

The Future of Drug Safety

PHARMACOVIGILANCE

January 26, 2007

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**IOM Committee on the Assessment of the US Drug
Safety System**



Sponsors

The study was commissioned by the FDA and sponsored by:

- FDA
- CMS
- AHRQ
- NIH
- VA



Charge to the Committee

- Examine roles of FDA and other actors in the drug safety system, examine ongoing safety evaluation efforts, evaluate existing tools, organization and operations, and authorities.
- Make recommendations in the areas of organization, legislation, regulation, and resources to improve risk assessment, surveillance, and the safe use of drugs.



The Work of the Committee

- 6 Committee Meetings
- 3 Open, Information-Gathering Meetings
- 1 Workshop
- 3 Commissioned Papers
- 2 Visits to CDER
- >30 interviews with present and past FDA staff, managers and leadership
- Volumes of reading materials, including recent OIG and GAO reports



Some Committee Precepts (I)

- **An agency whose mission is “to promote and protect the health of the public” should not have to beg for resources to do its job.**
- ***The FDA’s credibility is intertwined with that of industry, and a robust drug safety system is in everyone’s best interest.***
- **Safety and efficacy are the Yin and Yang of every drug and are best weighed together over the entire lifecycle of a drug.**



Some Committee Precepts (II)

- *Understanding of a drug's risks and benefits inevitably changes over the drug's lifecycle.*
- **Timely approval and attention to safety can and should become complementary rather than antithetical goals**
- *The timely identification, confirmation, and communication of risks and benefits are the best measure of regulatory success.*



The Vision

A lifecycle approach to drug risk and benefit that engages the participation of all stakeholders:

- **FDA:** Enjoys a culture of safety supported by strong leadership and management; is adequately resourced to deploy state of the art strategies and technologies for active reassessment of risks and benefits over a drug's lifecycle; consistently bases regulatory decisions on rigorous science; encourages debate, teamwork, and scientific curiosity; has regulatory authority that is clear, flexible, and strong both before and after drug approval



The Vision (cont'd.)

- **Industry:** dutifully assesses new information, communicates rapidly to FDA, implements timely the changes intended to strengthen drug safety
- **Providers:** heed FDA communications, are cautious in using new drugs - especially off-label, are aware of industry influence and base therapeutic decisions on scientific evidence, become informed about and communicate to patients the risks and benefits of all proposed drugs



The Vision (concluded)

- **Academe:** contributes expertise, data, tools, and unbiased advice; is transparent in its dealings with FDA and industry
- **Other government agencies:** collaborate with FDA in making health care databases and search tools available for risk and benefit surveillance
- **Patients:** demand reliable and timely information from FDA and providers, become informed about the risks, benefits, uncertainties of proposed drugs



The Report

- Culture, Structure and Management of CDER
- Quality and Quantity of the Science
- Credibility of the Science
- Regulation
- Communication
- Resources



What the Committee Did and Did Not Do

- The committee did *not* attempt to undertake a systematic review of specific drug safety incidents of recent years.
- The committee did attempt to focus on areas of vulnerability in the drug safety system and make recommendations for strengthening them



Vulnerabilities in the Drug Safety System

- Chronic underfunding
- Organizational problems
- Unclear regulatory authority and insufficiently flexible regulatory tools
- Inadequate quantity and quality of postapproval data, inadequate capability to systematically monitor drugs' risks and benefits postmarket



The Recommendations

- A suite of 25 recommendations that aim to provide a cohesive, integrated approach to transforming drug safety:
- 8 directed to Congress
- 3 directed to the Secretary of HHS
- 14 directed to FDA/CDER



Key Messages

Carry the strengths of the preapproval process to the postapproval period

Adopt a lifecycle approach to drug risk and benefit

- In organization and functioning of CDER
- In terms of regulatory authority
- In the quality, quantity, and credibility of the science that underpins regulatory decision-making
- In communication with the public and patients

