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GaBI Educational Workshops

First Turkish Interactive Workshop on Regulation and Approval of
SIMILAR BIOTHERAPEUTIC PRODUCTS/BIOSIMILARS

2–3 March 2016, Hacettepe University, Ankara, Turkey

Regulatory frameworks for biosimilars: WHO and other perspectives

Elwyn Griffiths, DSc, PhD

3 March 2016

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

HACETTEPE UNIVERSITY
PPCI Pro Pharma Communications International

Regulatory frameworks for biosimilars: WHO and other Perspectives

Elwyn Griffiths

WHO Consultant

With Ivana Knezevic and Hye Na Kang

Ankara, Turkey, 2016

Outline of presentation

- Biosimilars- scientific / regulatory challenges
- Role of the WHO
- Discuss how biosimilars might be regulated
- Outline WHO Guidelines for Similar Biotherapeutic Products
- Briefly discuss some differences in details between jurisdictions- eg choice of reference product, differences in nonclinical evaluation - EMA, Health Canada, FDA Regulations

Arrival of Biosimilars

- Increasing number of patents/data protection for rDNA derived biotherapeutics expiring or have expired
- Biotherapeutics “similar” to an innovator product now coming to the market
- Expect to be licensed subsequent to the approved innovator product but **on the basis of a reduced data package**

Drivers and Interests

- Alternatives to innovator products expected more affordable – may contribute to increased **access**
- Global markets for biologicals growing and attractive - so considerable global interest
- Encouraged by World Health Assembly Resolution 2014 on biotherapeutics

- **Difficult and contentious issues**
- Relate not only to science but also to regulatory processes and to legal aspects, patents/data protection
- **Key question** how to handle the licensing of these products if relying in part, on data from innovator product – regulatory pathway ?

Considerable Consultation – national and international since 2004

- Better understanding of directions and challenges in the regulatory evaluation of the quality, safety and efficacy of “biosimilars”
- Exchange of information between regulators, the identification of key issues and gaps, and recommendations on the next steps
- Wide range of regulatory preparedness - EMA (Europe) well ahead
- Clear need for global road map
- **Discussed at ICDRA 2006**

International Conference of Drug Regulatory Authorities (ICDRA)

- Forum for discussing various regulatory issues and ways to strengthen collaboration.
- Guides regulatory authorities, WHO and interested stakeholders
- Recommends priorities for action in national and international regulation of medicines, biomedicines and herbals
- **In 2006 discussed the issues of biosimilars and proposed action by WHO**

Role of WHO

- Not a regulatory agency
- WHO has played a critical role in the biologicals field for over 60 years
- **Setting global norms and standards for biologicals**
- Promotes their implementation
- Regulatory capacity building
- Pre-qualification of vaccines

- **WHO Biological Measurement Standards (physical):** Calibrating national references , basis of quality control, regulation

- **WHO Written Standards** (Recommendations and Guidelines) **take a global perspective**

WHO BIOLOGICAL STANDARDIZATION ACCOMPLISHED THROUGH

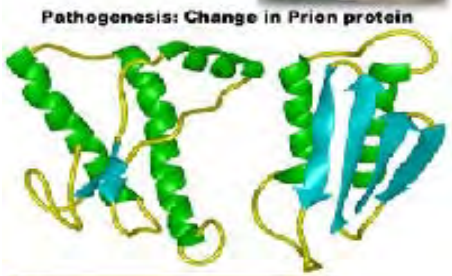
- Its biologicals programme – WHO Secretariat
- WHO Expert Committee on Biological Standardization (ECBS) (1st met1947)
- WHO Collaborating Centres
- Development of Biological measurement standards involves collaborative studies in numerous laboratories world wide
- **Written standards based on scientific consensus achieved through much international consultation**
- Involves pharmacopoeias, national regulatory authorities (including FDA,EMA), manufacturers associations (IFPMA,DCVMN,IGPA/EGA), academia

Biological standards – WHO products – also on line

Global written standards

Global measurement standards

Standards evidence base



Proposal for WHO Guidelines

- ICDRA, Seoul, 2006
- Clear need for global road map
- WHO requested to develop global regulatory consensus and guidance on biosimilars
- WHO Consultations on regulatory evaluation of “Biosimilars” 2006, 2007, 2008, 2009 - regulators and manufacturers
- Also on nomenclature (INNs)

What are the problems?

