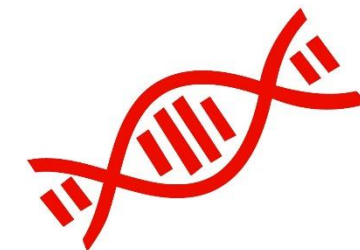


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Regulatory assessment of approved rDNA-derived biotherapeutics

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24 September 2019



Regulatory assessment of already approved rDNA- derived biotherapeutics

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September 2019



Outline of Presentation

- Briefly review scientific and regulatory background of rDNA biotherapeutics – differences from “chemical drugs”
- Arrival of biosimilars and their regulatory oversight
- Problems 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 immense 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 impact structure / function and have major effects on clinical performance of the product.

Consistency of production critical



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
- Over time Guidelines / Points to Consider **updated** in light of experience of production, use, development of new technologies and data.



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



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 is 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

- Current version of the *WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology* were adopted in 2013 (Replacement, not update, of 1991 guideline)
- *WHO Guidelines on evaluation of similar biotherapeutic products* (adopted in 2009)
- These emphasize that licensing of a biosimilar requires a **HEAD TO HEAD comparability exercise with a Reference Biotherapeutic Product, covering quality, non clinical and clinical aspects.**



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



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, e.g. 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



67th World Health Assembly 2014

- Resolution on biotherapeutics (BTPs) (WHA 67.21)
“Access to BTPs including similar biotherapeutic products (SBPs) and ensuring their Quality , Safety and Efficacy”
- Resolution on *regulatory system strengthening for medical products* (WHA 67.20) in which WHO was requested to provide guidance , especially on dealing with increasingly complex biological products
- Guidance on risk management strategies for dealing with already licensed “copy” rDNA biotherapeutics is one example of WHO’s work in this complex area



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, Colombia, 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, Switzerland, 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 biotherapeutics 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 reaction
- 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 are in the process of introducing new or updated regulations for biotherapeutics
- Include provision to re-assess products approved prior to the adoption of new regulations
- Important 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

- For example, 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 biologics



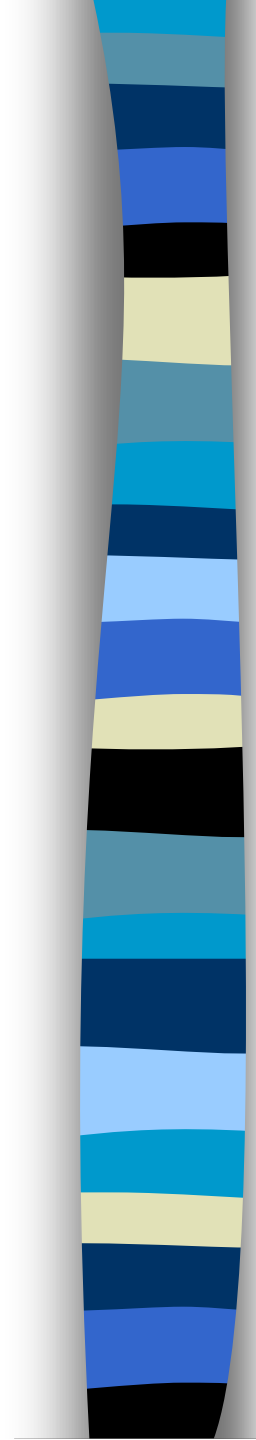
Canada : change in regulatory oversight of Low Molecular weight heparins (LMWHs)

- Manufacturers given **one year** to update their files to reflect data required for biologicals
- **By January 1, 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 January 1, 2010**
- Full biologicals submission with updates
- Yearly Biologics Product Yearly Report



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 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**



Other relevant WHO documents

- Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products (SBPs). Annex 2, WHO Technical Report Series, No. 1004, 2017
- Guidelines on procedures and data requirements for changes to approved biotherapeutic products, Annex 3, WHO Technical Report Series No 1011, 2018
- WHO Questions and Answers: Similar Biotherapeutic Products (posted on WHO Website. See WHO Technical Report Series, 1016, 2019)

Similar but not Identical
How to tell the difference?
Is a difference important clinically?



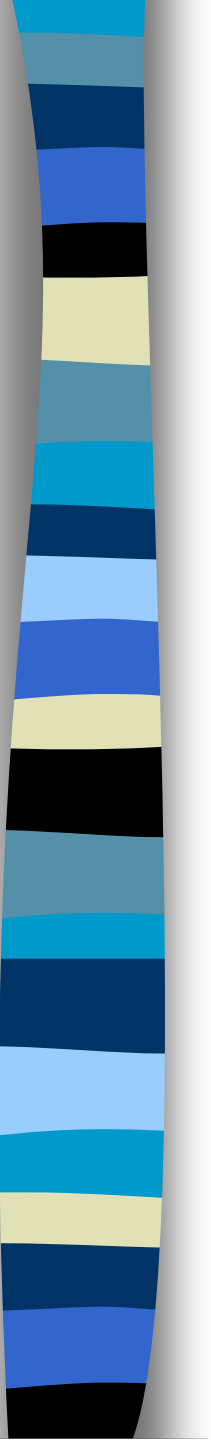
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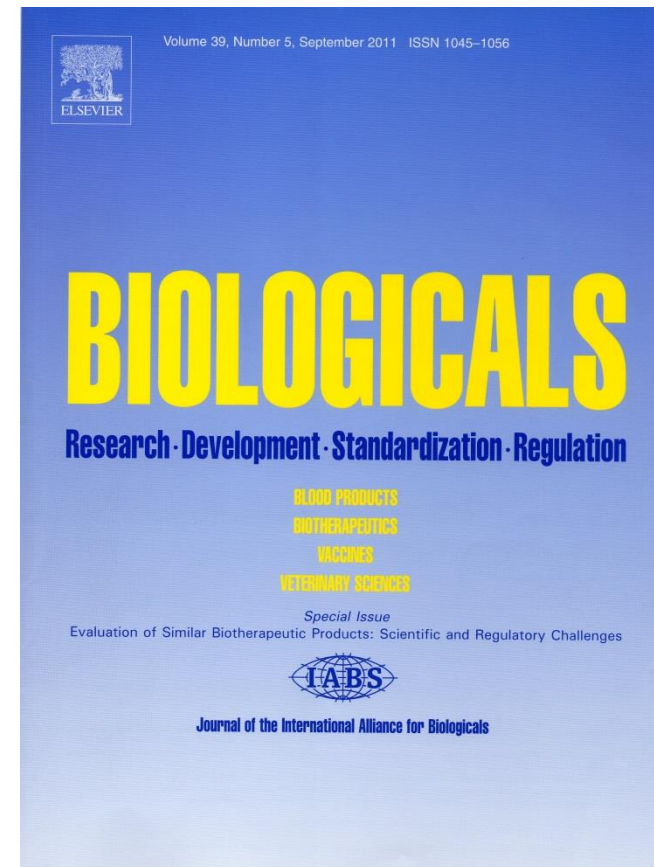
Further information can be obtained from:

WHO Biological standardization website -
www.who.int/biologicals



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**





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