

1 **Minutes of the DPTC Meeting**
2 **on 4 November 2005**

3 **ATTENDEES**

In person

Terry Tougas, *Chair* (Boehringer Ingelheim, IPAC-RS)
David Christopher (Schering-Plough, IPAC-RS)
Paul Curry (Solvay, USP, MBWG)
Bob Dana (Elkhorn Associates, PDA)
Ken Furnkranz (FDA, MBWG)
Sylvia Gantt (PQRI Executive Secretary)
Michael Golden (GSK, IPAC-RS)
Frank Holcombe (FDA)
Qian Li (FDA, MBWG)
Rik Lostritto (FDA, MBWG)
Lana Lyapustina (IPAC-RS Secretariat)
Guirag Poochikian (FDA)
Brian Rogers (FDA, MBWG)
Helen Strickland (GlaxoSmithKline, IPAC-RS)
Yi Tsong (FDA, MBWG)
Raj Uppoor (FDA)
Bruce Wyka (Schering-Plough, IPAC-RS)

By phone

Craig Dunbar (Alkermes, AAPS, MBWG)
Lee Nagao (IPAC-RS Secretariat)
Dan Malinowski (Pfizer, PhRMA)
Jolyon Mitchell (Trudell Medical, AAPS MBWG)
Chris Moreton (Idenix Pharmaceuticals, IPEC)
Rich Poska (Abbot, PhRMA)
Robert Seevers (Lilly, PhRMA)
Bob Wiens (Eli Lilly, IPEC)

4 **AGREEMENTS**

- 5 1. Two reports from the Mass Balance Working Group may be forwarded to the Steering
6 Committee. In addition, creation of a general consensus statement regarding flexibility of
7 limits may be considered for the draft guidance. In this case, an outline of how deviating
8 approaches can be justified would also need to be developed.
- 9 2. The Container Closure WG will update its workplan if much interaction with USP is
10 envisioned.
- 11 3. DPTC members will provide comments on the RFID report by 11 November.

12 **DISCUSSION SUMMARY**

13 *Opening*

14 Dr. Tougas opened the meeting and read the antitrust admonition: “Our discussions today are
15 subject to the anti-trust guidance applicable in the U.S. and E.U. Nothing discussed at this
16 meeting is intended to restrict the individual decision-making of any member company or to
17 represent an agreement to coordinate marketing or sales conduct. Those participating in this
18 meeting are instructed to avoid discussion of competitively sensitive subjects, including, but
19 not limited to, confidential marketing, sales, and pricing information.”

20 The objective of the meeting was to update on all of the DPTC Working Groups, and in
21 particular to hear reports from the Mass Balance Working Group (MBWG).

22 *The PSD Profiles Comparisons Working Group*

23 The Working Group is evaluating a combination of the chi-square ratio test and with a
24 population bioequivalence test on the “impactor sized mass”, i.e., mass on those impactor
25 stages that have a specific upper cutoff value. Currently the members of the group are
26 completing the assignment of naming a set of realistic profiles equivalent or inequivalent.
27 At the next meeting of the group, to be held later this year, these assessments will be
28 compared to those made by the combined test. If the test is not as robust as hoped, the
29 Working Group’s Recommendations will highlight situations where it is expected to work
30 well and situations where it may not, but at the moment no work is planned for developing a
31 different test. This situation is similar to a traditional BE assessment, where approaches
32 applicable for high 1st pass metabolism drugs may not be appropriate for other drugs.

33 The ultimate Recommendations document will also proscribe caveats and test method
34 considerations such as the necessity for a cross-over design.

35 Finalization and submission of the Recommendations to FDA is planned for the first quarter
36 of 2006.

37 *The Excipients Working Group*

38 The survey of excipient manufacturers, users and distributors was closed on 10/14/05, with
39 many usable surveys and much good information received. When the survey was designed, a
40 systematic approach to questions was used. Now the results will be analyzed and eventually
41 prepared in the form of a report. Particular attention will be paid to unusual responses or
42 practices that are inconsistent with current regulations. The systematic review and analysis
43 may take up to 3-6 months. No other deliverables are expected in the near future.

44 Eventually, a workshop may be considered based on the results of the findings, both to
45 highlight current good practices and to draw attention to the areas that might require further
46 work.

47 Dr. Poochikian stressed that in the QbD thinking, everything depends on precursors and it
48 would be important to understand how the testing of excipients relates to the physico-
49 chemical properties of the final drug product. He wondered whether that aspect would be
50 addressed in the Excipients WG effort, or whether the goal is only to update and modify
51 compendial test methods.

52 Dr. Moreton explained that the issue is not always in absolute values regarding particular
53 properties but in their variability from batch to batch. Excipient manufacturers are
54 sometimes required by pharmaceutical companies to produce material to specifications
55 beyond what manufacturing processes can deliver, and because such demands are often not
56 economical, they stop supplying to the pharmaceutical industry.

