

NATF's Official Position on Follow On Biologics

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Meet the first recipient
of an affordable
biologic for hemophilia.



He'll be 66 years old
when he finally gets it.

Welcome to Big PharmaWorld,
where their idea of meaningful progress on generic
biologics is monopoly pricing for years to come,
just by making minor changes to the formula.

It's called "evergreening." For patients in need of
affordable, life-saving biologics, it means a generation of
waiting on successive decades of market exclusivity before
the drug manufacturers would have to compete on price.

Biologic innovators deserve a fair return on investment,
but tweaking product formulas to maintain a monopoly
on price is more than wrong. It's just plain cruel.

Prove it's a new day.
Pass a real biogenerics
fix—one that puts
affordable life-saving
drugs in hands of
people when they
need them, not years
in the future.

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**For Some,
Waiting Isn't An Option**

Patients with life-threatening diseases need affordable biogeneric medicines sooner, not later. But some in Congress say it's better for them to wait 12 years. Many patients can't wait that long.

Representatives Henry Waxman and Nathan Deal, Senators Sherrod Brown, Charles Schumer and others have a better idea: Bipartisan legislation allowing generics to compete with expensive biotech medicines the way other generics already do with conventional brand-name drugs. That's real health care reform, right now.

Say "yes" to H.R.1427/S.726
"The Promoting Innovation and
Access to Life-Saving
Medicine Act."

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The Elements of NATF's Position Statement on FOBs

“The North American Thrombosis Forum, as a group of scientists, clinicians, and patient advocates involved with the care and development of new treatments for individuals with complications of thrombosis disorders, are greatly concerned about the potential of new highly complex biological agents derived from unfractionated heparin and heparin-like synthetic or semi-synthetic oligosaccharides.”

- *It is critical to include a multidisciplinary perspective in the legislative, regulatory, and approval processes for biosimilars*

The Elements of NATF's Position Statement on FOBs

“We thoroughly understand the complexity and high-risk nature of embarking upon the pathway to the production of a new biologic product. We absolutely do not wish to see impediments to this field of discovery and biologic development and as responsible partners we advocate the adoption of follow-on biologics that are demonstrated to be safe and effective.”

- *We must be perceived as partners in the effort to increase access to affordable, new and innovative treatments*

The Elements of NATF's Position Statement on FOBs

“If a follow-on biologic does not satisfy the same criteria for safety and efficacy as [was] demanded for the reference drug in a full clinical trial or the same criteria for the stringent pharmacokinetic assessments, it should therefore not be designated a follow-on biologic.”

- *The regulatory approval process to be developed by the FDA for biosimilars should be just as rigorous and comprehensive as it was for the reference pharmaceutical drug to ensure safety and efficacy and to define structure and function*

The Elements of NATF's Position Statement on FOBs

“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 strongly advocate that follow-on biologics 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.”

- *The FDA approval process must be flexible enough to accommodate scientific progress and clinical realities*
- *FDA must have the discretion to implement different regulatory guidelines for different types of biologics.*

The Elements of NATF's Position Statement on FOBs

“Interchangeability must be a prerequisite of any product to claim biosimilarity.”

- The criteria for claiming interchangeability must be clearly defined. The follow-on biologic must be equivalent to the reference product and this must be determined in well designed, well controlled, appropriately powered, and properly conducted clinical trials.”
- *Interchangeability should not be “preordained” for a biosimilar; it is a designation which must be earned not presumed*

The Elements of NATF's Position Statement on FOBs

“Indistinguishability with regard to safety and efficacy must be viewed as necessary and independent of the in vitro specifications”

The limitations of in vitro potency assessment are clearly demonstrated by:

Recent adulteration of UFH by the addition of chondroitin sulfate remained unidentifiable until 250 deaths had been directly implicated to this chemical impurity.

Treatment of hemophiliacs with FVIII FOB coagulant concentrates with pharmacological equivalence (as defined by pharmacokinetic and potency characteristics), resulted in development of antibodies against FVIII despite equivalent efficacy to reference product. Differences in viral attenuation procedures, an essential part of the manufacturing process as defined by regulatory authorities, were deemed responsible.

