

Science Board Sub-Committee Review of the National Center for Toxicological Research (NCTR) – May 2008

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The Science Board's National Center for Toxicological Research (NCTR) review Sub-Committee was asked to review the coordination between the NCTR and Food and Drug Administration (FDA) Product Centers with regards to the prioritization of joint projects and the utilization of resources. In preparation for this report the subcommittee met with NCTR senior scientists at their facility in Jefferson, AR on March 12, 2008. The subcommittee also met with senior staff from each of FDA Product Centers, including the Office of Regulatory Affairs (ORA), at agency headquarters in Rockville, MD on April 3, 2008.

These meetings with NCTR scientists and FDA Product Center senior scientific staff led to several observations:

- NCTR is a well run organization with unique scientific expertise that is committed to supporting FDA Product Centers and their regulatory roles. In contrast to the FDA Product Centers which are organized by product type for regulatory purposes, the central purpose of NCTR is science.
- FDA Center staff makes extraordinary efforts to fulfill their public health missions with less than adequate appropriations.
- NCTR and FDA scientists expressed the need to increase the opportunities for communication, both through IT (information technology) and direct contact, at all locations within the FDA. The postponement of the Science Forum program for budgetary reasons is viewed as a negative for scientific communication and interactions between scientists. A series of smaller science symposia known as the FDA Science Symposium Series have taken place that brings together FDA staff on specific topics that have public health importance in lieu of the larger Science Forum.
- A number of joint projects between NCTR and FDA Product Centers originate from direct scientist-to-scientist collaborations. This could be viewed positively and encouraged as scientific progress has a history of individual creativity and serendipity.
- Communication between NCTR and FDA Product Centers has improved with the addition of an experienced NCTR staff member stationed full time at agency headquarters.
- ✚ The Sub-Committee noted that special interest legislation, legislative micromanagement, earmarks and pressure from influential issue advocacy organizations may have negative effects on the prioritization of research projects within the NCTR and other Centers. The highest priority projects within a Center, or multiple Centers, can be affected negatively when the response to other interests take precedence. The Sub-Committee noted this in its visit to NCTR that specific resources had been

assigned to a project that had not prioritized or approved. From reviews of other Centers, it was clear that this is not confined to NCTR. The Executive Committee [described below] would have the accountability for determining the relative priority of unfunded special projects with respect to the FDA budget with the science of the special projects reviewed at the appropriate Center levels.

During this review it became clear that because each FDA Center regulates widely divergent products under unique legal and regulatory requirements that coordination with NCTR and across the agency will require an innovative approach to prioritization and coordination of scientific resources.

At this time the NCTR is one of three offices that falls under the agency's Office of Scientific & Medical Programs (OSMP) within the Office of the Commissioner. The OSMP reports directly to the Commissioner. The federal official designated to head OSMP is The Deputy Commissioner, Chief Medical Officer a position that is now vacant with the appointment of Janet Woodcock, M.D. to the position of Director, Center for Drug Evaluation and Research (CDER).

FDA Commissioner von Eschenbach, M.D. announced on April 9, 2008 the appointment of Frank M. Torti, M.D., M.P.H. as the FDA's Principal Deputy Commissioner and FDA's first Chief Scientist. The newly created Chief Scientist position stems from the Food and Drug Administration Amendments Act of 2007. NCTR will be reporting to the Principal Deputy of the Chief Scientist.

The Chief Scientist as a member of the agency's senior leadership team (see Recommendations), Dr. Torti will support the launch of the FDA Fellowship Program, which has the potential to attract up to 2,000 professionals of varying disciplines for a two year training program. As well, the new office will work to ensure the quality and regulatory focus of the intramural research programs of the agency, and place special emphasis on the importance of clinical research trials that are a part of the foundation of the FDA's regulatory structure.

