

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

VOLUME I

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University of Maryland
Shady Grove Campus 9640 Gudelsky Drive
Rockville, Maryland

A F T E R N O O N S E S S I O N

2 DR. LAMBORN: We will start the afternoon session.
3 We are going to change topics to the topic of the orally
4 inhaled nasal drug products, and we will start with an open
5 public hearing.

6 Orally Inhaled and Nasal Drug Products

7 Open Public Hearing

8 Overview of ITFG/IPAC-RS Collaboration

9 DR. CUMMINGS: Good afternoon.

10 [Slide]

11 My name is Harris Cummings. I am with the
12 Inhalation Division of Magellan Laboratories. I also sit
13 on the USP Aerosol Expert Committee.

14 I would like to start by thanking the advisory
15 committee for giving us time to speak this afternoon. In my
16 brief presentation, I am going to be introducing the
17 collaborative work of two groups concerned about issues
18 related to inhalation products.

19 [Slide]

20 These groups the Inhalation Technology Focus
21 Group, which is a focus group of the American Association of
22 pharmaceutical scientists and it is comprised of
23 pharmaceutical scientists who seek to advance the science
24 and technology and regulatory issues related to inhalation
25 products. The second group involved is the International

1 Pharmaceutical Aerosol Consortium on Regulation and Science,
2 which is an association of companies that develop and
3 manufacture inhalation products for the treatment of both
4 respiratory and non-respiratory diseases.

5 The work of the collaboration is to respond
6 through a science-based and data-driven process to the three
7 draft guidances which are shown here.

8 [Slide]

9 Both ITFG and IPAC-RS share the FDA's goal of
10 assuring the highest levels of safety, efficacy and quality
11 for orally inhaled products, and we also recognize the value
12 of having the guidance documents to facilitate the
13 development and approval of new medications. However, we
14 believe that significant differences still remain concerning
15 CMC and BA/BE issues in the draft guidances, and we believe
16 certain sections of the guidances need modification.
17 Finally, we are suggesting that additional meetings need to
18 occur which can provide the opportunity to discuss these
19 issues in depth in order to achieve the best possible
20 guidelines.

21 [Slide]

22 I would like to give a brief overview of the
23 completed work and also future commitments of the
24 collaboration to addressing these issues.

25 Following the publication of the draft guidances,

1 ITFG and IPAC-RS independently and together submitted
2 extensive written comments to the FDA. The collaboration
3 then organized and implemented the current process of
4 collecting and analyzing relevant data for both marketed
5 products and products under development.

6 Members of the collaboration participated in the
7 first OINDP subcommittee meeting in April of this year, and
8 at that time committed to collecting data and preparing
9 technical reports on the issues in the draft guidance.

10 It is the purpose of these technical reports to
11 describe the conclusions reached based on the data that are
12 collected, and to describe proposed modifications to the
13 guidances which are based on these conclusions. Today, we
14 have submitted four technical reports to the FDA, with
15 several more to follow.

16 [Slide]

17 The organization of the collaboration is shown
18 here. We have a steering committee with five technical
19 teams, and the technical teams are organized around the CMC
20 issues and the BA/BE issues.

21 [Slide]

22 The collaboration has certainly been a truly
23 industry-wide effort, with over 100 individuals from more
24 than 25 companies participating. The companies are listed
25 here, and they include pharmaceutical companies, contract

1 organizations, academic institutions and component
2 suppliers.

3 [Slide]

4 The technical teams are at different stages in
5 their work. All have collected and analyzed data. As I
6 mentioned earlier, four have submitted initial assessments
7 to the agency. In the talks that follow mine, a member of
8 each technical team will review the work of the team to date
9 and give examples of issues related to the guidances which
10 they believe warrant further discussion. They will also
11 explain plans for future work.

12 [Slide]

13 We are asking the advisory committee today to
14 support the continued scientific dialogue on these CMC and
15 BA/BE issues before the draft guidances are finalized, and
16 we ask you to support our request for meetings between the
17 FDA and the ITFG/IPAC regarding the collaborations technical
18 papers and data-based proposals to modify the draft
19 guidances.

20 [Slide]

21 In summary, ITFG and IPAC-RS recognize and
22 appreciate the agency's efforts in issuing the draft
23 guidances and the agency's initial steps towards a
24 scientific dialogue. We believe that a unique opportunity
25 exists now to produce the best possible guidances for

1 inhaled products, and would welcome the chance to work with
2 the FDA on achieving this goal.

