

SCIENCE ADVISORY BOARD MEETING

May 6-7, 1998

In attendance were: Science Advisory Board (SAB) members Marion Anders, Robert Anderson, William Bruce, Harold Davis, Tomás Guilarte, Joseph Rodricks, Marcy Rosenkrantz, Charles Wilkins and Lily Young; liaison members Norris Alderson/CVM, Joseph Contrera/CDER, Neil Goldman/CBER, Meredith Grahn/ORA, Mary Elizabeth Jacobs/CDRH, Barry Lindley/UAMS, Al Pohland/CFSAN; 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 began the meeting by requesting approval of the minutes from the June 5/6, 1997 meeting. There was one correction concerning Board member Robert Anderson's affiliation, with this exception the minutes were approved as written.

Dr. Anders called on Dr. Schwetz to give an update on Center and FDA activities since the last meeting. Dr. Schwetz reported on the current status of the search for a new Commissioner for the FDA. He reported the leading candidates were Dr. Jane Henney, former Deputy Commissioner for Operations and the current Deputy Commissioner for Operations and Acting Commissioner, Dr. Michael Friedman. This appointment is a Secretarial appointment with Senate confirmation. The position of Commissioner has been vacant since February, 1996. He reported that Dr. Friedman had moved forward in announcing the position of Chief Scientist of the FDA and the advertisement will begin early in June. He shared a copy of the position advertisement with members of the SAB.

Dr. Schwetz next introduced Art Norris who reviewed with the Board the makeup of the Executive Committee that Dr. Schwetz uses in managing the day to day operations of the Center. Mr. Norris explained that in addition to these senior managers of the Center Dr. Schwetz has invited on a three-month rotating assignment a division director to join the Committee along with a mid-level scientist who shadows him and participates in the activities of the Committee as well. With a series of overheads (Tab A) Mr. Norris described the new organization, along with the distribution of the personnel resources, that the Center is proposing, this includes two major offices, the Office of Research and the Office of Management and Systems. The new Deputy for Research will head up the Office of Research.

Following this presentation the Board questioned Dr. Schwetz about the DDR position and his/her ability to set their own research agenda and that of the research division directors. Dr. Schwetz said that he would continue to be a part of the planning along with the Executive Committee in setting the research agenda for the Center. He pointed out that the new DDR would also become a member of the Executive Committee and be an active participant in the day to day operations of the total Center. Dr. Schwetz was questioned about the qualifications of the deputy, and the fact that we were looking for a researcher, yet the position description indicates we are looking for a research manager. He explained that it was our intent to hire an individual who was at a transition point in their career where she/he was moving away from hands on research and interested in overall management and direction of a larger research organization such as we have at NCTR. In the process of this discussion Mr. Norris pointed out that we have identified a research search team for the purpose of identifying the potential candidates for this position. The team consists of five individuals from NCTR, five from the FDA, and from NCI, NIEHS and EPA. Dr. David Gaylor will serve as the chair of this committee, Dr. Anders, as chair of the SAB, will also serve on the committee.

Next, the director called on Mr. Attwood who discussed the 1998 budget and prospects for the 1999 budget. Ms. Anson discussed the current gaps analysis the Agency is conducting in developing its 1999 budget request. The NCTR budget for 1998 currently exceeds just over 38 million dollars, with seven million plus coming from Interagency Agreements (IAG) and Cooperative Research and Development Agreements. The majority of our IAG funding is coming from the National Institute for Environmental Health Sciences NTP program. Dr. Schwetz mentioned a new ability the Center is beginning to develop, with the help of NTP. in the area of photo-toxicity as a result of a request from the Center for Food Safety and Applied Nutrition and it's responsibility for cosmetics.

Next, Dr. Schwetz took time to recognize and present letters of appreciation and plaques to two retiring members of the Board, Dr. Lily Young and Dr. Harold Davis.

On the agenda next, was a presentation of the draft site visit report on the Information Technology Program, approval of which was held over from the last meeting. Dr. Rosenkrantz reported she had no further information to discuss with the Board, that they had a copy of the final report with an appendix discussing a minority view on one item (Tab B). Dr. Anders asked for a motion to accept the report, the motion was made and there was unanimous approval to accept it. With the report accepted by the Board, Dr. Anders requested an update from Ms. Anson on the recommendations contained in the report. Ms. Anson's update on the Center's progress on the recommendations contained in the report and it can be found at Tab C of these minutes.

Following Ms. Anson's presentation Dr. Rosenkrantz, who chaired the site visit, stated she was pleased with the thoroughness and completeness of the responses made by Ms. Anson and staff. (it should be noted that this formal response to a draft report was unusual, but because of a years delay in taking final

action on the report it was thought it appropriate, the progress report on of the draft recommendations be made).

As a final item of the morning, Dr. Schwetz called upon Meredith Graham the new director of the Arkansas Regional Laboratory, which is being constructed on the NCTR campus to provide an update to the Board. Ms. Graham reviewed the 20-year facility plan of ORA, which will consolidate 18 laboratories of the ORA into a nine laboratory complexes of which five will be mega-laboratories. ARL will be one the new mega-laboratories that will have about 170 people resulting from the closing of laboratories through out the Midwest. Dallas, Memphis, Detroit and Chicago are the first four laboratories that will be closed. She pointed out that all employees at those laboratories are being offered positions at the facilities, in Jefferson, AR.

After lunch Dr. Anders called on Drs. Doyle Graham and Tomas Guilarte to discuss their draft site visit report on the Center's Neurotoxicology Program. That report and it's recommendations can be found at Tab D. Dr. Silkker was asked to comment on the report.

He thanked the site visit team for their supportive comments. The issue raised concerning the number of protocols that the division is currently supporting, represents a 20% reduction over the past several years, and he said he expected this trend in the number of protocols to continue. This would be in keeping with the recommendations of the site visit team. Dr. Anders questioned Dr. Slikker and Dr. Schwetz concerning the intercenter neurobiology/Neurotoxicology-working group that was discussed in the report. This group is a paradyene for the virtual science center concept that Dr. Schwetz had discussed previously with the Board. After a brief discussion, Dr. Anders called for a vote, and the draft report was approved. He requested that Dr. Slikker be prepared to give the Board a formal report at its next meeting.

During the course of discussion on the Neurotoxicology program an issue was raised by Board members concerning the lack of research direction for the Agency as a whole. Along with that issue, there was raised the inability of NCTR scientists as well as scientists throughout the Agency to compete for Department research grants and in particular grants from the NIH. The Board considered and Dr. Anders suggested preparation of a letter to Dr. Schwetz and the Commissioner stating the need for an overall research plan for the Agency and a recommendation that the Agency should once again approach the Department about it's ban on FDA scientists applying for NIH grants. See Tab G.

Following a break the Board was presented the draft report on the site visit teams evaluation of the Center's Biometry and Risk Assessment Program. The report can be found at Tab E. During the course of the discussion an issue did arise as a result of one of the recommendations concerning the visibility of the Centers contributions particularly in the area of risk assessment. There is a lot of scientists recognition but that overall recognition of the Center's contribution is missing. Dr. Schwetz mentioned that this issue would be discussed later on in our agenda and the need for more publicity on the part of NCTR in developing its contribution in the whole area of toxicology. Dr. Anders then called on Dr. Kodel who provided some general comments on the site teams report and stated he would provide a written report at the Boards next meeting

Dr. Anders called upon Dr. Dan Sheehan to provide a progress report on the recommendations made the previous January as a result of a site visit report on the Estrogen Knowledge Base project. A copy of that report can be found at Tab F. In the course of Dr. Sheehan's report he mentioned that EPA will have to screen some 85,000 chemicals for potential endocrine disrupter activity . Of the 85,000 chemicals Dr. Sheehan estimated that 1% of them will be required for full blown testing at the cost of about 1 million per

chemical. It will be information from the initial screening that will populate the database that is currently being developed for endocrine disruptors.

The Board next took up the discussion of public information strategies for NCTR. During the course of the discussion it was pointed out that the Center has a problem similar to most scientific institutions where you have active publishing scientists. Individuals become known through their publications but the institution they're a part of is not known. The Board made it very clear that they have no doubt that the Center has good people and the trappings of the scientists are present on individual basis, but there needs to be the development of a corporate image for the Center. Different strategies were discussed including the development of more visibility on the WEB for the Center. One member opined that the Center's work could be divided into three areas, one in which its scientific expertise and individuals are available to help on specific tasks within the Agency. The second is the information the Center develops on specific substances, such as work to evaluate the carcinogenicity of specific substances. Finally, the last area which is the least understood and the least recognized is the Center's contribution to improve predictive models, which improves the efficiency and effectiveness of testing paradigms that are required by a regulatory agency. It is this last area which other centers find most difficult to incorporate into their guidance for the day to day evaluation of products that need regulatory decisions by the Agency. The Board concluded that the Center has missed opportunities in informing others in how importance of NCTR's contributions and, that rather than being in competition with them we are in partners in trying to improve the quality of the FDA regulatory processes.

Dr. Schwetz went on to present a concept of proposed national advisory board for NCTR that could be a subcommittee of the full SAB, that would be charged with facilitating the use of Center research results.

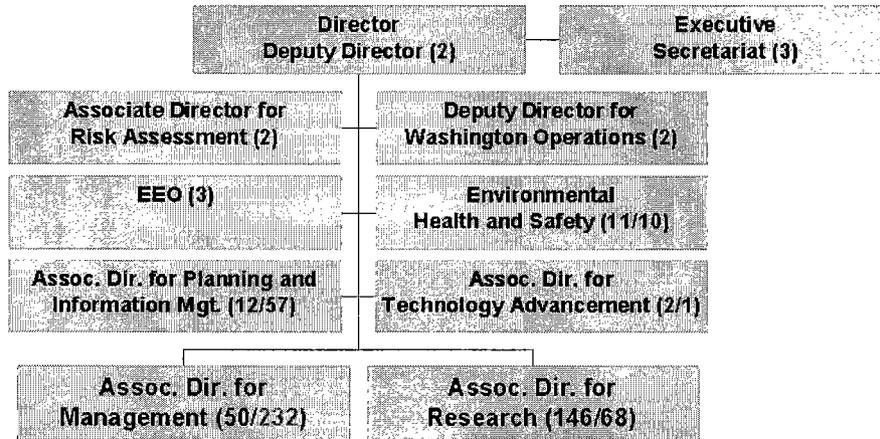
The Board discussed that this was not within the purview of the SAB, that it actually represented a conflict

with the current charter, which requires the Board to review for scientific quality and relevance of the research programs at NCTR. No action was taken by the Board on this matter.

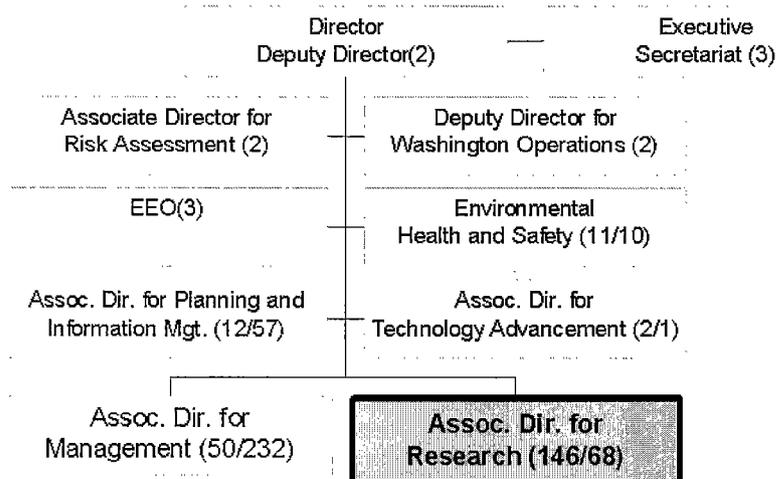
The final action by the Board was to request that site visits of the Center's three programs dealing with carcinogenesis research including the Divisions of Biochem Toxicology, Genetic Toxicology and the new Division of Molecular Epidemiology. The Board adjourned at 12:15 P.M.