- **Dealing with biologicals which differ from Chemical Drugs in many ways.**
- Biological starting materials and production processes - **inherently variable**
- Highly complex biological macromolecules
- Clinical performance can be affected by very slight changes in production process
- Biological methods (bioassays) needed to characterize product - potency (activity), immunogenicity, safety - **inherently variable**
- **Standardization** of processes essential

Other Issues

- Terminology – biosimilars, subsequent- entry biologics, follow on biologics
- Need to be regulated as biologicals
- Type of regulatory pathway which could allow a reduction in data package for licensing
- How to demonstrate “similarity” to innovator
- What should be the comparator / reference product
- Degree of “similarity” needed to qualify as a biosimilar
- Potential immunogenicity issues
- Extrapolation of indications from originator
- Interchangeability / substitutability

Biosimilars are not Generics

- **Agreed** Biosimilars **should not** be regulated under generic (chemical) drugs regulations – additional considerations essential
- Biologicals, by nature, are not “identical”
- **Agreed**, possible to license a new biological product on basis of its “similarity” with a well established licensed product
- Involves **extensive comparative** product characterization (quality) with comparator
- If quality data showed biosimilarity, reduced non clinical and clinical data package **possible**

WHO Guidelines on Evaluation of Similar Biotherapeutic Products

- Adopted by the Expert Committee on Biological Standardization in 2009 (WHO Technical Report Series 977 , 2013)
- Apply to well characterized/established products **“such as”** rDNA derived biotherapeutics. Vaccines, plasma products and their rDNA analogues **excluded –** WHO guidance available elsewhere.
- Could apply to polysaccharides (Heparins)

WHO Guidelines – Key Concepts

- **Similar Biotherapeutic Product** (SBP) is "similar" in terms of quality, safety and efficacy (Q S E) to an **already licensed** Reference Biological Product (RBP):
- **RBP** used as a comparator in **head-to-head** studies with the SBP in order to show similarity in terms of Q S E. Only an originator licensed on full dossier can serve as an RBP.
- **Allow choice of RBP –** nationally licensed and used product **or** one licensed and used in another jurisdiction
- RBP can not be an international/ pharmacopoeial measurement standard

WHO Guidelines - Stepwise approach

- **Demonstration of similarity** of SBP to RBP **in terms of Quality** is a **pre-requisite** for the reduction of the non-clinical and clinical data set required for licensure

- The same RBP should be used in the head to head Nonclinical and Clinical studies

- NRAs need to consider criteria regarding the acceptability of a non-national RBP, eg licensed and widely marketed in a country with well established regulatory framework , experienced in evaluating biotherapeutics and with established post-marketing activities

WHO Guidelines (2009)

- **Emphasize Head to Head** Comparability Exercise - applies to Quality, Non clinical and Clinical aspects.
- Discuss statistical design and analysis of equivalence / non-inferiority clinical trials for SBPs. Both maybe acceptable
- Clinical studies should **be designed to detect possible differences in safety and efficacy** not to repeat phase III studies
- Comparability of **immunogenicity** is essential
- Need to justify extrapolation to other indications, and especially if based on non inferiority studies

WHO Guidelines (2009)
Issues Not Covered

- Aspects related to product use
- Jurisdiction specific issues will need to be defined by the NRA
- Requirements for non-national RBP
- Intellectual property issues
- Policy on interchangeability and substitution of RBP with SBP
- Labelling and prescribing information

WHO Guidelines for evaluation of similar biotherapeutic products (2009)

- Provide **globally acceptable principles** as a basis for setting national licensing requirements
- Never expected to resolve all issues
- Considered guidance from other bodies (EMA)
- Leave space to NRAs to formulate more specific requirements: sometimes there are legal constraints
- Several implementation meetings 2010 - 2015 - Seoul (global), Xiamen (global) , Accra (Regional).
- **Indicate considerable convergence in approach to biosimilars but some differences in detail between jurisdictions**
- Outcomes published , including case studies.