57 ***The Mass Balance Working Group***

58 Presentations were made by Dr. Rogers and separately by Mr. Wyka and Ms. Strickland (the
59 slides will be available on the PQRI website along with the minutes. These presentations
60 represented the two differing perspectives on the value of the mass balance measurement
61 obtained during aerodynamic particle size distribution (APSD) measurements. During the
62 Committee’s discussion, the following points were made:

- 63 • The aerodynamic particle size distribution (APSD) measurement has undisputed value for
64 orally inhaled drugs because of potential links between APSD and efficacy or safety.
- 65 • Some participants questioned the value of the mass balance measurement, which is
66 obtained during APSD test, as a product specification (which could fail a batch of
67 product) rather than a run qualification (which would only comment on whether APSD
68 measurement is valid). The main reasons for this position are: (1) the high variability of
69 the method regardless of product quality and (2) the fact that the consistent product
70 delivery is controlled through a separate and more accurate test (dose content
71 uniformity). In addition, it was pointed out that if truly malfunctioning units were
72 observed during mass balance, under cGMP this should still lead to a product
73 investigation. This is the case even if mass balance is used strictly as a run qualification.
- 74 • Other participants expressed that if a mass balance outside +/-20% is obtained in two
75 units out of the batch, and if that value is truly due to the “malfunctioning” units and not
76 to the random variability of the test, the batch should fail. As a result, they argued the
77 mass balance measurement should be part of a product specification.
- 78 • Dr. Poochikian encouraged companies to provide to the Agency on an individual basis
79 industry’s data regarding the issue of cascade impactor’s mass balance.

80 The Committee discussed submitting two reports to the Steering Committee and also creating
81 a consensus general language for the draft guidance, which would emphasize that different
82 limits might be considered on a case by case basis. In this case, it would also be important to
83 clarify what is required to obtain a deviation from the approach stated in the guidance, i.e.,
84 what type of data and what type of statistical tools would be appropriate for justification.
85 This outline could be presented in the form of a flow chart.

86 ***The Leachables and Extractables Working Group***

87 Agenda and posters for the December L&E Workshop are being finalized. As of the day of
88 the meeting, 70 registrants had enrolled in the Workshop. The complete text of the
89 Recommendations may not be available for the general public before the Workshop, but the
90 Introduction and Summary might be released to the workshop attendees. The PQRI member
91 organizations will also have an opportunity for a thorough review and comment on the draft.

92 ***The Container Closure Working Group***

93 The Working Group has lost several members in the last 12 months due to people’s
94 movement within and between companies, and there is currently an active recruitment effort
95 under way. In the short-term, the following activities are under way:

- 96 • Executing design of the experiment for range finding study;
- 97 • Preparing response to comments on the previously published USP stimuli article about
- 98 moisture vapor transfer rates; and possibly incorporating new approaches into USP test
- 99 methods;
- 100 • Engaging the USP Packaging and Storage Committee to ensure consistency of
- 101 approaches; and
- 102 • Considering another publication as a follow up to the previously published paper, and this
- 103 time illustrating how the proposed method could be implemented.

104 The focus of work is not so much on safety and efficacy of container closure systems but on
105 their interchangeability. The group's workplan may need to be updated to reflect the
106 increased focus on USP.

107 ***The RFID Working Group***

108 This group started working several months ago to address potential effects of exposure to
109 radiofrequency on pharmaceutical products, in particular on biologics. Last June, a risk
110 analysis was conducted that showed no need for generation of additional data.

111 During a meeting between Dr. Poochikian, Dr. Massa, Dr. Clark, Ms. Winkle and Dr.
112 Seevers, it was agreed that PQRI Recommendations to FDA would be prepared in the form
113 of a report. This report had been circulated to the DPTC members before this meeting. The
114 report drew upon studies by Accenture, as well as upon papers and information from the
115 NMR field, and showed that exposures to even orders of magnitude higher fields do not pose
116 significant risk of degrading pharmaceutical products.

117 Separately, a paper by a CDRH scientist had been recently released, which supported
118 conclusions in Dr. Seevers' report with respect to thermal effects. This new study, according
119 to Dr. Seevers, duplicates the results obtained in the cited Accenture study. For example,
120 based on models and extrapolations it showed that in all configurations, including worst-case
121 scenario exposures, the temperature increase was less than 1 degree, and only in one case it
122 rose to 1.7 degrees per hour, which is still less than the variability allowed for stability
123 chambers by ICH guidelines. Dr. Poochikian noted that he was aware of this CDRH study. .
124 Dr. Poochikian stated that reportedly someone from FDA (RFID Task Force?) would make a
125 presentation at a trade meeting on counterfeiting issues in the near future.

126 **NEXT MEETING/TELECONFERENCE**

127 Teleconference on 1 December.
128

Finalized on 22 December 2005