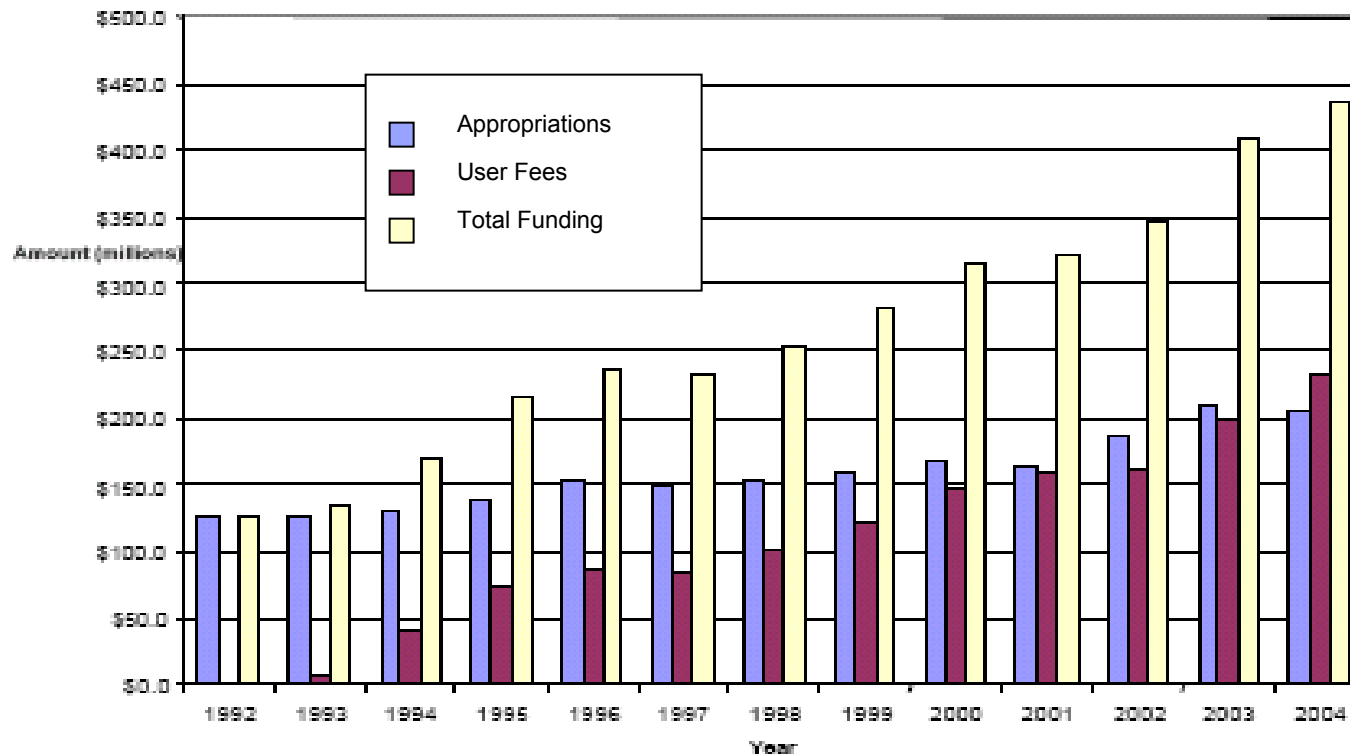


Resources

- Implementing the set of recommendations put forth in *The Future of Drug Safety* will require substantially increased resources.
- The committee strongly favors public funding, i.e., appropriations, but if that is not feasible, restrictions on use of PDUFA funds should be greatly reduced to allow management more flexibility to meet the agency's mission



