

**FDA-Industry PDUFA V Reauthorization Meeting**  
**January 10, 2011, 10:30-11:30am**  
**FDA White Oak Campus, Silver Spring, MD**  
**Building 32, Room 2390**

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**Purpose**

To continue discussion of the proposal for a phased-in requirement for electronic submissions in standardized formats during PDUFA V.

**Participants**

FDA

Wade Ackerman	OCC
Adam Kroetsch	CDER
Theresa Mullin	CDER

Industry

Jeffrey Francer	PhRMA
Sascha Haverfield	PhRMA

FDA and Industry discussed the agency's revision of the proposal to require electronic applications in standardized formats through guidance. The proposed revision would accelerate the timeline for requiring submissions in electronic common technical document (eCTD) format for certain types of applications by FY 2015, because a significant percentage of these applications were already being submitted in eCTD format as of FY 2009. Industry agreed to follow up with its members to get input regarding the feasibility of meeting the proposed accelerated timeframe.

Industry requested clarification on the agency's support of data standards content specifications through the Clinical Data Interchange Standards Consortium (CDISC) or Health Level 7 (HL7) exchange standards for regulatory submissions. Industry expressed concern that transitioning to HL7 would not be feasible for their member companies within the 3-4 year timeframe for implementing a requirement for electronic submissions specified in the proposal. FDA reiterated its intention to work with CDISC to develop content specifications for clinical data, and to consult with standards development organizations and other stakeholders before identifying standards for the submission of data other than clinical data. FDA agreed to solicit public input on the appropriate standards-developing organizations and standards to be used for the submission of data other than clinical data as part of the process outlined in the data standards enhancement proposal.

**FDA-Industry PDUFA V Reauthorization Meeting**  
**Premarket Sub-Group**  
**January 10, 2011, 10:30am - 12:30pm**  
**FDA White Oak Campus, Silver Spring, MD**  
**Building 31, Room 2442**

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**Purpose**

To continue discussion of proposals related to regulatory science, the pilot program for enhanced review transparency and communication, performance goals related to meeting management, and enhanced communication for emerging sponsors.

**Participants**

FDA

Ed Cox	CDER
Patrick Frey	CDER
John Jenkins	CDER
Chris Joneckis	CBER

Industry

Kay Holcombe	Genzyme
Hilary Malone	Pfizer
Sara Radcliffe	BIO
Jay Siegel	Johnson & Johnson
David Wheadon	PhRMA

**Regulatory Science Proposals**

FDA began the meeting by stating its interest in continuing discussions around four other proposals related to regulatory science:

- Advancing biomarkers and pharmacogenomics
- Ensure quality of patient-reported outcomes and other endpoint assessment tools
- Expand capacity for scientific advice to address complex manufacturing issues
- Ensure quality in non-inferiority and adaptive trial designs

FDA stated that these proposals represent new scientific areas where the agency is increasingly asked by sponsors for advice and consultation during the development process. Industry stated that many of FDA's regulatory science proposals were important and ideally should be funded either through congressional appropriations or user fees. Industry indicated that resolution of the entire package for user fee support would depend on completion of the ongoing discussions related to changes to the review model and that they would continue discussing FDA's proposals related to regulatory science. Industry also stated that it would be helpful in considering FDA's regulatory science proposals if the agency more clearly described the relevance to the application review process and the PDUFA program. FDA stated that it would add language to these proposals to reflect an outcome perspective.

**Pilot Program for Enhanced Review Transparency and Communication**

The discussion of this proposal began with Industry stating its concern regarding the requirement that applications be fully complete at the time of original submission and FDA's statement that unsolicited amendments will generally not be reviewed during the current review cycle. Industry requested that FDA accept additional application components during the 60 day filing period after original submission and that the agency reconsider its willingness to review unsolicited amendments if that information could address an issue in the application identified by FDA during its review. Industry suggested that delayed submissions should only include additional analyses of the data originally submitted; substantive new data would not be allowed. The agency stated that the intent of its proposal is to avoid

the submission of substantive information that should have been included in the original submission, and that the submission of additional information to address a problem raises questions regarding the completeness of the original submission. FDA stated that if the agency agreed to accept additional minor submissions during the filing period after original submission, the pre-submission meeting should be a requirement of the pilot program so that FDA and sponsors can agree on the contents of a complete application and the components of the application that will be submitted during the filing period. The agency noted that if it agreed to accept additional submissions during the filing period, it would only be during the first 30 days since review staff would need time to evaluate the delayed submissions to prepare for the internal filing meeting at Day 45. Regarding unsolicited amendments, FDA stated that it would consider an approach to discussing additional submissions in response to application issues communicated at mid-cycle or in the late cycle meeting with FDA.

