# Nonclinical Studies Subcommittee
# Advisory Committee on Pharmaceutical Science

## Discussion Document on Subcommittee Oversight

September 9, 2002 Meeting

**Recommendation:** The FDA is proposing that oversight of the Nonclinical Subcommittee (NCSS) of the Advisory Committee for Pharmaceutical Science (ACPS) be transferred to the National Center for Toxicological Research (NCTR) Science Advisory Board, with maintenance of a strong linkage to the Advisory Committee for Pharmaceutical Science through a liaison member.

**Background:** The Nonclinical Studies Subcommittee (NCSS) was formed in September 1999, under the oversight of the Advisory Committee for Pharmaceutical Science (ACPS), to identify scientific opportunities to improve nonclinical pharmaceutical development practices and to facilitate collaborative research approaches between FDA and its external constituencies to develop the information necessary to bring these opportunities into practice. The rationale for this subcommittee is based on the belief that collaborative approaches to new scientific opportunities are the most efficient way to improve product development and regulatory practice. It has become apparent that the most prudent approach within the FDA advisory committee structure is to separate the research oversight function from advisory functions directed at regulatory policy. NCTR is positioned better to provide support for research oversight while CDER is positioned better to implement regulatory changes in pharmaceutical review practices.

**History:** Recognizing the common interest among FDA, industry, government, and the public in advancing the scientific basis of pharmaceutical development and regulation, the NCSS was formed in 1999 to identify those scientific opportunities that could be advanced through collaborative research. In a series of meetings from 1999-2000, the Subcommittee met with invited experts in nonclinical pharmaceutical development to discuss opportunities for improving pharmaceutical practices, and concluded that a major need and opportunity was to establish improved linkage between nonclinical and clinical studies through utilization of better "accessible" biomarkers of adverse effect. Non-invasive imaging approaches were recognized as a means to bring monitoring of these biomarkers into more widespread clinical practice.

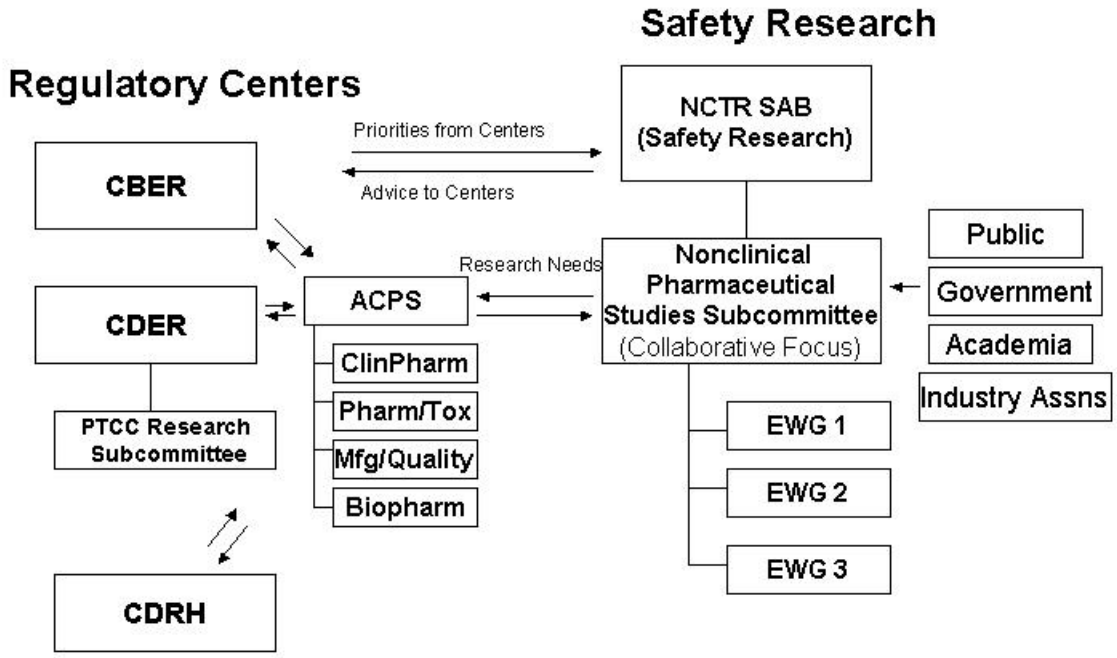
Two specific needs were selected for initial focus through discussions of the committee and with input from the Center for Drug Evaluation and Research (CDER) Pharmacology and Toxicology Coordinating Committee's (PTCC's) Subcommittee on Research. These two initial priorities are the needs for better biomarkers of 1) cardiac damage, and 2) vascular damage. Two Expert Working Groups (EWGs) were established in 2001 through solicitation of nominations through the Federal Register,

professional societies, the NCSS, the FDA, and other sources, and were charged to define the current status and to identify opportunities to improve current approaches for identifying and monitoring these two toxicities. These two EWGs are currently executing this charge.

