

1 **Minutes of the DPTC Meeting**
2 **on 25 January 2006**

3 **ATTENDEES**

Terry Tougas, *Chair* (Boehringer Ingelheim, IPAC-RS)
David Christopher (Schering-Plough, IPAC-RS)
Bob Dana (PDA)
Sylvia Gantt (PQRI Executive Secretary)
Michael Golden (GlaxoSmithKline, IPAC-RS)
Lana Lyapustina (IPAC-RS Secretariat)
Rich Poska (Abbot, PhRMA)
Bruce Wyka (Schering-Plough, IPAC-RS)

Clyde Anthony (USP), by phone
Frank Holcombe (FDA), by phone
Dan Malinowski (Pfizer, PhRMA), by phone
Chris Moreton (Idenix Pharmaceuticals, IPEC), by phone
Dan Norwood (Boehringer Ingelheim, IPAC-RS), by phone
Robert Seevers (Lilly, PhRMA), by phone
Russel Somma (IPS, ISPE), by phone

Absent:

Tony Amann (GPhA)
Guirag Poochikian (FDA)
Raj Uppoor (FDA)
Nakissa Sadrieh (FDA)
Vilayat Sayeed (FDA)
Bob Wiens (Lilly, IPEC)
Bill Williams (University of Texas, AAPS)

4 **AGREEMENTS**

- 5 1. The RFID Report has been approved. After finalization by Dr. Seevers and Dr. Tougas it will
6 be forwarded to the PQRI Steering Committee (SC) and subsequently to FDA. A peer-
7 reviewed publication based on the report was proposed by Dr. Seevers. The DPTC supported
8 this proposed activity.
- 9 2. Ms. Gantt will provide the finalized PQRI publication policy to the DPTC members.
- 10 3. Dr. Tougas will communicate to the SC the DPTC feedback discussed at this meeting.
- 11 4. The proposal for addressing statistical issues in specification-setting will be revised in the
12 next few weeks and re-submitted to DPTC for consideration.

- 13 5. In the next 2-3 months, Dr. Poska, Dr. Moreton and Mr. Golden will each provide more
14 detailed descriptions of the potential new topics they proposed at this meeting.
- 15 6. Dr. Norwood and Dr. Tougas will contact Dr. Sadrieh (the new FDA representative on the
16 Steering Committee) regarding the distribution of the L&E Recommendations to the
17 Workshop participants.
- 18 7. Ms. Gantt will send a reminder to the DPTC about the 1 Feb. deadline for comments on the
19 L&E Recommendations, and absent major comments the Recommendations would be
20 provided to the Steering Committee.
- 21 8. The L&E WG's presentation at the Society of Toxicology meeting has been approved.
- 22 9. Future drafts for comment to the DPTC should be circulated with a voting ballot with the
23 following choices: Approve. Approve with comments. Not approve (with explanation).
24 Abstain (with explanation).
- 25 10. The DoE protocol for the screening study by the Container Closure System has been
26 approved by the DPTC and the testing should commence.
- 27 11. The draft Mass Balance paper will be provided to the DPTC and the full MB WG after
28 finalization by the drafting team. The decision regarding disposition of the paper will be
29 made based on the majority of the returned votes.

30 **DISCUSSION SUMMARY**

31 *Opening*

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

38 The objective of the meeting was to discuss the following:

- 39 • Mission of the DPTC in light SC Discussions of Mission/Function of PQRI
- 40 • RFID Risk Assessment
- 41 • Proposal 'Development of Statistical Methods Related to Stability Testing'
- 42 • Other Potential New Projects
- 43 • Working Group Updates

44 ***Mission of PQRI and of DPTC***

45 Dr. Tougas invited the participants to discuss the new PQRI mission that is being discussed
46 by the Steering Committee and may be finalized at the upcoming 8 February SC meeting.
47 He reminded the participants that later, the DPTC mission would also need to be developed,
48 which had been started by Dr. Poska and Mr. Golden in the past.