3 I would like to again thank the advisory committee
4 and the agency for considering our comments and proposals,
5 and we are pleased to be able to participate in today's
6 meeting and hope to be able to contribute in future meetings
7 as well. Thank you very much.

8 DR. LAMBORN: It is my understanding we have a
9 series of presentations. Will you just take yourselves
10 through them?

11 BA/BE In Vitro and In Vivo Tests

12 DR. BORGSTROM: Good afternoon.

13 [Slide]

14 My name is Lars Borgstrom, and I am scientific
15 adviser at AstraZeneca, and today I speak on behalf of the
16 collaboration BA/BE group.

17 [Slide]

18 After the April 26 meeting of the OINDP system,
19 the collaboration made two different commitments with regard
20 to bioavailability and bioequivalence questions. We made a
21 commitment to develop a position paper on the BA/BE
22 question. We also made a commitment to respond to the
23 questions raised by the FDA at the April 26 meeting. On
24 August 30, the collaboration did submit these two technical
25 papers to FDA.

1 The collaboration has developed two position
2 statements, one on in vitro testing and one on in vivo
3 testing. I would like to read them out as a philosophical
4 background to our thinking.

5 [Slide]

6 In vitro testing is essential for pharmaceutical
7 product equivalence and should be included as part of the
8 BA/BE guidance for all nasal and oral inhalation products,
9 but is not currently sufficient for determining BE without
0 establishing in vivo BE.

.1 On the in vivo side we have the following wording,
.2 for bioequivalence approval, BA/BE guidance documents for
13 nasal and oral inhalation drug products for local action
14 should require use of validated human models for in vivo
15 testing for local and systemic exposure, efficacy and
16 safety. This means that we have agreed that in vitro as
17 well as in vivo testing is necessary.

18 [Slide]

19 Our assumptions that we have presented apply only
20 to locally acting drugs. Our discussions include both
21 nasally and orally inhaled drugs even though there is as yet
22 no published guidance on orally inhaled drugs. An obvious
23 comment is that this is an evolving scientific area and that
24 the position statements reflect the current state of
25 knowledge.

1 [Slide]

2 One of the findings on the in vitro side is that
3 it cannot be generally stated that the in vitro tests are
4 more relevant or discriminating than clinical studies for
5 bioequivalence. It probably often is so, but the used in
6 vitro method has to be validated with regard to the clinical
7 outcome. If so done, in vitro analysis should be more
8 discriminating as they tend to have a lower variability but
9 also here exceptions do exist.

10 Similar reasoning can be applied to the assumption
11 that for a nasal solution formulation in vitro studies
12 should be sufficient to declare bioequivalence. It could be
13 so, but the links between in vitro and clinical outcome are
14 yet not strong enough to support such a general statement.

15 Finally, in certain cases a correlation has been
16 shown between the in vitro outcome, lung deposition and
17 clinical effect but these correlations are not strong enough
18 to be predictive in a regulatory sense. Available
19 information can be used in the pharmaceutical development
20 work but not as a predictor for regulatory claims.

21 [Slide]

22 On the in vivo side, there is equivalence between
23 the old and new drug formulation. A similar situation is at
24 hand when a generic company makes a new formulation of an
25 approved drug. None of the extent of the testing

1 requirements should be negotiated with the agency.

2 [Slide]

3 During the discussion within the collaboration, we
4 have often been caught in a Catch-22 situation. There is,
5 of course, a need to establish validated links to be allowed
6 to predict the clinical outcome from in vitro data, but to
7 establish these links the company has to do a rather
8 extensive program and, thus, there is not anymore the need
9 for the links.

10 [Slide]

11 We would like to get an opportunity to meet with
12 the agency to discuss our findings and we are, of course,
13 also willing to address further questions that can be
14 raised. Thank you for your attention.

15 Responses to Agency's BA/BE Questions Raised at OINDP

16 Subcommittee Meeting

17 DR. HARRISON: Hi. Good afternoon.

18 [Slide]

19 I am Les Harrison. I am section head of clinical
20 pharmacokinetics at 3M Pharmaceuticals. I am also co-chair
21 of the BA/BE team, and I was an invited guest at the
22 subcommittee meeting in April, representing BA/BE for the
23 collaboration.

