The Development of Patient-focused Commercial Specifications through Understanding of Clinical Relevance and Criticality of Quality Attributes

January 28th 2019
Morning Session

The development of patient-focused commercial specifications through understanding of clinical relevance and criticality of quality attributes

Session Chairs:
Fiona Cornel, *Health Canada* and JR Dobbins, *Eli Lilly and Company*
Morning Agenda

How to Understand Criticality by *in vitro* / *in vivo* Testing
Marisa Joubert, Amgen Inc., Thousand Oaks, CA USA

How Can Prior Knowledge Support the Justification of Clinical Relevant Specifications?
Felix Kepert, Roche Diagnostics GmbH, Penzberg, Germany

Assessing Product Quality Attributes Utilizing Appropriateness Criteria and Efficacy and Safety Inputs to Establish Clinically Relevant Specifications
John Ayres, Pharma Safety Solutions, LLC, Indianapolis, IN USA

Regulatory Considerations for Setting Patient-focused Specifications
Mats Welin, Medical Products Agency (MPA), Uppsala, Sweden
Themes from the Morning Presentations

Criticality and ‘clinical qualification’ of product attributes can be assessed by various means – clinical (beyond pivotal), non-clinical, in vitro studies and prior knowledge/public knowledge.

Acceptance criteria should not be wider than ‘clinically qualified’ – but that does not mean just levels in the clinic – one can use other data to ‘clinically qualify’ – but statistics alone without justification isn’t acceptable.

Clinical relevance encompasses what is impactful in the clinic to patients and assures a consistent safety and efficacy profile.

ICHQ8 allows for Quality Risk Management including published tools and concepts and means described above. QRM should be a guide to the control strategy and consider route of administration, indication, dosage etc.

Gaining knowledge occurs throughout development and is based on understanding what ‘attributes’ the product actually has through analytical testing – this can evolve over time.
Themes from the Morning Presentations

Prior knowledge is valuable as often we have less clinical exposure, especially in pivotal studies, than the true variability of production.

An attribute’s impact on efficacy is somewhat easier to assess (PK/biomarkers and potency as well as in vitro studies) but safety impact in the clinic is not easy as you won’t get enough of the material into a patient and in vitro studies beyond immunogenicity are limited.

When using new technology it is important to have kept samples of early material to ensure if any new species appears that you know if it went into tox/clinical samples.

For a control strategy one can test where most appropriate (e.g. IPCs) and different limits can be used (reject, action, alert) – tests can be removed over time as we gain more knowledge – but can be added too!

One needs to consider PRIME/Breakthrough products with a different risk paradigm as so few lots in the clinic.
Themes from the Morning Presentations

Obstacles to going beyond clinical exposure can be a tendency not to ‘rock the boat’ based on older submissions, a desire to avoid questions from the agency with a risk averse dossier, willingness to adopt of new (and thus less familiar) technology etc.

When designing QTTP’s involve clinicians and consider new ways of doing clinical studies linking CQAs to outcomes, including the design of pharmacovigilence studies.
Themes from the Morning Presentations

For understanding immunogenicity risk, tools include cell line assays, PBMCs, mixed cultures, monocyte and Xeno-het mouse models (ability to be tolerant to an attribute but still retain ability to respond immunologically if tolerance is broken).

It was noted that when working with isolated species it is really important to understand what the material contains.

For HMW, even high levels of material did not break tolerance in Xeno-het or activate the in vitro assays. Prior/published knowledge and clinical data also has not shown any impact of HMW.

With partial molecules, PBMCs/Monocytes did respond but cell lines didn’t, so an attribute with potentially higher risk.

With Hydroxylysines, even high levels did not appear to induce any responses in the various assays.
Themes from the Morning Presentations

Prior/published knowledge is available for several examples of quality attributes:

Methionine oxidation in the Fc of MAbs impacting receptor binding/PK thus considered a CQA (but only if on both chains).

