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 (±3-sigma) :
  - Choices over ***data source***
  - Choices over ***amount of data***
  - Choices over ***basis of calculation***

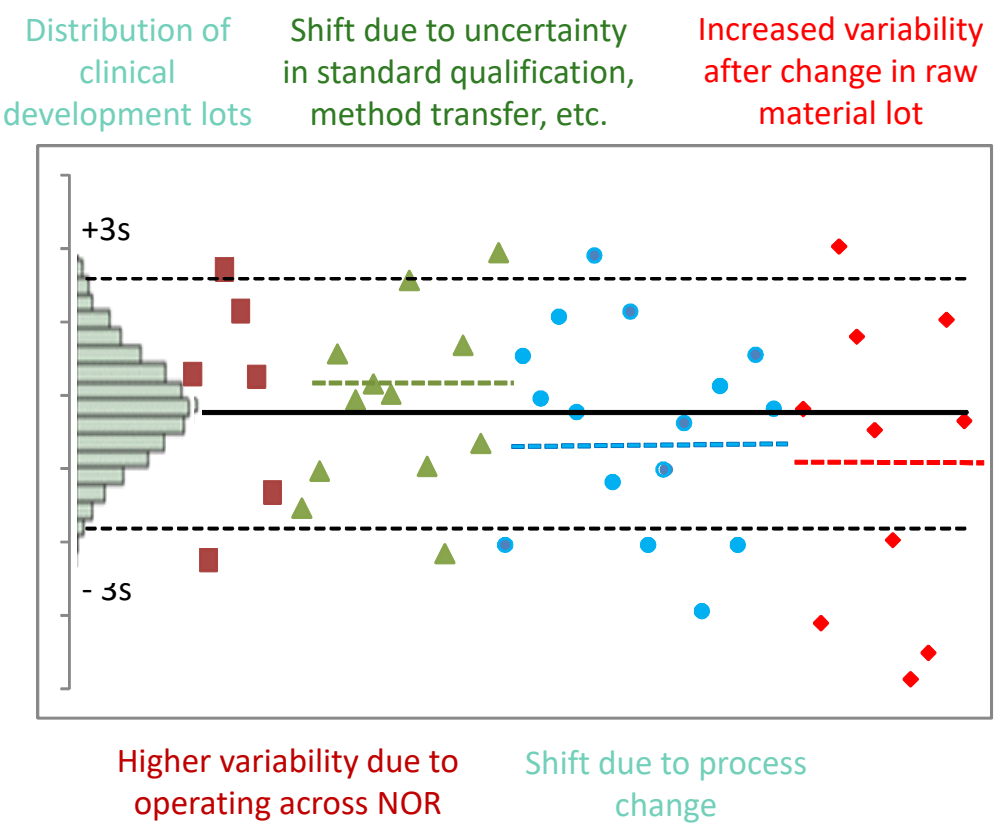
- Then there's ***data evolution*** during the global licensure process

