Elwyn Griffiths, DSc, PhD, UK

- Former Director General, Biologics and Genetic Therapies Directorate, Health Canada
- Chairman (2010–2015), Rapporteur (2016–2017) of the WHO Expert Committee on Biological Standardization

Regulatory assessment of already approved rDNA-derived biotherapeutics

Elwyn Griffiths, DSc, PhD

23 July 2017

Regulatory assessment of already approved rDNA-derived biotherapeutics

Elwyn Griffiths

Bangkok, Thailand

(July 2017)

Outline of Presentation

- Briefly review scientific and regulatory background of rDNA biotherapeutics - differences from “chemical drugs”
- Arrival and challenges of biosimilars
- 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 - **inherently variable**
- Highly complex products eg large protein molecules often glycosylated; some have more than one functional region. Some no “natural” equivalent
- Cannot be **fully** characterized by physicochemical properties **alone**
- Biological methods (bioassays) also needed to characterize product - potency (activity), immunogenicity, safety – **methods inherently variable**
- **Standardization** of processes essential

Critical Manufacturing Points

- Expression system – mammalian cells, bacteria, yeast, insect or plant cells etc
- Cell culture / fermentation / genetic stability : batch or continuous production
- DNA 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

Non-clinical and Clinical Evaluation

- **Non clinical evaluation**
- problematic for rDNA biotherapeutics; classic PD, safety or toxicological testing in animals (as for chemical drugs) of limited relevance
- DNA-derived biotherapeutics have unique and diverse structural and biological properties, **including species specificity**, immunogenicity and unpredicted pleiotropic activities. These properties pose particular problems in relation to nonclinical testing in animals
- pharmacological and safety evaluation need to take a large number of factors into account . Flexible case by case approach
- **Clinical**
- Usual extensive evaluation covering safety and efficacy, especially including immunogenicity studies

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** (eg EMA, US FDA, WHO)
- **Based on experience with biologicals** in general; provided framework for moving forward with the newer biotechnologies
- Original guidelines have been updated over time and developed by many other agencies

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 Workshops, Seoul, S Korea 2014 , Accra, Ghana 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**

Dealing with Biosimilars

- Considered that the well-established regulatory pathway for authorization of **generic versions** of small molecule drugs **not appropriate** – copies of biologicals not identical
- Regulatory framework and guidelines first develop by European Medicines Agency (EMA) in 2004 - 2005
- Followed by much international consultation led by WHO

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 seen worldwide - EMA (Europe) well ahead
- **Clear need for global road map**

Proposal for WHO Guidelines

- **International Conference of Drug Regulatory Authorities (ICDRA) Seoul, 2006**
- 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

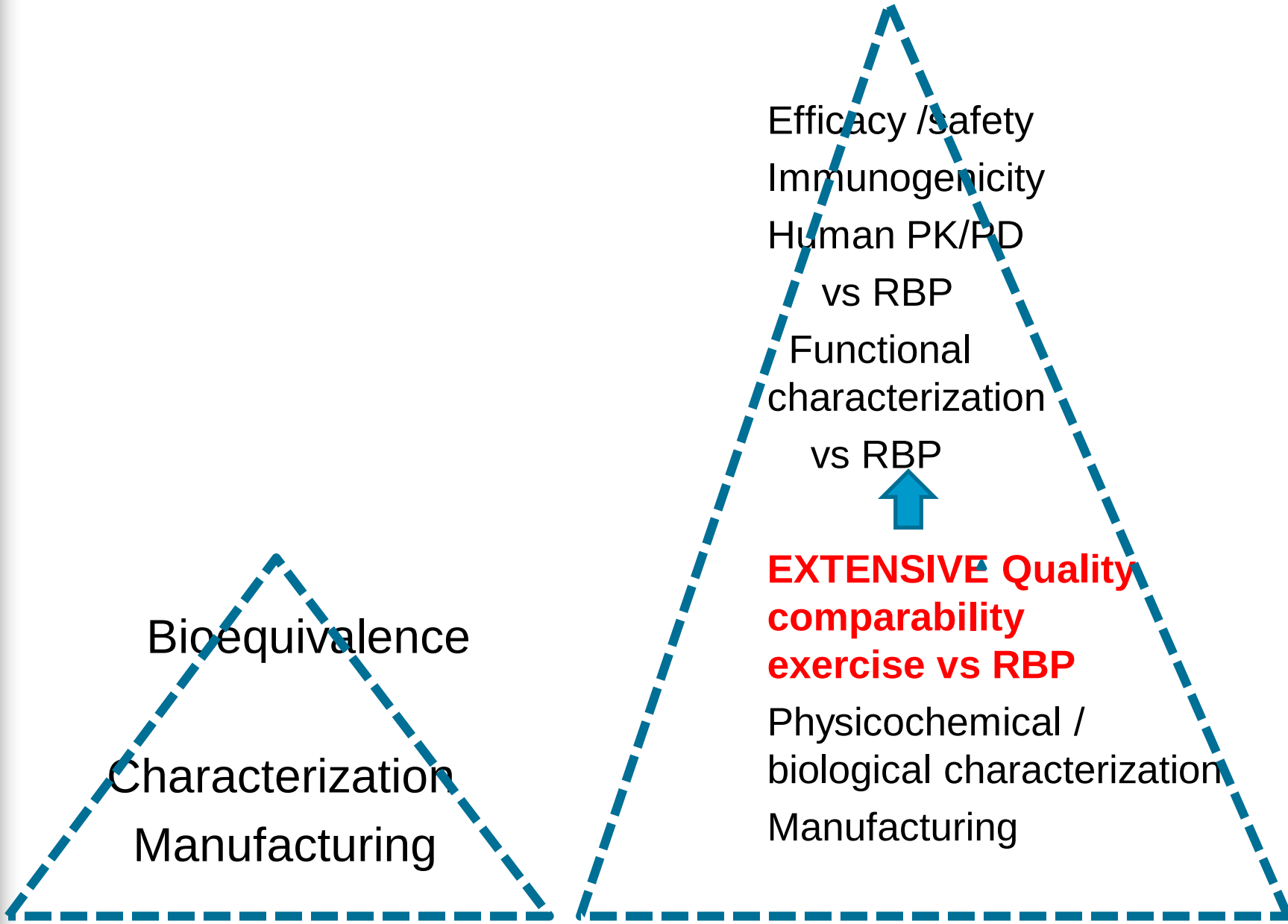
WHO Guidelines for evaluation of similar biotherapeutic products

