

Basis for Setting Acceptance Criteria

Representing EBE

Brian Withers, Director CMC Regulatory
Affairs, Abbott laboratories



Basis for setting acceptance criteria

Industry considerations:

- How to allow for Variability?
 - Different process used in Phase 1,2,3, commercial,
 - Different assays used at different stages
 - Limited Number of batches
- Clinical experience
 - Number of batches used in clinical studies can be limited
 - Linkage of some quality attributes to clinical outcome difficult
- To what extent can we use “other data”
 - “Prior Knowledge”
 - Product specific studies
 - Relevance of Quality Attribute
- How to not impede lifecycle improvements?



Sources of Variability

- Inherent variability
 - Based on biological system
- Introduced variability
 - Changes in manufacturing process during development will give variability
- Assay
 - Method variability
 - Method changes

Consistency

- We talk about ensuring consistency of the product
- BUT
- Should we not be more focused on answering the question “What is the acceptable level of variability that assures S&E”

Consistency vs Relevance to S and E? (1)

- How to balance these two?
- “Validation batches” can demonstrate consistency
 - DISCUSSION POINT: Do they alone indicate the variability that will be seen commercially?
- If we base specifications based only on consistency, we limit the ability to make future changes. Two examples in bit more detail
 - Glycoforms
 - HCP



Consistency vs Relevance to S and E? (2)

- Going beyond consistency
 - Use of additional process data
 - From pilot scale – design of experiments
 - From “prior knowledge”
 - From “Earlier “ processes
- Going beyond data from batches used in Phase 3 studies.
 - Use of Phase 2 data
 - Use of preclinical data
- Communication
 - CQA Risk Assessment
 - QTPP ranges justified based on S and E



Changes during Development (1)

- **DEVELOPMENT STRATEGIES DIFFER FROM COMPANY TO COMPANY AND ALSO FROM PRODUCT TO PRODUCT**
- From Tox to Phase 1
 - Cell line (e.g. polyclonal to monoclonal)
 - Formulation (Liquid to Lyophilised)
- From Phase 1 to Phase 2
 - Cell line (e.g. more productive clone)
 - Process (e.g. Scale change from Disposables)
 - Formulation Lyophilised to Liquid
- Phase 2 to Phase 3
 - Formulation (e.g. Vial to Syringe)
 - Process (e.g. Scale)
- Phase 3 to Commercial
 - Process (final “validated” process conditions)



Changes during Development (2)

- Discussion Point:
 - During development when we make changes the question is “Is the proposed material acceptable for the next phase of development?”
 - Is this the same as saying “the material used in phase 2 would be acceptable commercially?”
 - If so how do we use this information to help set specifications?



Sources of Data (1)

- Batch Analysis Data
 - Can be limited at scale
 - Validation (3 lots!!!??)
 - Demonstrate consistency, but do they give a sufficient measure of the future variability??
 - May never have been used in clinical setting
- Clinical experience
 - Number of batches in clinical can be small
 - Orphan indications – only one in phase 3
 - Not limited to Phase 3
 - Phase 2 will have often used higher doses
 - How much emphasis can be placed on this data?
 - Need to take account of stability data
 - Patients exposed to material with characteristics other than that indicated by batch release
 - Use of immunogenicity data.
 - Immunogenicity is not always a problem
 - ADA'S(APA'S?) do not necessarily impact on clinical effectiveness.



Sources of Data (2)

- Preclinical and Toxicology data
 - Batches may have differences compared to final commercial
 - DISCUSSION POINT
 - How to use this data?
 - Shows lack of toxicity, but immunogenicity across species difficult to interpret
 - Preclinical indicate PD ,mode of action etc
- In-Vitro assessments
 - Evaluation of stability in serum.
 - E.g., Assessment of Mab in serum shows significant deamidation within a relatively short period of time
 - Patient exposed to significant levels of deamidated product during clinical studies
 - Resulting S&E profile takes into account this exposure.
 - DISCUSSION POINT: Why would there ever be a need to set specification limits based on consistency?
- Post approval data e.g RMP, or Phase IV
 - Support Lifecycle approach to specifications



Analytical methods

- Change during development
 - How to compare data sets?
- “Normal Analytical method Variability”
 - Could be assumed that is accounted for by the variability of the batch analysis data.
 - BUT – Discussion Point
 - If only a small number of batches, should it be included as an additional source of future variability?
 - i.e. Insufficient tests to assume this source of variability included .
- Allowance for future improvements
 - Lifecycle of methods
 - “QbD” for Analytical method

Pharmacopeia Requirements

- Ph.Eur sets standards
 - Sub Visible particles
 - Endotoxins
 - Sterility
 - Visible appearance
 - Etc
- DISCUSSION POINT
 - What are the circumstances where we need to go beyond the standards set by the Ph.Eur?