- . . . 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***

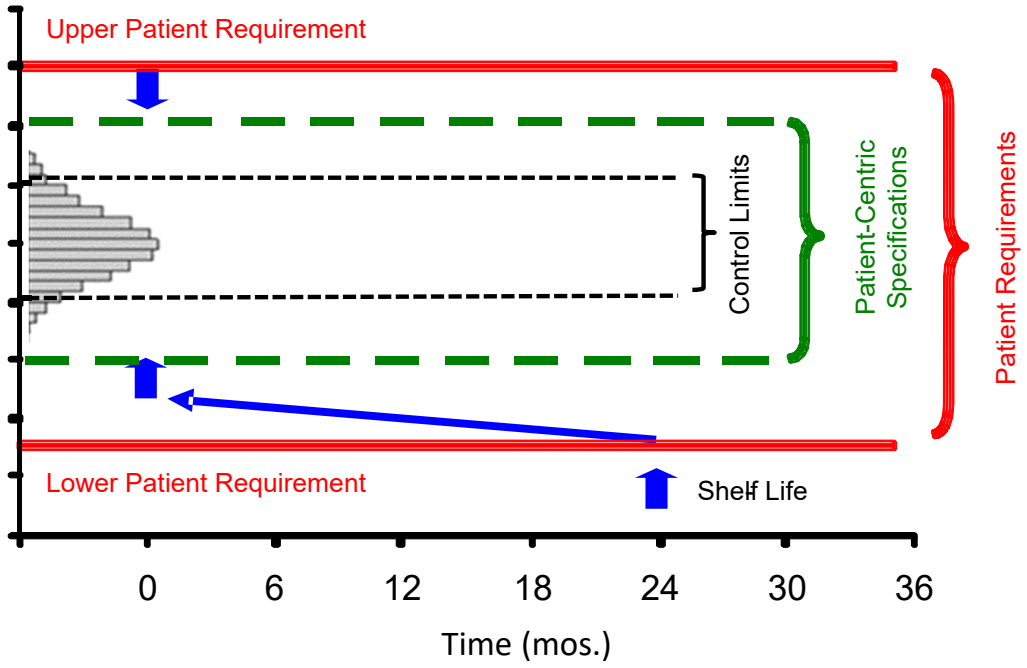


What is “quality” in QbD?

- 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

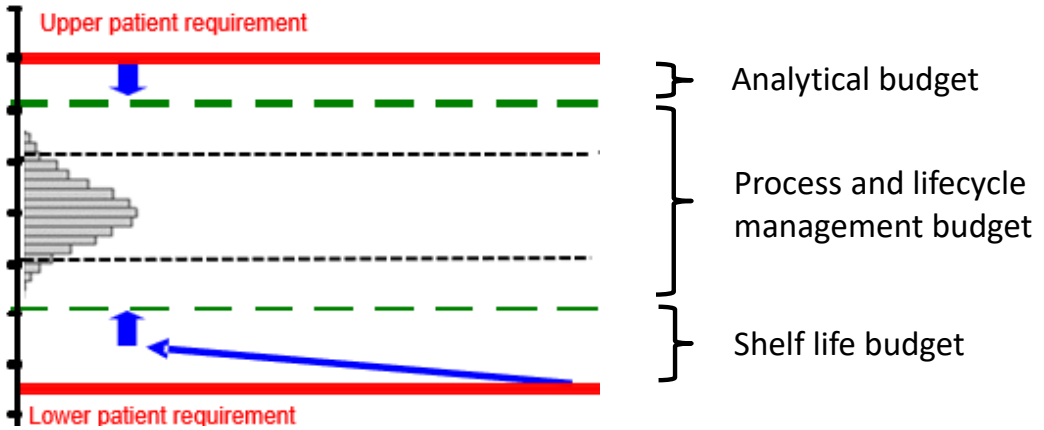
Quality Control (patient risk)

- *Control limits* formulated to help manage process consistency

Manufacturing Control (manuf. risk)

Building quality into the "product"

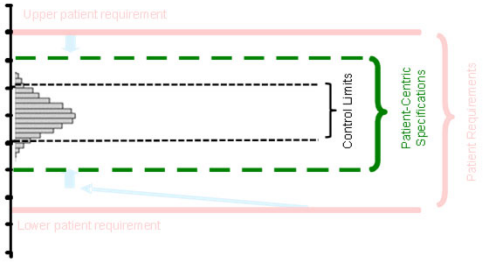
- Limits which are built on ***patient requirements*** can be the basis of ***target development ranges*** and ***approaches to lifecycle management***
  - *"Budget" allocation*



