

Minutes of the DPTC Meeting on 8 June 2005

ATTENDEES

In person

Terry Tougas, *Chair* (IPAC-RS)
Tony Amann (GPhA)
Clyde Anthony (USP)
Douglas Ball (IPAC-RS)
David Christopher (IPAC-RS)
Jon Clark (FDA)
Bob Dana (PDA)
Sylvia Gantt (PQRI Executive Secretary)
Michael Golden (IPAC-RS)
Christopher Morton (IPEC)
Guirag Poochikian (FDA)
Robert Seevers (PhRMA)
Rajendra Uppoor (FDA)
Bruce Wyka (IPAC-RS)

Via Teleconference

Lee Nagao (IPAC-RS Secretariat)
Richard Poska (PhRMA)
Russ Somma (ISPE)
Bob Wiens (IPEC)

DECISIONS MADE

1. Dr. Seevers was directed to provide to the DPTC further information such as bioassay data, to support absence of non-thermal effects of RF exposure on biological materials
2. The two groups representing the two different PSD mass balance proposals should each present their proposals to the DPTC during the September 2005 face to face meeting. The DPTC will provide a technical assessment of the two proposals with respect to how they address the objectives of the Working Group's work plan. The DPTC will present their assessment to the Steering Committee for consideration and decision.

DISCUSSION SUMMARY

Opening

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

The objective of the meeting was to review progress of the DPTC Working Groups.

Leachables and Extractables Working Group

Mr. Ball and Dr. Poochikian provided a detailed presentation on the working group recommendations. Mr. Ball presented background information and discussed the rationale behind, and derivation and use of the safety thresholds for OINDP. Dr. Poochikian described the best practices recommendations for testing for extractables and leachables in OINDP. Mr. Ball noted that the recommendations will consist of two main parts: the derivation and justification of the safety thresholds and the best practices.

In response to questions, Mr. Ball and Dr. Poochikian noted the following:

- The recommendations will address all OINDP (e.g., MDIs, DPIs, products for nebulization, nasal sprays). Thorough extraction studies should still be performed for DPIs, although it would be expected that the concentration and number of leachables would be very different (generally lower) for DPIs as for MDIs.
- The recommendations stress an integrated approach to control of extractables in components, encouraging safety risk assessment stages as early as materials acquisition in order to decrease the possibility of “11th hour” surprises involving detection of a bad actor compound during last stages of development.
- The analytical evaluation threshold (AET), which would be used by chemists assessing extraction and leachables studies results, is based on the safety concern threshold (SCT), developed to control potential carcinogens. The AET is an estimate of the SCT. The AET is a relative value which will depend on analytical methods, specifically difference in the response factors, and the drug product configuration (e.g., actuation per dose).
- If a leachable is below the qualification threshold, then a company would not need to qualify that leachable. However, depending on the compound, the company may feel that some information on that compound may still be needed to further justify their decision, such as literature references or structure-activity relationship studies.
- For the FDA, a correlation between extractables and leachables profiles means that there exists a reliable and predictable trend in which extractables exist in higher concentrations than the leachables. After this trend is established, then a sponsor can rely on extraction studies and profiles for routine quality control, rather than leachables profiles for routine quality control.
- It was acknowledged that in some cases asymptotic levels may not be obtained, as extraction is a kinetic phenomenon and it is possible to encounter an infinite sink of compounds diffusing out of a test article. .

Participants discussed several topics related to the presentation. Dr. Tougas noted that industry is still required to look for some “bad actor” compounds that are known to be absent from the material being used, thus having to prove a negative. He explained that in his opinion if a material does not contain or use a particular compound and there is negligible risk of its being

present, then the proof of its absence should not lie in an analytical assessment, but rather in documentation that states that such compound or compound type was not used as an ingredient.

Dr. Poochikian explained that there have been cases in the last few years where “bad actors” were still found in spite of the sponsor having compositional information from the material supplier. He noted that in some cases changes may occur upstream of which the supplier and sponsor may not be aware.

