



## ORGANISATION OF PHARMACEUTICAL PRODUCERS OF INDIA

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### OPPI POSITION PAPER ON BIOSIMILARS

#### Background

**Biopharmaceuticals and Biosimilars** : Biopharmaceutical drugs can be broadly defined as those medicines produced using a living system or genetically modified organism. They are different from traditional chemical medicines in many ways. Size is one of the most obvious distinctions: the molecules of a biopharmaceutical medicine are much larger, have far more complex spatial structures and are much more diverse (“heterogeneous”) than the chemical molecules which make up classical drugs.

The conditions in which biopharmaceuticals are produced largely define the final product. The process defines the product quality. **Any alteration to the manufacturing process may result in a completely different product.** Additionally proteins are relatively unstable, introducing additional measures in their storage, formulation and delivery. The criticality of the manufacturing process can be emphasized with the example of the increased incidence of pure red cell aplasia (PRCA) in patients being treated with Erythropoetin. Extensive investigation revealed that most likely change in excipient and manufacturing process may have caused the incidence of PRCA. No matter what the ultimate cause or causes of PRCA may be, the foregoing demonstrated the potential for immunogenicity from even slight changes in any facet of the manufacturing process for a biotechnology-derived protein product.

Biosimilar medicines are follow-on versions of original biopharmaceutical medicines. Biosimilar medicines are intended to have the same mechanism of action as the original biopharmaceutical medicines, and are designed to treat the same diseases as the innovator’s product.

There is considerable debate surrounding the definition, licensing and marketing of biosimilar medicines. The crux of this debate rests on the differentiation between biosimilar medicines and traditional generic copies of chemical medicines. **Whereas generics of chemistry based medicines are identical in the molecular structure and therefore copies of the original product, based on a strict definition of “sameness”, a corresponding definition cannot be established for biosimilar medicines because of their nature and the complexity of their manufacturing process. Here post-translational modifications are dependent of the host cell and the process.**

**Main Issues:**

- Small changes in the manufacture of biopharmaceutical and biosimilar medicinal products can dramatically affect the safety and efficacy of the therapeutic molecule.
- The very nature of a biologic means it is practically impossible for two different manufacturers to manufacture two identical biopharmaceuticals if not identical host expression systems, processes and equivalent technologies are used. This has to be demonstrated in an extensive comparability programme. Therefore a generic biopharmaceutical cannot exist.
- Substitution issues: by contrasts with the situation applicable for generics or “copies” of chemical entities, biosimilar medicines can be “similar” but not “identical” to the innovator reference products. The “similar, but not identical” nature of biosimilar medicines means that substitution of the innovator product with a biosimilar product could have clinical consequences as patients could respond differently to the two products. To guarantee the efficacy and safety of biosimilar products, these products should only be approved following the submission of appropriate data generated with the biosimilar drug. This data should include pre-clinical tests and clinical trials with a significantly relevant number of patients to establish the safety and efficacy of the biosimilar drug.
- Currently there are no clear Indian guidelines for the approval of biosimilars which will ensure the approval of efficacious and safe biosimilar drugs.

**Regulatory Approvals in US and EU**

**European Union** : Since the past few years, the EU has worked to establish a science-based procedure for supervising and authorizing the regulatory approval of generic biological products. In February 2006, EMEA (European Medicines Agency) released final guidelines containing details of clinical, non-clinical and quality expectations for biosimilar protein therapeutics. These guidelines were themselves an expansion of the general guideline released in September 2005 and of two earlier documents, a note for guidance containing non-clinical and clinical issues (December 2003) and a quality guideline (also December 2003). The EMEA’s work in developing regulatory and scientific guidance documents has enabled the EU to be the first major governmental body to authorise a biosimilar product. As of date, the European Commission has granted 2 approvals for biosimilar drugs.

**USA** : A series of key events and statements regarding follow-on proteins set the stage for the controversy surrounding FOPs (follow on proteins) in the U.S. The innovator industry filed several citizen petitions challenging the use of Section 505(b)(2) to approve FOPs. The Biotechnology Industry Organisation (BIO) filed a citizen petition in April 2003 objecting to the use of this section to approve a biologic without a “full complement” of non-clinical and clinical data.

However, till date no legislation is in place for approval of such products. Nevertheless in May 2006, the US FDA approved a recombinant human growth hormone (rhGH) after a legal battle. This product has been called a biogeneric because its active ingredient is Somatropin, the same as Genotropin, another recombinant human growth hormone that has been on the market since 1998.