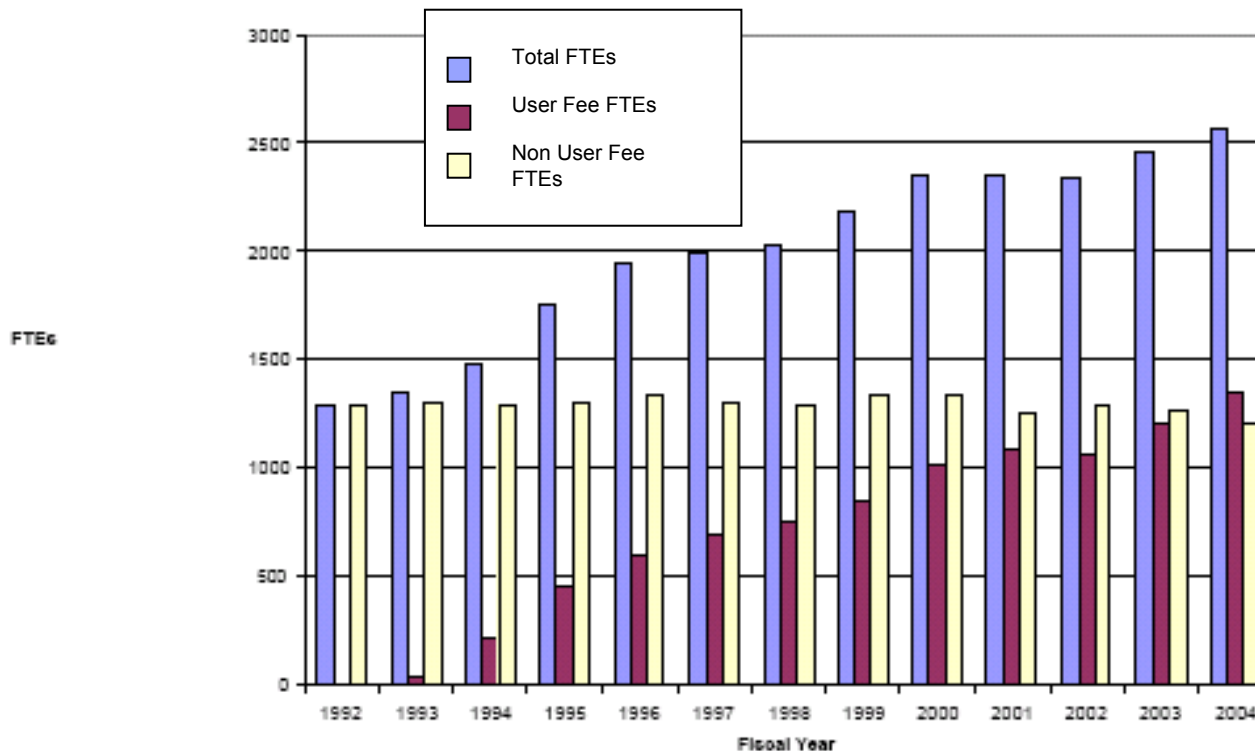
History of CDER Funding



Source: PDUFA White Paper (FDA, 2005, available at <http://www.fda.gov/oc/pdufa/whitepaper11-10/whitepaper11-10.html>). As cited in *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (IOM, 2006).



History of CDER Staffing



Source: PDUFA White Paper (FDA, 2005, available at <http://www.fda.gov/oc/pdufa/whitepaper11-10/whitepaper11-10.html>). As cited in *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (IOM, 2006).



CDER Structure and Organization: Challenges

- A complex, dedicated organization under great and varied external pressures
- Instability of leadership in the Office of the Commissioner does impair agency function
- Imbalance in resources, staffing, capabilities, formal role, and authority between premarket and postmarket offices and functions



CDER Structure and Organization: Challenges

- CDER lacks a systematic approach to identifying possible premarket safety problems and translating them into high-quality postmarket studies.
- Requested postmarket studies are often devised hastily and may be poorly designed or prove to be unfeasible.
- CDER lacks authority to force sponsors to complete their commitments or initiate new studies



CDER Structure and Organization: Recommendations

- A 6-year fixed term Commissioner to stabilize agency leadership, insulate it from some external pressures
- Appointment by DHHS Secretary of external Management Advisory Board to advise FDA Commissioner



CDER Structure and Organization: Recommendations

- A plan and support for cultural change
- Incorporation of safety goals into PDUFA goals letter
- Postmarketing safety staff be integrated into the drug review process and share post approval authority with drug review staff



CDER Structure and Organization: Recommendations

- Incorporating a lifecycle approach to risk and benefit into various aspects of CDER's culture and communicating that fact to all stakeholders could help bring speed and safety into optimal balance.
- Safety and efficacy must always be in balance, and the ideal organizational solution is a team approach to assessing both.



