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

ORALLY INHALED AND NASAL DRUG PRODUCTS SUBCOMMITTEE
OF THE ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

Tuesday, April 26, 2000

8:30 a.m.

CDER Advisory Committee Conference Room
5630 Fishers Lane
Rockville, Maryland

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1 possible, delineate between these two sets of formulations
2 and make it very clear what testing is required for which
3 one because our fear is that we come to the FDA and we are
4 going to be expected to meet all the requirements for a
5 nasal solution or a respiratory solution and they don't
6 really apply to a buckle solution.

7 Thank you very much.

8 DR. LEE: Thank you.

9 Next comes a series of presentations by two groups
10 that have been very active in this area. Dr. Cummings?

11 **AAPS Inhalation Technology Focus Group (ITFG)/**
12 **International Pharmaceutical Aerosol Consortium (IPAC)**
13 **Collaboration Technology Teams**

14 **Overview of the ITFG/IPAC Collaboration**

15 DR. CUMMINGS: Good afternoon. Thank you for the
16 opportunity to speak today.

17 [Slide.]

18 My name is Harris Cummings. I am with Magellan
19 Laboratories and Research at Triangle Park, North Carolina.
20 In the next few minutes, four minutes, I believe, I would
21 like to provide a brief overview of the collaboration
22 between the Inhalation Technology Focus Group and the
23 International Pharmaceutical Aerosol Consortium in
24 addressing the recent draft guidances from the FDA and to
25 express the extent of interest and commitment on the part of

1 industry to support the further development of these
2 guidelines for inhaled products.

3 [Slide.]

4 Two groups are involved in this collaboration, the
5 Inhalation Technology Focus Group which is the focus group
6 of the AAPS is comprised of pharmaceutical scientists
7 concerned with inhalation products.

8 [Slide.]

9 Also represented is the International
10 Pharmaceutical Aerosol Consortium which is an association of
11 manufacturers of aerosol products.

12 [Slide.]

13 Shown here are the three draft guidances which I
14 think we are all pretty familiar with by now.

15 [Slide.]

16 As far as perspective of the two groups, both the
17 ITFG and IPAC are in full agreement as to the value of the
18 new guidance documents and welcome their issuance. In
19 addition, we agree with the BA/BE and statistical issues
20 including the questions surrounding dose content uniformity
21 presented by the subcommittee today.

22 We do, however, believe that, in addition to these
23 important questions, there are many significant CMC issues
24 particularly related to testing and specifications that
25 still need to be addressed. In addition, we believe that

1 these difference can and need to be resolved through a data-
2 driven and science-based approach to achieve the best
3 guidances possible, a process which IPAC and ITFG have
4 started and are prepared to continue to support.

5 [Slide.]

6 The ITFG/IPAC collaboration was proposed in the
7 IPAC statement at the June '99 workshop as a part of a
8 consensus-building process involving collaboration with the
9 ITFG. The collaborative work between the two groups began
10 in September of 1999.

11 [Slide.]

12 The structure of the organization is as shown on
13 the slide and it consists of the steering committee and five
14 technical teams. The steering committee provides general
15 oversight and review for the five technical teams which are
16 shown in the slide and the technical teams are formed based
17 on the general technical subjects found in the three
18 guidances.

19 As you can see, CMC issues are the primary concern
20 of the documents and of the technical teams.

21 [Slide.]

22 The significance of the concern and commitment on
23 the part of industry is also reflected in the number of
24 companies involved in this collaboration. Individuals for
25 more than twenty companies representing a broad spectrum of

1 industry, including manufacturers, contract organizations
2 and component suppliers participate in this collaboration.

3 In addition to the approximately 85 individuals
4 who participate directly in the steering committee and
5 technical teams are many times that number of scientists at
6 member companies who work on collection and evaluation of
7 data.

8 [Slide.]

9 In the presentations that follow mine, a
10 representative of each of these technical teams will present
11 the current activities of the team and future work which the
12 team plans and the commitments that each team is willing to
13 make to further the work of the subcommittee. This includes
14 generation of data, technical papers and recommendations and
15 even a willingness to meet with the subcommittee, if
16 desired.

17 [Slide.]

18 Finally, the pharmaceutical industry, as
19 represented by the IPAC/ITFG collaboration, is committed to
20 a science-based and data-driven process of establishing best
21 practices for the FDA guidances. Large amounts of work have
22 already been completed in this process and even more has
23 been committed to by the member companies of this
24 collaboration.

