

From: Ram Sasisekharan [mailto:rams@MIT.EDU]
Sent: Sunday, February 11, 2007 3:38 PM
To: 'Janet Woodcock'
Cc: ajaz.hussain@sandoz.com
Subject: RE: IFPAC- Thank you and follow-up - wrt CRITICAL PATH

Rec'd 3/6/07
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Dear Janet,

It was a pleasure seeing you again in Baltimore at the IFPAC meeting and once again thanks for your motivating presentation. As you point out there is much to be done and it is so important for the nation that this is done right.

I am writing to you based on a comment you made in your talk with respect to the "rising public expectations about the prospects for new therapies based on new biomedical discoveries" and that "gaps" exist among academia/NIH, the FDA, and the bio/pharma industry. I would like to share a specific personal experience that highlights the challenges that result in the formation of these kinds of gaps, and how the Critical Path Initiative does provide a framework for a solution. At the outset I do concur with your view that, fundamentally, 'translational research' is different from what it takes to make drugs really work, especially ensuring drug safety.

Ajaz and I have been working together for quite a few years with great interest in defining pathways for follow-on or generic versions of complex drugs, which in part was covered by my talk at the IFPAC meeting. I have had the opportunity to witness all sides that have been involved in defining a regulatory pathway for low-molecular weight heparins [LMWHs], one of the best examples within the complex molecule space. These complex molecules are mixtures of many different structurally related components - the drug's microheterogeneity - that in aggregate provide the biological activity. I have worked on this family of molecules for many years at MIT. I got my tenure here based on the ability to sequence them and cloned the first heparin degrading enzyme, which earned me my PhD from Harvard Medical School with Bob Langer. From what I have seen in the way the LMWH regulatory framework for the approval of generic LMWHs, there are fundamental issues that underscore a "gap" between where the science currently exists and the accurate appreciation and implementation of the science by the regulatory agencies. There is a lack of harmony between the FDA and EMEA. Very simply put, the EMEA is at one end of the spectrum, taking a non-scientific approach by requiring clinical trials (more a check-the-box approach rather than driven by a hypothesis), while the FDA may be almost at the other end of the spectrum, potentially facing a uphill task of justifying its approach and ensuring confidence in its decisions and in the quality of generic products approved in US.

For LMWHs, numerous scientific studies have demonstrated that drug effects are controlled by the microheterogeneity within the drug (I am happy to provide you with the appropriate scientific literature). Recent advances in analytical methods do enable us to capture all aspects of microheterogeneity for these molecules to ensure therapeutic equivalence. In addition, a robust understanding of the source of microheterogeneity and the development of effective controls (including raw material specifications and in-process tests) is essential to avoid drift in future batches. This, taken together with an appropriate PK/PD study (biomarker based) ensures a rigorous framework for these complex molecules. In other words, what the science is capable of delivering to minimize risk is significantly more detailed than what the agencies might potentially require. Given the very divergent FDA and EMEA perspectives, this example may provide for an opportunity to demonstrate a scientific approach to integrate in the three dimensions of the Critical Path framework. The Critical Path initiative is indeed visionary and does aim to address these kinds of gaps. Bridging important scientific advances to help regulatory challenges will always put the FDA in a leadership position.

Hopefully, the example here is an illustration of how these gaps can be bridged within your framework, resulting in a high quality product for the benefit of public health and safety.

Again, it was a pleasure seeing you again at IFPAC.

Sincerely,

Ram

Ps. I understand and am sensitive to the potential conflict with the example I have chosen, to illustrate the above issues, due to Sandoz-Momenta interests in this area. However, given the significance and the key role that science (which is in my area of expertise) and Critical Path plays in this issue, I feel obligated to personally communicate some of the scientific concerns I have.

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