



EUROPEAN GENERIC AND BIOSIMILAR MEDICINES ASSOCIATION

European Biosimilars Group
EGA sector group

Biosimilar Product Labelling

The view of the Biosimilar medicines Industry

Ingrid Schwarzenberger, Sandoz
Brussels, 2 February 2016

PATIENTS

Increasing patient access



QUALITY

Quality, safety and efficacy



VALUE

Investors in innovation



SUSTAINABILITY

160.000 jobs across Europe



PARTNERSHIP

Key partners for public health





European Biosimilars Group
EGA sector group

EGA Vision 2020



To provide sustainable access to high quality medicines for all European patients



European Biosimilars Group
EGA sector group

EGA Vision 2020

EGA VISION



PATIENTS



QUALITY



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SUSTAINABILITY



PARTNERSHIP



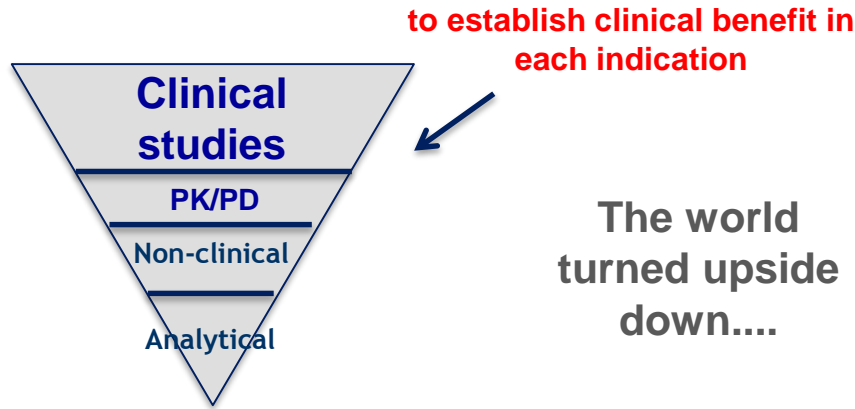
Safe and efficacious Biosimilars are on the EU market for more than a decade

- The biosimilar paradigm has evolved and the regulatory framework is continuously updated since 2005
 - 2005: science-driven conceptual approach
 - 2016: science-driven knowledge-based approach
- **Successful regulatory biosimilar framework** resulted in currently 20 biosimilar marketing authorizations in the EU (7 different molecules) - with confirmed safety and efficacy: Biosimilars behave as expected ¹
- The demonstration of biosimilarity relies on:
 - The foundation → **extensive structural and functional characterization**
 - The comprehensiveness → **totality-of-the-data from all levels of the comparison**
 - The confirmation → **selective and tailored clinical studies**
- **The role of clinical studies differs completely** for biosimilar development and originator development
- **Biosimilarity (comparability) applies to all biologics** during their life-cycle

¹ EC representative at Workshop on Biosimilars, 6 Oct, 2015: “Since 2006, EU-approved biosimilar medicines have already generated more than 400 million patient days of clinical experience worldwide”.

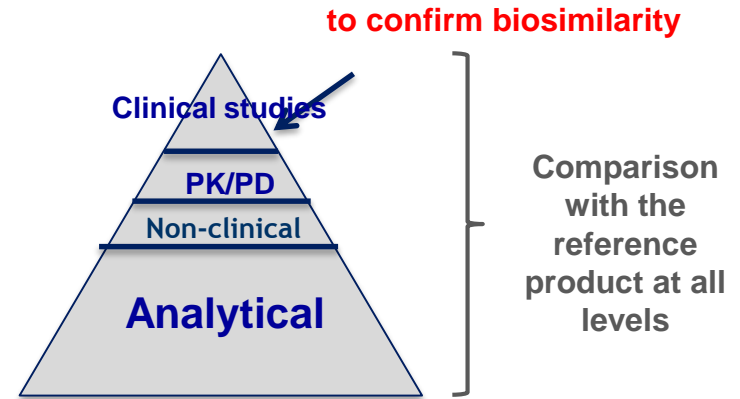
Biosimilar development ensures similarity to the reference product at all levels

Originator development



- New active substance
- Establishment of clinical benefit
- Clinical study to establish clinical benefit
 - Positive benefit/risk profile in each indication targeted

Biosimilar development



- Known active substance
- Establishment of analytical similarity
- Clinical study to confirm biosimilarity
 - Sensitive model to detect potential differences
 - Potentially, different study design, different endpoints and patient populations



Information to Physicians and Patients can be improved

- Need for an improved general information on medicines was/is acknowledged by all in multi-stakeholder discussion platforms (eg. EC DG GROW)
- Important aspects to understand prior one can envisage solutions:

Availability

- Which information?

