Drug Safety and FDA “Revitalization” Legislation

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House and Senate FDA “Revitalization” Bills

- Senate:
  - S. 1082, “Food and Drug Administration Revitalization Act” (FDARA)
  - Passed May 9, 2007 93 – 1

- House:
  - H.R. 2900, “Food and Drug Administration Amendments Act of 2007” (FDAAA)
  - Passed July 11, 2007 403 – 16
Major Components of the Legislation

- The bills would reauthorize laws sunsetting on September 30, 2007:
  - Prescription Drug User Fee Act (PDUFA IV)
  - Medical Device User Fee and Modernization Act (now MDUFA)
  - Pediatric Research Equity Act (PREA)
  - Best Pharmaceuticals for Children Act (BPCA)

- The bills also include new provisions and authorities, including:
  - Drug safety / Risk Evaluation and Mitigation Strategy (REMS) framework
  - Civil penalties
  - Clinical trial registry and results database
  - FDA Advisory Committee conflicts of interest
  - The Reagan-Udall Institute for Applied Biomedical Research
  - Pediatric devices
  - Anti-counterfeiting
  - Antibiotics (Senate)
  - Follow-on biologics “placeholder” (Senate)
PDUFA IV and Drug Safety

- Increases allocation of user fee revenues for drug safety activities by graduated amounts -- a total of $225 million over five years (in the House bill this is reduced if appropriations increase)

- Both bills broaden PDUFA-funded postmarket safety-related activities
  - Strikes PDUFA III three-year restriction on use of fees for postmarket safety activities
  - Fees can be used for:
    - Reviewing safety information on approved drugs, including adverse event reports
    - Developing and using improved data collection systems
    - Developing and using improved analytical tools to assess potential safety problems (including accessing external databases)
Risk Evaluation and Mitigation Strategies (REMS)

- The legislation provides a statutory framework for integrating risk evaluation and mitigation into drug reviews.
  - An evolution from PDUFA III, which provided funding for development of FDA risk-management guidances and review of voluntary risk minimization plans.
  - Many of the risk minimization tools in the legislation are already in use in existing drug approvals (under Subpart H / Risk Minimization Action Plans (RiskMAPs))
REMS Standards

- **House:**

  - A REMS proposal may be required for NDAs, BLAs, ANDAs, and major supplements if, based upon a series of factors, FDA “determines such a strategy is necessary to ensure that the benefits of the drug involved outweigh the risks of the drug.”

  - FDA would consider:
    - A statement by the sponsor stating whether a REMS or postmarket study/trial is needed, and characterizing the patient population, seriousness of the disease, expected benefit, duration of treatment, and seriousness of known or potential adverse events
    - The background incidence in the population likely to use the drug, the availability and safety of a drug or other treatment, if any, for such disease or condition to which the safety the drug may be compared, and whether the drug is a new molecular entity

  - May be required post-approval if based on new safety information
    - Submission within 120 days after notification
REMS Standards

- Senate:
  - An applicant may voluntarily include a proposed REMS “if there is a signal of a serious risk with a drug.”
  - FDA may require a REMS proposal “if based on a signal of a serious risk with a drug, a [REMS] is necessary to assess such signal or mitigate such serious risk.”
REMS Submissions

- Processes for moving existing drugs with distribution or use restrictions (Subpart H) into REMS framework
  - Would be deemed to have REMS, with assessment requirement

- House bill would allow the Secretary to “require the applicant to submit information regarding its marketing plan and practices for the drug” to determine whether such activities could undermine the REMS
  - Does not authorize Secretary to direct any changes to the marketing plan or practices
REMS Requirements: Senate Bill

- The REMS shall include
  - the FDA-approved professional labeling; and
  - a timetable for submission of assessments of the REMS.

- REMS may require
  - post-approval studies;
  - post-approval clinical trials;
  - a Medication Guide or patient package insert;
  - a risk communication plan;
  - pre-review for certain advertisements or specific disclosures in advertisements about serious risks, protocols for use, or date of approval; and
  - use and distribution restrictions.
REMS Requirements: House Bill

- The REMS for a drug or biologic **must** include:
  - a timetable for submission of assessments

- The Secretary **may** require one or more of the following elements:
  - a Medication Guide or patient package insert;
  - a risk communication plan;
  - use and distribution restrictions; and
  - pre-review of advertisements.
Postmarket Study Requirements

- Independent of the REMS framework, the House bill would allow the Secretary to require post-approval studies or trials “if the Secretary becomes aware of new safety information” in order to:
  - Assess a known serious risk related to the use of the drug involved
  - Assess signals of serious risk related to the use of the drug
  - Identify a serious risk
REMS: Use and Distribution Limitations

