What is meant by patient-centric quality standards?

Phil Krause

Independent consultant

Biologicals
Volume 88, November 2024, 101796

Editorial

A vision for patient-centric specifications for biologicals

Philip Krause, Cristiana Campa, Andrew Chang, Shawn Novick, Barbara Rellahan, Tim Schofield, Dean Smith

https://doi.org/10.1016/j.biologicals.2024.101796

Definitions related to Quality Standards

- *Specifications* define the tests and acceptance criteria for tests performed to release product lots, assuring that products will be acceptable for their intended use and yield the expected outcomes associated with labelling.
- *Critical Quality Attributes* (CQAs) are properties or characteristics of a product that should be within an appropriate limit, range, or distribution in order to assure the desired product quality (ICH Q8 (R2)1.
- ***Patient-centric Definition of Quality*** (PCDQ) includes ranges or distributions of CQAs that assure the desired product quality (i.e., quality standards). The PCDQ is supported by scientific knowledge or evidence. For a specification to be considered patient-centric, it must be consistent with the PCDQ.
- *Quality Target Product Profile* (QTPP) may include a proposed PCDQ as one of its elements.

Specifications and the PCDQ are different concepts because the PCDQ is defined in the context of the potential impact on product safety and/or efficacy and motivates the control strategy, while specifications are a component of the control strategy that define the tests and acceptance criteria a product must meet to be released.

Harmonizing around patient-centric quality standards

- Different approaches to setting specifications in different regulatory jurisdictions can lead to varying global expectations for the identical product, with major disadvantages for developers and patients.
- It is not “patient-centric” if differing specifications influence product distribution, which has the potential to lead to regional differences in product quality. Once acceptance criteria have been registered, it is very difficult and time-consuming to coordinate changes across multiple National Regulatory Agencies (NRAs), which can lead to overly complicated global supply chain networks and potential drug shortages.
- Ambiguity regarding whether specifications are intended to support quality or consistency is a major cause of differing expectations around the globe.
- Additionally, some developers are requested by regulators to tighten specifications after approval as more manufacturing data become available, potentially resulting in clinically acceptable batches that yield test results consistent with the PCDQ being rejected.
- Harmonizing around a scientifically valid approach could solve these problems
  - Build on QBD, product and process understanding
  - Support ICH Q8-12
  - Timely given ongoing update of ICH Q6

What should patient-centric quality standards look like?

- Commercial product is expected to have quality consistent with the safety and efficacy profile established at the time of authorization.
- The PCDQ must be defined in terms of its relationship to safety and efficacy and is influenced by the product's defined safety and efficacy profile in pre-licensure clinical studies.
- While the PCDQ describes a range on a CQA for which safety and efficacy has been established, whether through preclinical or clinical studies or as supported by prior knowledge, there is no requirement to identify the entire range that would ensure safety and efficacy for any CQA.

Sources of information to support Quality standards: Clinical studies

- Based on ranges in the levels of product attributes evaluated in the clinical development program.
  - This may include results from early dose-ranging studies or formulation studies
  - Where feasible, test product spanning an appropriate range in the level of key attributes to define the PCDQ.
  - For example, regulators have endorsed clinical testing of some vaccines using product at end-of-shelf-life potency to define a minimum efficacious potency level.
- There may be tension between studying product with attributes that carry some risk to efficacy and failing to obtain adequate data to support reasonable specifications for commercial product, and discussion of plans for obtaining such data should be discussed with regulators.
- Clinical data from different indications for the product may also be useful.
- PK/PD data from clinical studies can also provide key insights into attribute ranges that are associated with efficacy.

Sources of information to support Quality standards: Preclinical studies

- in vitro model systems examining pharmacology, toxicology or immunogenicity, and analytical studies examining structure-function relationships can provide data relevant to the potential biological impact of an attribute and the degree of sensitivity of a product to changes in certain attributes
- PK/PD data

Sources of information to support Quality Standards: Prior knowledge

- Prior knowledge from related products, including from products manufactured on the same platform (e.g., mAb, mRNA vaccine, etc.), can also provide key information.
- Prior knowledge relevant to attribute criticality and the potential (or lack of potential) for there to be a clinical impact within a proposed specification range.
- Prior knowledge based on clinical exposure to relevant products or relevant *in vitro*/*in vivo*/*in-silico* data, publications etc. may also inform assessment of the likelihood that the attribute will influence safety or efficacy.
- E.g., PCDQ for host cell proteins can be established based on known safety of other products containing the same host cell proteins, and determination of whether certain glycosylation patterns are relevant to efficacy may be informed by preclinical models.
- E.g., PCDQs may also be readily established for attributes that influence potency and stability. For example, if pH influences stability, the PCDQ for pH should be established to assure adequate potency and purity at end of expiry.