Mr. Golden noted that as technology continues to improve and allowing detection of lower and lower amounts of the small list of “bad actors,” recommendations for limits of quantitation or limits of detection should be developed for such compounds. Dr. Poochikian replied by stating that even 1 ppm, for instance, of such compounds could be of concern since the clinical effect of the compound may vary from patient to patient. Further, he noted that the cumulative effect of multiple leachables is unknown and could be of concern.

In response to a question, Mr. Ball explained that some compounds although not genotoxic, may have other safety issues such as sensitization or irritant potential, and therefore should be considered for risk assessment if above the qualification threshold. He clarified that sometimes on a case by case basis, a product may have one or two leachables above the qualification threshold, and that these leachables could be exempt from a full safety qualification if the sponsor can justify that the compound is safe at levels above the qualification threshold.

Dr. Upoor noted that it would be helpful to have a database of extractables/leachables from commonly used materials that could be publicly shared. He noted that such databases likely exist within companies, but are not divulged publicly. Development of such a database could be a potential extension to the current leachables/extractables project. Mr. Ball agreed and noted that such a database could be used to revise the USP in-vivo tests <87> and <88> currently being required, but which many industry and regulatory scientists find not meaningful or value-added. Participants agreed that such a database could be developed as a separate project, but should not be added on to the current Working Group’s activities since this is not part of their work plan objectives.

Mr. Ball added that a colleague at the MHRA had expressed interest in the PQRI L&E recommendations and noted that there will likely be much interest in the recommendation in Europe.

In response to questions about the timeline for completion of the recommendations, Dr. Nagao noted that the working group will attempt to meet an end of June deadline for submission of the recommendations to the DPTC.

The RFID Working Group

Dr. Seevers reported on his progress obtaining information on potential non-thermal effects on biotechnology products/materials. He noted that he had spoken with protein NMR experts, who informed him that high field NMR is routinely done to analyze proteins but that no non-thermal effects have been observed in such studies. He summarized his findings in a table which compared parameters for high field protein NMR and RFID, such as RF frequency,

power, exposure time, protein concentration and distance of sample from RF antenna.

Dr. Seevers explained that two frequencies are generally used in RFID: 13.56 MHz, also known as high frequency (HF) and 902-928 MHz, or ultra high frequency (UHF). The protein experts stated that 13.56 MHz would not cause any thermal or non-thermal effects. According to the NMR experts he spoke to, 13.56 MHz reader would pose negligible risk of thermal or non-thermal effects because of its low energy. Exposure time of biological material in the NMR could be up to several days. Exposure time of biological material to RFID is on the order of milliseconds, although the worst case scenario suggested by FDA is 16 hours.

Dr. Seevers said that most commercial firms are using roughly 600-800 MHz range. This is about the same range as used in RFID technology. WalMart, he said, claims to use a 900 MHz RFID system. Their technology is actually using 902-928 MHz. 915 MHz is generally the frequency that would be used in a loading dock scenario because at this frequency the reader can read labels over long distances, such as several meters. In the pharmaceutical arena, companies appear to want to use ranges of about 13.56 MHz. At this frequency the readers could only read within distances of inches. Dr. Seevers noted that it is not possible to mix and match technology. Thus, the integrated circuit and label to be read by a 13.56 MHz reader, will not respond to a 915 MHz reader.

Dr. Seevers reminded participants that thermal effects from RF exposure using RFID technology have been shown to be non-zero, but also minimal – not more than 1° C. Thermal effects are seen in NMR studies where samples may boil unless they are actively cooled. Sometimes denaturation of the sample may occur due to the increase in temperature. This same denaturation is observed when heating the sample to the same temperature in the absence of the RF field.

Dr. Poochikian noted that biological effects would not be detected via simple observation. However, Dr. Uppoor noted that biological effects would be detected in the NMR spectra.

Dr. Poska stated that any non-thermal effects would not occur in the milliseconds that products would be exposed to RF from an RFID reader. A worst-case scenario would be exposure of about 1 minute. 16 hours as proposed in the FDA letter is outside of the design space for the RFID scenario.