TAB A – Overheads

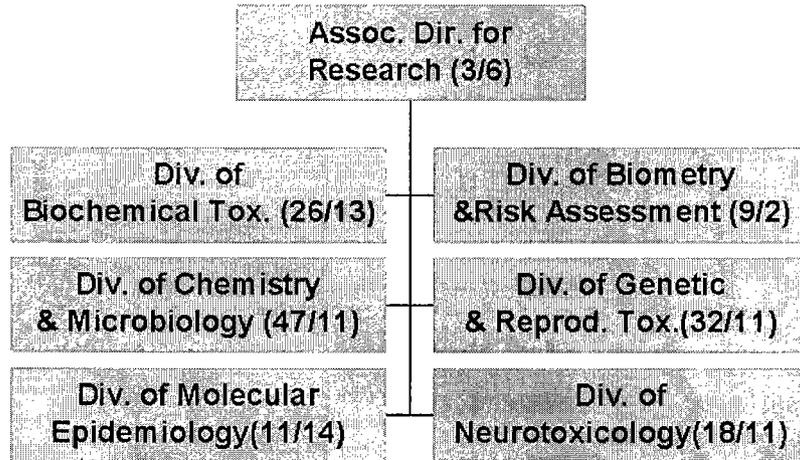
Old Organization



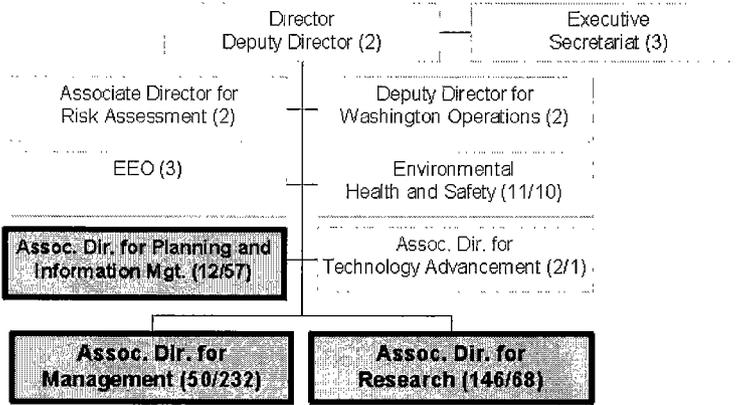
Old Organization



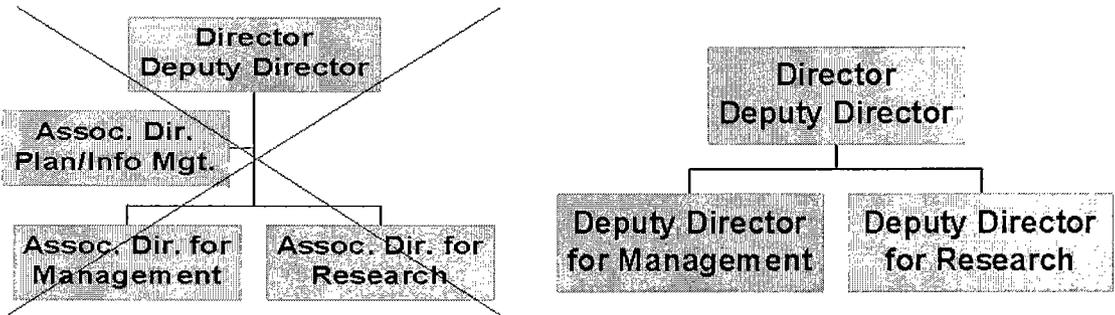
Old Organization



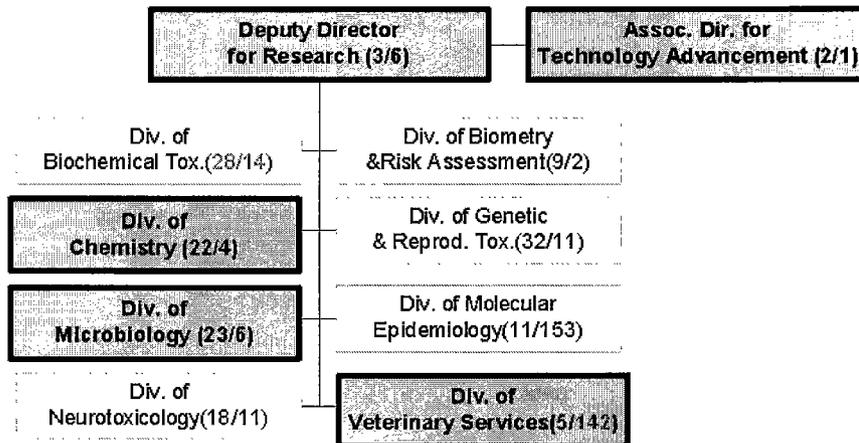
Old Organization



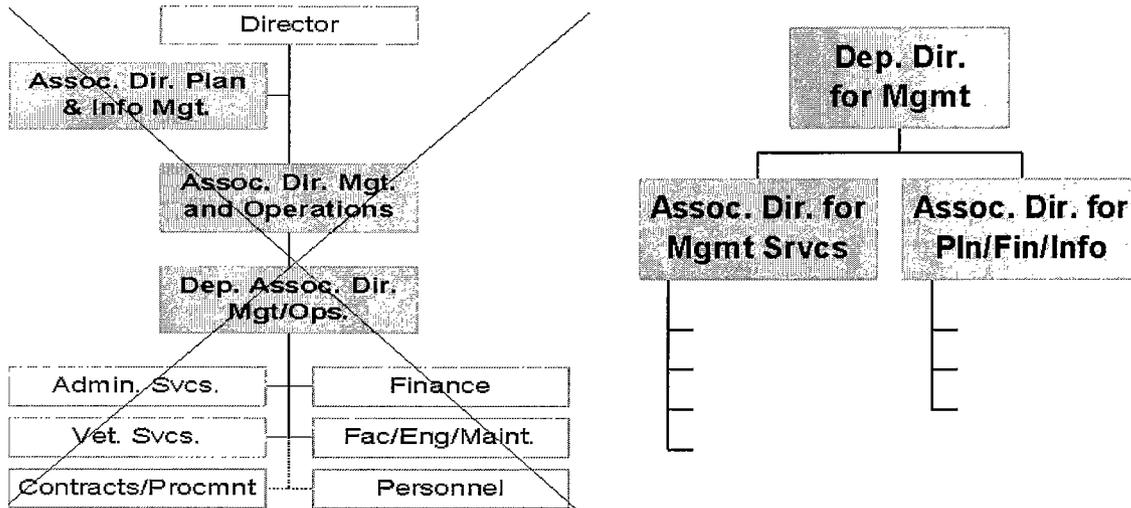
New Organization



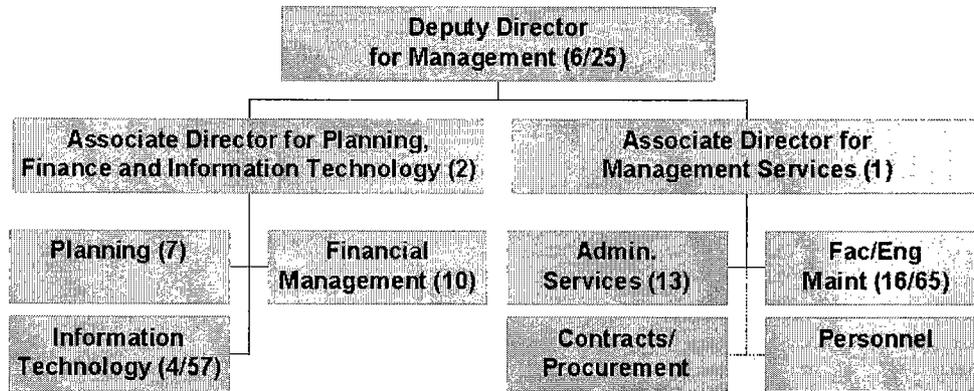
New Organization (Research)



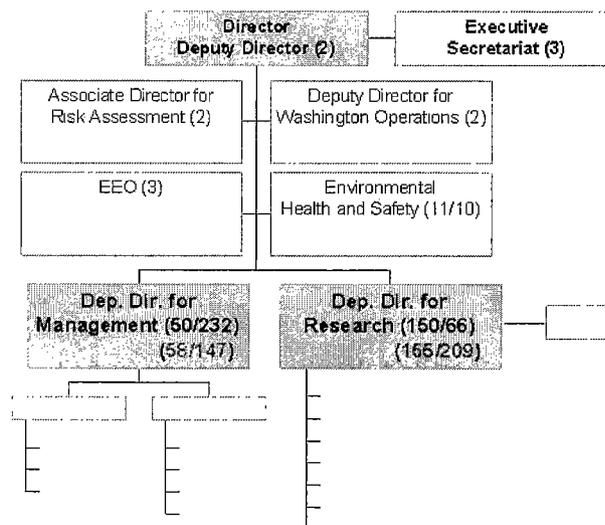
New Organization (Management)



New Organization (Management)



New Organization



TAB B

**SAB Review of NCTR Information Management
Program**

SAB Review of NCTR Information Management Program

The review occurred on May 1-2, 1997. The Site Visit Team (SVT) consisted of the following individuals: Marcy E. Rosenkrantz, Chair and member of the FDA SAB, Tomás R. Guilarte, member of the FDA SAB, Jeanette Clay, FDA, E. Glenn Rogers, FDA, and Kathleen Johnson, FDA. The format was a series of presentation by individuals from the contracting group and government project managers. There was an opportunity for the directors of the different NCTR scientific divisions to present their views about the positive and negatives aspects of the IM program. There was also a tour of the facilities and presentation of capabilities (hardware and software) associated with the IM program.

The charge of the SAB team was to evaluate three aspects of the program:

1) Infrastructure and Equipment

Is the infrastructure and equipment appropriate for the job.

Is it positioned for future growth?

Is the infrastructure under-utilized relative to the investment?.

2) Services provided

Do the services meet the scientific needs of the various divisions?

Are they suited to the administration?

Is NCTR properly connected to other sister agencies of the FDA? is there sufficient training for users?

3) Information Management Personnel

Is the leadership knowledgeable and poised to satisfy future needs?

Is the contracting mechanism adequate?.

Our comments and recommendations are directly tied to the charge to the SVT and will be presented in turn.

Infrastructure and Equipment

In general it appears that the infrastructure and equipment is adequate for the needs of the administration and scientific divisions. Planning for future needs seems to be proactive and in consultation with administrators and scientists.

NCTR has deployed several different computer-processing platforms within the center to support its many business needs. There are some legacy VAX platforms that the center is in the process of migrating to DEC Alpha architecture. The local area network appears to be robust to handle the majority of the centers traffic despite the occasional traffic bottlenecks that occur. Although SVT didn't get a good sense of the systems management operation, the network support group has done an outstanding job in the design and implementation of the FDDI ring, building in redundancy and the support of the entire network.

The mix of server operating systems, LANs and DBMS software seen at NCTR is different than in other components of FDA, but seems to be effective for local requirements. Because most NCTR applications operate independently of other FDA components, the lack of compatibility is not of

significant concern. However, the variety of systems in use is of concern. It results in the need for multiple types of system management expertise and increased resource requirements for support.

Network issues appear comparable to those experienced by other components of FDA. Troubleshooting of complex networks is an increasing problem, and Centers have developed their own expertise to complement the services provided by the FDA Network Control Center (NCC). Connectivity between FDA components is supported centrally by the NCC, while local problems are diagnosed and resolved at the NCTR. The Center's recent acquisition of network monitoring software parallels activities in other Centers and seems to have resulted in a very effectively managed network.

There was a reference by one user to a network-related problem that is a familiar problem in other FDA Centers. The user indicated that their desktop computer is so tied to the network that when the network is down, they can't do any stand-alone work on their PC. Careful development of network logon scripts and end-user training is required to provide alternative boot-up procedures that will allow users to operate without the network. This may be an area that can be explored and implemented as Windows 95 roll-out proceeds.

The mix of desktop computer models and operating systems prevalent in NCTR is typical of other components of FDA. This can be a limiting factor for growth - e.g. roll-out of Windows95 and Office 95/97 require high-end PCs for adequate operation. In addition, the mix can increase the complexity of support of desktop computers and reduce support personnel productivity.

With the new Agency standard for a network operating system and electronic mail, Microsoft Windows NT and Exchange, NCTR has a major migration ahead if it is to comply and convert from Novell. It may not be critical that this conversion be made if electronic mail interoperability through Internet can be established.

Recommendations

The center (if it hasn't already done so) should consider routing traffic to reduce network bottlenecks. The SVT was not sure how many different protocols are running on the network, but with the diverse system platforms in place there is certain to be a lot of Across-talk on the LAN. The center should ensure that either the network has a 95% or better up time or that the environment provides an alternative means for the scientific applications to continue to run when the network goes down.

As resources permit, low-end computers should be phased-out and replaced with state-of-the-art PCs. In addition, users should all be migrated to Windows95 for their primary desktop computer (used for electronic mail, word- processing and standard applications). Users who have DOS-based software that they must continue to use, should have alternate PCs available. However, user support provided for these systems should be minimal. It is not unreasonable to ask that the office, document, and e-mail systems within NCTR be compatible with the rest of the FDA, and that the NCTR staff be able to use those systems..

The center should consider the costs of migrating the ADABAS database over to the new architecture. The conversion and migration costs should be compared to the cost over the long-term of maintaining legacy equipment and software.

2) Services provided

The services provided by IM are utilized widely with some services being used much more heavily than others. For example, the InLife system appears to be essential for the large scale animal studies which are on-going at NCTR. The computational science component of the program is also very important for the development of new research directions at NCTR.

These new research areas include but are not limited to the development of knowledge bases such as the Estrogen Knowledge Base and the Fetal Imaging and Reconstruction project. If fact, it was apparent from the presentations that the computational sciences area of the IM program is rapidly expanding and demands from the scientific divisions may grow exponentially. It is likely that this component of ROW=s contract may be expanded in the near future

It is apparent that the scientific needs of the NCTR staff are of their primary concern and any systems put into place by the FDA at large should be flexible and extensible. In this regard, it is important that the expectations of the NCTR staff for the IM services by contract and Federal IM program employees be set appropriately.

The personnel of the IM contract is one of the biggest infrastructure assets because in the majority of the cases, individuals have been at NCTR for a number of years. They feel they are part of NCTR and its IM program rather than part of a contract. Contract personnel have intimate knowledge of how the system works. Also, in many cases they have developed friendly and collaborative working relationships with the scientists. This is an unique aspect of the contract.

In general, the SVT believes that the contract is providing a very valuable service for a reasonable price.. There was general agreement that the cost of the IM contract is very low compared to the cost in Information Management Services at other government institutions and in industry. The current cost of the contract is \$3.84M and covers 54 fte=s from ROW. At an average cost of ~\$71,000/fte, this is considered by any measure to be a bargain. The average cost of IM services elsewhere is approximately twice that cost.

The ratio of computer support staff to employees (government and contract) initially appears much higher than in other FDA Centers. This ratio is skewed somewhat by the presence of statistical, computational science and experimental liaison support that is atypical of other Centers. For example, in CDRH, there are no computer support staff dedicated to scientific projects; rather, the scientists involved in these projects have developed the necessary computer expertise in order to provide their own support.

The components of the NCTR IM support staff that have parallels in other FDA components are the Software Engineering, Systems Support and User Services groups. NCTR has 40.1 FTEs (36.5 Contract/3.6 government) involved in these aspects of support for the approximately 540 total NCTR staff, or a ratio of 1:13.5. This overall ratio is significantly higher than for other FDA Centers. There are proportionately more dedicated Systems Support and Software Engineering staff at NCTR than at most FDA Centers. For example, at CDRH, the ratio is 1:84 vs. 1:45 at NCTR for

Systems Support and 1:68 vs. 1:49 for Software Engineering. This may explain the generally satisfied end-user group.

The ratio of User Services staff (10.9 FTE) to NCTR staff is 1:50. In other FDA Centers, the ratio ranges from 1:40 to 1:200, with three of five Centers falling very close to the same ratio observed at NCTR. User support is handled very differently among the FDA Centers. Some have dedicated, central staffs, while other utilize a combination of central staff, and local office automation liaisons in the program areas. NCTR follows the centralized approach which seems to work very well.

NCTR appears to have a generally satisfied end-user group. While there are always complaints from end-users about a customer service group, these complaints appeared to be minimal at NCTR and can probably be diminished by increased communications regarding priorities and perhaps more discussion aimed at lowering user expectations to a more realistic level.

