



1 **Minutes of the DPTC Meeting**
2 **on 11 August 2004**
3 in Rockville, MD

4 **ATTENDEES**

<i>In person</i>	<i>By Phone</i>
Terry Tougas, Chair (Boehringer-Ingelheim, IPAC-RS) Clydewyn Anthony (USP) David Christopher (Schering-Plough, IPAC-RS) Frank Holcombe (OGD/FDA) Sylvia Gantt (PQRI Executive Secretary) Lana Lyapustina (IPAC-RS Secretariat) Chris Moreton (Idenix, IPEC) Guirag Poochikian (FDA) Rich Poska (Abbot, PhRMA) Russ Somma (IPS, ISPE) Rajendra Uppoor (FDA) Bob Wiens (Eli Lilly, IPEC)	Tony Amman (GPhA) Michael Golden (GlaxoSmithKline, IPAC-RS) Dan Malinowski (Pfizer) Lee Nagao (IPAC-RS) Bill Williams (University of Texas, AAPS)

5 **DECISIONS MADE**

- 6 1. The paper prepared by the Container Closure Working Group, entitled “Basis for Using
7 Moisture Vapor Transmission Rate Per Unit Product in The Evaluation of Moisture-Barrier
8 Equivalence of Primary Packages for Solid Oral Dosage Forms” will be forwarded to the
9 Steering Committee for approval. The minor changes suggested by the DPTC at the meeting
10 will be incorporated into the paper in parallel and approved by email.
- 11 2. Ms. Gantt will provide assistance to the Container Closure Working Group with organizing
12 meetings and teleconferences.
- 13 3. The Container Closure Working Group will provide a draft of the pre-screening protocol for
14 the MVTR study to DPTC for comment in the beginning of the 4th quarter, before the next
15 DPTC meeting.
- 16 4. The Excipients Working Group will revise its draft working plan based on the DPTC
17 comments and will resubmit it to DPTC for review.
- 18 5. Mr. Poska will take over from Mr. Moreton the responsibilities as DPTC liaison to the
19 Excipients Working Group.
- 20 6. The current Excipient Working Group will complete the work plan proposal. Once the
21 Steering Committee approves the work plan, additional members will be recruited. Names of
22 the candidates for populating the Excipients Working Group should be forwarded to Ms.
23 Gantt.

- 24 7. The Leachables and Extractables Working Group should prepare its recommendations for
25 PQRI review and submission to FDA by the end of 2004.
- 26 8. The Leachables and Extractables Workshop should be planned for the fall 2005. The issue of
27 leachables in products other than orally inhaled and nasal (e.g., ophthalmics, otics,
28 parenterals) may be included in the program of the Workshop.
- 29 9. The interim recommendations from the Mass Balance Working Group should be prepared
30 and submitted to FDA.
- 31 10. The Mass Balance Working Group should nominate an appropriate Chair to replace Dr.
32 Tougas in light of his new responsibilities. The candidate recommended by the Working
33 Group should provide a CV and a statement of interest. The DPTC will have to consider and
34 ratify the candidate selected by the Working Group.
- 35 11. After the submission of the interim recommendations to FDA, the Mass Balance Working
36 Group will have to consider its plans for the period until the safe harbor provisions for data
37 sharing are created.
- 38 12. The Profile Comparisons Working Group's paper may be published in the International
39 Journal of Pharmaceutics, provided that the IJP copyright conditions are acceptable to PQRI.
40 The copyright conditions will be discussed by the Steering Committee and ECAS.
- 41 13. The new format for the DPTC Tracking Form will be presented to the Steering Committee
42 for comment.
- 43 14. The next face-to-face meeting of the DPTC is tentatively scheduled for 3 November 2004.
44 Going forward, the DPTC schedule will include 3-4 face-to-face meetings a year and more
45 frequent teleconferences.
- 46 15. At the next meeting, the Committee will focus primarily on future directions of DPTC and
47 will only briefly review reports from the working groups. Prior to the meeting, all members
48 should inquire within their organizations and canvass the issues that need to be addressed,
49 potentially through DPTC.

50 **DISCUSSION SUMMARIES**

51 *Opening*

52 Dr. Tougas opened the meeting and read the antitrust admonition: "Our discussions today are
53 subject to the anti-trust guidance applicable in the U.S. Nothing discussed at this meeting is
54 intended to restrict the individual decision-making of any member company or to represent
55 an agreement to coordinate marketing or sales conduct. Those participating in this meeting
56 are instructed to avoid discussion of competitively sensitive subjects, including, confidential
57 marketing, sales, and pricing information."

