensitive set of checks and balances to manage manufacturing consistency, but also to improve knowledge about the process and analytics. As with design of an integrated vaccine control strategy, design of a robust and agile QMS should be rewarded with improved process capability (and thereby vaccine supply). As such, the adoption of patient requirements and PCS should be accompanied by a good faith effort to manage manufacturing consistency, and appropriate oversight (e.g., through inspections and use of quality metrics) by authorities.

In addition to international guidelines, local statutes and compendia should be aligned to this paradigm. Some laws may impede adoption of new approaches, while compendia should relegate authority for the review and approval of product specifications to regulatory agencies. In addition to the varieties of modern vaccines, different development approaches may be taken by companies, including advanced levels of product characterization, strategic designs of processes and analytical methods, and uses of clinical or patient-centric information to inform specifications. These are often company-specific efforts, which are difficult to address in overarching laws or with compendial requirements.

Finally, cultural boundaries need evaluation, with the goal of bringing clinical, preclinical, and CMC together in the quest to link product control with patient outcomes. The same is true within and across regulatory agencies as well as between industry and authorities. The strength of patient-centricity, as well as science- and risk-based development should drive harmonization of principles and practices, and thereby harmonization of vaccine quality.

All in all, patient requirements and PCS contribute to an integrated control strategy aimed at ensuring that vaccine products are safe, effective, and available. Its foundation rests on information from clinical and preclinical studies, *in vitro* application of both old and new technologies, and prior knowledge from vaccine platforms. Guidances should converge on this principle, beginning with the revision of ICH Q6B for specifications, and Q1 for the assessment of stability. Application of principles in USP General Chapter <1220> and ICH Q14 can complement these revised guidelines in helping to achieve the vision of QbD. While some approaches have been successfully used to model PCS, others will follow and lead to a new normal in the development of vaccine control strategy, as well as a more facile administration of innovative process and analytical changes.

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VACCINEINSIGHTS

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SPOTLIGHT

EXPERT INSIGHT

Risk-based approach to leverage prior knowledge & statistical modeling during process development & process characterization of multivalent vaccines

Brenda Carrillo Conde, Elizabeth Rainbolt, Aili Cheng, Khurram M Sunasara & Aparna Deora

The use of prior knowledge, platform processes, and family approaches is increasingly being discussed by drug developers and regulators. The concepts can be applied to product design, process development, process validation, analytical method validation, extractable/leachable testing, stability, and overall control strategies. This article will highlight the benefits of using these approaches, along with appropriate statistical modeling, to develop a risk-based approach for process development and process characterization for vaccines.

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INTRODUCTION

Multivalent vaccines provide protection against multiple strains (serotypes/serogroups) or antigens within the same strain of a pathogenic bacteria or viruses by targeting key antigens. Multiple drug substances targeting multiple antigens are combined into a multivalent

drug product vaccine. Typically, each antigen drug substance is separately manufactured by parallel or sequential manufacturing processes. A conservative development strategy would entail extensive process characterization studies (i.e., standalone studies for each antigen) resulting in significantly long development timelines. This approach treats each new drug substance as a new process to be fully characterized, utilizing methods like design of experiments (DOE) to generate antigen-specific predictive models without incorporation of prior knowledge for understanding the impact of process parameters on product quality and step/process performance.

Pfizer and other companies leverage experience gained over years of developing some of the most impactful vaccine platform technologies (i.e., mRNA and polysaccharide conjugate vaccines) for progressing new vaccines. For new antigens, a platform approach has the potential to significantly streamline development timelines and reduce process characterization efforts as it builds on extensive prior knowledge and platform process steps [1]. This approach may also achieve efficiencies in regulatory approval of new vaccine candidates.

The pace of process development and simplification of process characterization studies will depend on how analogous the process steps are to each other. To that end, a risk-based methodology has been established to provide structure to the use of platform approach by:

1. Identifying the extent of fitting of a unit operation within our prior knowledge;
2. Assessing if it can be further identified as platform step; and
3. If the antigen shares physicochemical and/or processing characteristics with past and current antigens to be grouped within a family.

