A Framework for Ensuring Quality with Patient-Centric Specifications

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Two control strategy paradigms

• **“Inside-out” approach**
  - Process, formulation, and analytical development are carried out independently resulting in a *specification reflecting “what is seen”* in manufacturing
  - *Layers of limits are built from the inside out* (e.g., unit operations → release limits → shelf life) and used to manage control of the product
  - The *limits are justified* based on clinical, preclinical, or *in vitro* experience; or prior (clinical) knowledge

• **“Outside-in” approach**
  - Prior (platform) knowledge is used to *forecast variability* in the component parts of the control strategy
  - Clinical, preclinical, and *in vitro* studies are performed to support *patient requirements which reflect “what is needed”* by patients
  - *Quality by design* is used to *build quality into* the process, shelf life, analytical, and lifecycle management that fit together within this requirement
Outline

• Issues with current practice related to specifications
• What is “quality” in QbD?
• Building quality into:
  ➢ Specifications
  ➢ The process
  ➢ Shelf life
  ➢ Analytical procedures
  ➢ Lifecycle management
• Summary messages
Issues with current practice related to specifications
Choices, choices, choices ...

• There’s disharmony over choices when specifications are based on manufacturing data ($\pm$3-sigma):
  ➢ Choices over *data source*
  ➢ Choices over *amount of data*
  ➢ Choices over *basis of calculation*

• Then there’s *data evolution* during the global licensure process

• . . . and lack of foresight regarding:
  ➢ Changes over the product lifecycle
  ➢ Changes over shelf life
Issues with current practice related to specifications
Lack of acknowledgement of changes over the product lifecycle

- The distribution of clinical and early production lots does not represent the long-term experience with the process.

- **Release limits** need to be wider to cover:
  - Operating in a broader range (NOR) than used to produce clinical lots
  - ... as well as routine and unexpected lifecycle changes.

- The consequences of ignoring this are supply shortages and frequent & burdensome global regulatory interactions.
What is “quality” in QbD?

- Industry and regulatory authorities should build consensus around the definition of quality. This is implied in current guidelines:
  - ICH Q6B states that the specification “… establishes the criteria to which a … drug product … should conform to be considered acceptable for its intended use;”
  - ICH Q8A(R2) states that “a control strategy is designed to ensure that a product of required quality will be produced consistently;”
  - ICH Q8A(R2) further defines the quality target product profile (QTPP) as “A prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product,” and goes on to say that the QTPP should include “Drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product” (emphasis added).
Building quality into the “specification”
An “outside-in” viewpoint

- Analytical limits are used to:
  - … **ensure quality** throughout shelf life
  - … and **control manufacturing**
  - Scientifically/clinically justified minimum and/or maximum **patient requirements**
  - **Patient-centric specifications (PCS)** calculated to predict that patient requirements are met at release and throughout shelf-life
  - **Control limits** formulated to help manage process consistency
Building quality into the “product”

- Limits which are built on *patient requirements* can be the basis of *target development ranges* and *approaches to lifecycle management*

- **“Budget” allocation**

  - The *process and lifecycle management budget* represents the target range for process development, with room for lifecycle management (CPV & ChgMgmt)
  - The *shelf life budget* represents the target shelf life
  - The *analytical budget* represents the analytical target profile *(driven by the ATP)*
Building quality into the “process”

- Patient-centric specifications are an important driver during process development - using design of experiments (DOE)
  - **Step 1: Establishment of CPPs** (CMPs) from screening studies
    - Working with a **process budget** within the patient-centric specifications
    - A process parameter which **may impact quality** (falls “outside” the budget) is a **CPP**
    - A process parameter which **has no impact on quality** (is well inside of budget) is **not a CPP**
Building quality into the “process” (cont.)

- **Step 2: CPPs are taken into a response surface design**
  - The process budget (PB) is used to define a region yielding acceptable performance (design space)
    - Region determined by lower PB bound (shown with confidence bound)
    - Region determined by upper PB bound
    - The design space is reported as ranges depicted as an inscribed rectangle
Building quality into the “process” (cont.)
An “inside-out” approach

- Manufacturing is typically limited to the normal operating range (NOR)
- Which projects to manufacturing control limits

- However, setting the specification limits to these make them the de facto budget
- And the design space (DS) is reduced to the NOR

A “design space” can’t be developed, and the process (and lifecycle management) budget is restricted to the NOR – no opportunity to move or assess changes or improvements
Building quality into “shelf life”

• A **target shelf life** should be driven by commercial supply requirements (e.g., FPI, inventory, transport, regulatory testing, use)
  ➢ Note: “inside out” uses ICH or common practice to **calculate shelf life if there’s a specification representing quality at EOSL**
  ➢ . . . or **predicts the EOSL limit**

• Product is formulated; **storage and hold times** (internal and external) are optimized

• Studies can be **designed to reduce uncertainty** in the estimation of loss rates and thereby the impact on the release limit (“outside in” or PCS)
Building quality into “analytical procedures”

- **Follows QbD principles and tools** with:
  - **Product** = reportable values; “patient” = decision maker
  - **Critical method attributes**: accuracy, linearity, linearity, total analytical error
  - **Acceptance criteria**: analytical target profile (ATP) informed by the analytical budget; validity criteria which predict acceptable performance
  - **A method operable design region (MODR or DS)** where method parameter ranges are determined which ensure acceptable performance
  - **An analytical control strategy**
    - Including change management (e.g., standard qualification, method bridging)
Building quality into “lifecycle management”

- The lifecycle management budget supports change management
  - A margin ($\Delta$) can be established which is associated with adequate process capability (low manufacturer's risk of an OOS)
    - While the patient is protected by patient-centric specifications (PCS)
  - An equivalence (or noninferiority) test might be performed to demonstrate conformance to the margin
    - Using a two one-sided test (TOST)
    - $90\%$ CI falls within $\pm \Delta = $ equivalent

- Change management protocols can be designed (viz., to minimize decision risks)
Summary messages

• The practice of setting specifications to manufacturing variability is subject to *disharmony, complicates the application of QbD*, and is behind *supply disruptions* and *time-consuming regulatory interactions*

• Analytical limits should be used to:
  1. *Ensure patient quality* (safety & efficacy) – *quality control*
  2. *Ensure manufacturing consistency* and *encourage innovation* – *manufacturing control*

• All components of the control strategy can be derived from “*patient requirements*”; which can result in efficiency by building a *shared definition of “quality”* into the most important components
Thank you!

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