58 Dr. Tougas welcomed the participants, especially the new DPTC members, Dr. Williams and
59 Dr. Amman. The Committee agreed that Dr. Lyapustina would attend DPTC meetings to
60 take notes. The participants reviewed and approved the proposed agenda with additions.

61 *The Container Closure Working Group*

62 Mr. Malinowski presented a final draft of the paper, which had been revised per DPTC's
63 previous comments. In response to questions, Dr. Moreton and Mr. Malinowski explained
64 that the appendices are based on the previously existing data supplied by companies, as an
65 illustration of how the approach proposed in the body of the paper could be applied.
66 Experiments to verify the approach, including the equations, are being planned, and will be
67 conducted as a second phase of the work after the paper is submitted for publication. The
68 Committee members recommended that this be clarified in the next revision, but approved
69 the paper for distribution to the Steering Committee for comment and approval.

70 In parallel with the work on the paper, the Working Group is planning screening experiments
71 for the MVTR test. Prescreening is also being planned. Dr. Jim Burgum is ensuring that
72 statistical design is appropriate before full-scale study is initiated. The DPTC will be
73 receiving a draft prescreening protocol for comment in the beginning of the fourth quarter,
74 before the next DPTC meeting.

75 The third direction of the Group's work is focused on data mining. The details of the
76 questionnaire will depend on the results of prescreening. When prepared, the request for data
77 will be posted on the PQRI website. In response to questions, Dr. Moreton and Dr. Poska
78 explained that safe harbor provisions are not necessary for this data mining because the
79 identity of specific products will not be declared, and the survey will not be asking for failing
80 data but for evaluation of different types of packaging with and without dessicant. Some
81 commented that although compliance concerns may not be an issue here, the resource
82 requirements still may be. However, DPTC was assured that direct participants on the
83 Working Group are prepared to share the data.

84 *The Excipients Working Group*

85 Mr. Wiens presented slides outlining the work plan of the Excipients Working Group. The
86 initial step would be to conduct an industry survey to assess current industry practices and
87 use of alternate methods for qualification of excipients. Based on the survey results, an
88 action proposal would be formulated, followed by a white paper or other deliverable. The
89 overall goal of the effort is to move away from multiple and redundant pharmacopeial tests
90 and large dossiers, to a more harmonized and streamlined control strategies, focusing on
91 critical attributes and processability (to support PAT). Some expressed doubts that critical
92 attributes could be decided a priori because, for a given excipient, they will depend on the
93 specific product where it is used.

94 DPTC members noted a concern that due to the liability associated with the USP-NF
95 branding, suppliers of excipients stop marketing pharmaceutical grade excipients. The lack
96 of mutual recognition of pharmacopeial standards world-wide also deters excipient suppliers
97 from marketing pharmaceutical grade materials. FDA representatives on the DPTC stressed

98 that FDA, for its part, accepts tests conducted according to non-USP methods, as long as they
99 provide equal or better control. Industry representatives recommended that this message be
100 communicated to the entire community more clearly and more consistently. Concerns were
101 also raised with inspectors' not accepting on-line tests for continuous processes in lieu of
102 final 'batch' tests.

103 The DPTC recommended that the Excipients Working Group develop its workplan further,
104 specify its focus on the US, and lay out plans for working with international groups, such as
105 the Pharmacopeial Discussion Group (PDG), to carry out international harmonization.

106 ***The Leachables and Extractables Working Group***

107 Dr. Nagao reported that the Chemists of the Leachables and Extractables Working Group are
108 preparing their recommendations. The Toxicologists have finalized the Threshold
109 Justification paper, and are now finalizing a document explaining the recommended
110 interaction between chemists and toxicologists for identifying and safety-assessing
111 leachables and extractables. In response to a question, Dr. Nagao clarified that both
112 development and routine-control issues are addressed by the Working Group. All
113 recommendations from the Working Group are scheduled for completion and submission to
114 FDA by the end of this year. The DPTC approved this plan. Dr. Poska asked how this
115 recommendation would be incorporated into FDA documents, in light of FDA's current re-
116 thinking of the use of guidances. Dr. Poochikian indicated he would prefer to see the PQRI
117 leachables and extractables recommendations be published as a guidance.

