Summary of outcomes and key messages from previous GHS meetings:

Meeting the challenge of clinically relevant specifications

Phil Krause

Former Deputy Director, FDA/CBER/OVRR

Independent Consultant

With thanks to many

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Editorial

A vision for patient-centric specifications for biologicals

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

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How do we define clinically relevant quality? The CRDQ:

- *Patient-Centric* means that patient outcomes drive our strategies and their implementation. While all approved products may achieve favorable benefit-risk to patients, in the current context we talk about how to use specifications and control strategies to accomplish this.
- *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.
- ***Clinically Relevant Definition of Quality*** (CRDQ) includes ranges or distributions of CQAs that assure the desired product quality (i.e., **quality standards**). The CRDQ is supported by scientific knowledge or evidence. For a specification to be considered clinicall-relevant, it must be consistent with the CRDQ. Note that we previously called this the Patient-Centric Definition of Quality.
- *Quality Target Product Profile* (QTPP) may include a proposed CRDQ as one of its elements.

Specifications and the CRDQ are different concepts because the CRDQ 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.

The CRDQ and associated specifications connect clinical and CMC domains

- Clinically Relevant Specifications: A set of tests and acceptance ranges to which product quality attributes should conform for the product to be safe and effective when used as labeled.
- 21 CFR 211.160 (b) Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity.
- Appropriate = clinically relevant and related to safety and efficacy
- Note that the regulatory definition does not say anything about use of specifications to monitor the manufacturing process

Example 1

- Product evaluated and approved in many countries, supported by studies consistent with the absence of a rare, serious, but plausible adverse event
- Regulator A licenses the product without an upper limit on a critical quality attribute (CQA) plausibly associated with this adverse event
- Regulator B later raises concern that the clinical studies supported product safety only when this CQA was at or below levels tested in the safety studies, and sets an upper limit on the CQA

Example 1 (cont)

- This leads to differences in products released in each country, with bias towards use of product with higher levels of the CQA in country A
- Post-marketing surveillance identifies AEs in country A
- This leads to heightened concern about AEs in country B

Example 2

- Manufacturer proposes “wide” release criteria for a CQA
- Regulator A is fine with this, because this can reasonably be supported by clinical data
- Regulator B requests narrower release criteria based on process improvements and the manufacturer’s demonstration of tight process control
- Manufacturer agrees to the narrower release criteria in country B, without telling regulator A
- Regulator A finds out, but does not want product marketed in country A to be biased in favor of outliers, so requests narrow release criteria as well

Harmonizing around clinically-relevant 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 does not help the patient 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

Ideally,

- Harmonization of specifications is an important goal of product development
- Specifications (CQAs) are set based on internationally agreed-upon scientific principles
  - Specifications must be clinically relevant wherever feasible
- 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

What should clinically relevant 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 CRDQ 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 CRDQ 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.

Linking quality between clinical and manufactured lots

- Via the combination of manufacturing process consistency and specifications, we seek to assure that future lots will have the safety and efficacy of the product during development
- We should thus evaluate parameters that are important for safety and efficacy, and provide as close a link to safety and efficacy as possible
- Parameters that provide this link are generally viewed as CQAs
- Specifications are the acceptance criteria for a specific validated test

Potency is defined based on clinical relevance

Specific ability or capacity **of the product**, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, **to effect a given result**.

[21 CFR §600.3 (s)]

Nonetheless, potency assays may be variable and results can encompass both manufacturing and assay variability

Precision of potency assays can influence confidence in results, whether for release or on stability assays

Defining quality: Key clinical parameters

- Lower clinical limit (LL): the lowest level at which we have confidence the product will be efficacious
- Upper clinical limit (UL): the highest level at which we have confidence the product will be safe

- Most clinical endpoint trials can only rigorously test one of these, and one or both may be supported by other data , yet we need to have confidence that product will be safe and effective

Defining clinically relevant quality (LL and UL)

- Attributes of lots used in clinical studies (usually phase II and phase III)
- Sometimes, immunogenicity or pharmacokinetic data may be used to bridge responses across different levels of an attribute
- If there is no evidence to support safety and effectiveness of product at attribute levels below or above those tested in clinical studies, those levels may presumptively define the LL and UL
- Assay variability for attributes of lots tested in clinical studies may create some uncertainty, mitigated by use of different lots in the clinical studies
- For some attributes, LL and UL might be dependent on product characteristics needed to assure other aspects of product quality (e.g., tertiary structure, pH)

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., CRDQ 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., CRDQs may also be readily established for attributes that influence potency and stability. For example, if pH influences stability, the CRDQ 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, or it isn't possible to evaluate ranges for all CQAs? ("traditional approach")

- A developer may justify a CRDQ 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 CRDQ 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 the broader "enhanced" 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.

