

1 **Minutes of the DPTC Meeting**
2 **on 3 November 2004**

3 **ATTENDEES**

In person

Terry Tougas, *Chair* (Boehringer-Ingelheim, IPAC-RS)
Jon Clark (FDA)
Rajendra Uppoor (FDA)
Sylvia Gantt (PQRI Executive Secretary)
Lana Lyapustina (IPAC-RS Secretariat)

By phone

Tony Amann (ACN Pharma, GPhA)
David Christopher (Schering-Plough, IPAC-RS)
Frank Holcombe (OGD/FDA)
Chris Moreton (Idenix Pharmaceuticals, IPEC)
Lee Nagao (IPAC-RS)
Rich Poska (Abbot, PhRMA)
Russ Somma (IPS, ISPE)
Bob Wiens (Eli Lilly, IPEC)
Bruce Wyka (Schering-Plough, IPAC-RS)

4 **DECISIONS MADE**

- 5 1. Dr. Tougas will request the Steering Committee to facilitate Agency's internal discussions
6 regarding the profile comparisons test, and will explain that the Profile Comparisons WG's
7 timeline is being extended by 3 months.
- 8 2. The DPTC will review and comment on the draft experimental protocol, to be provided by
9 the Container Closure Working Group in late November.
- 10 3. Dr. Norwood will be invited to present at the next face-to-face DPTC meeting on the draft
11 recommendations prepared by the Leachables and Extractables Working Group.
- 12 4. The Excipients Working Group's workplan has been approved and now enters the
13 implementation phase.
- 14 5. The DPTC will discuss potential future projects at the next face-to-face meeting.
- 15 6. FDA will consider appropriate actions regarding comments to the Blend Uniformity
16 guidance; there is no action for the DPTC regarding this matter at this time.
- 17 7. The next face-to-face DPTC meeting will be held the day before the Steering Committee
18 meeting (which is currently planned for 10 February 2005).

19 **DISCUSSION SUMMARY**

20 *Opening*

21 Dr. Tougas opened the meeting. The following antitrust admonition was read: "Our
22 discussions today are subject to the anti-trust guidance applicable in the U.S. Nothing

23 discussed at this meeting is intended to restrict the individual decision-making of any
24 member company or to represent an agreement to coordinate marketing or sales conduct.
25 Those participating in this meeting are instructed to avoid discussion of competitively
26 sensitive subjects, including, confidential marketing, sales, and pricing information.”

27 Dr. Tougas introduced the following objectives for the meeting: (i) to update on the DPTC
28 working groups, (ii) to report on the strategic meeting of the PQRI Steering Committee; and
29 (iii) to discuss the matter raised in Tom Garcia’s email.

30 *The PSD Profiles Comparisons Working Group*

31 Mr. Christopher provided an update on the PSD Profile Comparisons Working Group. He
32 reminded the participants that particle size distribution (PSD) of orally inhaled and intranasal
33 products is an important characteristic that was recommended in the 1999 FDA draft
34 guidance as one of the in-vitro measures for bioequivalence comparisons when approving
35 generic products or changes in innovator products (e.g., formulation or vendor change). The
36 PSD Profile Comparisons Working Group has thoroughly studied the chi-square test
37 proposed in that guidance, identified its capabilities and limitations, and in the process
38 developed statistical tools for assessing any profile comparisons test. Last spring, the
39 Working Group, with contribution from FDA scientists, developed 38 scenarios (based on
40 real CFC MDI data) for “test-driving” the chi-square test. Currently, the FDA scientists on
41 the Working Group are reviewing and discussing these scenarios with others at the Agency
42 (including a supervisory chemist and medical staff) in order to bring their internal
43 recommendation regarding equivalence or inequivalence of the given profiles.

44 To illustrate the need for such input, Mr. Christopher provided examples of several profiles,
45 highlighting four specific scenarios, which the current test will not be able to distinguish
46 consistently. If the FDA scientists indicate that any of the four scenarios should be
47 considered inequivalent, a more discriminating test needs to be considered by the Working
48 Group (some possible alternative tests have been under development within the Working
49 Group on a parallel track).