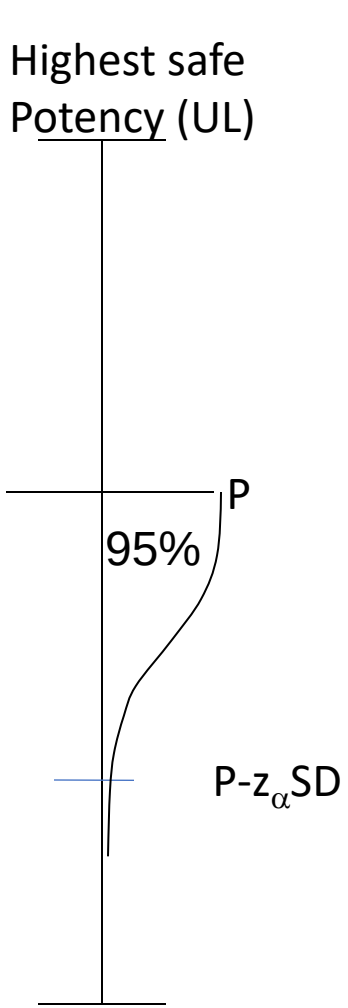
What if the only relevant information is from the batches used in the clinical trials?

- A developer may justify a PCDQ for a given CQA based on assuring that marketed product will be as similar as possible to that shown to be safe and effective pre-licensure.
- This is sometimes done by establishing specifications only as broadly as is consistent with the ability to manufacture the product while remaining aligned with the quality, safety and efficacy profile studied pre-licensure.
- As long as this range is justified in terms of its potential impact on safety and efficacy, this range represents a PCDQ for that attribute.
- BUT:
  - Once specifications are set in this manner, there is no justification for further narrowing of those specifications based on future manufacturing data.
  - Variables include: which lots to include, how many lots to include, diverse views on statistical approaches, and divergent health authority expectations.
  - Usually more conservative than broader approach that accounts for other relevant information, which could limit patient access to additional product lots that are clinically equivalent,
  - Increases the challenges of implementing chemistry, manufacturing, and control (CMC) changes and the likelihood of product shortages.

