Bundesamt für
Sicherheit im
Gesundheitswesen
BASG

Rethinking Biosimilars

Live or Death of a Concept

Dr. René Anour

AGES, Chair EMA BMWP

Biosims in a nutshell

Like generics but for biologics

Bundesamt für
Sicherheit im
Gesundheitswesen
BASG

- Copies of Biologics
- But not identical (most biologics are too complex to just copy)
- Biologics often cost thousands of Euro/shot
- Biosimilars are important to increase access to these highly effective drugs
- Experience shows: even in high access countries, access improved

Last year at Biobridges

Reducing the clinical program of biosimilars

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Everyone talked about it
- No one could name conditions
- BMWP reinitiated
- Concept Paper (aka Letter of Intent) planned

Concept Paper and Reactions

Draft Discussed at CHMP in December 23

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Letter of Intent saying …

We have a problem:

„The biosimilar void“

We have a problem pII

Losing clinical models

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- The first wave of Mabs has passed
- No good clinical models and large effect sizes
- Now we have small effect sizes
- Complex models
- Co treatments and orphans

A typical example

Comparability in a Cancer setting

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Nivolumab
- Setting for a clinical trial
- Advanced melanoma (on top of chemo)
- BOR within 24 weeks
- Equivalence Margin mathematically preserves 50%

What does that mean?

Bundesamt für Sicherheit im Gesundheitswesen
BASG

In an extreme case, a response that is 50% lower and happens six months later would formally be considered similar.

→ And HPs insist on such trials and base their trust upon them

Further problems

- Small effect sizes → huge trials
- Orphan settings – what can (should be) accepted

But also the positive needs to be menioned…

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- A number of papers analysing retrospectively the connection between quality and clinical comparability
- No case identified, where clinical showed difference not observed on quality
- No prospective value, but still!

Reception of the Concept paper

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Surprisingly uncontroversial
- Some WPs: We will decide later …

So, what's the consequence

„Just" changing everything

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Drafting a Reflection Paper on the tailored clinical approach
- Rethinking product specific guidance
- Review the Tailored Scientific Advice

Bundesamt für
Sicherheit im
Gesundheitswesen
BASG

Reflection Paper on a tailored clinical approach in Biosimilar development

A call to work for streamlining Biosimilar MAA

René Anour, AGES, Chair BMWP

History and Scope

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- A lot of experience has been gained in 17 years of the Biosimilar MAA
- Product specific guidelines allow tailoring for „simpler“ molecules
- Publications analysed retrospectively the correlation between Analytical/Functional level with comparative efficacy trials
- All Biosimilars technically included

Why do we believe, the work is needed

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Technology and Understanding in establishing Quality Comparability has evolved.
- Only 50% of Biologics getting off patent in near future have biosimilar candidates in Pipeline
- Current and upcoming Biosimilars include molecules where sensitive and meaningful clinical models for comparability are unavailable (or difficult to conduct)
  - Small effect size
  - Add on therapeutics
  - Orphan medicines

Goal of the Reflection paper

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Streamline the development and evaluation process while maintaining the highest standards of safety and efficacy

Explore guiding principles how analytical/functional testing (together with PK) can serve as a base for B/R.

How is the current status?

Drafting groups instituted

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- BMWP has installed a quality and a clinical drafting groups
- Both groups work in parallel and liaise once a month
- Focus will be on quality part

Current Timeframe

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Relevant WPs will be included for comments in October
- Presentation to CHMP
- Out for Consultation (2025)

The future role of PD

Is ist still the saviour?

Bundesamt für Sicherheit im Gesundheitswesen
BASG

In the past: PD study could lead to waiving efficacy if:

- PD Marker is validated surrogate for efficacy
- PD Marker is validated surrogate for pharmacological action

How often was that done?

The role of PD is heavily discussed…

A first approach

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Hardly any biologic has validated biomarkers in place

Qualification long process

Only more simple biosimilars have been auhorised in the past based on PD

What would it change, if we emphasized the meaning of PD?

PD should not be a default when evaluating a reduction of clinical data

Which molecules should be excluded?

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Can one make a „black and white“ list?
- What should be the criteria?

Immunogenicity

The very reason we were having trials in the first place

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Should highly immunogenic biologics be excluded?
- Controversial
- My take: No, if characterisability is good
  - Some immunogenicity will be evaluated in PK trial

Therapeutic Dose in steep part of Dose/Response

Aka small differences might have bigger impact

Bundesamt für
Sicherheit im
Gesundheitswesen
BASG

- Should those drugs be excluded?
- Clinical performance more easily influenced
- My take: No, if characterisability is good
  - We still have exposure!

Complex Biologics

Hard to characterise?

Bundesamt für
Sicherheit im
Gesundheitswesen
BASG

- What are those even?
  - Mixtures?
  - Therapeutic platforms
  - Unclear mode of action
- Yes, such products could/should be exluded
- However …
  - Technology evolves fast (will not be stated explicitly)
  - Are they even feasible for Biosim Development at all

How will Quality be compared (differently)?

Two worlds will be merged – first thoughts

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Fusion of classical quality comparability and methodology

Better communicate criticality

Prespecification for Attributes of high impact

Emphasize quality control sytems

Allow for flexibility for the less important attributes.

Bundesamt für Sicherheit im Gesundheitswesen
BASG

An example of EMA regulatory “flexibility”

Dr. René Anour, AGES,

Chair EMA Biosimilar Medicinal Products Working Party

The Tailored Scientific Advice

A tool for abreviated approaches

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Allows for evaluating tailored approaches already
- Uptake has been limited
- Process currently undergoing revision
- Stronger Uptake expected when guidance is adapted
- Input from applicants Welcome to make process more useful
- Is a separate form of Scientific Advice REALLY needed?

Example 1 – Biosimilar Eculizumab

Excipient „Sorbitol“ as source for discussion

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- First Biosimilar Candidate for Soliris
- Comparability on all levels demonstrated (without a CES!)
- Formulation contains Sorbitol (as opposed to originator)
- Issue for patients with Fructose Intolerance (as opposed to originator)

Instead of raising doubts regarding biosimilarity …

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Adapted PI and Pharmacovigilance measures

- Contraindications for fructose intolerant patiens and babies/children below 2 (Section 4.3. of the PI)
- Pharmacovigilance Measures: included in the Risk Management Plan
- educational materials: physician's guide, patient's/parent's information brochure, and patient safety card.

(European Medicines Agency: Information for the package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human use; EMA/CHMP/460886/2014).