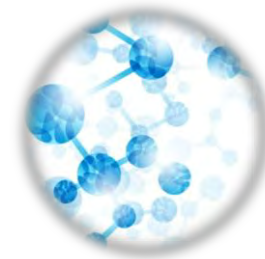




14 June 2016, Hilton Bogotá, Colombia

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- Chairman of the WHO Expert Committee on Biological Standardization



# Regulatory assessment of already approved rDNA-derived biotherapeutics

Elwyn Griffiths, DSc, PhD  
14 June 2016



# **Regulatory assessment of already approved rDNA- derived biotherapeutics**

**Elwyn Griffiths**

**Bogota, Colombia**

**14 June 2016**



## Outline of Presentation / Resumen

- Briefly review scientific and regulatory background of rDNA biotherapeutics - differences from “chemical drugs”  
(Regulacion de productos biotecnologicos )
- Arrival of biosimilars and their regulatory oversight
- Problem with some products already on the market? What is the problem ? / **Cuál es el problema?**
- **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 / Terminología

## Different names

- **Biotechnology Products** / Productos biotecnológicos
- Biotherapeutic Products / Productos biológicos terapéuticos
- Biotherapeutics

## All considered to be

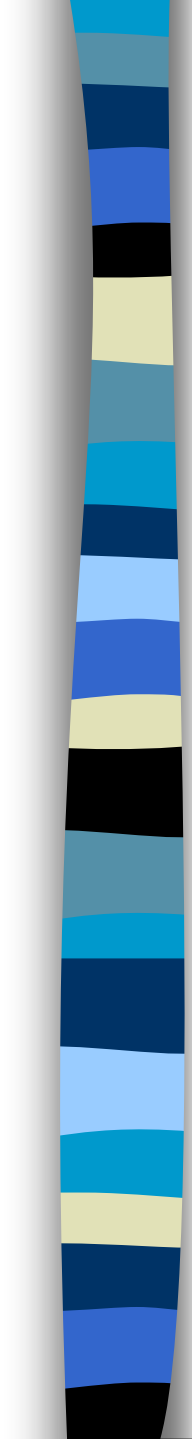
- **Biologicals** / Productos biológicos (mundial)
- Biological medicines / Medicina biológico
- Biologics (North America) / Productos biológicos (Norte América)



# 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**



# Regulatory oversight

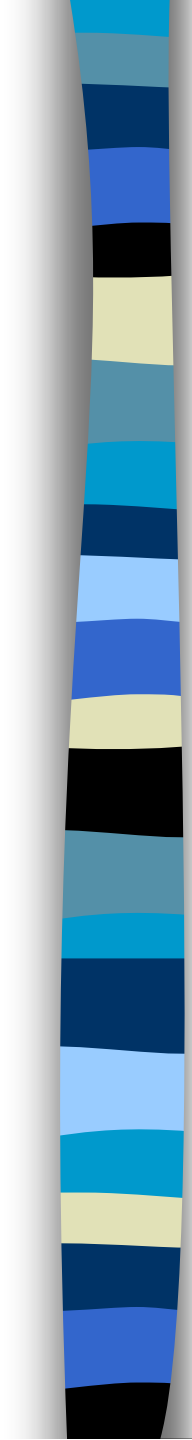
- **REGULATORY MEASURES** put in place **very early on** in development of biotechnology products - **regulated as biologicals**
- **GUIDELINES** on production and quality control rDNA derived proteins **also developed early on** (e.g. EMA, US FDA, WHO)
- **Based on experience with biologicals** in general;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



# Role of WHO

## (Organización Mundial de la Salud)

- 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.



