Reunion del Grupo de Tabajo OMS sobre la regulacion de productos biologicos terapeuticos
Seul, 2008

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Development of WHO Guidance on Similar Biological Products

- International Conference of Drug Regulatory Authorities 2006 – recommendation to WHO
- Expert Committee on Biological Standardization 2006 – endorsed recommendation
- WHO consultation on biosimilars held in Geneva, 19-20 April 2007

WHO consultation on biosimilars held in Geneva, 19-20 April 2007

- Generic approach for pharmaceuticals does not apply to “similar” biologicals
- WHO should develop a global regulatory guideline for “biosimilar” products

Aim

- Aim: to provide a globally acceptable set of principles for the evaluation of these biological products covering both licensing and post marketing surveillance.
- Licensing - based on the **reduced CLINICAL data package** but without compromising the quality, safety and efficacy of these products.

WHO consultation on biosimilars held in Geneva, 19-20 April 2007

- Recognized divergent approaches for regulatory oversight of similar biologicals in different countries due to:
  - Different situations with innovative products (small vs big markets)
  - Different regulatory frameworks

- Approaches elaborated should aim for better access to **biotherapeutics of assured quality** at **affordable price** worldwide

Development of WHO Guidance on Similar Biological Products

- **Drafting Group Established** – German Regulatory Authority (BFarM), Health Canada, Korea FDA,US FDA, NIBSC UK,
- **Meeting, Bonn, March 2008**

  - to discuss key issues in draft WHO guidance document

  -to develop plan of action for further development of the document

  -plan for Seoul consultation

Outcomes Bonn Meeting

- A number of key policies were clarified, including terminology, scope
- Two approaches to licensing subsequent entry biologicals / biosimilars to be proposed
- 1) Biosimilar approach

  2) Stand alone approach

Problems with Terminology

- Term “biosimilars” gives impression that WHO recommends European approach, - not the intention
- Original draft guideline called -- licensing approaches for biosimilar / follow on /subsequent entry biologicals
- Title refers to product, not pathway

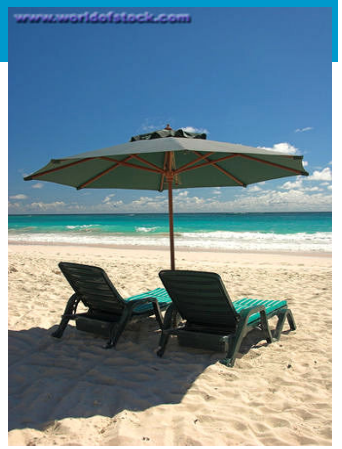
Problems with Terminology

- In Bonn decision made to call document – **WHO guideline on licensing approaches to subsequent entry biological medicinal products (SEBs)**
- Overall title refers to product type and covers the two regulatory pathways:
  - Biosimilar approach:
  - Stand alone approach

Definition of SEB

- SEB is a biological medicinal product developed to be “similar” in terms of quality, safety and efficacy to an already licensed, well established, reference medicinal product marketed by an independent applicant.
- Two different approaches (biosimilar and stand alone) that might be used worldwide for proving similarity of products developed subsequently to the originator products.

Two approaches proposed



1. **Biosimilar approach**

- thorough comparability exercise to prove similarity of the SEB to the chosen Reference Product in terms of quality, safety and efficacy

- demonstration of biosimilarity will lead to the license and use of the product that is similar to the Reference Product and **may allow extrapolation to other indications of the Reference Product.**

Stand alone approach

- based on the own data on quality, safety and efficacy to support proposed indications
- However, non clinical and clinical data package could be reduced
- Head to head clinical comparison with an originator product also possible

Stand alone approach

- Quality: full dossier always required
- Reduced clinical data package on justification, comparability against well established product recommended
- Extrapolation to other indications is limited – **disadvantage**
- **Not unlike a submission for an innovative product but with less non-clinical and clinical data on justification**

Reference Product / Comparator

- In **biosimilar approach** , the Reference Product / Comparator should be one licensed by full data package, and used throughout the comparability exercise. Allows flexibility like Canada - but some NRAs may require nationally licensed product
- Use in **stand alone approach** not critical but could be used in head to head clinical studies. “Standard of care” product could be used

Scope- March Document

In principle - all biologicals

- In practice, majority of the products that are subject of licensing with reduced clinical data are recombinant DNA-derived proteins ie well characterized biologicals
- Other categories of products to be considered as the techniques for their characterization become available

Draft WHO Guideline March 2008

- Sent out for consultation to industry, both innovative and generic, national regulatory authorities, Developing country manufacturers and national regulatory authorities
- Lots of detailed comments received
- Discussed in WHO consultation held in Seoul, May 2008

Consultation in Seoul – May 2008

Broad consultation with relevant experts

- Better understanding of the current situation: examples in Korea, China, India, Iran, Latin American countries
- Thailand reported considerable incidence of red cell aplasia. Unknown origin except that innovative industry point finger at biosimilar products (erythropoetin type) marketed with little regulatory oversight. Postmarket surveillance being set up to better monitor use and effects. No evidence its due to biosimilars.

Consultation in Seoul , May 2008

- Concern that stand alone approach may lead to double standard expressed
- Patient safety - essential
- Proposals for revision made – section by section
- Innovative and European generic industry wanted only European style Biosimilars approach
- May not be suitable for global use

Consultation in Seoul – key outcomes

- Scope redefined: well characterized biologics re-introduced; vaccines not to be included (covered by WHO documents)
- Two approaches (Biosimilars and stand-alone) should be clearly distinguished and text clarified : re-structure document
- Terminology to be improved to avoid misunderstanding (comparability exercise, similarity, reference product, comparator etc)
- Outcome of evaluation should be biotherapeutic product of assured quality independently of the pathway that was used for its evaluation (biosimilar or stand alone)

Consultation in Seoul – key outcomes

- **Reference product**
- Biosimilar approach: the same throughout the whole evaluation
- Stand alone: comparability in terms of safety and clinical efficacy
- **Nonclinical:** demonstration of similarity in terms of toxicity testing only was considered as a reasonable option for biosimilar approach
- **Clinical**: Demonstration of the equivalence in both approaches; however, non-inferiority is also acceptable in stand alone approach.

WHO Guidance

- Extensive for vaccines
- Little for biological therapeutics (some but not recent)
- Need to include considerable guidance for stand alone pathway
- Intention to develop guidance for biological therapeutics –but will come after present guideline.

Other relevant issues to be mentioned

- INN – link between nomenclature and regulation of biological therapeutics
- Interchangeability and substitutability to be explained
- Patent, intellectual property and data protection – mention only
- Mechanisms for sharing the information on adverse events

Name of Guideline

- Much discussed in Seoul and afterwards by email.
- Attention paid to problems of Spanish translation
- Needed title to cover both approaches: biosimilars and stand alone
- **New proposed title : WHO Guidelines on Abbreviated Licensing procedures for Biologic Therapeutic Products**
- **Refers to regulatory pathways not product**

Next Steps

- Revision of the draft guidelines: June-July
  - Revised draft to be prepared by 20 June and circulated to all participants of Seoul meeting for comments by mid July
  - Comments incorporated and WHO BS document for the ECBS finalized by 31 July
  - Public consultation 2 months
- ICDRA report – mid September 2008
- Expert Committee on Biological Standardization – 13-17 Oct 2008