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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 assessment of already approved rDNA-derived biotherapeutics

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Regulatory assessment of already approved rDNA-derived biotherapeutics

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Ankara, Turkey

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Outline of Presentation

- Briefly review scientific and regulatory background of rDNA biotherapeutics – differences from ‘chemical drugs’
- Arrival of biosimilars and their regulatory oversight
- Problem with some products already on the market? What is the problem?
- **How to deal with products already on the market – updating regulations**

Biotherapeutic Products

- Last 30 years seen revolution in rDNA-based and related biotechnologies
- Opened new exciting vistas for global public health – disease diagnosis / treatment / prevention / correction defective genes
- Cutting – edge of biomedical research
- Economically fastest growing sector in pharmaceuticals

What are they?
Terminology

Different names

Biotechnology Products

Biopharmaceuticals

Biotherapeutic products

Biotherapeutics

All considered to be

- **Biologicals**
- Biological medicines
- Biologics (North America)

Quantum Jump

- Sequencing nucleic acids
- Ability to 'word process' genes – **'cut, copy, paste' DNA sequences**
- **Express human genes in foreign cells (bacterial, mammalian, plant, yeast, insect) and produce clinically useful biological macromolecules / products**
- **Great progress also been made in ability to purify and to characterize biological macromolecules in great detail**

Biotherapeutics – What are the issues?

- **Differ from Chemical Drugs in many ways**
- Biological starting materials and production processes- **inherently variable**
- Highly complex products, e.g. large protein molecules often glycosylated; some have more than one functional region. Some no ‘natural’ equivalent
- Clinical performance cannot be **fully** predicted from physicochemical characteristics **alone**
- Biological methods (bioassays) also needed to characterize product – potency (activity), immunogenicity, safety – **inherently variable**
- **Standardization** of processes essential

Critical Manufacturing Points

- Mammalian cell bank / bacterial host / plant or other expression system
- Cell culture / fermentation
- Sequence / translational events
- Separation and purification of product
- Characterization of resulting protein + glycosylation or other modifications
- Bulk product testing (drug substance)
- Formulation
- Final product testing (drug product)

Slight changes in process can have major effects on clinical performance of the product. Consistency of production critical

Product characterization

- Means **more** than routine quality control tests
- Expect **several** parameters to be evaluated by different techniques, **not just one**
- Protein sequence, secondary / tertiary aspects, glycosylation, phosphorylation, oxidation, lipidation, etc.
- Product / **host cell** related impurities (including residual DNA; **Viral safety validation**)
- Potency (biological activity)
- Formulation implications and Stability
- Release QC testing – a subset of the product characterization tests; specifications set

Regulatory oversight

- **REGULATORY MEASURES** put in place **very early on** in development of biotechnology products – **regulated as biologicals**
- **GUIDELINES** on production and quality control rDNA derived proteins **also developed early on**, e.g. EMA, US FDA, WHO
- **Based on experience with biologicals** in general; provided framework for moving forward with the newer technologies

Role of WHO

- Not a regulatory agency
- WHO is a specialized agency of the United Nations system
- Key role in ensuring global availability of vaccines and biologicals of assured quality
- **Setting global norms and standards and promoting their implementation**
- WHO assessment and regulatory capacity building of National Regulatory Authorities

WHO Guidelines for Biotherapeutic Products

- Original WHO Guidelines published in 1991
- Replacement adopted in 2013 – not update
- Extensive science-based guidelines now **include new sections on non clinical and clinical evaluation** of rDNA proteins which were lacking in the original
- Also section on **manufacturing changes**
- **Cross refer to latest WHO cell substrates recommendations 2010** as well as to other relevant documents, such as those on TSEs and on sourcing of raw materials
- WHO Implementation Regional Workshops, Seoul 2014, Accra 2015.

WHO Guidelines for Biotherapeutic Products 2013 – Scope

- All biologically active proteins used in treatment of human diseases which are prepared by rDNA technology
- Protein products used in *in vivo* diagnosis, e.g. monoclonal antibodies
- Protein products intentionally modified by pegylation, conjugation with cytotoxic drug or modification of DNA sequences
- Quality section applies to rDNA derived vaccine antigens – but not nonclinical and clinical sections since other guidance in place

New Challenges

- New production processes / product types will raise new scientific / technical / regulatory issues
- Important to recognize and adequately deal with scientific/technical issues early
- Ensure sound scientific data base available on which to make regulatory decisions
- Ensure regulatory position adequately reflects scientific advances - **international dimension**
- Well illustrated by arrival of biosimilars