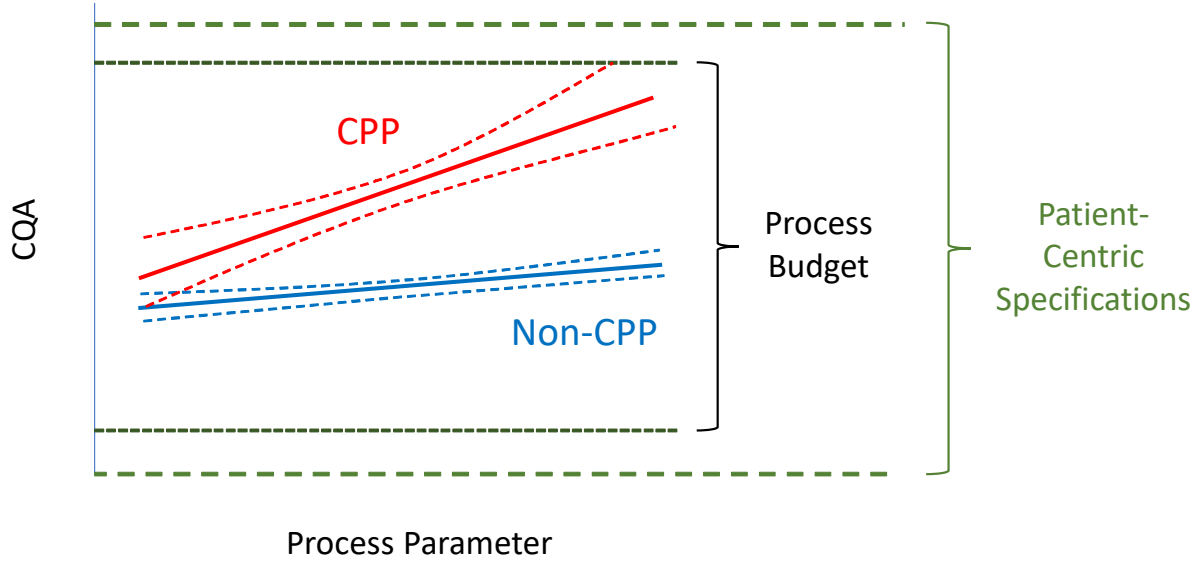
- The "***process and lifecycle management budget***" represents the target range for process development, with room for lifecycle management (CPV & ChgMgmt)
- The "***shelf life budget***" represents the target shelf life
- The "***analytical budget***" represents the analytical target profile ***(driven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

Driven by the QTPP & lifecycle

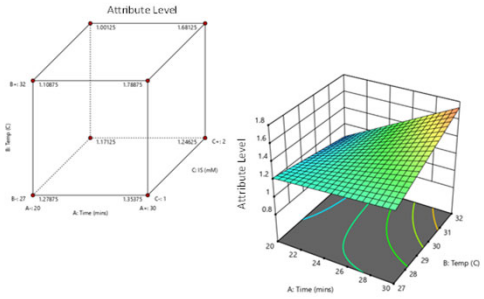
Building quality into the "process"



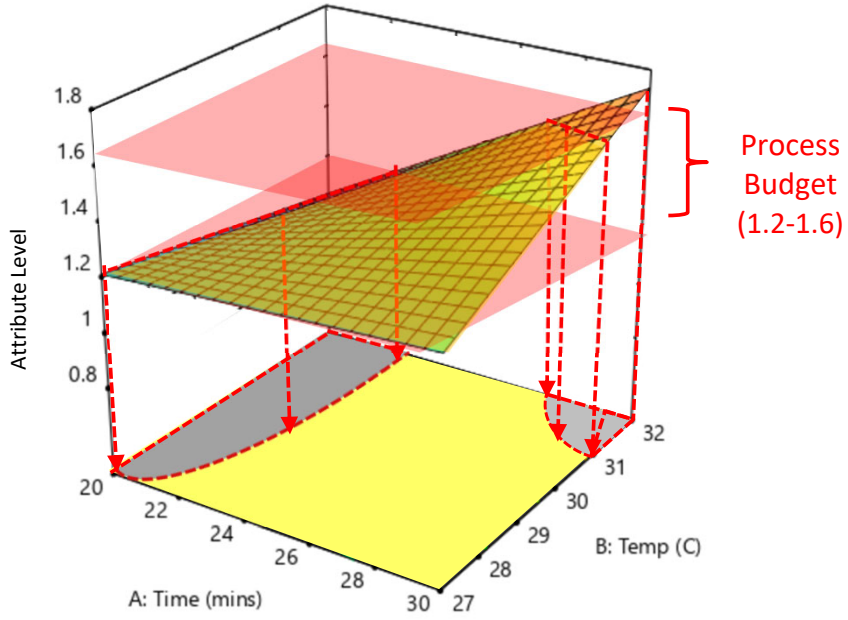
- Patient-centric specifications are an important driver during process development - using ***design of experiments (DOE)***
  - ***Step 1: Establishment of CPPs*** (CMPs) from screening studies
    - Working with a ***process budget*** within the patient-centric specifications
    - A process parameter ***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***