Regulatory Authority: Challenges

- Authority is unclear—interpretations of the statute are subject to “climate change”
- Authority is not sufficiently nuanced—major options are “bully pulpit” or withdrawal, actions dependent on successful negotiations with the sponsor, which may be prolonged



Regulatory Authority: Recommendations

- Congressional clarification of agency's enforcement authority
- Congressional authorization of a flexible and enforceable “tool kit” of regulatory options that may be applied at or after approval, e.g., conditions and restrictions on promotion and distribution, postmarketing studies



Regulatory Authority: Recommendations

- A special symbol on labels and promotional materials to remind providers and inform consumers that a drug is “new” and knowledge about its benefits and risks is limited
- FDA review of accumulated data on safety and effectiveness 5 years after the approval of a new molecular entity



Regulatory Authority: Take Home Message

Approval should not be the “last call” for realistic and effective regulatory action on drug safety.



Communication: Challenges

- Limited public awareness that new drugs carry some uncertainty, and that all drugs have risks and benefits
- Lack of systematic external input on strategies of risk communication to meet the needs of consumers and patients most effectively



Communication: Recommendations

- New FDA advisory committee for consumer and patient communication issues
- A communication plan for the new Office of Drug Safety Policy and Communication to ensure that the most timely and useful information is made available to patients and providers



The Science of Drug Safety: Challenges

- The post approval process suffers generally from inadequate data and informatics resources, and specifically from CDER's limited scientific capabilities and resources, especially in epidemiology and informatics
- Limited role for advisory committees, and lack of assured epidemiology expertise on committees
- Not enough information is made available to the public



The Science of Drug Safety: Postulate

Major components of drug safety assessment:

- Generation of hypotheses from safety signals
- Strengthening of safety signals
- Conduct of confirmatory studies
- Evaluation of risk management programs
- Continuing systematic evaluation of risks and benefits



The Science of Drug Safety: Recommendations

- Improve the utility of the existing Adverse Event Reporting System (AERS)
- Provide the intramural and extramural scientific resources needed to enhance CDER's ability to generate and test drug safety hypotheses



The Science of Drug Safety: The AERS

In 2004 the AERS received 422,889 reports:

- ~21, 500 from individuals
- ~162,000 from manufacturers (expedited)
- ~90,000 from manufacturers (serious)
- ~149,000 from manufacturers (other)



The Science of Drug Safety: Recommendations

- Establish a public-private partnership to prioritize, plan, and organize funding for confirmatory drug safety, efficacy, and effectiveness studies
- Ensure scientifically valid and timely evaluations of Risk Minimization Action Plans



The Science of Drug Safety: Recommendations

- Register at clinicaltrials.gov all Phase 2-4 clinical trials if data are intended to be submitted to the FDA pre- or postmarket
- Post on a government website, such as clinicaltrials.gov, structured field summaries of results of all efficacy and safety studies



The Science of Drug Safety: Recommendations

- Post all NDA and sNDA review packages on FDA website
- CDER should regularly and systematically analyze all postmarket study results and make public their significance for the integration of risk/benefit information



Demonstrate Commitment to Research

- Appoint Chief Scientist in the Office of the Commissioner to oversee the quality and regulatory relevance of intramural and extramural research
- Include research capacity in FDA mission statement, and
- Request and apply resources to support intramural research, as approved by Chief Scientist



The Science of Drug Safety: Recommendations

These Recommendations will require funds for scientific personnel, enhanced informatics capacity, and access to more and better data, as well as for intramural and extramural research aimed at strengthening the science on which FDA's regulatory processes and actions are based.