25 Thank you very much for your consideration.

1 DR. LEE: Thank you very much.

2 The next presentation is on BA/BE by Steve Farr.

3 **Presentation on the Work of the BA/BE Team**

4 DR. FARR: Thank you, Dr. Lee. Good afternoon,
5 ladies and gentlemen>

6 [Slide.]

7 I am Steven Farr. I am actually from Aradigm
8 Corporation in Hayward, California. I am grateful for this
9 opportunity to present to you today on behalf of the BA/BE
10 in vitro and in vivo Test Team. Over the course of a number
11 of meetings, the team is about through collection and
12 evaluation of relevant information, a series of data-driven
13 position statements that I wish to share with you today.

14 While the team used the current draft BA/BE
15 guidance document pertaining to aerosol products for nasal
16 application, it believes the findings are generally
17 applicable to in vitro and in vivo testing of products that
18 are both orally inhaled as well as nasal products.

19 [Slide.]

20 In the slide that you have in front of you, it
21 really describes the team's work that has lead to the
22 following propositions. And these were agreed to at the
23 last meeting. With respect to in vitro testing, we strongly
24 agree that it is essential for pharmaceutical product
25 equivalence to have these tests and they should be included

1 as part of the BA/BE guidance for oral nasal and oral
2 inhalation products.

3 But it is not currently sufficient for BE approval
4 without establishing in vivo BE. In other words, in vitro
5 testing is not sufficient to establish bioequivalence in the
6 absence of in vivo testing.

7 Turning to in vivo tests for BE approval, in other
8 words to establish product quality through the measurement
9 of bioequivalence, the guidance documents for nasal and oral
10 inhalation drug products should require the use of validated
11 human models for testing for local and systemic exposure
12 efficacy and safety.

13 [Slide.]

14 These working propositions are associated with
15 certain assumptions that define their applicability. The
16 team recognizes that its BA/BE recommendations apply to
17 locally acting drugs only as per the current draft guidance
18 for nasal aerosols and sprays. However, the team's comments
19 apply to both orally inhaled and nasal drug products, but it
20 is recommend that these dosage forms should be treated in
21 separate guidances.

22 It is further recognized that the scientific and
23 clinical bases for developing BA/BE guidance are evolving so
24 the working propositions created by the team only reflect
25 the state-of-the art knowledge.

1 [Slide.]

2 Based on currently available information, the team
3 has reached the following conclusions. Current in vitro
4 tests, namely dose-content uniformity and particle-size
5 distribution, may be used to estimate lung deposition but
6 their predictability with respect to bioequivalence has not
7 yet been shown.

8 Furthermore, the in vitro tests described in the
9 current draft guidance are not necessarily more relevant or
10 discriminating than clinical studies for the measurement of
11 bioequivalence. Systemic PK/PD studies will estimate local
12 exposure which will contribute to safety but may not
13 estimate local delivery which will contribute to efficacy
14 and local tolerance.

15 In turn, efficacy studies alone of a locally-
16 acting agent cannot establish bioequivalence since they will
17 not assure comparable safety through systemic exposure. So,
18 bearing in mind these preceding conclusions, the team
19 believes that in vitro alone are not sufficient to assess
20 product quality for bioequivalence.

21 Indeed, the guidance should not distinguish
22 between testing requirements for nasal suspensions and
23 solutions for in vivo BE.

24 [Slide.]

25 In closing, I just would like to inform the

1 subcommittee that the team is committed to prepare a
2 technical paper by the end of June this year to support the
3 conclusions described today. The purpose of the paper will
4 be to highlight areas where there is sufficient data to draw
5 conclusions and where there is not enough data at present,
6 and also to review technical documentation related to BA/BE
7 issues addressed by the team.

8 In addition, the team will be prepared to address
9 the BA/BE questions which have been posed during today's
10 meeting.

11 Thank you.

12 DR. LEE: Thank you.

13 The next up is Dr. Bo Olsson addressing the
14 specifications.

15 **Presentation of the Work of the Specifications Team**
16 **(Dose Content Uniformity/Particle Size Distribution)**

17 DR. OLSSON: Good morning. My name is Bo Olsson,
18 AstraZeneca. I am grateful for this opportunity to present
19 the statement of the CMC Specifications Technical Team.

20 [Slide.]