# 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 biotechnological 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 of biosimilars with RBP: concept not well understood and used
- Lack of expertise and capacity for evaluation of biotherapeutics at NRA



# Outcomes of implementation workshops

- **Recognition that 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 the 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



# 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 4 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.



# Extensive Global Consultation

- A topic discussed at 5 WHO /Regional Workshops on Biotherapeutics 2012 to 2015 – Bogota (Columbia), Xiamen (China), Bangkok (Thailand), Seoul (South Korea), Geneva (Switzerland)
- Two rounds of Public (web based) consultations (2014 , 2015)
- Comments from NRAs/NCLs: 31 countries in 6 WHO regions- AFRO, EMRO, EURO, PAHO, SEARO, WPRO
- Manufacturers and Manufacturers Associations
- Pharmacopoeias, others ( APEC)



# Main outcomes of consultations

- A very useful document
- Agreement to emphasize a stepwise 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 eg 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**



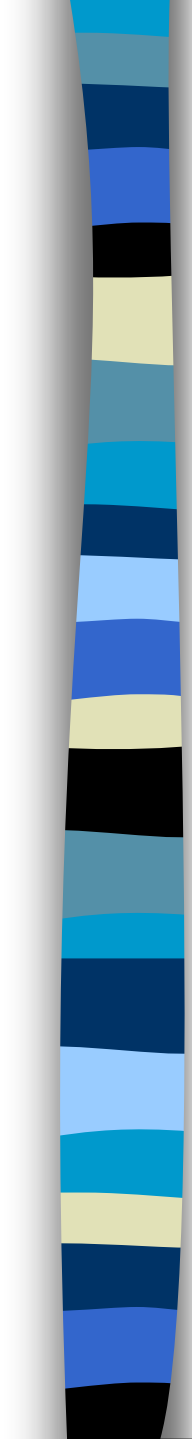
# Stepwise Regulatory Review of biotherapeutics already on the market

- 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.



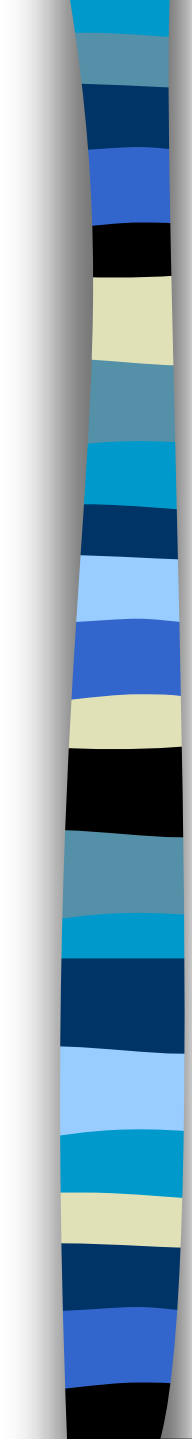
# Points to consider in a Stepwise Product Specific Regulatory Assessment

- 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 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 / biosimilars – reflect regulatory convergence
- **Include provision to re-assess products approved prior to the adoption of the new regulations**
- Provide for **interim transitional period**
- Very timely to consider the topic of regulatory assessment of approved products from a global perspective
- Examples of principles, Canada and Peru



## 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 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



# 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 2 years and clinical data within 5 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



# 67<sup>th</sup> 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



# 67<sup>th</sup> 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;

*Regulatory Assessment of Approved rDNA derived Biotherapeutics 2015*

- 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 (e.g. EMA) had in fact revised their guidelines becoming more aligned with WHO, e.g. source of reference product: extent and nature of non clinical and clinical studies required: in specific circumstances confirmatory clinical trial may not be necessary





# Responding to World Health Assembly Resolution

- However, meeting 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
- WHO Guidelines on post-approval changes for biotherapeutic products also under development
- These developments will be reported to the 69<sup>th</sup> World Health Assembly (2017)



# MUCHAS GRACIAS THANK YOU

Further information can be obtained from-

- Biological standardization website -  
[www.who.int/biologicals](http://www.who.int/biologicals)
- Contact persons: Dr Ivana Knezevic  
email: [knezevici@who.int](mailto:knezevici@who.int) : Dr Hye Na Kang  
email : [kangh@who.int](mailto:kangh@who.int)