The support of NCTR information management activities almost entirely through contract is atypical of other FDA Centers. In fact, NCTR's experience with contract support appears to be extremely positive, with stable, flexible and productive staff available for projects. In other parts of FDA, there have been a number of negative experiences with software development through contract that have resulted from delayed deliveries, cost overruns, and delivery of inappropriate end products. NCTR's approach with contracting demonstrates several key approaches that should be borrowed by the rest of FDA: contractors working on-site where they can readily interact with government staff, and contracts which are performance-based rather than fixed cost or cost-plus.

A recent "Best Practices" working group study of FDA Help Desk procedures was completed by the Rockville-based FDA Centers. While NCTR did not participate in this working group, it appears that their user support practices are comparable to the best practices of other FDA Centers. NCTR utilizes a single-point of contact approach for calls and a call-tracking database application. It conducts user satisfaction follow-up and maintains performance metrics. The Center provides: phone diagnosis as well as dispatch to the user location as required; user training, both through classes and one-on-one; and user guides and other documentation.

The User Support staff has almost an impossible task in providing user assistance to the NCTR campus. They provide support to over thirty applications running on four to six different operating systems. The help desk is utilizing knowledge bases and a problem reporting system to track the requests that come in. Problems that don't fall into their purview or are more technical than the expertise on the help desk are forwarded on to different contract personnel for resolution. Once the problem is referred to the next level the problem is no longer tracked by the help desk and becomes the responsibility of the specialist to work with the user to resolve the problem.

There is also a training component to the User Support function that provides on-site training to both government and contract personnel. To their credit, the training staff has provided almost three thousand hours of training to government and contract personnel on various software components.

In the area of software engineering, NCTR faces a dilemma with regard to the legacy systems supported in Adabas and Paradox and new systems being developed in Oracle. It is regrettable that the re-engineering of the Multi-generation support system could not have been completed in Oracle rather than Adabas due to technical and/or practical considerations. This will perpetuate the

disconnect between legacy and new systems and will limit the possibilities for data integration, as well as the sharing of software modules between systems. As it stands now, software developers must either specialize in one environment or another, or, if attempting to utilize all three DBMS's, cannot easily develop or maintain proficiency in any single one.

There also appears to be a tendency to develop applications in-house instead of utilizing commercial, off-the-shelf software (COTS). It can be self-serving to have contract staff integral to the decision-making on software platforms and design. While many NCTR projects require very specialized applications that must be written in-house, some applications could use COTS packages. For example, the user services Help Desk software was written in-house. There are a variety of COTS Help Desk software packages available, and used elsewhere in FDA, that could be used in NCTR and would provide functionality well beyond that of the in-house package. Another example might be the inventory system that the software engineering manager observed required a re-write.

Also in the area of software engineering, there appeared to be shared confusion among users about what the priorities for software development were and how the priorities were determined. It would appear that NCTR management should more openly advertise the priorities for support that have been set and more clearly indicate to user groups when their project did not make the cut and why. One method of prioritization of software projects that is used in CDRH/FDA has proved beneficial. Once a year, the six CDRH Offices, through an "Information Management Council," propose information systems projects that require continued or new support. The IM staff works with the Offices to develop resource estimates and a project list is generated, indicating the resources required vs. those available. Offices then prioritize their requests, and where appropriate, endorse other Office's proposed projects. A support plan is then proposed by the IM group to the Center Director who makes adjustments to priorities where deemed appropriate. The project plan is used to guide work during the year and is used to lower expectations for support when users have not been made aware of support decisions, but is adjusted during the year if new, major initiatives arise, or if user requirements change or fail to materialize. The Information Management Council is also used for discussion and decision-making on other IM issues, such as where new investments are made, when major migrations (such as a change in electronic mail product) are made, etc. This council ensures that program impact is considered in these initiatives, so that technical direction is coupled with program priorities.

Recommendations

There are areas of user support that NCTR might be able to improve upon and benefit from other FDA experience. The NCTR user support service attempts to support users in any software that is requested. This spreads resources too and requires user support staff to be expert in all areas. Most other FDA Centers limit software application support to a list of "standard" packages and dictates that users are on their own if they choose to use other packages. Some FDA Centers have proceeded towards much more standard desktop installation procedures and controls than has NCTR. While some end-users at NCTR expressed a strong need for flexibility, there are methods employed by other Centers that implement user roles in Windows95 and enforce required policies, but allow for "power" users to install their own software. These standard installation procedures and controls can reduce the complexity of support that results when configurations can be easily modified by the end-user. In addition, network-based desktop management software and routines can be utilized to upgrade desktop software, eliminating the need to visit each desktop for software version upgrades. The Agency's new Information Systems Architecture proposes the use of Microsoft SMS for enhanced network management of desktop computers. If implemented at NCTR, it should result in more effective use of support resources both for upgrades as well as trouble-shooting.

Future IM contracts at NCTR should carefully spell out what systems the contractor will support and provide training for. Any other systems that staff wish to use should be supported by the staff themselves. It is unreasonable to ask that contractors provide continuing low level support for legacy systems like DOS and its software, when the rest of the organization is clearly moving toward the next generation of Windows operating systems. If users wish to introduce their own software they will have to do so at their own risk and discretion. The concept of the Power User discussed above is strongly recommended for NCTR staff who require specialized or legacy software.

NCTR management should consider what level of support is reasonable and design the follow-on contracts accordingly. The User Services contract could be designed to provide on-line tutorials accessible from any web browser so that people could work through the tutorials as needed. User Services training in office software may not need to be an on-going service; weekly or even monthly courses in MS Word may not be required. However, User Services could be used to identify, test and demonstrate software packages that are relevant to the NCTR staff scientific needs (e.g. lab management s/w, plotting packages, statistical analyses packages, etc.) Once adopted by NCTR, use of these software packages could be included in the training program for a short amount of time before being transferred for inclusion in the on-line tutorials always available.

Management should consider establishing computer-savvy individuals in each program group to serve as liaisons with the user support group, to serve as local experts, and to clarify requirements for equipment and software installation. This was an area of concern expressed by the user group.

We also believe that there might be room for improvement and restructuring of the IM contract so that it may provide a greater service to the specific needs of each scientific division. Because there are so many different software packages deployed within the center, the help desk should identify a standard set of software that can be supported. Care should be taken, however, to give the user an alternative to get problems resolved, i.e., knowledge bases, vendor support numbers, etc.

Resolutions to problems that are referred to the specialist currently should be captured in the help desk database. The help desk should track the problem to its conclusion and the resolution logged into the database for future reference. It isn't clear how priorities are set when problems are referred to specialists by the help desk and how problems get escalated for resolution within the organization. A structure for determining priorities should be implemented by management. The help desk should establish guidelines and procedures that clearly indicate how problems are escalated and what the acceptable response times should be for various types of reported problems. Statistics should be captured on the number and types of problems being referred to the specialist(s) to determine trends or to determine if there is a need for more scientific computing expertise. The help desk should track all calls through to resolution. The contractor should be tasked to do an analysis of all problem calls every quarter to identify trends and problem areas and to provide the results of that analysis in a report to the government.

If Adabas cannot be phased-out, NCTR should develop a plan for integration of Adabas data with Oracle, such as through a data warehouse, or through client-server tools that can talk with both databases. There were some discussions that indicated the need to integrate program-oriented data with administrative data that is maintained in Paradox.

COTS packages should be explored for applicability before any in-house effort is begun in order to save development and maintenance resources.

NCTR has demonstrated significant accomplishments in use of state-of-the-art computing and where possible, other FDA components and researchers should be encouraged to share the software which has been developed. For example, the Estrogen Knowledge Base in development should be used by FDA as a model for how scientific and product data can be organized and made available within the Agency. Algorithms for image capture, manipulation and analysis could be of great benefit to other scientists. Expanded use of the Internet should be encouraged for distribution of data and programs that can be shared with the public.

3) Information Management Personnel

The services provided by the IM program are categorized into six areas which are: 1) administration, 2) systems, 3) software engineering, 4) experimental support/statistics, 5) computational sciences, and 6) users services. The IM organization supports the infrastructure and scientific computer resources of the NCTR. It provides contract management and oversight for 54 contractors who support IM in its effort to provide IT support for all aspects of the NCTR mission. The contractor provides IT support for such areas as travel, finance, library science, science, research, etc.; however, the primary mission or focus of the contract is to provide IT support for scientific and research efforts.

The SVT felt that one of the biggest concerns of the divisions may be related to how the resources are distributed by the administration. There was a concern that outside contractual work may begin to take a greater portion of the available resources and projects which may be of high scientific value but small in scope may not be prioritized appropriately either because they are small or do not bring in funds. In order to avoid this, there need to be open lines of communication and continuous discussions between the administration and scientific directors. An equitable distribution of the IM

resources amongst the scientific divisions is important in order to keep them competitive and capable of reaching their goals.

To address some program management and oversight concerns, NCTR has developed an innovative approach for improving contract management that utilizes someone from the user community as the IM Project Officer. The Project Officer provides government oversight for the contract efforts for a specific NCTR group/division. This approach appears to be successful and has improved the level of contractor oversight for one group/division and has given that user base a specific government person to call. The result is a user base with a sense that the IM organization is responsive and cares. This approach has not been used for other areas/divisions within NCTR who have also indicated that they desire more government oversight. Although this approach has decreased some user concerns, the Project Officer is responsible for overseeing and monitoring at least 18 active task orders. This works at some level only because NCTR has a very stable contractor environment, i.e., the same individuals have been providing support for over 20 years. If truly new contractors were to win the next contract award, any Project Officer may have difficulty adequately overseeing and managing the contractor.

There is a great deal of value in having a government Project Officer who addresses and resolves the government user=s issues and concerns with contractor support. The ability of the IM organization to provide sufficient oversight of the contractor is almost impossible by virtue of the ratio of government to contractors and, more importantly, because of the diversity of functional areas supported by the contract. Although there are five government employees in the IM organization, it is not clear how many, if any, are dedicated to contract oversight and management.

In discussions with some of the user community not served by a specific Project Officer, it was not clear to them where they needed to go and with whom they needed to talk in order to get their concerns addressed in a timely manner. They expressed concern about having contract staff prematurely pulled off of tasks in mid stream resulting in loss of time, loss of man-hours, and loss of historical data.

Because of NCTR's fairly recent expansion of the IM program=s contract support into the area of computational science and statistical support, there are some areas of potential concern. The contract manager appears to be strongly oriented to these new, sophisticated areas of support. NCTR Management must decide to what extent is this part of the bread and butter of IM support requirements in NCTR, management must be wary that software maintenance and user support areas are not neglected.

The primary purpose of the contract efforts is to support the scientific and research efforts of NCTR. The contractor openly expressed a bias towards the sciences versus the administrative efforts. The contractor indicated during their briefings that the interesting things are in the IT efforts to support the scientific and research efforts. It is there that the challenging and creative work is done. For these reasons, areas such as support for the pure administrative functions and support for the library function may not be getting the full attention of the contractor.

It was clear that NCTR has a very productive and synergistic relationship between government and contract staff. The NCTR staff has demonstrated creativity and effective management in their use of

contract mechanisms that allow for such a relationship. In future contract negotiations, NCTR should beware of losing the strong incentives for quality work that are linked with the performance-based contract agreement.

In addition, NCTR has had a history of stability with contract support staff who have stayed with the organization through changes in contract management. This has resulted in stable, competent support. The computational science support relies on young, relatively inexperienced staff who were likely hired at fairly low salaries. Due to the demand for such experience as will be gained with the sophisticated computing projects at NCTR, it is possible that these contract staff members will be tempted away with higher salaries available in the industry, and there may be significant turn-over in this segment of contract support. Other components of FDA have experienced significant project delays resulting from frequent turn-over of contract staff that is typical of the software consulting industry in the Washington D.C. area. A key to avoiding severe impact from turn-over is to have adequate government involvement in projects and expertise in the technology so that continuity is provided.

Recommendations:

The IT support provided by the contractor cuts across all aspects of the NCTR mission. It appears that a significant portion, if not all, of the IT expertise in scientific computing that is needed to support the NCTR scientific community resides with the contractor. This is somewhat disconcerting. To facilitate oversight of the contractor and to be able to evaluate the contractors approach and solutions, the IM organization should have on staff its own expert in scientific computing with broad experience in the application of IT in a scientific and research environment.

NCTR should provide the IM Project Officers an opportunity to receive the needed training to keep abreast of advances in scientific computing technology. NCTR might also consider removing the scientific computing aspect from the current contract and renegotiating the scientific computing tasks as a separate item structured in a research contract, not as part of the rest of the IM contract. In any event, NCTR should thoroughly research the current state of the art in visualization, knowledge bases, etc. NCTR management could then structure tasks to include research ongoing at other institutions in relevant areas, and include the use of COTS instead of relying solely on contractors. At least one member of the SVT is concerned that work on some tasks related to scientific computing under the IM contract may be duplicating efforts already well under way in the development of the knowledge base methods and in the visualization of complex multi-dimensional data sets. Particularly relevant research in these areas is proceeding briskly at several major research institutions, in industry, and at NIH.

An excellent example of the management structure to be employed is in the reassignment of Jon Appeget to work more closely with a particular division. This model should be employed for every division. NCTR staff need to know who the IM director is for his or her area. When potential conflicts arise it is up to the NCTR management team to set priorities and mediate conflicts. NCTR staff who use the IM services needs to be educated about the communication lines available to them.

If it is not possible to employ the same innovative Project Officer solution for other divisions, the SVT suggests that the IM organization consider assigning each IM staff member responsibility for

the care and feeding of a specific division. That person would be the Project Officer for all Task Orders for that division and would be the government individual the division would call for any problem. If possible, no one person should have oversight responsibilities for more than one division.

Because of the number of contractors, the range of topics and expertise required by the contractor and the shortage of government staff to provide oversight, the government should request that the contractor bring onto the contract an IT Program Manager. The IT Program Manager's primary job would be to provide the detailed day to day management of the tasks and the task orders and to work with the government Project Officer(s) to establish priorities and the allocation and movement of resources across tasks.

