Regulatory Evaluation of Biosimilars / Subsequent Entry Biologicals

Elwyn Griffiths

Biologics and genetic Therapies Directorate, Ottawa, Canada

Health Canada Santé Canada

Biotechnology Derived Medicines

- On the market since the early 1980s (recombinant DNA derived products as well as products from novel cell lines)
- Regulatory oversight (guidelines) put in place early on during their development- maximized their safety and efficacy
- They are best characterized biological medicines- well characterized biologics

Health Canada Santé Canada

Biotechnology Derived Medicines

- Recently new products appeared on the horizon – called Biosimilars / Subsequent entry Biologics

- This has led to a flurry of activity both with the manufacturers and regulatory authorities worldwide – **how to handle these products**

Health Canada Santé Canada

Requests to WHO for Action on Biosimilars/Follow on Biologicals

- International Conference of Drug Regulatory Authorities , Seoul, 2006
- **WHO requested to develop global regulatory consensus and guidance**
- WHO Expert Committee on Biological Standardization (2006)
- **Recommended WHO organize a meeting to review the issues in depth and develop a consensus on global needs/priorities**

Health Canada Santé Canada

International perspective on regulation of biosimiars

- **WHO consultation on biosimilars held in Geneva, 19-20 April 2007**
- Participants – regulators from Australia, Brazil, Canada, China, European Union, Germany, India, Iran, Japan, Switzerland, South Korea, UK and USA
- Generic and innovator manufacturers associations, including developing countries
- Academia.

Health Canada Santé Canada

WHO Consultation on Biosimilars, April 2007 - remit

- Review current directions and challenges in the regulatory evaluation of the quality, safety and efficacy of biosimilars
- To explore the need for, and form of, possible WHO regulatory guidance
- Expected outcomes - exchange of information between regulators, the identification of key issues and gaps, and recommendations on the next steps.

Health Canada Santé Canada

Biosimilars / Subsequent entry biologics

- Why this interest in biosimilars / subsequent entry biologics?
- What are they?

Health Canada Santé Canada

Background - Drivers

- Increasing number of patents/data protection for biological medicinal products expiring in coming years – some already expired
- Biologics “similar” to an innovator product now coming to the market- copies of the original innovator product
- Licensed subsequent to the approved innovator product **but on basis of a reduced non-clinical and clinical data package**

Health Canada Santé Canada

Background - Drivers

- Control of chronic diseases major challenge for public health systems
- Innovative biotherapeutics very successful but cost often prohibitive limiting their wide use, particularly in developing countries
- Biosimilars expected more affordable than innovator products - may contribute to their increased access
- **Difficult and contentious issues**

WHO Biosimilars consultation-outcomes

- Different NAMES given by different jurisdictions
- **Follow-on Biologics/protein products** (USA, Japan)
- **Biosimilar Products** (EU)
- **Subsequent-entry Biologics** (Canada)
- **Biogeneric products** used in India

WHO consultation- outcomes

- **Agreed** – biologics **do not** meet criteria for true GENERICS and **should not** be regulated under generic pharmaceuticals regulations where they exist
- Biologics are not “identical” by definition
- They are complex in nature and production
- Need for **some** clinical efficacy and safety data but **possibly less** than for an original innovator product- by now we already have much experience of the type of product and information on the mechanism of action

Biotechnology Products

- Manufacturing complex
- Very sensitive to production parameters
- Nature of cell substrate and growth conditions / downstream processing
- Minor changes can have major effects on biological activity
- **Key issue potential immunogenicity**

Health Canada Santé Canada

Potential immunogenicity

- Cannot be predicted
- Can happen with innovator product
- Biosimilars/ subsequent entry biologics need to move forward carefully, **no track record yet**

Biotechnology Products

- Nevertheless, considerable technological and methodological advancements in the characterization of proteins since many of the original recombinant DNA products were licensed
- **Enables detailed product characterization**
- Types of products considered – rDNA insulin, growth hormone, erythropoetin, various cytokines and interferons

Biotechnology Products

- Companies wishing to enter the biosimilar market need to acquire new skills in the **biologicals** field
- In manufacturing and product characterization
- In non clinical testing
- In clinical trials and regulatory compliance, pharmacovigilance issues

Health Canada Santé Canada

Not Generics

- Regulators agreed - possibility of licensing a new biological product on basis of “similarity” with a well established licensed product
- Expect extensive product characterization
- But with an abridged non clinical and clinical data package (case by case)
- Sometimes with head to head direct comparison with a **reference product at all stages** of the study, product characterization, non-clinical, clinical studies (EMEA)

Regulatory directions

- Some authorities already established regulatory pathways for biosimilars (EU)
- Others close to doing so (Canada)
- Yet others, developing countries in particular, do not have a regulatory framework for such products
- Generally same issues highlighted