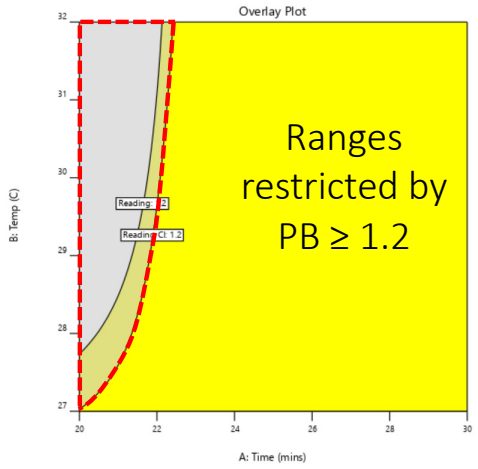


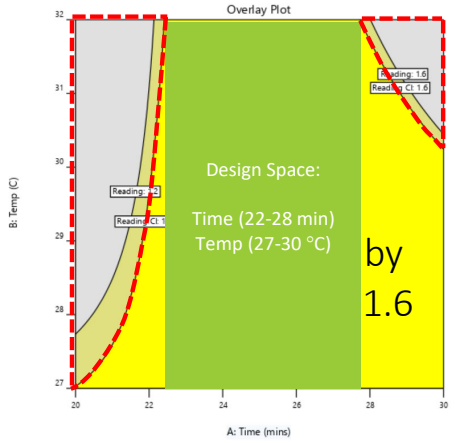
Building quality into the “process” (cont.)