Bridging pre-licensure and post-licensure results

- Goal: Make sure that product released after licensure behaves similarly to that tested in pre-licensure clinical studies
- This can be assured if measures of the CQAs for lots produced after licensure are similar to those of safe and effective clinical lots
- Assumptions:
  - Process remains in control: within-lot variability does not increase after licensure
  - CQAs are relevant to clinical performance

Relating specifications to quality

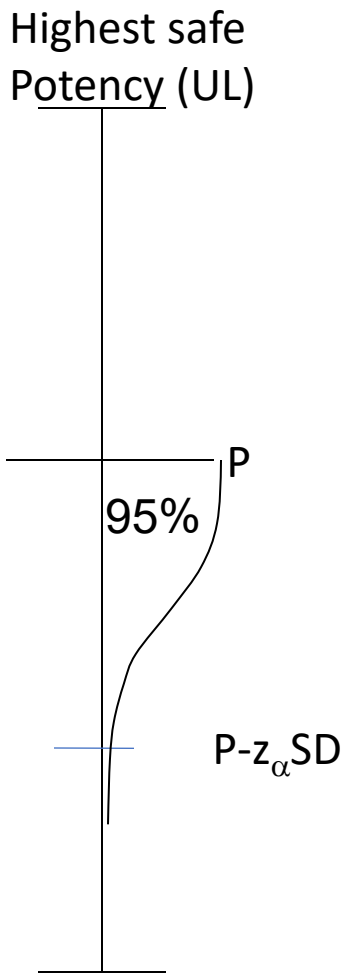
- Any specification, regardless of how established, is associated with a corresponding LL and/or a UL. Evidence should support safety and effectiveness of product in this range
- Prelicensure (e.g., dose ranging studies) is the best time to collect data to support LL and UL
- Specifications should not be set in such a way that allows product to be delivered with attributes beyond the LL-UL range

Specs, CQAs, and the CRDQ

- CRDQ is established 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 CRDQ (describing ranges on CQAs needed to assure product safety and efficacy) implies that specifications can be clinically relevant only when they are aligned with a CRDQ.
- All CQAs should have a CRDQ, but not all CQAs need 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 (outside-in approach). 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 (inside-out approach).

Modeling assay variability in specifications

Quality Standard



Quality Standard

- Potency is the CQA
- Quality standard is the CRDQ (LL and UL)
- The specification defines the test result that assures we will meet the CRDQ
- 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 specifications

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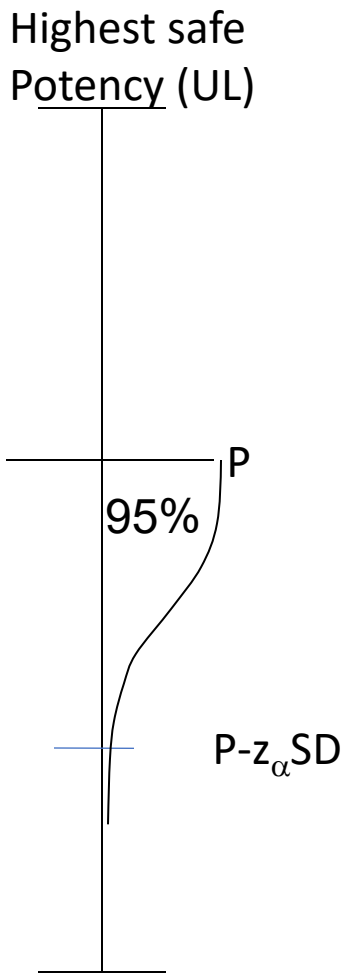

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- Minimum potency (P_{Min}) should provide assurance that the 95% lower bound exceeds LL
- This model can also be used to determine how stability should influence relationship between release and end-expiry specifications

