NOVARTIS

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Federal Trade Commission
Office of the Secretary
Room H-135 (Annex F)
Washington, DC 20580

December 22, 2008

Re: Emerging Health Care Competition And Consumer Issues – Project No. P083901

Dear Commissioners:

The Novartis Group of companies (Novartis) is pleased to submit a supplement to our previous response to the FTC docket on the important subject of the competitive effects of Follow-on Biologics (FOBs). In this response we elaborate upon selected points in our submission of September 29, 2008, as well as reiterate them in the context of the discussions that took place at the Federal Trade Commission's (FTC) Workshop on November 21, 2008.

Novartis is the European pioneer and leader in the global development and manufacture of both innovative and generic medicines. With our Sandoz business unit, for both simple and more complex biosimilars, we are uniquely positioned to continue to support the Commission's enquiry. Our input is informed both by actual data from our success with biosimilars in the market and by our experience as to what it takes to create and launch subsequent versions of previously-approved biologic products when their patents have expired. Our experience has been achieved with the regulatory systems as they currently exist both in the European Union (EU) and the United States (U.S.). A new pathway for FOBs under the Public Health Service (PHS) Act would enhance the selection of products available as reference products, and allow head-to-head competition when the patents on these products expire, providing of course, the pathway is appropriately designed to enable, rather that stifle, that competition. A bad pathway is worse than no pathway at all if it is not designed to be immediately available and implementable by regulators. It has to be usable by sponsors to increase access to these life-saving medicines by clearly allowing for the possibility of interchangeable FOBs to those biologics on which the patents have already expired. It must also facilitate the development of FOBs to the biologics of the future, even those that have yet to be approved as innovator products, by there being no limitation on the PHS Act biologics that can ultimately be used as reference products.

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The discussion at the workshop was informative and valuable for its breadth of coverage, as well as for the perspectives presented by the many stakeholders. However, it may also be that this breadth obscures the simplicity of the fundamental legislative elements necessary to enable the access to market for FOBs. Market access by interchangeable FOBs will precipitate competitive pricing and greater availability for patients. In this supplement we are suggesting that the FTC report in Spring 2009 refocus on the core elements needed to enable this market-based competition to occur and thereby the Commission facilitate the concomitant increase in access to the critical biologics that we all support.

Novartis believes that the key to access and competition for off-patent biologics is a simple delegation of authority to the Food and Drug Agency (FDA) to allow them to license FOBs - our rationale being that market competition is predicated on market access, which in the US requires an FDA license. This authority can allow the Agency to apply the science-based and data-driven regulatory standards to FOBs that they apply today to the licensure of innovator biologics (the ones that all stakeholders will always know the least about at the point of initial approval) and require that all sponsors of all biologics continue to demonstrate safety, purity and potency as is currently required by the PHS Act. The sponsor, in its FOB application, will be expected to identify a previously-approved biologic, and provide the data by which the FDA can judge if the FOB and its reference product are comparable and interchangeable.

Comparability is the established international "sameness standard" for biologics,[1] and one with which the FDA has had extensive experience since leading the world in the development of the concept by its publication of U.S. guidance in April 1996.[2] The FDA has been making comparability decisions for innovator products, before and after their sponsors make manufacturing changes based on sponsor-provided data, for a long time. These regulatory determinations by the Agency presuppose that the products are interchangeable and there is no change made to the label of the product before and after the manufacturing change or any indication that such a change has even occurred. For all intents and purposes the products are considered to be the same by the FDA, by health care providers and by patients. Hence, Novartis believes and asserts this is the established "sameness standard," on which FOBs can safely be licensed today.

An innovator making a manufacturing change using comparability has no choice and cannot elect for its product to be other than interchangeable – if it is comparable then it is interchangeable. That comparability is a very high regulatory standard of sameness is further evidenced by experienced innovators having had challenges achieving it for their own products. These failures are rarely made public and are usually corrected, but insofar as the products themselves have not been marketed with differences that affect safety, purity or potency of the products, the FDA is demonstrably doing its job. In identifying such comparability failures to the sponsors, FDA has shown that it has the ability to recognize them before such products are marketed and made available to patients.[3] Consequently, in the U.S., comparability has an exemplary safety record.[4,5] The public can have confidence that the FDA will be able to maintain these same high science-based, data-driven standards to FOBs if given the authority by Congress to do so.

The most public comparability failure occurred with Eprex (epoetin alfa) in Europe, and this has been frequently cited by the product's own sponsor in the FOBs debate.[6] A manufacturing change that had been encouraged by regulators to reduce a theoretical risk from naturally-sourced materials[7] led to a change in the product that was not detected by the sponsor or regulators ahead of the formulation change, and it resulted in a 25 fold increase in the incidence of the rare, but sometimes fatal, Pure Red Cell Aplasia.[8] This manufacturing change has not been instituted in the U.S., and all the epoetin alfa products currently marketed in the U.S. continue to contain human serum albumin (the replacement of which was the cause of the PRCA problem). While still early, and with all using Eprex as their reference product, the biosimilar epoetin products in the EU have not demonstrated any similar safety problems. The post-market monitoring of the biosimilars is appropriately strict for all products after the Eprex events.

