

The Future of Drug Safety: Recommendations of the IOM

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Current Problems

- *Chronic underfunding*
- *50% user fee-based*
- *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 Report

- *Culture, Structure and Management*
- *Quality and Credibility of the Science*
- *Regulatory Authority*
- *Communication*
- *Resources*



Structure & Organization

- A 6-year fixed Commissioner term [Rec. 3.1]
- Management Advisory Board [Rec. 3.2]
- Integration of postmarketing safety staff into the drug review process [Rec. 3.4]



The Science of Drug Safety

1. Signal Generation

Improve the Adverse Event Reporting System
(AERS) [Rec. 4.1]



The Science of Drug Safety

2. Signal Strengthening and Testing

Resources to generate and test drug safety hypotheses [Rec. 4.2]

- Increase intra- and extramural program that can access data from large and automated data bases
- Incl. drug utilization patterns and background incidence rates for adverse events
- Active surveillance for specific drugs



The Science of Drug Safety

3. Confirmatory Studies

Public-private partnership to prioritize, plan, and organize funding for confirmatory drug safety and efficacy studies [Rec. 4.3]

- *RCTs or high-quality observational studies*



The Science of Drug Safety

\$ 1 million budget for postmarketing safety studies proved insufficient to answer key questions about CV risks associated with ADHD drugs



The Science of Drug Safety

- Scientifically valid and timely evaluations of Risk Minimization Action Plans (RiskMAPs) [Rec. 4.4]
- Enhance internal epidemiologic and informatics capacity [Rec. 4.6]



Science of Drug Safety

- Chief Scientist to oversee intramural and extramural research [Rec. 4.7(a)]
- Majority of advisory committee members free of significant conflicts [Rec. 4.10]
- All Phase 2-4 clinical trials in clinicaltrials.gov [Rec. 4.11]
- CDER should synthesize postmarket study results and explain their significance to the public [Rec. 4.13]



Regulatory Authority

- Flexible and enforceable “tool kit” of post approval regulatory options, e.g., conditions and restrictions on promotion and distribution, and completion of postmarketing study commitments: [Rec. 5.1]
 - Drug labels and warnings
 - DTC advertising
 - Restricted use
 - Performance of studies
 - Active surveillance



Regulatory Authority

- Clarification of enforcement authority [Rec. 5.2]:
 - Fines
 - Injunction
 - Withdrawals
- New drug symbol on labels and promotional materials [Rec. 5.3]
- Restricted initial DTCA [Rec. 5.3]
- 5 year review of accumulated data [Rec. 5.4]



Communication

- Communications advisory committee and plan
[Rec's. 6.1, 6.2]



Resources

- Substantially increased resources. [Rec. 7.1]
 - *Appropriations*
 - *Flexibility in use of PDUFA funds*



Take Home Message

- *FDA the nation’s “trusted intermediary” between the pharmaceutical industry and the end users (physicians, pharmacists, and the patient)*
- *FDA must be in command of all the data, and that data and CDER decisions must be credible*



For More Information

- Report available at www.nap.edu
- Study Web site www.iom.edu/drugsafety



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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.