Specs and the PCDQ

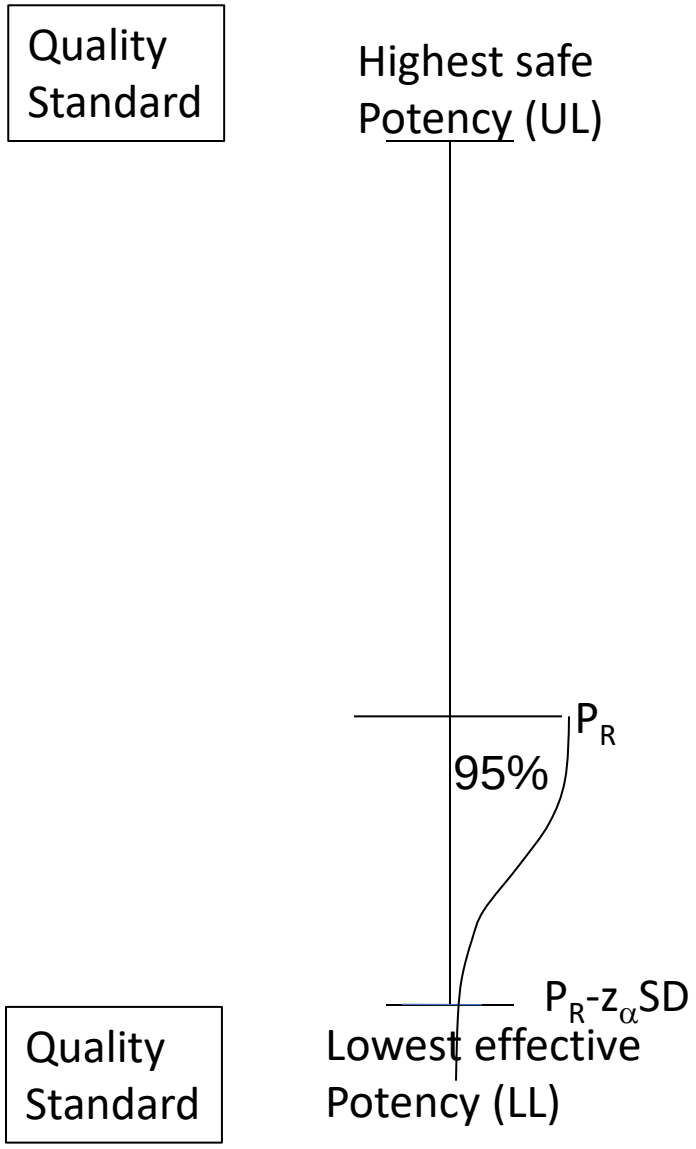
- PCDQ is defined in the context of the potential impact on product safety and/or efficacy and motivates the control strategy
- Specifications are a component of the control strategy that define the tests and acceptance criteria a product must meet to be released. Specifications often account for **assay variability and product stability**, which provides assurance that the PCDQ will be met through shelf life.
- However, the close relationship between specifications (as acceptance criteria on tests intended to measure CQAs) and the PCDQ (describing ranges on CQAs needed to assure product safety and efficacy) implies that specifications can be patient-centric only when they are aligned with a PCDQ.
- All specifications should be derived from CQAs, but not all CQAs require a specification
- The relationship between specifications and PCDQ can be modelled, e.g. with assay variability and stability data
- Where substantial knowledge is obtained to establish a PCDQ, specifications may be directly derived from the PCDQ range. Alternatively, a PCDQ can also be proposed with reference to a desired specification range, and justified on the basis of appropriate information, as may occur when a developer needs to be able to assure that a manufacturing process will consistently yield a product that meets the PCDQ.

Modeling assay variability in release specifications



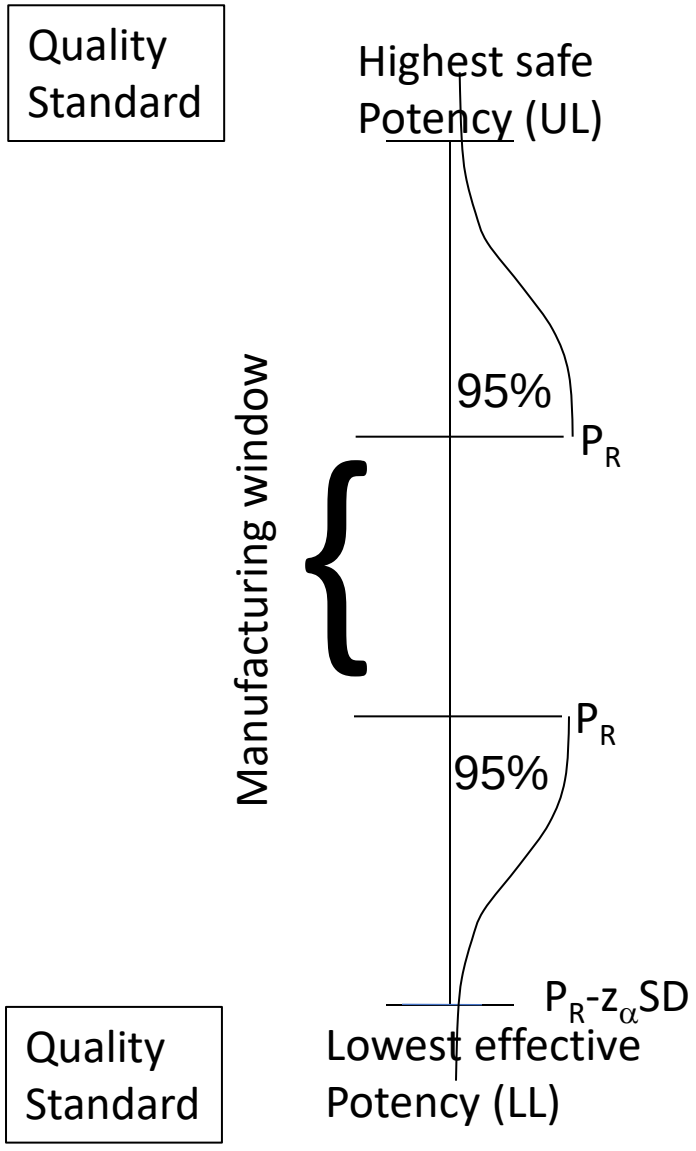
- A lot released with a mean potency of P may have actual potency less than (or greater than) P, due to assay variability
- Releasing a lot with a potency of P is tantamount to saying that the 95% lower confidence bound on this value is acceptable
- Thus, it is important to know:
  - the 95% lower bound on potency
  - Whether this 95% lower bound exceeds “LL”, the lowest potency believed to be effective