Summary

- Lets have a discussion!!!!!!

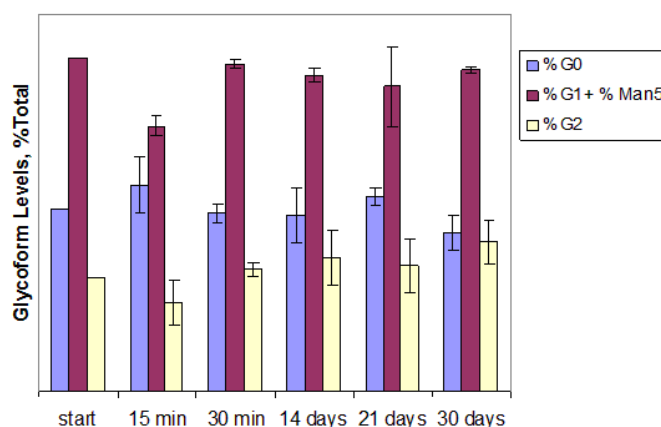
Thank –You

- Acknowledgements
 - Karin Sewerin
 - Christoph Lindenthal -Roche
 - Margit Jeschke - Novartis
 - Mark Schenerman - Medimmune

Glycoforms

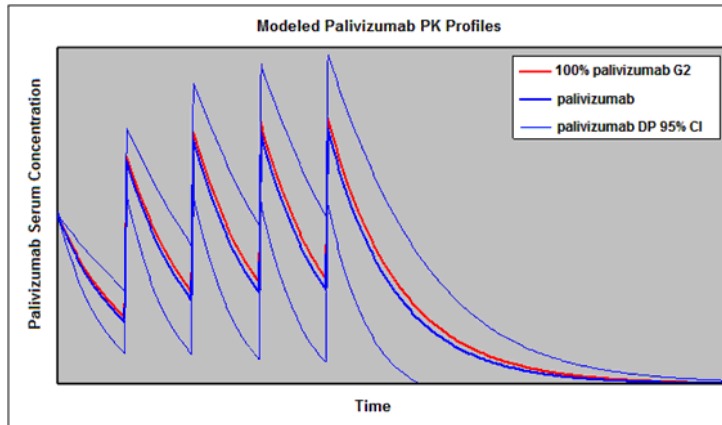
- If we set specifications for glycoforms based on consistency this could limit the ability to improve yields in the post approval setting.
- If specifications based on impact on S & E considerations wider limits can be supported.
- Example
 - Assumptions
 - No ADCC activity
 - Possible impact on pK
- Study/Assessment
 - Determine the behaviour of individual glycoforms in and model effect of pK
 - Determine ranges which will yield acceptable pk
 - Set specifications based on these limits
 - Wider than those based on batch analysis

Glycoform levels in palivizumab isolated from human serum PK samples



From: Schenerman, MA, Axley, MJ, Oliver, CN, Ram, K, and Wasserman, GF. (2009) "Using a Risk Assessment Process to Determine Criticality of Product Quality Attributes". in *Quality by Design for Biopharmaceuticals*. Eds: Rathore, AS and Mhatre, R. John Wiley & Sons, New Jersey, pp. 53-84.

Seasonal modeling of palivizumab and G2 glycoform PK profiles



From: Schenerman, MA, Axley, MJ, Oliver, CN, Ram, K, and Wasserman, GF. (2009) "Using a Risk Assessment Process to Determine Criticality of Product Quality Attributes". in *Quality by Design for Biopharmaceuticals*. Eds: Rathore, AS and Mhatre, R. John Wiley & Sons, New Jersey, pp. 53-84.

Phase 2 to Phase 3

- Example: Phase 2 vs Phase 3 dosing
 - In phase 2 half X , X , or 2X mg EOW studied.
 - In Phase 3 X mg EOW used.
 - Dose for phase 3 was selected based on "efficacy considerations" rather than any limitations based on safety.
 - When dealing with attributes such as aggregates, process and product related species should we consider these to be "clinically qualified" at limits based on the higher exposures used in Phase 2?
 - If not why not?
- Discussion point –How can the earlier data be used?



Specifications Limiting Design Space