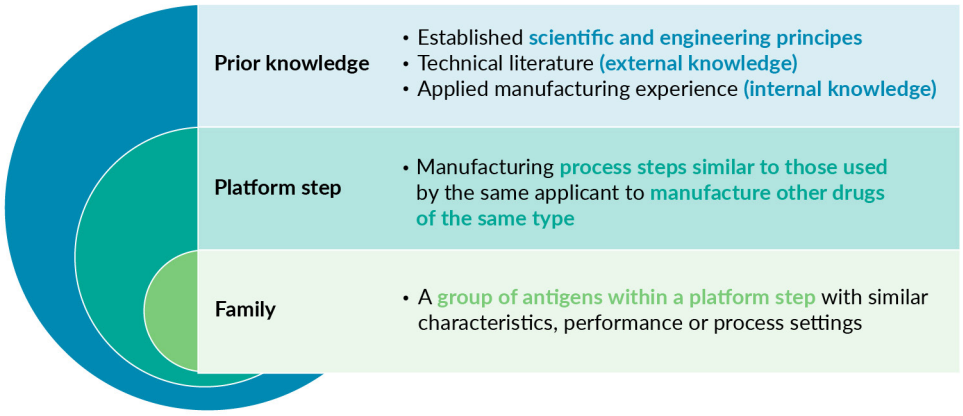
These three key concepts (prior knowledge, platform step, and family) form the basis of Pfizer's risk-based strategy and are defined below (and shown in Figure 1). As discussed later in the section covering risk-based approach, the level of simplification in development and process characterization design increases with the tier level (i.e., progressive application of outlined concepts).

Prior knowledge

Per ICH (i.e., Q8, Q10, and Q11) and EMA guidelines, prior knowledge includes

FIGURE 1

Summary of concepts used in risk-based strategy.



Prior knowledge defined in ICH Q8(R2), ICH Q10, ICH Q11, and EMA/CHMP/BWP/187162/2018. Platform step adapted from platform manufacturing definition in ICH IQ11.

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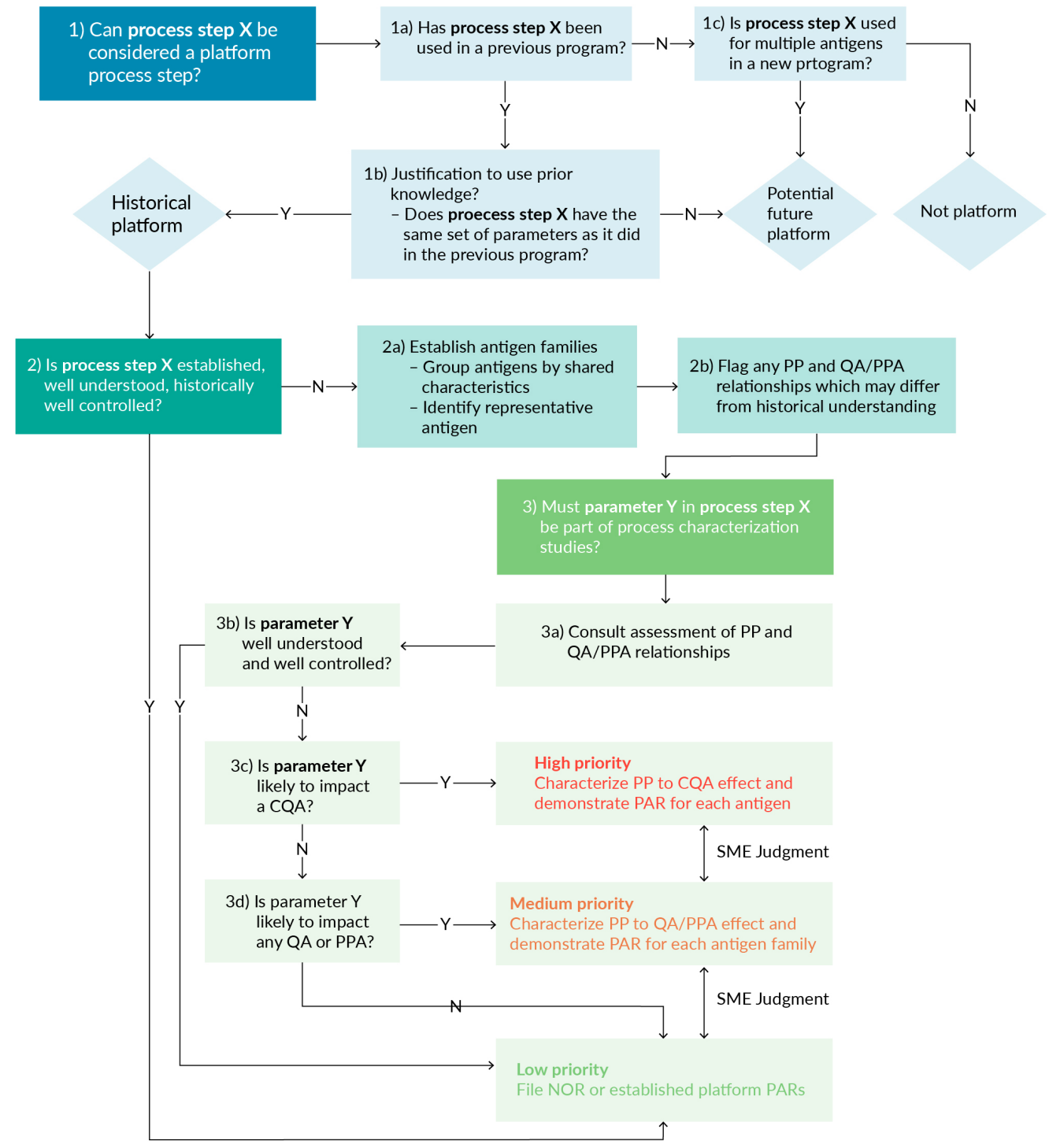
FIGURE 2