Charged variants of Mabs show moderate impact on bioactivity but not FcRN binding.

Looking at material extracted from patients, deamidation occurs in vivo – so lowering relevance to setting lot control testing or limits.

Glycosylation appears to impact in a molecule specific manner, so generalities should be approached with caution.
Morning Panel Discussion

John Ayres, *Pharma Safety Solutions, LLC, USA*

Gerald Gellermann, *Novartis Pharma AG, Switzerland*

Marisa Joubert, *Amgen Inc., USA*

Jochen Felix Kepert, *Roche Diagnostics GmbH, Germany*

Anthony Ridgway, *Health Canada, Canada*

Mats Welin, *Medical Products Agency (MPA), Sweden*
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity.

**Immunogenicity Testing**

Immunogenicity models in general are not directly predictive of what will happen in humans. However, they are useful to risk rank attributes and provide some assurance of potential for immunogenicity. A ‘low’ prediction using these models on their own might not be acceptable to rank the criticality of an attribute but using additional prior knowledge, clinical data, etc., a totality of evidence can help justify the final control strategy.

The Xeno-hat model presented was IgG2 specific but transgenic mice can be created for any protein. Mice solely transgenic for tolerance for a particular protein in general can have suppressed immune systems – so adding in wild type genes brings back a robust immune response.

When characterizing aggregates it is apparent that a partially folded structure is more immunogenic whereas totally degraded and normal structures appear less or non-immunogenic.
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity.

**Immunogenicity Testing**

Although not directly linked to clinical outcome, PBMC assays are being used to screen molecular candidates. Apart from antibody immune responses, clinical adverse events such as injection site reactions, hypersensitivity etc all need to be looked at that could elude to immune responses occurring.

**Further Justification of Criticality**

To maximize the value of non pivotal clinical studies – e.g. Phase 2 and dose range studies, it would be good to have them look for events (e.g. immunogenicity). Even though not there may not be enough patients might not get statistical significance, they can be informative and give some level of assurance.

The use of aged material within expiry in clinical studies should be encouraged to allow for testing of attributes that increase over time.
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity.

**Further Justification of Criticality**

For attributes where there are regulatory/compendial limits (e.g. Host Cell DNA or Endotoxin) it may not be required to have limits based solely on clinical exposure or process capability. Although it is important to have some level of control testing (IPC with action limits) to ensure that consistency in process does occur and an unexpected result is investigated.

Some attributes can be ‘validated out’ based on process capability (HCP or DNA). One needs to consider the whole clinical picture when assessing risk - disease type, patient population, route etc.

Getting samples back from patients seems to be getting more activity across companies. Regulators consider it a useful tool to understand what is actually happening in patients and valuable for gathering of knowledge.
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity.

**Further Justification of Criticality**

Although several companies have specifically put end of shelf life material in clinic to expand specification limits, there hasn’t been a challenge in pushing process limits to create more higher levels of attributes in the clinic. If one only uses data when running in the middle of the process control limits, will this reflect what could occur in day to day manufacture.

Even though one can’t power clinical studies to look for direct clinical impact for individual attributes, ‘some patients got it’ appears a better approach than no data in the clinic at all.
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity

Other considerations

There were no examples of companies giving a higher level of a specific attribute in a clinical study beyond what would reasonably be expected during normal manufacturing as deemed unethical.

An interesting discussion occurred where a company is producing two products to be given together - should one link specification limits between the two drugs?

Although no answer, it was a paradigm worth considering.

During development you will likely have less criticality data and thus more specifications early on – as you gain more knowledge you can remove specification tests.

It was proposed that one shouldn’t have specifications way beyond what you have put into patients because you can’t ignore what your process capability is.

Is it time to revisit ICHQ6B? Many agreed that it could be updated but no need to rewrite it - maybe Q&A clarification of content.
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity

Other considerations

It was recommended to have clinicians who understand CMC and product involved with specification setting early on during development and QTTP formations as well as when deciding if to make process changes (e.g. might contribute to a safety monitoring plan if going into the clinic).

