Making Medicines Affordable

EGA's Perspective on the Draft Quality Guideline

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Introduction

Many thanks for an excellent, science-based guideline!

Overview:

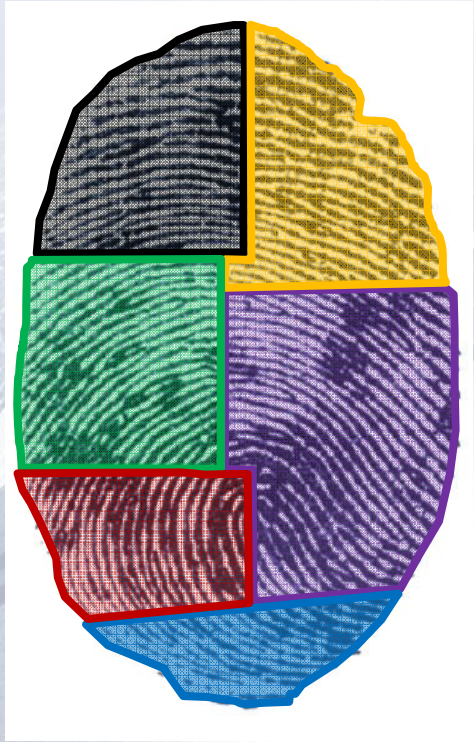
1. Quality target product profile
2. Different/novel expression systems

Biologics are understood extremely well today

Primary structure e.g.:
- LC-MS intact mass
- LC-MS subunits
- Peptide mapping

Impurities e.g.:
- CEX, cIEF acidic/basic variants
- LC glycation
- Peptide mapping deamidation,
- oxidation, mutation, glycation
- SEC/FFF/AUC aggregation

Biological activity e.g.:
- Target binding
- Activity
- F_c receptor binging
- ADCC
- CDC
- Apoptosis
- *In vitro* immunogenicity



Higher order structure e.g.:
- NMR
- CD spectroscopy
- FT-IR

Post translational modifications e.g.:
- NP-HPLC-(MS) N-glycans
- AEX N-glycans
- MALDI-TOF N-glycans
- HPAEC-PAD N-glycans
- MALDI-TOF O-glycans
- HPAEC-PAD sialic acids
- RP-HPLC sialic acids

Combination of attributes e.g.:
- MVDA, mathematical algorithms

Data integration provides more knowledge and certainty than the sum of the individual data

1. QTPP and similarity acceptance criteria

Relevant factors:

a)Variability observed in reference product

→ defines the target for product development

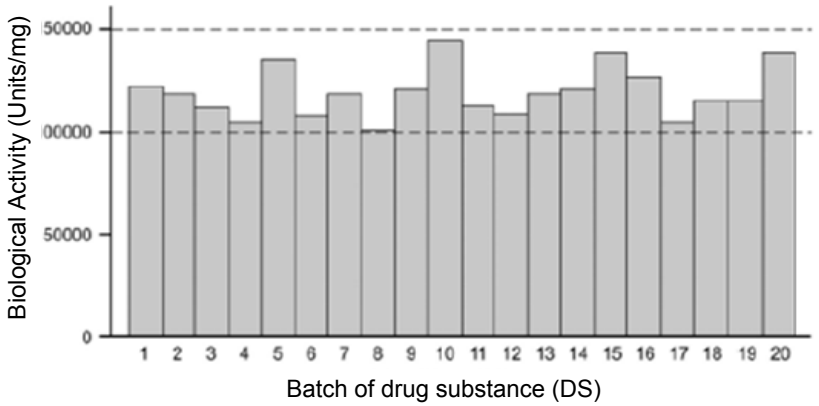
b)Criticality of attributes

→ Clinical relevance impacts the similarity acceptance criteria

a) Variability of the reference product

Batch-to-batch

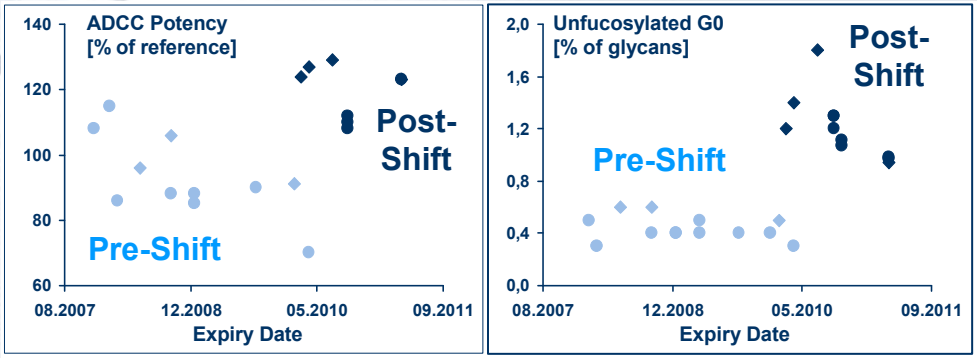
- Non-identicality is a normal principle in glycosylated proteins
- No batch of any biologic is “identical” to the other batches
- Variability is natural even in the human body and usually not problematic



