Kay Bailey Hutchison, Chairman
Bill Hughes, Staff Director

347 Russell Senate Office Building
Washington, DC 20510
202-224-2946
http://rpc.senate.gov

SENATE REPUBLICAN POLICY COMMITTEE

Legislative Notice

No. 13 April 30, 2007

S. 1082 – The FDA Revitalization Act

Calendar No. 120

S. 1082 was reported by the Committee on Health, Education, Labor, and Pensions (HELP) on April 24, by a vote of 15-6, with an amendment in the nature of a substitute. No written report.

Noteworthy

- Pursuant to a unanimous consent agreement, the Senate began consideration of S. 1082 on Monday, April 30 for debate only (no roll call votes). The U.C. does not limit time or amendments.

- S. 1082 reauthorizes prescription drug and medical device user fee legislation, reauthorizes two pediatric drug programs, includes expanded drug safety authority for the Food and Drug Administration (FDA), and creates a pediatric medical device improvement act.

- Six of 10 Republicans on the Committee on Health, Education, Labor, and Pensions (HELP) voted against reporting this bill. However, at press time, Committee staffers were working on a managers' amendment that they hoped would address many of these concerns.

- No Statement of Administration Policy has been released, but Health and Human Services Secretary Leavitt sent a letter to Chairman Kennedy on April 17 voicing concerns about the bill, in particular its proposals on expanding FDA's drug risk review and mitigation authorities.

- The House Energy and Commerce Committee has not yet reported an FDA reauthorization bill.

- The programs to be reauthorized will expire at the end of fiscal year 2007.

Background

The Food and Drug Administration Revitalization Act is a combination of six different pieces of prescription drug and medical device legislation. Four are reauthorizations – the Prescription Drug User Fee Act (Title I), the Medical Device User Fee and Modernization Act (Title III), the Best Pharmaceuticals for Children Act (Title IV), and the Pediatric Research Equity Act (Title IV). These acts expire September 30 and are all to be reauthorized for five years.

In addition, the HELP Committee included new drug safety legislation, which expands the authority of the Food and Drug Administration (FDA) to assess and manage drug risks (Title II). There is also new legislation to encourage specialized pediatric medical device development incorporated into Title IV.

Committee Markup

On April 18, the HELP Committee reported S. 1082 by a vote of 15-6. All committee Democrats and Independent Senator Sanders voted in favor of reporting the legislation, joined by Ranking Member Enzi and Republican Senators Hatch, Alexander, and Roberts. Six Republicans voted against reporting the bill: Senators Gregg, Burr, Isakson, Allard, Murkowski, and Coburn.

The Republicans who voted against the bill voiced a number of concerns, primarily about the expanded FDA authorities that some say could serve to slow the approval of safe drugs and could unnecessarily restrict access to medications. Since the bill was reported April 24, the HELP Committee has been working with these Members to address these issues through the expected managers' amendment. These concerns included:

- Senator Gregg, over the proposed FDA standard for whether to apply additional safety requirements to a given drug through Risk Evaluation and Mitigation Systems (REMS) as part of post-approval surveillance, as well as provisions regarding information technology for drug safety;

- Senators Coburn and Murkowski, over the restrictions on distribution and use of given drugs, particularly in regions where health care specialists are unavailable; and

- Senator Allard, over the bill's limitation on pediatric research incentives found in the reauthorization language of the BPCA.

While he supported the bill, Senator Roberts expressed concern over the provision authorizing FDA to ban advertising for a given drug for up to two years; as of publication, this provision is being renegotiated.

The following is a list of all of the committee amendments:

Amendments Adopted or Accepted:

- Senator Coburn's amendment, to subject "medical" marijuana to FDA approval, including a review of its safety and efficacy (11-9).

- Senator Brown's amendment, to require FDA to assist the Federal Trade Commission with an investigation into drugs licensed by brand-name drug companies to compete with generic versions of their products (voice vote).

- Senator Burr's amendment, to set deadlines for negotiations between FDA and drug companies over labeling changes for drugs (voice vote).

Amendments That Failed:

- Senator Gregg's amendment, to limit the expanded FDA drug safety authority provisions in the bill (9-12).

