Klinikum rechts der Isar
Technische Universität München

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory reflections on biosimilar development and statistical methods used at quality level

- *EMA draft reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development*
- *Comments received during public consultation phase of EMA*
- *workshop - content and outcomes*

4th Annual Biosimilars Forum

Presented by Ina-Christine Rondak on 18 October 2019
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Disclaimer

The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties nor the TU München.

Conflicts of interest: none

Outline

Objectives and timelines of EMA draft reflection paper

Comments received during public consultation

EMA workshop

Overview and summary of discussions

Learnings and way forward

Reflections on statistical aspects at quality level – history and timeline

2013

BSWP drafted and published **concept paper**

2014

BSWP drafts reflection paper with input from **BWP, BMWP, QWP**

2017

Mar

CHMP adopts **draft reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development**

Mar

End of 1 year public consultation phase

May

Creation of **multi-disciplinary drafting group** representing all involved working parties: **BSWP, BWP, BMWP, QWP**

2018

Sep

Release FDA guidance 1 (biosimilars)

May

Multi-disciplinary **workshop** on draft RP held at EMA with Industry and EU network experts

Meeting report and presentations available on website.

2019

Jun

Withdrawal FDA guidance 1 (biosimilars)

May

Release FDA guidance 2 (biosimilars)

Nov

EMA's Brexit preparedness business continuity plan (**BCP**):
Scaling back of guideline development

Future

Finalisation of reflection paper

Objectives of draft RP

Areas of interest

- Pre- and **post-manufacturing change**
- **Biosimilar** development
- **Generic** development

Scope

- Focus on methodological aspects
- Raise open issues from statistical perspective
- Address questions related to:
  - **Objectives** of comparisons
  - **Sampling** strategies
  - **Sources of variability**
  - **Options** for statistical inference and acceptance ranges

Aim

- Establish a **common language**
- Improve understanding among experts from various disciplines
- **Trigger discussion** vs. impose rules
- Discuss case studies and likely limitations hampering statistical inference
- Point out meaningful alternatives

Overview of general comments received during public consultation of draft RP

- Concerns/Reservations
- Conflicts/Shortcomings
- Support

Comments on draft RP

Concerns and reservations

- **"*Statistical testing should not become a pass/fail criterion without reflection of context and involvement of CMC experts*"** (n=8 commenters/15)
- Totality of evidence-based decision making shall not be endangered
- Scope of reflection paper is too broad, we need more specific reflections dependent on the setting
- Where is the gap for biosimilars, we have a good system in place
- Content of reflection paper expected to impose additional hurdles → adverse implications for healthcare systems and payers

Comments on draft RP

Conflicts and shortcomings

- **RP gives no answer to question: What is similarity?**
- Can „consistent manufacturing" ever be compatible with shift/drift in means?
- **Is „equivalence testing of means" meaningful in presence of shift/drift in means?**
- RP promotes equivalence testing of means, this is in contradiction with other ICH guidance
- Statistical tools using intervals are unnecessarily depreciated
- Specifications already provide sufficient control since they are clinically qualified

Comments on draft RP

Conflicts and shortcomings: biosimilar setting and special issues

- **Considering lower variability for the BS a problem contradicts GL**
- Systematic within-specs changes not addressed in RP
- Elaboration on question which DPs are from the same DS (dependence)
- (unknown) age of RMP batches important source of variability, not sufficiently addressed in RP
- Stability data comparison not sufficiently covered
- RP tends to disregard a well-developed continued process verification (CPV) program, which could be used to support/replace a small comparative study
- RP does not adequately cover multiplicity and dependencies between QA

Comments on draft RP

Support

- **Overlooked topic & regulatory reflection/guidance needed**
- RP well thought through giving proper scientific considerations
- **Nature of inference widely misunderstood** & appropriate inferential statistical assessment will result in **better decision making** (i.e. stat. inference better option than some qualitative approaches seen)
- General scientific principals are the same for biosimilar setting and pre-post-change but different rigor in different settings of comparing QAs meaningful
- For biosimilars: imbalance of information about RMP and BS
- Larger samples/collection of more relevant information to be rewarded/incentivised