FDA also stated that additional resources would be required under this proposal to ensure that the appropriate drug safety staff are involved in the additional meetings for applications under the pilot program and to address Industry's request for earlier involvement of safety staff during review.

### **Meeting Management Proposals**

FDA proposed that after a sponsor's submission of a Type C meeting package, the agency would determine whether a face-to-face meeting or a written response is needed to sufficiently address the issues identified in the meeting package. Under this proposal, the Type C meeting PDUFA performance goal would be satisfied by either holding a meeting or sending a written response to the sponsor. Industry agreed to this proposal. FDA agreed with Industry's original proposal to classify post-action meetings in the case of a complete response letter as Type A, although the agency stipulated a requirement that the request for this meeting should be received within the 3 month window following issuance of the complete response letter.

### **Enhanced Communication for Emerging Sponsors Proposal**

Industry discussed a revision of its proposal to enhance FDA-sponsor communication during drug development for sponsors without an FDA-approved product. Industry proposed a process where eligible sponsors could submit written requests for answers to simple and clarifying questions that would be linked to a previous interaction with the agency. Industry's proposal included a telephone consultation prior to FDA submitting its written response to the questions. The stated intent of this consultation is to walk the agency through the issue. Industry also proposed an option for post-response communication should sponsors require additional clarification of FDA's written response to the question. Industry proposed that FDA verify eligibility for this program by querying the Orange Book or other appropriate database to determine if the sponsor has an FDA-approved product. Industry further proposed that this type of communication be limited to only one request per IND per year for pre-IND and End-of-Phase 2 (EOP2) inquiries only.

The agency agreed to limit this proposal to pre-IND and EOP2 inquiries only; however, the agency proposed to link these requests for clarification to a specific previous meeting with FDA where minutes were issued. FDA stated that the scope of these requests for clarification should be limited to the topics discussed at the previous meeting; new issues raised in the request for clarification would be considered a new meeting request. Furthermore, the agency also stipulated that the request for clarification must be received within 3 months after the meeting occurs with FDA. FDA proposed a response time of 45 days from the date of receipt for these requests.

FDA stated that it has not conducted an analysis to determine the resource implications for this proposal. Industry noted that some sponsors do not have the need for this process, yet would pay user fees to support this proposal.

**FDA-Industry PDUFA V Reauthorization Meeting**  
**REMS-Sentinel Sub-Group**  
**January 10, 2011, 10:30am - 11:30pm**  
**FDA White Oak Campus, Silver Spring, MD**  
**Building 32, Room 3502**

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**Purpose**

This meeting was the third meeting of a negotiation Sub-Group focused on the PDUFA V proposals for Sentinel and for standardizing and integrating REMS into the healthcare system. This meeting focused only on continuing discussions on Sentinel.

**Participants**

FDA

Debbie Henderson      CDER  
Rachel Behrman        CDER  
Jayne Ware             CDER

Industry

Paul Eisenberg            Amgen  
Florence Houn            Celgene  
Rob Kowalski             Novartis  
Andrew Emmett            BIO

**Pilot Sentinel as a Tool for Evaluating Safety Signals**

FDA discussed its revisions to the Sentinel proposal based on feedback from Industry during a teleconference held on January 7, 2011. In particular, the revised proposal included provisions for a transparent, public process for determining which activities would be funded under the Sentinel proposal, benchmarking progress on activities, and evaluating activities to measure success toward designated goals.

FDA and Industry discussed additional revisions to the proposal that involved:

- Clarifying the Sentinel activities that would be funded by this proposal to assure activities would emphasize safety issues that affect classes of drugs or multiple products;
- Including both an interim assessment in FY 2015 as well as a final assessment in FY 2017 to evaluate the utility of Sentinel in guiding future regulatory actions to manage safety issues; and
- Adjusting the resource estimate to include both the interim and final assessments.

FDA agreed to revise the proposal to incorporate the line-edits made during this meeting. The group agreed that once those changes were made, the proposal was ready to be presented to the Steering Committee.