24 [Slide]

25 Today, what I would like to summarize are the

1 responses that the BA/BE team prepared in answer to the
2 agency's questions that were proposed during the
3 subcommittee meeting.

4 [Slide]

5 To answer the questions, what we did, we formed
6 small working groups for members of the BA/BE team and also
7 from other experts within the collaboration. We used the
8 scientific data that we could find. We used the literature
9 and also company experiences to prepare our answers. The
10 answers were reviewed by the entire BA/BE team, and we had
11 to reach consensus for all answers. This process took
12 several months and we submitted to the agency a report at
13 the end of August.

14 [Slide]

15 In general, what we found as an overview is that
16 the FDA, indeed, raised some difficult technical issues
17 during the April 26 meeting, and it is our opinion that most
18 of these issues are still open. What we were able to do is
19 provide additional scientific substantiation for many of the
20 subcommittee's answers. In add, we were able to provide
21 responses where the subcommittee's answers were limited.
22 So, going forward, what we really need is more opportunities
23 to digest what we have found and to continue to address
24 these difficult questions. We appreciate the pas
25 opportunities we have had to really dialogue with the

1 agency, and we hope that this continues.

2 [Slide]

3 What I would like to do now is really walk through
4 what our responses were to the questions that were raised by
5 the agency, and they were divided really into two main
6 areas, in vitro and in vivo.

7 Looking first at in vitro, one focus was profile
8 analysis, and the question was should all stages of the
9 cascade impactor be examined for BA/BE, and we agreed with
10 the subcommittee and the answer there was yes for us.

11 [Slide]

12 The second question under profile analysis was
13 should a statistical approach be used and, if so, how about
14 chi-square? We agreed with the subcommittee that, yes, a
15 statistical approach should be used and chi-square may be an
16 appropriate metric but further assessment is needed. And,
17 this is a position where we could help as a collaboration
18 because we have many real data sets within our members that
19 could be used here. In fact, we are attempting to get
20 clarification from the agency that this effort would be
21 useful before we actually undertake this new and probably
22 large effort.

23 [Slide]

24 The next question in the in vitro area focused on
25 DPIs. Here, we were very fortunate. Within the

1 collaboration we have really the key DPI manufacturers and
2 we could bring a lot of technical expertise to answer this
3 question as well.

4 The first part of the question was what design
5 features would be needed for determining pharmaceutical
6 equivalence. Our as was fairly general here, pretty much
7 all the formulation and device elements would be needed.

8 [Slide]

9 The second part of this question though allowed us
10 to get a lot more specific in terms of listing what type of
11 tests would be needed. I draw your attention to the second
12 bullet where we did actually customize some of these
13 requirements to the uniqueness of DPI. Here, we are saying,
14 in the second bullet, that particle size distribution
15 certainly should be measured across a range of airflows and
16 a realistic range of temperatures and humidities.

17 [Slide]

18 In the in vivo area, the question we are focusing
19 on is, first, local delivery of nasal aerosols -- local
20 delivery really meaning local efficacy. The first question
21 was what about the clinical designs that were presented?
22 Are they reasonable for BA/BE and are there alternatives?

23 We agreed with the subcommittee here that really
24 the proposed guidances for the clinical tests were
25 reasonable and that the traditional treatment study probably

1 is still the most appropriate design. However, a real key
2 here is that the statistical requirements need to be
3 discussed in an open forum so that we can really better
4 evaluate these type of tests.

5 [Slide]

6 The second question for nasal delivery was if you
7 can establish bioequivalence for SAR, SAR standing for
8 seasonal allergic rhinitis, can you get bioequivalence
9 transferred for other indications?

10 Here, the subcommittee did not really answer that
11 question, but what we came up with was an answer that, yes,
12 we thought that you could be able to transfer indications
13 once you establish BE for the SAR, at least in adults.

14 The second bullet certainly says that in children
15 you need to be more cautious and you need to assess if the
16 safety can be transferred as well.

17 [Slide]

18 Also in the in vivo area, the next series of
19 questions focused similarly to the nasal but now for
20 steroids, and they asked again what type of testing is there
21 for steroids and are there alternatives.

