



# NATF OFFICIAL POLICY STATEMENT REGARDING THE PROTECTION OF PATIENT SAFETY AND PATIENT RIGHTS ON MATTERS OF FOLLOW-ON BIOLOGICS

## BIOSIMILAR BIOLOGICS ARE NOT IDENTICAL: PATIENT SAFETY CONCERNS FROM SCIENTIFIC AND CLINICAL EXPERIENCE

Assuming that all biosimilars are interchangeable may result in adverse clinical consequences. Recent examples include the treatment of individuals who developed acquired antibodies against their FVIII coagulant protein after receiving plasma derived concentrates of equivalent efficacy but which had undergone different viral attenuation procedures as part of the manufacturing process. The final FVIII products were indistinguishable from their pharmacokinetic and potency characteristics; however, *in vivo*, the modified product was associated with significant adverse immunologic events. The resulting neutralizing antibodies in these individuals rendered them difficult to treat and at increased risk for both bleeding and resistance to treatment with already commercially available safe products.

Another scientifically humbling observation was made in 1998 when a commercially available recombinant human erythropoietin preparation induced antibody mediated pure red cell aplasia despite a prior history of clinical safety and efficacy. This adverse effect was temporally associated with a formulation change in the composition of the stabilizing excipient; other biological products employing similar stabilizing strategies did not produce similar complications.

Of concern is the advent of new biosimilars derived from unfractionated heparin and heparin-like synthetic or semi-synthetic oligosaccharides. The limitations of *in vitro* potency assessment are nowhere more evident than documented by the recent adulteration of unfractionated heparin by the addition of chondroitin sulfate to the active pharmaceutical ingredient. This adulteration remained identifiable even after chemical modification to produce derivative forms of unfractionated heparin, namely some of the approved low molecular weight heparin preparations. The significance of this event cannot be minimized as just an issue of chemical impurity since it was directly implicated as the cause of death in over 250 individuals.

Because many biological substances have multiple activities, only some of which may be known today, even indistinguishable activity *in vitro* cannot guarantee interchangeability *in vivo* or more importantly when the product is used in the treatment of specific disease. It is evident that final specifications for commercial products and the physical and chemical procedures for their evaluation **must be equal** to the challenges which will accompany the introduction of biosimilars into the marketplace.

**Indistinguishability with regard to safety and efficacy must be viewed as necessary and independent of the *in vitro* specifications.** It must be appreciated



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that the current goals and design of most clinical trials emphasize short term safety and efficacy; however, such studies are **inadequate** to recognize the long term consequences of what appear to be only subtle and initially irrelevant differences.

The pharmaceutical industry and medical care providers should be focused on the legitimate goal of biosimilars to be interchangeable with the ultimate need to provide lower cost therapeutic alternatives. Most imperative is to assure that this aim is not subverted by our ignorance of properties that could not be predicted to be important or even adulteration of a product which might not be readily detectable.

### **POINTS TO CONSIDER:**

- 1. Interchangeability must be a prerequisite of any product to claim biosimilarity.**
  - a. The criteria for claiming interchangeability must be very well defined. The biosimilar must not be inferior to the reference product and this must be determined in well designed, well controlled, appropriately powered, and properly conducted clinical trials
  - b. Post-market surveillance and pharmacovigilance strategies must be implemented and enforced to establish long term safety and efficacy. This is particularly critical when the biosimilar is expected to be used “off-label.”
  - c. The benefits of interchangeability are intended to achieve cost savings, which could easily be lost if safety and efficacy are not incontrovertibly established for the biosimilar. Unanticipated adverse events, if of higher frequency and severity than with the reference product, whatever the cause(s), may prevent biosimilars from ever providing their potential economic advantages.
  - d. Because biosimilars may differ from the reference pharmaceutical product in unknown ways, they must be excluded from being used themselves as reference products. This is important in order to prevent propagation of unrecognized clinically significant differences among the products. Laboratory comparisons must similarly employ the innovator product as the reference for all relevant properties.
  - e. If a biosimilar does not satisfy the criteria defined for the full clinical trial or for the stringent pharmacokinetic assessments, it should therefore not be designated a biosimilar.



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- f. As a means of avoiding inadvertent, but potentially devastating mistakes, agents that fall under 1e, may be considered for market availability only under a separate name and upon fulfilling the rigors of the Food and Drug Agency for approval.
2. **Potency is an *in vitro* assessment of activity, and it must be demonstrated such that potency differences between products cannot predispose them to dosing errors.**
  - a. The biological activity of a biosimilar must use the same unit of biologic activity as the reference product.
  - b. Potency of the biosimilar and the reference must be equivalent so that they will exhibit comparable pharmacokinetic properties *in vivo*
3. **We recognize that current reference products may become associated themselves with formerly unappreciated safety issues.** This may be a moving target in clinical medicine. As such, we advocate that biosimilars be evaluated with respect to those newly appreciated complications even if at the time of licensure the reference product could not have been similarly evaluated.
4. **Lower cost biosimilars may lead to their more widespread use in the medical patient population.** Consequently, cohorts of individuals, who would not otherwise have received this class of product because of cost, may actually be identified to demonstrate unanticipated consequences or benefits from the medication. Only post market surveillance will provide the opportunity to identify these host related phenomena and to relate genotypes and phenotypes.

### **Discussion**

The comments provided above and the examples which illustrate them reflect the experience of experts who share a common perspective that lower cost pharmaceuticals must be safe and effective. Our experience with complex biologics and the care of patients who would potentially benefit from them compel us to express these cautionary notes. To that effect, we thoroughly understand the complexity and high risk nature of embarking upon the pathway to the production of a new biologic product. We do not wish to see impediments to this field of discovery and biologic development and as responsible partners, we advocate the adoption of biosimilars whenever they are demonstrated to be safe and effective.



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## **North American Thrombosis Forum (NATF)**

The North American Thrombosis Forum (NATF) is a multi-disciplinary organization founded with the objective of improving patient care through the advancement of thrombosis education. This unique approach includes conversation among and involvement of patients, advocates, office-based physicians, hospitalists, nurse practitioners, nurses, pharmacists, physician assistants, and hospital administrators. All educational programs are designed to allow and encourage patients and their families to interact with the professionals who carry out research, provide clinical care, or work on public policy or advocacy issues related to thrombosis. Further information is available on the NATF website, <http://www.natfonline.org>.