Accessibility

- Which support / vehicle / tool?

Suitability

- What for ? Which purpose?
- Which audience?



Are we facing a transparency issue?

- **Most of the sought for information already exists e.g.**
 - The basis for authorisation (EPAR + EPAR summaries in several EU languages)
 - The instruction for use of a medicinal product (SmPC)
 - The experience and signal detection (PSURs, ADRs)
 - EMA Policy 0070 on publication and access to clinical-trial data
 - National prescribing guidelines (where applicable)
 - Other...

Availability

→ Does not appear as the primary concern



For today's discussion: Can labelling increase accessibility and suitability?

Accessibility

- Which support / vehicle / tool?

Suitability

- What for ? Which purpose?
- Which audience?

- Labelling is one important and regulated source of information on the instruction for use of a medicine
- Labelling forms an integral part of the EU regulatory framework and potential changes should be considered in a holistic manner
- There may be more effective ways to provide tailored information other than the product information



Focus on the medicinal product label: what is the purpose?

The Label - what it does



- Informs healthcare professionals and patients on how to use the medicine safely and effectively¹
- Is updated if use changes (new indications, new safety information, restrictions in use, ...)

The Label - what it does not



- Does not recapitulate the development and assessment history of the product (neither pre- nor post-approval)
- Does not describe the approval pathway

Suitability

- The label of a medicinal product is an instruction for use of the product
- It is not a history book about the product's development and approval history

¹ EU Commission - Notice to Applicants: A Guideline on Summary of Product Characteristics (SmPC), September 2009

Biosimilars refers to the reference product in all aspects - including the label

The approval of a marketing authorisation confirms

- **Biosimilarity** = “Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy”¹
- **Clinical performance will be equivalent**
 - no scientific reason to expect otherwise
 - track records confirm the scientific reasoning
- “The posology and route of administration of the biosimilar must be the same as those of the reference medicinal product.”¹

➤ **The same label is applicable for the biosimilar - as communicated and issued by EMA²**

¹ EMA overarching guideline

² EMA QRD general principles regarding the SmPC information for a generic/hybrid/biosimilar product



Recent requests for “transparency” only serve as a barrier to biosimilar use

- The main argument put forward:
 - “Transparency“ on (especially) clinical data for a biosimilar would be needed so that the doctor can make an “informed decision” which product is best for which patient
- The question is:
 - Why focus on biosimilars and on SmPC/PIL when the apparent issue is rather a question of suitability (language) and accessibility to information (which tool, which platform)?
 - If information on product development, product registration and product life-cycle is deemed important, why restrict the discussion to Biosimilars?
- This narrow focus only leads to confusion and defeats the initial ‘information’ objective of the label
- If information on the different versions of biological substance is needed, which vehicle is the most appropriate?

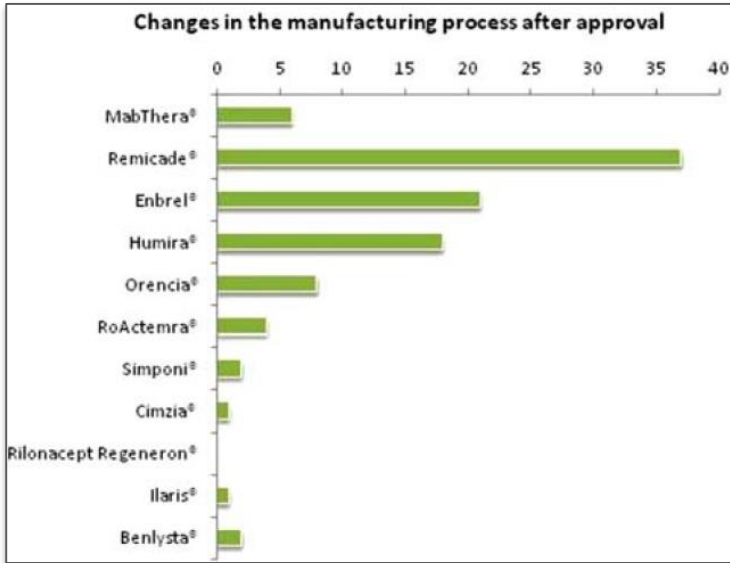


The reality is: strategies vary, not the strict regulatory supervision

- All medicines have options for their
 - development (eg, clinical studies, comparability)
 - regulatory approval (eg, full dossier, biosimilar, adaptive pathway)
 - life-cycle (eg, manufacturing changes)
- For all biologics, variability is an inherent features - there are only “versions” of biological medicines¹
 - no batch is “identical” to another; they are only comparable wrt Q,S,E
 - analytical data has been used for 20 years to control this variability: for batch-to-batch consistency, for major manufacturing changes, and now for biosimilars
- **Strict regulatory supervision** and constant adaptation to scientific evolution ensures a robust framework
 - **Where regulators give approval for biologics: the variability is deemed “clinically not relevant”, the use of the product(s) remains the same and therefore the label remains the same**