**FDA-Industry PDUFA V Reauthorization Meeting**  
**January 10, 2011, 1:30pm – 4:00pm**  
**FDA White Oak Campus, Silver Spring, MD**  
**Building 31, Room 2442**

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**Purpose**

To update the FDA-Industry Steering Group on the current status of Sub-Group discussions and to discuss Sub-Group proposal recommendations to the Steering Group on benefit-risk and patient-focused drug development, rare diseases, meta-analysis, and piloting Sentinel.

**Participants**

FDA

Wade Ackerman	OCC
Ed Cox	CDER
Patrick Frey	CDER
Debbie Henderson	CDER
John Jenkins	CDER
Chris Joneckis	CBER
Brian Kehoe	OL
Theresa Mullin	CDER
Donal Parks	CDER
Bob Yetter	CBER

HHS

Roger McClung	ASL
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Industry

Annetta Beauregard	EMD Serono
Paul Eisenberg	Amgen
Andrew Emmett	BIO
Jeffrey Francer	PhRMA
Sascha Haverfield	PhRMA
Kay Holcombe	Genzyme
Florence Houn	Celgene
Paul Huckle	GlaxoSmithKline
Rob Kowalski	Novartis
Hilary Malone	Pfizer
Sara Radcliffe	BIO
Jay Siegel	Johnson & Johnson
Mark Taisey	Eisai
Helen Thackray	GlycoMimetics
David Wheadon	PhRMA

The Sub-Groups discussed the following proposals for recommendation to the Steering Group:

**Benefit-Risk / Patient-Focused Drug Development**

The Ad-hoc Sub-Group discussed the proposal to extend the agency's ongoing work to develop an enhanced structured approach to benefit-risk assessment and communication. This proposal would include a series of public workshops throughout PDUFA V for obtaining patient and other stakeholder perspectives to better establish the clinical context (i.e., severity of the treated condition and the adequacy of the existing treatment armamentarium) for certain therapeutic areas that would be identified through a public process. FDA stated that during PDUFA V, the agency will publish a five-year plan for public comment. The plan will include public workshops during PDUFA V to discuss frameworks and approaches to benefit-risk assessment and lessons learned as these approaches have been implemented in drug review. FDA will also revise the relevant agency review and memo templates, and train review and management staff to fully integrate the use of the enhanced structured benefit-risk assessment framework into the regulatory review process during PDUFA V. The proposal also includes an evaluation component to assess the impact of using the enhanced structured benefit-risk assessment framework in the drug review process.

Industry acknowledged that the revised proposal reflected the agreed revisions discussed at the Sub-Group meeting. The Steering Group agreed that this proposal could be added to the package of proposed recommendations.

## **Rare Diseases**

The Premarket Sub-Group discussed the proposal to advance development of drugs for rare diseases. This proposal would increase the agency's capacity in CDER and CBER to focus on rare disease product development. It includes guidance and policy development related to rare disease drug development, increased outreach to patient organizations and industry regarding development of such drugs, a public meeting to discuss complex issues in clinical trials, staff training related to review and approval of drugs for rare diseases, evaluative tools to measure the success of these activities.

The Steering Group agreed that this proposal could be added to the package of proposed recommendations.

## **Meta-Analyses**

The Premarket Sub-Group discussed the proposal to ensure quality in meta-analyses. This proposal includes convening a public meeting to discuss scientific approaches and methods for the conduct of meta-analysis and to facilitate stakeholder feedback regarding the use of meta-analysis in the regulatory review process; publishing a draft guidance for public comment that describes FDA's intended approach to use meta-analyses in the regulatory review process; publishing the final guidance after consideration of comments received; and staffing a dedicated review team to evaluate different scientific methods and to explore the practical application of scientific approaches and best practices for the conduct of meta-analysis.

The Steering Group agreed that this proposal could be added to the package of proposed recommendations.

## **Sentinel**

FDA and Industry discussed the proposal to pilot Sentinel activities during PDUFA V. Under this proposal, FDA would conduct a series of activities to determine the feasibility of using Sentinel to evaluate drug safety issues that may require regulatory action, e.g., labeling changes, Post Market Requirements or Post Market Commitments. These activities will be designed to further evaluate safety signals that have served as the basis for regulatory action(s) and to help determine the utility and validity of the Sentinel System to evaluate other types of signals in population-based databases. The proposal includes a provision for a transparent, public process to determine the activities that will be studied with a focus on issues that affect classes of drugs or multiple products. Interim and final assessments during PDUFA V will evaluate the utility of Sentinel in informing future regulatory actions to manage safety issues.

