

MINUTES OF THE TELECONFERENCE
OF THE PQRI PSD MASS BALANCE WORKING GROUP ON
25 MARCH 2002

I. PARTICIPANTS

Terry Tougas (Boehringer Ingelheim), Chair
Sylvia Gantt (PQRI)
Lana Lyapustina (IPAC-RS)
Margareth Marques (USP)
Jolyon Mitchell (Trudell Medical)
Brian Rogers (CDER/FDA)
Bruce Wyka (Schering-Plough)

II. OPENING

Dr. Tougas welcomed the participants and especially Dr. Marques, who is temporarily replacing Dr. Zaidi as the USP representative. Dr. Marques briefly reviewed her background and explained that she had served as the USP liaison to the USP Aerosol Expert Committee for a number of years.

Dr. Tougas proposed, and the participants agreed, that the objectives of the teleconference be the following: (i) to identify leaders for driving the implementation of individual steps of the work plan, and (ii) to review and revise as needed the timelines in the work plan.

Dr. Tougas noted that he had made a presentation on the work plan to the Drug Product Technical Committee (DPTC) on 28 February. Ms. Gantt confirmed that the DPTC is currently reviewing the work plan and will provide its comments to the Working Group in the near future.

III. DISCUSSION

Responsibilities

The participants agreed that the following Working Group members will assume primary responsibility for preparing initial drafts for the Group's review, and otherwise spearheading the effort on individual steps of the work plan:

<i>Step #</i>	<i>Description</i>	<i>Leaders</i>	<i>Initial Draft Due Date</i>
Step 1.	Prepare preliminary draft of the <i>Investigational Tree</i> based on the Working Group's experience.	Dr. Mitchell and Mr. Wyka	13 May
	Develop and conduct a survey of the industry to obtain data on all known causes and frequencies of failure for the mass balance determined via cascade impactors.	TBD	TBD
	Analyze survey results and finalize the <i>Investigational Tree</i> , based on reported causes and frequencies of MB failure.	TBD	TBD
Step 2.	Discuss an experiment to compare variances of the delivered dose as determined in a USP DCU apparatus as opposed to those determined in a cascade impactor.	Dr. Tougas and Dr. Furnkranz (to be confirmed)	13 May
	Design and conduct the above experiment.	TBD	TBD
	Prepare a document defining how PSD Mass Balance should be used for product quality control.	TBD	TBD
Step 3.	Prepare and publish a <i>Good Cascade Impactor Practices</i> paper, which would include the <i>Investigational Tree</i> developed in step 1.	Dr. Mitchell, Mr. Wyka and Dr. Rogers	TBD
Step 4.	Discuss data inclusion/exclusion criteria for the eventual data-mining which would aim to establish general procedures and limits appropriate for MB as a PSD run qualification.	Dr. Tougas and Dr. Rogers	13 May
	Based on PSD data gathered through data-mining, establish what general procedures and limits are appropriate for mass balance as a PSD run qualification.	TBD	TBD
Step 5.	Make recommendations for FDA's CMC Draft Guidances for OINDP.	TBD	TBD

Timelines

The Working Group reviewed and slightly revised the timelines for completing these steps and agreed on the following:

**STEP 1 DEVELOP INVESTIGATIONAL TREE
TIMELINE**

- Prepare initial draft of the *Investigational Tree* **by 13 May 2002.**
- Identify statisticians with expertise in survey analysis and probabilistic risk assessment **by the end of May 2002.**

- With the participation of statisticians, draft the survey for investigation of causes and frequencies of MB failure **in June-July 2002**.
- Finalize survey **in July-August 2002**.
- Send out the survey **in September 2002**, to as many companies and testing laboratories as possible (via IPAC-RS, ITFG, PhRMA, GPhA, EPAG).
- Collect answers by **November 2002**.
- Clarify ambiguities in submitted questionnaires **in December 2002-February 2003**.
- Perform statistical analysis of submitted data **in February-April 2003**.
- Finalize the *Investigational Tree* within the WG **in May - June 2003**.
- Prepare a written report of findings of step 1 **in July-August 2003**.
- Present the report, with the developed *Investigational Tree* to the PQRI DPTC and SC **in September 2003**.
- Present the report, with the developed *Investigational Tree* to the wider scientific community through a presentation at a PQRI workshop, or conference, or a publication in **Q4 2003**.

