DUKE UNIVERSITY MEDICAL CENTER
DUMC 31175 • Durham, NC 27710
Victor F. Tapson, MD
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Division of Dockets Management
Food and Drug Administration
Re: Docket # 2003-P-0273
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

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DUKE UNIVERSITY MEDICAL CENTER

Victor F. Tapson, M.D.
Professor of Pulmonary & Critical Care Medicine
Director, Pulmonary Vascular Disease Center

May 28, 2010

Division of Dockets Management
Food and Drug Administration
Re: Docket # 2003-P-0273
5630 Fishers Lane
Room 1061, HFA-305
Rockville, MD 20852

Dear Sirs:

Over the last year, I have monitored the debate over the potential approval of generic forms of certain complex biologics that are critically important to cardiopulmonary physicians, including myself, who manage 'at-risk' and treat patients with thromboembolic diseases. These are not benign or innocuous medical conditions and often carry dire consequences. In particular, the class of agents commonly known as the low-molecular-weight heparins or LMWHs (FDA Docket #2003-P-0273) has attracted my significant attention.

During this time, I have involved myself as a leader or participant in scientific, clinical and educational programs where the concerns of physicians, pharmacologists, pharmacists, and allied health care professionals have been voiced (i.e., Society of Hospital Medicine, Case Managers Society of America, international Union of Angiology, North American Thrombosis Forum). These positions are based and supported by clinical or scientific data, or both. The statements and positions of several organizations are also becoming increasingly noticeable and my professional perspective is consistent with most of the elements of these statements.

The current consideration of approving a generic LMWH without pre-approval clinical evidence of effectiveness and safety generated from adequate controlled clinical studies increases the risk: benefit equation for patients, clinicians, and society significantly. This is unacceptable and inconsistent with the progress made in the management of thrombosis dating back decades since the discovery of heparin.

There are currently three LMWH products available in the United States. The current product labeling of these products has a longstanding caution against their interchangeable use based upon differences in pharmacokinetic properties and anticoagulant profiles. Clinical data produced through randomized clinical trials by the sponsors of the various branded LMWH clearly supports this recommendation. The LMWH have a common biologic origin, vary in manufacturing process, and each is incompletely characterized.

I understand that certain limited studies focused on immunogenicity have been requested by the Agency and I agree with this action. However, I am unconvinced that *in vitro* or preclinical testing is adequate assessment of the potential for a generic LMWH to produce immunogenic consequences including heparin-induced thrombocytopenia. More importantly, it is not nearly enough data for a complex biologic compound that has multiple uses and applications in both acute patient treatment and chronic patient management. The need for increased access for medications is very important, but not at the risk of deleterious consequences to patients or society. I urge the Food and Drug Administration require that a

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potential generic LMWH produce data from adequate controlled clinical trials for comparable indications of use with the branded LMWH.

Only through the availability of such data can we maintain the healthcare standards of patient care and maintain the basis of treatment guideline recommendations that assist the clinician community of this country in making therapeutic decisions and assurance patients are receiving reliable therapies.

If you have further questions or require additional information or would like to meet with myself, please contact me at the contact information found on the bottom of this letter.

Sincerely,

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