Risk-based strategy to design streamlined process characterization studies.



CQA: Critical quality attribute; NOR: Normal operating range; PAR: Proven acceptable range; PP: Process parameter; PPA: Process performance attribute; QA: Quality attribute; SME: Subject matter expert.

knowledge from "established biological, chemical and engineering principles, technical literature, as well as applied development and manufacturing experience from similar products or processes." [2–5]. Historical information and experimental data can be

leveraged to support the development of a commercial manufacturing process and expedite scientific understanding. When a new vaccine candidate uses a platform technology, the new experience and knowledge gained will become part of the prior knowledge for a future program.

Platform step

Per ICH Q11, platform manufacturing is defined as "the approach of developing a production strategy for a new drug starting from manufacturing processes similar to those used by the same applicant to manufacture other drugs of the same type." [3] For the purpose of this strategy, the scope of platform definition is focused on specific process steps. When a new vaccine candidate moves into development, a process step is assessed for suitability within an established platform manufacturing step. The outcome of the assessment directs process characterization studies and the extent to which prior knowledge and suitable models will be leveraged.

Family

A family is defined as a group of antigens within the context of a given platform step with similar physicochemical characteristics (e.g., viscosity, chemical features), performance (e.g., target quality profile and/or specification), or process settings. This definition extends to antigens within the same multivalent vaccine program or across vaccine programs using the same platform process step. To categorize an antigen family, antigens are assessed for similar physicochemical and/or processing characteristics to group them and identify representative or worst-case antigen(s) (e.g., most dissimilar in characteristics that could impact the performance of the evaluated step) for process characterization studies. Data (knowledge) obtained for those antigens can be applied to other antigens of the same family. This family approach can aid in establishing acceptable ranges and assessing parameter criticality with greater efficiencies compared to antigen-by-antigen approaches.

We present herein an overview of two synergistic approaches:

1. A statistical approach to harness prior knowledge; and

2. A risk-based approach for systematically categorizing plans and defining the scope for process characterization work.

STATISTICAL APPROACH

As mentioned earlier, part of the prior knowledge comes from development and manufacturing experience. If used effectively, statistics contribute to process understanding and prior knowledge accumulation from the following three aspects:

1. Experimental design: statistical design of experiments (DOE) allows us to collect properly planned data to accumulate valuable knowledge and experience about the manufacturing process. The effort on proper statistical design is justified because the collected data and the resultant predictive models reflect the cause-and-effect relationship, not just apparent correlation. Design of experiment is the foundation for model building and should always be considered before data collection.