- ***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

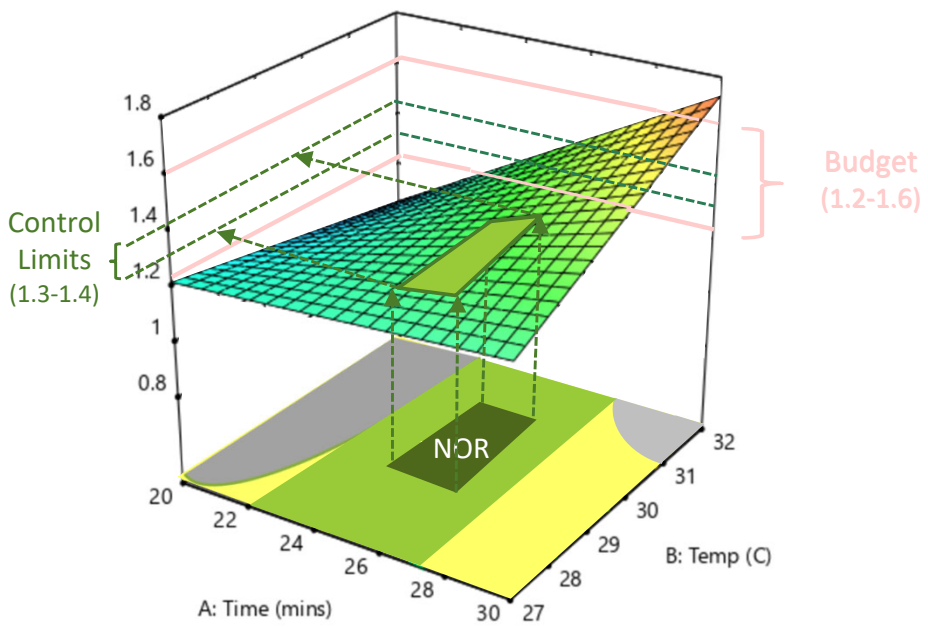




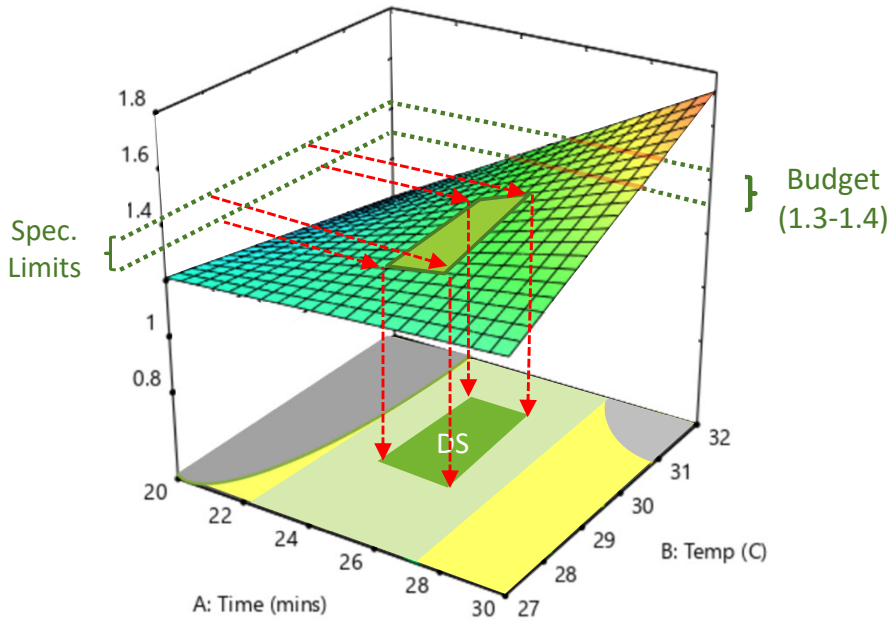


Building quality into the “process” (cont.)
An “inside-out” approach

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

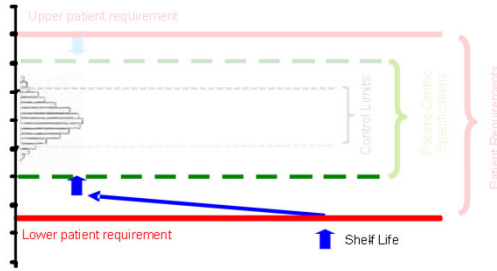


- However, setting the specification limits to these make them the de facto budget
- And the design space (DS) is reduced to the NOR



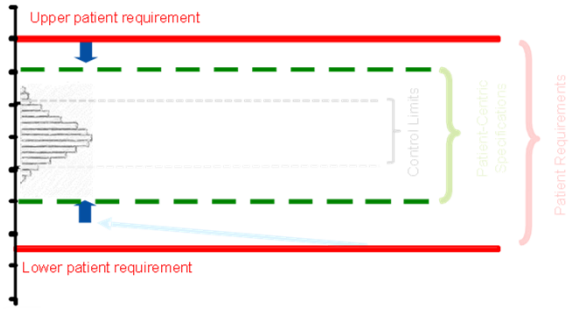
- A “design space” can’t be developed, and the process (and lifecycle management) budget is restricted to the NOR – no opportunity to move or assess changes or improvements

Building quality into “shelf life”