Dr. Poochikian explained that it would be advantageous to provide data that would support the calculations and information provided by Dr. Seevers. He also inquired about risks posed by the accompanying magnetic field.

Dr. Seevers explained that if data were to be gathered, PQRI would need to fund Michigan State University (MSU) to do the non-thermal effect exposure studies. He further noted that it was not clear how gathering information on one product would provide adequate data. He noted that the calculations show that the relative risk of effect may be estimated using the inverse square law, with the RF source as the point source. In this case the risk would be calculated as 1 over 1000 squared, which amounts to a risk of one in a million for non-thermal effects or effects from the magnetic field.

Dr. Moreton noted that the MSU study would likely not be value added and would not be necessary since the calculations, which are based on fundamental scientific laws, demonstrate such a low risk of non-thermal effect.

Dr. Seevers noted that he had obtained the information that the DPTC had asked for, namely he had provided technical input from protein NMR experts and had performed a risk assessment on non-thermal effects. Based on this information, he inquired how the Working Group should proceed. Are more studies needed or is this sufficient information to finish the information gathering stage? He noted that if no further studies are needed, then this information should be used to revise the FDA RFID guidance to address biotechnology products.

Dr. Clark clarified that the information is very valuable, and that it should be taken forward within PQRI for discussion on how it should be made public, before any changes to existing guidance are considered. Dr. Tougas agreed that the information has great value and noted that it is important to publicize the risk assessment as soon as possible, while decisions about guidance are being made.

Dr. Poochikian said that he disagreed. He explained that at this point, the information is all theoretical, and that effects of RF on bio-activity are not addressed. He noted that some minimal level of evidence is needed to support the calculations. Dr. Seevers noted that there may be very little data available since negative results (i.e., results showing no effect) are rarely published.

Dr. Seevers agreed to provide the equation for conversion of RF to magnetic field so that magnetic field strength would be clarified, and to provide within his risk assessment literature references to development of high field protein techniques using exposures over several days. He clarified that he would only be addressing non-thermal effects since it has been established that there are negligible thermal effects even after several hours of RF exposure.

In response to a question, Dr. Clark clarified that the purpose of the output of the working group is to provide peer reviewed information for gaps in current knowledge on RFID. He noted that this information could be both sent to FDA as part of a recommendation and could be published.

Dr. Seevers explained that after he performs his agreed actions, he would not have much more time to devote to this project. He emphasized that the work is not worth publishing without FDA review and co-authorship, and that if he is to devote anymore time to the project, he would like some assurance of FDA involvement and therefore an effective outcome. Dr. Seevers asked Dr. Poochikian if data were to be obtained, if Dr. Poochikian would be satisfied. Dr. Poochikian noted that he would have to examine the data first and then would consider if further work was needed.

Dr. Tougas asked if extrapolation from protein structure data would be sufficient to demonstrate lack of structural and biological effect of radio frequency exposure. He noted that protein structure data shows no effects under energy and conditions that are orders of magnitude above what biological materials would be exposed to via RFID. Dr. Poochikian said that biological effects would still need to be addressed, and that this could be done by examining

bioassay results.

Dr. Seevers noted that if Dr. Poochikian agreed that provision of information on NMR protein studies, bioassay results from biological materials exposed to RF fields, and risk assessment is sufficient to address non-thermal effects of RFID, then he would proceed to consolidate this information for submission to the DPTC. Dr. Poochikian agreed to consider this information.

The DPTC agreed on the following next steps:

- Dr. Seevers will provide the equation for conversion of RF to magnetic field, and provide within his risk assessment literature references to development of high field protein techniques using exposures over several days
- Dr Seevers will compile and submit to DPTC information on NMR protein studies, bioassay results from biological materials exposed to RF fields, and his risk assessment regarding non-thermal effects of RFID

The PSD Mass Balance Working Group

Dr. Tougas reported that at the Steering Committee's direction, the DPTC should assess the PSD Mass Balance Working Group situation. He reminded participants that some members of the Working Group had proposed an "indefinite hiatus" of the Group due to reasons described in previous minutes, teleconferences and meetings. He explained that in the Steering Committee's opinion, a Working Group cannot simply decide to stop without thorough internal review of the reasons for a proposed termination of activities. Because the problem stems from two different views within the group regarding the appropriate use of the mass balance measurement, and because this is a technical issue, the Steering Committee concluded that the DPTC should review and provide to the Steering Committee a technical assessment of the two positions. The Steering Committee will then include this assessment in their deliberations regarding ways forward for the Working Group.