2. Model prediction: quantitative predictive models can be built based on not only the data of the antigen of interest but also the prior knowledge established from similar antigens or the antigens from the same family. The Bayesian statistics provides a framework that allows us to leverage the quantitative prior knowledge in the model prediction and risk assessment. The recently published book *Case Studies in Bayesian Methods for Biopharmaceutical CMC* [6] includes a collection of Bayesian applications in multiple areas like

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leveraging prior knowledge in shelf-life prediction, specification setting, analytical method equivalence, analytical comparability, and experimental designs.

3. Data mining: companies with a long history of drug development usually have rich development and manufacturing data across multiple modalities and products. This large historical data set enables the use of numerous data mining tools that can be applied to help quantitatively summarize the prior knowledge from relevant historical data. Such quantitative prior knowledge can then be used to build valuable informative priors for both Bayesian model predictions and experiment designs for further evaluation. Generally, building and applying Bayesian predictive models is not a challenging task either mathematically or computationally. However, one of the key inputs for Bayesian models is the probability distribution of the relevant parameters. Such distributions are called priors. Without proper collection and summarization of the historical data and prior knowledge, the prior distributions could be too wide to carry any valuable information. Such priors are usually called 'noninformative priors'. Although Bayesian predictive models can still be built using noninformative priors, the real benefit of the Bayesian approach can only be manifested when informative priors are utilized.

RISK-BASED APPROACH

This section outlines the strategic approach for designing a streamlined process characterization plan for new vaccine candidates by applying the previously defined concepts (i.e., prior knowledge, platform steps, and family approach). The purpose of this approach (illustrated by the decision tree shown in Figure 2) is to be used as guidance for teams to define the scope and scale of process characterization studies for new vaccines. Upon reaching the last part of this decision tree, each process parameter in a platform step is assessed for its anticipated impact on critical quality attributes/quality attributes and process performance attributes by leveraging prior knowledge, defining the terminal categorization high, medium, or low priority for study.

This process is intended to be used as part of Pfizer's risk assessment process and additional project-specific considerations may be taken to finalize the process characterization plan for the development of a new vaccine product. The first two sections of this decision tree enable simplification of process characterization studies by:

1. Identifying the platform step: assess whether a specific process step is operated as part of established platforms. This can guide the extent of prior knowledge that can be leveraged for the design of a process characterization plan. If identified as a platform step, the risk assessment process is simplified and previous study designs for characterization studies (e.g., DOE) can be repeated.

2. Establishing antigen families: once a process step is identified as a platform step, either it is identified as a well-established operation or the antigens sharing this same platform step are assessed for identification of antigen families. If the platform step is identified as a well-established operation, process characterization studies could be eliminated or reduced (e.g., testing the edges of process parameters using one/multiple factor[s] at a time [OFAT/MFAT]) to confirm unit operation performance. To categorize a family, antigens are evaluated for similar physicochemical and/or processing characteristics to group them and identify a representative and/or worst-case antigen(s). When identified as family, process characterization studies can be performed using a representative or worse-case antigen, instead of repeating each characterization study across all antigens within a product. Additional simplification is

gained if the family extends to a previously characterized product, in which case studies can be designed to confirm performance and applicability of the platform.

The application of this systematic approach can significantly enhance efficiencies by eliminating redundancies in process characterization studies and shifting focus from performing full characterization studies to confirming the applicability of the platform and prior knowledge.

CONCLUDING REMARKS

The substantial manufacturing experience and process characterization knowledge, collectively known as 'prior knowledge' [2], gained during the establishment of platform technologies, can be leveraged to increase efficiencies in the development of new vaccine candidates. Expanding risk-based and statistical assessments to platform strategies could similarly be applied to process validation (e.g., using the family approach to matrix process validation studies [7]), extractables and leachable testing, analytical method validations (e.g., risk-based approach to apply platform method strategy for validation and tech transfer), stability strategies and overall control strategies. The use of platform strategies, such as those described in this article, could enable accelerated market availability of key lifesaving vaccines.