- Senator Roberts's amendment, to strike the provisions giving FDA the authority to delay television ads for newly-approved drugs and to require FDA review of drug advertising (10-11).

- Senator Allard's amendment, to retain the pediatric research incentives in the Best Pharmaceuticals for Children Act (BPCA) (10-11).

- Senator Coburn's amendment, to add specific provisions related to RU-486 (9-12).

- Senator Coburn's amendment, to strike restrictions on the practice of medicine (10-11).

- Senator Gregg's amendment, to provide exclusions from FDA restrictions drugs developed out of the Biomedical Advanced Research and Development Authority (BARDA) and used in the event of a biological attack (9-12).

Amendments Offered and Withdrawn:

- Senator Clinton's amendment, to eliminate the bill's sunset of the Pediatric Data Collection program (section 505B of the Food, Drug and Cosmetic Act).

- Senator Brown's amendment, to place limits on pharmaceutical companies' involvement with citizen petitions against generic drugs.

- Senator Hatch's amendment, to provide additional authorities regarding antibiotics and enantiomers.

- Senator Hatch's amendment, to deal with information being released appropriately.

Bill Provisions

[Based on information provided by the HELP Committee and FDA]

Title I — Prescription Drug User Fees

The Prescription Drug User Fee Act (PDUFA) was passed in 1992 to address the speed and predictability of the review and approval process of new drug applications by FDA. PDUFA has been reauthorized and updated every five years since.

Today, user fees fund about half of new drug review costs. They have helped FDA increase new drug review staff two-fold between 1992 and 2004 – from 1,277 full-time equivalent staff to 2,503. The median approval time for priority new drug applications and biologics license applications decreased from 13.2 months in 1993 to 6.4 months in 2003. Since the start of PDUFA, FDA has approved over 1,000 new pharmaceutical drugs and about 100 new biologic drugs. According to FDA, before PDUFA, only about 8 percent of new drugs worldwide were launched first in the United States, but today that figure is about 50 percent.

Absent legislative action this fiscal year, FDA would be unable to continue to collect user fees for the new prescription drug review program after September 30. Per the Act's instructions, FDA officials worked with the drug industry to develop a proposal for Congress on PDUFA reauthorization in advance of expiration. Title I largely reflects those recommendations.

Section 103 of the bill sets an overall amount for user fees in 2008 of nearly $393 million (will be adjusted upward annually based on FDA's 2007 workload). This section also expands drug user fees for post-approval drug safety programs.

Section 104 refers to FDA review of voluntarily submitted drugmaker television advertisements. Currently, some drugmakers voluntarily submit their ads to FDA. FDA can ask them to change their ads but cannot force them. They can only "recall" the drugs – which is very rare. Section 104 gives FDA the authority to collect user fees from drugmakers submitting ads to the agency. This is intended to help FDA hire more staff to make advertising reviews better and faster.

Title II — Drug Safety

Even after a drug comes to market, FDA has various tools it can use to reduce drug risk to the public. Some of these tools are communication, further studies, further clinical trials, or even restrictions on distribution. Title II expands FDA's use of these tools. Under this bill, for certain drugs found to present enough of a risk, FDA would require the drugmaker to work with the agency to develop a specific strategy, using these types of tools, to evaluate and mitigate that risk. These FDA-drugmaker strategy plans are named risk evaluation and mitigation strategies (REMS).

Subtitle A – Risk Evaluation and Mitigation Strategies

Subtitle A of Title II establishes a system of routine active surveillance for post-market drug safety through a public-private partnership. The partnership would aggregate data from Federal and private health databases containing information for at least 100,000,000 covered lives and support the analysis of utilization and safety data from these databases and from FDA. The subtitle also requires the use of other surveillance approaches to supplement these networked databases. This would be supported with $30 million in appropriations.

However, for some drugs flagged by the surveillance system, additional tools are needed to manage serious risks; in those situations, the FDA would be able to require and approve a risk evaluation and mitigation strategy (REMS) for these drugs. Drugmakers would propose a strategy and FDA would approve it after structured negotiations, if necessary. For drugs with new active ingredients, the strategy would be reviewed at 18 months and three years. For other drugs, there would be a REMS strategy review at three years. A REMS strategy would also be reviewed in labeling supplements and when FDA requests a review based on new safety information.