21 Our focus has been on dose-content uniformity and
22 particle-size distribution as the key attributes. For the
23 industry, internationally harmonized guidelines is the key
24 component for timely and cost-effect development of safe and
25 efficacious drug products. A tremendous amount of work has

1 gone into establishing a range of harmonized guidelines
2 between the United States, Europe and Japan through the ICH
3 process.

4 The Technical Team on CMC specifications believes
5 that orally inhaled nasal drug products are amenable to the
6 principles set forth by ICH. Particularly, the ICH
7 Guideline Q6A on specifications provides a process for
8 establishing specifications and the extended application to
9 inhaled dosage forms is being encouraged by the document.

10 [Slide.]

11 The ICH Q6A recommends a data-driven process for
12 specification setting. Based on pharmacopeial standards,
13 results from development and from pivotal batches and a
14 reasonable range of analytical and manufacturing
15 variability. We concur with Q6A that it is important to
16 consider all of this information and we don't believe it is
17 justified to apply a single standard specification to the
18 wide range of different products that are on the market and
19 in development.

20 [Slide.]

21 Based on the collective experience, the
22 Specifications Team has posed the hypothesis that the
23 current state of OINDP technology may not allow general
24 compliance with the DCU specifications in the draft
25 guidances.

1 To address this question, to date more than twelve
2 companies have initiated the process to collect a worldwide
3 blinded database of more than 45 products to examine actual
4 DCU capability of these products. Our target is to have an
5 initial assessment of the database by the end of July.

6 It is our position that the format of
7 specifications should be based on sound statistical
8 practices such that they can be translated into quality
9 requirements. We propose to work with the subcommittee and
10 the agency to investigate using this database, alternate DCU
11 specifications which may better serve this purpose.

12 This includes those approaches presented by Dr.
13 Walter Hauck this morning.

14 [Slide.]

15 Also, for particle-size distribution data, we have
16 initiated a process to collect a database. The target date
17 for initial assessment is, again, by the end of July. The
18 purpose of this survey is primarily to examine the relevancy
19 of the mass balance criterion as a product specification
20 versus a system-suitability requirement. But it may also be
21 used for looking into profile comparison techniques as well.

22 [Slide.]

23 In summary, we believe that the achievements of
24 ICH should be taken advantage of in the FDA guidances and we
25 are collecting a wide database which we hope can provide

1 useful information for the subcommittee and the agency.

2 Thank you for your attention.

3 DR. LEE: Thank you.

4 The next subject is tests and methods. Carole
5 Evans?

6 **ITFG/IPAC Technology Team: CMC Tests and Methods**

7 DR. EVANS: Good afternoon.

8 [Slide.]

9 My name is Carole Evans from Magellan
10 Laboratories. My role in this series of presentations is to
11 give an overview of the work and approach of the Test and
12 Methods Team. The team has reviewed the draft CMC guidances
13 and has identified areas where the FDA approach differs from
14 that which we in industry feel is meaningful and scientific
15 justified.

16 [Slide.]

17 As a result of this review, we have identified
18 four general concerns. Firstly, while recognizing there are
19 certain key tests which are required for all dosage forms,
20 we feel that the requirement for certain other tests should
21 be driven by a critical review of the data and that the
22 guidance should, therefore, distinguish between these two
23 categories of tests.

24 In some instances, the language used in the
25 guidance was ambiguous. For example, we are uncertain of

1 the intent behind the requirement for a stability-indicating
2 method of dose delivery of MDIs. We would recommend a
3 change in wording to, for example, a validated method free
4 from bias.

5 We feel that the guidances should be further
6 edited to clarify the requirements for each dosage form
7 possibly separating each dosage form into individual
8 guidances. Finally, the team would like to strongly
9 recommend further harmonization of requirements with other
10 pharmacopeial and international standards; for example, the
11 control of synthetic impurities should be aligned with ICH.

12 [Slide.]

13 The team has started its work by reviewing the
14 diagram for metered-dose inhalers and has identified several
15 areas for comment. These are shown here. The scope of the
16 comments vary from simply requests for clarification of
17 wording and calls for harmonization to suggestions for
18 alternate approaches to testing.

19 For example, in some cases such as the requirement
20 for moisture testing, the guidance should indicate that the
21 need for this test should be driven largely by the
22 development data. There are other tests such as plume
23 geometry or spray pattern which did not offer meaningful
24 performance characterization or redundant component
25 controls. These, therefore, should not be required.

