

SCIENCE ADVISORY BOARD MEETING  
JUNE 5-6, 1997

In attendance were: Science Advisory Board (SAB) members Doctors Anders, Anderson, Bruce, Rosenkrantz, Wilkins and Young; liaison members Drs. Alderson, Cavagnaro, Collins and Jacobs; and NCTR, and ROW staff (complete list of attendees is available through the executive secretary).

The meeting of the SAB to the National Center for Toxicological Research (NCTR) was called to order at 9:00 a.m. by the Chair, Dr. Anders. He introduced new Board members, Doctors Robert Anderson, West Virginia University and School of Environmental Education; Marcy Rosenkrantz, Associate Director, Super Computing Technologies, Cornell Theory Center, Cornell University; and Dr. Charles Wilkins, Professor of Chemistry and Associate Dean for Physical and Mathematical Sciences, Dept. of Chemistry, University of California, Riverside. Following introductions he asked for approval of the January 29-30, 1996 minutes, the minutes were approved as written.

Mr. Norris began the Director's report by addressing the NCTR budget, Interagency Agreements, and describing the Senior Biomedical Research Service, a new personnel system for scientific personnel. The Board received a draft of NCTR's strategic plan, and was requested to provide comments, especially as they relate to the Center's strategies and vision for the future.

Dr. Schwetz reviewed with the Board organizational and personnel changes that occurred since the last SAB meeting: the termination of the Caloric Restriction Program and the transfer of that staff to other existing divisions; his serving as Acting Director for Reproductive and Developmental Toxicology; and the decision not to fill the position of the Associate Director for Research. He also discussed the Center's Interagency Agreement (5.5 million) with the National Institute of Environmental Health Science/National Toxicology Program (NIEHS/NTP), and discussed a task order under this agreement to examine low level exposures to endocrine disruptors in multi-generations

He reported that the Center is developing Cooperative Research and Development Agreements (CRADA's) that will help speed up the process of developing the Estrogen Knowledge Base (EKB), and a project in the neurotox area that will provide a data base on the toxicity of a class of chemicals in the primate.

Discussing the consolidation of FDA's Office of Regulatory Affairs (ORA) field laboratories, Dr. Schwetz reported that the new Arkansas Regional Laboratory facility, to be located on campus, will eventually house 150-170 research staff, (mostly microbiologists and chemists). As part of this consolidation a new joint quarantine facility is currently under construction with completion scheduled for this fall.

Next, he discussed a report prepared by the FDA Science Board's Subcommittee on FDA Research. This Report looked at: research across the Agency: the kinds of research that should be undertaken; the appropriate models for peer review of intramural research; how to develop an infrastructure of research within the Agency so that FDA accesses the best outside experts; and how to develop novel approaches to the organization of laboratory research within the Agency.

The Report concluded that: FDA lacks the culture of good science and communication; existing research programs are not consistent in quality and mission relatedness; science management practices are

generally poor; center directors and others managing the research of the Agency are not doing their job in assuring that what needed to be supported was, and the research not worth supporting, eliminated; the quality of electronic technology was uneven across the Agency; the scientific communication throughout the Agency is inadequate; the organizational structure has not promoted uniformly high quality science; center loyalty sometimes gets in the way of loyalty to the Agency; that the decreasing budget is a problem; and we are not using external resources to the extent that we could.

The Report recommended that: FDA create a virtual science center within the Agency to take advantage of scientific resources that exist FDA wide; and that it be headed by a Chief Scientist, and the position be situated within the office of the Deputy Commissioner for Operations.

Dr. Schwetz went on to report that the Agency had begun efforts to address the recommendations in the report, namely: the development of more consistent peer review practices across the agency; the development of an expertise data base; and the beginning of the development of an FDA-wide research plan. In discussing the recommendation for better communication the SAB members, liaisons, and staff reviewed options for improvement. Some ideas discussed, were the use of FDA Today and the FDA Consumer as a means of information dissemination. The use of the Internet was also discussed.