Dr. Tougas asked participants for their input on how the DPTC review and assessment could best be accomplished. He also noted that several members of the DPTC, such as himself, Dr. Poochikian and Dr. Christopher, were also active on this Working Group, and asked participants for guidance on ways to ensure that the DPTC assessment process is unbiased.

In response to a question, Ms. Gantt noted that the PQRI by-laws do allow for formation of an unbiased ad hoc group to review PQRI work.

Dr. Clark asked for further details on the background of the issue and on PSD mass balance as a specification. Dr. Tougas and Mr. Wyka noted that the Working Group had been discussing whether PSD mass balance is appropriate as a specification or as a run qualification.

Mr. Golden noted that the process was frustrating because it seemed that the Working Group was almost finished with its work, and then at the "11th hour" a new proposal was put forth. Others in the Group then statistically assessed this new proposal, and when they came back with results demonstrating that the new proposal was more stringent than the existing one,

the process was ended.

Dr. Tougas explained further frustrations, noting that the original proposal had been a compromise between the two differing views within the group, and at the time had seemed to satisfy both parties. Specifically, it proposed that the mass balance measurement should be included on the specification sheet, but that it should first be considered a run qualification, that is, if results are outside of established limits, then the method should be re-examined. Only if there is evidence suggesting that results outside established limits were not due to method/analyst issues, then the product should be assessed. The new proposal is a return to using PSD mass balance solely as a product specification.

Dr. Tougas noted that the new proposal subverts the DDU PTI effort as well as FDA's new initiatives because it adds to the DDU assessment a mass balance test that operates under the zero tolerance paradigm and penalizes the producer for increased testing.

Dr. Tougas explained that most of the Working Group members had understood that if the statistical evaluation of the new proposal showed that it was no more stringent than the original proposal then it should be considered further, but that if it was more stringent, then it would not be acceptable over the original proposal. The statistical evaluation showed that the new proposal was more stringent, increasing the producer risk. At this point, the authors of the new proposal stated that they had not agreed with these aforementioned caveats, and the discussions degenerated from that point.

In response to a question, Dr. Tougas clarified that the statistical evaluation was through an OC (operating characteristic) curve that shows both consumer and producer risk. The OC curve plots the probability of acceptance of a batch as a function of the true batch mean at an assumed standard deviation. The curves are based on a specified quality standard (sampling plan and acceptance criteria). He emphasized that it is the quality of the batch that is being established, not the quality of an individual unit, and therefore it is the mean and variability of the batch that is being assessed.

Participants discussed the controversy behind use of PSD mass balance as a specification for product quality. Dr. Clark stated that the Working Group had formed because of the requirement in the guidance for PSD mass balance measurements as a product specification. Dr. Tougas and Mr. Golden confirmed his statement. Mr. Golden explained that the PSD mass balance assessment as a measurement of product quality, specifically the quality of the dose, is a 4th to 5th generation redundancy in testing. There are better ways, he said, to measure the quality of the dose (e.g., DDU). Dr. Tougas explained that there exists fundamental disagreement regarding the value of PSD mass balance via cascade impaction as a measure of product quality, when tests such as DDU are already being done on the product. He explained that use of cascade impaction in this way is like conducting a DDU measurement, except that instead of squirting the sample into one beaker and measuring the amount, you would be squirting the sample into ten beakers and adding up the amounts in all ten beakers to determine the amount of the original sample.