1 [Slide.]

2 Our approach has been to develop position
3 statements on each of these areas and the outline of those
4 is provided in our written statement. We plan to collect
5 data with regard to most of these position statements. In
6 cases where the request is simply for rewording or for
7 further harmonization, we will not be collecting data.

8 [Slide.]

9 We are currently in the process of collecting the
10 data. This data will allow us to evaluate and, where
11 necessarily, refine our position statements. To date, we
12 have only addressed the guidance with respect to metered-
13 dose inhalers. It is our intent to repeat the process for
14 other dosage forms.

15 [Slide.]

16 After we have completed this process, we would
17 like the opportunity to share our recommendations with the
18 subcommittee and the agency. We believe that data-driven
19 recommendations will be helpful to the subcommittee and,
20 ultimately the agency, in creating stronger guidances. We
21 hope we can continue this discussion on critical CMC issues
22 by providing these documents and welcome an opportunity for
23 further dialogue.

24 Thank you.

25 DR. LEE: Thank you very much.

1 Next up is leachables and extractables. Dr. Dave?

2 **Presentation on the Work**

3 **of the Leachables And Extractions Team**

4 DR. DAVE: Thank you, Vincent. My name is Kaushik
5 Dave. Actually work for Schering Plough. However, this
6 afternoon, I represent the Extractable and the Leachable
7 Team. What I will present is the opinion of the team based
8 on reviewing the draft guidances.

9 [Slide.]

10 The team recognizes the importance of control of
11 extractables and leachables from the point of view of
12 patient safety and quality of these inhalation products.
13 The team is committed to providing information in this area.

14 [Slide.]

15 Just to give you some background with regard to
16 definitions, extractables is what one observes when one uses
17 solvents. Leachables is what appears in the product. Just
18 to put it in some other words here, I hope that you can
19 extract as much as you can from this presentation and, from
20 my perspective, I hope a lot of this leaches in.

21 [Slide.]

22 Just to share with you; the team has identified
23 four particular areas of focus which are listed up there.
24 The general approach which the team is taking is collecting
25 data from several companies and what we plan to propose to

1 do is analyze the data and make some recommendations in
2 these four areas.

3 I will, over the course of the next couple of
4 minutes, just go over these four areas briefly.

5 [Slide.]

6 The first area of interest is what we have defined
7 as analytical characterization of extractables. We feel
8 that the guidelines are not particularly clear and, perhaps,
9 it may be advantageous to propose slightly different
10 language and clarification. For example, we feel that there
11 is a need for clear definition of what a critical component
12 is from an extractable point of view.

13 [Slide.]

14 The second area of interest is what we have
15 defined as analytical characterization of leachables. The
16 real question here is do we really need to be extractables
17 and leachables testing commercially since we are looking at
18 pretty much the same phenomenon.

19 The draft guidelines have identified this and has
20 alluded to the fact that if a correlation can be established
21 between the leachables and extractables, perhaps, there
22 could be some reprieve from leachable testing. But, then,
23 the question becomes what is a correlation here. The
24 guidelines are not very forthcoming.

25 Keeping in mind that we are looking at trace

1 analysis here, firstly. Secondly, we are trying to compare
2 extractables, which is a solvent-based phenomenon to
3 leachables which is formulation-dependent. Can we really
4 come up with a correlation and what kind of correlation
5 should that be?

6 What the team proposes to do is, after reviewing
7 data, come up with a working definition of a correlation.

8 [Slide.]

9 The third and most important area of discussion in
10 the team is safety qualifications of leachables. We feel
11 that this is an extremely important area where there is a
12 need for discussion and understanding as to what are the
13 requirements. Simple questions like, "What is the criterion
14 for qualification? How do we determine the levels? Does
15 ICH apply here? If it does, do we compare it to the active
16 ingredient. They are not chemically related; does that make
17 sense?"

18 Again, the team has formed a working group
19 composed predominantly of toxicologists from the industry
20 they will be reviewing this closely and making some
21 recommendations.

22 [Slide.]

23 The fourth and final area of discussions in the
24 team is is this the right way of approaching control of
25 components, testing them at the end. Shouldn't we building

1 quality into components instead of looking for quality at
2 the end? Again, there are a lot of systems out there,
3 quality systems, which would insure that quality components
4 are produced and also those quality systems will include
5 change control and audit.