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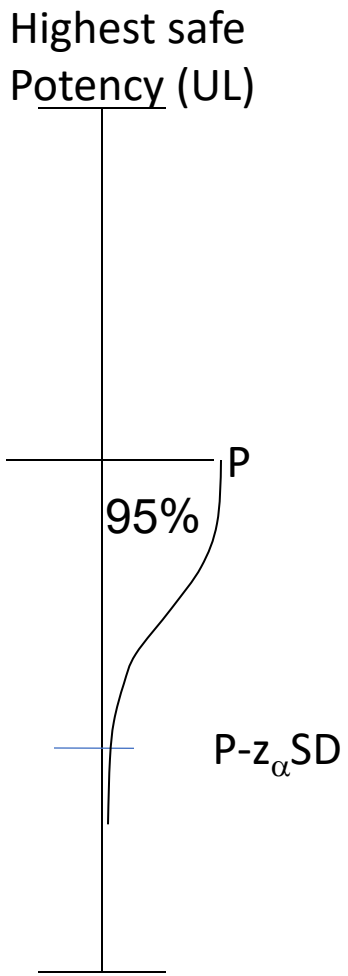

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- Minimum potency (P_{Min}) should provide assurance that the 95% lower bound exceeds LL
- This model can also be used to determine how stability should influence relationship between release and end-expiry specifications
- Similar considerations apply for upper limits

How reliable is the assay near LL?

- Thought experiment: If two lots of product have the same assay result, but one was manufactured with process mean 1 log lower than the result, and the other with process mean 1 log higher than the result, which lot likely has the higher potency?
- If the manufacturing process is under control, then the manufacturing process independently provides information about the likelihood that the potency of any individual lot is in an expected range
- For example, if we have equal confidence in the assay and the process, the true potency will likely be best estimated by the average of the assay result P and the average (target) potency of manufactured lots P_T

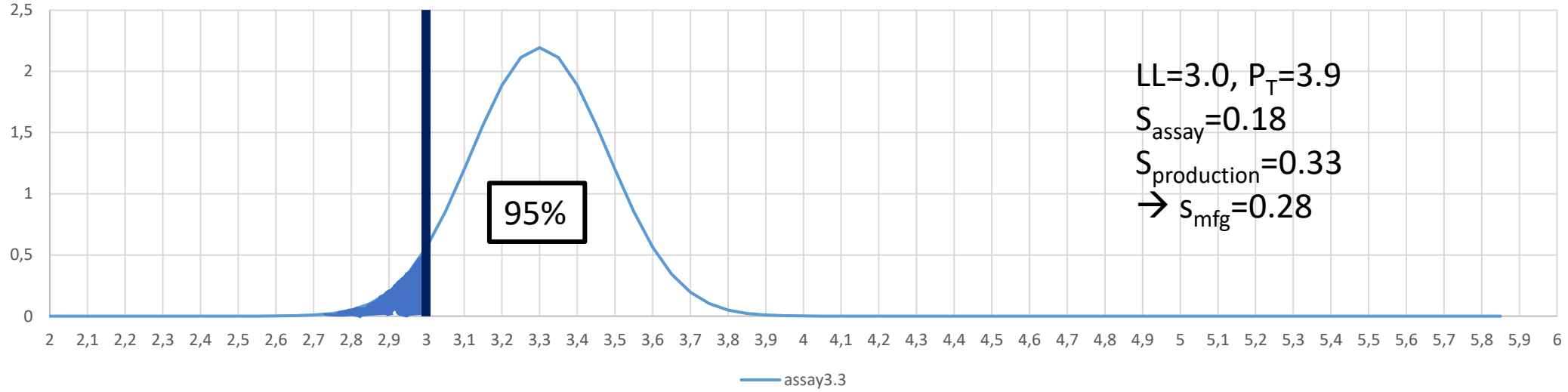
Implications

- If the manufacturing process is under control, extreme assay results are generally more likely the result of assay variability than manufacturing variability
- This makes individual assay results even less well suited to assessing process consistency

- Process control can be estimated by assessing variability of potency across lots (which includes both assay and manufacturing variability), and comparing with assay variability
  - e.g., $s_{total}^2 = s_{assay}^2 + s_{manufacturing}^2$ if assay and manufacturing variability are independent of each other

- Can we use this information to obtain better estimates of product potency than are obtained by using only the assay?

