

Development of Patient-Focused Commercial Specifications

Understanding of Clinical Relevance and Criticality of Quality Attributes

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The CASSS chemistry, manufacturing, and controls (CMC) Strategy Forum on 23 January 2019 in Washington, DC, was entitled, “The Development of Patient-Focused Commercial Specifications Through Understanding of Clinical Relevance and Criticality of Quality Attributes.” This forum covered the definition, identification, control, and management of patient-focused attributes throughout the life cycle (from discovery through approval) of biological products, including vaccines. Participants investigated how to differentiate through the product development life cycle which attributes are “clinically meaningful” from those applied for manufacturing capability and/or process consistency. Speakers explored which attributes have been identified as critical quality attributes (CQAs) and which have been shown to have no clinical relevance in addition to how those determinations were reached.

In addition, participants discussed developing a life-cycle approach to clinically meaningful specification development. Approaches were addressed for establishing CQAs using modeling (e.g., molecular and immunogenicity analysis), prior knowledge, and both nonclinical and clinical experience. Differences were explored between CQAs that require specifications — for example, bioburden, sterility (for aseptic products), and



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content/potency — and product-specific attributes that are shown to be clinically relevant CQAs. The forum not only described clinically meaningful attributes, but also considered how to set associated acceptance criteria or limits.

MORNING SESSION: KNOWLEDGE AND DATA

The morning session, “Data-Driven Approaches to Establishing Criticality of Quality Attributes,” predicated that understanding the CQAs of a biopharmaceutical and its potential risk to patients is foundational to establishing patient-focused specifications. The session described approaches to leveraging product-

specific and prior knowledge to inform the assessment of CQAs. Discussion began with the use of in vitro and in vivo model systems to evaluate attribute severity and potential influence on product safety and efficacy. Appropriate use of prior knowledge in justifying specifications was presented. Clinical considerations were explored, including the use of appropriateness criteria, efficacy data, and safety inputs to explore criticality and define clinically relevant specifications. The session ended with a regulatory perspective on attribute criticality and setting patient-focused specifications. Fiona Cornel (Health Canada) and JR Dobbins (Eli Lilly and Company) chaired this session.

The first presentation was **“Case Studies for Advancing Critical Quality Attribute Understanding and Building Prior Knowledge,”** by Marisa Joubert (Amgen). Joubert noted that criticality and “clinical qualification” of product attributes can be assessed by a number of means: clinical trials (beyond pivotal studies), nonclinical evaluations, in vitro studies, and prior knowledge/public knowledge. Acceptance criteria should not be broader than “clinically qualified,” but that does not restrict them to clinical levels. Companies can use other data to qualify a product clinically, but statistics alone without justification will be unacceptable.

Tools for developing understanding of immunogenicity risk include cell-line assays, peripheral blood mononuclear cells (PBMCs), mixed cell cultures, monocytes, and Xeno-het mouse models (1). The latter are immune-competent heterozygous mice developed by crossbreeding a human Ig-tolerized XenoMouse model with a C57BL/6J wild-type mouse.

All those can tolerate a therapeutic but still retain their ability to respond immunologically if that tolerance is broken by an attribute, such as high levels of a particular posttranslational modification. Joubert noted that when developers are working with isolated species, it is vital to understand what the sample material contains. Even material with high levels of molecular-weight (HMW) species did not break tolerance in Xeno-het mice or activate the in vitro assays. Neither prior/published knowledge nor clinical data have shown HMW impact. For low-molecular-weight (LMW) species, material with high levels of partial molecules generated a response in PBMCs/monocytes but no response in cell lines, indicating that partial molecules are an attribute of potentially high risk. With hydroxylysines, even high levels appeared not to induce response in any assay.

The second presentation was **“How Can Prior Knowledge Support the Justification of Clinical Relevant Specifications?”** by Jochen Felix Kepert (Roche Diagnostics). He noted that ICH Q8–11 provide guidance on how to define product quality with respect to

CMC FORUM SERIES

The CMC Strategy Forum series provides a venue for biotechnology and biological product discussion. These meetings focus on relevant chemistry, manufacturing, and controls (CMC) issues throughout the life cycle of such products and thereby foster collaborative technical and regulatory interaction. The Forum strives to share information with regulatory agencies to assist them in merging good scientific and regulatory practices. Outcomes of the Forum meetings are published herein to help assure that biopharmaceutical products manufactured in a regulated environment will continue to be safe and efficacious. The CMC Strategy Forum is organized by CASSS—Sharing Science Solutions (formerly the California Separation Science Society), and is supported by the US Food and Drug Administration (FDA).