Also reviewed was the process ORA utilized in concluding and recommending the move to co-locate with NCTR in Jefferson, Arkansas, six laboratories throughout the Midwest. He reported the ORA's Chicago lab's dioxin capability had already been moved into newly renovated space within the NCTR and that we were completing the construction of a new joint quarantine facility.

The next item on the agenda was the site visit team (SVT) review of the Estrogen Knowledge Base (EKB) project. Drs. Anders and Rosenkrantz were members of the team. Dr. Anders presented the report (TAB -6) to the Board, stating the goal of the EKB was to deploy computer based tools that would enable researchers and regulators to extrapolate data from known estrogenic agents to predict the estrogenic activity of new compound formulations. The SVT was asked to focus their review on five issues: (1) the technology of knowledge based development, (2) the soundness of concepts about estrogen biology and toxicology, (3) the adequacy of resources for the project, (4) the relative priority of the EKB project at the NCTR, and (5) the prototypical value of the EKB for the development of other toxicology databases.

On the first issue, the SVT recommend the initial focus be on use of classification tools rather than QSAR tools; that in developing this knowledge base NCTR look at what has been used by other researchers in computational models; that the focus be on things such as the estrogen receptor binding assay, which is widely used, recognized in the field and something that can be quantified; that there be some focus on phytoestrogens, as there is literature in terms of binding assay results available, and they represent a family of diverse chemicals that will test the robustness of the model. A classification model which predicts classes of activity should be encouraged as an early step, and any use of classification models should include some estimate of error. As for the soundness of concepts in estrogen biology and toxicology being pursued the SVT was positive in their review. In looking at the adequacy of the resources for the project, it was concluded that there should be a balance between toxicological sciences and computational sciences, these two have to work in some kind of harmony, with a proper distribution of resources, to make the project successful. The SVT in addressing the relative priority of the EKB felt it should be given a high priority, because of its importance to the scientific community. The SVT was not sure how the users would

view its priority, saying it won't be used and it won't have the impact it should if the user doesn't see it as value. In addressing the prototypical value of the EKB for the development of other toxicology knowledge bases, they opined that biology was going to have an important influence on whether the transfer of this technology would be successful. They felt this was an opportunity for NCTR to identify those areas where you can find the biological step that lends itself to the development of knowledge bases. They said resource considerations will also become a factor in whether or not this could be applied widely to other knowledge bases. In summary, the SVT was highly supportive of this activity, and because it is a prototype project, they felt it was important that the SAB be kept informed of its progress. They cautioned that the goals had to be realistic.

Concluding the presentation Dr. Anders recommended that the draft report be accepted, this was seconded and the report was approved as written. A lengthy discussion followed on how best to put resources together, how to form partnerships/collaborations with other organizations both within and out of the government and industry.

Discussion of the next round of site visits and SAB assignments followed. Dr. Schwetz touched briefly on the reviews that had already taken place, noting that the SVT looked at both research and non-research programs. Facilities management was one area he proposed be reviewed, the plan would be to bring in engineers from within and outside the FDA to review our engineering and operation resources and how we manage the facilities. The first reviews to begin the second round will be the Biometry and Risk Assessment Program followed by the Neurotoxicology Program, with a report back to the full Board in late March or early April.

Dr. Rosenkrantz presented the draft SVT report of the Information Management Program (TAB 3). The team was charged with examining: the appropriateness of the infrastructure and equipment and whether the infrastructure was being utilized properly relative to the investment that was made; the services provided, and whether they meet the needs of the various constituencies and are they suited to the administration; whether the Center is positioned for future growth; if NCTR's properly connected to other entities of the FDA; the contracting mechanism to see if its appropriate and/or adequate; and finally examining the IM personnel/leadership.

The team reported that the Center had an extremely diverse infrastructure, particular attention was paid to the VAX system and the migration to an alpha cluster, and the mix of desktop computers and operating systems that go along with those machines. They said it was a robust network and the people handling the networking services were doing an outstanding job. In looking at the LANs and database management systems, they reported that, though they are not the same as the rest of the FDA, they felt with the networking team at the Center there would be no problem making NCTR inter-operable with the rest of FDA.