50 Mr. Christopher explained that in order to recommend a most appropriate test for profile
51 comparisons to FDA, the Working Group needs to have pre-determined “targets” for the test
52 to declare equivalent or inequivalent; and this is a decision point and a rate-limiting step at
53 the moment. Mr. Christopher stressed, however, that all Working Group members are active
54 and engaged, and the slow progress is due to the complexity of the issue and the need to
55 consider various perspectives.

56 In order to allow FDA scientists sufficient time to reach internal consensus, the Working
57 Group would like to extend its workplan by 3 months. Mr. Christopher requested the help of
58 the DPTC and Steering Committee to facilitate Agency’s internal discussions.

59 The Working Group is also preparing a scientific paper describing its findings to date. A
60 draft should be available for the DPTC review by the end of the year.

61 During the DPTC discussion, Mr. Christopher further clarified the following:

- 62 – the PSD profile comparison test is a strictly in-vitro comparison;
- 63 – the chi-square test as proposed in the draft guidance requires 30 cascade impactor
- 64 runs of the Test product and 30 cascade impactor runs of the Reference product;
- 65 – this test is not intended nor appropriate for release or stability testing;
- 66 – the test compares the performance of a Test to the Reference, not of a product to a
- 67 specification;
- 68 – to minimize the variability not related to the product (“noise”), such as instrument or
- 69 operator variability, the profile comparison test should be conducted in cohorts,
- 70 similar to the cross-over design used in clinical trials;
- 71 – according to the draft guidance, the 30 units of Test and Reference product should
- 72 come from 3 respective lots (10 units from each lot); in this way, lot-to-lot variability
- 73 is included in the comparison; and
- 74 – when PQRI and FDA develop a safe harbor for data collections, the Working Group
- 75 may consider a prospective study to supplement information in its existing database.

76 It was agreed that Dr. Tougas will request the Steering Committee to facilitate Agency’s
77 internal discussions regarding the profile comparisons test, and will explain that the Profile
78 Comparisons WG’s timeline needs to be extended by 3 months.

79 ***The Container Closure Working Group***

80 Dr. Moreton briefed the DPTC on the 27 October teleconference of the Container Closure
81 Working Group, as follows:

- 82 – the white paper prepared by the Working Group will be published in the
- 83 *Pharmacopeial Forum* in January 2005;
- 84 – a new FDA representative on the Working Group Susan Zuk reported that the 2nd
- 85 draft of the BACPAC-II guidance would be forwarded to FDA internal group in
- 86 November;
- 87 – the Working Group discussed the experimental protocol for the ranging study to test
- 88 the hypothesis of moisture permeability of different packages; and specifically the
- 89 way to fill and treat blister packages. The draft protocol will be provided to the
- 90 DPTC for review in late November;
- 91 – to conduct the planned experiments, the Working Group will rely on the
- 92 manufacturing capabilities of its member companies; the experiments are expected to
- 93 start in early 2005; the exact timeline will depend on the coordination of schedules.

94 ***The PSD Mass Balance Working Group***

95 Mr. Wyka provided an update on the PSD Mass Balance Working Group. He noted that
96 much progress was made at the face-to-face meeting at the end of July, where the first draft
97 of recommendations was outlined based on the industry and FDA experience. There are
98 several issues that need to be resolved, but the Working Group hopes to finalize its

99 recommendations by the end of the year. A scientific paper presenting the statistical
100 justification of the recommendation is also under preparation. If a safe harbor for PQRI data
101 is established in the future, the Working Group may assess various sources of MB variability
102 in the next phase of its work.