CQAs and the use of quality risk-assessment tools (2–5). Adoption of the principles described in those guidelines could enable alternative approaches to setting specifications as described in ICH Q6B (6). The presentation discussed how knowledge from similar products can be leveraged during CQA assessment and how such information can be translated into setting of specifications. Although some knowledge might be applicable across molecules, other information will not be and therefore would need to be assessed by product. Kepert offered examples that illustrate the opportunities and limitations in using prior knowledge to support clinically relevant specifications.

The third presentation was **“Assessing Product Quality Attributes Utilizing Appropriateness Criteria and Efficacy and Safety Inputs to Establish Clinically Relevant Specifications,”** by John Ayres (Pharma Safety Solutions). He described that adopting clinically relevant specifications is not a new concept and dates back to the early 2000s, when the US Food and Drug Administration (FDA) embarked on its “Pharmaceutical CGMP Initiative for the 21st Century: a Risk Based Approach.” Development and adoption of ICH Q8–11 provided a structured way to define a product’s critical quality attributes (CQAs), design space, manufacturing process, and control strategy for

establishing specifications tied to the quality target product profile (QTPP). Although progress has been made, limitations persist that have stymied the realization of establishing registered specifications limited to direct clinical impact. Ayers looked at some of those impediments encountered in achieving the goal of risk-based and clinically relevant specifications along with the utility and shortcomings of clinical inputs to establishing relevant acceptance criteria. He examined the effect of institutional/cultural normative behavior, risk aversion, and the impact of uncertainty and economic drivers affecting innovator/industry and regulatory interaction. And he presented a paradigm to assess drug substance and drug product batches with CQAs that fall outside pivotal clinical trial exposure levels but within the inherent variability of a capable and well-controlled manufacturing process.

The last presentation of the session was **“Regulatory Considerations for Setting Patient-Focused Specifications,”** by Mats Welin (Sweden’s Medical Products Agency, MPA). ICH Q6B states that because specifications are chosen to confirm quality rather than to characterize a product, biomanufacturers should provide their rationale and justifications for including and/or excluding testing for specific quality attributes (6). In addition, “specifications should be based on data obtained for lots used in pre-clinical and clinical studies. The quality of the material made at commercial scale should be representative of the lots used in preclinical and clinical studies” (6). The outcome of a 2011 workshop of European Medicines Agency and industry experts was in line with Q6B, stating that clinical qualification is considered to be the most important aspect of setting acceptance criteria. But the principles of setting acceptance criteria will depend on the nature of the tests used.

Authorities expect acceptance criteria for tests of critical product-specific attributes to be based on clinical justification. Welin covered common issues identified in assessing biological medicinal products, including

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Immunogenicity models are not **DIRECTLY predictive of what will happen in humans — but they are useful to rank attribute risks.**

both the selection of what to test for and how to set acceptance criteria for those attributes. For obvious reasons, criticality of the attributes will influence the need to control them batchwise. Prior knowledge can be considered when assigning criticality, but its applicability must be justified.

Alternatives to testing at both the drug substance (DS) and drug product (DP) levels have been accepted in the past. Regarding the acceptance criteria applied, applicants frequently claim that clinical results have been considered in justifying those criteria. In the end, however, limits often are set without clinical justification. Instead, they are based on statistical calculation from all batches. Setting limits based on results from batches used in clinical trials could be difficult because often only a small number of batches are used to do so, and those may not mirror the full range of variability actually seen in commercial production.

Welin discussed how certain evaluations can be performed to justify clinically relevant specifications that are wider than the ranges seen in batches used for clinical trials. Those evaluations include making use of prior knowledge, understanding structure–function relationships, making use of dose-finding studies, and so forth.

MORNING PANEL DISCUSSION: BEST PRACTICES AND CLARIFICATIONS

A panel discussion concluded the morning session. The attendees of the CMC Strategy Forum were asked to discuss best practices as well as any other aspects of the session that needed further clarity. This panel discussion included John Ayres (Pharma Safety Solutions), Gerald Gellermann (Novartis Pharma), Marisa Joubert (Amgen), Jochen Felix Kepert (Roche Diagnostics), Anthony Ridgway (Health Canada), and Mats Welin (MPA). The panel topics, questions and responses/discussion were as follows.

