NONCLINICAL STUDIES SUBCOMMITTEE OF THE ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

December 14, 1999
Holiday Inn, The Ballrooms
Two Montgomery Village Avenue
Gaithersburg, MD

Academic Representatives
*John Doull. M.D., Ph.D. (Chair)
Jay Goodman, Ph.D.

Consumer Representative
*Gloria Anderson, Ph.D.

Industry Representatives
Jack Dean, Ph.D.
Jack Reynolds, DVM
Joy Cavagnaro, Ph.D.

FDA Representatives
Kimberly Topper (Executive Secretary)
James MacGregor, Ph.D.
David Essayan, M.D.
Eric Sheinin, Ph.D.
Frank Sistare, Ph.D.
Dave Lester, Ph.D.
Jerry Colling, Ph.D.
Joseph DeGeorge, Ph.D.

Invited Guests
G. Allen Johnson, Ph.D.
Richard Frank, M.D., Ph.D.
Gwyn Morgan, Ph.D.

* Members of the Advisory Committee for Pharmaceutical Science

These summary minutes for the December 14, 1999, meeting of the Nonclinical Studies Subcommittee of the Advisory Committee for Pharmaceutical Science were approved on 9 March

I certify that I attended the December 14, 1999, meeting of the Advisory Committee for Pharmaceutical Science Nonclinical Studies Subcommittee and that these minutes accurately reflect what occurred.

Kimberly L. Topper
Executive Secretary

John Doull, M.D., Ph.D.
Chairperson

The Chair, Dr. John Doull, called the December 14, 1999 meeting of the Nonclinical Studies Subcommittee of the Advisory Committee for Pharmaceutical Science to order at 8:40. The conflict of interest statement was read and the subcommittee members were introduced.

Dr. Jim MacGregor introduced the FDA objectives and explained the subcommittee was to act as a steering committee for collaborative projects, identify the appropriate experts, charge them and monitor the progress of the expert groups to help focus in the appropriate opportunity areas. He stated the areas we need to have additional research are: relationship of endpoints to health, relationship to outcomes in established assays, relationship between laboratory models and man, and reproducibility, accuracy, sensitivity and robustness. He explained that we were looking to work in the areas of defining science - not Regulatory issues, bridging technologies, (animal to human) and asked the question, "What should we be doing with opportunities and limited resources?"

Dr. Jack Reynolds provided the industry perspective stating that we need to focus on those technologies that allow us to make the bridge, so we could measure the same thing in laboratory models and then make key measurements in the clinic. He defined the general classes of biomarkers and said he has seen the value in partnering with regulatory agencies and sees this as a win/win situation.

Dr. Jerry Collins talked about his current collaborative work with PET issues and reinforced that this process was not to look at specific products, regulatory issues or GMPs. He asked what specific ways can this consortium of academic, industry, and government labs work together to facilitate the nonclinical aspects of PET imaging probe development.

Dr. Richard Frank presented the industry side of the PET issue and encouraged consideration of the drug impact target and determination of clinical benefit. He said there were four kinds of measurements that were taken with PET: tissue metabolism, tissue blood flow, tissue pharmacokinetics, and ligand-receptor interaction. The advantages inherent to PET are 1) quantifiable, in familiar units, 2) exact attenuation correction, 3) resolution to mm, 3D images, 4) isotopic substitutions in physiological traces of drugs, 5) Repeat measures, rapid results, small "n", 6) minimal perturbation of system, and 7) mechanistic relevance, correlation with "gold standard." The disadvantages to using PET are 1) radiation exposure, 2) time to develop new tracers, 3) validation required (not unique), and 4) infrastructure required. He encouraged FDA to look at where the best benefit will be derived from the collaborative research; we have to assess carefully the value added as measured against logistics and the costs.

Dr. Dave Lester introduced the topic of MRI and the potential for use in the drug development process. He believed that MRI was a potential project because it

would provide a rapid, sensitive and predictive initial screening for toxicity. This would give complete data sets reducing the number of animals because it could be done in vivo.

Dr. Johnson discussed the actual use of MRI/MRM in research and explained the processes they were using. The unique attributes of MRI/MRM are nondestructive, proton stains, inherently 3D, and inherently digital - web based atlas. Dr. Johnson acknowledged that there was a backlog on getting equipment at the present time.

After all the presentations were given there was extensive discussion on the MRI/MRM issue. A question and answer session ensued. The session ended with a reminder not to lose focus of the overall goal, there is a need for standards and a need to "pool" existing data.

Dr. Sistare presented 4 Biomarker Research Proposals of Regulatory Interest that industry, academia, and NIH may want to help solve. These include further evaluation of troponin T as a biomarker for cardiac toxicity, skin photocarcinogenicity tissue biomarkers (inducible), drug-induced vasculitis, and drug-induced hepatotoxicity. His vision would be for a collaborative effort defining improved panels of biomarkers for specific toxicities that cut across species and build into a practical format. In summary, collaborative research approaches will benefit all partners by: 1) identifying useful safety biomarkers to reduce human morbidity/mortality, 2) improving drug development go/no-go decision making, 3) delineating when interspecies differences may be (ir)relevant to the human situation (preventing clinical holds/impasses), and 4) improving regulatory decision making with more/better clinical and nonclinical signals.

Dr. Morgan described the International Life Sciences Institute (ILSI) project. He explained it was being done to advance the scientific basis for the development and application of genomic and proteonomic technology to mechanism-based risk. He believes that tissue biomarkers give us a very important understanding of a mechanism, and from that we are able to assess the same pathophysiologic effects then in man. He questioned what the implications are of an effect on biomarkers whose relevance in predicting hazards to humans is not yet known? He feels that the research would be very useful in gaining confidence in the value and utility of biomarkers by means of collaboration and corroboration of the observations made.

Dr. Reynolds introduced the topic of the challenges of early entry into clinical trials. He encouraged the clarification and articulation of the potential value and benefits if an early clinical program. He repeated that the committee's objective was to evaluate the potential application if new technology tools for application in nonclinical and early clinical trials.

Dr. DeGeorge presented on facilitating early drug development, safety issues from the FDA point of view. His presentation focused on 1) use of single dose studies and screening INDs, 2) issues in toxicology study design, and 3) guidance on IND format and content. He concluded that there are areas where nonclinical and clinical research could shape agency and industry guidance. Decisions and identification of focus and approaches to address the research questions would necessitate broad cooperative efforts.

Dr. Eric Sheinin discussed the CMC (chemistry, manufacturing and controls) issues for screening INDs. He reiterated that the Phase 1 Guidance had all the requirements for chemistry.

The committee held extensive discussions and came to the following consensus:

1) FDA should establish a standardized approach for use of biomarkers in nonclinical studies in collaboration with representatives from ongoing biomarker initiatives.

2) Broader expert groups should be formed for biomarkers and imaging and bring decisions back the NCS Subcommittee - focus on specifics.

3) Bring together experts in imaging technology and clinical application area and the experts should identify knowledge gaps in imaging and should help facilitate communication on technology.

4) The committee should work with stakeholders to bring this project into the forefront.

The meeting was terminated at 5:26.

See also The Pink Sheet dated 1/03/2000: http://medlib.cder.fda.gov/dml_Pink/