103 Mr. Wyka reviewed for the DPTC members the initial draft of the recommendations using a
104 flow-diagram, which included the possibility for a limited re-testing and re-centering the
105 target mass balance. Among the issues currently under discussion are:

- 106 – the number of allowed re-testing cycles (2 or 3);
- 107 – the range for the expected mass balance results (± 15 or 20% LC)
- 108 – the allowed direction of re-centering (only -5% or $\pm 5\%$ LC); and
- 109 – the use of a new or the same unit for re-testing.

110 Some of these issues could be analyzed via operating characteristic (OC) curves using typical
111 variabilities seen in these products, as illustrated in the slides circulated before the DPTC
112 meeting. After the Working Group's statisticians verify these OC curves, FDA will discuss
113 them internally, after which that the work on the recommendations could be continued and
114 completed.

115 During the DPTC discussion, Dr. Amann commented that the cascade impactor test is very
116 variable. Dr. Tougas agreed that the mass balance measurement significantly depends on the
117 testing system and not only on the product. For this reason, the current draft
118 recommendation regards mass balance as a composite measure of both the system
119 suitability/performance and the product acceptability/performance.

120 ***The Leachables and Extractables Working Group***

121 Dr. Nagao updated the DPTC on the progress of the L&E WG. She explained that at the
122 October face-to-face meeting, the Working Group reviewed draft recommendations and
123 agreed on timelines for revising and completing them. The WG chemists reviewed their
124 specific chapters, which are based on their earlier work; and the WG toxicologists reviewed
125 the justification of their proposed thresholds. The WG recommendations are being kept at a
126 general, non-prescriptive level. The Working Group plans to finalize them by the end of the
127 year and to provide them to the DPTC for review in early 2005.

128 Dr. Nagao highlighted the need for briefings on these recommendations before the entire
129 document is circulated for formal review to the DPTC, Steering Committee and PQRI
130 member organizations. Dr. Tougas proposed that Dr. Norwood be invited to present his
131 Working Group's recommendations in person at the next DPTC meeting.

132 Furthermore, the Working Group in collaboration with ECAS is planning a PQRI workshop
133 in the fall of 2005, in order to explain its Leachables and Extractables recommendations to a
134 broader audience. This workshop will be mentioned in general presentations to be made by
135 the WG members at the RDD Europe and PDA conferences in May 2005.

136 ***The Excipients Working Group***

137 Mr. Wiens reported that the revised workplan has been submitted to the Steering Committee
138 and approved with no further comments. The Working Group will now start implementing
139 the plan. No action is required of the DPTC at this time.

140 ***The RFID Working Group***

141 Ms. Gantt informed the DPTC that the RFID Working Group, chaired by Dr. Tougas, is
142 preparing a workplan, which should be completed by the end of November. The first phase
143 of the workplan is projected to be completed in the spring of 2005.

144 ***PQRI Strategic Planning***

145 Dr. Tougas shared with the DPTC members the highlights of the strategic planning meeting
146 held by the PQRI Steering Committee in September 2004. He explained that all Technical
147 Committee Chairs presented to the SC an update on their projects, which was followed by a
148 constructive discussion about future directions of the Institute. In particular, the Drug
149 Product and Manufacturing Technical Committees identified several areas of potential
150 synergism, where constructive collaboration would be helpful in order to address the many
151 aspects of the Agency's 21st Century initiative. The Steering Committee also considered
152 international initiatives but agreed not to duplicate current ICH efforts. The DPTC members
153 agreed, but noted, however, that unlike ICH, PQRI could create practical guidance on
154 specific issues, and set standards based on science and research. Several members
155 underscored the unique nature of PQRI, where scientific issues could be jointly discussed.

156 The DPTC members agreed to continue their own strategic discussions at the next face-to-
157 face meeting, to be held in early 2005.

158 ***Tom Garcia's Email***

159 The participants considered the situation described in Tom Garcia's email. Dr. Clark further
160 explained background and potential options for dealing with that situation. It was agreed that
161 DPTC does not need to take any action on this matter at this time.

162 **NEXT MEETING/TELECONFERENCE**

163 To be confirmed by email (will depend on the Steering Committee's schedule)

164

Finalized on 10 January 2005