

# Regulatory Review and Approval Process: Across the Globe

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# Health Canada Publishes Draft Approval Guidelines for Biosimilars

- Global Insight Perspective:

Health Canada is making rapid progress with approval of guidelines and is expected to have cheaper copies of biotech products on the market earlier than the USA.

# Global Report: Moving Towards Generic Biologics

- European Medicines Agency (EMA) has guidelines in place to address comparability when companies introduce changes into their manufacturing process.
- At the heart of the problem is what further tests will be required on biosimilar products.

# Global Report: Moving Towards Generic Biologics

- Originator companies claim comprehensive testing for all biosimilars
- Generic counterparts believe testing should be minimized
- Biosimilar approval structure in the EMEA are significantly more comprehensive than those of US FDA

# Global Report: Moving Towards Generic Biologics

- In the EU, legislation was passed in 2003. At that time, results of toxicological, pharmacological or clinical trials were not required for demonstration of safety and efficacy.
- Since then, EMEA has issued seven guidance documents to improve the safety and efficacy.

# Global Report: Moving Towards Generic Biologics

- European law requires pre-clinical and clinical data to support approval of biosimilar products
- Aisling Burnard, Chief Executive of UK Bio-industry, says “Ultimate goal of the guidelines should be to ensure patient safety”

# Global Report: Moving Towards Generic Biologics

- EU and EMEA have continued to move forward in bringing two recombinant human growth hormone (HGH) products to the patients:
  - Omnitrope
  - Valtropin

# Industry View

- Biosimilars shake up the Biologics market
- Take necessary steps to prepare or risk being left behind
- Biopharma companies cannot afford to sit back and wait for the Guidelines. Those who are not ready will be left behind.

# World Health Organization Policy For Biosimilars

- Represented at the meeting were the regulatory authorities of Canada, European Union, South Korea, Japan, Australia, Belgium, Poland and USA.
- China and India, which produce the bulk of APIs for the world, were not represented.

# World Health Organization Policy For Biosimilars

- WHO indicated that they are considering development of regulatory guidelines on biosimilars.
- Any regulatory guidelines developed by an organization that has no regulatory power over member nations will have very little impact. But it will give license to manufacture these products in several member nations.

# WHO Draft Guideline June 2008

- The intention of the guideline is to provide a general set of principles for evaluation and licensing of biotherapeutics on the basis of the reduced clinical data package but without compromising the quality, safety and efficacy of these products.
- Two approval pathways
  - **Biosimilar pathway**
  - **Clinical comparability pathway**

# Industry Views of Biosimilar Development in Japan

- Japan is unlikely to produce more than a handful of biosimilars domestically in the near future.
- Regulatory guidelines will be needed for Japanese developers to plan and initiate production of biosimilars.

# JAPAN

Recent draft guidance (17-Sep-2008) on the “Quality, Safety and Efficacy of Follow-on Biologics”

- A **Follow-on biologic** is a drug to be developed by a different marketing approval holder as a drug that is bio-equivalent/quality-equivalent to biotechnology derived drug already approved domestically. A Follow-on biologic must be developed on the basis of data obtained from a comparison with the comparator bio-drug demonstrating bio-equivalence/quality-equivalence in respect of quality, safety and efficacy; or similar data.

# ARGENTINA

## Registration and Registry Modification of Biological Medicinal Products

- “Similar Biological Medicinal Product” is a medicinal product that has been shown, by similarity studies, to be similar in terms of quality, safety, and efficacy to a biological medicinal product taken as reference which has already been authorized by the health authority. The present definition is applicable to those products that may be broadly characterized, such as proteins obtained by recombinant DNA techniques and polypeptides and highly purified natural proteins

# MALAYSIA

Guidance document and guidelines for registration of biosimilars in Malaysia made final August 2008

- The information in this guidance is adopted from the EMEA guidelines, in particular the Guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substances, with some adaptations for Malaysian applications.

# Biosimilars: Indian Generic Companies and the Drug Regulators

- Dr Reddy's laboratories, the country's third biggest drug-maker, will form joint ventures with world's biggest biotech companies to make biosimilars and take on companies such as Ranbaxy, Reliance Life Sciences, and Biocon.

# India Readies for Generic Biologics Market

- Asia's Biologics Business: Biocon, Intas, Ranbaxy, Dr. Reddy's and Wockhardt
- India makes 30-40% of the world's vaccine at WHO-approved facilities
- Are the Indian Drug Regulators ready for the new, more challenging form of generic drugs?

# India Readies for Generic Biologics Market

- Biocon President says: Our plants have been inspected by European regulatory agencies and we have been able to comply with their standards.
- Asia's bigger challenge in selling to the regulated markets will be, the possible regulatory request for additional clinical trials to prove that the biosimilars are as safe as original product.

# Global Challenges

- Swiss drug-maker Novartis wants to sell Omnitrope in USA.
- Urbana court has ruled that FDA has not presented compelling reason for its delay in approval of this drug.
- Heart of the problem: Verifying the safety and efficacy of copies of biotech drugs without data from clinical trials.

# Global Challenges

- Australia and Croatia have approved Omnitrope
- India produces large quantities of vaccines with WHO guidelines
- Asia can sell their biosimilars in non-US markets without doing any clinical testing

# Global Challenges

- EMEA has put in place abbreviated approval guidelines for four categories of biosimilars:
  - Human Growth Hormone, Somatropin
  - Recombinant granulocyte-colony stimulating factor (G-CSF)
  - Insulin
  - Erythropoietin
- Ranbaxy of India has announced joint venture with Zenotech Laboratories, for the first biosimilar product in India (G-CSF)

# Biologics Price Competition and Innovation Act of 2007

Sponsored by Senators Kennedy, Hatch,  
Clinton and Enzi

- Under the approval process in the bill, a biosimilar applicant will be required to demonstrate that there are no clinically significant differences in the safety, purity and potency between biosimilar product and branded product by using analytical, animal and human testing.

# Collective Wisdom

- Standardization subcommittee (SSC) of International Society on Thrombosis and Hemostasis (ISTH) USA, has collectively made following recommendation for one of the biologics, which is a very complex molecule:

Generic version of

Low Molecular Weight Heparin (LMWH)

# Collective Wisdom

- Efficacy and safety of a biosimilar LMWH has to be demonstrated in clinical trials for every indication to be approved by the regulatory authorities.
- Based on the heterogeneity of the LMWHs, all biosimilar LMWHs have to demonstrate their non-inferiority, compared to the originator products, in preclinical and clinical investigations.

# Collective Wisdom

- Experts from different countries have met several times in the last two years in Boston, USA (under NATF Platform) and in New Delhi, India (under SASAT Platform) and drafted editorials and white papers on the subject.
- These experts reached the same conclusion as that of experts from SSC of ISTH and EMEA:  
*Clinical and pre-clinical trials are essential  
for the approval of biosimilars*

# Regulation of Follow-on Biologics: Ensuring Quality and Patient Safety

- We very much want oral anti-coagulants. We want cost-effective biologics, biogenerics, biosimilars, follow-on biologics and cheaper copies of biotech products.
- In a global market, there should be Uniform Global Regulatory Review and a Global Approval Process.
- All countries of the world are Looking at this lucrative platform, yet the regulatory process is different in each one.

# Conclusions

- In view of WTO agreements, globalization of economy and marketing, it is critical to come up with Global Review and Global Approval Process.
- Biosimilars are complex biologic products, unlike their simple generic molecules.
- To protect public health and patient safety, it is critical and essential that the regulatory standards for their approval should not be solely determined on the basis of cost-effectiveness.