6 Actually, we have a technical team, the Supplier
7 QC, which is looking into this.

8 [Slide.]

9 Finally, the team is committed to offer databased
10 technical reports and recommendations to the agency and the
11 subcommittee over the course of the next three to four
12 months. Also, secondly, the team is available to evaluate
13 any extractables or leachables issue which the subcommittee
14 or the agency would like us to.

15 Thank you very much.

16 DR. LEE: Thank you.

17 The next issue concerns supplier quality control.

18 Mr. Hansen?

19 **Presentation on the Work**
20 **of the Supplier Quality Control Team**

21 MR. HANSEN: Thank you and good afternoon.

22 [Slide.]

23 My name is Gordon Hansen from Boehringer Ingleheim
24 Pharmaceuticals. I would like to take the next few minutes
25 to present an overview of the work of the ITFG/IPAC Supplier

1 Quality Control Supplier Qualification Team. This
2 collaboration has presented a unique opportunity for
3 representatives from the pharma industry and component
4 suppliers to collaborate on a review of the key issues in
5 the draft CMC guidances which relate to the testing and
6 qualification of inhalation-device components and
7 excipients.

8 [Slide.]

9 The draft CMC guidances focus extensively on
10 testing of components as well as excipients. A core theme
11 of the CMC guidances with respect to these components is
12 that tight standards and extensive testing by the pharma
13 manufacturer are required in order to assure batch-to-batch
14 quality of components and excipients.

15 [Slide.]

16 The team, in reviewing these guidances, has
17 drafted a thesis or vision statement which may be described
18 as follows. The qualification and control of critical
19 components in the area of performance-related physical
20 testing, extractables and leachables and excipients should
21 be achieved by a combination of appropriate scientific
22 practices, cGMP controls and supplier qualification systems.

23 [Slide.]

24 The first step for the team was to collect data on
25 current GMP practices. A survey of suppliers was conducted

1 to evaluate quality and compliance practices at all stages
2 of component, excipient, raw-material and active-substance
3 manufacture. Information was obtained from fifty-three
4 suppliers from raw materials through finished component
5 manufacture.

6 [Slide.]

7 The results of the survey are shown on this slide.
8 One is that the level of cGMP awareness and compliance in
9 the component and raw-material supply chain is improving but
10 improvement needs to continue. Secondly, there are specific
11 cGMP program elements which remain to be generally accepted
12 and implemented especially early in the supply chain.

13 [Slide.]

14 Some general observations were also made from the
15 survey in that there are no generally accepted cGMP
16 guidelines for the component supply chain but guidelines do
17 exist for the control of bulk excipient manufacturers which
18 have been drafted by IPEC, which is the International
19 Pharmaceutical Excipients Council.

20 [Slide.]

21 The team proposes the following: the team endorses
22 the IPEC guideline for the control and cGMP compliance of
23 excipients and it encourages its broader acceptance. The
24 team also proposes that an industry-wide initiative be
25 established to develop a cGMP guideline for component

1 suppliers. This collaboration would be a unique, perhaps
2 unprecedented, partnership between suppliers, the pharma
3 industry and the agency in designing a system which assures
4 product quality by building it in rather than by extensive
5 testing by the end user.

6 [Slide.]

7 The team also requests that the agency partner
8 with the pharma industry and component suppliers by first
9 formally recognizing the value of the cGMP guideline for
10 component suppliers by acknowledging in the guidance
11 documents that if sufficient supplier mechanisms are in
12 place, appropriate reductions in testing will be considered.

13 We also ask that the agency help establish key
14 elements and expectations for the cGMP guideline for
15 components and participates in reviewing and commenting on
16 draft guidelines.

17 Thank you for your time.

18 DR. LEE: Thank you.

19 Now comes the concluding presentation by this
20 group, Cynthia Flynn.

21 **Concluding Presentation on ITFG/IPAC Collaboration**

22 DR. FLYNN: Good afternoon.

23 [Slide.]

24 My name is Cynthia Flynn. I work for Aventis
25 Pharmaceuticals. I would like to take this opportunity to

1 provide you the concluding remarks concerning the ITFG/IPAC
2 collaboration.

3 [Slide.]