49 The participants made a number of suggestions for consideration by the Steering Committee,
50 regarding the original and new missions of PQRI, the SUPAC model, the role of FDA in
51 PQRI, the process for populating PQRI working groups and for ensuring technical capability
52 of each group. The participants noted that several working groups have been successful in
53 building consensus (BU, L&E, Profile Comparisons) but some groups have not (MB, RFID),
54 and the new process for publishing the majority and minority opinions where consensus
55 could not be reached should help resolving those issues through a broader scientific
56 discussion in peer-reviewed journals. DPTC stressed however that in general, working
57 towards consensus should be the primary objective.

58 The DPTC stressed that all organizations, but above all FDA as the regulatory agency
59 dealing with scientific issues, should be bringing new projects for PQRI's research. DPTC
60 acknowledged that project timelines should be managed more rigorously in the future.

61 ***The RFID Working Group***

62 Dr. Seevers explained that the comments received on the draft RFID report are minor in
63 nature. The DPTC agreed that Dr. Seevers and Dr. Tougas should finalize the report and
64 forward it the Steering Committee for subsequent submission to FDA. The DPTC further
65 recommended that the report be published in peer-reviewed literature, e.g., in the journal
66 *Pharmaceutical Technology*. Ms. Gantt agreed to circulate the revised PQRI publication
67 policy to the DPTC members after the meeting.

68 ***Proposal for Statistical Issues in Specification and Shelf-Life Setting***

69 Dr. Tougas reviewed the background for a research proposal related to statistical issues in
70 specification setting and establishment of products' shelf life for time dependent quality
71 attributes. He explained the statistical flaw in current guidelines and regulatory approaches
72 to setting of products' specifications and shelf life, namely the inherent
73 contradiction/mismatch between the limits derived from *average* batch performance and the
74 decisions based on *individual* test results. Mr. Christopher commented that this issue had
75 also been often discussed within the PhRMA CMC statistics group and regularly comes up in
76 various workshops. He confirmed that PhRMA CMC statistics group would be interested in
77 this PQRI effort.

78 The DPTC agreed that this proposal might have value especially if viewed more broadly than
79 just setting the shelf life. The participants commented that it would be well aligned with the
80 Quality by Design principles. They mentioned that the current initiative to align safety and
81 efficacy with product specifications is leaving unclear the details for setting control criteria.

82 For example, for impurities, the tox limits may provide an upper ceiling for acceptance
83 criteria but the control specifications would be well within those tox-defined limits, and the
84 process for arriving at appropriate control limits is currently not well established. The
85 participants felt that an open, comprehensive technical discussion by the experts in this field,
86 and some common recommendations in this area would be of much value. Dr. Tougas
87 explained that having a dedicated person (e.g., a graduate student) to investigate this issue,
88 while having that person's advisor as a resource and the PQRI working group as a discussion
89 forum could be the most efficient way to address this issue.

90 The DPTC recommended that the present draft proposal be revised so that the background
91 and context be better clarified. It was also recommended that coordination with the
92 Manufacturing TC be considered. The DPTC agreed that Dr. Tougas, Dr. Schwenke (BI),
93 Mr. Christopher and potentially Dr. Sandell (AstraZeneca) should revise the proposal and
94 resubmit it to the DPTC.

95 ***Potential New Topics***

96 DPTC members mentioned the following potential topics (and agreed to prepare more
97 detailed descriptions for the next face-to-face meeting):

- 98 1. Statistical issues in setting products' shelf life. (Per above, to-be-revised UNL
99 proposal).
- 100 2. Statistical methodologies for setting specifications. (Need to establish methods and
101 approaches that both FDA and industry can use.)
- 102 3. Dissolution specification in light of QbD. (Dr. Hussain had approached PhRMA
103 about this issue last fall).
- 104 4. Clarification of the terms "design space", "critical process parameter", "critical
105 quality attribute". (Currently there are many varying definitions within FDA, USP,
106 industry, etc.)
- 107 5. ICH Climate Zone IV stability issues and scientific justifications. (Concerns of India,
108 other Asian countries).
- 109 6. Alcohol interactions with modified-release products.
- 110 7. Modification of the Arrhenius equation for prediction of chemical stability to
111 incorporate the effect of moisture (water activity).