DECEMBER 2007 REVIEW of the NATIONAL CENTER for TOXICOLOGICAL RESEARCH (NCTR)

The Science Board Subcommittee on Science and Technology previously reviewed the NCTR in its December 2007 report "FDA Science and Mission at Risk." The complete findings of this review can be found in Appendix G of the Science Board's report. The two members of the original NCTR review subcommittee were in agreement on how best to address the issues associated with NCTR. There appears to have been a disagreement between the subcommittee members and the review writers who apparently injected a recommendation to close NCTR. This recommendation was never presented to

the Sub-Committee members. The current Sub-Committee is in agreement with the original recommendations and mirror the original review.

The five findings of the December 2007 review as listed in Appendix G of “FDA Science and Mission at Risk” are presented in apposition with the findings of this subcommittee.

Finding 1 – December 2007 Report:

- Despite efforts to better integrate NCTR’s programs with those of other Centers with the Agency, geography/distance continues to be an issue.

May 2008 Finding: This subcommittee did focus on geography as a potential impediment to communications between NCTR and FDA. Staff that was interviewed expressed the opinion that communication could be accomplished with improved IT capabilities, increased travel budgets, and increased opportunity for knowledge sharing through programs such as the agency’s Science Forum and the Science Symposium Series.

Finding 2 – December 2007 Report:

- The NCTR submitted suggestions to the Subcommittee for a means of establishing an Agency-wide process for prioritizing research that is used by NCTR with the other FDA Product Centers in leveraging resources from NIEHS [National Institute of Environmental Health Sciences] to conduct safety and toxicity assessment of FDA nominated compounds to address specific regulatory issues.

May 2008 Finding: A recurring theme repeated throughout this review from both NCTR and FDA scientists is the need for better methods to prioritize not only FDA nominated compounds for National Toxicology Review (NTP) but critical science issues agency wide. As we understand the complex processes within the agency, there appears to be a number of formal and informal systems (ad hoc) to determine the prioritization of projects. These systems appear to be working. Our impression is that a more centralized final decision making process would be more efficient and would reduce the duplication of expensive technology.

Finding 3 – December 2007 Report:

- Safety Pharmacology studies at NCTR need to be expanded. An agreed upon priority setting process for all research in the Agency and increased funding for research is needed.

May 2008 Finding: As noted in the December 2007 review, the agency must undertake the steps necessary to create a better priority setting system.

Finding 4 – December 2007 Report:

- Priority-setting within NCTR must be coordinated and compatible with the processes used in other Centers within the Agency. This is an Agency issue. NCTR developed a strategic plan (2007-2011) that was vetted with the other centers to get agreement before it was issued in January 2007.

May 2008 Finding: The FDA Product Centers are very supportive of the role that NCTR has played, or is now playing, in their regulatory missions. There is still a need for the agency to directly address the issue of priority setting.

Finding 5 – December 2007 Report:

- The NCTR must be more supportive in assisting/supporting the programmatic needs of CDER, CFSAN, CVM and other Centers.

May 2008 Finding: As stated above the FDA Product Centers are supportive of the role that NCTR has played, or is now playing, to meet their regulatory missions. Both NCTR and FDA recognize that more resources are needed to address this issue.

Additional Findings from the May 2008 NCTR Review.

- Both NCTR and other FDA scientists recognize the importance that IT can play in the collaborative process. In addition, both groups acknowledge the importance of face-to-face contact such that occurs at meetings and symposia in the scientific process.
- Several of the Centers are engaged in projects that appear to have originated from Congress, either as ear marks or legislation, issue advocacy groups, or pressure from individual members of Congress. The December 2007 Report noted Congressional earmark programs without giving details. The question must be raised as to the extent that politics and special interests have influenced project prioritization across the agency.

Recommendations from the December 2007 Report

The following are the four recommendations made in the December 2007 reports as they appear in Appendix G of "FDA Science and Mission at Risk."

- Enhance the incorporation of safety pharmacology in the NCTR's mission.