Modeling assay variability in release specifications



- A lot released with a mean potency of P may have actual potency less than (or greater than) P, due to assay variability
- Releasing a lot with a potency of P is tantamount to saying that the 95% lower confidence bound on this value is acceptable
- Thus, it is important to know:
  - the 95% lower bound on potency
  - Whether this 95% lower bound exceeds "LL", the lowest potency believed to be effective
- Minimum release potency (P_R) should provide assurance that the 95% lower bound exceeds LL
- This model can also be used to determine how stability should influence specifications

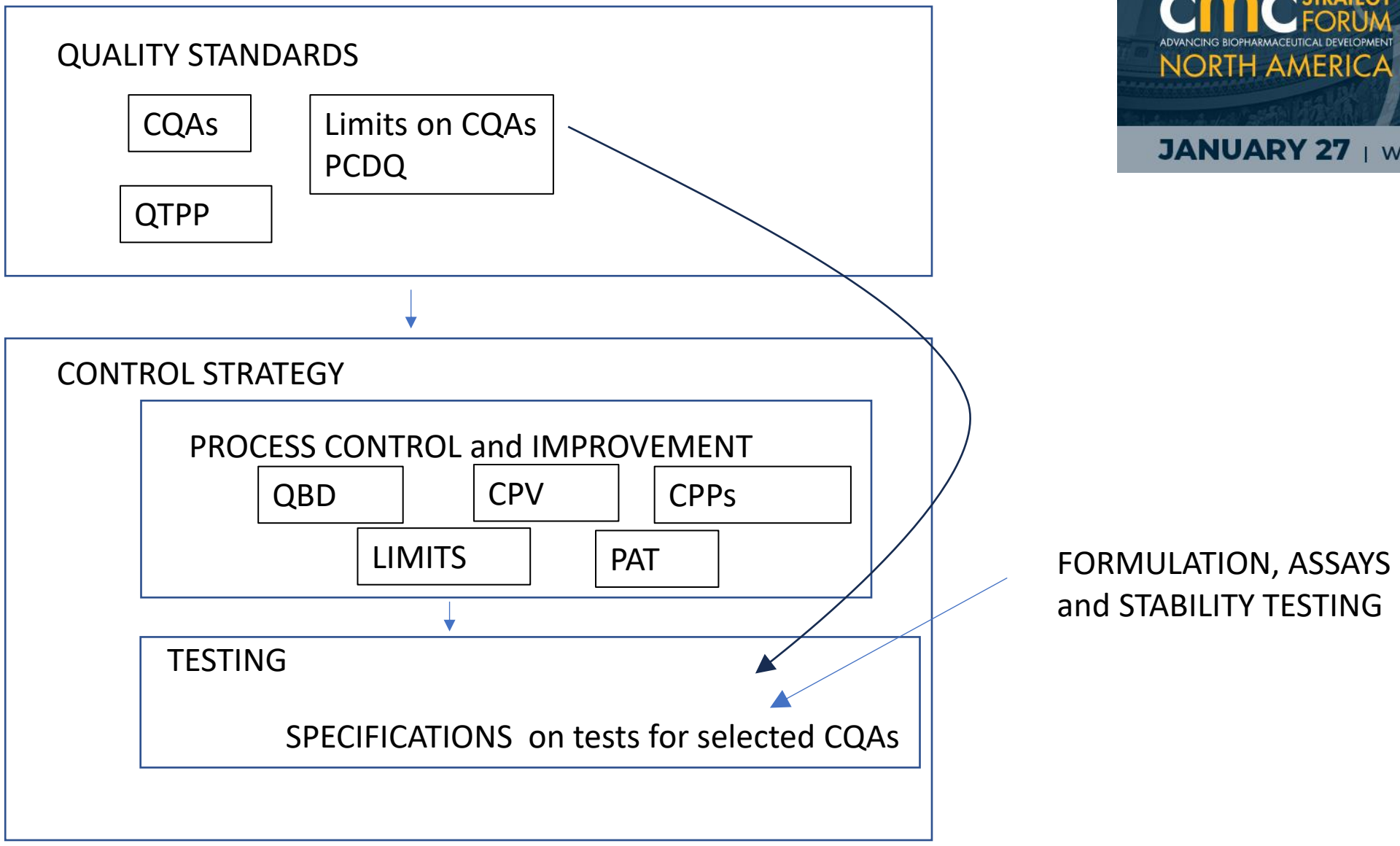
Modeling assay variability in release specifications