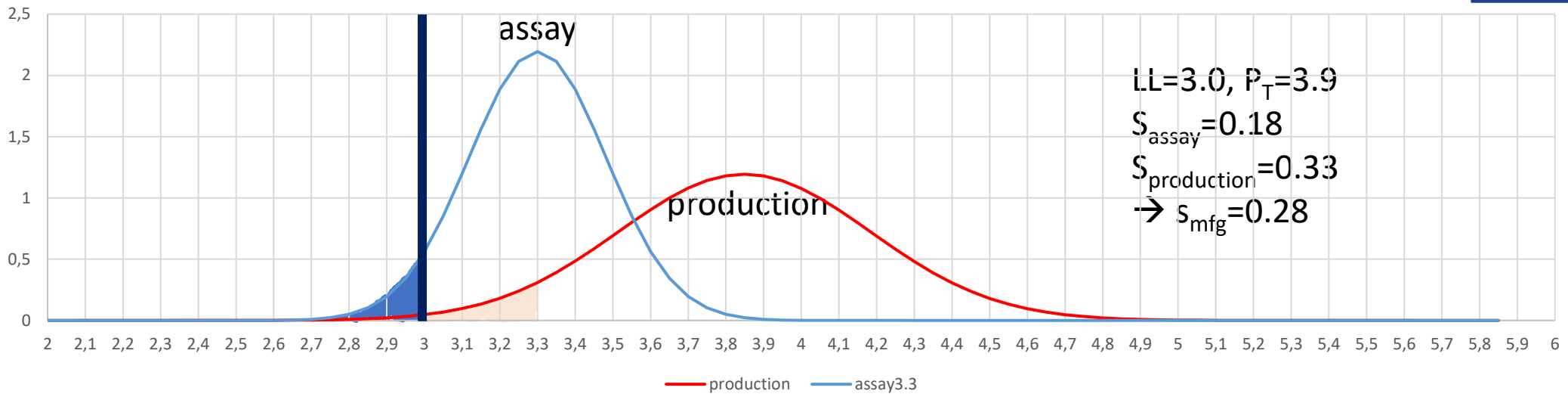
Spec is based on clinical limit



- Lower clinical limit is 3.0 (logs), so we desire to assure that manufactured product is released with true potency above that level
- Based on the standard error from the assay validation S_{assay} of 0.18, we set the lower release limit at 3.3, which provides 95% confidence that a batch released at a potency of 3.3 will exceed a true potency of 3.0: (3.3 - 0.18 * 1.65 = 3.0)