4 I trust that during the last six presentations, we
5 were able to demonstrate the very high level of commitment
6 and the massive amount of work that has been completed by
7 more than 85 pharmaceutical scientists working in the
8 foreground of this effort as well as the hundreds supporting
9 them in the background which represent more than twenty
10 companies to address key concerns in draft CMC and BA/BE
11 guidance documents.

12 ITFG and IPAC is committed to collecting and
13 assessing all relevant data which becomes available to this
14 collaboration. More importantly, we are committed to
15 sharing those findings in a very timely fashion with this
16 subcommittee and the agency.

17 ITFG/IPAC anticipates that this information will
18 be useful to the subcommittee in its deliberations and also
19 to the agency in the preparation of the final CMC and BA/BE
20 guidances. In addition, we believe that this information
21 will assist in the creation of a very high-quality document
22 which the industry and agency can use in designing the
23 dosage forms of the future.

24 [Slide.]

25 I just would like to take the time, then, to

1 review very briefly the deliverables which the technical
2 teams are committed to providing and the time frames
3 associated with those deliverables. Firstly, the BA/BE team
4 is committed to preparing a technical paper on BA/BE that
5 have been highlighted in the previous presentation. This
6 will be completed by the end of June.

7 In addition, that team will attempt to address as
8 many questions as possible as have been raised during this
9 meeting.

10 The Specifications Team is committed to
11 completing, by the end of July, an initial statistical
12 assessment of the actual DCU and particle-size database
13 which is collected by this collaboration. We would very
14 much like to share this initial assessment with you and with
15 Dr. Hauck in order to help your endeavors.

16 The Test and Methods Team is committed to
17 completing, within the next three to four months, the
18 technology paper outlining the key MDI tests. In addition,
19 in the future, we also plan to do similar work for other
20 dosage forms, as was alluded to by Carole in the previous
21 presentation.

22 The Leachables and Extractables Team is committed
23 to also completing a technical report within the next three
24 to four months as well as to making recommendations within
25 the next three to four months concerning leachables and

1 extractables.

2 Lastly, the Supplier Quality-Control Technical
3 Team is volunteering to ask as a co-leader with the agency
4 in developing a cGMP guideline for component manufacturers.

5 [Slide.]

6 I would like to point out to the committee that it
7 should be noted that the work of the collaboration deals
8 with not only BA/BE issues, which have received substantial
9 emphasis today, but also places a significant amount of
10 emphasis on four critical CMC issues, not just the DUC
11 issue.

12 [Slide.]

13 The collaboration of ITFG/IPAC is very convinced
14 of the need for a science-based interactive dialogue and is
15 requesting that the agency continue the subcommittee
16 process. We are also requesting that the collaboration be
17 given the opportunity to provide the deliverables that I
18 just described in the next three to four months for the use
19 of the subcommittee and agency in order to assist in the
20 resolution of the various CMC, BA/BE issues.

21 [Slide.]

22 I would like, then, to conclude my remarks by
23 acknowledging several groups. First of all, we would like
24 to express our deep gratitude to the agency for holding this
25 meeting and allowing us to present the work that has been

1 completed to date of the ITFG/IPAC collaboration.

2 We would also like to thank the members of the
3 subcommittee for considering our comments and proposals and
4 we look forward to working with them in the future. I would
5 like last to acknowledge the very hard work of all of those
6 people I was talking about, the 85 in the foreground and the
7 hundreds in the background, for the commitment, constructive
8 collaboration, that they have given to the ITFG/IPAC
9 collaboration.

10 Thank you for your attention.

11 DR. LEE: Cynthia, may I ask you one quick
12 question? What is the size of the team, how many members?

13 DR. FLYNN: The entire team? Or a specific
14 technical team?

15 DR. LEE: A specific technical team.

16 DR. FLYNN: They vary, depending on the technical
17 team. So you would have to tell me exactly which one. We
18 have a total of 85 members when you add up all the steering
19 committee and all the technical-team members. There are
20 five technical teams.

21 DR. LEE: So divide by five. Ten or fifteen? Can
22 someone be on several teams?

23 DR. FLYNN: In some cases, there are, but not in
24 all cases; no.

25 DR. LEE: And then the position paper that you

1 will develop or deliver will be a consensus document?

2 DR. FLYNN: Correct.

3 DR. LEE: Thank you.

4 That concludes the presentations by those two
5 groups. Now we have two more to go. Next up is on CMC
6 issues by Dr. Neugebauer.