22 [Slide]

23 Our answers there again were pretty much in
24 agreement with the subcommittee. We thought that a
25 comparative dose-response trial with pulmonary function

1 measurements is still the standard and still reasonable, but
2 we do also recognize that the variability for this trial is
3 large and the metrics really are not that sensitive. Just
4 like for the nasal area, what is really needed here is some
5 type of statistical input to help us really sort this out.
6 Here, again, the collaboration could help. A number of our
7 member companies have done comparative clinical studies on
8 steroids which could be useful if there were an open forum
9 where this could be discussed to get at the appropriate
10 statistical requirements.

11 [Slide]

12 To answer the question about other biomarkers, it
13 is our feeling that really there are none that have been
14 established thus far that can be used. However, we were
15 very intrigued by the crossover design that was suggested by
16 Ahrens during the April 26 subcommittee meeting, and that
17 actually has the potential of fulfilling what we are looking
18 for in this area but it is premature to really accept it at
19 this point in time.

20 [Slide]

21 The last question focused on PK issues and asked
22 the question if you can show in vitro documentation as well
23 as PK documentation establishing bioequivalence, is that
24 sufficient?

25 Here, the subcommittee seemed to lean toward

1 answering no, and what we said was, yes, there could be
2 situations where in vitro data plus PK may be relied on.
3 The requirement there is that PK there would somehow have to
4 be shown to be a surrogate marker for the clinical efficacy
5 documentation, and we do admit that no drug at this point in
6 time can do it.

7 We went further as well and said that if you can
8 show in vitro and in vivo correlation for safety and
9 efficacy, it may be even possible to waive all clinical
10 studies.

11 [Slide]

12 In summary, the number of questions posed by the
13 FDA on the guidance have underscored a number of open
14 issues, and we feel that most of those issues are still
15 open, and the BA/BE team collected a substantial body of
16 information that, hopefully, bears on some of these issues,
17 and what we would like to do is encourage that examination
18 continues, utilizing existing avenues and we can have the
19 OINDP subcommittee consider them, go through PQRI. We can
20 have another broad workshop. Dialogue between the
21 collaboration and the FDA is certainly welcome. And, there
22 is also the possibility of federal research grants. We
23 would love to see the studies that we talked about of Ahrens
24 for steroids funded and actually taken to fruition. We hope
25 that the agency and, indeed, this advisory committee is

1 receptive to our comments and continues to dialogue with the
2 public before finalizing the current draft guidance or
3 issuing further guidances. Thank you.

4 ITFG/IPAC-RS Technical Team CMC Specifications

5 DR. Olsson: Good afternoon.

6 [Slide]

7 My name is Bo Olsson. I am formerly scientific
8 adviser at AstraZeneca. Now I am with Microdrug
9 Development. I am a member of the aerosol expert committee
10 of both the United States and the European Pharmacopeia. I
11 speak here today on behalf of the CMC specifications team of
12 the collaboration. In this team we have focused on dose
13 content uniformity and particle size distribution
14 specifications.

15 [Slide]

16 At the OINDP subcommittee meeting this spring, our
17 team posed the hypothesis that the current state of OINDP
18 technology may not allow general compliance with the dose
19 content uniformity specifications in the draft FDA CMC
20 guidances.

21 At the same meeting, the agency raised the
22 question if there should be a single content uniformity
23 standard for all orally inhaled and nasal drug products.
24 They also posed the question if FDA should continue
25 development of the proposed statistical approach to

1 evaluating content uniformity.

2 Our approach in addressing these questions is to
3 collect the worldwide database to investigate the actual
4 dose content uniformity capabilities and appropriate
5 statistical approaches.

6 [Slide]

7 We have now collected data and this unique
8 database comprises a total of 46,000 observations for 77
9 products originating from 10 companies. So, it is truly a
10 multi-company effort. These products are on the market or
11 in late development, meaning from Phase IIB, Phase III or
12 NDA stage.

13 Our initial assessment of the data was submitted
14 to the FDA this summer, and it is now available on the FDA
15 web site.

16 We have further developed and submitted a plan for
17 continued analysis of the database, which we will discuss
18 with the agency on Monday next week.

19 [Slide]

20 From the initial assessment, we found that for the
21 key requirement in the draft guidances, namely that no
22 observations may be outside 75-125 percent of the label
23 claim, most products do not comply; 68 percent of the
24 products in the main analysis show results outside these
25 limits. Yet, the grand mean dose in the database is at 100

1 percent of labeled claim.