- An FDA priority setting process, such as the one currently used by NCTR in conjunction with the NIEHS/NTP program should be applied and coordinated across the Agency.
- NCTR is applauded for collaborative research that leverages funding from other agencies to support Agency regulatory need.
- Since the NCTR has a non-regulatory charter, the staff can focus on integrated research across program disciplines that provide identification of biomarkers of toxicity, development of new technologies to facilitate review, and new methods development and validation.

Recommendations of the May 2008 Science Board Subcommittee Review of the NCTR

1. There was a great deal of positive evidence from NCTR and the FDA Product Centers that the NCTR provides a valuable and integrated resource for a wide variety of collaborative projects that are directly related to the regulatory functions of the collaborating Centers.
2. Physical distance is not a barrier to collaborations, but is characterized by the same functional differences that occur between laboratories two floors away, or two buildings away. Due to chronic budgetary inadequacy, this “distance” has been magnified by the increasingly difficult travel budgets for science, as well as the antiquated IT capabilities for efficient and effective functioning between Centers. The Sub-Committee recommends:
 - a. In agreement with the major recommendation of the Sub-Committee for the “FDA Science and Mission at Risk” Report, we strongly urge the creation of modern IT and communication systems to increase efficiency and capabilities between Centers and enhance familiarity with the expertise and interests within the Agency. Many current collaborations have been based on the chance of “knowing someone who has the technological capability at hand,” rather than exposing and harnessing the total capabilities within the organization to enhance the knowledge base and thus the agency’s regulatory mission.
 - i. Two very important capabilities have been damaged by the lack of relatively minor budgetary needs. The first of these was the postponement of the very successful FDA Science Forum that was held annually in Washington, DC, and offered a pan-FDA scientific and integration opportunity valued independently by all the Centers who met with the Sub-Committee. The second was the lack of project-related

travel budgets so that those accountabilities that require face to face interaction for maximal efficacy can continue. Both of these issues could be solved by a sufficient budget that is flexible and administered centrally [to be discussed below].

- ii. It is clear that the IT systems for effective interactions would benefit cross-Agency communications. IT recommendations have been described in the “FDA Science and Mission at Risk” report and are enthusiastically supported by this Sub-Committee.
 - iii. Large corporations with worldwide operations are using IT technology to enhance communications and allow staff to efficiently identify experts and colleagues with shared interests. For example, General Electric has linked their ~350,000 employees into ~50,000 communities of practice using commercially software called SourceCentral. We recommend using similar IT technology to improve Agency-wide communications for better utilization of resources.
 - iv. Center staff indicated that databases of scientific projects were being developed in some Centers. There is also an agency wide database under development with the official title of “FDA Research Database” with the goal of sharing information throughout the organization. These IT initiatives should be encouraged and their availability should be adequately funded.
- b. The communication and structure of Science at the FDA needs an effective central structure to enhance the interaction between the Centers and the senior FDA administrators. This will provide needed high level prioritization between Centers to avoid unnecessary duplication of capabilities and resources and enhance the clear necessity for effective inter-Center interactions.
 - c. These recommendations were made in the “FDA Science and Mission at Risk” report and will be expanded upon below.

Supplemental Comments for Informational Purposes Only

- 3. The prioritization of projects and the collaborative sharing of technical expertise amongst a large number of defined customers or clients in large organizations have been accomplished in many ways in the private sector. The Sub-Committee strongly recommends the creation of an Executive Team that is directly accountable to the Commissioner. The Executive Team would include Center leadership other functional elements within

the agency such as IT and food safety and drug safety. Some Centers have developed their own effective prioritization structures, generally with intra-Center accountabilities, but the cohesive leadership of accountable individuals structured for communication and integration across the Agency must be clear. The organization chart of the FDA at the Commissioner's Office level shows a reporting structure that illustrates the difficulties in managing a large organization. The Commissioner is a political appointment with overall accountability, but the mission of the FDA in food safety, drug safety, and hundreds of other legal mandates must be managed in an efficient way in the day to day functioning of the agency.

