

2006 Cardiovascular Biomarkers And Surrogate Endpoint Symposium

September 18-20, 2006

Bethesda North Marriott Hotel & Conference Center
Bethesda, Maryland

The FDA Critical Path Initiative – Opportunities and Challenges

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(views do not necessarily reflect FDA policy)

It is a real pleasure to be here. Over the past several years changes within the agency have given us an historic opportunity to work together to move biomarkers forward in ways that are useful for society, for sponsors and for patients. I would like to start by just refreshing your memory about the Critical Path Opportunities List that the agency put out in March 2006 and comment briefly about where I think we are going with these opportunities. From there, I would like to move into a brief general discussion of biomarkers. I know this has been discussed extensively and I expect a lot of my comments will echo those that others have made before me and comments perhaps some of the other will make the rest of the morning including the international speakers, which I am really looking forward to hearing. Then, finally I will end with some comments about where I think that FDA's role is in supporting the development, uptake and efficient use of novel biomarkers.

In March 2006, under Dr. Woodcock, the agency issued the Opportunities List for the Critical Path Initiative. The intent of the opportunities list was to identify those opportunities that the agency saw as particularly high value. That is, those things that if accomplished could make material differences in the way we develop medical products for patients. We identified a total of 76 of these opportunities. The important point is that these opportunities were not things that the FDA said would be done by the agency itself. This was a list that said with your help, with outside help, with input from a variety of stake holders, we would like to have people work with us to accomplish these tasks, these tasks that we view as very high value for drug product development and medical product development in general. On that list were a variety of things related to cardiovascular diseases. These were the six areas of focus that the opportunities list identified. Number one is better evaluation tools. I believe that is "regulator speak" for biomarkers from discovery through development, manufacturing, and product release. The other ones I am not going to comment on because I want to focus my attention on the development of better evaluation tools, which I am going to equate for this talk with the development of biomarkers.

As many people have said, historically the development of biomarkers has been inefficient, unfocused and siloed. It has relied on individuals within laboratories making observations, then writing abstracts, making presentations, talking with their colleagues,

gradual uptake in a field in a relatively haphazard way that results in years, if not decades going by before a biomarker is in broad use. And also there are extensive periods of time before any notions of surrogacy are raised and sufficient data are generated. However, the other challenge has been that when people have talked about biomarker development, they have focused heavily, I would say, at least in public, on establishing surrogacy. That is, for every biomarker identified, the first question is, “is it a surrogate for clinical benefit?”. That is a very high hurdle. There are relatively few established clinical surrogates and I’d suggest that there are more efficient, more useful ways to think about biomarkers than simply whether or not they are capable of providing surrogacy information. These payoffs, I would suggest, are the historic challenge, the opportunities that drug product developers, the agency and other parties have to revolutionize, to reinvigorate medical product development. Through the better use of these biomarkers, I really believe that we can make a more efficient system to develop new products. I think biomarkers give us the opportunity to obtain much better information about dosing than we would obtain if we strictly rely on clinical outcomes in relatively large clinical trials. I think it gives us a better opportunity to plan those Phase III trials with the best doses possible. I think they give us a better opportunity to better understand the disease state, to better understand the patients that we want to enroll in trials, to increase the probability of trial success and identify populations that have the greatest likelihood of responding to a targeted therapy. And in that sense, it is consistent with one of the larger goals of the FDA, which is to move the goal of personalized medicine and make it possible for us to give individualized information to patients about their chances of benefiting and having risks from the use of a single medication. Obviously part of that is to allow us to predict and hopefully ameliorate or prevent adverse events.

One notion of biomarkers that I think has received a lot of attention is the notion that biomarkers can be useful for understanding the long-term consequences of the use of a product. We have relatively limited long-term data on the effects of those anti-hypertensive medications including effects on blood pressure and things that we might otherwise think are valuable. We believe those effects persist. They are difficult to obtain and difficult to measure in uncontrolled settings and I think that biomarkers could play a role in giving us more information there.