At the end of the day, using the principals of a risk based, patient focused process allows a company to use resources appropriately to look at what is critical versus measuring every attribute, critical or not or regardless of level in product.
Afternoon Session

Developing Patient-focused Specifications

Session Chairs:
William Egan, GSK Vaccines and Anthony Ridgway, Health Canada
Afternoon Agenda

Best Practices for Setting Patient-focused Commercial Specifications
Darrin Cowley, AstraZeneca, Gaithersburg, MD USA

Justification of Specifications Compared using Traditional versus a Risk-based Approach
Gerald Gellermann, Novartis Pharma AG, Basel, Switzerland

IQ Consortium Biologics Working Group on Specification Setting Strategies
Juliana Kretsinger, Eli Lilly and Company, Indianapolis, IN USA

Clinically Relevant Specifications: Case Study and Summary of Discussion at the BioPhorum Development Group Meeting
Taro Fujimori, AbbVie Bioresearch Center, Inc., Worcester, MA USA
Themes from the Afternoon Presentations

There is a difficulty in setting specs when we have less lots in the clinic as we get better with yields and purity early during development. There won’t be enough data to make statistically justified limits.

A step-wise approach can be used to develop the control strategy. Understanding what your attributes are, taking all data available to assign criticality, developing methods that focus on critical quality attributes, measure the attribute where it can actually be controlled and to remove redundant testing (e.g. between DS and DP).

Controlling quality attributes through raw material and process controls can allow for reduced testing - the ‘overall control strategy’, not focused just on lot release assays ‘testing quality in’.

Start with clinical exposure – add on statistical process variability – add prior knowledge based on clinical exposure of other relevant products – add on in vitro/animal data/publications.

One can move testing from DS to DP (e.g. potency) and move many to IPCs or process control measures (e.g. pH, osmolality).
Themes from the Afternoon Presentations

An example was presented about Asp-329 for an IgG1 where it is impacting for potency but only at higher levels. Studies showed that it was created under conditions not seen during manufacture (high temperatures and pH). Negligible amounts occur over time or are found in the product. Using this data it was justified not to have a specification.

When justifying specifications there can be a traditional or risk based approach. Traditionally we have clinical production lots where we can add on stability increases for an attribute and add on statistical variation of batch production. In a risk based approach looks at criticality of attributes and potential impact on safety and efficacy.

A cumulative approach was described were worse case impact of all variants changing over time and what impact they have on potency. If all was acceptable it allowed for increasing specification limits and/or moving testing to in-process. The use of the quality system to monitor these process controls reduces the overall risk and need to have the attribute on the specification.
Themes from the Afternoon Presentations

The Innovation and Quality IQ consortium was described whereby their mission is to identify challenges for biologics development and share best practices and advance new technologies etc. The specifications working group has worked on early phase and patient focused specifications.

For early phase specifications, 80% of companies use platform specifications. 60% use ‘report results’. ‘Compare to reference’ is a popular identity test specification. There was often extra testing beyond lot release, to gather more information.

Patient focused specifications is a term replacing clinically relevant specifications. Based on existing tools and data, can we build a standard approach for justifying ranges beyond clinical experience?

Case studies were presented using clinical experience in different trials, indications and doses and tying in PK modelling with acceptance of 80-120 comparability that allowed for an assessment of impact that could provide for wider oligosaccharide limits.
Themes from the Afternoon Presentations

Lifecycle management of specifications can include additional studies of Mechanism of Action, improved analytical technology, expansion of indications etc. that may allow revisiting of specifications.
Afternoon Panel Discussion

Barry Cherney, Amgen Inc., USA
Fiona Cornel, Health Canada, Canada
Darrin Cowley, AstraZeneca, USA
Taro Fujimori, AbbVie Bioresearch Center, Inc., USA
Gerald Gellermann, Novartis Pharma AG, Switzerland
Juliana Kretsinger, Eli Lilly and Company, USA
Kavita Ramalingam Iyer, Merck & Co., Inc., USA
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity.