STEP 2 COMPARE PSD MB AND DCU VARIANCES

TIMELINE

- Prepare a preliminary draft protocol for comparing variances of the delivered dose as determined in a USP DCU apparatus and in a cascade impactor, **by 13 May 2002**.
- Identify statisticians with expertise in uncertainty analysis **by the end of May 2002**.
- With the participation of statisticians, prepare a mature draft protocol for prospective research (*e.g.*, characteristics of the products on which the experiment will be performed, the exact experimental procedure, and the procedure for data analysis), **by July 2002**.
- Ask for input from wider scientific community to improve the draft protocol **in September -November 2002**.
- Conduct experiment **in January-March 2003** by a neutral party (FDA laboratories or academic laboratories or CROs).
- Summarize results in a paper **in May-June 2003**.
- Paper will be sent to DPTC, SC for review and approval before publication.

STEP 3 DEVELOP GOOD CASCADE IMPACTOR PRACTICES

TIMELINE

- Start in **June 2002**.
- Finish in **June 2003**.
- Eventually publish (after review and approval by DPTC and SC of PQRI), in DIA Journal, or Journal of Aerosol Medicine, or Journal of Aerosol Science, or Pharmacopeial Forum, or other appropriate publication.

STEP 4 DETERMINE APPROPRIATE PSD MB LIMITS

TIMELINE

- Draft data inclusion/exclusion criteria by **13 May 2002**
e.g.,
 - number of actuations per determination;
 - type of impactor;
 - flow rate; and
 - product status (*e.g.*, approved after a certain date, in development after a certain stage, *etc.*).
- Identify statisticians with expertise in analyzing large sets of QC data (*i.e.*, designing a data template for an industry-wide survey, compiling submitted data, and analyzing the database) by the **end of May 2002**. Use internet sites of pqri.org, ipacrs.com, epag.co.uk, and other contacts for soliciting interest.
- With the participation of statisticians, develop survey template – **June-August 2002**.
- Evaluate appropriateness (qualitatively and quantitatively) of the ITFG/IPAC-RS PSD database. Obtain approval of data sponsors to use relevant parts of the ITFG/IPAC-RS PSD database. **September - October 2002**.
- Issue solicitation for additional data, possibly through FDA FTEs and industry (data-mining). **September - October 2002**.
- Complete data collection by **December 2002**.
- Clarify ambiguities and resolve inconsistencies in assembled data. – **January - February 2003**.
- Analyze data and prepare a draft report. **March-April 2003**.
- Finalize the report within WG. **May - June 2003**.
- Send paper to DPTC, SC for approval.
- Publish.

**STEP 5 MAKE RECOMMENDATIONS FOR CMC OINDP DRAFT GUIDANCES
TIMELINE**

- Prepare a recommendation, finalize it within the WG, send to the DPTC and SC for review and approval, and submit to the FDA. **Q3-4 2003.**

Outstanding Clarifications

Dr. Rogers agreed to clarify how much time would be required for mining cascade impactor data from the FDA files in step 4 of the work plan. In response to a question, Dr. Lyapustina noted that in IPAC-RS's experience, industry data mining could be accomplished in two months. Dr. Rogers estimated that the Agency might require close to three or more month. He will consult internally at the Agency and provide the Working Group with a realistic estimate in the near future.