Issues with biosimilars /subsequent entry biologics

- Definitions and terminology
- Which regulatory pathway?
- Scope of products – only proteins ? Polysaccharides (Heparins)?
- Proof of similarity – potential immunogenicity
- Focus on abridged clinical studies
- The comparator / reference product
- Extrapolation of indications
- Interchangeability / substitutability

Scope

- rDNA proteins only ?
- All well characterized proteins?
- Polysaccharides?
- Low Molecular weight Heparins – heterogenous 3000-5000MW- molecular weight varies, pharmacopoeial specifications insufficient
- EU consider heparins as biosimilars- developing guidance document

WHO Conclusions and Recommendations

- Biosimilars / subsequent entry biologics here to stay - issue is in providing appropriate regulatory oversight
- Regulatory oversight just evolving on global scale
- Wide range of regulatory preparedness for these products - the EMEA perhaps being the most advanced.

WHO Conclusions and Recommendations

- Agreement that clarification / harmonization of **terminology** important
- Agreement that a **WHO guideline** on key concepts would be helpful
- Not prescriptive – draw attention to issues and possible ways of addressing them

Health Canada Santé Canada

WHO Drafting Group Established

- Drafting Group established to develop first draft of WHO guidance
- FDA, KFDA, Germany, Health Canada, UK,
- Industry to be consulted
- Timelines – first draft March 2008
- **WHO Consultation, Seoul , May 2008**

Health Canada Santé Canada

WHO Consultation on Biosimilars - April 2007

- Meeting report currently in press in the journal Biologicals (Elsevier)

Health Canada Santé Canada

Regulatory directions and perspectives-European Union

- EU legislation amended to define biosimilar and regulatory process
- Guidelines in place – general and product specific
- Cover non-clinical and clinical requirements
- Several biosimilars approved by EMEA
- **Not generics**

EMEA Guideline on Similar Biological Medicinal Products

		comparability exercise
Quality	- Full	+
Non Clinical	- Reduced	+
Clinical	- Reduced	+

Published 2005 – **Biosimilars approach**

Health Canada Santé Canada

Regulatory directions and perspectives- USA

- Legal pathway exists for review and approval of smaller well characterized proteins under Food, Drug & Cosmetics Act
- Other biotherapeutics (eg cytokines) fall under Public Health Service Act and no abbreviated authorization presently possible
- Proposed modifications and development of clear pathway under consideration

Health Canada Santé Canada

Regulatory Approach in Canada

- Moving towards a Canadian regulatory framework for subsequent entry biologics (biosimilars)
- Abbreviation SEBs

Health Canada Santé Canada

Drivers for Regulatory Framework in Canada

- An increased number of biologic drug patents expiring
- Public demand for affordable alternatives to innovator biologics
- Changes in global market dynamics for biologic drugs
- Increase in number of inquiries and submissions for SEBs

A Major Challenge for SEBs

- Unpredictable nature of the immunogenicity of all biologic products
  - Most biologics induce antibodies
  - Manufacturing changes can cause unexpected changes in immunogenicity
  - Current analytical methods cannot fully predict biological properties
  - Immunogenicity of biologics may have serious clinical consequences
- Need for enhanced post-market surveillance for new biologic drugs, including SEBs

Canadian Context

- A Regulated Marketplace, but unlike USA & Europe:
  - Smaller in market size
  - Unlikely to be primary target for subsequent entry biological development and submissions

Canadian Context

- Existing Regulatory Framework
  - Enables Minister to approve New Drugs (including SEBs) based on sufficient evidence of safety and efficacy
  - No specific regulations to prevent SEB, but existing framework not a best fit for SEBs
- Division of responsibilities for product safety (federal government) and delivery of health care (provincial government)
  - Approval of SEBs will not address interchangeability with its reference product

The SEB Project at BGTD

- Biologics and Genetic Therapies Directorate (BGTD) is leading the Health Canada Working Group (WG) on SEBs. WG initiated in December 2005.
- Representation from BGTD, Therapeutic Products Directorate (TPD), and Marketed Health Products Directorate (MHPD). Consults with Legal Services when required.
- A Fact Sheet for SEB published in July 2006 outlining the interim regulatory approach for SEBs.