2 [Slide]

3 From this, we conclude that our hypothesis that
4 orally inhaled products are not generally in compliance with
5 the draft guidances is supported by data. Additionally, the
6 database shows a relatively large difference between
7 products and also between product types, suggesting that a
8 single one size fits all specifications is unsuitable.

9 [Slide]

10 To follow-up the initial assessment, we intend to
11 continue with a more thorough investigation, specifically on
12 the compliance with the more complex criteria in the
13 guidance system we have done so far, and we will also
14 investigate the interesting approach taken by ICH for dose
15 content uniformity, and we will try to assist in the
16 development of Dr. Hauck's approach of statistical
17 hypothesis testing to dose content uniformity.

18 [Slide]

19 Turning now to particle size distribution, we have
20 committed to examine the relevancy of the mass balance
21 requirement as a product specification versus as a system
22 suitability requirement, and also to investigate if fewer
23 than 3-4 stage groupings can provide equivalent control.

24 Again, our approach has been to collect the
25 worldwide database to investigate actual PSD capabilities.

1 [Slide]

2 This database comprises a total of over 3600
3 individual particle size distributions from 35 products.
4 Our initial assessment of the data was submitted to the
5 agency and is also available on their web site. We are now
6 developing a plan for further analysis of the PSD database.

7 [Slide]

8 The draft guidance mass balance requirement is
9 that the total mass of drug collected on all stages should
10 be within 85-115 percent of the labeled claim. The key
11 finding from the database is that only 4 of the 35 products
12 showed no results outside 85-115 percent. The median
13 product had 5 percent of the observations outside these
14 limits.

15 [Slide]

16 From this, we conclude that products do not in
17 general comply with the proposed mass balance requirement,
18 and that, therefore, the proposed requirement is not
19 suitable as a drug product specification but it could well
20 be appropriate as a system suitability requirement with
21 limits defined on a case by case basis.

22 [Slide]

23 To follow-up the initial assessment, we would
24 continue the analysis of the PSD database to investigate
25 further the relevance of the mass balance criterion, and to

1 compare different metrics and sets of criteria for
2 characterizing protein size distribution of OINDPs. We are,
3 of course, willing to meet and discuss with the agency.

4 [Slide]

5 In conclusion, we feel that many unresolved issues
6 surround CMC specifications for DCU and PSD. To address
7 these issues, our team has collected and is analyzing DCU
8 and PSD data. We strongly encourage continued discussions
9 by all interested parties before CMC draft guidances are
10 finalized. It is our firm view that developing
11 statistically sound specifications based on real data is
12 essential to creating a scientifically credible program of
13 product quality control. Thank you for your attention.

14 CMC Tests and Methods

15 DR. EVANS: Good afternoon. My name is Carole
16 Evans. I am here to present the work of the tests and
17 methods team

18 [Slide]

19 The team's objective in its work has been to
20 assist the agency in developing CMC testing requirements
21 that provide valuable information about product quality. We
22 hope to do this by providing data-driven commentary on the
23 testing requirements contained in the draft guidances.

24 [Slide]

25 I would like to start with some initial comments

1 on the draft guidances and general observations. Firstly,
2 to clarify the requirements for each of the four dosage
3 forms included in the draft guidances, the guidances should
4 be further edited or separate guidances developed for each
5 dosage form, thus making the testing requirements for each
6 dosage form more readily understood.

7 Secondly, in some instances, the language in the
8 guidances is ambiguous, and where we have addressed these
9 they will be addressed by written comments not supported by
10 data.

11 Finally, the need for certain tests should be
12 driven by an evaluation of the data generated in dearily
13 development.

14 [Slide]

15 We have reviewed the draft guidances and
16 identified areas for comment. We started our work with the
17 MDI test requirements. We have got work in progress on
18 other dosage forms. But as the work for MDI is further
19 along, I am going to focus on these today.

20 The team has developed position statements with
21 respect to the tests listed here. These are the tests where
22 we felt that the consensus industry viewpoint diverges from
23 that of the agency. In particular, we focused on those
24 areas where we are able to generate data to test our
25 position statements. We believe that by conducting this

1 data-driven commentary we can make a commentary of a
2 different flavor to those already submitted earlier this
3 year.