The designation of an IM government person to be the Project Officer for all administrative functions and one for the library function should also be considered. This would provide the government increased ability to deal with problems as they arise. SVT suggests that these types of IT efforts be defined by their own separate task orders and supported by contractors whose experience and expertise are in these types of efforts. Another alternative would be to have separate contracts to support the non-scientific and non-research areas.

Appendices

After a draft of the final report was presented to the board a dissenting opinion was presented in the form of a memo. The memo is presented here as Appendix A. In, The SVT chair, Marcy Rosenkrantz subsequently submitted a response to that memo. The contents of that response are presented as Appendix B. The memo presented in Appendix A has been edited only by adding letter delineation to help the reader of Appendix B.

Appendix A

COMMENTS ON FINAL REPORT submitted by J. Clay and E. Glenn Rogers

1. Introduction

a) A fundamental comment made to the Chair during our initial review of the draft document is still valid in the final document. It was our understanding that the task of the SVT was to accomplish a review of the NCTR IM Program, not a review of the IM contract as stated in the final report. If the purpose of the review is different, observations and comments made will have a very different fundamental perspective.-

2. Infrastructure and Equipment

a) Paragraph beginning with "The mix of server operating systems, LANs and DBMS software ...resource requirements for support " and specifically the sentence "Because most NCTR applications operate independently of other FDA components, the lack of compatibility is not of significant concern " This statement is incorrect. Kathy Johnson and the OIRM staff had submitted comments on the initial draft indicating changes to this sentence. We had changed the sentence to read "Compatibility with the rest of FDA is important at the infrastructure level, especially with regards to word processing and electronic mail. The final report does not include this change.

b) Paragraph starting with "Network issues appear comparablethe FDA Network Control Center (NCC), which, by its remoteness, is ineffective in dealing with local problems - This is a review of NCTR s IM Program and not a review of the NCC. The statement as written appears to be judging the NCC versus focusing on any NCTR problem/issue because the NCC is not local to NCTR. (Note: Katherine Johnson has made an effort to get this changed in both the initial draft and the final report. Hopefully, this change has now been made

c) Paragraph starting with "AWith the new Agency standard for a network.....It may not be critical that this conversion be made if electronic mail inter-operability through Internet can be established. - Although it may not be viewed by one of the contributors as critical, the establishment of standards and an Integrated Systems Architecture (ISA) is the direction of the agency and is consistent with the intent of the Information Technology Management Reform Act (ITMRA)

d) Paragraph beginning with "As resources permit, low-end computers should be phased out . It is not unreasonable to ask that the office, document, and e-mail systems within NCTR be compatible with the rest of the FDA, and... " The last sentence of this paragraph is inconsistent with the paragraph referenced above in 2.b but it is consistent with the direction of the Agency.

e) Paragraph beginning with "It is apparent that the scientific needs of the NCTR staff "

It is not clear what this paragraph is attempting to convey to NCTR.

f) Paragraph beginning with "The components of the of the NCTR IM support staff that have parallels in other " and the succeeding paragraph.

The OIRM staff cannot confirm nor deny the statistical data contained in those paragraphs as they pertain to other FDA Centers

g) Paragraph beginning with "NCTR appears to have a generally satisfied end-user group perhaps more so, than in other FDA Centers..." -

The comment is subjective and the OIRM staff has no additional information that would allow us to support that statement. We do agree that there will always be complaints from end-users about customer service and that the complaints at NCTR appear to be minimal

3. General Comment:

The SVT was asked to review the IM program and make subjective recommendations/comments. This subjective approach will logically result in a subjective report. The SVT Chair had a significant challenge to pull together the final report and we appreciate all of her work. We would strongly recommend that future subjective reports of this nature be developed in a manner such that any dissenting views are captured and reflected in the final report.

Appendix B

Response to Appendix A item 1a

The word "contract" in the title and later in the body of the report has been changed to program where appropriate. There are places in the report where we specifically mean contract and not program. Those instances of the word have not been changed. I think I found all instances of the word and changed them where appropriate. If I missed any, please let me know and I will make the needed changes.

Response to Appendix A item 2a

See the remainder of the paragraph in question and recommendation paragraph 2. "It is not unreasonable to ask that the office document and e-mail systems within NCTR are compatible with the rest of the FDA." However, the paragraph in question deals with the operating systems, LAN and DBMS systems at NCTR. We should not confuse the method of sending the e-mail and documents (the LAN) with the s/w used to compose the e-mail and documents (MS Office). If interoperability can be insured using the network already in place at NCTR, mail and document traffic should arrive and be readable everywhere.

N.b. The Internet has been existing quite nicely for some time using a variety of local networks (and office automation products). It is rare that e-mail is so corrupted during transmission as to make it un-readable.

Response to Appendix A item 2b

It was changed as of Wednesday morning, 6/4/97, in response with my apologies to an e-mail from Kathleen Johnson.

Response to Appendix A item 2c

The SVT was convened to evaluate the IM program at NCTR not the efficacy of the ISA standards. I'm sure that the intent of the ITMRA was to save the taxpayer money by insuring compatibility not merely to achieve uniformity at any cost. If interoperability can be achieved isn't that better than fixing something that we have already complimented for its efficiency, etc. "If it ain't broke, don't fix it."

Response to Appendix A item 2d

I do not believe there is an inconsistency here. The paragraph in 2b refers to the operating systems, LAN and DBMS. This sentence was moved to its current position, because it deals with office s/w products. See my comments on item 2b above.

Response to Appendix A item 2e

It is merely attempting to convey to the NCTR that they got their message across. Their research is paramount to them. And the IM program should support their scientific efforts by providing services that are flexible, etc.

Response to Appendix A item 2f

This comment was submitted to the report by a member of the SVT who was asked to present information that compared the way NCTR's program with IM programs as they are carried out in other parts of the FDA. I have no reason to doubt the word of the member submitting the data.

Response to Appendix A item 2g

I will respectfully remove the offending part of the sentence (sic)....

Response to Appendix A item 3

Peer reviews are by their nature a mixture of subjective and objective criticisms and comments. Such reviews have been the mainstays of scientific investigation and have helped maintain the integrity, independence and excellence of scientific research, everywhere. I personally do not want to see the process changed.

In defense of the final report presented here, the chair respectfully maintains that the text of all the inputs from all members of the SVT were integrated into the final version with only a minimum of editing to maintain a consistent style and format. Those comments therefore cannot be discerned as separate comments in the final report. Comments that were substantially and substantively duplicated by other members of the SVT were not duplicated in the final report.

TAB C

**Response SAB Site Visit Review
NCTR Information Management Program
May, 1997**

Response: SAB Site Visit Review
NCTR Information Management Program
May 1-2, 1997

The Information Management Program Staff very much appreciate the comments and suggestions of the Information Management SAB Site Visit Team (SVT). In reviewing the NCTR Information Management (IM) Program, the SVT was charged with evaluating these aspects of the IM Program (1) Infrastructure & Equipment, (2) Services Provided and (3) IM Personnel. It is gratifying to be recognized by the SVT for the following:

- (1) the provision of A infrastructure and equipment (that) is adequate for the needs of administrative and scientific divisions . . . Planning for future needs is proactive and in consultation with administration and scientists . . . very effectively managed network.≡
- (2) the provision of Athe computational science component of the program . . . (is) very important for the development of new research directions at the NCTR . . . personnel of the IM contract (are) one of the biggest infrastructure assets . . . valuable service for a reasonable price (to a) generally satisfied end user group.≡
- (3) A . . . a very productive and synergistic relationship between government and contract staff.≡

To ensure that the information exchange regarding the review and recommendations is complete, this response is structured to update/clarify/respond to comments and /or recommendations within each of the three aspects reviewed by the SVT.

(1) Infrastructure and Equipment

Page 1, Paragraph 7: A There are some legacy VAX platforms that the center is in the process of migrating to DEC Alpha architecture.≡

Update: We are proud to announce that the migration to the Alpha platforms is complete and the VAX platforms have been removed from the computer room. One MicroVax remains to support a laboratory automation package that is being replaced by September 30, 1998.

Page 2, Paragraph 1: A However, the variety of systems in use is of concern.≡

Update: NCTR is currently undergoing a centerwide migration to the new FDA Office tool standards (MicroSoft (MS) Windows 95 and MS Office 97) with completion estimated by December 1998. As of January 1, 1999, support for DOS-based applications, Windows 3.1 and e-mail other than MS Exchange/Outlook will cease. The only support to DOS or Windows 3.1 applications will be limited to necessary laboratory PC support. All nonstandard software outside the previous exception will be supported only by the individual user.

Recommendations

Page 2, Paragraph 6: A The center (if it hasn't done so) should consider routing traffic to reduce network bottlenecks.≡

Clarification/Response: The Center has not experienced network bottlenecks. NCTR=s upgrade to FDDI was a planned move to prevent network bottlenecks/cross-talk and also provide the Center with network growth capacity. NCTR has 99% uptime and has ensured that scientific software is available on per machine basis to prevent downtime.

Page 2, Paragraph 7: AAs resources permit, low-end computers should be phased out and replaced with state-of-the-art PCs.≡

Response: Since the establishment of the FDA PC Bulk Buy contract in FY 97, NCTR is phasing out low-end computers and replacing them with Micron PCs using an FDA Bulk Buy contract. We have replaced 205 PCs and have 100 remaining to be purchased before the end of FY 98.

Page 3, Paragraph 2: "The center should consider the cost of migrating the ADABAS database to the new architecture. The conversion and costs should be compared to the cost under the long term of maintaining legacy equipment and software.≡

Response: Prior to initiation of the rewrite (January 1997) of the NCTR Breeding and Inlife systems an analysis of requirements was conducted. The resulting white paper defined the functions that were needed, evaluated and defined ancillary systems requiring modification or replacement, looked at DBMS options, identified Year 2000 associated issues, and outlined costs to either modify, rewrite or purchase a COTS package to achieve the functionality needed.

The decision was made to rewrite the Breeding and Inlife systems into a common system with capability to support multi-generation studies using the ADABAS. This decision was based on sunk costs in functional ADABAS-based software applications, breadth of ancillary integrated systems that would require extensive rewrite and validation in another DBMS, the ease of use of middleware to integrate data, and the quite limited time frame requirements. A more extensive cost analysis of converting this ADABAS system to Oracle following completion of the multi generation system vs maintenance of this new system is something we will look at in FY 99.

A more extensive discussion follows. Migration of data from ADABAS to Oracle would be a small part of migration; the ADABAS file structures were developed from logical data models upon which relational normalization to at least third normal form were performed. Mapping of ADABAS files to Oracle tables would be straightforward. The primary effort would be in replicating the person-decades of software development invested in ADABAS-based software applications. An entire suite of related applications (Study Definition, Table Maintenance, Error Correction, Inlife and Breeding System Reports, statistical data extractions, and others) are written against an integrated database schema of which the raw data from Inlife and the Breeding System are just a part. Some of the development effort-for example, functional requirements analysis - would not have to be repeated, but rewriting the applications and validating them to Good Laboratory Practices standards would entail an effort of such magnitude that all other software development would come to a standstill for some years. The current level of support for existing ADABAS applications - exclusive of the Multi-Generation Support System rewrite of Inlife and Breeding - is that of routine maintenance and upgrades. That would still be the case subsequent to any migration, thus yielding no net gain in the area of continuing support. In terms of legacy hardware (a point raised in this context), ADABAS runs on NCTR=s Alpha cluster. In the unlikely event that Software AG decided not to support ADABAS under Open VMS, ADABAS runs quite well under many varieties on Unix on many hardware platforms. A port is quite simple.

NCTR chose ADABAS as an appropriate DBMS technology for several reasons. ADABAS file structures allow data structures, arrays, structures of arrays, and arrays of data structures. This physical representation allows a much more congruent mapping of the time-series data prevalent in scientific data to physical storage than does the relational model. The semantic mapping between data and its physical representation has proven to be of considerable utility in reporting and analysis of data. ADABAS is more efficient in CPU and disk storage utilization. For example, ADABAS applies sophisticated data compression algorithms to both base data and index data, yielding in many cases more than a two-to-one compression of data. Migration to Oracle would require purchase of significantly more disk storage than required by ADABAS. Finally, Software AG is the ninth-largest software vendor in the world, and the third largest DBMS vendor (after Oracle and IBM). ADABAS is well represented in industry, commerce and state and federal governments; there is no question of Software AG=s continued presence in the marketplace and support of its products.

NCTR=s decision to develop the Multi-Generation Support System with ADABAS as the DBMS was predicted upon both of the above considerations. The development effort was considerably shortened by reusing both ancillary systems and the existing well-characterized database schema.

(2) Services Provided

Page 5, Paragraph 3 and Page 7, Paragraph 5: A COTS packages should be explored for applicability before any in-house effort is begun in order to share development and maintenance resources. There are a variety of Commercial off-the-shelf software (COTS) Help Desk software packages available, and used elsewhere in FDA, that could be used in NCTR and would provide functionality well beyond that of the in-house package.≡

Clarification: As a first step in software development, we maintain a knowledge of COTS applications for scientific and administrative systems and ensure availability of COTS packages as evaluation units for applicability and possible cost savings and effectiveness in addressing the need. An example of COTS packages recently purchased is WinLIMS, a laboratory information management system. For the most part we adopt a hybrid strategy buying or using Software Development Kits (SDK) that make packages adaptable. We have reviewed available COTS help desk packages. The help desk software currently in use was developed in-house at less cost than purchase of a COTS package.

Page 5, Paragraph 4: A. .there appears to be shared confusion among users about what the priorities for software development were and how the priorities are determined.≡

Update: We do not disagree with this comment. An interim solution has been to provide a detailed list of software engineering projects to each Division Director (DD) during quarterly planning reviews to allow them to reassess individual divisions= priorities. A listing of SW engineering projects will be included in the FY 99 operational planning and budgeting process to facilitate prioritization. We thank CDRH for their recommendation.

Recommendations

Page 6, Paragraph 2: A. .limit software application support to a list of Astandard≡ packages . . . ≡

Response: As mentioned previously (page 2, paragraph 1, update) following conversion to Agency standards the user support will be limited to standard packages for desk top applications.

Page 6, Paragraph 3: AFuture IM contracts at NCTR should carefully spell out what systems the contractor will support and provide training for.≡

Response: This recommendation of the SVT is being implemented in the new contract. The scope of work for a new contract specifically defines systems and training for which the contractor will be responsible.