**Rationale:** The Subcommittee has decided to place its major focus on biomarkers of toxicity. As the activities of the Subcommittee expand through collaborations and the formation of additional EWGs, the support of a center with sufficient resources and an advisory committee structure focused on this disciplinary area will be required. The FDA Center with principal research responsibility for toxicology research is the National Center for Toxicological Research (NCTR). The membership of the NCTR SAB consists of recognized experts with extensive experience in toxicology research and safety evaluation. The multi-disciplinary ACPS, administered by CDER, is reorganizing its disciplinary focus to include four disciplines that will focus on advising change in regulatory practice and policy aspects of clinical pharmacology, manufacturing and product quality, microbiology, and pharmacology and toxicology. Moving the oversight of the NCSS, which is charged with proactive research and development of new and improved approaches to safety evaluation, to the NCTR SAB, which is already focused on the research and developmental aspects of toxicological practice, will provide improved support, feedback, and oversight. Maintenance of a strong linkage with the ACPS Pharm/Tox Subcommittee will provide an appropriate multidisciplinary regulatory interface through which the NCSS can receive advice and to which the NCSS can provide research findings that can underpin regulatory recommendations.

**Linkages:** Linkages with other key Advisory and interest groups are necessary for effective operation of the Subcommittee. These groups, and the proposed linkages, are illustrated below.

With input from the product regulatory centers (using appropriate existing committees and organizational structures) and from experts from outside FDA, the NCSS will identify research priorities that: 1) have the potential to improve regulatory practice and pharmaceutical development, 2) are of common interest to FDA, industry, and the public, and 3) that have the potential to be supported jointly by these sectors. Expert working groups will define specific research options in the context of the current state of knowledge and practice. The NCSS will forward recommendations on approaches to the SAB for discussion and endorsement, will serve as a steering committee to collaborative projects undertaken, and will present findings to the SAB. The SAB and NCSS will then present results that can serve as the basis of regulatory changes to the ACPS and the regulatory Centers for evaluation and action.




## Key Linkages and Interactions

To ensure effective linkages with key bodies, the following membership criteria are suggested.

- The Advisory Committee for Pharmaceutical Science
  - It is recommended that NCSS membership include one member of ACPS. This member would provide a direct link with the ACPS, and would be responsible to keep ACPS informed of NCSS activities and to solicit input about these activities from ACPS. Minutes and reports of activities would go to ACPS, and at appropriate times joint meetings may be held to make recommendations and seek advice.
- Pharmaceutical and biotechnology industry organizations, FDA centers, NIH, public and consumer groups
  - Membership on NCSS would continue to include one from PhRMA, one from BIO, one from each involved FDA center, and one consumer representative. EWGs will have liaisons from each involved FDA center. At appropriate times, input will be sought from appropriate Center organizations, such as CDER's PTCC Research Subcommittee. Currently, one NCSS member is Co-Chair of this CDER Subcommittee.
- National and international organizations involved with harmonization of safety assessment practices
  - Responsibility for FDA coordination of the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) and for Safety Testing Guidelines developed by the Organization for Economic Cooperation and Development (OECD) currently resides in the NCTR Washington Office. Executive coordination of the

NCSS and the NCTR SAB would be managed from this same Office and would include the FDA Coordinator for these activities, facilitating communication and coordination of NCSS activities with ICCVAM and OECD. It is anticipated that new methods and approaches that arise from NCSS activities would become part of the ICCVAM and OECD processes.

**Resources for Collaborations:** The FDA will provide the necessary funds and administrative support for meetings of the NCSS and its EWGs; industry members will be expected to provide their own travel funds. Funds for proposed collaborations will be identified through discussions with proposed collaborators and interested institutions, and may include intramural resources of collaborators and extramural funding programs. It is envisioned that resources and funding will come from a variety of sources, depending on the specific goals and existing research programs within the collaborating sectors.

FDA and interested collaborators will be expected to identify current research activities that could be brought together to leverage more effective collaboration and consortium-based approaches. Previous experience has shown that successful funding can be achieved when interested parties are engaged appropriately. Numerous examples exist of collaborations that have arisen from such focused discussions among interested parties, including ongoing research in the two areas of current NCSS focus. A formalized structure of identifying mutual goals and developing consensus on priorities should facilitate this process. The Health and Environmental Sciences Institute (HESI) of the nonprofit International Life Sciences Institute (ILSI) successfully uses a similar mechanism to that proposed here to identify and conduct collaborative research on pharmaceutical development, and FDA has participated in a number of these collaborations. FDA is proposing to identify its own priorities through a similar process, using the established FDA advisory committee system. Longer-term goals may be funded through joint advocacy for public funding from agencies such as FDA or NIH.

Collaborations will use appropriate administrative vehicles such as CRADAs, MTAs, interagency agreements, informal collaborations, and grants or contracts. Expert groups will be asked to identify opportunities for new practices, research needs to bring new findings into regulatory practice, and potential resources appropriate to the specific objectives identified. Once priorities have been identified and consensus on approaches achieved, it would then be the responsibility of the potential collaborators to provide or obtain the resources necessary to achieve the objectives identified.