- A lot released with a mean potency of P may have actual potency less than (or greater than) P, due to assay variability
- Releasing a lot with a potency of P is tantamount to saying that the 95% lower confidence bound on this value is acceptable
- Thus, it is important to know:
  - the 95% lower bound on potency
  - Whether this 95% lower bound exceeds "LL", the lowest potency believed to be effective
- Minimum release potency (P_R) should provide assurance that the 95% lower bound exceeds LL
- This model can also be used to determine how stability should influence specifications
- Similar considerations apply for upper limits

Integrated control strategy

- The integrated control strategy is used to manage product consistency while assuring that the product will meet expectations for quality embedded in the PCDQ, and comprises
  - manufacturing process design,
  - control of the manufacturing process (including control of material inputs, critical process parameters, and use of in-process limits)
  - quality/risk management system
  - testing (including adherence to specifications)
- The process should be designed to assure that product of defined safety and effectiveness will be consistently produced.
  - Incorporating QbD principles, including strategies for process design, identification of critical process parameters, principles of design space or process knowledge, process analytical technologies, strategic post licensure change management, and quality and risk management systems, can help to assure a robust manufacturing process.
- The quality/risk management systems typically include routine and non-routine controls which monitor and assure, among other things, process consistency, and product quality and stability.
  - The control strategy also may include continuous/continued process verification (CPV) which may lead to process improvements. CPV typically includes consistency elements such as internal trending limits that are based on historical process performance with the intent of identifying unexpected performance events (e.g., OOT events).
  - The trend limits also act as early warning signs of a potential issue and result in corrective and preventive actions as needed to ensure consistent process performance. Trending of test results and other strategies may trigger investigations that help to improve manufacturing and assure that the process remains under control.



Patient-centric quality standards support patient-centric specifications

Specs and product control

- Batch release testing is required by regulators to assure that each product lot meets the pre-defined expectations for quality embodied in the specifications and thereby the corresponding PCDQ. These specifications, in turn, may inform process design because the process must be capable of consistently delivering product that meets specifications.
- Critically, in a patient-centric paradigm, specifications play a role in quality assurance, but are separate from methods to assure manufacturing control.
- Lot release testing is not intended to be the primary assessment of manufacturing control, but instead an important assessment of product quality.
  - When a robust quality system, including CPPs, alert and action limits, a robust analytical strategy (for in-process and specification tests), appropriate statistical modeling, etc. is in place, while specifications provide confirmation of product safety and efficacy, they provide no added value in manufacturing control.
  - Setting narrow acceptance criteria for the purpose of monitoring process consistency, as is sometimes considered an appropriate interpretation of ICH Q6 Guidelines, does not work, in part because it is unclear how an individual result on a single batch should be interpreted in the context of process performance.
  - Indeed, if assays are imprecise and the process is inherently consistent, extreme test results may more likely be the result of assay variability than an out-of-control process, especially where specifications have been set tightly around manufacturing variability.
- In a patient-centric paradigm, the PCDQ should be based on expected patient outcomes, and specifications are defined in a manner consistent with the PCDQ.
  - Because product is manufactured using a process designed to produce consistent product, it should be very unusual that a lot would fail to meet its specifications.
  - Thus, in the context of a well-designed manufacturing process and control strategy, specifications play a confirmatory role assuring a batch will meet its intended safety and efficacy profile.