Advisory Committees

- Regularly include expertise in epidemiology and public health
- Review all New Molecular Entities prior to or shortly after approval



Conflict of Interest on Advisory Committees

- A substantial majority of members (60%) should be free of significant conflicts of interest (as defined in FDA Guidance)
- Waivers should be issued sparingly, and
- FDA should routinely analyze whether voting patterns are influenced by COIs



For More Information

- Report available at www.nap.edu
- Study Web site www.iom.edu/drugsafety
- Email Drugsafety@nas.edu



INSTITUTE OF
MEDICINE

Complete text of
recommendations,
as they appear in the report

Recommendations

- 3.1: The committee recommends that the FDA Commissioner should be appointed for a six-year term of office. The Commissioner should be an individual with appropriate expertise to head a science-based agency, demonstrated capacity to lead and inspire, and a proven commitment to public health, scientific integrity, transparency, communication, and inclusion.
- 3.2: The committee recommends that an external Management Advisory Board be appointed by the Secretary of HHS to advise the FDA Commissioner in shepherding the Center (and the Agency as a whole) to implement and sustain the changes necessary to transform the Agency's/Center's culture—by improving morale and retention of professional staff, strengthening transparency, restoring credibility, and creating a culture of safety based upon a lifecycle approach to risk-benefit.



Recommendations

- 3.3: The committee recommends the Secretary of HHS direct the FDA Commissioner and Director of CDER, with the assistance of the Management Advisory Board, to develop a comprehensive strategy for sustained cultural change that positions the agency to fulfill its mission, including protecting the health of public.
- 3.4: The committee recommends that CDER appoint an ODS/OSE staff member to each NDA review team and assign joint authority to OND and ODS/OSE for post-approval regulatory actions related to safety.
- 3.5: To support appropriate balance between the agency's dual goals of speeding access to innovative drugs and ensuring drug safety over the product's lifecycle, the committee recommends that Congress should introduce specific safety-related performance goals in PDUFA IV in 2007.



Recommendations

- 4.1: The committee recommends that in order to improve the generation of new safety signals and hypotheses, CDER (a) conduct a systematic, scientific review of the AERS system , (b) identify and implement changes in key factors that could lead to a more efficient system, and (c) implement statistical-surveillance methods for the automated generation of new safety signals.
- 4.2: The committee recommends that in order to strengthen and test drug safety hypotheses, CDER should (a) increase their intramural and extramural programs that can access and study data from large automated databases and (b) include in these programs studies on drug utilization patterns and background incidence rates for adverse events of interest, and (c) develop and implement active surveillance for specific drugs.



Recommendations

- 4.3: The committee recommends that the Secretary of HHS, working with the Secretaries of Veterans Affairs and Defense, develop a public-private partnership with drug sponsors, public and private insurers, for profit and not for profit health care provider organizations, consumer groups, and large pharmaceutical companies to prioritize, plan, and organize funding for confirmatory drug safety and efficacy studies of public health importance.
- 4.4: The committee recommends that CDER assure the performance of timely and scientifically-valid evaluations (whether done internally or by industry sponsors) of Risk Minimization Action Plans (RiskMAPs).
- 4.5: The committee recommends that CDER develop and continually improve a systematic approach to risk-benefit analysis for use across the FDA in the pre- and post-approval settings.



Recommendations

- 4.6: The committee recommends that in order to improve the postmarketing assessment of drugs, CDER build internal epidemiologic and informatics capacity.
- 4.7: The committee recommends the Commissioner of FDA demonstrate commitment to building the scientific research capacity of the Agency by:
 - a. Appointing a Chief Scientist in the office of the Commissioner with responsibility for overseeing, coordinating, and ensuring the quality and regulatory focus of the agency's intramural research programs.
 - b. Designating the FDA's Science Board as the extramural advisory committee to the Chief Scientist.
 - c. Including research capacity in the mission statement of the FDA.
 - d. Applying resources for support of intramural research, approved by the Chief Scientist.
 - e. Ensuring that adequate funding to support the intramural research program is requested in FDA's annual budget request to Congress.