4 [Slide]

5 This slide summarizes the processes that we have
6 used for each of these tests. For some tests water, spray
7 pattern, plume geometry, shot weight, and for the
8 requirement to control temperature and humidity in particle
9 size distribution we are in the process of collecting and
0 analyzing data to test our position statements for these
.1 tests.

.2 For further tests we have simply drafted comments
.3 on the requirements for MDIs, such as those for impurities
.4 and degradation products where we are simply requesting an
15 alignment with ICH requirements, or for dose content
16 uniformity where we have suggested alternate wording that we
17 think is clearer. Finally, we have collected data from the
18 scientific literature with respect to particle size
19 distribution methodologies and pressure testing for single
20 propellant and co-solvent mixture formulations.

21 [Slide]

22 We are currently in the midst of analyzing our
23 data on MDIs but do have some preliminary findings to bring
24 to you today. We have collected data for many products and
25 have shown so far that tests for spray pattern, water

1 content and shot weight often don't provide meaningful
2 information about product performance. For example, the
3 guidance requires that spray pattern testing be performed to
4 evaluate proper performance of valves and actuators, and the
5 data to date does not indicate a correlation between the
6 parameters of the devices and spray patterns gathered.

7 Further, there is a wide body of literature that
8 lends support to the use of validated and alternate methods
9 for particle size distribution and we will be submitting a
10 paper outlining those.

11 Finally, the literature suggests that for single
12 propellant and co-solvent mixtures the pressure testing is
13 outcomes a sensitive approach for determining the
14 appropriate ratios present. We feel that the integrity of
15 the propellant alcohol mixture is better controlled by
16 direct analysis of the alcohol content.

17 [Slide]

18 As I said, we are still in the process of
19 analyzing our data. With respect to MDIs, we will be
20 submitting technical papers containing our conclusions and
21 recommendations to the agency, and the expected date is
22 December of this year.

23 We are continuing with other dosage forms and
24 will, early next year, collect data and analyze data with
25 respect to those other dosage forms. Like the other teams

1 who are presenting here today, we would welcome the
2 opportunity to meet with the agency to discuss our findings
3 and data, and to try and work with the agency to address any
4 other questions raised. Thank you.

5 CMC Leachables and Extractables and

6 CMC Supplier Quality Control

7 MR. HANSEN: Good afternoon.

8 [Slide]

9 I am Gordon Hansen. I am associate director of
10 preclinical analysis at Boehringer Ingelheim
11 Pharmaceuticals.

12 [Slide]

13 Today I will be reporting on the work of two
14 technical teams, the leachables and extractables team and
15 the supplier quality control team. Both of these teams are
16 comprised of scientists from pharmaceutical companies and
17 component suppliers with broad experience in the
18 characterization of leachables and extractables. The team
19 supports the agency's activities in developing the draft
20 guidances and recognizes and supports the need for clearly
21 stated and scientifically sound requirements with respect to
22 leachables and extractables in inhalation products.

23 The team believes, however, that these guidances
24 could benefit from additional study and dialogue. The team
25 is committed to working with the agency and the subcommittee

1 to discuss these topics in detail.

2 [Slide]

3 After careful review, the team has identified key
4 issues which we believe could be strengthened by the add of
5 more detailed and clarifying language. For example, what
6 are appropriate reporting and identification thresholds for
7 leachables and extractables? How is a correlation between
8 leachables and extractables established? What are
9 appropriate practices for establishing safety of leachables?
10 Is extractables profiling appropriate for control of
11 component composition, and which critical components should
12 be subject to routine extractables testing?

13 In looking at just one of these issues in more
14 detail, currently the issue of reporting levels for
15 extractables and leachables is not well defined and is
16 currently substantially more stringent than is outlined in
17 ICH Q3B. Is 1 mcg per canister sufficient, or are detection
18 limits required that are lower than that? The situation at
19 present appears to be driven by advances in scientific
20 technology rather than pharmaceutical science.

21 The following steps have been taken by the team in
22 order to investigate these issues in more detail: The team
23 has collected drug product specific leachables and
24 extractables data in order to investigate the concept of
25 correlation. The team has also formed a toxicology working

1 group to address toxicology issues for leachables. The team
2 has investigated current supplier practices for the control
3 of component composition and extractables profiles.