Schneider, C. K.: Biosimilarity: A better definition of terms and concepts. *25th Annual DIA EuroMeeting*, 04-06/03/2013, Amsterdam

Manufacturing changes

- Manufacturing changes are made frequently
- Differences in attributes often larger than batch-to-batch variability
- Such changes are stringently controlled by regulators and approved only if they do NOT lead to clinically meaningful differences

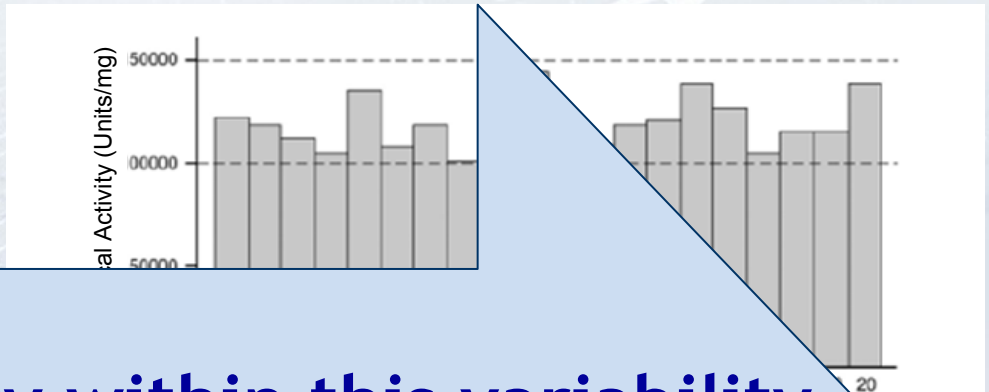


Schiestl, M., *et al.*: Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceuticals. *Nature Biotechnology*, 29: 310-312, 2011

a) Variability of the reference product

Batch-to-batch

- Non-identicality is a principle in glycosylated prote
- No batch of a identical" to the othe
- Variabi bod



Safety and efficacy within this variability have been demonstrated in clinical studies and by real-life experience with the reference product

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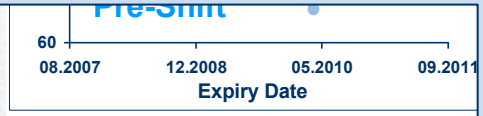
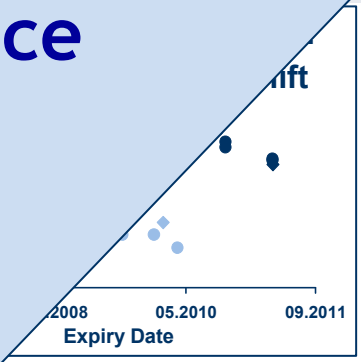
approved

clinically





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b) Clinical relevance (criticality) of the attribute 1/2

Systematic criticality assessment must be performed on all quality attributes

- **Impact on safety and efficacy is what matters**
- **Much is known about the clinical relevance of the various quality attributes**
  - Has been managed well after manufacturing changes
  - Structure-function relationships studied systematically
  - Much known from literature and previous experience

b) Clinical relevance (criticality) of the attribute 2/2

- **The culprits are well known, e.g.**
  - Sialylation ↔ PK
  - Fucosylation ↔ ADCC
  - Gal-α1,3-Gal ↔ immunogenicity
  - Aggregates ↔ immunogenicity

- **Criticality should be evaluated in a systematic and quantitative way**

Acceptance criteria are based on RP variability AND clinical relevance

- Two elements impact acceptance criteria:
  - Variability of reference product
  - Clinical relevance of attribute
- Flexibility for attributes with no clinical impact is higher
- One-sided ranges for similarity exercise often appropriate (e.g. less aggregates acceptable)
- EMA may want to describe this risk-based approach in more detail in the guideline

2. Different/novel expression systems

Different and novel are separate things

- Different expression systems that provide similar attributes and have equal or better safety track records

  → Doable

- Novel expression systems that have NO safety track records

  → Challenging

2. Different/novel expression systems: Examples

- **"Doable": CHO instead of SP2/0**
  - Closely related systems (hamster, mouse)
  - CHO has even better safety track record
  - Provide similar attribute profiles, but CHO avoids some issues (e.g. Gal-α1,3-Gal)
- **"Challenging": Algae instead of CHO**
  - Very different systems
  - Algae have no track record
  - Provide very different attribute profiles

Summary

- The **target** for development is determined by the **variability** in the reference product
- The **similarity acceptance criteria** depend on the **clinical relevance** of the attributes in addition to RP variability
- Therefore, a purely statistical approach to setting acceptance criteria is insufficient
- If a **different expression system** is used, it must still yield a **comparable CQA profile**