We have an opportunity now to really change the way we historically move products from discovery to marketing. We can change the paradigm so that biomarkers are considered and discussed with regulators throughout the span of the product development, rather than at the end of the medical product development when you are trying to explain an adverse event or obtain a dosing. Give better information to the regulators early on, at the Pre-IND phase, or at the EOP2 meeting about what biomarkers you are planning on using and how you plan on what kinds of information you want to draw out of those biomarkers. I think having that opportunity, giving the regulators that chance to hear your thinking about how you want to use the biomarkers will make them more receptive to the more complex uses of biomarkers. I believe that we have to focus and make general across therapeutic classes the development of biomarkers. The notion that biomarkers are segregated in some particular therapeutic area is a luxury that we cannot afford any longer. We need to provide a general path to clear regulatory

development and approval of the biomarkers and then we need to support their use broadly across therapeutic areas.

Obviously cardiovascular medicine is the focus of this talk today, but there are a variety of therapeutic areas that would benefit, I believe, from more efficient and focused use of biomarkers. I also recognize that we need to work in collaboration with outside groups to qualify biomarkers. This group is part of that effort. I have talked before about the need for collaborative efforts such as this because no single group can solve these issues. We need to find a ways to support government/academic/industry collaboration to move these biomarkers forward. There is a need for good communication. What is found in cardiovascular world has to be translatable and has to be communicated in an appropriate way to the development of products for pulmonary areas or other areas that need new medications. What is the FDA's role? I think regulators in general need to provide a convening mechanism. A centerpiece of Dr. Woodcock's vision for the Critical Path Initiative, in general, and biomarker development in specific, is the use of consortia. Provision is that it is more efficient for us to be working together in appropriate mechanisms than try to work separately to move biomarkers and other Critical Path activities forward. Biomarker qualification for the agency, for the regulators, is largely one process. That is, we need to provide clarity and process. The FDA has chosen to focus its initial attentions on safety biomarkers. There is a lot of information available and in some sense it is interesting for preclinical focus.

The guiding principles are that given there are multiple interested parties in biomarker development and that no group has all of the resources necessary to move a biomarker to surrogacy, to efficient use, and broad application, cooperation through consortia can lead to more efficient product development and better outcome for all of us. This coordinated sharing requires protecting commercial interests, but we think that there are a lot of opportunities for sharing this information broadly. The sharing requires a common language, and a data structure. To the extent that we can implement and utilize a common data structure, that allows us to send information between trials and between therapeutic areas much more efficiently is of benefit. The regulators job then is to provide to the developers a pathway to share the results. On example of this kind of activity is the recently formed Biomarker Consortia that is involving the NIH Foundation, the Food and Drug Administration and PhRMA. This group has been formed to look at a wide range of biomarkers for focus. They are going to pilot the initiative in oncology, which is looking to qualify an imaging biomarker, FDG-PET. It is an opportunity to identify a surrogate for therapeutic response to oncology products. We have other consortia as well that are ongoing around specific disease areas. These consortia sometimes involve interactions with the agency and a single sponsor or the industry with an academic partner that is interesting in helping to move the guidance and move other aspects of the Critical Path forward. In order to provide a pathway forward, we need to decide how best to move biomarkers, what particular information we need to obtain, how best to give regulatory feedback about the acceptance of a biomarker, and its utility in various therapeutic areas.