- a. The "FDA Science and Mission at Risk" report recommended that the position of Chief Scientific Officer created. We fully concur with this recommendation.
- b. In the course of our review Commissioner von Eschenbach announced the appointment of the Agency's first Chief Scientist as mentioned above. Because this is a new position we are unsure of the responsibilities of this position within the reporting structure of the Office of the Commissioner. The function of the Chief Scientist Science Director and the Executive Committee are described in greater detail below.
- c. Comments earlier in this review alluded to the potential influence of politics into the prioritization of science within the FDA. The politicalization of the agency has contributed to a loss in public confidence in the agency's ability to fulfill its public health mission. We suggest that the position of Chief Scientist not be a political appointment and that this position be filled from the ranks of senior FDA career scientists.

Overview of Recommended Functions of the Chief Scientist and the Executive Committee

- The Chief Scientist reports directly to the Commissioner.
- The Chief Scientist should be Chair, or Co-Chair of an Executive Committee that has accountability for the prioritization of projects across the Centers, including NCTR and the FDA Product Centers.
- The "FDA Science and Mission at Risk" review recommended that Deputy Director for Science be created within each Center. These Deputy Directors would have reporting responsibilities to their respective Center.

Directors and to the Chief Scientist. It is suggested that these Deputy Directors represent their Centers on the Executive Committee.

- The Deputy Directors for Science would be responsible for organizing and managing science within their Centers consistent with Agency science priorities and Center needs. These individuals should have the vision necessary to direct a highly skilled team of researchers, clinicians, support staff and trainees, creating and delivering a wide-ranging program of fundamental, enabling, and translational applied research within the mission of FDA. These individuals also should be experienced research group leaders with an established track record of accomplishments in “cutting-edge” science relevant to their Center and commitment to the collaborative ethos that underpins effective multidisciplinary research activities.
- The current system provides opportunities for priorities to be set within a Center, and each Center has evolved its own method of setting these priorities. We would strongly suggest the Executive Committee mentioned above have accountability for the allocation of the FDA budget. The Executive Committee would provide the overall operating direction for the Centers, the interactions and synergies between the Centers, and the interactions of the FDA with other federal agencies. The Center Directors have filled the void with internal prioritization procedures, but have not been able to coordinate cross-Center prioritization adequately. This situation could be blamed on the chronic shortage of resources and budget, but the FDA needs to be structure to efficiently, effectively and transparently manage an adequate budget.
- During this review there were numerous examples of NCTR cooperating with other Agencies with regard to responses to serious threats, particularly in the areas of food safety and drug safety. Emergency situations are handled with great expertise, skill and involvement, although sometimes at a serious costs to other capabilities. The occurrence of two or more food emergencies simultaneously could seriously impact abilities to respond to either and certainly would impact on-going support of important, non-emergency high priority projects and activities. This becomes even more critical when there is no budgetary relief with which to manage the interplay between Centers. The effect on each may be variable but still affects each Center’s ability to prioritize the most important parts of their portfolios. A structural and clearly accountable Executive Committee could address these issues of effectiveness and efficiency across the whole Agency.
- This Executive Committee would meet with the Center Directors periodically in person or by video conferencing to determine priorities within the scope of the FDA’s mission. Interactions between Center

Directors, as well as specific inter-Center collaborations and consultations, would be enhanced by having a framework of accountable leadership who would be available for immediate direction and integration, as new and challenging problems arose.

- The Commissioner has the final accountability for the function of the FDA but clearly needs to efficiently delegate accountabilities in a structure that provides communication, discussion and transparency. The Commissioner would Chair the Executive Committee maintaining ultimate accountability but would have an operational team for discussion, prioritization, and implementation. The current Associate and Assistant Commissioners could be incorporated into appropriate Center or Executive structures, rather than remaining somewhat independent.