### **Purpose**

Global biopharmaceutical market is estimated at U.S.\$ 63 bn of sales in 2005. The Indian Biotechnology industry is also gaining momentum, with revenues of over U.S.\$ 2.0 billion in 2006, 70% of which is Biopharmaceuticals. There are 40 National Research Laboratories in the country employing 15,000 scientists. There are more than 300 college level educational and training institutes offering degrees and diplomas in biotechnology, bio-informatics and the biological sciences, producing nearly five lakh students annually. The Dept. of Biotechnology, Ministry of Science & Technology, Government of India has also issued "National Biotechnology Development Strategy" which gives key policy interventions for the accelerated growth of this sector. Given this backdrop, biotechnology is certainly the next big frontier for the Indian economy. This exploding scenario can put immense pressure on the government to facilitate the growth of biogenics without stringently regulating the equivalence issues. This emphasises a need to establish guidelines for the approval of biogenics in India, on lines of regulated markets.

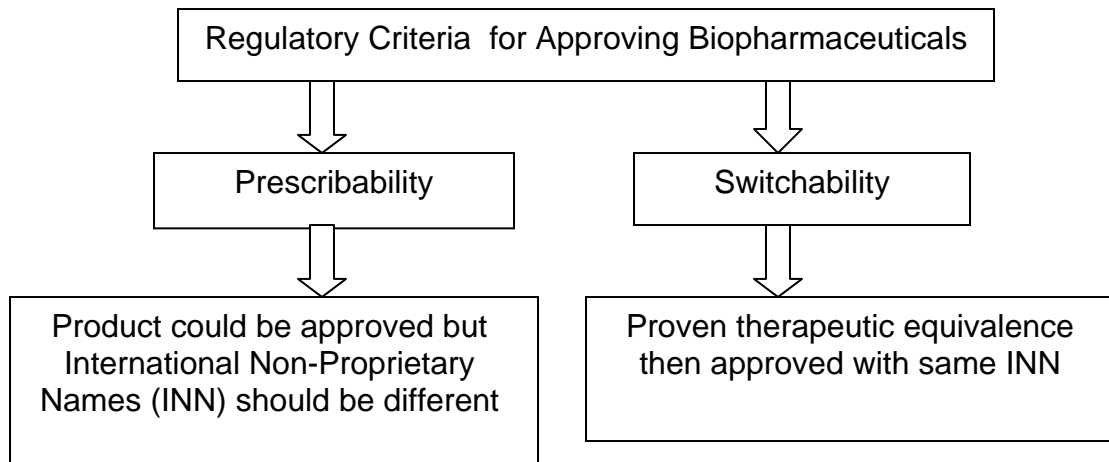
### **Approach**

The standard generic approach (for oral formulations it means the demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) is normally applied to chemically derived medicinal products. Due to the complexity of biological/biotechnology-derived products, the same generic approach is scientifically not appropriate for these products. The "similar biological medicinal products" approach, based on a comparability exercise, will then have to be followed.

The following approaches could be considered:

1. Like vaccines, we could consider classifying all biologicals as 'new' drugs in order to bring all biological approvals in the purview of Central Drugs Standard Control Organisation (CDSCO). It may be appropriate to mention here that the State FDAs are empowered to grant manufacturing licences without new drug approvals if the drug is more than 4 years in the Indian market. In that context, it is indeed ironical that while the US FDA is struggling to grant approval for biogenics, our State FDAs can easily approve biogenics if the product is available in India for greater than 4 years without any substantial data. Moreover, as bioequivalence approach is not scientifically appropriate for biogenics, all applications in India should be submitted in the Appendix 1 format rather than the 1A format requiring complete data submission like a new drug.

2. We have to consider establishing Regulatory criteria for the approval and consideration for comparability to the innovator product These would be on the basis of '**prescribability**' and '**switchability**'.
- Prescribability** essentially means a clinical setting, where a clinician prescribes the product for the first time based on its characterization during clinical trials.
  - Interchangeability** (or **switchability**) refers to a clinical setting when a clinician transfers a patient from one product to another based on its bioequivalence data.



### **Conclusion**

Our first choice would be Approach 1 discussed above that would classify Biopharmaceuticals alongwith with vaccines as biologicals. If this is not possible, Government should consider creation of Indian Guidelines for the Regulatory approval of therapeutic Biopharmaceuticals that should be prepared as a consensus document and legislated. This will ensure not only efficacy and quality but also patient safety.

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