Division of Systems Biology

Response to Scientific Advisory Board Subcommittee Review

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Views expressed in this presentation are those of the presenter and not necessarily those of the U.S. Food and Drug Administration

First Cause – Thank You!

We are grateful for the positive and constructive nature of the comments and recommendations in the draft report. Your comments are valuable to us as we determine the best ways to address critical needs of the FDA as we move forward over the next 5 years

Thematic Areas Reviewed

- Division Organization
- Clinical/Translational Metabolomics and Proteomics
- Doxorubicin/Cardiotoxicity Markers
- TKI Markers and Mechanisms
- Alternative Drug-Safety Models
- Food Safety Technology
- Computational Modeling
- Precision Medicine

Division Organization

1. *Is the organization optimal for the utilizing staff expertise?*
   - We are reviewing the Divisional structure.

2. *How might computational technologies be integrated?*
   - We are developing collaboration opportunities within NCTR, FDA, and other HHS resources that would address our data-integration/computational needs.

Clinical/Translational Metabolomics and Proteomics

1. *For 'omics approaches, validation of candidate biomarkers should be a clear strategic focus*
   - The Division has engaged a dialogue with the newly formed FDA Drug Development Tool Qualification team to identify biomarkers that may be of sufficient high priority to warrant a development (i.e., validation) effort.
   - We have begun developing putative "Context of Use" (COU) statements that would guide biomarker qualification.
   - We have considered steps toward validation of biomarkers of Drug-Induced Mitochondrial Injury (DIMI) (palmitoyl carnitine and cytochrome C).
   - We are also engaging the Predictive Safety Testing Consortium (PSTC) of the Critical Path Institute, and HESI for interest in this and other biomarker work.

Clinical/Translational Metabolomics and Proteomics

2. *"In the case of MALDI imaging, the group could quickly become field leading."*
   - We appreciated the encouragement and do intend to leverage this technology and expertise within the FDA and greater biomedical research community.
3. *Regarding sample and data quality: "..these activities support the overall FDA mission, especially as it pertains to data submission."*
   - The Division appreciates the affirmation of this effort; we will indeed support and further it.
   - The Division is one of the leaders in a recent data quality workshop.

Doxorubicin/Cardiotoxicity Markers

1. *The Subcommittee noted a need for more specific 'omics-based biomarkers, based on the injury specific to the anthracyclines.*
   - The Division appreciates the affirmation of these efforts.
2. *The Subcommittee also noted the need to evaluate the mechanism of sunitinib cardiotoxicity and potentially other TKIs (tyrosine kinase inhibitors).*
   - We appreciate the encouragement for the current project.
   - We have designed this and are developing other studies in collaboration with colleagues in FDA review divisions who are familiar with the issues of TKI-induced cardiotoxicity.

Doxorubicin/Cardiotoxicity Markers

3. *The subcommittee recommended an increased focus on clinical studies and clinical context.*
   - This is an important point that we take very seriously.
   - The Division already has proteomic results from a clinical study of doxorubicin-treated breast cancer patients.
   - The Division has also established a collaboration with a pediatric oncology group at Arkansas Children's Hospital.
   - As noted earlier, developing draft Context of Use (COU) statements promptly after a putative biomarker discovery provides the groundwork for a subsequent development strategy, including clinical studies.

Doxorubicin/Cardiotoxicity Markers

4. *The Subcommittee noted the closer relevance of genetically diverse animals to the human population and the issue associated with using an inbred animal model.*
   - We agree completely and can point to studies where using outbred animals results in variable responses to treatments.
   - We believe that you need a homogenous population to identify biomarkers, which can then be tested for individual responses in in a genetically diverse strain.

TKI Markers and Mechanisms

1. *The Subcommittee encouraged data mining as a means of developing hypothesis of TKI adverse effects.*
2. *The Subcommittee also noted the value of including drug properties when analyzing human data*
   - We appreciate the encouragement and the advice for future work.

Alternative Drug-Safety Models

1. *The Subcommittee noted, but the advantages and caveats of using iPSC-derived cardiomyocytes as models for mechanistic studies of cardiotoxicity.*
   - The Division appreciates the encouragement of these efforts and critical insights
   - We recognize that this model can address only certain questions and any results would need to be extended to *in vivo* or clinical studies.

Alternative Drug-Safety Models

2. *Opioid exposure on neurodevelopment*
   - The Subcommittee affirmed our *in vitro* efforts and noted caveats with the system.
   - We appreciate these comments and will closely monitor initial studies.
3. *In vitro models of male reproductive toxicity*
   - The Subcommittee noted the overall direction of this study may need to be more clearly defined.
   - We thank the Subcommittee for their comments and insight.
   - We are working to establish collaborations that would strengthen the research.

Food Safety Technology

1. *RAPID-B Technology*
   - The Division appreciates the Subcommittee's positive comments on the RAPID-B technology and its application in many arenas.
2. *The Subcommittee encouraged exploring the integration of RAPID-B with genomic platforms used in pathogen monitoring*
   - The Division has placed an ORISE fellow who has been developing the technology in a laboratory at CFSAN as a means of integrating RAPID-B with other technologies.
   - The collaboration will provide feedback on the complementarity of RAPID-B with established CFSAN approaches.

Computational Modeling

1. *Responses to questions posed by the Division*
   - The Division appreciates the Subcommittee's detailed comments which will be helpful in moving forward in the field.
2. *The Subcommittee noted the importance of a quantitative description of the applicability domain*
   - The Division agrees a careful approach to developing an AD is essential and we are exploring several avenues.

Computational Modeling

3. *The Subcommittee strongly favors the use of dose or concentration when modeling toxicity endpoints*
   - The Division agrees the modeling toxicity data in an only binary fashion impacts the computational model.
   - In the case of the PLD model presented, only binary data was provided.
   - Our intent is to move forward with endpoints based on dose or continuous data (wherever possible).

Precision Medicine

1. *The Subcommittee strongly endorses NCTR's unique, non-genetic approach to precision medicine, with research on the effects of gender, age, and obesity using animal models, data mining and omics technologies.*
   - The Division greatly appreciates the Subcommittee's affirmation and support of the direction we are taking.

Precision Medicine

2. *The Subcommittee expressed concerns about the use of an in vitro model to test hypotheses derived from mining of in vivo data*

   - The use of an *in vitro* rat hepatocyte model is driven by the practical issue of narrowing the number of drugs that would be evaluated in an *in vivo* animal model.
   - The central hypothesis is that gene expression data can predict age and sex-specific differences in PK/PD. If our initial results support this, we will tackling mining the growing human gene-expression data to extend our investigations.

Precision Medicine

3. *The Subcommittee uniformly supported and was enthusiastic about our efforts to evaluate the effects of obesity on drug safety and efficacy*
   - The Division greatly appreciate the Subcommittee's support for this effort.

Precision Medicine

4. *The review team called attention to the selection of obesity model, organ systems examined and pharmaceutical interventions used*
   - The choice of obesity model is critical; the one chosen is supported by prior reports in the literature.
   - The initial focus on doxorubicin-induced cardiotoxicity is indeed driven by our historical comparators.

Precision Medicine

4. *The review team called attention to the selection of obesity model, organ systems examined and pharmaceutical interventions used (cont)*
   - We appreciate the Subcommittee's advice and will certainly include their suggestions on expanding our focus in the future, including a consideration of efficacy and not just toxicity.
   - In addition, we are collaborating with several CDER laboratories to address a variety of obesity-dependent endpoints.

FDA U.S. FOOD & DRUG ADMINISTRATION

Thank you!


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