Participants reviewed the status of soliciting statistical support. Dr. Mitchell inquired, and Dr. Lyapustina confirmed that she had contacted certain experts from NIST but no statisticians have come forth yet. Dr. Rogers offered to inquire about availability of statisticians at the Agency, and the participants agreed that Dr. Rogers should do so. Working Group members emphasized that in order to meet the timeline agreed on this teleconference, the statisticians should be identified by the end of May 2002.

Dr. Mitchell asked whether additional time should be allowed in the work plan for receiving input and feedback from the broader scientific community on the work of this Working Group. Participants considered this question and agreed that the timeframe agreed above already allows for such input.

In conclusion, Ms. Gantt noted an important milestone reached by PQRI, namely that the recommendation developed by the PQRI Blend Uniformity Working Group has been approved by the PQRI Steering Committee for submission to the FDA.

IV. AGREED ACTIONS

The participants agreed that:

- Dr. Rogers will contact FDA statisticians to solicit their interest and availability for helping with the Working Group's necessary statistical work.
- Dr. Mitchell and Mr. Wyka will prepare an initial draft of the Investigational Tree by the end of April.
- The timeline for step 1 of the work plan should accordingly be offset by 2 month compared to that proposed on 25 February.
- Dr. Tougas and Secretariat will confirm Dr. Furnkranz's willingness to serve as a co-leader of Step 2 of the work plan.
- Statisticians with experience in survey analysis and probabilistic risk assessment should be identified by the end of May, and these statisticians should be involved in drafting the survey, starting in June 2002.

- A preliminary draft protocol of the experiment for comparison of PSD and DCU variances will be prepared late April-early May and discussed at the next face-to-face meeting of the Working Group on 13 May. Statisticians with expertise in uncertainty analysis should be identified by the end of May, and these statisticians should be involved in preparing the protocol. A mature draft will be prepared by July 2002. The protocol will be reviewed and finalized in September-November 2002, the experiment will be conducted in January-March 2003, and the results will be analyzed in May-June 2003.
- The preparation of the *Good Cascade Impactor Practices* document should start in June 2002 and be completed in June 2003.
- Dr. Tougas and Dr. Rogers will draft the exclusion/inclusion criteria for data gathering in step 4 by the time of the next face-to-face meeting of the Working Group on 13 May.
- Dr. Rogers will clarify how much time would be required for mining the CI data from the FDA files in step 4.
- Ms. Gantt will clarify the PQRI policy for receiving outside input on the Working Group's Work Plan.¹

V. NEXT TELECONFERENCE/MEETINGS

The next teleconference of the PSD Mass Balance Working Group is scheduled for **Thursday, 25 April at 10:00 AM (US EDT)/15:00 UK TIME.**

The next face-to-face meeting of the Working Group is scheduled for **Monday, 13 May 2002, 11:45 AM- 2:15 PM (Arizona/Pacific Time)** [2:45-5:15 PM Eastern Time/19:45-22:15 UK TIME] in the Aster I Conference Room of the Westin La Paloma in Tucson, AZ. At this meeting, the Working Group will review the initial drafts prepared by the Working Group members as listed above.

VI. ADDRESSEES

PQRI PSD Mass Balance Working Group:

Ken Furnkranz (CDER/FDA)
Martin Lavery (Aventis)
Margareth Marques (USP)
Deborah Miran (GPhA)
Jolyon Mitchell (Trudell Medical)

Brian Rogers (CDER/FDA)
Terry Tougas (BI), Chair
Bruce Wyka (Schering-Plough)
Kahkashan Zaidi (USP)

Copy:

Jeffrey Blumenstein (Pfizer, DPTC)
Sylvia Gantt (PQRI)
Sid Goldstein (Prasco, DPTC)

Chris Moreton (DPTC)
Guirag Poochikian (FDA, DPTC)
PQRI PSD Profile Comparisons WG

¹ After the teleconference, Ms. Gantt provided this clarification. The Working Group chair was advised that the work plan should not be circulated outside of PQRI member organizations until the PQRI Steering Committee approves the work plan.