Sponsor considerations

- CQA ranges that provide manufacturing, stability, and lifecycle flexibility can be supported when sufficient knowledge is available to justify that the range assures predicted safety and efficacy. Considerations include:
  - availability of technologies and models for defining limits
  - constraints on clinical material manufacture and clinical trials conduct
  - prospect of utilizing relevant knowledge across relevant products
  - anticipated product life-cycle changes to support shelf-life extensions, to address in-use considerations, or to improve drug delivery or product tolerability
- Companies are less likely to make the investment in obtaining this knowledge if it is unclear that regulators will allow this definition of product quality to influence the product control strategy, or if having provisionally accepted this approach at licensure, regulators subsequently require tightening in line with improving assay or process capability.
- Therefore, establishing a PCDQ to support specifications provides manufacturers flexibility when appropriate but assures that all attributes are controlled to levels that maintain safety and efficacy consistent with that demonstrated during preclinical and clinical development.

Key Principles

- The patient-centric approach is premised upon the development of limits that predict safety and efficacy of a biological product and should be distinguished from limits that are calculated based upon the variability of CQAs during routine manufacturing. Defining the PCDQ as a part of specifications development comes with a proactive vision for product development. Here, clinical and CMC studies are designed and conducted to address priority issues with an eye towards reduction of risks to process and patient outcomes.
- A consequence of this patient-centric approach is that quality standards (i.e., the PCDQ) are at the heart of the control strategy for critical quality attributes. As long as specification acceptance criteria ranges are aligned with the PCDQ, product quality will be confirmed by a passing test.
- Developers may collect information to define ranges that support a broader PCDQ for key CQAs in order to extend the acceptable range of the corresponding specifications, and thereby enable continued process improvement while assuring product supply.
- The manufacturer is rewarded for investing in process and product understanding and development of a Quality/Risk management system, and not penalized by being required to tighten acceptance criteria to reflect what is seen in a moment of time, or disincentivized to improve method or process capability.
- It is recognized that as developers and regulators gain experience in implementing the patient-centric approach, strategies for establishing, implementing, and harmonizing the PCDQ will evolve.

