Effective uses of Release and Control limits to Manage Manufacturing and Patient Risks

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A viewpoint on quality
– “line of sight”

– “Line of sight” is the concept of knowing where you’re going to facilitate development and increase the likelihood of regulatory and commercial success
  – Development of the **commercial control strategy**

– Some current paradigms
  – Quality target product profile (qTPP)
  – Analytical target profile (ATP)
  – Lifecycle management

– Early manufacturing and shelf-life modeling can be used to inform development
  – Points to priorities in the development of the process and the commercial control strategy
  – Informs nonclinical and clinical studies to support the control strategy
A vision for the control of potency

- Justified minimum and maximum potency requirements
- *Release specifications* determined to ensure (with specified confidence) that potency meets its quality requirements throughout shelf-life
- *Control limits* and associated rules to monitor and manage manufacture
The big picture

Process Operating Conditions ($x$)

$y = f(x)$

Quality Attributes ($y$)

$z = g(y)$

Surrogate outcome ($z$)

$p = h(z)$

Clinical Outcome ($p$)

$x_{\text{limit}} = f^{-1}(y_{\text{limit}})$

Design Space

$y_{\text{limit}} = g^{-1}(z_{\text{limit}})$

Specifications

$z_{\text{limit}} = h^{-1}(p_{\text{limit}})$

Translational Medicine
Defining quality: $z = g(y)$

- Strategic clinical development
- Potency example
  - Dose ranging
  - Expiry potency study
  - Clinical stability
Underlying clinical dose response facilitates design and minimum potency determination

– Perform manufacturing modelling to establish required potency range
  – Simulate potencies from dilutions of a target material (note: all doses needn’t be tested – defined as \( T/dil \))
– Underlying theoretical kinetics can be utilized to facilitate clinical design and analysis
  – A design with more doses allows kinetics modeling and minimum dose determination
  – Too few doses does not support modeling – risk of a higher expiry potency

* AVAX Case Study, Control Strategy (ISPE)
An expiry potency can be manufactured to support a target or compendial minimum

- Approaches
  - Dilution to minimum dose
    - Pro – easy to target
    - Con – not representative of “degraded” product
  - Aged at labeled storage temperature
    - Pro – representative of aged vaccine
    - Cons – difficult to achieve a specific target and/or long time to achieve targeted expiry potency
  - Accelerated aging to target
    - Pro – able to target within a feasible time
    - Con – accelerated aging may be nonrepresentative of naturally degraded vaccine
Accelerated aging facilitates targeting and yields a precise estimate of potency

- Use interim stability data to forecast “pull time” and to define expiry potency
- Stability data can be combined with release data to obtain a more precise estimate of potency of aged material
Stability data for a clinical lot can be used to estimate potencies that subjects received

- Vaccine potency decreases over the course of a clinical study
- The release potency of a clinical lot is not representative of what subjects received
- Statistical modeling of clinical stability data can be used to estimate potencies that individual subjects received
- The individual potencies can be used to model the kinetics and thereby the minimum potency requirement
Process characterization studies can be utilized to simulate the distribution of CQAs across ranges in the CPPs.

Utilizing normal variation in CPPs translates into variation in CQAs.

Target P(OOS) \(\approx 0.3\%\) (3-sigma capability)
Building quality: \( y = f(x) \)

Cont.

- Output from one unit operation an input to the next  
  \( y_{t+1} = f(x, y_t) \)

- Statistical uncertainty – Bayesian analysis
  \( y_{t+1} = f(x, y_t) + e(\text{process parameters}) + s \)
Managing quality: $x_{\text{limit}} = g^{-1}(z_{\text{limit}})$

Specifications

- Current practice is to use clinical lot and/or full scale development lot data to set Drug Substance and Drug Product limits
  - 2/3-sigma or tolerance limits
- Issues with current practice
  - Does not account for shelf-life
  - Limited data/experience early in the lifecycle of a product
  - Does not account for product lifecycle events
    - Process change/improvement
    - Method transfer
    - Standard qualification
    - Comparability
Managing quality: $x_{\text{limit}} = g^{-1}(z_{\text{limit}})$

Release specifications revisited

- Additional considerations
  - The need for a “clinically” valid endpoint ($z_{\text{limit}}$)
  - Evaluated end-to-end to forecast DS & DP release and shelf life risks
    - DP release limit protects the customer
    - DS release limit protects the manufacturer
  - Formulation characterization predicts lot-to-lot variation

\[
x_{\text{limit}} = y_{\text{limit}} + b \cdot t + t_{df} \cdot \sqrt{(t \cdot s_b)^2 + s^2}
\]

or through modeling and simulation of formulation characterization outcomes
Managing quality
The product lifecycle

– The specifications at release should also account for routine events which occur over the commercial lifecycle of a biopharmaceutical
  – Distribution of clinical development lots manufactured at “set points”
  – Forecast variability due to ranges in process parameters
  – Shifts due to events related to analytical method maintenance
  – Shifts due to events related to process changes/improvements
  – Increases in variability due to changes in unverified process factors
Managing quality
Comparability

- After a process change, method transfer, standard change, etc.
- A margin ($\Delta$) can be established which has low risk of an OOS if the margin is reached (manufacturer's risk) while the patient is protected by the release limit.
- An equivalence test (“equivalent or better”) is performed to demonstrate conformance to the equivalence margin (upper confidence bound falls within the equivalence margin).

![Graph showing shelf-life limit, release limit, control limits, and time (mos.)](image)

Equivalent

$\Delta$

Not equivalent
Managing quality
Continued process verification (CPV)

- Management of the process
  - What is the natural behavior in the process? Are individual batches independent? What are the failure modes?
  - Track & trend campaigns and batches within campaigns
    - Control limit on campaign average
      \( (\bar{y}_{\text{campaign}} - \bar{y}_{\text{campaigns}}) \)
    - Control limit on batch \( (\bar{y}_{\text{Batch}} - \bar{y}_{\text{campaign}}) \)
    - ... or control of \( s_{\text{Batch}} \)
  - Drift in impurity level due to “instability” of some process factor
    - Column stability
    - Buffer degradation
    - Standard degradation

Campaign effect

Drift

Impurity

Batch

Release Limit

Shelf-life Limit

Control Limits
Summary

- Line of sight facilitates process and analytical development and helps ensure a strategic control strategy

- Specifications should be distinguished from control limits
  - Specifications help manage customer risks
  - Control limits help manage manufacturing risks

- Development studies (characterization and stability) inform limits which may be used in addition to limited commercial scale manufacturing data to develop the control strategy

- Limits should also be considered in the context of routine product lifecycle events to ensure robustness and to apply risk based approaches to lifecycle management

- Statistical modeling and testing provide a basis for evaluating, communicating and controlling the risks to product quality and supply
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