The Steering Group agreed that this proposal could be added to the package of proposed recommendations.

The Sub-Groups provided updates on the current status of discussions on the following proposals:

### **Proposals to enhance regulatory science**

FDA stated that the agency considers it important to continue discussing the proposals regarding Quality-by-Design, non-inferiority and adaptive trial designs, patient-reported outcomes, and biomarkers and pharmacogenomics (refer to minutes from [September 27](#) and [October 12](#) for discussions of these proposals). The proposals related to regulatory science will continue to be discussed in the Premarket Sub-Group.

## **Pilot Program for Enhanced Review Transparency and Communication**

The Premarket Sub-Group stated that the pilot program for review of new molecular entity new drug applications (NME NDAs) and original biologics license applications (BLAs) during PDUFA V would not be an optional program. The Sub-Group stated that it is exploring a way to allow submission of minor additional information during the 60-day filing period that would not adversely impact FDA's ability to plan its review, and it is considering an approach to discussing additional submissions in response to application issues communicated at mid-cycle or in the late-cycle meeting with FDA. The agency explained that the intent of its original proposal was to avoid the submission of substantive information that should have been included in the original submission, and that the submission of additional information to address a problem raises questions regarding the completeness of the original submission. The Sub-Group also noted that this proposal includes interim and final evaluations of the success of the pilot program.

## **Meeting Management Proposals**

The Premarket Sub-Group stated that Industry's original request for a Type C2 meeting for written responses-only would be addressed by sponsors submitting a Type C meeting package with a request for either a face-to-face meeting or a written response. After receipt of the package, FDA would evaluate the issues and determine whether the agency agreed with the sponsor's request. There would be no change to the current performance goals for Type C meetings, whether conducted face-to-face or through a written response. The Sub-Group also stated that it agreed that meetings regarding risk evaluation and mitigation strategies (REMS) and post-marketing requirements would be classified as Type B meetings, post-action meetings after a complete response letter or a clinical hold would be classified as Type A meetings, and that submission of background packages for Type A meetings would be required at the time of the meeting request.

The draft proposal to address these modifications will be discussed at a future Steering Group meeting.

## **Enhanced Communication for Emerging Sponsors**

FDA discussed its concerns about this proposal as communicated during the Premarket Sub-Group meeting. The agency stated that sponsors should certify that they have no approved application and are eligible to receive this kind of communication, rather than FDA determining a sponsor's eligibility. FDA also stated that requests for this type of communication should be linked to a previous meeting with the agency where minutes were issued. In addition, the agency stated that requests must be submitted within 3 months after the meeting with FDA, and FDA would respond within 45 days of receiving the request for clarification. Industry stated that the ability to discuss the issue with FDA in a telephone consultation before submitting the request clarification was an important part of their proposal. FDA stated that it would consider allowing that possibility, but not as a formal commitment for each request for clarification, and further indicated that the implementation of this proposal would require additional agency staff resources.

## **Data Standards**

The Sub-Group addressed the proposal for a phased-in requirement of electronic submissions with standardized data during PDUFA V. The group discussed and agreed to clarify the most recent revision of the proposal to specify that the Clinical Data Interchange Standards Consortium (CDISC) would be used in developing clinical data standards, while a public process would be used to identify the appropriate standards development organization to develop standards for the submission of non-clinical data.

## **Improving human subject protection in clinical trial oversight**

The Ad-hoc Sub-Group reported on its initial discussion of the proposal to improve human subject protection in clinical trial oversight. FDA stated that this proposal would implement a quality systems approach in clinical trial oversight during PDUFA V. This would include FDA review of sponsor-developed plans to ensure quality in clinical trials before the protocols begin and “real-time” inspections while the trial is still ongoing. FDA stated that identification and active management of sources of variation at critical steps in clinical development should reduce delays in application review due to compliance issues that are not identified until after the trial has been completed. In response to questions from Industry participants in the discussion, FDA noted that it would revise the proposal to further define this approach for Industry, and how it is integrated into the drug review process.

## **Financial**

The Financial Sub-Group reported that it is currently discussing the three technical changes proposed by FDA (refer to minutes from [October 12](#)), the algorithm for the PDUFA V inflation adjuster, and the total cost of an FTE to be used for PDUFA V.