- Both bills permit FDA to require that a REMS include use and distribution limitations if required for the safe use of the drug
  - This can include training and certification requirements, dispensing in certain settings, documentation of safe use conditions, patient monitoring, registries
- The distribution and use limitations in the REMS must:
  - be commensurate with the specific serious risk listed in the drug’s labeling;
  - not be unduly burdensome on patient access;
  - be posted for public review within 30 days of imposition with an explanation of how the limitations will mitigate the safety risk; and
  - to the extent practicable
    • conform with elements used to assure safe use for other drugs with similar, serious risks; and
    • be compatible with established distribution, procurement, and dispensing systems for drugs.
REMS: Use and Distribution Limitations

- Both bills provide that REMS may include an implementation system that a company can use to
  - “[M]onitor and evaluate implementation” of REMS requirements by physicians, pharmacists, and other health care providers who are responsible for implementing REMS requirements; and
  - “work to improve implementation” of REMS requirements by health care providers.

- The House bill could also require companies to stop distribution of the drug to healthcare providers who fail to adhere to the REMS requirements after notice and opportunity to remedy
REMS Timetables and Dispute Resolution

- The House bill would require submission of REMS assessments annually for the first three years after approval, with an overall assessment at seven years.

- In the Senate bill, reviews would be required at 18 months and three years.

- Both bills include processes/timelines for the resolution of REMS-related disputes, including a review conducted by the Drug Safety Oversight Board (DSOB).
Both bills would require the Secretary, through the Drug Safety and Risk Management Advisory Committee, to evaluate whether various REMS elements:

- assure safe use of a drug;
- limit patient access; or
- place an undue burden on the healthcare system
REMS Enforcement

- Failure to follow a REMS requirement would render a drug misbranded
- Both bills include civil penalties for manufacturer violations of REMS requirements
  - The House bill provides penalties of $250,000 per violation (up to $1 million) in a single proceeding, and for continued violations after the Secretary has provided notice penalties of $10 million per violation (up to $50 million).
  - The Senate bill provides for a penalty of $250,000, doubling every 30 days (up to a $2 million maximum).
Post-Market Surveillance and Assessment

- Both bills provide $25 million for FDA to establish systems for post-marketing “surveillance and assessment” or data mining.
- Both create private-public collaborations to collect and analyze post-market prescription drug data.
  - The Senate bill aims for a public-private partnership in which the agency would pool data from federal and private health databases and hire private research groups to investigate priority safety signals.
  - The House bill would direct FDA to consult with experts to develop methods of integrating and analyzing data from multiple sources and then require it to enter into partnerships to allow the analysis of available data from various sources to support identification of safety signals.
- The bills do not explicitly include manufacturers in these partnerships.
Safety Labeling Changes

- Both bills provide new frameworks for safety-related labeling changes

- Under the Senate bill:
  - A company would notify FDA if it becomes aware of new safety information that it believes should be included in the labeling, and then FDA and the company would enter into discussions in accordance with a specific timeline.
  - If supported by reasonable scientific evidence, the Secretary may request that the company submit a supplemental application.
  - Provides for the resolution of disputes by the DSOB.
  - If the company does not make a ordered labeling change, the drug would be deemed misbranded.
Safety Labeling Changes

- The House bill goes further than the Senate version:
  - Authorizes the Secretary to order safety-related labeling changes based on new safety information
  - Provides timelines for discussions between the company and FDA, and permits accelerated timeline if the Secretary believes the labeling change is “necessary to protect against a serious public health threat.”
  - Explicitly preserves the existing Changes Being Effected (CBE) regulation (i.e., 21 C.F.R. § 314.70)

Impact on preemption of state law failure to warn claims in product liability suits?
Dissemination of Safety Information

The Senate bill would establish, one year after enactment, a website devoted to pharmaceutical data and risk communication that includes:

- Patient labeling and packaging inserts
- Professional labeling
- Medication Guides (where applicable)
- Link to the entry in the new clinical trial registry data bank
- Most recent safety information, alerts, recalls, and warning letters from FDA
- REMS publicly available information
- Guidance documents and regulations related to safety
- Summaries of assessed and aggregated data from the new surveillance system “to provide information of known and serious side-effects”
- Allows patients and others to submit adverse drug event reports
- Information about properly disposing of medications
Dissemination of Safety Information

The House bill would go further, requiring FDA to collect, analyze, and publish an array of “emerging” safety information including:

- A summary analysis of the adverse drug-reaction reports received for recently approved drugs;
- A biweekly report based on a screening of the Adverse Event Reporting System (AERS) database;
- A report to Congress on the Office of Surveillance and Epidemiology recommendations and consultations on post-market safety activities;
- An annual review of the entire backlog of post-market safety commitments to determine which require revision or elimination; and
- The development of “postmarket safety performance measures…as measurable and rigorous as the ones already developed for premarket review.”
DTC Advertising

- The House bill would require that all DTC advertisements to include the statement:
  - “You are encouraged to report adverse effects of prescription drug medication to the FDA. Log onto www.fda.gov/medwatch or call 1-800-FDA-1088”

- Both bills establish civil penalties for “false or misleading” DTC advertisements.
  - House bill: $250,000 to $500,000
  - Senate bill: $150,000 to $300,000
Reagan-Udall Foundation

- Both the House and Senate bills would establish the Reagan-Udall Foundation to lead collaborations amongst FDA, academic research institutions and industry to support FDA’s mission to modernize medical, veterinary, food and cosmetic product development.

- The collaborations would be focused on Critical Path activities, including projects to:
  - bolster R&D productivity;
  - provide new tools for improving safety in regulated product evaluation; and
  - making regulated product development and safety more predictable and manageable.
Reagan-Udall Foundation

- The Foundation would have a Board of Directors with 12 members:
  - 4 from industry;
  - 3 from academic research organizations;
  - 2 from FDA and NIH;
  - 2 from patient advocacy organizations; and
  - 1 representing health care providers.

- The Foundation will be financially supported by industry and donated funds.
  - The Commissioner could transfer between $500,000 and $1.25 million in appropriated funds to the Foundation.
Reagan-Udall Foundation

- The House bill also authorizes the FDA Commissioner to enter into “Critical Path Public-Private Partnerships” to implement the Critical Path Initiative.
  - An eligible entity is defined as an institution of high education, a tax exempt organization.
  - The entity must have experience personnel and clinical expertise and be capable of developing and evaluating methods and processes to increase efficiency of medical product development and more accurately identify the benefits and risks of new and existing medical products.

- The bill would authorize $5 million for FY08 and such sums as necessary for FY09-12.
Office of the Chief Scientist

- The bills would also establish an Office of the Chief Scientist within the FDA Commissioner’s Office
- The Office of the Chief Scientist would:
  - Oversee, coordinate, and ensure quality and regulatory focus of the intramural research programs; and
  - Identify and solicit intramural research proposals across FDA through an advisory board composed of employees and experts in trial design, epidemiology, pharmacovigilance, basic science, and public health.
Anti-Counterfeiting Technology

- Both bills contain provisions relating to the adoption of anti-counterfeiting technology.
- The Senate bill would require:
  - A standardized numerical identifier that is unique to each drug package, harmonized with international consensus standards, and applied at the point of manufacturing and repackaging within 18 months of enactment.
  - For the 50 prescription drugs with the highest US sales, overt optically variable counterfeit-resistant technologies that could be seen with the naked eye, are similar to what is used to secure US currency, are manufactured and distributed in a secure and controlled environment, and include additional nonvisible features (including forensic capability) within 2 ½ years of enactment. The bill would also allow for the use of other technologies with a comparable security function.
- The House bill requires the Secretary to “develop standards and identify and validate effective technologies for the purpose of securing the prescription drug distribution system against counterfeit, diverted, subpotent, substandard, adulterated, misbranded, or expired drugs.”
Clinical Trial Registry and Results Database

- Both bills would require the public registration of clinical trials post-Phase I
- They differ over posting of clinical trial results
  - The House bill would establish a results database within one year of enactment, spelling out specific requirements for the content of results submissions
  - The Senate bill provides for a negotiated rulemaking, with a final rule issued within two and a half years of enactment.
Advisory Committee Conflicts of Interest

- The Senate and House bills would largely codify current FDA practices for granting waivers for advisory committee members with a “financial interest.”
  - “Financial interest” is defined under 18 U.S.C. § 208(a), which prohibits a government employee from participating “personally and substantially” in any “particular matter” in which his/her family has a financial interest.
- The House bill would also limit advisory committee meetings to one financial conflict-of-interest waiver per meeting.
Conclusion

- Drug safety legislation will create important new industry responsibilities and FDA authorities
  - Largely reasonable, but some troubling provisions still need to be worked out
  - Details of regulatory implementation will be critical
- Congress will continue to focus on FDA drug safety and marketing
  - Additional legislation
  - Investigations
- Will the legislation build confidence in FDA and industry?
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