Recommendations

- 4.8: The committee recommends that FDA have its advisory committees review all NME either prior to approval or soon after approval to advise in the process of ensuring drug safety and efficacy or managing drug risks.
- 4.9: The committee recommends that all FDA drug product advisory committees, and any other peer review effort such as mentioned above for CDER-reviewed product safety, include a pharmacoepidemiologist or an individual with comparable public health expertise in studying the safety of medical products.
- 4.10: The committee recommends FDA establish a requirement that a substantial majority of the members of each advisory committee be free of significant financial involvement with companies whose interests may be affected by the deliberation of the committee.



Recommendations

- 4.11: To ensure that trial registration is mandatory, systematic, standardized, and complete, and that the registration site is able to accommodate the reporting of trial results, the committee recommends that Congress require industry sponsors to register in a timely manner at clinicaltrials.gov, at a minimum, all Phase 2 through 4 clinical trials, wherever they may have been conducted, if data from the trials are intended to be submitted to the FDA as part of an NDA, sNDA, or to fulfill a postmarket commitment. The committee further recommends that this requirement include the posting of a structured field summary of the efficacy and safety results of the studies.
- 4.12: The committee recommends that FDA post all NDA review packages on the agency's website.
- 4.13: The committee recommends that the CDER review teams regularly and systematically analyze all postmarketing study results and make public their assessment of the significance of the information with regard to the integration of risk and benefit information.



Recommendations

- 5.1 The committee recommends that Congress ensure that the FDA has the ability to require such postmarketing risk assessment and management programs as are needed to monitor and assure safe use of the drug product. These conditions may be imposed both before and after approval of a new drug, new indication, or new dosage, as well as after identification of new contraindications or patterns of adverse events. The limitations imposed should be commensurate with the specific safety concerns and benefits presented by the drug product. The risk assessment and management program may include:
- a) Distribution conditioned on compliance with FDA-initiated changes in drug labels.
 - b) Distribution conditioned on specific warnings to be incorporated into all promotional materials (including broadcast DTC advertising).
 - c) Distribution conditioned on a moratorium on direct to consumer advertising.
 - d) Distribution restricted to certain facilities, pharmacists, or physicians with special training or experience.
 - e) Distribution conditioned on the performance of specified medical procedures.
 - f) Distribution conditioned on the performance of specified additional clinical trials or other studies.
 - g) Distribution conditioned on the maintenance of an active adverse event surveillance system.



Recommendations

- 5.2 The committee recommends that Congress provide oversight and enact any needed legislation to ensure compliance by both FDA and drug sponsors with the provisions listed above. FDA needs increased enforcement authority and better enforcement tools directed at drug sponsors, which should include fines, injunctions, and withdrawal of drug approval.
- 5.3 The committee recommends that Congress amend the FD&C Act to require that product labels carry a special symbol such as the black triangle used in the UK or an equivalent symbol for new drugs, new combinations of active substances, and new delivery systems of existing drugs. FDA should restrict DTCA during the period a product label carries the special symbol.



Recommendations

5.4 The committee recommends that FDA evaluate all new data on new molecular entities no later than 5 years after approval. Sponsors will submit a report of accumulated data relevant to drug safety and efficacy, including any additional data published in a peer reviewed journal, and will report on the status of any applicable conditions imposed on the distribution of the drug called for at or after the time of approval.



Recommendations

- 6.1: The committee recommends that Congress enact legislation establishing a new FDA advisory committee on communication, composed of members who represent consumer and patient perspectives and organizations. The committee will advise CDER and other centers on communication issues related to efficacy, safety, and utilization during the lifecycle of drugs and other medical products, and will support the Centers in their mission to “help the public get the accurate, science-based information they need to use medicines . . . to improve their health.”
- 6.2: The committee recommends that the new Office of Drug Safety Policy and Communication should develop a cohesive risk communication plan that includes, at a minimum, a review of all Center risk communication activities, evaluation and revision of communication tools for clarity and consistency, and priority-setting to ensure efficient use of resources.



Recommendations

7.1 To support improvements in drug safety and efficacy activities over a product's lifecycle, the committee recommends that the Administration should request and Congress should approve substantially increased resources in both funds and personnel for the Food and Drug Administration.

