Table 3: Setting Specifications with Limited Batches and Analytics to Understand Process and Assay Variability

SESSION 1:
FACILITATOR: Harold Taylor, *Merz Pharmaceuticals GmbH*
SCRIBE: Birgit Schmauser, *BfArM, Federal Institute for Drugs and Medical Devices*

SESSION 2:
FACILITATOR: Cari Sänger - van de Griend, *Kantisto BV*
SCRIBE: Marta Germano, *Janssen Infectious Diseases and Vaccines*

SCOPE:
According to ICHQ6B (1999) "*Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization and should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product*". This guideline further suggests the following considerations for setting acceptance criteria: "*Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency and data from stability studies, and relevant development data*".
The choice of product quality attributes to be controlled by specifications may be easily justified by evaluating their impact on safety and efficacy, which can be taken into account in the definition of critical quality attributes, CQAs. Such evaluations are, however, not always straightforward, especially if only few batches have been manufactured or used in a clinical or preclinical setting. Without a good estimate of the variability of CQAs, it may be difficult to clinically or statistically justify acceptance criteria for release testing. A number of different approaches to circumvent these difficulties will be discussed at this roundtable.

QUESTIONS FOR DISCUSSION:
1. What is the current practice in specification setting and which considerations weigh the most: clinical relevance, manufacturing process capability, or analytical capability?
2. How do you deal with specifications on which you have little knowledge about clinical relevance?
3. Do you leverage knowledge from similar products and processes when setting acceptance criteria and justification of specifications?
4. What strategies do you apply, for example, for accelerated programs which typically would not need manufacturing of several batches? Do you have experience with setting provisional acceptance criteria at the time of filing, and changing them to final acceptance criteria post-approval?
5. To circumvent the lack of knowledge about manufacturing process variability, do you have experience with replacing end-product specifications by control of process parameters or starting materials, in the context of an integrated control strategy?

DISCUSSION NOTES:
Session 1:

Short introduction about general limitations in quantification due to the particularly challenging situation that the amount to be quantified may be very, very low and the sensitivity of a method may not be challengeable to the same extent.

Further limitations may result from the fact that:

- the drug is related to an orphan disease
- no historical data are available
- data are available from characterization level only

1. What is the current practice in specification setting and which considerations weigh the most: clinical relevance, manufacturing process capability, or analytical capability??

DRAWBACKS

- Time pressure limits
    - Management against statistics, against quality
- No consecutive data available
- Available data may not be representative

PRACTISE

- Specifications may be derived from platform knowledge
    - E.g. early phase with adaptations
    - For consistency batches (usually 3) ± 15% deviation from platform specification allowed
- Clinical validation of specification
    - Inter-product variability versus data points collected
- Toxicological qualification
    - The dirtiest batch ever should be used
        - Analytics: uncertainty is super crucial
    - Relevance of results
        - e.g. host cell protein
            - theoretical versus practical considerations
        - e.g. host cell DNA
            - WHO specification as starting point

2. How do you deal with specifications on which you have little knowledge about clinical relevance

- Relevance of QAs with a limited number of batches (~1, accelerated review)
    - Measure everything that can be measured
        - Observation with batches: first
        - Relevance of QAs: later
        - Classical methods are applied as a starting point
            - Others may be added later
        - Are platform methods specific enough for each product?
    - Important to generate data
        - Specifications may initially have “reporting limits”

3. Do you leverage knowledge from similar products and processes when setting acceptance criteria and justification of specifications

- Setting of specs early on may not be smart
- Risk assessment should estimate exposure in clinical trials
    - Platform knowledge may guide this
- Role of agencies´ own risk assessment
    - Relevance of scientific content
    - Confidence in thinking process

4. What strategies do you apply, for example, for accelerated programs which typically would not need manufacturing of several batches? Do you have experience with setting provisional acceptance criteria at the time of filing, and changing them to final acceptance criteria post-approval?
    - HISTORICALLY: provisional acceptance criteria at the time of filing
    - NOW: authorization agreement post marketing
    - Originator – Biosimilar
        - Reanalysis of originator data does not "impact" originator product safety evaluation
5. To circumvent the lack of knowledge about manufacturing process variability, do you have experience with replacing end-product specifications by control of process parameters or starting materials, in the context of an integrated control strategy?
    - E.g. DNA specification
        - Getting rid of the specification based on platform knowledge at the time of licensing
        - Re-introduction of specification in other markets
        - If there is no danger to a particular Quality Attribute why should it be measured?

Session 2:
Considerations regarding setting specifications based on clinical experience versus specifications based on the manufacturing process capabilities

- Need to know how to apply statistics, and involve the statistical department as much as possible
- Five is generally considered to be the minimum number of batches for statistical significance
- Batches during development are generally manufactured at target settings; it would make sense to go to the edges of the process parameters
- Regulatory agencies only accept specifications based on clinical experience ("specifications need to be clinically relevant"); this means that you may need to tighten the specifications if the clinical experience is less broad that the manufacturing process variability
- Applying good statistics is key. For example, for setting acceptance criteria, tolerance intervals (and not confidence intervals) should be calculated. Also, it needs to be taken into account whether the data are (expected to be) normally distributed
- In case of biological assays, it is not unlikely that the analytical variability will be larger than the manufacturing variability; this may mean that in some cases the

specification may need to be based on method variability, whereas it would be desirable that the specification would be broader than the method variability
    - If you base specifications on results for the tox batch, make sure there are as little changes as possible in the manufacturing process
    - You can consider using development or engineering batches to justify specs, but they need to be representative for the clinical batches

- How to you set specifications for new products for which there is no or very little prior knowledge, or when you only make one batch during early development?
    - In such cases you could base control on process control ("the process is the product")
    - You can use prior knowledge for similar products (platform-type specifications), or take into account scientific considerations

- Regarding the specifications themselves:
    - Include the smallest, yet reasonable number of methods/quality attributes in specifications, do as much as possible in characterization
    - Specifications for potency should be relative to the reference standard/material