The SVT recommended that: network bottlenecks be reduced and phasing out low end computers. NCTR should migrate users to Windows 95 for their primary desktop use, that e-mail, document handling, and word processing be uniform and utilize the Agency standard; that only a few legacy PCs be kept to support jobs that could only be done on them. There was no agreement reached among the team concerning the need to migrate immediately to Agency standard for network operating systems. They felt the IM contract employees were a major infrastructure asset and were providing excellent service at a reasonable price. The SVT looked at data warehousing and the need to make current database management systems

compatible and inter-operable with ORACLE, saying it was an important issue, and how to make this work should be seriously investigated. Also of importance to the SVT was making sure that a distinction be made between what in-house software development efforts will be engaged in versus using commercial off-the-shelf software that's widely available, has been tested, and found robust. The SVT noted that scientific computing efforts at the Center were increasing and had to be looked at carefully in terms of the other efforts supported, as this technology will continue to take on more and more resources unless priorities are appropriately set.

The SVT observed that user services were doing a good job and in their opinion were in peril of suffering burnout. They recommended: limiting the software applications and operating systems they support; using off-the-shelf software to better track help desk calls; look at training, maybe use on-line tutorials and courses that have been developed by the software vendors. In looking at the scientific computing area, they said it was important to develop a plan, for an ADABAS-ORACLE integration using things like client-server tools.

They opined that it was important there be a management structure in place, that users within individual functional areas have liaison person to mediate priorities. Because scientific computing requirement was increasing the team felt there was a need for someone within the government staff with the expertise to make sure that it is a collaborative process, so the directions and priorities being set up are being driven by the Center priorities, with scientific computing help from the contractors. They suggested that if these people didn't exist, that resources be used to train people. They suggested that in looking at the IM contract the Center think about splitting the contract so that you have user services and administration in one and scientific computing in another contract, saying that it may be a better way to assure that resources are being devoted to Center priorities.

In the discussion that followed Dr. Rosenkrantz reviewed the disagreement among the team members concerning the need for the Center to immediately migrate to FDA's networking operating system standard. As a result Dr. Rosenkrantz recommended deferring acceptance of the draft report while she tries to work out the differences. She allowed that if this couldn't be accomplished she would submit and forward the draft to the Board with a minority report. A motion was made to accept this suggestion, it was seconded, and passed.

Dr. Lay, in the absence of Dr. Thompson, Director, Division of Chemistry opened the morning session presenting the Board with a progress report on the Analytical Methods Development Program (Appendix A). In responding to the SAB recommendations, he said they'd developed a mission statement that helped to lead the FDA into the 21st century in the area of analytical methods development by not only looking at current needs but trying to anticipate needs into the future. Dr. Anders noted the statement was silent about support for the investigative mission of NCTR. Dr. Lay said, that for various reasons the Division had focused on internal projects at the time of their review and that some of the strongest research efforts were in the collaborations with other Center research divisions. He said they interpreted the SVT critique as a suggestion that they develop a strong chemistry-centered program, while continuing to collaborate with others. He stated there were four areas they felt they could significantly contribute to in a chemistry-centered way and develop a strong internal research program that involved the development of regulatory and research analytical methods. Other focal areas were in the role and creation of new hardware and new methods to do things that haven't been done before, not only developing new methods for new classes of chemicals or chemical compounds but also biologics, and they could also contribute in the areas

of computational chemistry, bioanalytical chemistry and measuring DNA adducts. He said they had an active program in staff visits/exchanges, presentations in FDA science symposia, and other symposia nationally and internationally, and the publishing of much of their methodological work in the scientific literature.

Concluding, he said they couldn't support all the long-short term goals recommended, but they were going to seek a proper balance between the establishment of a strong chemistry centered program with the increased requirements for chemistry support from the other divisions. Dr. Anders commended him on the programs responsiveness.

There being no public participation the meeting was adjourned.

Respectfully submitted,

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Ronald F. Coene

May 6, 1998