Immunogenicity Testing:

Immunogenicity models in general are not directly predictive of what will happen in humans. However, they are useful to rank attribute risks and provide some idea of the potential for immunogenicity. A “low” prediction based on these models alone might not be acceptable to rank the criticality of an attribute, but they can help justify the final control strategy when combined with additional prior knowledge, clinical data, and the totality of evidence.

The Xeno-het model presented during the main session was specific to immunoglobulin G2 (IgG2), but transgenic mice can be created for any class of protein. Mice that are transgenic solely for tolerance of a particular class of protein can have suppressed immune systems in general — and back-crossing with wild-type mice can add in wild-type genes to confer a more robust immune response.

When characterizing aggregates, it is apparent that a partly folded structure is more immunogenic than totally degraded and normal structures, which appear to be less or even nonimmunogenic. Although not directly linked to clinical outcomes, PBMC assays are being used to screen molecular candidates. And apart from antibody immune responses, clinical adverse events such as injection-site reactions and hypersensitivity should be examined to determine whether an immune response is occurring.

Further Justification of Criticality: To maximize the value of nonpivotal clinical studies — e.g., phase 2 and dose-

ranging studies — their data should be reviewed for signs of adverse events (e.g., immunogenicity). Even though such studies may not be powered to provide statistical significance for adverse events, they can be informative and provide some level of assurance. Using aged material (within expiry) in clinical studies should be encouraged to allow for tracking of attributes that change over time.

For attributes with regulatory/compendial limits (e.g., host-cell DNA or endotoxin) limits may not have to be based solely on clinical exposure or process capability. However, some level of control testing (in-process controls with action limits) is important to ensuring that the biomanufacturing process remains consistent and that unexpected results are investigated. Some attributes (e.g., host-cell proteins and DNA) can be “validated out” based on process capability.

Developers need to consider the whole clinical picture when assessing risk: disease type, patient population, route of administration, and so on. Getting samples back from patients and performing CQA evaluation studies is becoming more common. Regulators consider that practice to be a useful tool that helps developers understand what is happening in patients and thus is valuable for knowledge gathering.

Although several companies have put end-of-shelf-life material in the clinic specifically to justify widening specification limits, forum participants had seen no reports of companies pushing process limits to create material with higher levels of attributes in the clinic for purposes of justifying wider limits. Data generated from batches run in the middle of a given set of process-control limits might not reflect the realities of long-term commercial manufacturing.

Clinical studies cannot be statistically powered to look for direct clinical impact for each of a given molecule's CQAs. However, using material with a broad range of a particular attribute in clinical studies still could be used as one aspect of justification for specifications.

No one knew of any companies giving a higher level of a specific

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attribute in a clinical study — which might be deemed unethical — beyond what reasonably would be expected during normal manufacturing.

Other Considerations: An interesting discussion arose over a company's producing two products meant to be given together: Should that company link the specifications of those drugs? Although no consensus was reached, forum participants agreed that it was a strategy worth considering.

Typically during early development, fewer data are available to inform a CQA risk assessment, so more tests may be needed. As more knowledge is gained over time, removal of some specification may be justified.

Acceptance criteria that are well beyond what have been put into patients should not be used because of both the lack of clinical experience and the necessity of considering process capability and consistency.

Is it time to revisit ICHQ6B? Many participants agreed that the guideline could be updated but saw no need to rewrite it. A questions-and-answers clarification of content might help.

Panelists suggested that clinical-trial physicians should understand CMC. They should be familiar with product safety and efficacy issues involved in specification setting, generation of quality target product profiles (QTPPs), and assessment of process change risk.

Such individuals could contribute to a safety monitoring plan being developed for clinic use.

In summary, using the principles of a risk-based, patient-focused process allows a company to use resources appropriately by establishing the criticality of attributes and designing a testing strategy based on that criticality assessment.

AFTERNOON SESSION: SPECIFICATIONS

The second session of the day,

“Developing Patient-Focused Specifications,” highlighted the difficult task of establishing clinically meaningful specifications for product attributes that are deemed necessary to ensuring the continued safety and efficacy of a drug product (whether vaccine or therapeutic protein). William Egan (GSK Vaccines) and Anthony Ridgway (Health Canada) chaired this session.

