Bundesamt für Sicherheit im Gesundheitswesen
BASG

The Biosimilar Tailored Approach

The quest of Sisyphos?

René Anour, AGES, Chair EMA Biosimilar Medicinal Products Working Party (EMA BMWP)

What “everyone“ says

Entirely sure … are we?

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Clinical trials for Biosimilar are unnecessary
- They are insensitive
- Why are we still doing them
- They should not be required since YESTERDAY

In principle: Yes

There are some good reasons …

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Technology in characterisation has advanced
- For most orginators MOA is known
- We still have the PK
- Retrospectively: no cases where clinical difference was not “anticipated“

But how exakctly…

How can Quality PROSPECTIVELY account for clinical comparability

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Puzzled Looks
- People shy away
- How to deal with uncertainty?
- Will we have more failed applications?
- What accounts for similar efficacy/safety/immunogenicity with what margin?

Maybe it is not THAT simple

And nobody knows - YET

The general philosophy

Clinical trials – a blunt instrument?

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- address slight differences shown at previous steps.
- Cannot justify substantial differences in quality attributes
- **confirm comparable clinical performance** of the biosimilar and the reference product.
- Reference: Guideline on similar biological medicinal products (https://www.ema.europa.eu/en/similar-biological-medicinal-products)

When are efficacy trials necessary?

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Per default: required

- RCT, using efficacy endpoints.

- population should generally be sensitive for detecting potential differences

- In general, an **equivalence design** should be used. The use of a **non-inferiority** design may be acceptable if justified. It is recommended to discuss the use of a non-inferiority design with regulatory authorities

What about safety?

Important throughout clinical development

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- captured during initial PK and/or PD evaluations as part of the pivotal clinical efficacy study.
- normally be collected pre-authorisation
- their amount depending on the type and severity of safety issues known for the reference product. The duration of safety follow-up
- As regards immunogenicity assessment, applicants should refer to existing CHMP guidance (EMEA/CHMP/BMWP/14327/2006 Rev 1, EMA/CHMP/BMWP/86289/2010)

Product specific Guidance

Most do not strictly require an efficacy trial

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- recombinant granulocyte-colony stimulating factor
- low-molecular-weight heparins
- recombinant human insulin and insulin analogues
- interferon beta
- recombinant erythropoietins
- recombinant follicle-stimulating hormone
- somatropin
- Monoclonal antibodies

- https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar#-product-specific-biosimilar-guidelines-section

Exceptions to the usual

When can efficacy trials already be omitted?

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- PD markers as established surrogate for efficacy
  - If not reflected in product specific Guidance – seek EMA feedback

- A **comprehensive** and meaningful quality comparability is available and allows for a **tailored clinical approach**

The Tailored Scientific Advice

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Preassessment of Quality to allow for tailoring of clinical program

- EMA offers tailored scientific advice on development programmes of new biosimiliar medicines.

- The tailored procedure advises developers on the studies they should conduct, based on a review of the quality, analytical and functional data they already have available

Reference: https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance#scientific-advice-on-biosimilars-section

Are there examples for Monoclonals?

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Feasibility vs Comprehensiveness

- 2 Eculizumab Biosimilars (Bekemv and Epysquli)
- Small PD studies (n=42/n=50) in PNH patients.
- Efficacy based on LDH/breakdown of RBC

→ Tailored approach based on feasibility

- https://www.ema.europa.eu/en/medicines/human/EPAR/epysqli
- https://www.ema.europa.eu/en/medicines/human/EPAR/bekemv

The Future

How the need for comparative efficacy trials might evolve

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- It is planned to issue a **concept paper** outlining high level principles regarding a tailored clinical approach based on quality data

- Scope: tbd

Some really preliminary ideas …

How could this be approached

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Explain for stupid clinical experts (like myself)

Group quality attributes around clinical parameters

How well can e.g. the mode of action be covered?

WHAT IS A RELEVANT DIFFERENCE AND WHY

Methodology and Quality

Not the closest allies so far

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- *Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development*

- Criticality assessment needs to include:

  - Why and for what is this critical
  - What is a relevant difference
  - What is the best method to measure this (sometimes confirmatory statistics make sense, sometimes they dont)

Some Considerations

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Which changes in QA which impact
  - occurrence and detection of deviation
- Every CQA : similar or not
- Use a prespecified rule for an overall decision based on singular decisions.
- One-size-fits all not realistic

So is it going to be easy?

The rock is not over the top … yet

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Absolutely not!
- Discuss any concept with regulators beforehand
- Argue with science not policy
- Engage, when guidamce will be put out for consultation

Bundesamt für
Sicherheit im
Gesundheitswesen
BASG

Thank you!