¹ EMA overarching guideline

Variability of biologics is controlled and not relevant for the label



C. Schneider, Ann Rheum Dis March 2013 Vol 72 No 3

Examples: Major manufacturing changes of biological products are allowed and occur frequently

- Rituximab with altered ADCC (a potential mode-of-action of the product)
- Etanercept with altered glycosylation (50% enrichment of G2F decreased to 30%)
- Aranesp with change of master cell bank resulting in significant changes in glycosylations

M. Schiestl et al. Acceptable Changes in Quality Attributes of Glycosylated Biopharmaceutical; Nature Biotechnology (2011) 29:310

Q, S, E are deemed comparable with no expected clinical meaningful difference

Approved indications remain the same (no systematic confirmatory clinical trials)

Use of the product stays the same

Label remains the same



The biosimilar label must remain useful, informative for its purpose, and fair

Suitability and Accessibility can be improved outside the medicine's label

Biosimilar analytical data in the label is not useful in guiding use of the product

- Providing analytical data to those not skilled in interpretation will confuse stakeholders
- Analytical data from manufacturing changes are currently not reported in the label

Biosimilar preclinical data in the label is not useful in guiding use of the product

- Preclinical data from animal studies is regarded as least informative for the biosimilarity assessment
- With the active substance of the biosimilar being known, preclinical studies only provide some „comfort“ that nothing seriously had been overlooked in the analytical assessment
- Updated biosimilar regulatory guidance reduced the need of animal studies significantly

➤ Analytical data proves “sameness” to regulators; it is not useful in the label

➤ If policy changed, the label of all biologics should include analytical data from manufacturing changes

Preclinical data supports “sameness” to regulators; it is not useful in the label



The biosimilar label must remain useful, informative for its purpose, and fair

Biosimilar clinical data in the label is not useful in guiding use of the product

- The role of biosimilar clinical trials differs from their traditional role in originator development: confirmation of “sameness” and do not reproof of safety and efficacy
- Designs often use different endpoints, treatment duration and statistical justifications to demonstrate sameness
- PK/PD comparisons are often more informative for biosimilars than comparative safety & efficacy studies
- Biosimilars with proven analytical similarity in all measurable parameters may have more streamlined clinical programs than biosimilars that need clinical studies to exclude clinical relevance of differences seen in the analytical assessment
- In the very few cases where manufacturing changes required clinical studies, these were at maximum conducted in one indication (and extrapolated to all other indications) and were not included in the label

- HCPs and patients will interpret the lesser amount of clinical data (or different approach) as lower level of evidence
- Providing specifics of clinical trial designs and data in the label will only confuse stakeholders
- If policy changed, the label of all biologics should include clinical data from manufacturing changes (or justify the lack of it)



EMA has chosen the right scientific approach for the biosimilar label

- EMA has followed through the science-based conceptual approach for Biosimilars and decided that the biosimilar label should be the same as that of the reference product ¹:
 - Based on the demonstrated biosimilarity between the biosimilar and the reference product and upon approval, the biosimilar product has a comparable quality, safety and efficacy profile
 - Confirmed by real world evidence (10 years in the EU)
 - Therefore, the safety and efficacy data of the reference product are equally relevant for the biosimilar product
 - The approved biosimilar products in Europe follow the reference product labels
- This is the correct scientific and legal approach and should be maintained!
- The trust in the regulatory approval process of biologics should not be undermined - and surely not for biosimilars only

¹ EMA Communication on SmPC for Generic and Biosimilar Products,



- Transparency is not an issue at the moment
- Suitability and accessibility of available information on medicines
 - Best achieved in multi-stakeholder set up where the EBG is engaged
- Transparency cannot be a ‘pick & choose’ exercise: a fair, consistent and holistic approach is required
 - For all medicines, development and life-cycle, across registration pathways
 - Unbiased information is a key pillar to communication
- **EU regulators have followed through the Biosimilar concept and have approved the same label as for the reference product**
 - the right scientific and legal approach - fit for purpose