7 **CMC Issues**

8 DR. NEUGEBAUER: My name is Ken Neugebauer. I am
9 the Director of Marketing for Solvay Fluorides responsible
10 for the NAFTA region. I am speaking on behalf of and
11 presenting the comments of Ms. Anja Pischtiak, Product
12 Manager of Pharmaceutical Aerosols for Solvay Fluor based in
13 Hanover, Germany.

14 [Slide.]

15 Solvay Fluor is a manufacturer of the propellants
16 HFA227 and HVA134a used in inhalation drug products,
17 marketed by Solvay under the trade name of Solkane, would
18 like to make two comments on the major excipients and MDIs,
19 the noncompendial propellants 227 and 134a. The comments
20 relate to the draft guidance for industry, metered-dose
21 inhaler and dry-powder inhaler drug products chemistry,
22 manufacturing and controls documentation.

23 [Slide.]

24 The first point. Lines 288 to 295 identify a
25 requirement for a toxicological qualification of the novel

1 excipients 134a and 227 but do not give directives of what
2 comprises a toxicological qualification. The consortia
3 IPACT I and II have submitted to the FDA extensive safety
4 data on 134a and 227 intended for inhalation which may
5 sufficiently demonstrate the toxicological suitability of
6 the novel excipients 134a and 227 for use in medical
7 products including MDIs.

8 Solvay believes that the uncertainty of the
9 requirements for a toxicological qualification of the pure
10 excipients strongly inhibits the pharmaceutical industry
11 from reformulating its CFC-containing products to HFAs.
12 Therefore, we propose that a definition for the
13 toxicological qualification of the noncompendial propellants
14 HFA134a and HFA227 be added to the draft.

15 The second point we want to make, lines 381 to 405
16 show impurity acceptance-criteria limits for 134a impurity
17 by impurity, which are given in such detail, strictly
18 process related. Solvay, for example, uses for the
19 manufacturer of 134a pharma a process starting from
20 trichlorethylene which is not mentioned in the FDA
21 specification.

22 However, it is present in trace, but detectable,
23 amounts in our product and, therefore, is specified by
24 Solvay. While Solvay has four additional impurities not
25 shown in the specification quoted by the FDA, sixteen other

1 impurities that are listed in the draft specifications are
2 not contained in Solkane 124a as manufactured by Solvay.

3 Therefore, Solvay proposes to replace detailed
4 impurity-by-impurity limits with acceptance criteria based
5 on toxicological tests performed both for HFA134a and for
6 HFA227.

7 [Slide.]

8 I submit, with these comments, Solvay's
9 specification--that is impossible to read; I apologize. I
10 will get a clearer copy for publication. Basically, this is
11 our specification for 134a with detailed description of all
12 of the impurities listed and comparison for what Solvay
13 manufactures in the draft guidance.

14 [Slide.]

15 This slide is the specification for Solkane 227
16 pharma as filed currently with the FDA to be added to the
17 draft guidance in case the 134a specification remains. The
18 227 specification is currently omitted.

19 Finally, I have included with my submission that
20 we agree in principle with comments previously submitted by
21 IPACT as published in the August 1999 Gold Sheet. Again, I
22 am submitting them with the key points highlighted for the
23 committee.

24 Thank you very much.

25 DR. LEE: Thank you very much.

1 The final speaker of this session is on growth
2 effects of nasal steroids by Dr. Schenkel.

3 **Growth Effects of Nasal Steroids in Children**
4 **and Differences among the Steroid Preparations**

5 DR. SCHENKEL: Good afternoon. I want to thank
6 the committee for allowing me to speak about this issue.

7 [Slide.]

8 I am a practicing allergist. I am Director of
9 Valley Clinical Research Center in Easton, Pennsylvania. I
10 have been involved in a number of clinical trials looking at
11 differences among the various nasal corticosteroids. What I
12 am going to be talking about in the next few minutes is
13 exactly that, the differences among the steroids in a
14 clinical setting.

15 You have heard a lot today about trying to look at
16 in vitro models and how to tell differences among the
17 steroids. I am going to point out to you the fact that
18 there are differences, not just in bioequivalence but in
19 what I have called bioactivity, particularly in the
20 pediatric population and particularly the effects on growth.

21 I would urge the subcommittee to look at this very
22 carefully. It has already been looked at by the FDA in
23 terms of acknowledging a new pediatric labeling for nasal
24 corticosteroids.