The range of values explored in clinical trials have the potential to become the acceptable ranges for those specifications. But with a well-controlled and consistent manufacturing process, the investigated range of attributes can be so narrow that they lead to over-narrow specifications set relative to what might be necessary clinically. Following product licensure, the need for expanded specifications could become apparent over time along with the realization that they might have been set too narrowly. This session explored strategies that might help companies during clinical development to arrive at a set of clinically meaningful specifications that are not bounded strictly by manufacturing consistency.

The first presentation of the afternoon session was **“Best Practices for Setting Patient-Focused Commercial Specifications,”** by Darrin Cowley (AstraZeneca). He opened by describing that, according to ICH Q6, a specification “should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product” (6). Clinical manufacturing has not been as reproducible or productive historically, often producing significantly variable final-product attribute levels throughout

a clinical program. That has enabled commercial specifications to be based on both “clinical exposure” and product-specific clinical manufacturing history. Over time, however, biomanufacturing has become more consistent, bioreactor productivities have increased, and accelerated approval pathways have limited significantly the number of batches manufactured and used in the clinic — all of which subsequently have minimized the levels of product-specific attribute variability introduced into the clinic.

Unfortunately, the commercial specification-setting philosophy hasn't evolved to address this new reality and retains its strong foundation in process consistency. To overcome the unintended consequences of manufacturing advances, Cowley said, we must incorporate elements of ICH Q8–11 (2–5) to make informed risk- and science-based decisions when setting specifications. Industry and regulators alike must leverage the vast amounts of prior knowledge available to improve their understanding of how attribute levels affect potency, immunogenicity, and so on. Once a common understanding of attribute risk has been realized, then specification setting can shift from clinical experience/process variability to yield attribute-centric specifications focused on safety and efficacy.

The second talk was **“Justification of Specifications Compared Using a Traditional Versus a Risk-Based Approach,”** by Gerald Gellermann (Novartis Pharma AG). He compared traditional assessment with an advanced and risk-based approach for definition and justification of specifications, discussing putative impact(s) on manufacturing process and life-cycle management. The traditional approach focuses on consistency; the advanced approach provides opportunities to use present understanding of structure–function relationships for analyte molecules. The latter approach enables definition of limits that can extend outside those determined by clinical experience. If indicated, such a potentially extended definition would be required to incorporate more worst-case assessments as the basis for predicting

future manufacturing variability. Such scenarios provide the basis for designing robust commercial manufacturing processes and further facilitate efficient product life-cycle management.

The third presentation was **"IQ Consortium Biologics Working Group on Specification Setting Strategies,"** by Juliana Kretsinger (Eli Lilly and Company). She described the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ) as a technically focused organization of pharmaceutical and biotechnology companies sharing a mission: to advance science and technology to augment the capabilities of member companies to develop transformational solutions that benefit patients, regulators, and the broader research and development community. In 2017, IQ's biologics leadership group initiated a working group to discuss strategies for phase-appropriate specifications.

The first effort from that working group focused on early phase specification practices. Responses from a survey among IQ member companies to understand current practices were integrated into a manuscript that recently was accepted for publication in the *Journal of Pharmaceutical Sciences* (7–8). The paper offers guidance on strategies for defining early phase specifications, and it includes platform specification examples.

The working group's second focus is to develop an industry-aligned view on commercial specification-setting best practices, with an emphasis on defining patient-focused commercial specifications. The IQ working group includes members that represent a broad range of companies working on biologics, thus enabling preparation of a guidance that addresses a similarly broad range of questions and concerns. Kretsinger shared highlights of current thinking to support forum discussion on specification-setting strategies.

The final presentation of the session was **"Clinically Relevant Specifications: Case Study and Summary of Discussion at the BioPhorum Development Group Meeting"** by Taro Fujimori (AbbVie Bioresearch Center). Focusing on expectations for companies to establish

and use clinically relevant specifications, he presented a case study of clinically relevant specifications. The case study had been discussed at a BioPhorum Development Group meeting, and Fujimori shared a summary of the outcomes. The mission of the BioPhorum Development Group is to connect process development organizations within (currently) 24 biopharmaceutical member companies, provide an effective environment for them to collaborate on shared issues, and accelerate improvement across the biopharmaceutical development community.