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VACCINEINSIGHTS

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SPOTLIGHT

Building faster technology platforms for mRNA vaccines manufacturing: analytics hold the key

Iulia Oita, Katleen Braet & Leonie wyffels
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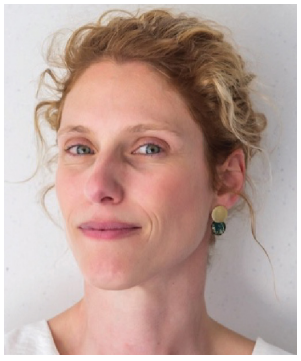

VIEWPOINT

"One way to add more value to the analytical toolbox and compensate for the initially intense effort to establish the toolbox is to design the analytical procedures to be 'platform-like' from the beginning..."

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mRNA vaccines are a versatile new technology, able to respond quickly to global health crises. Moreover, given their specific characteristics, mRNA vaccines are interesting candidates to be established as a platform technology. The recent alignment in all necessary steps for the successful manufacturing of mRNA-based vaccines, either conventional or self-amplifying, now provides defined development goals for platform establishment. However, any successful establishment of a technology platform requires a diverse analytical toolbox. Setting up an analytical toolbox during the early stages of platform development requires significant investment in time and resources. Here, we discuss several potential approaches to accelerate progress and avoid analytics becoming a bottleneck.

The availability of a platform technology is expected to speed up drug development by providing a consistent framework for the development process, manufacturing, and control strategies [1,2]. Whether it's a small, ambitious biotech or a well-resourced big pharma company, the aim is the same: to successfully build a platform and continuously apply ever-increasing knowledge across different products to enable fast delivery of the desired pipeline.

In the post-COVID world, mRNA vaccines are among the most interesting candidates to be established as a platform technology [3–5] as demonstrated by their ability to respond quickly to global health crises, bringing new technologies to patients sooner [6,7]. mRNA-based vaccines inspired new strategies for preclinical roadmaps, new concepts to speed up drug development, and novel CMC strategies [3,6,7].

The necessary steps required for successful manufacturing of mRNA-based vaccines, either conventional or self-amplifying, are relatively well-known and described in the literature [4,5,8,9]. Because of the fast evolution of the field of mRNA vaccines and this relative clarity on the different technological steps required for their manufacturing, mRNA vaccines are listed in a recent EMA guideline as amenable for platform approach, among more mature product groups such as monoclonal antibodies or viral vectors [3]. Yet, mRNA-based vaccine platform principles are still under development and the typical platform-related "prior knowledge" is currently building up whilst addressing the specific shortcomings of mRNA-based vaccines related to safety, efficiency, and stability.

The recent resolution of all necessary steps required for successful manufacturing of mRNA-based vaccines, either conventional or self-amplifying, are relatively well known and described in the literature [4,5,8,9]. Notably, standardization efforts from WHO [9], *US Pharmacopoeia* [8], and *European Pharmacopoeia* [10] aim to provide clarity on regulatory expectations and enable setting the development goals for platform establishment. However, to bring these goals to life, a diverse analytical toolbox, integration of standardized critical quality attribute (CQA) lists for each mRNA product family, and analytical procedures applicable at platform or product level are all needed. This toolbox will then act as *the* knowledge generator, essential for the evolution and survival of the platform.

During incipient platform development, the availability of an analytical toolbox is typically a key bottleneck since it requires massive knowledge intake and a significant investment in time and resources [3,11]. However, the platform analytical toolbox has the potential to become an efficient long-term accelerator when developed strategically. With this in mind, are there any possibilities to reduce the impact of analytics on the speed of early platform development stages?

Since at mRNA platform level, standard CQAs are no longer a mystery [8], the focus can now shift to prioritize the essential analytical tools required for process and product development and define acceptable levels for critical product-specific characteristics, for example, double-stranded RNA. Despite some specific features (large, highly charged, fairly heterogenic, and relatively unstable), the essential analytical tools for mRNA vaccines are the same as all drug development candidates: analytics for quantification,

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evaluation of purity, and potency. These analytical tools will provide the answer needed to prioritize process parameters based on product impact and to define meaningful and effective control strategies [4]. Among them, purity methods will essentially drive the process development and provide an understanding of product purity profiles from the early stages. Considering the array of possible process-related impurities and the mRNA-specific stability profile, the purification process for RNA is only going to be as robust as the analytics available to characterize it [12]. Keeping in mind mRNA characteristics, a combination of analytical procedures based on different principles (e.g., capillary gel electrophoresis, anion exchange high-performance liquid chromatography, ion-pairing high-performance liquid chromatography, analytical flow field flow fractionation, next-generation sequencing) may be needed to solve the purity puzzle rather than using a single methodology. While some procedures will remain product-specific and are less amenable to platform standardization, the availability of platform knowledge can speed up their analytical development time by using the same set of starting conditions, or the same approach for method development, or by targeting impurities or RNA-related products expected to be formed based on prior knowledge.