Page 6, Paragraph 4: AThe User Services contract could be designed to provide on-line tutorials accessible from any web browser so that people could work through the tutorials as needed.≡

Response: This recommendation is currently being implemented. A Web-based training course is now being offered.

Page 7, Paragraph 1: A Management should consider establishing computer-savvy individuals in each program to serve as liaisons with the user support group, to serve as experts, and clarify requirements for equipment and software installations.≡

Response: In December 1996, NCTR established the Information Technology User Group (ITUG). The ITUG is chartered to represent each NCTR division/office, to serve as liaisons for their respective division to the Information Management Staff (IMS) in identifying, evaluating and recommending hardware and software, to address user needs, and to serve as a resource within each division. The IMS has also distributed a reference/resource list of government IMS that defines the contract support areas for which the IMS staff is the primary contact. On the research side of the house, Leonard Unruh (IMS staff member) functions not only a primary contact for scientific computing questions but also troubleshoots for hardware and software problems with scientific IT support equipment.

Page 7, Paragraph 2: AWe also believe that there might be room for improvement and restructuring of the IM contract so that it may provide a greater service to the specific needs of each scientific division.≡

Response: The recommendations of the SVT noted here are being taken into consideration in the next contract. On February 24, a meeting of office and division directors and PI=s and IM staff was held to discuss computer needs anticipated through 2004. This information is being incorporated in the Statement of Work requirements of a new contract.

Page 7, Paragraph 3: AResolutions to problems that are referred to the specialist currently should be captured in the help desk database.≡

Response/Clarification: We feel it is important to clarify the help desk procedures. All help requests, including those which are referred to specialists, are currently captured in the help desk database. All help desk calls are tracked to their conclusion, and the problem resolutions are logged into the database. Our technicians also currently use this database as a reference tool to assist in solving future problems.

Several other points were mentioned in the SVT=s draft regarding the collection of statistics and performing analyses on help desk calls, priority setting and problem escalation, and acceptable response times. The following information will more completely describe help desk management.

Information currently captured on every help desk call includes the following: requester name, division, and location; call date and time; problem category and application; problem description; problem resolution; staff assigned and time spent; closure date and time. Analyses of help desk call data has been completed on three separate occasions during the past two years. The data has indeed helped to identify trends and potential problem areas. In addition, the information has helped us develop plans for end-user training and identify training needs for our contract staff. We agree that an analysis of calls Abeing referred to the specialist(s)≡ would provide additional trend information and would help determine if there is a need for more scientific computing expertise.

Our current help desk procedures for priority setting and problem escalation allow for flexibility and appropriate response to critical and non-critical problems. Most help desk calls are handled and closed by the technician on the first telephone call. Occasionally technicians must go to the requester=s office or lab to resolve the problem. Assignments are made by our contract Help Desk Coordinator. If the technician is unable to resolve the problem on the first telephone call or trip to the requester, the Help Desk Coordinator enlists the specialist, who works with the end -user and technicians to resolve the problem.

Problems which have the end user Adead in the water,≡ involve NCTR senior management, and/or involve approaching deadlines are assigned the highest priority and are solved first. The Help Desk Coordinator follows up on calls assigned to specialist(s) to ensure that the end-user is satisfied and that the help request is closed in the database. We respectfully suggest that flexible procedures such as these enable us to provide quick and appropriate response to end-user problems.

The SVT report suggested the use of Aacceptable response times≡ for various types of problems. We operate with the philosophy that the acceptable response time for dealing with end-user problems is As Soon AS Possible. We take all reasonable measures to solve problems quickly and thoroughly. We currently provide timely support for the volume of ~500 calls per month. We make every effort to keep the end user informed of progress on the request.

Page 7, Paragraph 4: AIf ADABAS cannot be phased out, NCTR should develop a plan for integration of ADABAS data with Oracle such as through a data warehouse or through client server tools that can talk with both databases.≡

Response: We do realize the utility - even necessity - of data integration across disparate data sources. However, this can be achieved at higher levels of abstraction than that of physical storage in a particular vendor=s DBMS. To address this, NCTR has budgeted for the purchase of Software AG=s Entire SQL Server. This is a middleware product which allows a Ametadata≡ layer to be superimposed on ADABAS file structures. This metadata layer models ADABAS file structures as relational tables, thereby permitting any SQL-compliant tool to access ADABAS data. We will, therefore, be able to access ADABAS from the Developer 2000 tool we now use for Oracle. Conversely, Software AG=s Natural LightStorm, with which we are developing the Multi-Generation Support System, can natively access relational databases using embedded SQL, thus permitting access to Oracle data from systems developed in LightStorm. This allows us to be able to use the tool most appropriate to the problem in hand.

Oracle has its own strengths, and we are using Oracle in a number of current and planned software development projects.

Software Engineering staff have not found any difficulties in acquiring and maintaining proficiency in multiple DBMSs and associated development tools. Data modeling and relational normalization are performed in the same manner irrespective of the target DBMS. The software tools used - Natural LightStorm for ADABAS and Developer 2000 for Oracle - are both event driven, object-oriented GUI toolsets. Analysis, design and development paradigms are, therefore, similar for both environments. While the occasional confusion arises when trying to use a Natural LightStorm event as a Developer 2000 trigger, this is no different than knowing and using both COBOL and FORTRAN. While a number of Paradox applications are still supported, these are all administrative systems, which will be replaced by forthcoming Agency-wide Administrative Systems Automation Project (ASAP) modules. Any administrative or management systems not supplanted by ASAP will be rewritten in Oracle. As this occurs, Paradox applications will gradually disappear.

NCTR has chosen to retain ADABAS because it is a technology fully suited to its intended use; migration to any other DBMS would effect no gain but rather cause a significant loss of time and money; data integration can be achieved via middleware, and experienced staff are available to exploit its usefulness.

Page 7, Paragraph 6: A NCTR . . . should be encouraged to share the software which has been developed. . . expanded use of the Internet should be encouraged for distribution of data and programs that can be shared with the public.≡

Response: The use of the Internet for distributing data and programs is under discussion within the FDA and an Agency response is being developed. There are security issues that impact a final decision. NCTR staff have proposed several options to pursue in an attempt to ensure accessibility of the Estrogen Knowledge Base (EKB) data for collaborative studies.

(3) Information Management Personnel

Page 8, Paragraph 2: AThe SVT felt that one of the biggest concerns of divisions may be related to how resources are distributed by the administrators≡ (time allocation stats; priority of division).≡

Clarification/Update: As noted earlier (Page 5, Paragraph 4) improved communication is a principal goal of the IMS. Through quarterly distribution of task information, a better understanding of resource commitment is being achieved.

Page 8, Paragraph 4: AAlthough there are five government employees in the IM organization, it is not clear how many, if any, are dedicated to contract oversight and management.≡

Clarification: Attachment 1 (NCTR Information Management Points of Contact) defines the role of each government IM specialist. Mr. Ron Barsh serves as Project Officer for the NCTR IM contract for all services; Mr. John Appleget serves as co-Project Officer for the statistics component of the NCTR IM contract. Mr. Ken Weis provides network management direction and oversight; Ms. Shirley Dawson provides user support management and oversight; Mr. Leonard Unruh provides liaison to contract scientific computing and provides direct support to researchers for Hardware and Software concerns. Attachment 1 has been mailed to every user at NCTR, has been made available on the NCTR intranet and has been issued as an electronic news item.

Page 9, Paragraph 2: A. . .administration functions and support for the library function may not be getting the full attention of the contractor.≡

Clarification: Although the current contract is specific in its requirement that it support NCTR's scientific mission, infrastructure support is provided which includes development and support of administrative databases and systems that support our science focus. In that vein, the contractor has developed an entire suite of administrative, management and financial support systems. Since FDA headquarters is now working on a wide range of these types of systems, such as the Administrative Systems Automation Project (ASAP) and the Hyperion initiative, we are now limiting our support to routine maintenance and to ensuring year 2000 compliance. We are, however, continuing to develop new and enhance existing administrative/management support systems which are uniquely NCTR or are not being addressed by FDA headquarters initiatives. Support of the library function includes providing linkage to

searches and provision of on-line requests for reprints, etc. There is a need identified for more web enabled applications and development of a library web page and appropriate links to same. This is being considered as we develop a new scope of work.

Recommendations

Page 9, Paragraph 5: AIt appears that a significant portion, if not all of the IT expertise in scientific computing . . . resides in the contractor . . . the IM organization should have on staff its own expert in scientific computing.≡

Response: The NCTR management agrees with this recommendation for obtaining government expertise in scientific computing. A position description for such an expert is being developed. Approval for recruitment will be sought later this year.

Page 9, Paragraph 6: ANCTR should provide IM Project Officer . . . training . . . NCTR should consider renegotiating the scientific computing tasks as a separate item . . . ≡

Response: In defining the needs of the NCTR community for IT support through FY 2004, these valuable recommendations have been included in the discussions.

Page 10 Paragraph 2: ANCTR staff who use IM services need to be educated about the communication lines available to them.≡

Response: As noted earlier (page 8, paragraph 4 clarification), communication lines for all users have been defined and circulated via multiple vehicles. The ITUG provides an additional linkage to IM services and quarterly meetings are held with DDs to gain information on their requirements for IT services.

Page 10, Paragraph 3: A If possible no one person should have oversight responsibilities for more than one division.≡

Response: As clarified earlier, with limited staff, each IM staffer has principal responsibility for a specific area of oversight on the contract. Division liaisons have been identified through the ITUG and the role of this user group is being looked at with an eye to expansion.

Page 10, Paragraph 4: AThe government should request that the contractor bring onto the contract an IT Program Manager . . . to provide day to day management of tasks . . . ≡

Response: Within the current contract structure, day to day management is the duty of the Contract Manager who is assisted in these duties (administration and scientific) by a business manager (general administration) and two department managers (systems and software management). As we redefine the IM needs and develop a new scope of work, the SVT recommendations regarding both scientific and administrative contract management requirements have been important considerations.

Page 10, Paragraph 5: AThe designation of an IM government person to be the project officer for all administrative functions and one for the library should also be considered.≡

Response: The IM needs to the Year 2004 were discussed with office managers, DDs and principal investigators (PIs), on February 24, 1998. Several options are being explored to ensure that the most efficient and effective structure is developed to ensure support across the spectrum of NCTR IM needs.

In summary, the NCTR Information Management Program very much appreciates the valuable advice provided by the SVT. The IM program:

X is already phasing in state-of-the-art PCs to support standard architecture infrastructure

- (in conjunction with FDA),
- X will limit application support to a list of standard packages by January 1999,
 - X is redefining the new contract statement of work to spell out systems and servers be supported,
 - X has implemented on-line tutorial training,
 - X is actively communicating with all DDs via one-on-one meetings, e-mail and information flyers, and has established designated IM government staffers as primary contacts for areas served within the contract,
 - X has established and is expanding the roll of the ITUG,
 - X has ensured that retention of ADABAS fully suits its intended use while being able to integrate data with the FDA via middleware, and
 - X has opened the lines of communications with users to facilitate development of the most appropriate vehicle/vehicles to ensure access to all support and servers required in the IM arena through year 2004.

TAB D

Program Review of the Neurotoxicology Division

NATIONAL CENTER FOR TOXICOLOGICAL RESEARCH
SCIENTIFIC ADVISORY BOARD SUBCOMMITTEE
PROGRAM REVIEW OF THE
NEUROTOXICOLOGY DIVISION
January 27-28, 1998

Subcommittee Members

Doyle G. Graham, M.D., Ph.D. (Chair), Ad Hoc Member

Thomas Burbacher, Ph.D. Ad Hoc Member

Deborah Cory-Slechta, Ph.D., Ad Hoc Member

Tomas Guilarte, Ph.D., NCTR, SAB

James O'Callaghan, Ph.D., Ad Hoc Member

1.0 Program Overview

1.1 Introduction

We agree with the opinion stated in the previous review of the Division of Neurotoxicology, conducted on January 7-8, 1993, that the Division is a valuable resource to both the scientific and regulatory missions of the FDA. There is no question that the development of drugs and devices and the provision of a safe food supply will continue to be confronted by issues of neurotoxicity and that the FDA is well-served by maintaining a strong Division of Neurotoxicology at NCTR. Further, the Division as it currently exists is a unique resource with capabilities that are not duplicated elsewhere.

1.2 Existing Neurotoxicity Program

The Subcommittee greatly appreciates the leadership provided to the Division by Dr. William Slikker. He demonstrates a clear vision for what the Division should be and is dedicated both to excellence of the research conducted and to its relevance to the mission of the FDA. He has a sound relationship with superiors and has excellent interactions with the scientists and staff within the Division. Possessed of a warm personality, a

dynamic style, strong managerial skills, and the ability and desire to nurture the career development and welfare of personnel in his Division, he is seen as an extremely effective Division Director and a valuable member of the leadership team at NCTR. The Subcommittee proposes that the next steps in Dr. Slikker's growth as a leader involve working with his staff to develop sound rationales for setting priorities and making the hard choices regarding what efforts should not be continued, what programs need to be consolidated, etc.

There is concern that the lack of growth in funding of the Division, paralleling the overall meagre funding of the FDA, will make it more and more difficult for the Division to conduct basic research and to respond to immediate needs of the other FDA Centers. The Subcommittee feels strongly that both missions are important to the existence of an excellent Division and that they are complimentary. Another general concern that surfaced had to do with the reward system within the FDA in which promotions are largely based on the number of publications rather than the impact of the researcher's publications on the FDA and on the field of neurotoxicology. This emphasis is a potent stimulus to conduct high dose, short-term studies that lead to frequent publications, whereas the Center representatives express a strong need for data from chronic low dose experiments.

The subcommittee is sympathetic to the forces toward an ever-expanding number of research projects, given the many needs of the FDA and the desire to advance the overall understanding of neurotoxic injury. We urge that the Division strives to do fewer projects well than more projects superficially. In this vein, we would discourage the further development of neurophysiological techniques and a major effort in the study of TSE/BSE other than a supportive role in a larger FDA effort.

