

**Stakeholder Meeting on PDUFA V Reauthorization**  
**November 17, 2010, 2:00 – 5:00 PM**  
**Hubert H. Humphrey Building, Washington, D.C.**  
**Room 800**

---

**Purpose**

To discuss Advisory Committee (AC) meetings, comparative effectiveness research, off-label prescribing, Risk Evaluation and Mitigation Strategies (REMS), and stakeholder comments and proposals for PDUFA enhancement.

**Participants**

FDA

Wade Ackerman	OCC	Donal Parks	CDER
Jane Axelrad	CDER	Jayne Peterson	CDER
Daniel Brounstein	CDER	Matt Sullivan	CDER
Patrick Frey	CDER	Andrea Tan	CDER
Andrea Furia-Helms	CDER	Robert Temple	CDER
John Jenkins	CDER	Terry Toigo	OSHI
Brian Kehoe	OL	James Valentine	OSHI
Patricia Kuntze	OER	Bob Yetter	CBER
Theresa Mullin	CDER		

Stakeholders

Jeff Allen	Friends of Cancer Research
Jeanette Baldonado	Arthritis Foundation
James Baumberger	American Academy of Pediatrics
Cynthia Bens	Alliance for Aging Research
Marcie Bough	American Pharmacists Association
Marc Boutin	National Health Council
Paul Brown	National Research Center for Women & Families
Rebecca Burkholder	National Consumers League
Kevin Cain	National Health Council
Lauren Chiarello	National Multiple Sclerosis Society
Adam Clark	FasterCures/The Center for Accelerating Medical Solutions
Allan Coukell	The Pew Charitable Trusts
Christin Engelhardt	Pancreatic Cancer Action Network
Steve Gibson	The ALS Association
Amanda Grimm	American Academy of Dermatology Association
Robert Guidos	Infectious Diseases Society of America
Tamar Magarik Haro	American Academy of Pediatrics
Suzanne Henry	Consumers Union
Darby Hull	Consumer Federation of America
Angela Jeansonne	American Osteopathic Association
Julia Jenkins	Kakkis EveryLife Foundation
Lisa Joldersma	BlueCross BlueShield Association
Stephanie Krenrich	Cystic Fibrosis Foundation
Martha Nolan	Society for Women's Health Research

Angela Ostrom	Epilepsy Foundation
Mark Pascu	Leukemia and Lymphoma Society
Kate Ryan	National Women's Health Network
Drew Saelens	Men's Health Network
John Schall	Parkinson's Action Network
Marissa Schlaifer	Academy of Managed Care Pharmacy
Roslyne Schulman	American Hospital Association
Andrew Sperling	National Alliance on Mental Illness
Lisa Swirsky	Consumers Union
Kerry Thompson	National Association of Free Clinics
Bill Vaughan	Consumers Union
Mary Lee Watts	American Association for Cancer Research
Michael Werner	Alliance for Regenerative Medicine
Celia Wexler	Union of Concerned Scientists
Patrick Wildman	The ALS Association

### Advisory Committees

FDA stated that the agency holds Advisory Committee (AC) meetings to seek highly specific and independent expert advice on complex issues. AC meetings also increase awareness of public health issues, facilitate public input, and increase the credibility and integrity of FDA's decisions. ACs are composed of voting members, which include consumer and patient representatives, and non-voting members, which include Industry representatives. FDA also stated that the agency is responsible for conducting conflict of interest screening and determining eligibility for participation in ACs. FDA follows criteria for determining if an individual should be recused and is also responsible for granting conflict of interest waivers. FDA noted that since fiscal year 2006, when 57 waivers were granted for 13 PDUFA meetings, the number of waivers issued has steadily decreased, with 6 waivers issued in 2010 for 40 PDUFA meetings.

### Comparative Effectiveness Research

FDA stated that the legal standard for approving new drugs does not require that they perform better than existing therapies. The Food, Drug, and Cosmetic Act (the act) requires that new drugs demonstrate substantial evidence of effectiveness which is defined in the act as "adequate and well-controlled investigations." FDA regulations describe the essential characteristics of adequate and well-controlled investigations, including that the study design must allow a valid comparison with a control group to provide a quantitative assessment of the drug's effect. Several recognized control groups are identified in the regulation, including placebo control and active treatment control. One exception where a comparative study is required is when a lack of effectiveness or inferior effectiveness to existing treatment options is potentially harmful. FDA noted that comparative studies can often require enrollment of very large numbers of patients, making them very difficult and expensive to conduct, particularly in the case of demonstrating a comparative advantage for a symptomatic benefit.