It goes without saying that, especially during the early days of platform establishment, analytical development is time-consuming, which in turn has an impact on timelines for process development. Speeding up analytical development timelines is thus an obvious solution to manage overall process development timelines. A possible approach is to think in 'development loops' as proposed in [6], focusing on the essential characteristics of analytical procedures and applying them as soon as possible on 'real' process samples. At the start of process and product development, a fully validated method is not a must. The 'mandatory space' of the analytical development includes elements able to provide understanding of the limitations of analytical procedures (matrix interferences, bias sources, causes of variability). Keeping in mind the subsequent development stages, limited variability and transferability to a GMP environment would be desirable, but not mandatory during very early stages, rather features belonging to the 'optimal space' described in [6]. At the beginning of process and product development, applying the analytical procedures will function as 'customer feedback', adding essential knowledge to improve the analytics along the way. Each 'development loop' may help analytical procedures evolve towards improved selectivity, sensitivity, accuracy, or precision. Retaining material from relevant preclinical batches, such as key process development batches or batches used in animal studies, can bridge later information obtained during early development such as the presence or levels of certain impurities, providing a better understanding of pre-clinical or clinical study data.

One way to add more value to the analytical toolbox and compensate for the initially intense effort to establish the toolbox is to design the analytical procedures to be 'platform-like' from the beginning of platform establishment [3]. This might involve including a wide product range and the largest expected sample matrix ranges, considering also potential in process control samples. Adding a phase-appropriate robustness assessment would also be useful for troubleshooting or change impact assessment. In this way, essential knowledge needed to speed up the development of new products and build tolerance for major development changes will also become available.

Understanding performance and limitations of the analytical procedures as soon as possible can further increase the value of the knowledge generated by making all the data representative. This provides the basis for a better understanding of analytical results and a thorough assessment of batch-to-batch consistency, and increases the value of pre-clinical studies. It will also help in comparing data across different platforms, by giving an unbiased view of how representative pre-clinical

batches are and evaluating the impact of changes inherent throughout the development process.

In conclusion, the impact of analytical development on timelines can be reduced by prioritizing the essential analytics required for process development, working in 'development loops', implementing 'platform-like' thinking, and qualifying the methods as soon as possible.

BIOGRAPHIES

IULIA OITA is CMC-Manager at Ziphius Vaccines, where she has been since 2022. She is a pharmacist by training and received her PhD in Pharmaceutical Sciences from Vrije Universiteit Brussel in 2012. She has worked for over 15 years in the pharma industry, involved in pre-clinical and clinical analytical development of small and large molecules. In her current position she coordinates outsourced and internal analytical activities.

KATLEEN BRAET is CMC-Manager at Ziphius Vaccines, where she has been since 2022. She is a biotechnologist by training and received her PhD in Medical Sciences from Ghent University in 2003. She has worked for several years in academia in the field of phage display and antibody engineering at Ghent University, Queensland University, and the Mater Medical Research Institute. In 2013, she started a career in the IVD industry conducting research to enable improved performance and efficient manufacturing of diagnostic biomaterials. In her current position she coordinates outsourced and internal manufacturing activities.

LEONIE WYFFELS is R&D director at Ziphius Vaccines, a biotechnology company focused on the development of self-amplifying mRNA based vaccines and therapeutics. She gained over 15 years of experience in both academia (University of Arizona, USA; University of Antwerp, Belgium; University Hospital Antwerp, Belgium) and industry (Ablynx, a Sanofi company) in 'bench to bedside' drug development, GMP manufacturing and quality control of biological products. She obtained her degree of Pharmacist and PhD in Radiopharmaceutical Sciences at the University of Ghent, Belgium.

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