Input from representatives of other FDA Centers was very helpful. It is clear that the activities of the FDA Intercenter Neurobiology/Neurotoxicology Working Group has led to growing communication between these Centers and the Neurotoxicology Division of NCTR. While we would caution that the Division activities should not be dictated solely by Center requests, we do see that these interactions can keep the Division abreast of needs across the FDA and can facilitate coordination of research activities. It was apparent that the senior leadership in the FDA Centers is sometimes less than fully supportive of these scientific interactions, focusing instead on their own turf and power issues. We see this situation as a challenge for the leadership of the FDA; the middle management simply must not be allowed to erect barriers to the collegial interactions that have been established in this working group and that stand to benefit the FDA as a whole.

2.0 Focal Research Areas

2.1 Role of Aromatic Amines in Neurotoxicity

A considerable degree of expertise in the dopaminergic and serotonergic neurotoxicity of substituted amphetamines has developed within the Division over the past decade. While it is not inherently obvious why a focus on drugs of abuse should exist within the Division, it is recognized that the original basis of this research effort grew out of a NIDA-funded IAG. Importantly, this knowledge base, gained through years of work on these compounds, has resulted in the development and implementation of critical technologies in the areas of biochemical, molecular and cellular neurobiology. The approaches and data bases developed, in turn, have now been applied to more real-world problems of direct interest to Centers within the FDA. Thus, this program has matured to the point where it is poised to make a critical contribution to the mission of the FDA by providing information regarding the neurotoxic potential of widely prescribed agents that affect aminergic systems, such as methylphenidate, dexfenfluramine and phentermine. Over-the-counter decongestants, antitussives and "herbal" remedies also fall into the category of potential aminergic neurotoxicants that will be the focus of research into this important area of neurotoxicology.

Since the last SAB review this program has developed the capability to use extracellular microdialysis not only as a tool to assess neurotransmitter release, but also to assess local levels of the administered drug through a novel fluorescence derivitization technique. This is an important advance, as it allows functional determinations of drug action at the target site to be correlated with local brain levels of the agent in question. This dose-to-target-to-effect relationship is often missing or ignored in studies of the potential neurotoxic effects of aminergic acting agents that have vastly different pharmacokinetic properties among species. Thus, in an animal model, these data will allow for more accurate risk assessment to be conducted with a knowledge base relating neurotoxic endpoints with drug levels at the putative target region of the brain. The capability to collect such data represents a critical Division resource and should be maintained.

Recent literature on substituted-amphetamine neurotoxicity shows that core temperature is an important (sometimes referred to as a nuisance) variable that predicts neurotoxic outcomes. A careful review of the literature will show that what is now almost common place knowledge can be traced to the results of studies initiated within the Division of Neurotoxicology as part of this focus area. These data are of direct relevance to the human condition, in that elevated core temperature/drug interactions associated with environmental/workplace conditions,

can potentially result in neurotoxicity. There was little evidence that this issue has been raised with the appropriate FDA Centers. This issue may be of particular relevance to the case of fenfluramine, not only with respect to the question of neurotoxicity, but also with respect for the potential of this compound to cause heart valve pathology. It seems clear that the database on the role of core temperature in fenfluramine neurotoxicity should be applied to the design of any non-human primate study on the potential neurotoxic and cardiotoxic actions of this agent.

Defining what constitutes a neurotoxic response is not easy, and a proven approach to this problem is embodied in the makeup of the Division, i.e., a multidisciplinary program. Work in this focus area is well integrated with the development and application of novel techniques for assessing neural damage (Histochemical Methods Development). Importantly, this has allowed for the direct comparison of dosing paradigms that result in, e.g., transmitter related changes or seizures that are (or are not accompanied) by evidence of underlying neural damage. Such information can be used by the Agency to differentiate NOELs for reversible changes, such as in transmitter dynamics, with NOELs for neural damage. Preliminary data have been gathered on heat shock proteins, aberrant induction of tyrosine hydroxylase and neurotrophic factors. To relate such changes to the neurotoxic condition, efforts should be continued to obtain the cellular localization of such changes in comparison to known patterns of neural damage under a given dosing regimen.

The proposed future directions of this program are diverse and somewhat far afield. Examining (and understanding) the role of NO, glutamate, trophic factors, heat shock proteins etc, underlying the neurotoxic effects of even a single agent will require a great deal of effort to bring to fruition. A clear-cut rationale for these choices is missing and a prioritization, at a minimum, is in order. In this and other focus areas there has been a tendency to concentrate on acute exposures. Given the relevance of the current research to compounds of concern to the Agency and the potential role of temperature in neurotoxicity, it seems timely to undertake low-level, chronic dosing studies where core temperature is manipulated to mimic the real-world environment.

2.2 Oxidative Stress-Induced Neurotoxicity

The program in oxidative stress-induced neurotoxicity headed by Dr. Ali has been very productive during the past five years. In response to the previous SAB review in 1993, the laboratory has established collaborations with other researchers in neurotoxicology, both within the FDA and with investigators at NIDA and at several universities in the US and abroad, has established tissue culture facilities, and has expanded the use of molecular biology techniques.

The central hypothesis guiding this laboratory proposes that a number of neurotoxic events have generation of excess reactive oxygen species (ROS) as the primary event leading to tissue injury. While the scheme for production of ROS is for the most part correct, it should be noted that superoxide is not a product of MAO metabolism, but rather of the transition metal-catalyzed autoxidation of the catecholamines. While the laboratory has developed assays for ROS and for malondialdehyde as indices of oxidative stress, there may be more value in quantifying irreversible reaction products between proteins and products of lipid peroxidation (e.g., the pyrrole adduct and Michael addition products formed by 4-hydroxy-2-nonenal) and between proteins and peroxynitrite (nitrotyrosine).

The laboratory has made excellent use of genetically engineered mice. The mice that over-express CuZnSOD provide a very good model for testing whether superoxide anion plays a role in the genesis of cell injury; with this mouse model it was clearly demonstrated that the dopamine depletion associated with exposure to methamphetamine and MPTP both are mediated through the production of superoxide. In the case of MPTP, this did not result from redox cycling of MPP⁺, as is the case with paraquat, but rather from the direct injury to mitochondrial electron transport. Similarly, the NOS knockout mice serve as an excellent model for determining whether NO plays a role in the neurotoxicity of drugs; the experiments with methamphetamine show clearly that the homozygous NOS deficient mouse is less vulnerable to dopamine depletion.

Studies on manganese have shown that ROS production is greater with trivalent than with divalent manganese. Whether additional studies on manganese are justified should depend on whether the FDA anticipates regulatory concerns. Otherwise, the manganese studies have served their purpose as a model of oxidative stress in the brain. The studies on Ibogaine less clearly fit into a program on oxidative injury, though the toxic effects of this drug have high importance to the FDA.

Plans to study the neurotoxicity of iron have not been well developed. The deaths of children ingesting iron may not even have a neurotoxic etiology, so it is important that the investigators persist in their plans to investigate the toxicity of iron compounds through the examination of all organ systems. The protocol to study GHB are also incompletely developed and justified. It is not obvious how oxidative injury is a relevant mechanism. The possibility was raised that GHB may not be neurotoxic in the absence of ethanol. There is concern as well about the mercury proposal. Why is this a priority for the FDA? Will exposures levels planned for mercury vapor be at all relevant to human exposures?

2.3 Excitatory Amino Acids as Mediators of Age and Neuroanatomical Susceptibility to Neurotoxicants

The neurological consequences of excitatory amino acid receptor overstimulation (excitotoxicity) is an important area of study because excitotoxic mechanisms have been implicated in a number of neurodegenerative diseases. Emerging evidence suggests that a number of naturally occurring or anthropogenic chemicals or classes of chemicals interact with excitatory amino acid receptor subtypes to produce neurotoxicity. The review committee recognizes that the focus area of excitatory amino acid receptors and regional susceptibility to neurotoxicants is and should continue to be an integral component of the Division of Neurotoxicology at NCTR in order to serve the goals of the FDA in making regulatory decisions on chemicals which produce neurotoxicity via this type of mechanism.

A prominent example of the excellent work that has been carried in this area by Dr. Scallet, in collaboration with other division investigators, is with domoic acid. This work has utilized a number of histopathological methods, some of which have been developed or refined at NCTR, to identify the regional susceptibility of brain structures to domoic acid exposure. Extensive dose-response studies and temporal expression of neuronal damage have been performed in rodents and in non-human primates during the last five years. This has led to estimates of lowest acceptable levels and of concentrations of domoic acid in seafood. These data are very useful in risk assessment and regulatory decisions for the FDA. Overall, this has been a very fruitful and productive endeavor.

Domoic acid is an excellent example of a chemical agent with real world and FDA relevance that produces neurotoxicity by activating excitatory amino acid receptors. The last decade has witnessed an increasing interest both in academia and by pharmaceutical companies to develop excitatory amino acid receptor antagonists such as MK-801 (dizocilpine) for therapeutic use (e.g., stroke). Therefore, there is the potential for an increasing number of drugs that are excitatory amino acid antagonists whose neurotoxic potential will need to be assessed. The Subcommittee believes that this should be a continued area of research in this program.

Based on these comments, it is difficult to rationalize the current and projected increase in demand for personnel and resources to study the neurotoxicity of endocrine disrupters and develop an assay or biomarker for TSE/BSE. The rationale for the selection of these two projects is not clear, and the projects are clearly outside of the excitatory amino acid receptor focus area. The demand on time and personnel may compromise the continuation of the excitatory amino acid work. Although the proposed work on TSE/BSE maybe an important area of research for the FDA, the committee is not clear whether the Neurotoxicology division has the expertise to lead such an effort. It

may be more appropriate for the division to contribute to the development of a biomarker or assay in a multicenter effort to address this important concern.

It was also disappointing that there is no future direction or attempts at making associations between regional brain susceptibility to neurotoxicants and excitatory amino acid receptor expression. For example, data were presented in which low levels of domoic acid exposure only resulted in neuronal degeneration of the CA2 region of the hippocampus. A question that arises from these findings is whether CA2 neuronal degeneration is associated with the expression of an excitatory amino acid receptor subtype which is uniquely sensitive to domoic acid and only expressed in this region. This work can be performed by the mapping of excitatory amino acid receptor subtypes either by receptor autoradiography, immunohistochemistry or in situ hybridization techniques.

It is clear that the excitatory amino acid receptor focus area enjoys the collaboration of other senior scientists within the division. For example, the involvement of Dr. Schmued. However, there is no apparent involvement of Dr. Scallet in some of the other divisional studies such as those being performed by Dr. Paule in which there is a clear excitatory amino acid receptor theme, specifically, the CRADA work on MK-801 and remacemide exposures in monkeys. This is an opportunity in which Dr. Scallet could play an important role in assessing the neurotoxic potential of exposures to these excitatory amino acid receptor antagonists.

2.4 Neurohistochemical Methods Development and Validation

Dr. Schmued's development of The Histochemical Test Battery is seen as a very useful instrument for the FDA and other regulatory agencies, filling a need that has existed for a long time but never before adequately addressed. The Fluoro-Jade stain is seen as a major advance. This technique allows for the identification of dead cells, especially dead neurons even as rare events. It also lends itself to quantitative histopathology and to eventual automation. Since it most likely identifies necrotic, but not apoptotic cells, the inclusion of the TUNEL technique is justified. While the TBA technique will be useful in identifying oxidative stress in the period prior to tissue sampling, an added technique, such as the immunohistochemical detection of reaction products between proteins and 4-hydroxy-2-nonenal may prove to be more useful, as these products accumulate over time.

The Subcommittee thinks that it is now time to complete the matrix on the proposed stains applied to region of the brain for a number of model toxicants, as has been started for domoic acid and 3-NPA. With verification of this Battery, it then will be ready for wide-spread dissemination and incorporation into the routine evaluation of drugs and other compounds for their neurotoxic potential.

2.5 Disruptors of Energy Metabolism and Axonal Transport; Oxidative Stress-Induced Neurotoxicity

The program entitled "Disruptors of energy metabolism and axonal transport; oxidative stress induced neurotoxicity" was presented as "3 Nitropropionic acid induced neurotoxicity" by Dr. Binienda. The concept that liberation of free fatty acids secondary to calcium ion activation of phospholipases is a route to neuronal degeneration is not attractive, since it is the peroxidation of unsaturated fatty acids and the toxicity of the products of lipid peroxidation that constitute the relevant sequence of events. 3-NPA results in a loss of succinic dehydrogenase activity, an effect that can result in the preproduction of ROS and the stimulation of lipid peroxidation. The EEG studies on domoic acid intoxicated rats, on the other hand, do not have a compelling rationale and demonstrate such a high degree of variability that the technique is unlikely to yield useful information. The proposal to progress to visual evoked potentials meets with little enthusiasm, since the toxicants in question are neither specific toxicants for the visual system nor axon-directed toxicants. The Subcommittee sees little reason to continue the investment of resources in electrophysiologic techniques, since there is no obvious application to the ongoing projects in the Division.

2.6 Interspecies Extrapolation and Validation of Animal Models; Disruptors of Energy Metabolism and Axonal Transport

The program on Neurotoxicity of Aids Therapeutics represents a relatively new focus for NCTR. The research is strongly tied to NCTR's mission of meeting the real-world needs of FDA and should thus be supported with ample resources to accomplish the goals of the program. The collaborative effort that was developed for the E2502 Thalidomide Protocol is a clear example of how various programs within and outside NCTR can come together to work together on a very important public health problem. The clinical relevance of the protocol is clear and the involvement of clinical expertise is a major strength for this program. The endpoints examined for this protocol, while broad in scope, were, for the most part, appropriate. Some of the outcome measures (e.g., clinical chemistries) are valuable even though they may not be sensitive indicators, since the general health of the animal is an important factor in these studies. While the nerve conduction studies represent an appropriate functional

evaluation aimed at documenting peripheral neuropathy, the lack of a sensory assessment in the behavioral battery is a major weakness in the protocol, since the goal was to "determine if an animal model of peripheral neuropathy could be generated...". The positive neuropathology findings indicate that this model can be developed at clinically relevant doses. If further studies of nonhuman primates are conducted, ample resources should be allocated to include appropriate tests of sensory functions. The rationale to continue the use of the nonhuman primate model to "screen new agents for HIV" should, however, be considered carefully. In addition, if additional nerve biopsies are planned, it is strongly suggested that the Division send a technician to another institution to be trained in teased fiber techniques, so that the morphological assessments of peripheral nerve pathology can be of the highest quality. It would seem that more effort should be directed toward advancing the in vitro model system to address this problem prior to beginning a screening program using nonhuman primates. Given the likelihood from the in vivo studies that the primary injury is to myelin, cultures of Schwann cells or organotypic cultures of dorsal root ganglia would be the most obvious in vitro systems.