The Mab used in examples for the oligosaccharide profile of a Mab was not an approved product but the higher level beyond the clinical experience was not questioned during the filing process. Whether these findings would be applicable across all Mabs was discussed but there was no consensus if this was appropriate.

Mass spectrometry and other assay technology studies have been used with patient material to justify limits and got approval.

In the case of the asparagine deamidation case study where the levels were no longer tested, they included shipping and stability testing and were levels were low in product in the first place – 20-30x required to have impact.

An update on the progress of the multi attribute method revealed challenges in QC. However, MAM has replaced some tests under IND – the ETT team is still working with the company. Another company uses MAM in development labs but not QC.
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity.

A biosimilar has its own specifications and is showing similarity to the reference product. The sponsor will get reference product and do head to head clinical studies – can the information coming from those studies be useful for understanding criticality?

There is now a wealth of data for prior knowledge, including a long lifecycle of product data for the innovator over time. In terms of setting specifications, the biosimilar company uses prior knowledge from the innovator product if published.

What is the value of having clinical studies at the end of expiry – does it confirm the attributes that were selected are relevant? There was agreement it is valuable plus including in use conditions and time, but one must know what level of attribute is in those samples. There is a need to consider what type of study – extension, pivotal, number of patients, exposure time etc. and needs to be explained in a filing.

The cumulative approach presented focused on potency. For PK and other impacts one can use prior/public knowledge to understand which attributes could be impactful.
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity.

With PK modeling it could be more robust to look for PD as the 80-125 limits for bioequivalence are somewhat arbitrary.

There is a trend towards a more end to end control strategy with incoming material controls, IPCs, Real Time Release and not only specifications. Process control should assure the product quality appearing at lot release.

Regarding the use of animal models to assess safety and efficacy of attributes is was considered as useful- an understanding of how that links to humans is important but not always essential if looking for relative effects. Any data reduces the uncertainty. If you have a zero concern and there is no data to show anything to the contrary that should reduce the criticality of the attribute. If there is concern and this too can be substantiated through data outside the clinic, it suggests the attribute should be considered critical.
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity.

There is a need to provide the background of the animal models to regulators so they can understand how they work and their relevance. Where does such data go into a file? Usually in the justification of specifications or product characterization sections. It is a good practice to have a note to the reviewer where it is or as a road map.

The role of dose ranging studies, especially when looking at maximum tolerated dose, can provide some data on safety. Some studies can look at efficacy as well. Immunogenicity is harder to see from these smaller studies. But it does depend on the attribute you are looking at.

CAR-T cell products can fail specifications - if in clinical studies a patient can remove themselves from a trial and the medic can decide to dose regardless. If commercial regulators do lot by lot release then the agency can allow dosing if the manufacture starts a new trial - or require dosing under an IND. If the material is successful this can update and widen specifications.
The attendees of the CMC Strategy Forum are asked to point out aspects in the presented best practices that need further clarity.

With breakthrough products maybe the same approach as CAR-T cells can be used with product that doesn’t meet specifications still going into patients and expanding specifications over time.

There are many cases where expanded attributes are included in clinical studies and specifications have been widened.
Special Thanks to...

CASSS Staff:

- Karen A. Bertani, CMP, Director, Global Engagement and Knowledge Sharing (CMC Forum Manager)
- Stephanie L. Flores, CAE, Executive Director
- Julie Fowle, CMP, Program and Event Planning Specialist
- Anna Lingel, CMP, Exhibitor Relations and Technology Specialist
- Renee Olson, Senior Program Manager
- Catherine Stewart, Finance Manager

Audio-Visual Support:

Michael Johnstone
MJ Audio-Visual Productions