Elements of a REMS Strategy:

A REMS strategy will always include two elements: FDA-approved professional labeling and a timetable for periodic assessment of the REMS. When more elements are needed, a REMS strategy may include tools to assess, communicate about, or manage risks. FDA can apply these tools as long as certain standards, designed to ensure that new FDA authorities are applied appropriately and as necessary, are met. For example, FDA can require a drug-specific study when the routine active surveillance system is not sufficient to assess a serious risk.

FDA could also decide to restrict distribution, within limits, of a drug deemed particularly risky. But such restrictions can be lifted in public health emergencies.

In addition, the bill states that FDA could demand to review a television advertisement for a given drug earlier than normal, and even order a moratorium on ads for a given drug for up to two years if "necessary to protect public health and safety while additional information about serious risks of the drug is collected." While the bill only suggests these as possible tools and does not specifically recommend them for any particular circumstance, many Republicans have voiced some concerns about giving FDA such authority. Some believe the advertising restrictions are unconstitutional as free speech violations.

Compliance:

Civil money penalties will apply for a knowing violation of an element of a REMS.

Resources:

Increased drug user fees will be used to review REMS and for FDA's general drug safety activities. For FY 2008, $25 million; for FY 2009, $35 million; for FY 2010, $45 million; for FY 2011, $55 million; and for FY 2012, $65 million.

Science:

Subtitle A also includes provisions regarding the scientific environment at FDA. It promotes transparency, by posting the action package for approval for drugs, as well as requiring notice of meetings and agenda of the Drug Safety Oversight Board. Also required is a report on the integration of the staffs of drug safety and drug review in drug safety activities at FDA (in response to the Institute of Medicine drug safety report).

Lastly, Subtitle A also requires FDA's Drug Safety and Risk Management Advisory Committee to review priority drug safety questions and the effectiveness of aspects of the REMS process.

Subtitle B – Reagan-Udall Foundation for the Food and Drug Administration

Subtitle B establishes a foundation to lead collaborations amongst the FDA, academic research institutions, and industries. Collaborative research projects will be designed to bolster research and development (R & D) productivity, provide new tools for improving safety in regulated product evaluation, and, in the long term, make regulated product development and safety more predictable and manageable. The Foundation will be financially supported by industry and philanthropic-donated funds. A Chief Scientist at FDA will promote intramural research and coordinate it with efforts at the Foundation.

Subtitle C – Clinical Trials

To enhance patient enrollment and provide a mechanism to track subsequent progress of drug trials, the data bank at ClinicalTrials.gov will be expanded to include all phase II and subsequent trials, as well as devices. Currently, only clinical trials of drugs for serious and life-threatening conditions are required to register in the data bank.

In addition, to ensure that results of trials are made public, and that patients and providers have the most up-to-date information, results information will be added to this database. Information will be added only after the product in question has been approved or cleared for marketing. Results information will first come from existing FDA and National Institutes of Health documents, as well as peer-reviewed scientific publications. A negotiated rulemaking process will be used to determine when and how to add results information not captured under those conditions. Violations of these provisions will be subject to civil money penalties.

Subtitle D – Conflicts of Interest

Subtitle D requires disclosure of conflicts of interest of drugmakers' advisory committee members prior to an advisory committee meeting, and greater efforts by FDA to identify and recruit members of advisory committees.

Subtitle D – Other Drug Safety Provisions (Medical Marijuana)

This provision (offered by Senator Coburn during markup) subjects state-legalized medical marijuana to the full regulatory requirements of the Food and Drug Administration,

including a REMS strategy and all other requirements and applicable penalties of the Federal Food, Drug, and Cosmetic Act regarding safe and effective reviews, approval, sale, marketing, and use of pharmaceuticals. This provision would require those who produce, market or sell marijuana for medical uses to comply with the same rules that pharmaceutical manufacturers are legally bound to follow.

Title III — Medical Device User Fees

Title III reflects the agreement between FDA and industry for reauthorizing device user fees. A managers' amendment may make modifications.

The bill establishes an overall amount of $287 million in medical device user fees over five years, with $48 million in FY 2008. This is coupled with a fixed 8.5 percent annual increase (with no other adjustors), a further reduction of fees for small business, and the addition of other fees.