The further use of the rodent model should also be considered since positive findings have now been reported with this model. Appropriate tests of sensory function should also be a major part of any further studies using rats. This would provide valuable functional data which would complement the findings to date.

The E2501 protocol "Placental transfer and fetal distribution of the human immunodeficiency virus therapeutics.." is another clear example of a protocol with strong clinical relevance supportive of FDA's mission. The data related to the distribution of parent compounds and metabolites for AZT, d4T, ddC, and ddI, with particular reference to brain concentrations, clearly indicates that there may be important differences in these compounds in regards to their neurotoxicity potential.

2.7 Interspecies Extrapolation and Validation of Animal Models

Dr. Ferguson's efforts are directed towards the hypothesis that insults associated with developmental cerebellar stunting result in behavioral alterations similar to those of attention deficit hyperactivity disorder (ADHD). In support of that hypothesis, data were presented from groups of rats that had been exposed postnatally to MAM and to dexamethasone. While the findings were consistent with such a hypothesis, there were considerable concerns expressed about the validity of such a hypothesis, as well as the feasibility of actually addressing it. These concerns included the extent to which the cerebellum per se might participate in such behavioral disorders, given the

complexity of the brain, as well as the known involvement of other neurotransmitter systems and regions in activity changes in experimental animal studies (e.g., neonatal hippocampal lesions) and the difficulty of establishing such relationships. Attempts to differentiate such regional involvement on the basis of behavioral paradigms (e.g., use of spatial learning tasks to rule out hippocampus lesions) present problems since lesions of several regions have, in fact, been shown to alter spatial learning. In addition, the predictive validity of the behavior of rodents in open fields or other activity devices to serve as models for ADHD in humans, already a huge response class comprised of differing types of behavioral/attention deficits, does not appear to be recognized in the articulation of this hypothesis. The difficulties engendered by concurrent body weight loss and its concomitant biochemical underpinnings raises additional questions that would need to be sorted out. Given the significance placed on the ability of scientists in the Division to maintain a recognized presence in the neuroscience community at large, this formulation clearly needs extensive further critical review, revision and refinement if it is to be successfully received in that community. Additional mentoring of Dr. Ferguson in this process is strongly advised. An additional concern about these efforts is the extent to which they duplicate studies which have been published in the past by others.

The committee does recognize the importance to the Division of the ability to provide developmental behavioral assessments in many of the projects that are or will be underway. In that context, Dr. Ferguson's efforts and her ability to implement additional paradigms for such approaches take on additional significance. In so doing, the studies with MAM and dexamethasone provide an opportunity to validate the procedures that have already been set up and those proposed for implementation in the future. In fact, such validation is a necessary component of establishing such laboratories and do not require any hypothetical framework.

At the same time, proposed future studies related to DMFO and dexamethasone were thought to be highly relevant to FDA needs and do not need to be embedded in the larger overall hypothesis of a cerebellar stunting mechanism. Utilization of these compounds raises significant issues with respect to potential developmental insults in pediatric populations that have not been fully explored or evaluated and which have considerable implications from both mental health and economic standpoints. Such questions merit study by virtue of their importance to the Agency itself and for problems related to developmental disabilities. In fact, additional preliminary data from such studies may eventually lead to a more cogent hypothetical framework.

The Subcommittee also recognized that this line of research represents an attempt to develop the capabilities to look at the ontogeny of developmental disabilities, such as attention deficit hyperactivity disorder, and to identify the mechanisms by which they occur. This could represent a unique niche for Dr. Ferguson's efforts and

one which could be extremely useful for future questions that come to FDA about compounds with potential to induce central nervous system effects. Understanding the relationships between various brain regions/systems and behavioral deficits, developmentally induced or otherwise, of course, involves very complex questions that have occupied numerous scientific investigators' lifetimes and are not easily resolved. This program would likely benefit substantially from further efforts to critically evaluate what is known about ADHD in human populations, along with potential underlying etiologies as presented in experimental animal studies. It will be important to critically assess how questions about the role of specific regions could be explicitly addressed in an experimental context, as well as what would constitute an appropriate model of ADHD in rodents. These efforts would strengthen Dr. Ferguson's assertions and her ability to impact the field of developmental disabilities.

Dr. Paule's efforts provide the Division with a unique resource and capability. The ability to directly assess the same behavioral functions across species offers opportunities to rationally enhance predictive capabilities and thus impact risk assessment. Furthermore, identification of behavioral profiles in pediatric populations can then serve as a basis from which to examine the effects of specific manipulations of brain function (regions, neurotransmitter systems) in rats or non-human primates in order to mimic the effects observed in children, i.e., to identify their mechanistic basis. The ability to identify regions and systems involved in specific toxic insults would then provide a basis from which chemical therapeutic strategies can be evaluated. Thus, this approach offers numerous possibilities for future returns to the Agency. Dr. Paule's laboratory and program have been very productive, and his studies are highly regarded by his colleagues and peers. They have also served to establish collaborative networks to the extramural community that bring additional resources and recognition to NCTR.

There are some concerns about certain aspects of this resource. One relates to the variability of some of the paradigms used in the OTB and the difficulty that this may encumber with respect to detecting effects of treatments, particularly in the case of chronic low level-exposures or with compounds such as ramicamide. This may be compounded by the necessity of using rather small sample sizes in studies of non-human primates. Power calculations would provide an assessment of the capability to detect effects of a specified size based on current paradigms and their inherent variability and should certainly constitute a component of experimental design. But it would also be expected that by this time, an extensive enough database should be available with the non-human primate studies to permit further refinement of the behavioral paradigms in order to decrease some of this variability.

It would also be particularly useful to see a more detailed breakdown of the sensitivity of different paradigms in the battery to different classes of compounds. This kind of information could be very valuable in

furthering our understanding of the ways in which different neurotransmitter systems are involved in different behavioral domains. Dr. Paule's statement that most drugs tend to affect all of the paradigms in the battery might be a reflection of this variability. The committee recognizes that such efforts, both in terms of further refinement of the behavioral paradigms and more detailed elaborations of the differences between drug effects, may reflect a shortage of adequate personnel for Dr. Paule's program and it would certainly benefit from additional resources.

Similar issues arise with respect to the studies in children. The potential of these studies is very clearly recognized by the Committee, but at the current time it is very difficult to evaluate the status of these efforts since little information has been published. Again, this appears to reflect the absence of adequate personnel for what are very labor- and data-intensive approaches. Dr. Paule may also want to think carefully about the studies in all three populations in the future with respect to focusing efforts in particular areas. While there are numerous types of insults in children that would be of interest, the payoff for obtaining data from only a few children with any given problem, such as traumatic head injury, where each child displays a different deficit, may not be worth the efforts. Further, it may be more important to focus on those problems which can be evaluated and examined in depth across the three species.

3.0 Conclusions

The Neurotoxicology Division of NCTR is a unique resource that should be vigorously supported. While minor adjustments are suggested for setting of priorities, the overall direction of this Division is seen as very positive.

TAB E

**SAB Site Visit Team Review
NCTR Biometry & Risk Assessment Program
October, 1997**

**Science Advisory Board Site Visit Team
Review of the
NCTR Biometry and Risk Assessment Program**

*Little Rock, Arkansas
October 23-24, 1997*

Science Advisory Board Site Visit Team
Review of the
NCTR Biometry and Risk Assessment Program
October 23-24, 1997

Members

**Dr. Joseph Rodricks, ENVIRON International Corp., Chair
Dr. Robert Anderson, WV School of Environmental Education, Inc.
Dr. Elaine Faustman, University of Washington
Dr. Daniel Krewski, Health Care Canada**

Background

The Science Advisory Board of the Food and Drug Administration convened an Ad Hoc Site Visit Team (SVT) to review the Biometry and Risk Assessment Program (BRAP) at the National Center for Toxicological Research (NCTR). The SAB had previously commissioned a review of BRAP five years ago.

The SVT visited NCTR on October 23-24, 1997, to review the program. The BRAP program was presented by the Director, Dr. Ralph Kodell, along with staff scientists. Representatives from four of the five other FDA centers were in attendance, and provided additional information to the Team.

The SVT evaluated the Biometry and Risk Assessment Program with respect to scientific quality, productivity, and relevance to FDA programs. The SVT also considered the general nature of the program, the level of resources assigned to BRAP, and the balance between research in biometry and risk assessment and collaborative research with other NCTR divisions.

The SVT noted a number of changes in BRAP since the last review in 1992, including the appointment of Dr. Ralph Kodell as director in May, 1996.

The SVT wished to acknowledge the major contributions made by the outgoing director, Dr. David Gaylor, to the development of the Biometry and Risk Assessment Program at NCTR, and to the advancement of the field more generally.

General Comments

The SVT found the quality of scientific research within BRAP to be very high. The staff also exhibited a high degree of commitment to the program, and dedication to excellence in research. The SVT found the research program to have considerable breadth and depth. Except for the few discussed below, research projects conducted within BRAP appeared to be relevant to FDA's overall objectives.

Staff in the Biometry and Risk Assessment Program appeared to be responsive to specific risk assessment problems presented by other divisions within NCTR and other FDA centers. This responsiveness was also illustrated by the fact that staff are also involved in a number of important activities outside the FDA, including those sponsored by the National Research Council, International Life Sciences Institute, and the U. S. Environmental Protection Agency.

BRAP is an established center of excellence in risk assessment. It has or is developing all of the qualities needed to exercise a national leadership role in biometry and risk assessment. Because of its focus on risk assessment methodology, divisional programs will have important implications for all of FDA.

Recommendations

Based on its review, the SVT formulated a number of recommendations concerning the future of NCTR=s Biometry and Risk Assessment Program.

- X Although BRAP is generally well-managed and functions well as a unit, greater attention needs to be paid to program planning. Specifically, long-term research goals need to be established with much greater specificity. This strategic planning needs to be done in close cooperation with other divisions within NCTR and, perhaps more importantly, with other centers within FDA with attention to priorities, expected outcomes, and milestones. Unless such planning is undertaken, it is difficult to assess whether current activities and short-term goals will have the desired impact on FDA=s programs in the future, and whether or not planned activities are the most important ones for achieving long-term goals. Although investigator-initiated projects are not to be discouraged, there is a need for more top-down direction in program planning. The SVT found the director=s categorization of future research initiatives within the risk assessment paradigm established by NAS to be a particularly useful component of the current planning process.
- X The SVT felt that the program would be strengthened by establishing well defined research themes to which a number of staff could contribute. In addition to providing a basis for more clearly defining long-term objectives, this would promote greater interaction among scientists within BRAP. For example, the SVT observed that a number of projects were related to interspecies extrapolation. A number of other projects were designed to exploit data from a variety of sources to identify associations that could provide the basis for the establishment of general risk assessment principles. Although such research themes were apparent to the SVT, and could be identified as underlying several projects, collaborative efforts to integrate related projects on the basis of these themes appear not to have been undertaken.
- X The SVT recommends that greater efforts be made to coordinate BRAP research initiatives with the needs of other FDA centers. Based on FDA=s mandate, BRAP should play a major role in the scientific affairs of FDA as a whole. In addition to working more closely with FDA centers, the possibility of coordinating scientific research through the Office of Science should be explored. The SVT recommends that consideration be given to convening an annual

workshop with risk assessment specialists from within FDA to promote such interaction. Workgroups, perhaps organized by BRAP, and involving all relevant FDA scientists, could serve to make clearer BRAP=s important role in the Agency.

- X The SVT felt that BRAP needed to make a greater effort to communicate its research results and accomplishments, both within the FDA and externally, and their potential application. The SVT was concerned that existing communications take place primarily at the scientist-to-scientist level, and that BRAP=s contributions may not be highly visible at the Agency=s decision making level.**
- X The SVT observed that the success of a number of research projects in BRAP is critically dependent on the skills of a single scientist. To ensure the success of these projects, provisions for continuity of staff expertise need to be made. Whenever possible, the BRAP Director should ensure the maximum possible collaboration and mentoring within the program. In the case of the development of mathematical models of carcinogenesis, for example, the success of future research seems largely dependent on Dr. Qi Zheng.**
- X The SVT considered the use of summer faculty to be a particularly cost-effective way of augmenting the human resource complement within BRAP. It is recommended that this program be maintained or, resources permitting, expanded. Other extramural approaches to augmenting the BRAP program should also be explored. For example, small research contracts with risk assessment experts can often yield large program benefits.**
- X The SVT generally endorsed the future research program outlined by the director. However, the SVT felt it was particularly important to follow through on the proposed new food safety initiative to define risk assessment methods for microbiological hazards. It is clear that food borne microbial pathogens are an important, and possibly growing, public health problem for which the FDA has significant responsibility. The lack of well-established microbial risk assessment methods at present underscores the need for work in this area as a high priority. This work needs to be closely coordinated with other activities currently underway within FDA.**
- X he SVT noted that the concept of a threshold of regulation now applied to indirect food additives, may have much broader application within FDA. (Other potential areas of application include direct food additives, veterinary drug residues, and trace leachates from medical devices.) The SVT recommends that the broader applicability of the threshold of regulation concept be explored in collaboration with relevant FDA centers. The results of this review may have an impact on the intensity with which future research in this area is pursued.**
- X While of the view that ongoing research in pharmacokinetics and statistical methods in molecular epidemiology is of good quality, the SVT felt that the short**

and long term objectives of this research are not well described. This clarification is essential in order to evaluate the anticipated impact of further work in this area. At present these activities appear excessively diffuse, and should be curtailed until specific objectives, and the means to attain these objectives are fully described. The SVT suggests that exchanges between biometry and risk assessors are needed to strengthen the molecular epidemiology project, and that link ups with ultimate users of the information needed to be established to give the pharmacokinetic project some focus.