To simplify the descriptions, some values have been rounded

Manufacturing target is based on spec



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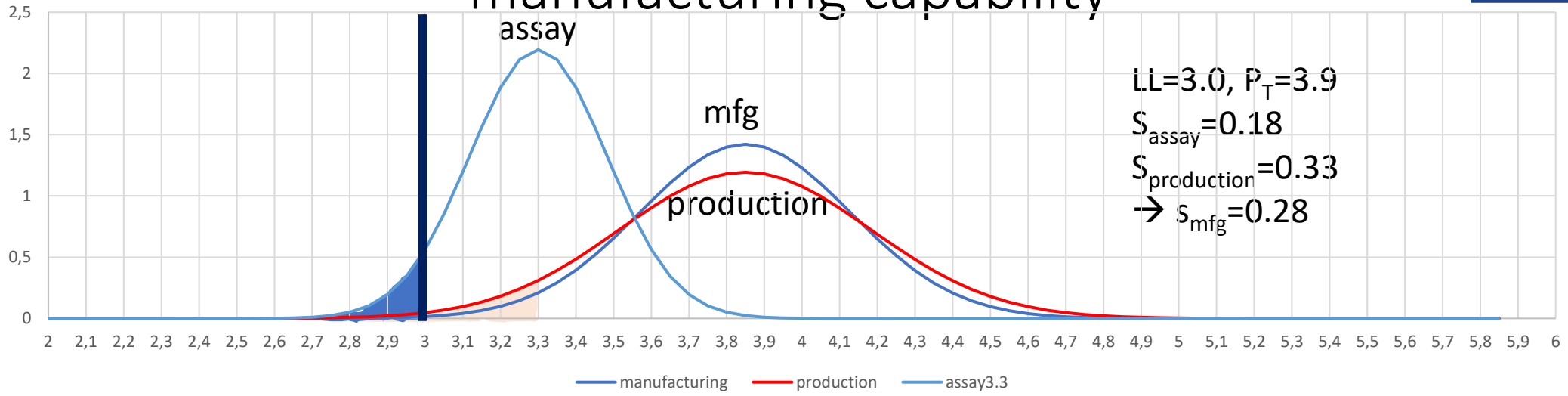
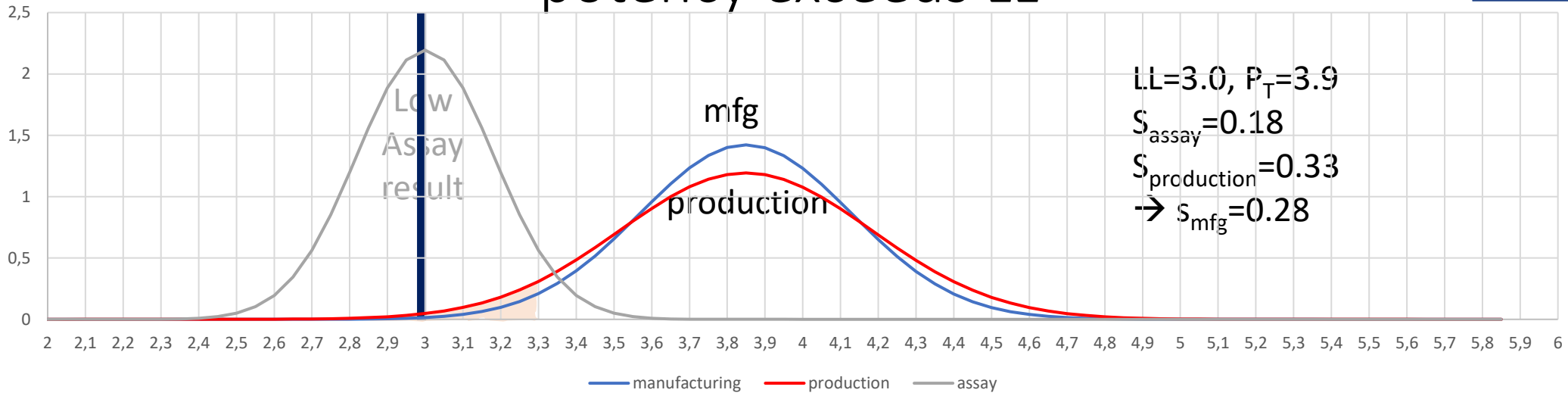
- If we target a manufacturing potency of 3.9, 95% of lots will have potency measurement that exceeds 3.3 (3.9-1.65*0.35=3.3). So 5% of lots will fail.
- **IF WE DON'T SET MANUFACTURING TARGET BASED ON LL OR SPEC, WE HAVE LOST THE CONNECTION TO CLINICAL OUTCOMES. IF THIS ISN'T FEASIBLE, WE NEED TO IMPROVE THE MANUFACTURING PROCESS.**

This strategy doesn't account for true manufacturing capability



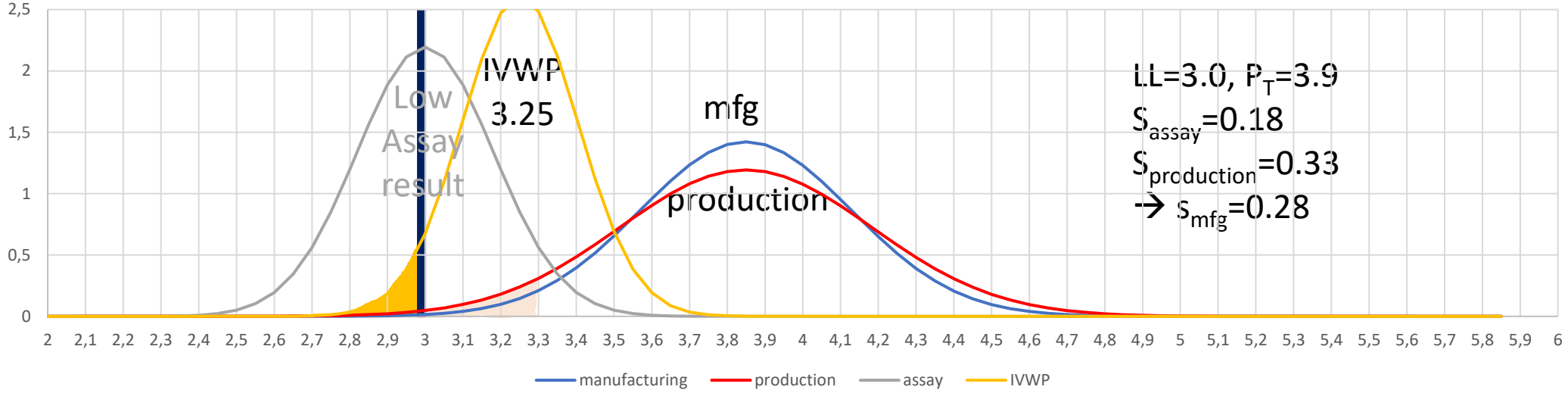
- If we target a manufacturing potency of 3.9, 95% of lots will have potency measurement that exceeds 3.3 (3.9-1.65*0.35=3.3). So 5% of lots will fail.
- s_{mfg} is calculated based on $s_{production}$ and s_{assay}, since $s_{production}$ encompasses both assay and manufacturing variability
- Based on manufacturing target and process variability, 99.87% of manufactured lots will have true potency above 3.0. So we would hope only 0.13% of lots would "fail" when the process is under control.
- There is a discrepancy between our release strategy and our manufacturing capability