Title III also includes an FDA-industry proposal to modify the current third-party inspection program. Provisions to clarify that device establishments can register and list products electronically are intended to increase the efficiency with which FDA manages this information.

Title IV — Pediatric Medical Products

Subtitle A – Best Pharmaceuticals for Children Act

Subtitle A reauthorizes the Best Pharmaceuticals for Children Act (BCPA), which is intended to help ensure that drugs used by children are safe for pediatric populations. BPCA generally provides six months of additional exclusivity (shielding them from generic competition) to drug manufactures who conduct safety and efficacy studies of drugs in pediatric populations.

This bill, however, provides for only three months of additional exclusivity to blockbuster drugs – those whose U.S. sales exceed $1 billion annually at the time FDA's written request for study is issued.

Subtitle B – Pediatric Research Improvement Act

Subtitle B reauthorizes the Pediatric Research Equity Act (PREA), and renames it the Pediatric Research Improvement Act (PRIA). To coordinate with the pediatric exclusivity provisions of the Best Pharmaceuticals for Children Act (BPCA), PRIA consolidates an internal FDA committee to review all issues of pediatric-related labeling and assessments. Doing so ensures that a drug that falls under PRIA or BPCA is reviewed both by experts for that particular drug and those with pediatric expertise.

If a company chooses not to pursue pediatric exclusivity for an already-marketed drug under BPCA, and no study is performed through NIH, the Secretary has the authority to require the submission of pediatric data for the drug. The proposed reauthorization of the program streamlines this process and helps get essential pediatric data for important drugs, while preserving the ability of companies to meet and discuss testing with the agency.

The bill requires two reports – one from the Institute of Medicine and one from the Government Accountability Office (GAO) – with the intent of providing better data on the number and ways in which the pediatric exclusivity rule is used, and of evaluating its contributions to ensuring overall pediatric drug safety.

Given the interaction between BPCA and PRIA, the legislation clarifies that these programs will continue to operate together with a five-year authorization period for both programs.

Subtitle C – Pediatric Medical Devices Safety and Improvement Act

Subtitle C is not a reauthorization. It is the Pediatric Medical Device Safety and Improvement Act, which aims to improve the process for approving pediatric medical devices and encourages research, development, and manufacture of pediatric devices through demonstration grants and incentives.

It is also intended to encourage pediatric medical device development for devices that only relatively few children need. A humanitarian device exemption (HDE) in current law permits a device to be marketed with less evidence of efficacy if it treats a condition affecting less than 4,000 persons, there is no other option, and follow-up efficacy data is collected. However, a company marketing a device pursuant to this HDE cannot currently make a profit.

This legislation modifies the existing HDE for medical devices to allow profit for HDE-approved devices specifically designed to meet a pediatric need. It maintains an existing requirement that a humanitarian use device is limited to one that treats and diagnoses diseases or conditions that affect fewer than 4,000 individuals in the United States per year. Profit would be allowed for up to 4,000 pediatric devices. The HDE exemption expansion sunsets in 2013 and a GAO report assessing the HDE exemption expansion and its impact on patients and manufacturers is required.

The FDA's Office of Pediatric Therapeutics will acquire enhanced authority to collaborate with NIH, the Agency for Healthcare Research and Quality, and subject matter experts in order to assess pediatric device R&D needs.

Also, demonstration grants, with tracked results, will be established for non-profit consortia to promote pediatric device development, manufacture and distribution. The bill will grant explicit authority to the FDA's Pediatric Advisory Committee to monitor pediatric devices and make recommendations for improving their availability and safety. This approach incorporates several recommendations of the Institute of Medicine, including improving the post-

market surveillance of medical devices used for children and expanding public access to post-market studies of pediatric medical devices.

Cost

The Congressional Budget Office estimates that S. 1082 would affect both discretionary and mandatory spending. Assuming appropriations are consistent with the bill, CBO estimates that implementing S. 1082 would reduce net discretionary outlays by $157 million in 2008. CBO also estimates that the net discretionary cost of implementing this bill over the 2008-2012 period would amount to $547 million. The CBO cost estimate is available at http://www.cbo.gov/ftpdocs/80xx/doc8033/s1082.pdf. In terms of mandatory spending, CBO estimates that S. 1082 would increase direct spending by $5 million over the 2008-2012 period and $150 million over the 2008-2017 period as a result of extending the exclusivity provisions which expire in current law. CBO also estimates that S. 1082 would have a negligible effect on federal revenues over the 2008-2012 period and would reduce federal revenues by $32 million over the 2008-2017 period.