Workshop on the draft reflection paper on statistical methodology for the comparative assessment of quality attributes

Workshop organisation and format

- **1.5-day workshop** on 3-4 May 2018 at EMA
- Organisation committee representing **all involved working parties**:
  - Biostatistics (BSWP)
  - Biosimilars (BMWP)
  - Biologics (BWP)
  - Quality (QWP)
  - and EMA Biostatistics Office
- **5 sessions**: each including 4 presentations followed by discussion
- **2 additional closed sessions for regulators only** at the end of each day to reflect on discussions

Scope and objective of workshop

- **Discussing comments received** during public consultation phase
- Better understanding challenges seen by industry and opportunities (e.g. illustrated by **case studies**)
- Discussion of methodological approaches and suitable alternatives
- Facilitating further progress and developments in this field

- **Multi-disciplinary scientific workshop** touching upon quality, manufacturing, statistics, and methodology areas. Corresponding expertise was sought from participants and external stakeholder could participate **by invitation only**

Participants

- **31 Industry participants**, representing industry associations (A3P, AAPS, APIC, EBE/VE, EFSPI, ISPE, Medicines for Europe)
- **31 EU regulators** from 21 national competent authorities and universities and 6 working parties and committees (BWP, BMWP, BSWP, PKWP, QWP and CHMP)
- 1 **FDA** representative (scope biosimilarity)

Highlights and key messages per WS-session

(more detailed WS report incl. presentation available on dedicated website)

A: Problem statements & challenges

Clear understanding of **fundamental concepts** and definitions is vital

Importance to **define clear objectives** of the comparison task

Discussion whether **general concepts** a**pplicable to all settings**

B: Case studies: pre/post change

Various definitions and interpretations of **'consistent manufacturing'** have different methodological implications

C: Case studies: biosimilars

Impact of **sources of variability** and **shifts/drifts** in reference product

E: Operating characteristics of existing criteria

Frameworks to explore OCs dependent on various factors needed

F: New strategies and alternatives

New strategies to improve **experimental design & statistical analysis**

Learnings from the workshop

1. **Different contexts** require **separate considerations**
2. **Clarification of terminology** and language (e.g. descriptive vs inferential, consistent manufacturing, etc.)
3. Important to understand **operating characteristics** (OCs) of methods used for comparisons and well understood frameworks to visualize OCs will be important to identify suitable similarity criteria
4. There is **no unique optimal** similarity **criterion**
5. Agreement that **quality of decision making can be improved**

Immediate recommendations after the workshop

- **Clarity about objective and weight** of comparative QA data comparison:
  - Inferential approach or 'just description'?
  - What are the implications if similarity is shown at quality level
  - What are the risks if wrong decisions are made?
- Reflections on **operating characteristics** of methods
- **Pre-specification**: what can be approached prospectively, e.g. by a (written) plan? More transparency regarding sampling approach and acknowledgment of limitations
- **Identification of important sources of variability** and possibility to **account for them in sampling and analysis**
- **Proposals** to be discussed e.g. in **Scientific Advice** procedures

What happened since then?

- Strengthened the newly emerged **multidisciplinary interaction**
  - Creation of a **multidisciplinary task force** from B/BM/BS/QWP to address comments received and WS outcome
- **Reflections by other stakeholders** seen in
  - Innovation Task Force meetings, Scientific Advices, Centralised Procedures
  - Scientific publications

What happens next?

- **Finalisation of Reflection Paper**
  - Will remain "reflection paper", not guideline
  - RP expected to become more general in nature (and shorter) based on learning that flexibility needs to be maintained
  - Reflection on impact of false positive conclusion on overall decision making
  - Framework for evaluation of similarity criteria via operating characteristics
  - Suggestions for prospective planning

- **Further implications** on other guidelines in areas of interest to be discussed
- Liaising with other regulatory regions to strive for **harmonisation**

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Questions and comments?

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