The agency remarked that one type of study design that is not often used can show whether a new therapy is effective in patients who have failed existing treatments. In a "randomized withdrawal" trial design, patients are given the new drug for a period of time and then some patients are randomly switched to the original treatment. FDA added that the information in large databases such as Sentinel could be informative in terms of comparative effectiveness, but its utility needs to be proven.

### Off-Label Prescribing

FDA also discussed off-label prescribing of approved products. The agency noted that if data indicate that certain off-label prescribing of a drug is harmful, then FDA could use labeling changes or other authorities to address those safety concerns. FDA also noted that the agency does take enforcement action against promotion of off-label use when it occurs.

### REMS

FDA discussed the agency's ability to require Risk Evaluation and Mitigation Strategies (REMS) under the FDA Amendments Act of 2007 (FDAAA) in both pre- and post-market settings. A REMS can include a Medication Guide, a communication plan, and elements to assure safe use. FDA described the six elements to assure safe use: healthcare providers who prescribe the drug have particular training, experience, or certification; healthcare settings that dispense the drug are specially certified; the drug may be dispensed only in certain healthcare settings; the drug may be dispensed to patients with evidence of safe-use conditions; patients must be subject to monitoring; and patients must be enrolled in a registry.

FDA noted that REMS must be designed to address the specific serious risks identified either before approval or in the post-market setting, and that the most serious preventable risks will lead to the most restrictive programs. FDA acknowledged that concerns have been raised about REMS that involve only a Medication Guide and noted that the agency is currently working on a guidance to address those concerns. FDA also received many public comments from the two-day public meeting in July 2010 and the public docket that was open through August 2010. The agency noted that it is still working through those comments. FDA also noted that it is engaged in efforts that will help the agency articulate the criteria needed to determine if a REMS is necessary, and the criteria needed to determine which elements of a REMS are needed to address the identified safety concerns. FDA is also working to standardize REMS materials and facilitate the use of existing pharmacy systems to implement REMS.

FDA noted that if the agency's understanding of a drug's risks occurred earlier in review of an application, then FDA and Industry could begin risk management discussions earlier. Stakeholders asked how they could be involved in discussions regarding REMS. The agency stated that the best mechanism for stakeholder involvement in the pre-approval setting is at an Advisory Committee meeting, because discussions of REMS before approval are confidential unless they are discussed at a public Advisory Committee meeting. In the post-approval setting, particularly if multiple drugs in a class are involved, the agency noted that there are more opportunities to engage stakeholders.

### **Discussion of Stakeholder and FDA Proposals**

Several stakeholder groups discussed their comments regarding PDUFA V reauthorization:

#### Union of Concerned Scientists

The Union of Concerned Scientists offered several suggestions for consideration:

1. Identify conflicts of interest proactively through requiring Advisory Committee members to read and sign forms regarding their obligations, and engaging the public in the vetting process.
2. Restrict the participation of conflicted members.
3. Make it easier for the public to track FDA progress in reducing the numbers of conflicted experts.

#### National Health Council

The National Health Council (NHC) stated that they are interested in hearing more information about the following FDA proposed enhancements:

1. Patient-focused drug development
2. Advancing biomarkers and pharmacogenomics
3. Advancing development of drugs for rare diseases

NHC commented that conflicts of interest need to be transparent and disclosed, but they also need to be managed so that FDA has access to the right expertise on Advisory Committees. NHC indicated that it can be difficult to find the expertise needed without waivers, especially in cases of highly specialized areas where the number of available experts is small. FDA noted that there have been cases in which late recusals from an AC due to a conflict of interest have led to a meeting cancellation and a delay in FDA's approval of the application. FDA stated that conflict of interest screening is an important aspect of maintaining trust in the AC meeting process; however a balance between ensuring trust in the process and obtaining the necessary expertise must be maintained.

FDA noted that biomarker review is a very resource-intensive process and its current capacity for this work is stretched. The agency also commented that lessons learned in development programs for rare diseases often translate to other development programs. The training provided to staff across FDA's review divisions will focus on the experience gained in clinical trials in small populations.

#### Patient, Consumer, and Public Health Coalition

Consumer's Union, National Women's Health Network, and the Union of Concerned Scientists/Scientific Integrity Program discussed concerns regarding the Sentinel Initiative. The coalition inquired about non-financial barriers to implementation and the current level of resources being spent on Sentinel. FDA stated that a PDUFA proposal is being discussed to add additional resources to the Sentinel pilot program.