Implementation workshops for BTP/SBP guidelines: Case studies & Publications

When	Topic of simulated case study	Publication
1st WS for SBP 2010	Special lecture: **Statistical considerations** for confirmatory clinical trials for SBPs	*Biologicals* 39 (5), 2011
	Comparing equivalence and non-inferiority approaches	
2nd WS for SBP 2012	The role of the **quality assessment (of mAbs)** in the determination of overall biosimilarity	*Biologicals* 42 (2), 2014
3rd WS for SBP 2014	**Efficacy study design and extrapolation**: Infliximab & Rituximab	*Biologicals* 43 (1), 2015
1st WS for BTP 2014	Special lecture: **Immunogenicity assessment** of biotherapeutic products: An overview of assays and their utility	*Biologicals* 43 (5), 2015
	Assessment of unwanted immunogenicity of mAbs: TNF antagonist & CD20 mAbs	

Canada

- Health Canada (NRA) possesses comprehensive and distinct regulatory frameworks for-
  - Pharmaceuticals
  - Generic Pharmaceuticals
  - Biologics
- Food and Drugs Act
  - Schedule D – Biologic Drugs List
- Food and Drug Regulations, Part C: Drugs
  - Division 2 - Good Manufacturing Practices
    - Annex to the GMP Guidelines, GMPs for Biologics
  - Division 4 - Schedule D (Biologic) Drugs

Health Canada

- **Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) (2010)**
- No new Regulations - existing regulations used because sufficiently flexible
- **Guidelines** clarify the fundamental principles, policies and regulations that will be applied to SEBs under New Drug Submission Pathway
- Clarify the quality, non-clinical, clinical and post market requirements for licensing SEBs
- Intention to harmonize as much as possible with other competent regulators and the WHO

Health Canada SEBs Guidance

- The term “subsequent entry biologic” (SEB) is used by Health Canada to describe a biologic drug that enters the market subsequent to a version previously authorized in Canada, and with demonstrated similarity to a reference biologic drug.
- SEBs are **NOT Generics**
- Term SEB chosen instead of “biogeneric” or “generic Biologic” so as to **clearly distinguish** between the regulatory process (and product characteristics) for SEBs and that used in Canada for generic pharmaceutical drugs.
- SEBs subject to existing laws on patents , data protection , IP

Health Canada SEB Guidelines

- State that comparative **side by side** (head to head) evaluation of quality , non clinical and clinical attributes of new product against Reference comparator product is essential
- The demonstration of biosimilarity of proposed SEB to Reference Biologic Drug in **terms of Quality** is a **pre-requisite** to a reduction in non clinical and clinical data.
- Provide guidance on **choice** and use of **Reference Biological Drug** (comparator product)

Health Canada – choice of Reference Biological Drug

- Canadian Reference - Authorized and marketed in Canada and with a history of safe use and effectiveness in Canada
- **Flexibility -** *Canada is a small market and some reference product choices may not be authorized or marketed in Canada*
- Although Canadian reference preferred, Health Canada allows use of Non-Canadian reference biologic drug but strictly defined

(Like WHO Biosimilars Guidelines)

Guidance on Non-Canadian reference biologic drug

- Sponsor must name biologic drug authorized in Canada to which the SEB will be subsequent
- Sponsor responsible for showing that the non-Canadian reference is a suitable proxy for the version approved in Canada. Same innovator company
- Should be from a jurisdiction that has an established relationship with Health Canada;
- Widely marketed in a jurisdiction that formally adopts ICH guidelines
- Has regulatory standards and principles for evaluation of medicines, post-market surveillance activities, and approach to comparability that are similar to Canada

Health Canada SEBs Guidelines

- Point out that authorization of SEB is **NOT a declaration of equivalency** with comparator
- Extrapolation of indications of the SEB to those of the RBD allowed on justification
- Once a Notice of Compliance (Market Authorization) is issued, the SEB is a new “stand alone” biologic drug and regulated accordingly. However, an SEB should not be used as a reference biologic drug for another SEB submission.
- Health Canada requires Risk Management and Pharmacovigilance Plans in place prior to issuing marketing authorization. Also Periodic Safety Update Reports (PSUR).