A low assay result very likely still means product potency exceeds LL



- An assay result of 3.0 is much more likely to be associated with a true potency above 3.0 vs. below 3.0
- A minimum release potency P_R of 3.3 may be more conservative than is needed to assure adequate potency of this product, if the manufacturing process is known to be in control.

Combining the data



- Combining assay & manufacturing information, using inverse variance-weighted potency, a measured potency of 3.0 would correspond to a mean potency of 3.25, with a 95% lower confidence bound of 3.0.
- Where we have this level of confidence in the manufacturing process, product could be released at the lower clinical limit.
- Instead of a 5% failure rate, the failure rate would be 0.6% (still conservative relative to true expected failure rate of 0.13%).

If the manufacturing process is under control, the target is set as specified, and $s_{mfg}<1.54s_a$, measured potency does not need to exceed LL in order to assure product quality

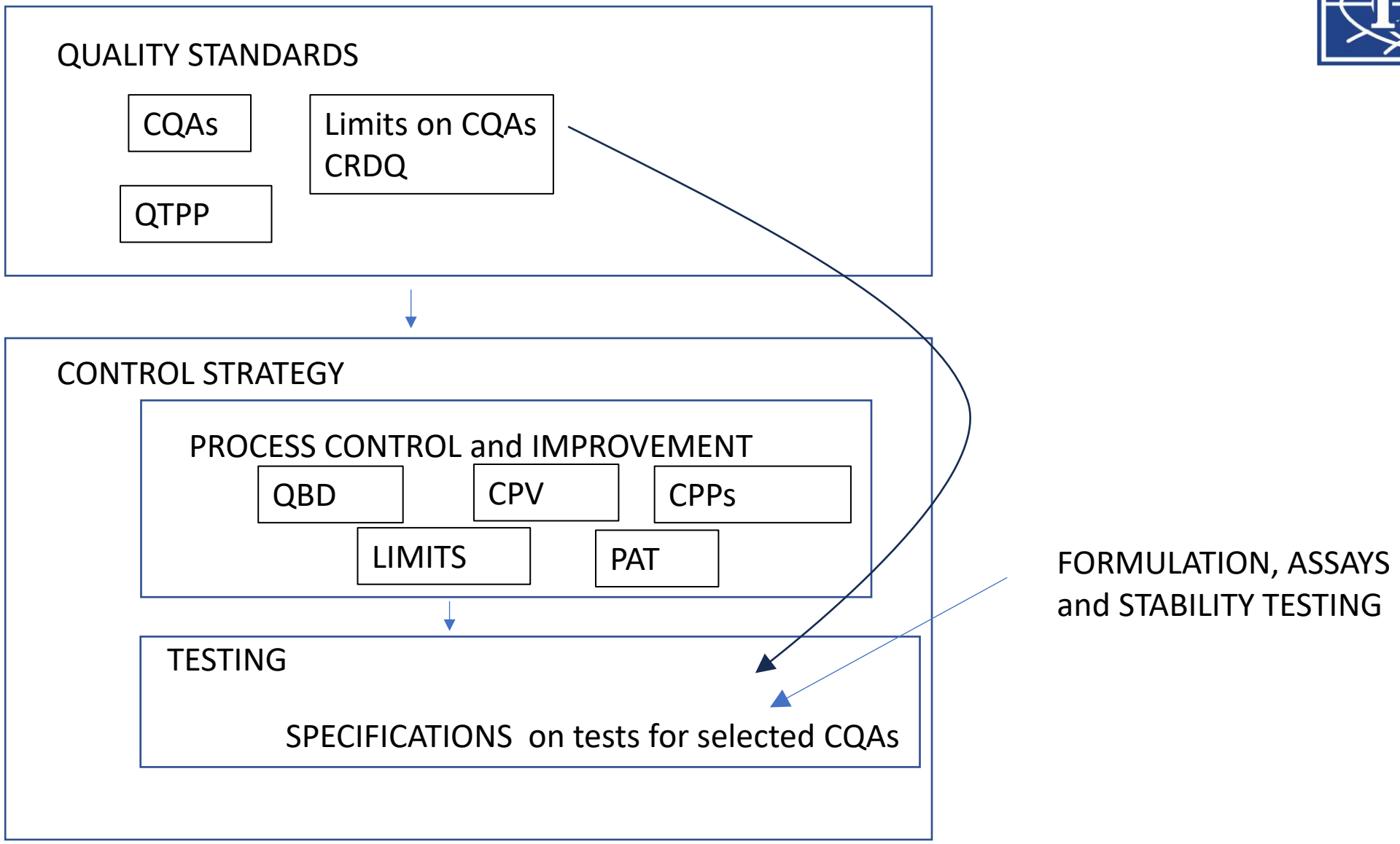
Specifications should not be used for process monitoring

