

1 **Minutes of the DPTC Meeting**
2 **on 11 May 2006**

3 **ATTENDEES**

4 Terry Tougas, *Chair* (Boehringer Ingelheim, IPAC-RS)
5 Bob Dana (PDA)
6 Frank Holcombe (FDA), by phone
7 Lana Lyapustina (IPAC-RS Secretariat)
8 Dan Malinowski (Pfizer, PhRMA), by phone
9 Chris Moreton (Idenix Pharmaceuticals, IPEC), by phone
10 Dan Norwood (Boehringer Ingelheim, IPAC-RS), by phone
11 Lee Nagao (IPAC-RS Secretariat)
12 Russel Somma (IPS, ISPE), by phone
13 Raj Uppoor (FDA), by phone
14 Bob Wiens (Lilly, IPEC), by phone
15 Bruce Wyka (Schering-Plough, IPAC-RS), by phone

16 ***Absentees***

17 Tony Amann (GPhA)
18 Clyde Anthony (USP)
19 David Christopher (Schering-Plough, IPAC-RS)
20 Michael Golden (GlaxoSmithKline, IPAC-RS)
21 Rich Poska (Abbot, PhRMA)
22 Nakissa Sadrieh (FDA)
23 Vilayat Sayeed (FDA)
24 Robert Seevers (Lilly, PhRMA)
25 Bill Williams (University of Texas, AAPS)

26 **EXECUTIVE SUMMARY**

27 The proposal for Arrhenius Equation Extension will be recommended to the Steering
28 Committee for endorsement as a new PQRI DPTC project.

29 The Specifications/Stability proposal will be recommended to the Steering Committee for
30 endorsement as a new PQRI DPTC project.

31 DPTC recommends further development of the MTC proposal ‘Specification Design and
32 Lifecycle Management’ before making a decision regarding its disposition.

33 DPTC approved the proposed Leachables and Extractables Training Course (20-21
34 September 2006)

35 **DISCUSSION**

36 *Opening*

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

43 The proposed objectives of the meeting were to discuss proposals for new projects and to
44 review updates from the Working Groups.

45 *General Overview of New Projects*

46 Dr. Tougas reviewed the process for approval of new PQRI projects. He reminded the
47 participants that Technical Committees are responsible for scientific and technical
48 assessment of proposed projects while the Steering Committee gives final approval from the
49 strategic portfolio perspective. Dr. Tougas noted a complicating factor in that new proposals
50 come from different directions, including directly to the Steering Committee. He encouraged
51 the DPTC to give a thorough consideration to the proposed new projects so that he could
52 report the Committee’s feedback at the upcoming meeting of the Steering Committee (on 12
53 May) where the portfolio of PQRI projects would be discussed.

54 In response to inquiries from Mr. Moreton, Dr. Tougas said that the roles of DPTC and MTC
55 would be considered and clarified at the upcoming SC meeting. The participants agreed that
56 MTC is to be more focused on process parameters, and the effects of changing parameters on
57 the product performance (which is established in clinical trials). By contrast, the DPTC
58 projects are to be more focused on product performance, development, characterization,
59 packaging, efficacy. The assignment of a new project to one committee or the other should
60 be done by the Steering Committee. Some projects may be administered jointly by DPTC
61 and MTC.

62 Dr. Tougas further noted that some of the proposed projects span several disciplines, such as
63 the ‘Quality by Design’ proposal, which may need to involve experts in pharmacokinetics,
64 formulation, process development and manufacturing. To accommodate the broad scope of
65 such projects, a special governance structure is being considered, e.g., with technical
66 oversight provided by a group comprising the chairs of the four Technical Committees (Drug
67 Product, Drug Substance, Manufacturing and Biopharmaceutics), and Mary Oats (Pfizer) as
68 the SC representative. Some of the DPTC members expressed doubts that this structure
69 would be more efficient than the currently existing, and urged a thorough discussion both by
70 the SC and TC members before the final decision is reached. The participants also stressed
71 that for such ‘superprojects’, people with direct and recent experience in the subject matter
72 (e.g., solid oral dosage forms) should be part of the overseeing body, in order to enable that

73 body to make appropriate decisions and recommendations. It was suggested that if specific
74 Working Groups are formed for such projects, the Chairs of those Working Groups become
75 part of the overseeing committee.