4 [Slide]

5 Similarly, the tox team has reviewed the current
6 industry practices for establishing the safety of leachables
7 and is drafting a strategy for incorporation into the team's
8 "points to consider" document which will be submitted later
9 this year.

10 The tox team is investigating current practices
11 for establishing the safety of leachables, and looking
12 forward as to what industry requirements should be for the
13 safety evaluation of leachables.

14 [Slide]

15 After the analysis of the available data, the
16 leachables and extractables team has developed the following
17 key points for the agency's consideration. These will be
18 included in the "points to consider" document to be
19 submitted to the agency by the end of the year.

20 These points are as follows: A leachables study
21 should be a one-time development study and not a routine
22 requirement. Secondly, a correlation is established between
23 leachables and extractables when each leachable can be
24 linked qualitatively to a corresponding extractable. Once a
25 correlation is established, leachables are controlled

1 through the routine extractables testing of critical
2 components which contact the formulation or the patient's
3 mouth or nasal mucosa. Finally, the team strongly
4 recommends that a process be developed for establishing
5 reporting, identification and qualification thresholds for
6 leachables.

7 [Slide]

8 The toxicology evaluation proposal consists of
9 adding a separate section to each guidance to describe the
10 toxicology evaluation process, including a flowchart.

11 Toxicological qualification should be performed
12 only on leachables, and only on those leachables that occur
13 above a data-supported threshold.

14 The guidelines should also distinguish between
15 genotoxic and non-genotoxic leachables.

16 The issue of testing USP 87 and 88, these tests do
17 have utility for extractables testing, particularly for
18 component suppliers, however, for a pulmonary product, where
19 there may be a substantial body of data, these tests may not
20 have added value when the entire package is considered.

21 [Slide]

22 The team's next steps will be, first, to submit
23 the "points to consider" by the end of this year. We will
24 request the opportunity to meet with the agency to discuss
25 team findings and consider appropriate strategy for how

1 toxicology thresholds can be established. In collaboration
2 with the supplier quality control technical team, we will
3 propose a control strategy which includes appropriate
4 testing criteria for ensuring relevant performance and
5 safety characteristics of critical components. As the other
6 teams presenting today, this team is willing to address
7 further issues and welcomes further dialogue with the
8 agency.

9 [Slide]

10 At this time, I would just like to take a last
11 minute or two to describe the work of the supplier QC team
12 which reported its findings during the April 26 meeting of
13 the OINDP subcommittee.

14 This team investigated the question what is the
15 current status of compliance in the component supplier
16 industry? This team conducted a survey of component
17 suppliers in order to evaluate the quality and compliance
18 practices at all stages of not only component but excipient,
19 raw materials and active drug substance manufacture.

20 Findings of this team were that there, indeed, are
21 no generally accepted guidelines for the components supply
22 chains but, in fact, IPEC has developed GMP guidelines for
23 the manufacture and compliance of excipient manufacture.
24 Indeed, this team has endorsed the more widespread adoption
25 of the IPEC guidelines. This team is eagerly awaiting

1 comment and guidance, and in consultation with FDA and the
2 identification of the proper venue, would like to
3 collaborate in the development of cGMPs for component
4 suppliers. A formal report summarizing these findings will
5 be submitted to the agency by the end of the year. Thank
6 you.

7 Concluding Remarks

8 DR. FLYNN: Good afternoon.

9 [Slide]

10 My name is Cyndy Flynn, and I am the director of
11 pharmaceutical sciences at Aventis.

12 [Slide]

13 I would like to take this opportunity to recap
14 some of the highlights of the previous presentations that
15 you have just heard. The collaboration is composed of more
16 than 100 pharmaceutical scientists who represent more than
17 25 companies and institutions who have been working to
18 address the key concerns in the draft CMC and BA/BE
19 guidances.

20 This collaboration is committed to collecting and
21 assessing all relevant data, and sharing these findings in a
22 very timely fashion with the agency. The collaboration
23 anticipates that these data-based conclusions and proposals
24 will be useful to the agency in its preparation of the final
25 CMC and BA/BE guidances, and that this will ultimately

1 benefit both patients and the pharmaceutical industry.