- Adopted by Expert Committee on Biological Standardization (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.**

Choice of Reference Biotherapeutic Product

- RBP should be an **innovator** product licensed on the basis of a **full data package**
- It should have been **in use for sometime** and have substantial history of safe and effective clinical performance (details of the clinical performance will be in the public domain)
- RBP can be product authorized/marketed in another jurisdiction (foreign RBP) if there are adequate data and use (WHO , Health Canada, updated EMA guidelines)
- Sometimes the RBP is referred to as an “originator “ product. This does not necessarily mean the first to be licenced . The RBP can be any licensed product which meets the above criteria but often it is the original first licensed product since this will have the largest data base of use.
- RBP **should not be** an international / national / pharmacopoeial measurement standard
- RBP **should not be** another biosimilar

Generics vs Biosimilars



WHO Guidelines for evaluation of similar biotherapeutic products (2009)

- Provided **globally acceptable principles** as a basis for setting national licensing requirements
- Never expected to resolve all issues- eg policy on interchangeability and substitution of RBP with SBP excluded (very much a national decision)
- Considered guidance from other bodies (EMA, HC)
- Leave space for NRAs to formulate more specific requirements: sometimes there are legal constraints
- **Several implementation workshops 2010 - 2015 - Seoul (global), Xiamen (global) , Accra (Regional). .**
- Outcomes published , including **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**

Lessons learnt from 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 meet the 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.
- **The lack of agreed terminology** for products developed as "copy" products but with only partial comparability to a reference **has compounded the problem** – terms like "biogenerics" and biosimilars incorrectly used
- Global agreement that the term "biosimilar" applies **only** to products licensed following full head to head comparability exercise (quality, non-clinical and clinical)

So what should be done with these already licensed products ?

- 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
- Following **extensive international consultation** WHO guidance on ***Regulatory Assessment of Approved rDNA-Derived Biotherapeutics*** – adopted in 2015 as an **Addendum** to the WHO Guidelines on rDNA products

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.*

WHO Addendum follows option 4 : Emphasis on a stepwise regulatory assessment in dealing with the problem

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 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

- Time 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 allowed to remain on the market for this period unless safety issues are recognized**

A stepwise approach protects the supply and authorization could be regularized following further regulatory evaluation

Points to consider in a Stepwise 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 Regulatory Assessment

- Type of disease - life threatening or not. Patients - paediatric , adult , geriatric,
- Seriousness of potential lack of efficacy / safety issues, including higher efficacy or immunogenicity (especially if antibodies could cross-react with native protein and induce devastating effects) (EPO, MGDF).
- 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 review process and timelines

Regulatory Assessment of Approved rDNA biotherapeutics

- A number of countries recently introducing new or updated **regulations** for biotherapeutics / biosimilars – reflects some regulatory convergence
- **Include provision to re-assess products approved prior to the adoption of the new regulations**
- Provide for **interim transitionary period** very much along the lines advocated in the WHO guidance on *Regulatory Assessment of Approved rDNA-Derived Biotherapeutics* – (2015)

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 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

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

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 (re-licensing process)
- Annual progress reports also needed.
- Failure to submit required data sets would result in cancellation of the license
- **The new Regulations came into force in 2016**

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 2015 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

Updated and New Guidelines for biotherapetuics and biosimilars

- Some NRAs (eg EMA, Health Canada, S Korea) have revised their guidelines on biosimilars (2014-2016), overall guidance becoming more aligned. US FDA biosimilars guidance became available in 2015
- EMA has overarching guidelines for biosimilars, also separate ones on quality and on non clinical and clinical issues. In addition there are a number of product specific guidelines.
- Because of the complexity of monoclonal antibodies **WHO Guidelines on evaluation of monoclonal antibodies as similar biotherapeutic products** were developed and adopted in 2016 as part of WHO's support to NRAs
- **Under development –** WHO Guidelines on Procedures and Data Requirements for Manufacturing Changes to Approved Biotherapeutic Products (expected to be submitted to ECBS in 2017)
- Updating the WHO biosimilars guidelines under consideration - maybe as Qs & As

THANK YOU

Further information concerning WHO guidelines can be obtained from-

- WHO Biological standardization website -

  www.who.int/biologicals

- Contact persons: Dr Ivana Knezevic
  email: knezevici@who.int

- Dr Hye Na Kang
  email : kangh@who.int