AFTERNOON PANEL DISCUSSION: Q&A

Another panel discussion followed the afternoon presentations. Barry Cherney (Amgen), Fiona Cornel (Health Canada), Darrin Cowley (AstraZeneca), Taro Fujimori (AbbVie Bioresearch Center), Gerald Gellermann (Novartis Pharma), Juliana Kretsinger (Eli Lilly and Company), and Kavita Ramalingam Iyer (Merck & Co.) participated. They addressed a number of topics ranging from test methods to different product modalities.

Justifying Limits: The monoclonal antibody (mAb) used in oligosaccharide profile examples mentioned at the forum was not an approved product, but no higher level beyond the clinical experience was questioned during the filing process for that product. Participants discussed whether such findings would be applicable across all mAbs, but there was no consensus about whether such an approach would be appropriate. Mass spectrometry and other assay technologies have been used to study patient materials for justifying limits, and those specifications were approved. And in the asparagine deamidation case study, the company included shipping and stability testing wherever levels had been low in the product to begin with in order to justify eliminating routine testing. Levels of 20–30× were necessary to make an impact.

Multiattribute Methods: An update on progress with the multiattribute method (MAM) of analysis revealed challenges in quality control (QC) at one company. However, MAM has replaced some tests

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under investigational new drug (IND) applications, and the FDA's Emerging Technologies Team (ETT) still is working with the company on that. Another company uses MAM in development labs but not in QC.

A **biosimilar** has its own specifications and must demonstrate similarity to a reference product. Sponsors will obtain reference-product samples and perform head-to-head clinical studies. But forum participants were unclear about whether the information coming from those studies would be useful for understanding attribute criticality. A wealth of data exists for prior knowledge of reference products, including a long history of product data from the innovator over time. To set specifications, a biosimilar company uses prior knowledge from the innovator product if that has been published.

Expiration Dates: The value of having clinical studies at the end of expiry was questioned. Can it confirm whether the attributes originally selected remain relevant? Forum participants agreed that it is valuable to introduce material near the end of its expiry into clinical studies. Companies must be able to estimate the level of an attribute in resulting samples based on clinical in-use stability and

Expanded attributes have been included in clinical studies, and specifications have been **WIDENED** consequently.

real-time stability studies. Developers need to consider the details of their clinical studies — e.g., extension, pivotal status, number of patients, exposure time, and so on — which then will need to be explained in a filing.

Pharmacokinetics and Pharmacodynamics (PK/PD): The cumulative approach presented earlier in the afternoon had focused on potency. For PK and other effects, companies can use prior/public knowledge to understand which attributes could be most influential. PK modeling could provide a more robust way to look for PD because the 80–125% limits for bioequivalence are considered to be somewhat arbitrary.

Animal Testing and Dose-Ranging Studies: Most participants considered animal models to be useful for assessing safety and efficacy of attributes. An understanding of how those results would relate to effects in humans is important, but not always essential (e.g., if developers simply are looking for relative effects). All data reduce uncertainty. “If you have zero concern,” was the consensus, “and you have no data to show anything to the contrary, then that should reduce the criticality of an attribute.” For attributes of concern, their importance can be substantiated through data outside the clinic — if that suggests that an attribute should be considered critical. In such cases, companies should provide background on the animal models to regulators to help them understand how the models work and how they are relevant to patient safety and product efficacy. Such data usually should be included in the “justification of specifications” or “product characterization” sections of a regulatory filing. It is a good practice to include a road-map note to reviewers describing where data can be found.

Dose ranging studies also can provide some data on safety, especially

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when designed to find the maximum tolerated dose of a product. Some studies can elucidate efficacy as well. Immunogenicity is harder to parse from these smaller studies, but that does depend on the product attribute under consideration.

Beyond Specifications: For chimeric antigen receptor (CAR) T-cell therapy products that fail specifications, a physician might decide to dose anyway. If commercial regulators require lot-by-lot product release, then they can allow such dosing if a manufacturer begins a new trial — or require dosing under an IND application. If the material proves to be successful, then that can provide additional data and justification to support widening specifications. With other breakthrough products, perhaps the same approach can be used in which product that doesn’t meet specifications still goes into patients to expand specifications over time.

In many cases, expanded attributes have been included in clinical studies, and specifications have been widened consequently. The trend is toward a more end-to-end control strategy with incoming material controls, in-process controls, real-time release, and not relying on specifications alone. Process control should ensure product quality at lot release.

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