Novartis believes the FDA will operate best if the Agency is empowered to concentrate its expertise and experience where it is most applicable, namely on the regulatory assessment of the data provided by any sponsor of a biologic, be it an innovator product or a FOB, and that the Agency should not be distracted by additional requirements that are better managed elsewhere. These potential distractions include issues connected to the patent estates of those innovator products that will form the reference products for FOBs. The Hatch Waxman Act,[9] however well intentioned, created a cumbersome and complicated patent listing/notification system that inextricably coupled the patent system to the regulatory process, causing difficulties for both innovators and generics. That system has restricted and delayed

competition, and ultimately patient access, to small molecule drugs. Meanwhile, the biotech industry has flourished with no such patent linkage.

The current "decoupling" of the IP and regulatory systems for PHS Act regulated biotechnology-based products should continue even as FOBs are enabled. Any connection between patents and regulatory approval is necessarily counterproductive to the efficiency of each and unfair to one stakeholder over another. It is far better to leave Title 35 alone and accept Hatch Waxman as the sole exception (and reflective of a very different state for the generic drugs industry in 1984 and the likely FOBs sponsors in 2008). Every other industry operates with patents independent of regulatory approvals, and the very complexity of the legislative efforts to date only serve to show how difficult it is to achieve any fairness by linking the two. If either an early artificial act of infringement of a patent has to be created or a regulatory approval delayed pending litigation, then incentives are changed, and competition and access are affected adversely. There is no good way to link patents and FDA approval, and having considered all the options long and hard, Novartis recommends that no attempt be made to do so. While sympathetic to the calls for "certainty" by both innovator companies and generics, we see no way that this can be achieved without patent rights being curtailed, which we do not support. Further, we caution that an early start to patent litigation is no guarantee to an earlier end. Not only is any link between the patent rights and the regulatory approval unable to assure certainty, but also Novartis believes that without the clarity of decoupling there cannot be a feasible FOBs pathway. Such a pathway is essential for competition to enhance access to these critically important products for patients.

An award by Congress of a fixed term of exclusivity for the innovator product during which it cannot be used as a reference product and during which the FDA cannot approve a FOB would be straightforward to implement, as it is a date certain counted from the approval date of the reference product. Novartis continues to support at a minimum the data exclusivity periods available in Europe. At the end of the innovator exclusivity period, the sponsor of a FOB must assess its freedom to operate, just as any sponsor of another innovator biologic. This is also akin to the situation faced by the sponsor of any other product in a high technology, patent-intensive space. Likewise, innovator product sponsors will have to decide if they believe their patents to have been infringed and sue to defend those patents if and when a FOB is launched. Those rights will be unaffected by a FOBs regulatory pathway.

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We commend the Commission for its interest in FOBs and in assisting the U.S. Congress in its efforts to ensure the creation of a regulatory pathway that will enable competition and access to valuable biologic medicines when patents expire. Novartis is confident that the FDA can apply the comparability standard consistently and fairly to all biologics, including FOBs, if given the authority to do so. As a proponent of FOBs and generic drugs, as well as an established and committed innovator of both biologics and small molecule drugs, Novartis looks forward to further assisting the Commission in its efforts to create an appropriate mechanism that is a win:win for all stakeholders, including the ultimate consumer, the patient. We strongly believe that FOBs can be an important component of the U.S. health care system, just as they already are in Europe, and that they will enhance access and competition for patients and by so doing fulfill unmet medical needs.

Kind regards

Robert Pelzer
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[1] ICH Q5E Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process June 2005, *available at:* http://www.fda.gov/Cber/gdlns/ichcompbio.pdf, last accessed December 7, 2008.
[2] FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products, APRIL 1996, *available at:* http://www.fda.gov/cder/guidance/compare.htm, last accessed December 12, 2008
[3] "Myozyme's zig-zags" Usdin BioCentury Volume 16, Number 48, October 27, 2008
[4] Woodcock J., et. al. The FDA's Assessment of Follow-On Protein Products: a Historical Perspective. Nature Reviews/Drug Discovery 2007; vol. 6; pp. 437-442.
[5] Woodcock testimony before the Waxman hearing, March 26, 2007 and transcript of that hearing.
[6] Bader F, "Immunogenicity of Therapeutic Proteins: A Case Report", Presentation by Johnson & Johnson at the FDA Public Workshop on Scientific Considerations Related to Developing Follow-on Protein Products, September 2004. *Available at*: http://www.fda.gov/cder/meeting/followOn/Bader.ppt, last accessed December 19, 2008.
[7] Consider reference to EMEA guideline about removing naturally-sourced materials
[8] FDA, "Information on Erythropoiesis Stimulating Agents (ESA) (marketed as Procrit, Epogen, and Aranesp)," *available at* http://www.fda.gov/cder/drug/infopage/RHE/default.htm, last accessed 16Dec08.
[9] Drug Price Competition and Patent-Term Restoration Act of 1984, also known as the Waxman-Hatch Act or the Hatch-Waxman Act.