76 ***‘Arrhenius Equation Extension’ Proposal***

77 Mr. Moreton reminded the participants that this work is building upon the work started
78 within the Container Closure Working Group. It relates to moisture influence on stability.
79 Several different equations have been suggested in the literature to describe these effects but
80 there is no universal relationship describing these phenomena. The purpose of such
81 equations is to better predict the slope from stability data. (References are included in the
82 paper provided by Mr. Moreton). The proposed work therefore would include one or two
83 studies to look at (a) degradation reactions involving water/moisture, and (b) degradation
84 reactions not involving water but promoted by the presence of water.

85 Dr. Holcombe commended the proposal in general but commented that the scope seems to be
86 broad. For example, even the first step – literature review – would involve more work than
87 might appear at first glance, because there are many types of water to consider, e.g.,
88 solvation, loosely bound, free, etc. Mr. Moreton agreed but noted that it all comes down to
89 water activity and therefore approximations of that activity would work. He further
90 explained that the proposed steps would be undertaken sequentially and not in parallel.

91 Other participants raised concerns related to the overall timeline (5.5 years) proposed for this
92 project. Mr. Moreton emphasized that this time is realistic, given the amount of work
93 planned. Furthermore, he explained that there would be intermediate deliverables along the
94 way even before the 5.5. year mark. For example, results of the literature review and
95 developed algorithm would be available within 12 months. It was recommended that the
96 proposal be amended to clearly indicate these intermediate deliverables.

97 In response to inquiries, Mr. Moreton assured the DPTC that if approved, the Working Group
98 could be populated relatively quickly because there are already several candidates ready to
99 undertake this work.

100 The DPTC agreed that from the technical and scientific perspective, the proposal is sound
101 and valuable, and should be recommended for adoption as a new PQRI DPTC project. Dr.
102 Tougas was actioned to convey this recommendation to the SC. Mr. Moreton agreed to
103 prepare draft slides for the SC discussion of this topic.

104 ***‘Stability/Specifications’ Proposal***

105 Dr. Tougas presented the revised proposal entitled “Establishing Acceptance Criteria for
106 Time Dependent (Stability Indicating) Quality Attributes and the Evaluation of Stability Data
107 for the Control of Pharmaceutical Products”. He explained that the overall objective of that
108 proposal is to take the existing approaches to evaluating stability data and put them into the
109 Quality-by-Design format, and in addition to correct one or two technical issues with the
110 current way of evaluating data.

111 During the DPTC discussion, Dr. Tougas further explained that the key considerations are
112 the following.

113 (1) How does a manufacturer identify critical quality attributes, especially stability indicating
114 attributes? (For example, should a company do a risk assessment of factors influencing
115 stability of process?)

116 (2) Once the critical attributes are selected, how should they be controlled? (Currently, there
117 is a chicken-and-egg situation with establishing shelf life and specifications, both of
118 which are derived from the same set of data based on process capability rather than on
119 product performance requirements).

120 (3) An additional problem is that of multiplicity, i.e., the increased probability of failure with
121 increased testing. It would be important to have such tests and acceptance criteria that
122 would not penalize more measurement (e.g., more batches, more replicates, more
123 properties measured).

124 Dr. Tougas also noted that in the EU, release specifications and end-of-life specifications are
125 not necessarily identical. In the U.S., this approach may not be as common, and the U.S.
126 practice needs to be brought more in line with the new regulatory paradigms.

127 Some participants asked how this project would interact with the other PQRI specification-
128 related projects. Dr. Tougas explained that the Steering Committee would have to consider
129 that aspect.

130 The DPTC agreed to recommend this project to the SC for adoption as a new PQRI DPTC
131 project.

132 ***MTC Proposal ‘Specification Design and Lifecycle Management’***

133 Dr. Tougas explained that Dr. Bird (MTC Chair) had proposed that this project be a joint
134 project under the DPTC and MTC leadership.

135 Dr. Holcombe commented that the paper describing this project is currently too vague to
136 enable a substantive discussion. For example, the paper seems to suggest that the project
137 would aim to define what is important for approval of a product but does not explain whether
138 the goal is to produce ‘a list of things to do’ for a risk-based assessment of a product or only
139 produce ‘concepts’ to consider – or, in other words, a list of things agreed upon, or a list of
140 things on which agreement would be needed between the sponsor and the Agency.

141 Other participants pointed to a substantial overlap between this and the QbD project, and
142 suggested that a merging of the two proposals might be considered.

143 The participants agreed to recommend that the proposal for this project be developed in more
144 detail before the final decision is made.