- At the time the specifications are set, there may not be enough manufacturing data to reliably predict future manufacturing performance
- If specifications are set too widely, this may introduce uncertainty about safety and effectiveness of marketed product
- Reduced flexibility to improve manufacturing process or assays
- Doesn’t give serious information about the process- it’s unclear how to extrapolate failure of a single lot to the process
- Lower chance of international harmonization if different regulators use different approaches

What are sources of confidence in manufacturing process consistency?

- Other process information, including CPPs, assay results on drug substance, etc.
- Testing strategies that are not linked to specifications, with trending and other statistical analysis of manufacturing/assay results over time (this information is not always shared with regulators)

- The primary purpose of drug product assay specifications should be to assure that true product attributes are between LL and UL



Clinically relevant quality standards support clinically relevant specifications

Manufacturing and specifications

- Specification setting needs to start with a link to clinical outcomes (i.e., the CRDQ), and should build in information about both the assay and the manufacturing process
- It is inappropriate to use narrow specifications to assure process control
- Consistent with QBD and 6-sigma, lower assay and manufacturing variability should support wider specifications and lower targets
- Process understanding could influence release decisions, theoretically justifying minimum release specifications that are closer to “LL” than would be justifiable based on assay variability alone
- This raises the intriguing question for the future: if manufacturing is under control, will we even need specifications in order to assure product quality?

- The primary purpose of drug product assay specifications should be to assure that true product attributes are between LL and UL

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 CRDQ, 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 and 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 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.
  - 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).

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 the paradigm of clinical relevance, 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, trending, 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 clinically relevant paradigm, the CRDQ should be based on expected patient outcomes, and specifications are defined in a manner consistent with the CRDQ.
    - 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.
- 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 CRDQ 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.

Advantages to the Patient

- Assurance of product quality
- Reduced likelihood of product shortages that may be caused by inappropriately narrow acceptance criteria.
- Earlier patient access to new or improved medicines.

Advantages to Developers

- 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 clinical relevance 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

- Reduced need to review “out-of-specification” results and to review specification changes that are unrelated to product quality
- Increasing confidence that batch approval is associated with quality and expected patient outcomes,
- 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: recommendations

- 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

Conclusions

- All specifications should support desired clinical outcomes. Explicit planning of how data will be collected to demonstrate this is important
- For any given product, the relationship between CQAs and predicted outcomes is important for product development, and general consensus on how to accomplish this is essential for harmonization of specifications
- Mathematical modeling of specifications, assay variability, process variability and stability provides a scientific foundation for harmonization