The SEB Project at BGTD

- A Draft Guidance document entitled *Draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)* released in January 2008.
- For comment
- Received lots – from both innovative and generic industry

Overview of basic concepts for Regulatory Framework

- Patient safety and options for alternatives in the biologics field are of paramount importance
- SEBs will be licensed based on **demonstrated similarity** to a chosen Reference Biologic Product.
- **SEBs are not "generics"**
- **Approval of SEBs will involve direct and/or indirect comparison (reliance) on data from already approved products**

Scientific Basis

Quality Requirements

- SEBs will be approved on **demonstrated similarity to a reference biologic product**, relying in part on publicly available information from a previously approved biologic drug, in order to present a reduced clinical data package as part of the submission

Scientific Basis

- Full Chemistry and manufacturing package
- Comparability between SEB and a Reference Biologic Product
- Extensive side by side characterization of SEB and **Reference Product**

Choice of Reference Product (Comparator)

- Licensed (and marketed) in Canada?
- History of safe use in Canada ?
- **Flexibility** required for when there is no Canadian Reference Product
  - Canada is a small market and some reference product choices may not be licensed or marketed in Canada

Choice of Comparator

- Possibility of allowing comparator that is licensed by a major regulatory agency with which Health Canada has a Memorandum of Understanding

  eg FDA or EMEA

Reference Product

- Availability of final formulated product only
- Use for comparative physico-chemical comparator needs unformulated drug substance
- “Generic” manufacturers have buy lots of final product and isolate active substance.
- Need to validate isolation process does not lead to changes in drug substance eg oxidation etc. Not easy

Scientific Basis

Non-clinical and Clinical Requirements

- Results from the Comparability Exercises determine the extent of data requirements
- **Clinical studies should be provided for each indication being sought (differs from EMEA)**
- **Depends on study design – clinical equivalence or non- inferiority -flexibility**

Non-clinical and Clinical Requirements

- The final SEB product should be used in pre-clinical and clinical studies.

- Pharmacokinetic and pharmacodynamic data essential but with other clinical studies on case by case basis

Clinical efficacy and safety trials (1)

- Comparative in nature to demonstrate the similarity in efficacy and safety profiles
- Design of the studies
  - Active control trial or matched historical controls (?)
  - Equivalence/non-inferiority trials; superiority trials (?)
  - Comparability margin has to be justifiable on clinical grounds . Some flexibility .

Clinical efficacy and safety trials (2)

- Safety data from sufficient number of patients and sufficient study duration to allow for comparison of the nature, severity and frequency of ADRs
- As feasible, studies should be sufficiently powered either to detect any clinically and differences in efficacy that are clinically important or to show that the efficacy of the SEB is not clinically inferior to that of the innovator.
- **The immunogenicity of the SEB** to be tested using state of the art methods to ascertain the effect of the immunogenicity of the product on both its efficacy & safety **(usually 12 month study expected)**

Clinical efficacy and safety trials (3)

- Neutralising antibody (if positive)
  - Further analyses of PK/PD, Efficacy and Safety are required
- Post-market risk management plan should include a systematic testing plan for monitoring immunogenicity

Anti-Growth Hormone antibodies

Month	Omnitrope	Genotropin
0	0/44	0/45
3	11/42 (26%)	0/44
6	14/42 (33%)	0/44
9	24/42 (57%)	1/44 (2%)

(Data from Andrew Fox Amgen) Omnitrope =SEB

Anti-Growth Hormone antibodies

- 89 patients studies .
- Detected about 30 fold higher chance of developing immune responses in children with growth deficiences with original omnitrope
- Purification process improved study repeated. Problem solved.
- Product (Omnitrope) approved in EU, US and Australia

Outcome of comparability study - Canada

- Agreed indication will **only** be that tested in comparative clinical study. Others may be assigned later with more clinical data.
- Interchangeability or substitutability with the comparator product separate issue and subsequent to market authorization
- Decision on interchangeability based on scientific and clinical data, **not automatically**

Health Canada Santé Canada

European Position

- Reference must be a licensed product
- Needed since object is to show product “similarity” and clinical equivalence
- Intention to assign all of the indications of the Reference Product to the biosimilar on basis of one clinical study
- Not the position in Canada

No Automatic Substitition

- In EU individual Member States **providing clarity in law** on substitution of biological medicines
- France and Spain (2007)
- Legislation to prevent automatic substitution of reference product with biosimilar
- Laws stipulate reference product and biosimilars are not identical and cannot be substituted at the pharmacy level automatically - need full opinion

Scientific Basis

Post-Market Requirements

- An enhanced post-market surveillance strategy will be required, as for all new biologic products
  - Hence a post-market safety surveillance plan is required prior to issuance of marketing authorization
  - The surveillance plan should be designed to monitor and detect both known adverse events and potentially unknown safety signals.
  - Any post-market risk management plan should include detailed information of a systematic testing plan for monitoring immunogenicity of the SEB.