118 In addition, the Working Group has proposed to hold a PQRI workshop to highlight its
119 recommendations to the FDA. The workshop would be held in the Washington area, for
120 about a day and a half; about a hundred or more attendees may be expected, from
121 pharmaceutical companies (QA, production operations, R&D), componentry suppliers, CROs
122 and FDA. The DPTC approved the concept of the workshop, recommended that it be
123 planned for fall 2005, and suggested that additional topics be considered for the program,
124 such as leachables and extractables in non-inhalation products. After some discussion, the
125 Committee agreed that in light of the extensive input received during the preparation of the
126 recommendations being finalized now, no pre-submission workshop is necessary.

127 Dr. Nagao further reported that USP is interested in working with the Working Group to
128 determine how extractables testing methods could be incorporated into USP. In July, a
129 teleconference was held with the participation of Dr. Poochikian (FDA, DPTC and USP
130 Aerosol Expert Committee), Dr. Porter (USP and member of the PQRI Leachables and
131 Extractables WG), Dr. Norwood (Chair of the Working Group) and Dr. Curry (USP Aerosol
132 Expert Committee). This dialogue will continue.

133 ***The PSD Mass Balance Working Group***

134 Dr. Tougas reminded the participants that the Mass Balance Working Group's data mining
135 and prospective experiment could not be conducted because of the current unavailability of a
136 safe harbor. In light of this obstacle, the Working Group agreed to develop interim
137 recommendations regarding the use of mass balance obtained from cascade impactors. Much

138 progress in developing the recommendations was made at a July face-to-face meeting of the
139 Group; the recommendations would promulgate a flexible approach to the 85-115%LC
140 limits. Dr. Tougas explained that the Working Group felt that after the safe harbor
141 conditions are created, there would be value in carrying out the originally planned data
142 assessments, especially the prospective experiment intended to quantify the different
143 contributions to the variability. He stressed that solving the issue of the safe harbor is of
144 extreme importance for PQRI as a whole. Before the safe harbor is established and after the
145 interim recommendations are submitted to FDA, the Working Group would have to consider
146 its role and activities.

147 The DPTC discussed the process of selecting a new Chair for the Mass Balance Working
148 Group, in light of Dr. Tougas' new role as a DPTC Chair. The participants agreed that the
149 Working Group should nominate a candidate, followed by the DPTC's consideration and
150 ratification.

151 *The PSD Profile Comparisons Working Group*

152 Mr. Christopher provided an overview of the Working Group's recent work. He reminded
153 the Committee that the performance of the chi-square method had been characterized with a
154 range of profiles and certain features were identified. The Working Group is now trying to
155 re-create the process followed by FDA originally to select a specific critical value. Once this
156 algorithm is established, the statisticians would be able to determine whether or not the
157 features of the chi-square test identified earlier affect the ability to make appropriate
158 decisions consistently. This algorithm would also be helpful to revise the test methodology if
159 needed.

160 To document its progress to date, the Working Group is preparing a paper, preliminarily
161 slated for the International Journal of Pharmaceutics. The DPTC approved the concept of
162 publishing such a progress report, but directed the Group to consult with the Steering
163 Committee and ECAS regarding potential copyright issues. The timing of the paper would
164 be clarified at the next DPTC meeting.

165 *Future Directions for DPTC*

166 The Committee discussed that with several of the Working Group nearing final stages of
167 work, the DPTC should consider future directions of work. The unique nature of PQRI was
168 mentioned on several occasions during the course of the meeting, and all participants agreed
169 that many regulatory science issues could benefit from being addressed in this forum.
170 Examples of such potential issues are: genotoxic impurities in API (Dr. Tougas would
171 consult with DSTC Chair Dr. Tway on this); ICH topics Q8 and Q9 and their implications for
172 FDA practice; good pre-clinical practices, e.g., methods for assessing permeability,
173 polymorphisms, etc. (probably starting with an industry survey). DPTC members were
174 directed to canvass their organizations for potential new projects and prepare for discussion
175 at the next DPTC meeting.

176 ***Administrative***

177 At the closing of the meeting, the Committee discussed the proposed new tracking form and
178 format of future meetings. Less frequent face-to-face meetings were agreed. The Steering
179 Committee comments on the tracking form were requested.

180 **NEXT MEETING/TELECONFERENCE**

181 *Face to face meeting:* tentatively on Wednesday, 3 November 2004 (location to be
182 determined).

183 *Teleconference:* to be scheduled as needed.

184 Finalized on 7 September 2004