Arrival of Biosimilars

- Increasing number of patents/data protection for biological medicinal products expiring
- Alternatives, ‘similar’ to innovator products, coming to market and **expected to be licensed on reduced data** package
- Expected more affordable – may contribute to increased **access**
- Considerable global interest
- **Difficult and contentious issues**
- Relate not only to science but also to regulatory processes and to legal aspects, patents/data protection
- **Key question was how to handle the licensing of these products if relying, in part, on data from innovator product**

WHO Guidelines for evaluation of similar biotherapeutic products

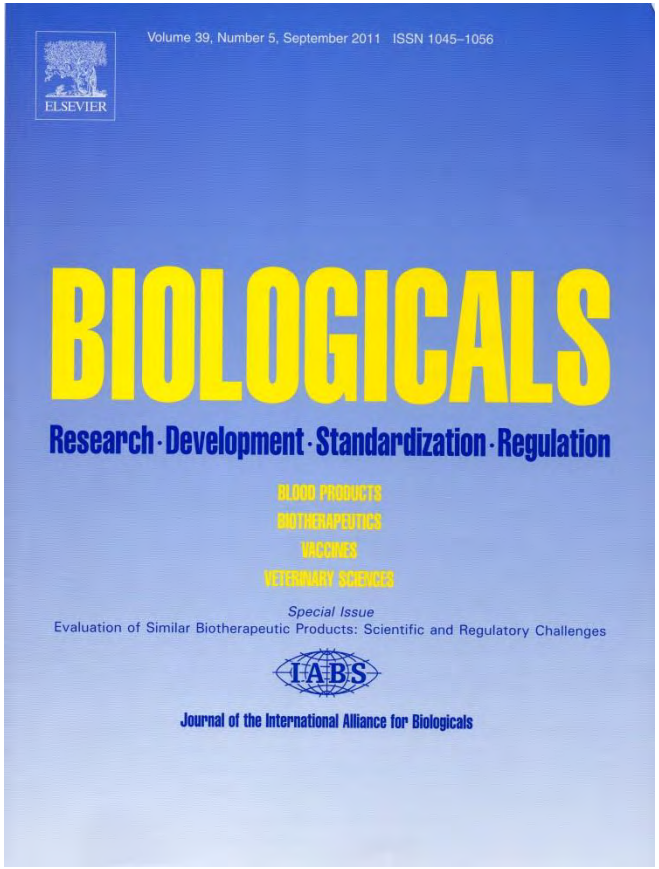
- Adopted by ECBS in 2009
- Biosimilars **should not** be regulated under generic drugs regulations – biologicals are not 'identical' and additional considerations are essential
- Possible to license a new biotherapeutic product (SBP) with a reduced data package on basis of 'similarity' with a well established licensed Reference Biotherapeutic Product (RBP) **as shown in a HEAD TO HEAD comparability exercise covering quality, non clinical and clinical aspects.**
- **RBP should not be an international / national / pharmacopoeial measurement standard**

WHO Guidelines for evaluation of similar biotherapeutic products 2009

- Provide globally acceptable principles as a basis for setting national licensing requirements
- Not expected to resolve all issues
- Considered guidance from other bodies in particular the EMA
- Leave space to NRAs to formulate additional/ specific requirements: sometimes there are legal constraints
- Implementation workshops – Seoul 2010, Xiamen 2012, Seoul 2014,Accra 2015
- Outcomes published as review articles and case studies

Review of the global situation up to 2011

- Special Issue journal Biologicals
- ‘Evaluation of Similar Biotherapeutic Products: Scientific and Regulatory Challenges’
- Biologicals Vol 39. No 5, September 2011
- Open access – **can be freely downloaded**



Outcomes of implementation workshops

- Increasing alignment between jurisdictions: noted importance of WHO in furthering standardized global approach, a convergence, but many challenges
- Most biotherapeutics in developing countries licensed by a stand alone approach with reduced data package rather than strict comparability exercise.
- Some countries have regulatory pathway for ‘non-innovative biotherapeutic products’ but requirements generally unclear
- Comparability studies with RBP: concept not well understood and used
- Lack of expertise and capacity for evaluation of biotherapeutics at NRA

Outcomes of implementation workshops

- **Identification of some 'copy' products licensed without adequate quality, safety or clinical data**
- Some 'copy' products licensed as 'biogenerics', a term which should not be used since it suggests a generic pathway.
- **Also, lack of harmonization of regulatory oversight of rDNA derived biotherapeutics in general (not just biosimilars)**
- Some licensed with data packages that did not follow current international regulatory standards
- Sometimes a range of different products on the market in one jurisdiction eg erythropoietin (EPO) in Thailand

The problem

- Slight differences in the product can have unintentional effects on clinical performance and safety – EPO and red cell aplasia
- Generally little known about the safety and efficacy of products licensed without adequate quality, safety or clinical data since pharmacovigilance is weak in most countries concerned.
- Lack of terminology for products developed as ‘copy’ products with only partial comparability to a reference has compounded the problem

So what should we do with these already licensed products ?

