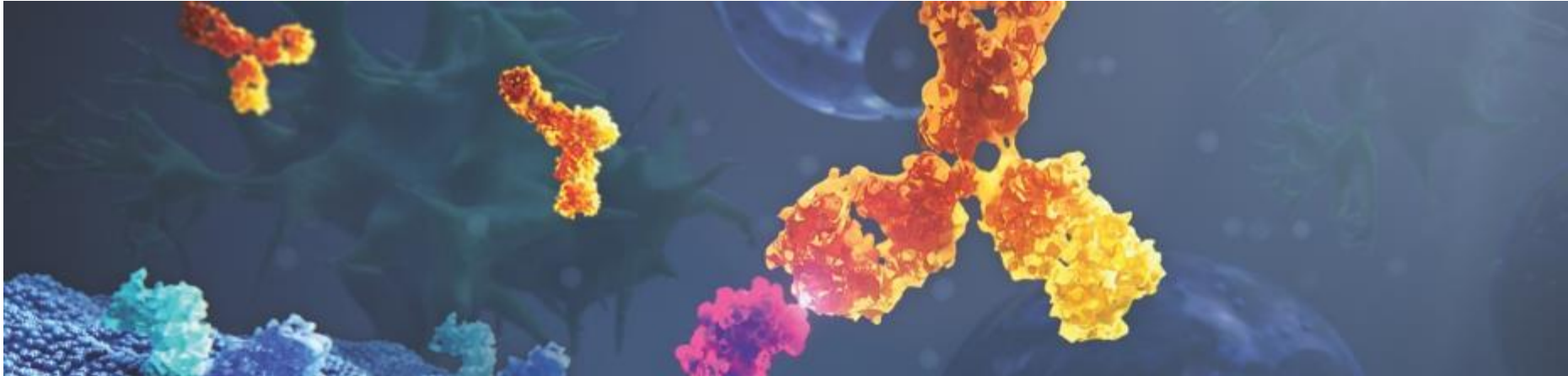


Strategies for Setting Patient-Centric Quality Standards

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Problem Statement – The Traditional Approach to Specification Setting

- Without a broader understanding of patient centricity with respect to quality attributes, a proposed control strategy (e.g., specifications and other CMC elements) is largely based on what material was provided during clinical trials, mainly at the pivotal stage.
 - Basing specifications on clinical trial material alone may result in specifications being set conservatively.
 - This particularly presents a challenge for products where only a limited number of batches are manufactured prior to submission of a dossier (e.g., products under accelerated pathways and cell and gene therapies).
- Overly restrictive specifications that are not based on patient-centric risks may result in the rejection of [otherwise/demonstrably] safe and effective products, and can lead to shortages or stock-outs.
- The traditional specification setting approach can also cause a higher lifecycle regulatory burden for both industry and regulators as new variations/supplements are often needed to adjust specifications post-approval.



Problem Statement – Applying a Patient-Centric Approach to Specification Setting, Continued

- Even if a Patient Centric approach to specification setting is deemed acceptable, without clear guidance, Industry / Regulators may be limited in fully implementing the approach.
- While there is general agreement that prior knowledge can be used to justify the design of the control strategy, there are no guidelines for industry on how to utilize various data sources (e.g., publications, modelling) to set specifications, the extent of supporting information expected, or where to put that data in a dossier to provide a comprehensive rationale for regulator evaluation.



Patient Centricity

- Fundamentally, the patient centric approach simply involves setting specifications based upon all available pertinent knowledge and information including data from:
 - Preclinical and Clinical trial materials,
 - Product specific knowledge from other studies (e.g. in vitro / in vivo animal studies)
 - Prior knowledge from related products and processes
- A critical facet of a PCQS approach is that “patient relevance” is not the same as clinical trial experience.
 - Patient relevance relates to the risk that a quality attribute may impact safety and efficacy when the product is administered within the potential exposure range.
 - A quality attribute can be considered to be “qualified” as clinically relevant based upon data that substantiates its relationship to safety and efficacy; this data is not necessarily limited to that generated from clinical trials.



Examples of Product Specific Knowledge Additional to Clinical Outcome Data

- Use of material in clinical studies closer to expiry with potential to have increased levels of certain quality attributes
- Taking serum samples from patients to see how product behaves in vivo
 - PK/PD of various glycoforms
 - Deamidation or oxidation
 - Clipped forms
- Incubating product in patient serum in vitro
- Purifying attributes and understanding their relationship to potency
- Non clinical studies



