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From: Robert Langer [mailto:rlanger@MIT.EDU]
Sent: Thursday, February 22, 2007 10:18 AM
To: Woodcock, Janet
Cc: Bob Langer; 'Ram Sasisekharan'
Subject: Re: IFPAC- Thank you and follow-up - wrt CRITICAL PATH

Dear Janet,

I am writing to follow up on the letter that Dr. Ram Sasisekharan sent to you last week. I fully support the points that Ram made in his letter to you. Ram obtained his PhD in my laboratory, and we have worked together on analytical technologies for the sequencing and characterization of complex sugars such as low molecular weight heparins [LMWHs] and glycoproteins both at MIT and Momenta Pharmaceuticals which we founded and are directors of.

I feel that generic versions of Complex Mixture Drugs represent an area where science is critically important. Specifically, technological advances now enable the accurate characterization and sequencing of these complex mixture drugs to identify and quantify all of the chemical components of the mixture. When applied to LMWH or glycoproteins such as EPO, such technologies can significantly enhance our understanding of the chemical constituents in the mixture and develop process conditions and controls for reproducible manufacturing of equivalent versions. Thus, demonstrating equivalence as well as creating appropriate structure-process relationships is now possible - translating some of your vision for the critical path initiative at the FDA into reality.

I believe from a scientific point of view that these advances are essential enablers for the review and approval of follow-on versions of complex mixture drugs such as Lovenox®. Without these tools, it is impossible to understand the structural subtleties potentially linked to both efficacy and safety. However, I am concerned that the pressures to approve generics rapidly has the potential to establish standards lower than the complete characterization and manufacturing controls possible with today's science. Thorough characterization of drugs such as Lovenox® includes measuring the microheterogeneity of sequences and functional groups using a combination of multiple high-resolution techniques. Further, mapping the microheterogeneity to the process conditions is essential to identify and control critical process parameters to ensure a reproducible process. Thus, complete characterization means a complete understanding of all of the chemical constituents in the complex mixture, their origin and control (in the form of raw material and process controls) to ensure equivalence to innovator batches now and in the future.

Lovenox® is a classic example of a drug where less than complete characterization could leave many questions unanswered. The mixture is broadly biologically active, binding at least 2 to 3 dozen targets (such as cytokines and growth factors), while the sequences responsible for the anti-Xa and anti-IIa activity are present in less than 15% of the mixture's constituents. Without establishing complete equivalence to an innovator drug which has been through the clinical trial process, it is impossible to predict unintended biological and clinical consequences. For example, heparins and LMWH are potent regulators of Fibroblast Growth Factors as well as Vascular Endothelial Growth

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Factors - two growth factors involved in angiogenesis and cell growth. These activities are not captured by measurement of Anti-Xa or Anti-IIa activity, necessitating thorough characterization. Complete characterization is the only way to ensure a substitutable product with equivalent efficacy and safety to the innovator product without the need for full clinical trials.

The FDA has long shown scientific leadership in ensuring the safety and efficacy of our nations pharmaceuticals. To have the requisite technology in hand and not take full advantage of its potential to ensure equivalence brings risks to the patients, the agencies reputation, and most certainly will weigh heavily in the ongoing debate over bio-generics. Ram, myself and others around the country have dedicated many years of work to ensure the analytic tools required for thorough characterization were available and the necessary high scientific standards were achievable. With these tools now available, the FDA can ensure equivalence of the generic LMWH products and the innovator drug. This will create the needed confidence among the patients and the physicians, and allow the agency to set the global standard for a complex scientific challenge.

If helpful, I will make myself available for any meeting, either a public or confidential group of advisors to fully evaluate these kinds of issues. Please let me know if you have any questions or I can be of any assistance.

Thanks for your consideration.

Best regards,

Bob Langer

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