- International Conference of Drug Regulatory Authorities (ICDRA) (Singapore 2010) discussed such situations and requested WHO to develop guidance on risk management strategies for ‘copy’ rDNA biotherapeutics already licensed as ‘biogenerics’.
- Essentially to develop approaches to evaluating these already licensed products according to WHO guidelines or for phasing them out in a reasonable period of time

New WHO Document – Regulatory Assessment of Approved rDNA-Derived Biotherapeutics

- Developed as an **Addendum** to the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology
- **Applies both to rDNA biotherapeutics and biosimilars**
- It underwent considerable public consultation and **adopted** by the WHO ECBS in October **2015**

First draft considered four options

1.Leave on the market and strengthen post market surveillance to identify possible adverse effects associated with use;

2. Withdraw from the market immediately

3. Withdraw only when a safety or efficacy problem has been identified;

4. Leave on the market for a specified period, during which time manufacturers would be required to submit appropriate missing data and a “risk management plan” for regulatory evaluation to support the continuation of the license.

Consultations – five rounds

- Regional workshop in Bogota Columbia, 2012;
- 2nd Implementation workshop for SBPs in Xiamen China, 2012;
- Panel discussion in International Conference on Biological Products in Bangkok Thailand, 2013;
- 1st Implementation workshop for BTPs in Seoul Korea, 2014;
- Informal consultation for RA doc in Geneva, April 2015.

Consultations – public

- 1st round, Feb – March 2014;
- 2nd round, Dec 2014 – Jan 2015.
- **Altogether very wide consultation**
- NRAs/NCLs: 31 countries in 6 WHO regions; AFRO (*Burkina Faso, Ghana, Kenya, Nigeria, Tanzania, Zambia*); EMRO (*Egypt, Iran, Jordan*); EURO (*Finland, Germany*, *Russia, UK*); SEARO (*India, Indonesia, Thailand*); PAHO (*Brazil, Canada, Chile, Colombia, Cuba, Panama, Peru, USA, Venezuela*); WPRO (*China, Japan, Korea, Malaysia, Philippines, Singapore*
- Manufacturers and Manufacturers Associations
- Pharmacopoeias, others (APEC)

Main outcomes of consultations

- Agreement to emphasize a step wise assessment approach (option 4)
- Should include a **product-specific** risk-benefit assessment to decide the appropriate action and timelines
- Product should be allowed to remain on the market during the review, that is for a specified period.
- Terminology was a big problem with early drafts – ‘copy’, ‘non-innovator’, ‘risk’ , ‘risk management plan’ but resolved in approved document
- Suggestion that providing examples would be very helpful

Regulatory Assessment of Approved rDNA – Derived Biotherapeutics 2015

- *Short Background*
- *Scope – deals primarily with all rDNA protein products but some aspects may also be relevant to other non protein biotherapeutics, e.g. polysaccharide products*
- *Summary of regulatory expectations for rDNA derived biotherapeutics including biosimilars*
- ***Stepwise review of products on the market***
- ***Points to consider in a stepwise regulatory assessment (product specific)***
- *Regulatory Actions*

Emphasis is on a stepwise regulatory assessment in dealing with the problem

Stepwise Regulatory Review of biotherapeurtics already on the market

- NRAs identify products licensed using data which do not meet current international regulatory standards
- NRA assesses identified products and data gaps
- NRA decides appropriate actions – involves risk-benefit considerations.
- Manufacturers informed
- Manufacturers propose (within short time period) a **Plan of Action** for dealing with the problem
- Manufacturers propose timelines to provide missing data and/or generate missing data.
- NRAs evaluate the action plan and agree next steps

Timelines

- Timeline for completing a review and providing new data will depend on the time needed to provide missing data or to generate these data taking into consideration **product specific aspects**.
- Finally, NRA evaluates all data submitted, including new data, and then decides on appropriate regulatory action
- **Product remains on the market for this period**
- The stepwise approach protects the supply and authorization could be regularized following submission of additional data, further regulatory evaluation and demonstration of acceptable benefit–risk profile.