S. 1082 would preempt any State or local government law that requires manufacturers of medical devices or drugs to register clinical trials and related information in a database. That preemption would be an intergovernmental mandate as defined in the Unfunded Mandates Reform Act (UMRA) because it would limit the application of State law. However, the costs of the mandate would be minimal and would be far below the threshold established in UMRA. Further, CBO estimates that the direct cost of those mandates would exceed the annual threshold specified in UMRA ($134 million in 2008, adjusted annually for inflation) in each of the five years that the mandates would be effective.

Administration Position

As of press time, no Statement of Administration Policy (SAP) had been issued. On April 17, Secretary of Health and Human Services Leavitt sent a letter to HELP Committee Chairman Kennedy, which is excerpted below:

> "The Administration strongly supports the reauthorization of the prescription drug user fee and medical device user fee programs….
>
> "Improved drug safety is not simply a matter of extending new legal authorities to FDA or requiring the Agency to engage in certain detailed activity. Indeed, extending these interventions or expanding the use of REMS is unlikely to result in improvements in drug safety as desired by the bill's sponsors.
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> "The better overall strategy is to ensure that FDA has the appropriate resources and the capacity to develop better scientific tools and approaches to drug review, including (1)

improving information available to the Agency; (2) improving its ability to evaluate this information; and (3) improving how that evaluation is communicated to the public."

Possible Amendments

Issue	Sponsor	Description
RU-486	DeMint	Require REMS strategy assessment for RU-486 within six months after enactment.
BCPA Market Exclusivity	Allard	Retain the pediatric research incentives in the Best Pharmaceuticals for Children Act (BPCA). This would remove the reduction of exclusivity incentives on blockbuster drugs from six months to three months. Failed during markup.
Television Advertising	Roberts	Require companies to submit television advertisements to FDA at least 45 days in advance but does not require FDA approval. Civil penalties for misleading or false ads.
Safe Internet Pharmacy Act (S. 596)	Gregg	Amend PHSA to require all Internet pharmacies to register with FDA and to meet certain requirements before dispensing prescription drugs.
Clinical Trials	Grassley	Senator Grassley may offer amendments based on his drug safety legislation (S. 648) or his legislation with Senator Dodd regarding clinical trials (S. 467).
HIV/AIDS	Burr	Exempt HIV/AIDS drugs from REMS if it causes a delay of more than 30 days (this amendment can be used for any disease).
Clinical Trials	Burr	Require generics to pay part of the costs of clinical trials required to be conducted by drug companies; require FDA to notify drug companies of non-compliance with REMS and give companies time to correct error(s) before instituting civil monetary penalties.
Antibiotic Research (withdrawn during markup)	Hatch	Insert provisions relating to antibiotic safety and safety of certain enantiomer drugs.

Issue	Sponsor	Description
BCPA Market Exclusivity	Stabenow	Reduce the research incentives in the Best Pharmaceuticals for Children Act to less than three months of exclusivity for blockbuster drugs.
Citizen Petitions	Brown	Allow FDA to continue reviewing a generic drug application while a citizen petition is being considered; require the party submitting petition to certify that information in the petition is accurate; and require the party to disclose any compensation from those who have a financial interest in its outcome. (Was withdrawn during markup.)
Extension of Pediatric Data Collection (withdrawn during markup)	Clinton	Eliminate sunset of Section 505(b) the FDCA from the bill.
Food safety, pet food	Durbin	Give FDA authority to mandate recalls of contaminated food products and to fine companies that do not properly report food contamination.
Biosimilar therapies	Clinton, Schumer	Based on their legislation (S. 623) to authorize the FDA to begin the process to approve generic versions of complex and expensive drugs called biologics or biotech drugs.
Importation	Dorgan	Allow and expand importation of drugs from Canada and other countries.

[Based on information shared by the HELP Committee]