Drug companies and medical product companies may be more comfortable sharing safety information because in some sense, it is not product specific. Whether or not that is true, it is true that safety is an early focus of product development and a lot of the early decision making revolves around safety. It is a useful place to start and I have two examples here of safety activities that are going on in the agency. The first is the electronic ECG database consortia. This is being spearheaded by Dr. Stockbridge, who has had a lot of help from Randy Levin in the informatics groups in the agency. The objective is to find a way to systematically look at ECG waveforms. The problem is that the ECGs are all sitting on paper, paper that is printed out at various speeds, paper that is sitting in warehouses, paper that is really impossible to turn into any data that you can analyze in any meaningful sense. There is a need to find a data standard to allow electronic submission of ECGs. Once we have that data standard, then we can start asking a lot of interesting questions. They set up that standard and worked with standard setting organization and provided a mechanism to submit ECGs. The FDA then partnered with an academic organization to construct this ECG warehouse. The next task is to identify the projects to look at, using that database to answer the ECG, the questions related to ECG waveforms with the intent of reducing the amount of information collected without changing standards of efficacy and safety. Another good example is the Nephrotoxicity Biomarkers consortia. This is the consortium that is focusing on the preclinical markers of nephrotoxicity, something that that has been a concern for drug product development for some time. In this case, we have a consortium between the FDA, sponsors and academics that has been set up through the C-Path Institute. Here again, the major function is to convene, to pull together the data that we have available to us on selected nephrotoxicity biomarkers and then perform additional studies if necessary with the intent of ideally locating, identifying a model for human drug induced nephrotoxicity and move those biomarkers into more broad use in therapeutic development. I think that both of these examples illustrate good uses of the consortium as a model for interactions between the FDA and outside interested parties. Both of them focus on programs can have high impact in terms of cost and efficient development of products.

One of the activities that CDER in particular has done in the last year to support the Critical Path and efficient development of biomarkers is the formation of the Office of Translation Sciences. That office is headed by Shirley Murphy, who has been with the agency for a number of years and was previously in industry. It also includes the Office of Biostatistics and the Office of Clinical Pharmacology because we recognize that their expertise is central in any sort of movements forward in the critical path. Her role is to facilitate Critical Path discussions with all aspects of the Center for Drug Evaluation and Research efforts around Critical Path.

I am going to end by describing a vision to you which involves two things. It involves biomarkers that give information about the disease state, about the metabolism of the compound, about the molecular targets of a therapeutic, as well as disease modeling that takes the information that you have about a variety of biomarkers and places it into the context of a disease and its progression and what you understand about its pathophysiology in a way to predict patient outcomes to predict patient responses to a

novel therapeutic. That model then, using biomarkers and disease models is updated as you obtain information throughout the product development. As new information contradicts earlier parts of the model, the model is changed. As it reinforces parts of the model, so be it, much to the better. The idea is that at the end of the day, you will have a much better integrated understanding of the therapeutic, its toxicities, how best to avoid them, its efficacies and what concentrations and what doses to choose from to obtain those efficacies. It will make the best efficient use of biomarkers, and rather than relying on a single biomarker to make all decisions, it appropriately recognizes the complexity of therapeutic development.

I would conclude that I believe more systematic development of biomarkers is essential. I don't believe that this is something that we should look at as a short-term project. The fact that this Cardiovascular Biomarkers and Surrogate Endpoints Symposium continues to have the successes that it has speaks to the interest in biomarkers that exist in the therapeutic areas. FDA is actively supporting biomarker development, including its role as part of supporting the Critical Path Initiative. Critical Path is an effort to harness industry, academic, and regulatory authorities to further the Critical Path opportunities list, including biomarker development. Again, consortia are the best mechanism for us to move forward along that path. There are barriers that exist to the greater use and integration of biomarkers into development, but I don't think that the status quo is an acceptable outcome. I think we have to be prepared to make the changes that are necessary to make fuller use of them. We are committed to making the regulatory changes that support that effort. There has been encouraging interest from academic sponsors and I hope that those groups are also interested in using this opportunity to move biomarkers forward.

Finally, we can work to move biomarkers toward greater integration as we are approaching an era of personalized medicine in order to deliver the right treatment to the right patient at the right time. It is the goal of FDA and other regulatory agencies to be the bridge to developments that are needed to make that future a reality.