- X The SVT observed that about 70% of staff time appears to be devoted to research projects originating within BRAP, and that about 30% of time is devoted to supporting activities originating outside the division. Since these percentages are not precisely determined at this time, the SVT recommends that the amount of time spent in these two areas be monitored more closely. Recognizing the importance of the support role played by BRAP to FDA programs, the SVT recommends that an appreciable minority of staff time continue to be devoted to supporting activities originating outside BRAP.**
- X The SVT was impressed with the results obtained from the aggregate analysis of existing data. For example, aggregate analyses of cancer bioassay data have identified strong associations between tumor incidence and body weight. Such analyses represent a cost-effective approach to research in risk assessment which has the potential to lead to important new results. The SVT wishes to encourage further analyses of this type, particularly in the area of predictive toxicology, and from rapid communication of results that may have agency-wide applications.**
- X While supporting efforts towards a unified approach to risk assessment for cancer and noncancer endpoints based on the benchmark dose, the SVT strongly cautions against the use of this initiative to hinder efforts to gain greater understanding of low dose risks using the best possible scientific information. The simplified procedures based on the benchmark dose should be viewed as procedures to be used when data are inadequate to permit a comprehensive biologically based assessment of risk. Similarly, this work should not preclude efforts to better characterize uncertainty in estimates of risk.**

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TAB F

Progress Estrogen Knowledge Base

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April 20, 1998

Dr. Marion W. Anders
Chair, NCTR Science Advisory Board
Professor & Chairman
University of Rochester
Department of Pharmacology
601 Elmwood Avenue
Rochester, New York 14642

Dear Drag,

Enclosed is a summary from Dr. Dan Sheehan of progress on the estrogen knowledge base since the review by the SAB. Clearly there has been progress, but not uniformly on all fronts. For example, the inability to use a large body of RBA data from another government lab (because of an unexpected problem with accuracy) is a setback. Receipt of money through the CRADA was slower than we expected, delaying the purchase of programs. Despite these problems, progress has been made as outlined by Dan.

There is one point in particular that I would like to discuss at the SAB meeting on May 6th. We are negotiating with EPA to receive the data from the validation phase of the EDSTAC testing program. We want to get these data but expected to get them later to help build the model. Resources will be needed whether we get the data now or later, but the real question is the impact of diverting resources now to receive the data that would otherwise be invested to continue model development so that we can use the data. I'm quite sure the most efficient way for the federal government is for us to get the data now and prevent duplication of effort by the EPA. I look forward to input from you and the rest of the SAB.

Sincerely,



B. A. Schwetz, D.V.M., Ph.D.
Director, NCTR, and
Interim Chief Scientist, FDA

Enclosure

cc: Ron Coene

RECENT ACTIVITY IN THE ESTROGEN KNOWLEDGE BASE PROGRAM

Daniel M. Sheehan
April 22, 1998

There were four major areas that the SAB commented on in their report. The presentation will be organized around these areas, and be followed by a look at the future and a summary of NCTR and outside funding to date.

Develop and populate the database

While incomplete, the code writing for the database is highly advanced. The code writing continues. The contract staff with expertise to support this effort have been asked to divide their time to address several sensitive and/or time critical projects not connected to the EKB which extended our deadline for this portion of the project. We have identified several collaborators and customers who await the completion of the database. Our need and applications for the database have already been described. Additionally, the EPA wants to use it for storage of data and references both for the Validation and Standardization phase and the actual screening and testing phases of the EDSTAC process. We are engaged in detailed conversations with them regarding their needs and will develop an IAG or MOU. In return for providing them the database, they will populate it with citations and old and new data. We have also joined a new consortium that seeks to organize an international toxicology database with limited access. Of the 10 presentations, the databases presented by Roger Perkins and Ed Thompson (P&G) were technically the highest state-of-the-art and both compatible and complementary. In collaboration with Ed Thompson, we seek to merge the databases and present it to the consortium as the prototype. We would get credits for use of the completed database, and hopefully some development money to help finish or customize the database. From the start, the database was designed to be extensible to many other purposes. One such purpose being explored currently is for a FDA project (see below).

Identify the users

We have identified four possible users of our technology. This was done by personal contact, and by participating in the FDA Science Forum and the FDA Endocrine Disruptor Committee. CDRH and CFSAN are interested in collaborating in a pharmacokinetic study of bisphenol A, which will get us started on filling the PBPK tier. Angelo Turturro wants to use our ER computational models for a regulatory investigation. CDER has provided us with a disc containing 11,000 chemical structures of drugs and other ingredients. We will search the database with HQSAR (see below) for chemicals predicted to bind to the ER. A retrospective project (CDER, NCTR, and OWH) to analyze the predictability of animal data for human outcomes will use the database we are developing. Additionally, EPA will make extensive use of this database for EDSTAC. Several barriers have impeded the ability to identify users. Because the CMA CRADA money didn't arrive until mid-March, the hardware and software have just been ordered, which has dramatically slowed model development. Likewise, we had planned to assay 50 chemicals for their RBA; we now need to assay 150 (100 active for QSAR plus 50 inactive, which when combined with the 100 will be used for classification models) because we determined, via personal communication, that the published data set we were going to use was compromised. Finally, to identify users more efficiently, we need to be able to show them what we have done and what we can do. We wish to make our capabilities known electronically, but this requires an Internet site, and FDA firewall issues have not allowed our Web site to be made available. We wish to put our models, developed with ER data generated at NCTR, on the Web site.

Develop other models

From the beginning, one of our objectives was to explore a variety of modeling software for use in predictive models. While our publications reflect our initial work with CoMFA and CODESSA codes, we have also explored classification models, artificial neural networks, and others. We plan to use the 50 inactive chemicals in the ER assay to provide data for this category of activity in classification models; the other 100 active chemicals will provide other categories of activity. Leming Shi has written a 50 page

feasibility and strategy document on classification models. Use of data from other models is critical for modeling, but the data quality and the structures of the chemicals for which data are available are significant limitations. Five usable published data sets which had some chemicals in common were used to compare the predictability between three different, commonly used assays for chemicals which bind to the ER (competitive binding assay; reporter gene assay; MCF-7 cell proliferation assay). Although as the biological complexity of the system increased there was increasing error in predicting activity from a competitive binding assay, reasonable predictivity was found. The error was associated primarily with two chemical classes: the antiestrogens and chlorinated chemicals, the first of which is known for partial agonist activities. These results demonstrate the utility of data mining techniques for discovering clues regarding mechanisms of action. An HQSAR model has been developed which predicts RBA's about 1,000 times faster than current models, and can thus be used for screening of large chemical data bases.

Focus on the bottom tiers

A revised EKB schematic is found in Fig.1. It should be clear from the foregoing that we are focused on the bottom tiers, but not exclusively so. In the lab, we have worked on the competitive binding assays for ER, AFP, and TEBG while conducting *in vivo* assays on methoxychlor and genistein. We have data suggesting in two cases that knowledge of the RBA's for AFP (a serum estrogen binder) and ER allows prediction of *in vivo* potency. Data collection is ongoing in all these areas. We are not using reporter gene nor cell proliferation assays, but as shown above, we are using results from published assays in data mining model development. Data from pharmaceutical companies and other corporate sources is essentially not available, and if work were done on such data sets, we could not publish the results. Furthermore, little data on lower affinity chemicals is available from these sources. Most of the pharmaceutical data is for high affinity chemicals, as the purpose of drug development for hormones is to obtain the highest potency chemical possible. We have used the few published robust data sets in an effective manner, e.g., the Kuiper data set on ER- β . We will receive from another government agency substantial data sets with the correct type and number of chemicals necessary for us to develop a variety of models. Additionally, we have just finished competitive binding assays with over two dozen phytoestrogens and this data set is being explored for use in QSAR models.

The future

We hope to be able to finish the database in about 6 months, assuming ROW personnel are available, and to be populating it with literature data being collected now by the EPA. New data from the EDSTAC will be entered as it is received. Once up, literature and data which we recover, as well as our publications and data sets will also be put on the site. Also, we hope to get the firewall issue resolved, so the Web site can be put on line. We expect that this will not only provide important publicity for NCTR, but also lead to other opportunities. Additionally, we will contact reviewers and scientists at the Product Centers and arrange meetings to demonstrate what the EKB can provide them. In presenting the EKB to the FDA Centers, it will be important to emphasize that the EKB is a prototype, and represents a new kind of tool. This is as important a message to get out to the reviewers as the type of specific help the EKB can bring to the reviewers.

We hope to obtain funding for finishing the database from EPA in the near future, and possibly from the database consortium. It is important to recognize this as an NCTR database that is extensible to other applications. The time spent by ROW personnel developing the database, and the outside funding obtained to support virtually all the software and hardware purchases, is an investment in a broad capability that can be used in a variety of ways.

With the Web site up, we expect all FDA employees to have access to our work. A FDA-wide announcement regarding our Web site and its contents appears to be the most efficient way to identify customers, along with the meetings with FDA personnel mentioned above.

Development of classification models will continue, and Leming Shi has been assigned this as a primary area for research. In addition, given the success of our data mining exercise, we expect to conduct further work in this area. Finally, QSAR, classification, and other models will be further developed. These will be compared against each other and also evaluated in combination.

We will continue to work in the bottom tiers, and will apply data from these studies to predict *in vivo* potency. It is clear that we need PBPK and Receptor-Based-Pharmacodynamic-Models to obtain reliable predictions, and we need to develop an organized approach to doing so that includes funding considerations, collaborations, and NCTR expertise. Likewise, for these models to be of use, we must derive general dose-response mathematical models (nonmonotonic, threshold, and nonthreshold) that can be customized for specific applications.

The budget

The budget from the inception of the EKB is shown in Table 1. Note that two-thirds of the money has come from outside resources, and that this has been used to purchase virtually all the hardware and software which now belongs to NCTR. This infrastructure will be used to support other projects. The other one-third has come from NCTR via contract funding, and is a modest amount when compared to many other NCTR projects.

Additionally, we expect to hear soon from the Burroughs-Wellcome fund whether we will be selected to write a full proposal for up to \$500,000 per year for up to five years. As mentioned previously, we expect some funding from EPA, and funding is also possible via the International Toxicology Database Consortium.

Publications

Tong, W., Perkins, R., Xing, L., Welsh, W.J., and Sheehan, D.M. QSAR models for estrogen binding to alpha and beta estrogen receptors. *Endocrinol*, 138:4022-4025, 1997.

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Sheehan, D.M., and vom Saal, F.S. Low dose effects of endocrine disruptors- a challenge for risk assessment. *Risk Policy Report*, 31-39, issue of Sept. 19, 1997.

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Dickerson, R.L., Brouwer, A., Gray, L.E., Grothe, D.R., Peterson, R.E., Sheehan, D.M., Sills, C., and Wiedow, M.A. Dose-response relationships. *Principles and Processes for Evaluating Endocrine Disruption in Wildlife*. In press, 1998.

Tong, W., Lewis, D. R., Perkins, R., Chen, Y., Welsh, W. J., Goddette, D. W., Heritage, T. W., and Sheehan, D. M. Evaluation of QSAR methods for large scale prediction of estrogenic compounds. *Journal of Chemical Information and Computer Sciences*. In press, 1998.

Sheehan, D.M., Willingham, E., Gaylor, D., Bergeron, J.M., and Crews, D. No threshold dose for estradiol-induced sex reversal of turtle embryos: How little is too much? Submitted *Environmental Health Perspectives*.

Fang, H., Tong, W., Perkins, R., and Sheehan, D.M. Quantitative comparison of *in vitro* assays for estrogen receptor-ligand binding. In preparation, *Environmental Health Perspectives*.

TABLE 1

EKB EXTERNAL FUNDING

<u>SOURCE</u>	<u>AMOUNT</u>
OWH (experimental; split with U Mo, Columbia)	\$ 185,000
OWH (computational; two grants)	\$ 325,000
CMA CRADA	\$ 300,000
EPA grant (U Mo, St. Louis)	<u>\$ 425,000</u>
Total	\$1,235,000

ROW CONTRACT LABOR & ODC FOR EKB

<u>GFY</u>	<u>HOURS</u>	<u>AMOUNT</u>
95	322	\$ 15,500
96	2,169	\$ 95,400
97	8,818	\$ 371,000
98	2,810	<u>\$ 113,300</u>
Totals	14,119	\$ 595,200

TAB G

Letter to Dr. Schwetz from Dr. Anders

UNIVERSITY OF
ROCHESTER
MEDICAL CENTER

SCHOOL OF MEDICINE AND DENTISTRY
DEPARTMENT OF PHARMACOLOGY AND PHYSIOLOGY

Rec'd 6/16/98/w

M. W. Anders, D.V.M., Ph.D.
Lewis Pratt Ross Professor and Chairman

June 8, 1998

Bernard A. Schwetz, D.V.M., Ph.D.
Director
National Center for Toxicological Research
HFT-1, 3900 NCTR Road
Jefferson, AR 72079-9502

Dear Bern:

At the 6-7 May 1998 meeting of the Science Advisory Board, we discussed issues relating to collaborative interactions between the Center and the Agency and the relationship of the research activities of the Center to the priorities of the Agency. Accordingly, the SAB approved these two recommendations:

"The Scientific Advisory Board of the National Center for Toxicological Research finds that some research programs of the NCTR would benefit from collaborative interactions with other centers in the Agency and that such interactions would exploit the scientific talent that is broadly present in the Agency. The Board also finds that mechanisms to support intercenter research projects are apparently lacking. Accordingly, the Board recommends that the Agency's Office of Science consider development of a funding mechanism for meritorious, intercenter research projects that support the mission of the Agency. The Board also recommends that the funding be peer-reviewed, limited in duration, and nonrenewable and be targeted at projects that are timely and important to Agency-wide research and regulatory activities."

"The Scientific Advisory Board of the National Center for Toxicological Research finds that although the research activities of the Center are supportive of its mission it is difficult to determine their relevance to the research priorities of the Food and Drug Administration. The Board also finds that a mechanism for setting Agency-wide research priorities is apparently lacking. Accordingly, the Board recommends that the Agency consider the development of Agency-wide research priorities. Research priorities should be developed with cognizance of the importance of collaborative research in helping the Agency fulfill its mission."

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Bernard A. Schwetz, D.V.M., Ph.D.
June 8, 1998
Page 2

The SAB would be pleased to discuss these recommendations with you and your colleagues.

Sincerely,



M. W. Anders, D.V.M., Ph.D.

MWA:sem
pc: Science Advisory Board