Health Canada SEBs Guidelines Labelling / Product Monograph

- A statement indicating that the product is a SEB
- Key data on which the decision for market authorization was made
- Tables showing the results of the comparisons between the SEB and reference biologic drug
- Indications approved for use
- No claims for bioequivalence or clinical equivalence between the SEB and reference biologic drug

- Interchangeability / substitution is the responsibility of Canadian Provinces , not Health Canada

Health Canada SEBs Guidelines Proposed Revision December 2015

- Released for comment
- Proposed revisions based on Health Canada's experience over past 5 years as well as international developments in regulation of SEBs
- Reference Biologic Drug – further guidance on its selection and better clarity on use of a non-Canadian reference
- **Immunogenicity** - guidance expanded to emphasize use of state of the art methodology
- **Clinical trial design** - use of most sensitive population
- New **separate section on Extrapolation**

Health Canada SEBs Guidelines Proposed Revision. Extrapolation

- New section with expanded information
- A Reference Biologic Drug may have more than one therapeutic indication but the abridged clinical studies will have studied only one.
- When biosimilarity has been demonstrated in one therapeutic indication , extrapolation to other indications of the Reference Biologic Drug may be possible – **but not automatic**
- Must be justified - mechanism of action, pathophysiological mechanisms of the disease(s) involved, safety profile ,etc
- Case by case considerations
- Sponsors encouraged to discuss with Health Canada

Health Canada SEBs Guidelines Proposed Revision 2015

- **New section** on Consultation with the Biologics and Genetic Therapies Directorate , Health Canada
- Encourages early consultation with Health Canada on various issues such as **choice of Reference Biologic Drug** and on **Extrapolation of indications**
- Plan to explore a Step wise review approach that will be complimentary to the SEB development process
- Launching a three year pilot involving Scientific Advice Meetings where Health Canada will provide advice early in the SEB development process
- Sponsors encouraged contact the Biologics and Genetic Therapies Directorate

European Medicines Agency (EMA)

- Guideline on similar biological products (2005) *(overarching guideline on biosimilars)*
- Guideline on similar biological medicinal products containing biotechnology derived proteins as active substances – Quality Issues (2006)
- Guideline on similar biological medicinal products containing biotechnology derived proteins as active substances – non-clinical and clinical issues (2006)
- **Revised 2014 (effective 2015)**

European Medicines Agency
EMA Revised

- **Change in requirements for the Reference Product (RP)**
- **Originally** single RP, licensed within the EU, had to be used throughout the comparability programme
- “To facilitate global development of biosimilars and to avoid unnecessary repetition of clinical trials”
- **Use of non - EMA authorized version of the RP possible** for certain non clinical and clinical studies
- However, for demonstration of biosimilarity at the **quality level**, side by side analysis of the biosimilar with an **EMA authorized Reference Product** must be conducted

European Medicines Agency
EMA Revised

- Applicant needs to provide data to **establish acceptable bridge** between the non EMA authorized and EMA authorized Reference Product
- Non EMA authorized Reference Product must be authorized by an NRA with similar scientific and regulatory standards as EMA (eg ICH countries)
- Closer alignment between WHO , EMA and Health Canada with respect to Reference Product
- **Other revisions in the text of the EMA Guidelines also align well with WHO text - new EMA text sometimes more precise**

European Medicines Agency
EMA Revised

- **New EMA text**
- A biosimilar should be **Highly similar** to the reference medicinal product
- **Extent and nature** of non clinical and clinical studies needed depend on the level of evidence obtained in previous step

- **WHO text**
- Comparability exercise designed to show SBP has **Highly similar** quality attributes when compared to the RBP
- **Amount of non clinical and clinical data considered necessary** depends on product class , the extent of characterization possible with state of art methods

European Medicines Agency
EMA Revised

- **New EMA**
- **In specific circumstances a confirmatory clinical trial may not be necessary,**
- This requires that similar efficacy and safety can be **clearly** deduced from the similarity of quality, biological, PK/PD profiles

- **WHO**
- Clinical trials usually required to show similar efficacy of SBP and RBP. **In certain cases** however, **comparative PK/PD** studies **may be appropriate** provided at least one PD marker is an accepted surrogate for efficacy . PK/PD often more sensitive than clinical endpoints

European Medicines Agency
EMA Revised

- **New EMA**
- **Increased immunogenicity** compared to the reference product may question biosimilarity**.**
- ***In vivo* non clinical evaluation** more focus on 3Rs - Replacement, Reduction, Refinement

- **WHO**
- If the antibody incidence is higher with the use of the SBP compared to the RBP, **the reason for the difference needs to be investigated.**
- *In vivo NC* evaluation of biological / PD activity **may be dispensable** if validated *in vitro* assays available

European Medicines Agency
EMA Revised Comparative Non clinical evaluation of SBP and RBP

- **Original**
- Quality characterization
- Nonclinical *in vitro*
- Nonclinical *in vivo*
- Clinical evaluation