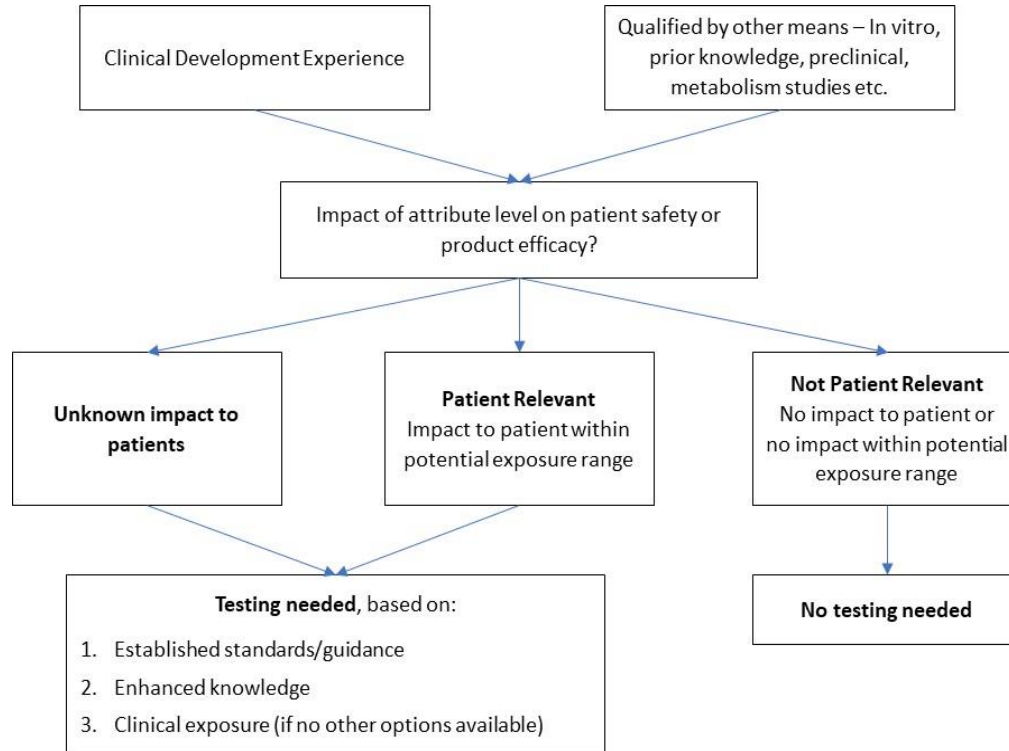
Ways to Increase the Value and Applicability of Prior Knowledge

- Prior knowledge needs to be documented in a form that is easily communicated/understood for use in process/product development activities and regulatory filings
- Industry needs to work with regulators to identify type and extent of information/data needed to support establishment of patient centric control strategies and specification ranges
- Industry needs to identify and address gaps in the understanding of attribute impact and publish findings in literature to build cross-product/cross-industry knowledge database
- Product developers and regulators need to share a consistent, scientific understanding of the available prior knowledge and level of understanding in order to facilitate the development of products

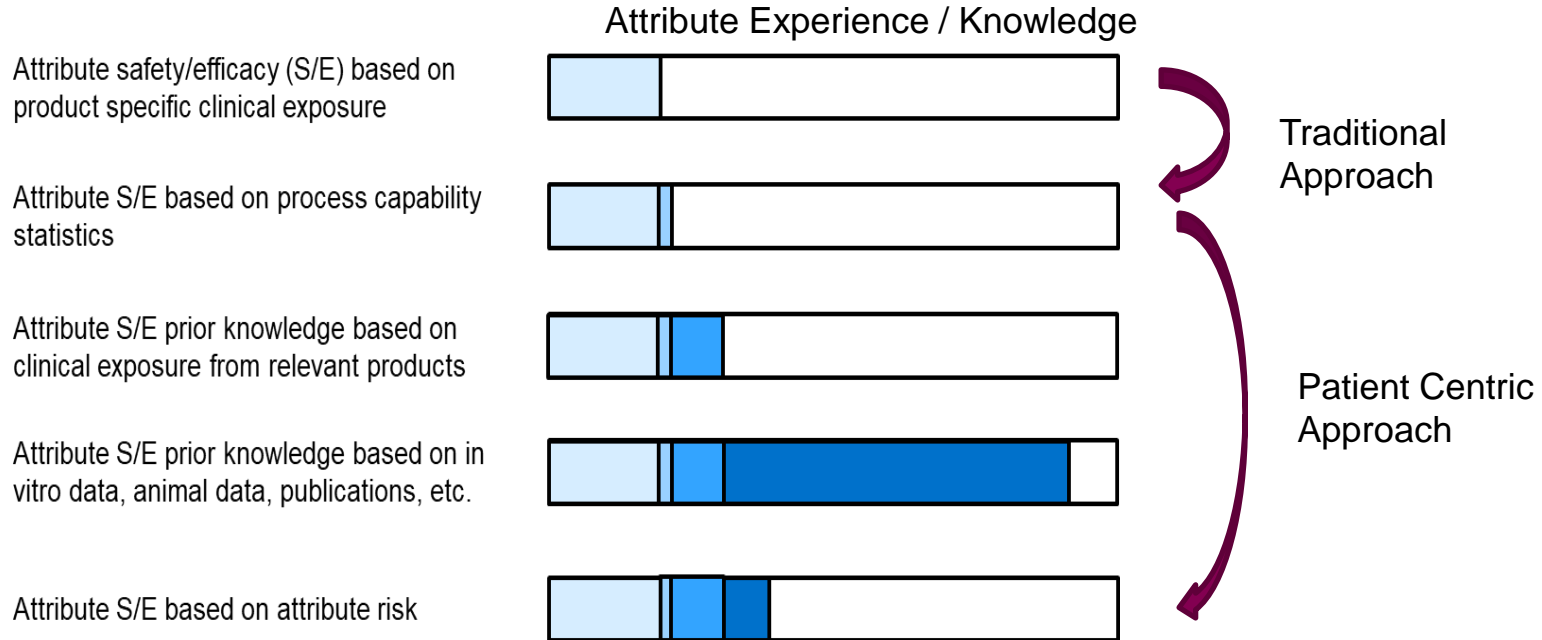


Patient-Centric Control Strategy

Pathways to differentiate the need for routine testing for a product quality attribute in the PCCS



Establishing Patient-Centric Acceptance Criteria



*Figure in Paper / Similar to figure in :
D. Cowley, CASSS CMC Strategy Forum, Jan 2019

**Requires Robust
Justification**



Acknowledgments

- PhRMA Patient Centric Working Group