112 ***The Leachables and Extractables Working Group***

113 Dr. Norwood reported that the L&E Workshop last December was successful, with over 160
114 total participants, including about 35 from FDA. The Working Group is now reviewing
115 comments from the Workshop. One of the main requests has been that the L&E
116 Recommendations be provided to the attendees. The DPTC recommended that Dr. Norwood
117 and Dr. Tougas contact Dr. Sadrieh (the new FDA representative on the Steering Committee)
118 regarding this.

119 Dr. Norwood further explained the proposed presentation at the Society of Toxicology
120 meeting, which will be based on the information already disclosed at the Workshop. The
121 DPTC approved this presentation.

122 Dr. Norwood noted that no major comments have been received on the L&E
123 Recommendations circulated at the end of 2005 for the DPTC review. DPTC agreed that
124 Ms. Gantt should send a reminder about the 1 Feb. deadline, after which date the
125 Recommendations should be provided to the Steering Committee.

126 The DPTC recommended that in the future, drafts to DPTC be circulated along with a voting
127 form.

128 Dr. Norwood noted that the Working Group is now considering plans for future publications
129 based on the prepared Recommendations.

130 ***The Container Closure System Working Group***

131 Mr. Malinowski reported that the Working Group is focusing the DoE screening study and
132 the protocol for testing blisters and bottles. Specifically, the group is now determining
133 appropriate storage conditions and identifying equipment for producing packages.

134 Mr. Malinowski noted that the draft protocol submitted to DPTC had elicited only minor
135 comments and he requested a formal endorsement of the proposed protocol. The DPTC
136 confirmed that the protocol should be considered approved and the study should commence
137 without necessarily re-circulating the document for another round of comment/approval.

138 Finally, Mr. Malinowski reported on the WG's recruiting efforts and explained that the
139 Group would like to have a balance of R&D and manufacturing experience and also to have
140 members that can provide laboratory or other resources for the required work. He indicated
141 that the WG had identified three promising candidates and would provide their CVs to the
142 DPTC for review and approval in the near future.

143 ***The Profile Comparisons Working Group***

144 Mr. Christopher reported that the "Interim Progress Report" has been revised based on the
145 reviewer's comments and the revised manuscript is currently under the Working Group's
146 review. The Working Group is also completing the evaluation of the capabilities of the
147 combined test (chi-square ration and impactor-sized mass tests), and plans to prepare a report
148 of findings by the end of Q2 2006. A peer-reviewed publication based on the findings is also
149 planned. The participants agreed that any follow-up work that might be considered based on
150 the WG's findings, should be presented to PQRI as a new project proposal.

151 ***The Excipients Working Group***

152 Dr. Poska reported that the Working Group is now drafting a report summarizing findings of
153 the survey. The draft should be available for the DPTC review in the near future. He
154 commended Dr. Uppoor for the excellent work with that Working Group.

155 ***The Mass Balance Working Group***

156 Mr. Wyka reported that drafting of the paper outlining the majority WG's position is nearing
157 completion. The DPTC agreed that after finalization by the drafting team, the paper should
158 be provided to the DPTC and the full MB WG for comment and voting, including the
159 following choices: "Approve"; "Approve with comments"; "Not approve (with
160 explanation)"; and "Abstain (with explanation)." The DPTC further agreed that the
161 decision will be made based on the majority of the returned votes, in accord with the current
162 PQRI publication policy.

163 In addition, as suggested at the 4 Nov. DPTC meeting, a draft language for the FDA
164 guidance has been proposed and will be discussed by the Working Group. The target is to
165 submit the proposed language to FDA and to sunset this WG by the end of Q1 2006.

166 **NEXT MEETING/TELECONFERENCE**

167 Ms. Gantt will circulate by email a schedule of DPTC meetings and teleconferences for 2006.

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Finalized on 21 February 2006