Advantages

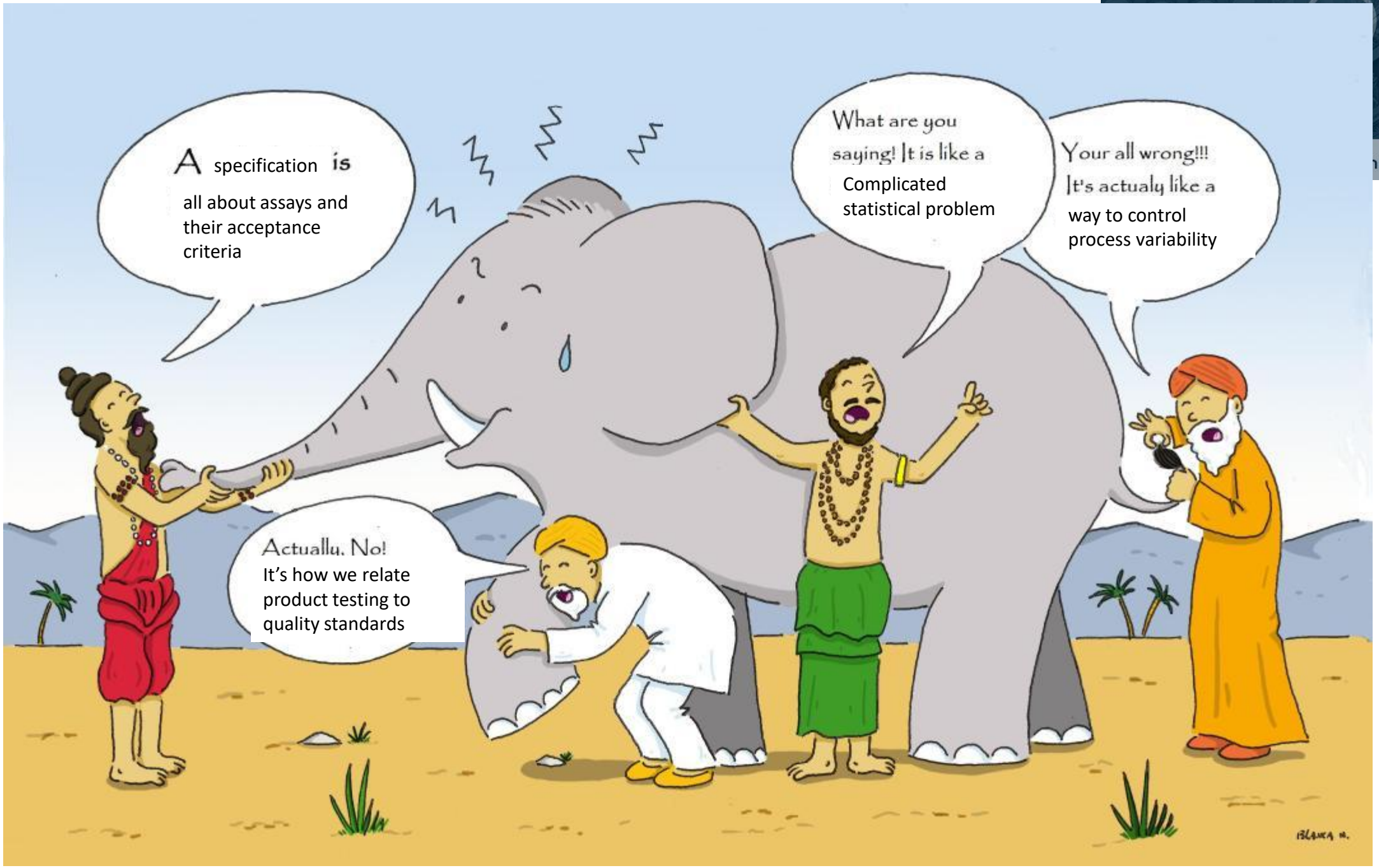
- Advantages for **the patient** of this approach include assurance of product quality, and reduced likelihood of product shortages that may be caused by inappropriately narrow acceptance criteria. Moreover, this approach will facilitate earlier patient access to new or improved medicines.
- Advantages to the **developer** may include fewer out-of-specification results, adequate shelf life, and room to monitor and control the process within the quality system, facilitating technology transfer and introduction of control strategy innovations during the product lifecycle. Harmonization of acceptance criteria on the basis of patient centricity reduces the risk of disparity of global reviews, and the need to change specifications over the product lifecycle. This also provides increased flexibility to monitor and to improve the product or process with fewer global regulatory interactions. A sound post licensure change management system that includes CPV will facilitate process monitoring and improvements.
- Advantages to **regulators** may include reduced need to review “out-of-specification” results and to review specification changes that are unrelated to product quality, while increasing confidence that batch approval is associated with quality and expected patient outcomes, leading to a more reliable global supply of medicines. Meaningful investment by the developer in understanding safety and efficacy leads to increased confidence in a manufacturer’s post licensure change management system, which facilitates routine manufacturing and analytical changes, reducing the burden on regulators to oversee these activities.

Implementation/Vision

- Global and regional guidelines should describe the relationship between quality standards (i.e., the PCDQ) and specifications
  - Potential implications for nonclinical and clinical study design could be included.
- Implementation by individual companies, with adequate supporting data and careful review by regulators empowered by companies to exchange data and perspectives with other relevant agencies, will provide the opportunity for industry to:
  - explore alternative strategies using current and evolving technologies
  - share their experiences
  - build scientific strategies which can be adopted and refined over time.
- With a broader body of experience, the patient centric approach will drive industry, regulators, ICH guidelines, and compendia towards consensus on acceptable strategies for establishing the PCDQ and corresponding control strategy, including specifications, and ultimately support harmonization of review and of product quality

Ideally,

- Specifications (CQAs) are set based on internationally agreed-upon scientific principles
  - Specifications must be patient-centric wherever feasible
  - This can only be accomplished where there is an appropriate quality standard (patient-centric definition of quality)
- There is a prospectively developed plan to develop data to support specifications
- Manufacturers come to all relevant regulators to discuss plan to obtain data to support desired specifications early in the process
- Harmonization of specifications is an important goal of product development
- Future discussions of specifications must recognize patient-centricity as their primary function. While each product is different, developers should be encouraged to invest in exploring attribute ranges and development of an overall control strategy including specifications that provides sufficient control over the applicable critical quality attributes, consistent with a PCDQ-based quality standard.


A specification is
all about assays and their acceptance criteria
Actuallu. No!
It's how we relate product testing to quality standards
What are you saying! It is like a
Complicated statistical problem
Your all wrong!!!
It's actualy like a
way to control process variability