- **Revised**
- Quality characterization
- Nonclinical ***in vitro***
- **Data review** decision on need for ***in vivo*** studies
- **YES** **NO**
- Clinical evaluation

US FDA Guidance for Industry 2015

- **Scientific Considerations in Demonstrating Biosimilarity to a Reference Product .**
- **Reference Product Exclusivity for Biological Products**
- US FDA has comprehensive regulatory frameworks for Pharmaceuticals, Generic Pharmaceuticals and **Biologics**
- Biologics License Application (BLA) –approved Biologic under Public Health Service Act (not Food & Drug Act)
- **New guidance clarifies the principles, policies and regulations that apply to biosimilars**

US FDA Biosimilars Guidance for Industry 2015

- Defines *biosimilarity* to mean “that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components”
- “No clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”
- **Reference Product must be a US licensed biological product**
- A non-U.S.-licensed comparator product can be used with an acceptable bridge to the U.S.-licensed reference product. Some other agencies (Korea) has similar regulation

US FDA Biosimilars Guidance for Industry 2015

- Generally aligned with EMA, WHO ,HC
- Stepwise approach to demonstrating biosimilarity - includes a comparison of the proposed product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness
- Indicate a ***totality-of-the-evidence*** approach to evaluate scientific evidence for biosimilarity. Same in EMA, HC and WHO except the language different.

US FDA Biosimilars Guidance for Industry 2015

- ***Extrapolation of Clinical Data Across Indications***
- If a product meets the requirements for licensure as a biosimilar, an applicant may seek approval for one or more additional conditions of use for which the reference product is licensed.
- Applicant needs to provide sufficient scientific justification for extrapolation
- ***Interchangeability***
- FDA requires evidence beyond that needed to demonstrate biosimilarity to determine interchangeability

Global Picture

- Increasing alignment between jurisdictions
- WHO Implementation workshops have been very useful, especially the case studies
- **Agreed** term “biosimilar” should apply **only** to products licensed following full head to head comparability exercise (Q, N, C)
- Products which do not meet these criteria could be licensed by other regulatory pathways (stand alone)
- Developing and regulatory evaluation of biosimilars is not easy. Needs a lot of expertise and experience
- New manufacturers with less experience of biologicals coming into field
- Products will need very careful evaluation by NRAs

67th World Health Assembly 2014

- First-ever Resolution on biotherapeutics (BTPs)(WHA 67.2) "Access to BTPs including similar biotherapeutic products (SBPs) and ensuring their Quality , Safety and Efficacy"

Requests Member States

- To "develop the necessary **scientific expertise** to facilitate development of solid, scientifically-based regulatory frameworks "
- Work to ensure that the introduction of new national regulations, where appropriate, does not constitute a barrier to access to BTPs/SBPs
- To develop or strengthen, national regulatory assessment and authorization frameworks

67th World Health Assembly Resolution on Biotherapeutics (WHA 67.2) 2014

- **Requests WHO**
- To support the development of national regulatory frameworks that promote access to quality, safe, efficacious and affordable BTPs, including SBPs;
- To encourage and promote cooperation and **exchange of information** among Member States in relation to BTPs/SBPs
- **To convene the WHO ECBS to update the Similar Biological Products Guidelines adopted in 2009 taking account of the technological advances for the characterization of BTPs and considering national regulatory needs and capacities**

Responding to World Health Assembly Resolution on Biotherapeutics (2014)

- A WHO Informal Consultation was organized in April 2015, to review the 2009 WHO Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) in detail
- Consultation concluded there was **no need to revise** these overarching WHO guidelines since the **evaluation principles described still apply.**
- Some other NRAs (eg EMA) had in fact revised their guidelines and overall guidance becoming more aligned.

Responding to World Health Assembly Resolution

- However, agreed that , because of their complexity, specific issues and consideration for the development and evaluation of **biosimilar Monoclonal Antibodies** did need further clarification and guidance
- The development of a WHO product specific document on the Regulatory Evaluation of Similar Monoclonal Antibody Products is underway
- A drafting group was established in November 2015
- These developments will be reported to the 69th World Health Assembly (2017)

Thank you for your attention
Further information can be obtained from :

- Biological standardization website -

  www.who.int/biologicals

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Similar but not Identical. How to tell the difference?

Pictures taken from:
http://savingsandclone.com/news/press_room.html