145 ***QbD Proposal***

146 Some of the DPTC meeting participants discussed that the proposed project seems too broad
147 and may need to be narrowed down on specific questions. In addition, this proposal needs to
148 be fleshed out to explain how it would relate to the MTC proposal discussed immediately
149 above. The participants also discussed the difficulty of establishing an appropriate
150 governance structure for this project., which spans several TCs.

151 ***Container Closure System***

152 Mr. Malinowski reminded the participants that at the previous DPTC meeting, the Working
153 Group was asked to review its Workplan and re-affirm its goals in light of FDA's diminished
154 interest in the PACPAC guidance. He explained that the MVTR work would try to reduce
155 regulatory burden for primary packaging changes, and therefore there was overwhelming
156 support within the Working Group for continuing this project based on the high business
157 need of the industry. The goal of the project remains to develop methods for selection of
158 primary packaging and assessing protection provided by such packaging.

159 For 2006, the Working Group has the following objectives:

160 (1) Execute screening DoE, which is the first step for designing a larger study (start with 3-4
161 materials, select duration of tests, open-box exposure, etc.).

162 This objective involves production and testing of packaging, and data analysis on the
163 screening study.

164 (2) Based on the initial article in the USP Pharmacopeial Forum, prepare a new draft for a
165 peer-reviewed publication.

166 This article will stress issues with current USP methodology, and will include real life
167 experiences based on the DoE data, so that industry can see things from the
168 regulatory perspective as well. The journal for this publication still needs to be
169 decided.

170 (3) Strengthen membership of the Working Group, recruit new members which could
171 contribute laboratory and other resources to the group's work.

172 CVs from several candidates had already been received and are being considered by
173 the Working Group.

174 A DPTC member strongly recommended that at least one supplier be included in the
175 Working Group, and one manufacturer of blister/strip packaging equipment. Mr.
176 Malinowski replied however that within the current PQRI policy, such suppliers and
177 manufacturers are not eligible for WG membership because they do not belong to any
178 of the PQRI member organizations. Dr. Tougas agreed to discuss this issue with the
179 Steering Committee.

180 ***Leachables and Extractables***

181 Dr. Norwood reported that comments on the Working Group's Recommendations are being
182 considered; he expressed hope that the revised Recommendations would be provided to the
183 DPTC the following week. In response to questions, Dr. Norwood further explained that
184 most of the comments had to do with the analytical threshold and very few with toxicological
185 threshold. Dr. Norwood noted that some publication plans are being discussed within the
186 Working Group and would be brought to the DPTC's attention at the next meeting.

187 Dr. Norwood reviewed plans for the L&E Training Course being planned for 20-21
188 September 2006. During the Workshop, Recommendations and experiences with laboratory
189 data would be presented. Based on the 2005 L&E Workshop, the Working Group expects a
190 substantial response to this offering. Dr. Norwood reviewed the projected budget and
191 attendance. A DPTC member encouraged the Working Group to include case studies in the
192 Training Course, e.g., explaining why a company may accept a lower limit but would have
193 difficulty meeting it over the life of a product. Dr. Norwood assured the DPTC that this and
194 other examples would be included in the program of the Training Course. The DPTC
195 endorsed the proposed Training Course and recommended its approval to the Steering
196 Committee. (The proposal has now been approved and the program has been posted at
197 http://pqri.org/workshops/leach_ext/pqrilandeworkshop.asp).

198 Finally, Dr. Norwood informed the DPTC of a proposed new member for the Working Group
199 – Dr. Paul Curry, who has extensive experience with L&E issues and will provide a link to
200 the USP, which had previously expressed an interest in publishing L&E methods as a
201 pharmacopeial chapter. The DPTC approved this addition.

202 ***Profile Comparisons***

203 Dr. Lyapustina reported that the Working Group is waiting for the final verification of its
204 computer code against the code used by FDA contractors. To date, some discrepancies in the
205 results had been found and the source of the discrepancies is being explored. The Working
206 Group still plans to complete its work on the Final Report by the end of the second quarter.
207 The Interim Report has been submitted to a peer-reviewed AAPS PharmSciTech online
208 journal.

209 ***Excipients***

210 Mr. Wiens reported that the Excipient Workshop proposal has been revised and re-submitted
211 to Ms. Gantt and the SC for final approval. The Workshop speakers will discuss such topics
212 as What regulations are needed? and What is critical for control of excipients? The DPTC
213 reviewed the proposed dates and logistics of the Workshop's organization. (The program has
214 now been posted at <http://pqri.org/workshops/Excipient/Excipient06.asp>).