Stand alone approach also possible in Canada

- Proposed regulatory framework also allows a stand alone approach
- Extensive product characterization but no head to head comparison with Reference Product
- Some abbreviated non-clinical and clinical evaluation on justification and case by case basis.
- Clinical studies can also be comparative

Stakeholder Consultation

- 5-6 June 2008 Ottawa
- Innovative industry associations, generic industry associations, patients groups, Provincial / Territorial representation
- WHO, EMEA (teleconference) Japan (teleconference)
- 100 + participants

Stakeholder consultation June 2008: Main points

- General consensus to move forward on proposed framework
- Patient safety paramount important
- Some disagreement – on use of Non-Canadian Reference Product
- Interchangeability / substitutability issues
- Draft will be revised to clarify some aspects

Flexibility and Balanced Approach

- Based international best regulatory practices
  - **Sound science**
- Enables **flexibility** to suit needs of Canadians and legislative framework
- International Collaboration with other National Regulator Agencies and through the World Health Organization

Next Steps in Canada

- Revision of guidance document based on comments received, out-come of the consultation
- Publication of finalized guidance document with comments received
- Continued collaboration with other international partners towards a harmonized approach
- Timeline: End 2008

Nomenclature Issues

- **International Non-proprietary Names (INNs)**
- Again a difficult and contentious issue
- Concerns of innovator pharmaceutical industry regarding automatic substitution

International Non-proprietary Names (INNs)

- WHO INN programme initiated in 1950
- Assigns non proprietary names to pharmaceuticals so that each can be recognized globally by a unique name
- INNs are essential part of the regulatory process in many countries – an INN is required for licensing (eg EMEA)

International Non proprietary Names (INNs)

- Used in pharmacopoeias, labeling, product information, advertising and other promotional material, drug regulation and scientific literature, and as a basis for product names, e.g. for generics.
- INNs facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients
- Tool in worldwide pharmacovigilance

International Non proprietary Names (INNs)

- Pharmaceuticals (eg ibuprofen)
- Some Biologicals (eg natalizu**mab**)
- Biotherapeutics, including rDNA derived – cytokines , interferons, monoclonal antibodies
- Genetic therapy products
- Not vaccines or naturally derived blood products

Health Canada Santé Canada

INN Challenges

- **Generic drugs are assigned SAME INNs as the innovator drug** (even if produced different routes).
- No guidance covering biosimilars- **new**
- Assign SAME INN as innovator product?
- Assign DIFFERENT INN **to indicate biosimilar** product?
- Why and on what basis?

Health Canada Santé Canada

WHO Consultation on INNs for Biosimilars, September 2006

- Representatives of the WHO Expert Committee on INNs
- Representatives of Regulatory Authorities of Australia, Canada, European Union, Japan, South Korea, USA

Health Canada Santé Canada

Task

- Exchange views on issues relating to nomenclature of biosimilar products in different regulatory settings
- Advise WHO on INN policy for these new products.
- Views of innovative and generic industry on naming biosimilars available in writing

Health Canada Santé Canada

How should INNs be assigned?

- Should INNs be used to reflect a **REGULATORY PROCESS** (eg extent of clinical trials for approval) ?

- Should INNs be based only on description the medicinal substance **(scientific product characterization**) irrespective of the regulatory package developed and accepted for approval ? **(traditional)**

Health Canada Santé Canada

Present situation

- Different **innovator biologicals** can have SAME INN even if slight differences in glycosylation (interferon beta-1a)
- Significant differences in isoforms lead to distinctive INN name (epoetin alpha: epoetin beta) – different producer cell lines

Conclusions/Agreement

- Assignment of INNs should be **independent** of the regulatory process
- Term “Biological” based on scientific considerations
- **Term “Biosimilar” is a regulatory and legal concept**
- Two should be clearly differentiated

Health Canada Santé Canada

Conclusions/Agreement

- Decisions on interchangeability or substitutability should be based on appropriate scientific and clinical data (not available to INN Committee), **not on INNs**
- For pharmacovigilance purposes INN is **only one** component of **biological product** identification
- Additional identification needed (Lot Number, product identifier)

Health Canada Santé Canada

Possible WHO Codes

- Recommendation for WHO to draw up list of internationally agreed **codes to reflect different production processes** (such as E. coli, yeast , CHO cells etc) .
- Use of such codes discretionary and used in labeling when regulatory authorities wished to distinguish different production systems.

Recommendations on biosimilars

- No distinctive INN designation to indicate biosimilar
- **Naming of Biosimilars should be handled in way as stand alone biologicals**
- Need to explain clearly to stakeholders **limitations of INNs for biologicals**

Health Canada Santé Canada

Final conclusions

- Regulatory oversight of so called “biosimilars” / subsequent entry biologics evolving rapidly
- No question that they will become a future major player on the world market
- Expectation this will open up global access
- **Need to move forward BUT carefully**

Health Canada Santé Canada

Muchas Gracias

- Thank you
- Merci Beaucoup
- Diolch yn Fawr

Health Canada Santé Canada