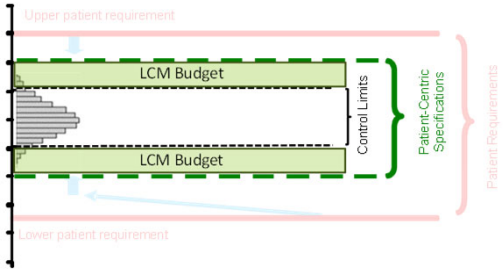
- A ***target shelf life*** should be driven by commercial supply requirements (e.g., FPI, inventory, transport, regulatory testing, use)
  - Note: ***“inside out”*** uses ICH or common practice to ***calculate shelf life if there’s a specification representing quality at EOSL***
  - . . . or ***predicts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

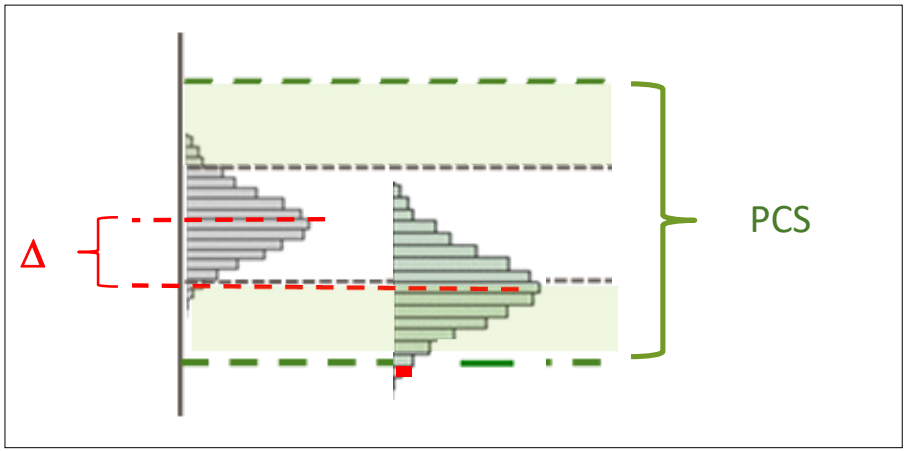


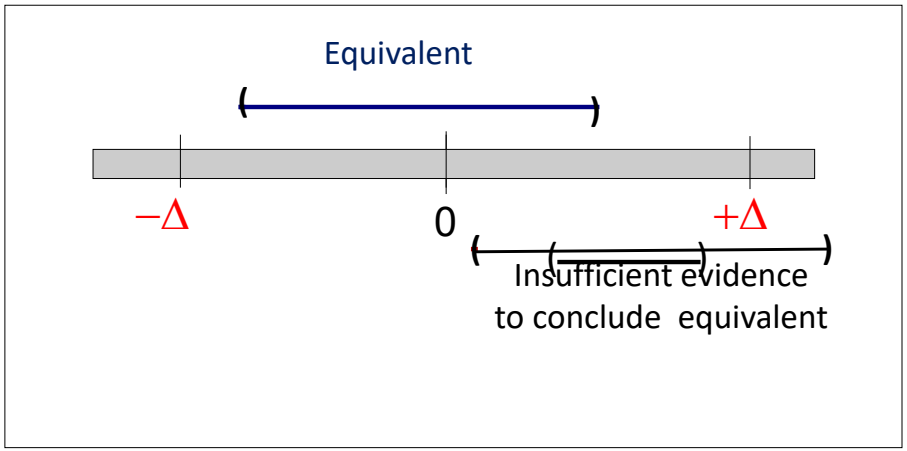
- *Follows QbD principles and tools* with:
  - *Product* = reportable values; *“patient”* = decision maker
  - *Critical method attributes*: accuracy, linearity, linearity, total analytical error
  - *Acceptance criteria*: analytical target profile (ATP) informed by the *analytical budget*; validity 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 (Δ)*** 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 ***±Δ*** = ***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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