In 1998 a commercially available rh-EPO induced antibody mediated PRCA 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. (reaction of active peptides with components of the rubber stopper?)

The Elements of NATF's Position Statement on FOBs

“...indistinguishable [potency] differences *in vitro* cannot guarantee interchangeability *in vivo*...”

“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 [due to *in vivo* activity variability].”

- *The biological activity of a follow-on biologic must use the same unit of biologic activity as the reference product.*
- *Potency of the activity units of follow-on biologic and the reference must be equivalent so that they will exhibit comparable pharmacokinetic properties in vivo.*

The Elements of NATF's Position Statement on FOBs

- Drugs that do not possess pharmacologic similarity in vivo and in vitro may be considered for market availability only under a **separate name** and upon fulfilling the rigors of the Food and Drug Agency for approval.
- The decision whether interchangeability is possible with respect to FOBs should be made on a case-by-case-basis by the FDA.
- In the clinical arena substitution by PBMs should be prohibited unless authorized by the prescribing physician after consulting with the patient.

The Elements of NATF's Position Statement on FOBs

“Lower cost follow-on biologics may lead to their more widespread use in the medical patient population. ...Only post market surveillance will provide the opportunity to identify ...host [and product] related [adverse] phenomena...”

- *Post licensing registries which are less cumbersome and more user friendly should be developed by FDA for both the reference drugs and FOBs*

The Elements of NATF's Position Statement on FOBs

“Because follow-on biologics 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...”

The Elements of NATF's Position Statement on FOBs

- NATF does not address the issues of
 - Exclusivity
 - Patent litigation

BUT

 - For reference products, exclusivity periods following approval should be harmonized with the European Union (EU)
 - FDA approval of biosimilars should not be contingent upon the resolution of patent litigation (National Health Council)



CALL TO ACTION

- NATF must mount an aggressive educational effort to urge all Americans, particularly those in a position to direct manage patient health (physicians, nurses, pharmacists, patients), to learn about and the risks of biosimilars in relationship to patient safety.
- NATF should highlight for the American public and Congress the fact that biosimilar biologicals have a very different potential for generating adverse events, compared to chemical compounds and generic drugs; biosimilars are not generics
- NATF supports the approval of generic chemical compounds

CALL TO ACTION

- Organizations such as NATF must work to minimize the potential recognized (and be vigilant for currently unrecognized) risks of FOBs by supporting FDA efforts to establish adequate, comprehensive, and stringent approval processes
- NATF should continue to emphasize the scope of the population, which will be affected by the FDA approval of antithrombotic biosimilars and the implications thereof, eg. deep vein thrombosis and pulmonary embolism are diagnosed in 400,000 Americans years and contribute to at least 100,000 deaths each year

CALL TO ACTION

- Biosimilars, which do not meet the standards of the reference pharmaceutical product, may introduce considerable morbidity, possible mortality, and certainly could reverse any cost savings
- NATF should continue to remind the American public and Congress of the past examples of unpredictable consequences caused by previously FDA approved FOBs
- We need to constantly emphasize that NATF is not taking its position as a result of commercial interest – rather, we are a group of scientists, clinicians, and patient advocates who concerned about and involved in the care and development of new treatments for individuals with complications of thrombosis disorders,. The members of NATF are stakeholders in the healthcare system and we are committed to monitor, improve, and influence the clinical care outcomes and the public policy which affect those with thrombotic diseases

CALL TO ACTION

- NATF should alert Congress to the needs of FDA to accomplish their mandate to approve follow-on biologics or biosimilars only when there are data to support such use. We need to advocate for the conduct of rigorous and well conducted and adequately powered clinical trials, which are the only known mechanism to obtain the safety and efficacy data which FDA requires for its deliberations.
- Americans in positions to guide, direct, or manage patient care need to express their concerns regarding the FOBs in public forums, particularly in clinical, regulatory, educational and political arenas.