2 [Slide]

3 Based upon the data that has been collected and
4 analyzed to date, the technical teams have concluded that
5 certain aspects of these draft guidelines need to be
6 revised. As described in the earlier presentations by my
7 colleagues, the technical teams have prepared or are in the
8 process of preparing specific data-based proposals for
9 modifying the draft guidances.

10 [Slide]

11 This slide is a summary of the technical papers
12 which have been prepared and submitted to date. Two papers
13 have been submitted in the summertime by the specifications
14 team; two papers by the BA/BE team, in the summertime also,
15 have been submitted; and the tests and methods team is in
16 the process of getting ready to submit a paper concerning
17 MDIs, in the month of December; and the leachables and
18 extractables team will also be submitting a technical paper
19 in December.

20 [Slide]

21 This slide is a summary of the numerous CMC and
22 BA/BE issues which have been presented to you today, which
23 remain of great concern to the collaboration.

24 What needs to be highlighted here is that the
25 collaboration sees that the majority of the issues revolve

1 around CMC issues, not necessarily only around BA/BE issues,
2 although these are also very important to the collaboration.

3 [Slide]

4 We believe that it is of utmost importance that
5 the collaboration's data-based conclusions and proposals for
6 modifying the draft guidances be given full consideration
7 before these guidances are finalized. As was mentioned in
8 the morning session by Dr. Toby Massa on another topic, it
9 has been found by industry that it is far more productive
10 and efficient to have the comments of industry incorporated
11 prior to finalization of these guidances rather than
12 afterwards.

13 Hopefully, we have been able to demonstrate to you
14 that these issues are of a very complex nature and that they
15 have generated a huge industry response, and this has been
16 demonstrated by the attendance levels at the June, '99 AAPS
17 meeting as well as at the April 26 subcommittee meeting
18 where we had a packed house.

19 In addition, at least 20 comment letters have been
20 received concerning these guidance documents which comprise
21 hundreds of pages of comments. In addition, there has also
22 been this massive effort on the part of the collaboration to
23 try and address these issues.

24 [Slide]

25 The collaboration, therefore, strongly recommends

1 that the agency continue to work towards resolving these
2 very important CMC and BA/BE issues by utilizing all
3 available existing avenues for in-depth interactive and
4 scientific dialogues. Some of these are listed on this
5 slide that could potentially be used, and I am sure there
6 are many others. We feel that such dialogues will ensure
7 that the guidances bring maximum value to regulators,
8 industry and, most importantly, to the patients and
9 physicians.

10 [Slide]

11 We would also respectfully request that the
12 Advisory Committee for Pharmaceutical Science support the
13 need for continuing scientific dialogue on these very
14 important issues before these draft guidances are finalized.
15 We would also request that the committee endorse our request
16 that opportunities be found for continued dialogue between
17 the FDA and the collaboration concerning the very unique and
18 valuable inter-company databases we have been able to
19 collect to date.

20 [Slide]

21 Finally on behalf of my colleagues, I would like
22 to express our gratitude to the agency for holding this
23 meeting. We very much appreciate the opportunity to present
24 our work, and we thank the agency and the committee for
25 considering our comments and proposals. Thank you.

1 DR. LAMBORN: Thank you. A couple of points of
2 clarification -- this may seem a little bit of a reverse
3 order of the way things should be done because of the need
4 to have the open public hearing at the time it was
5 scheduled. The material that has been presented to this
6 point has been part of the open public hearing. We do have
7 a subcommittee report, which Dr. Adams is going to present.

8 The other thing is that ultimately the
9 subcommittee will continue to bring items back to this
10 committee, and this is, in a sense, the advisory body that
11 will ultimately recommend to the FDA, not the subcommittee
12 but clearly a subcommittee was needed to move this forward.

13 Subcommittee Report

14 DR. POOCHIKIAN: Good afternoon.

15 [Slide]

16 My name is Guriag Poochikian. I am the chair of
17 the OINDP CMC working group. I am also a member of the USP
18 expert aerosol committee.

19 In April of this year, the OINDP subcommittee of
20 this advisory committee met under the leadership of Dr.
21 Vincent Lee, who is the chairman and professor at USC.
22 Unfortunately, Dr. Lee is not able to make it today so I
23 will try to summarize briefly and report the main discussion
24 points. My intent today is to be a messenger only. I am
25 not an advocate of any position today.