Participants asked about the availability of data to support either side of the argument. Dr. Tougas said that currently the data available is from the IPAC-RS database of MB results,

which shows the general variability of mass balance measurements. The database consists of thousands of mass balance results. Participants asked if a particular product could be tested, and Dr. Tougas reminded them that this was proposed but that lack of safe harbor assurance did not allow performance of these experiments. Additionally, if the experiments were to be done, the chosen lab would need to use an approved and validated method.

Dr. Tougas explained that the IPAC-RS data showed that the proposed FDA guidance specification limits are not acceptable as they impose about a 5% failure rate for products. Mr. Christopher asked if a comparison of the mass balance results and DCU results was performed. Dr. Tougas said that this type of data was not obtained.

Dr. Tougas explained that there are two questions fundamental to the discussions about the PSD mass balance assessment. First, is the PSD mass balance assessment a test that represents an important quality attribute of the drug product for each batch that is not already being controlled in a better way by other tests? This question cannot be answered experimentally, but rather through an assessment of the control strategy. Second, are the proposed FDA guidance limits reasonable? This question can be answered experimentally, and the IPAC-RS data was obtained to address this question.

Dr. Tougas and Mr. Golden further explained that collection of sample from the various plates of the cascade impactor often caused high variability in MB results. Dr. Clark noted that if the measurement technique can have higher variability than the batch then a hard look should be taken regarding the usefulness of the technique for that particular purpose.

Mr. Christopher noted that the Working Group had earlier proposed experiments to assess the variability of mass balance results, and to compare cascade impactor and DDU results. However, an FDA participant in the Working Group said that he did not care about results comparing cascade impactor and DDU and that such results would therefore be inconsequential.

Dr. Clark emphasized that things have changed at the FDA and that FDA is encouraging industry to look at variability. This stance, he said, is contained in a number of publicly available FDA documents.

Participants discussed how the DPTC should review and assess the concerns of both Working Group parties. Mr. Wyka proposed that each party should present their views and proposals to the DPTC in separate presentations. Dr. Uppoor agreed that both parties should present, the DPTC should discuss and assess the technical merits of both sides. Dr. Tougas noted that a structured discussion would be essential and wondered if the DPTC should provide to each party an outline of issues or questions that should be addressed in the presentations. He further wondered if the topics should be addressed together in one presentation or separately and if discussions of each side should be done in the absence of members of the Working Group.

Participants discussed these questions and considered approaches to maintaining an unbiased review of the presentations. They agreed on the following next steps:

- The two groups representing the two different mass balance proposals should each make separate presentations to the DPTC during the September 2005 face to face meeting
- The presentations should describe the proposals and how these proposals address the objectives and goals of the approved work plan for the PQRI PSD Mass Balance Working Group
- The DPTC will discuss each of the presentations, and provide a technical assessment of the two proposals with respect to how they address the objectives of the work plan. The DPTC will inform the parties if further information is needed to develop the assessment
- The DPTC will present this assessment to the Steering Committee for consideration and decision
- Dr. Tougas and Dr. Poochikian should be involved in the development of whichever presentation he supports, and should be involved in the assessment. However, other members of the Working Group should do the actual presentations
- All members of the DPTC, whether or not they are members of the Working Group, are welcome to attend the presentations and contribute to the assessment

The PSD Profile Comparisons Working Group

Mr. Christopher the Working Group is evaluating the combination of the chi-square ratio and the new test using the collected scenario information. Mr. Christopher reminded participants that the Working Group should reach consensus on a recommendation by the end of 2005.

The Container Closure Working Group

Dr. Morton reported that he had been in contact with Dr. Malinowski, and that this Group is getting back on schedule. Currently the Group is proceeding with developing its experimental studies.

The Excipients Working Group

Mr. Wiens and Dr. Somma reported that the questionnaire had been reviewed and approved by the DPTC and the Steering Committee, and will be implemented on-line.

NEXT MEETING/TELECONFERENCE

Scheduled DPTC meeting dates for the remainder of calendar year 2005.

July 13	Teleconference
August	No meeting

September 14	In-person – FDA – Rockwall II – Room 7204
October 17	Teleconference
November 1	In-person – FDA – Rockwall II – Room 105