Points to consider in a Stepwise Product Specific Regulatory Assessment

- Number of 'problem' products on the market as well as alternatives licensed by experienced NRA which meet current standards
- Is the product manufactured and licensed in a country with an NRA well experienced in evaluating biotherapeutics ?
- Is actual product on the market comparable to that used in the experienced manufacturing country?
- Extent to which the submission dossier meets WHO Recommendations and Guidelines
- Level of use and consequence of treating or not treating a disease (supply issue)

Points to consider in a Stepwise Product Specific Regulatory Assessment

- Type of disease – life threatening or not. Patients – paediatric, adult, geriatric
- Seriousness of potential lack of efficacy / safety issues, including higher efficacy and immunogenicity
- Effectiveness of pharmacovigilance in monitoring possible adverse reactions
- Traceability issues
- Expertise and capacity of NRA in licensing biotherapeutics
- Possibility of regulatory evaluation support by experienced NRA (mentoring)
- Transparency- informing healthcare professionals of ongoing review process and timelines

Regulatory Assessment of Approved rDNA biotherapeutics

- Number of countries now introducing new or updated regulations for biotherapeutics
- Include provision to re-assess products approved prior to the adoption of the new regulations
- Very timely to consider the topic of regulatory assessment of approved products from a global perspective
- Need a document which is useful and uses terminology which can be easily understood

Increasing alignment/convergence between jurisdictions

- Recently, several Latin American countries – Mexico, Chile, Uruguay, Peru – finalized or proposed new or updated regulations for licensing and for license renewals of biotherapeutic products, including SBPs.
- Include provision to re-assess products approved prior to the adoption of the new regulations
- Also provide for an **Interim transition period**
- These regulations are good examples of aligning with WHO's regulatory framework for biotherapeutics and increasing **regulatory convergence** between jurisdictions.

Examples to illustrate process

- **Canada** – change in regulatory oversight of heparins (2008–2010) included interim arrangements
- **Brazil** – change in regulatory oversight of heparins involving need for full dossier and re-evaluation of products already approved in light of safety issues
- **Thailand** – changes to bring regulatory oversight of Erythropoietin (EPO) up to date through re-evaluation of EPO already on the market – in light of red cell aplasia incidence.
- **Peru and Mexico** have finalized or proposed new regulations for biotherapeutics and biosimilars and both have interim arrangements for products already licensed under previous regulations.

Canada: change in regulatory oversight of Low Molecular weight heparins (LMWHs)

- LMWHs are derived from unfractionated heparin by different methods of heparin depolymerization
- Each has a specific molecular weight distribution that determines its **anticoagulant activity and duration of action**
- Not demonstrated to be pharmacologically and clinically equivalent
- They are biologicals
- Several were licensed in Canada as pharmaceutical drugs. Health Canada regulations for biologics (biologicals) require submission of more data than for chemical drugs.

Canada: change in regulatory oversight of Low Molecular weight heparins (LMWHs)

- **In 2008**, Health Canada recognized the importance of the biological origin of LMWHs and a need to better support heparin new drug submissions, particularly the proposed 'biosimilar' LMWHs
- A **risk based plan of action developed** to transfer the review of heparins and LMWHs, from the Therapeutic Products Directorate (TPD, responsible for pharmaceuticals), to the Biologics and Genetic Therapies Directorate (BGTD, responsible for biologics and related complex drugs)
- This involved a transitional period to allow manufacturers to update their files to reflect data requirements for biologicals

Canada: change in regulatory oversight of Low Molecular weight heparins (LMWHs)

- Manufacturers given **one year** to update their files to reflect data required for biologicals
- **By 1 January 2009**
- Certificates of Analysis for 20 consecutive lots of each product marketed in Canada
- Must reflect current USP requirements and include Nuclear Magnetic Resonance (NMR) and Capillary Electrophoresis (CE) results
- Number of lots sold in Canada per year
- **By 1 January 2010**
- Full biologicals submission with updates
- Yearly Biologics Product Yearly Report

Proposed plans in Peru

- March 2015 Peru issued draft new regulations for registration of **full dossier biotherapeutics** and of **biosimilars**
- Transitional provisions proposed for biotherapeutics licensed prior to new regulations
- In the case of a ‘copy’ product licensed without a full dossier, manufacturer given 60 days to notify NRA of intention to renew registration using the SBP pathway
- Failure to do so would result in the cancellation of the license
- A Risk Management plan required within 6 months of new regulations coming into force as well as chemistry, manufacturing and control data

Proposed plans in Peru

- For a **'full dossier' product**, all necessary quality, non clinical and clinical data to be submitted within 1 year
- For proposed **biosimilars,** comparability data required within two years and clinical data within five years
- Annual progress reports also needed.
- Failure to submit required data sets would result in cancellation of the license

The stepwise approach

- The length of the interim transition period will be country and product specific
- It will depend on a number of aspects, including whether there are already recognized safety issues in the country, as well as the points raised in the stepwise regulatory assessment section of the proposed document

Expected value of the New WHO document on Regulatory Assessment of rDNA derived biotherapeutics

- Raise awareness of the products currently available (licensed with limited data)
- Strengthens available guidance
- Screening check-list for dialogue between regulator and manufacturer
- **Emphasizes regulatory oversight throughout the life-cycle of a product**
- Indicates WHO updating regulatory information on a regular basis

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

- Biological standardization website -

  www.who.int/biologicals

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