25 It is well known that oral corticosteroids can

1 sensitive assays that are being developed, we do have an
2 ability to measure or detect plasma concentrations after
3 oral inhalation in nasal products although we do have some
4 cases where we are still struggling with the measurement of
5 these plasma concentrations, or detecting and quantifying
6 these concentrations.

7 So I would actually say that we do require that
8 pharmacokinetic-based bioavailability studies be conducted,
9 both to understand from a clinical pharmacology perspective
10 as well as the product-quality perspective. However, for
11 orally inhaled and nasal drug products intended for local
12 action, it is multiple aspects that have to be address.
13 Bioavailability and bioequivalence cannot be solely
14 addressed based on pharmacokinetics.

15 But, because of the accuracy and, wherever
16 possible, we say pharmacokinetic studies are the first
17 choice to characterize the systemic exposure. However, that
18 alone is not sufficient. You need additional
19 pharmacodynamic data from a safety perspective as well as
20 clinical efficacy data where appropriate.

21 Thank you.

22 DR. LEE: Thank you very much.

23 Dr. Harrison, you have the last words, but you
24 only have twenty minutes.

25

Industry View

1 DR. HARRISON: Good afternoon. I want to thank
2 you for allowing me to be the last presenter.

3 [Slide.]

4 My topic is PK and PD studies for systemic
5 exposure of locally acting drugs. I am giving an industry
6 viewpoint.

7 [Slide.]

8 The value of PK for OINDP is that it measures
9 systemic absorption or systemic exposure. Both terms are
10 used in the guidance. I look at them as interchangeable.
11 Really, what they are doing is measuring systemic safety.
12 PK is an established bioequivalence metric. It can be
13 standardized. It can be validated. It is discriminating.
14 So certainly it has an awful lot of pluses for it.

15 [Slide.]

16 There are some concerns, however, with PK that
17 were raised. One is the low doses that are given nasally
18 and by inhalation, what limitations that imposes. The assay
19 lower limit of quantitation; there is quite a bit of
20 variability that is encountered in PK studies for the nose.
21 There could be draining of excess dose so that you really
22 don't get a good dose response. And, for oral inhalation,
23 the dosing technique is quite critical.

24 [Slide.]

25 What I want to do is address those concerns up

1 front. The first one is low doses. That really is not so
2 important anymore. The bottom line is can you quantitate.
3 With the new advances in analytical techniques, you can
4 usually do it. Low dose is not a big issue, I think,
5 especially when you have a therapeutic dose range, as has
6 been proposed in the new guidance--the nasal guidance, that
7 is--you can go, say, one puff, two puffs or even up to four
8 puffs. Whatever is recommended in the dosing
9 recommendations, it is fair game to use in the PK study.
10 That also will help in analytical sensitivity.

11 So that gives you a lot more dose options than
12 doing a PK study. To me, that is a good idea. The nasal
13 route, you may be limited by drainage on how much you can
14 give but, again, there is sensitivity there even for that.

15 [Slide.]

16 Looking at the assay lower limit of quantitation,
17 with LC mass spec/mass spec, now, you have got tremendous
18 capabilities to go into the peak of gram per ml range. In
19 many cases, you can get down to about 10 to 20.

20 What I have listed there are commercial assays
21 that are actually available. Say, if you were a generic
22 firm, you could find those assays available right now. For
23 BDP that is important because it has got a 17
24 monopropionate metabolite that is really the primary
25 material in plasma and it is the most active and there are

1 assays for that as well as BDP.

2 So you can do a good kinetic analysis of BDP as
3 well. Again, because the equipment is so pervasive, you
4 could get an analytical lab to help you out with whatever
5 assay you wanted, I believe. So that is not a big issue
6 anymore, either.

7 [Slide.]

8 Variability is a concern. There is large
9 intersubject variability. There is large intrasubject
10 variability. There is also variability with the dosing
11 technique. That needs to be addressed.

12 [Slide.]

13 This is just a slide showing, in one of the
14 treatments given nasal formoterol, perhaps an example of a
15 beta agonist, the variability you are seeing here with about
16 an N of 27 is roughly on the order of about 40 or so
17 percent. That is fairly typical. It is also, say, typical
18 of a topical product or a variable oral product and it is
19 something that would could live with.

20 DR. HAUCK: Here, with a N of 12, the variability
21 is a little bit higher. This is nasal triamcinolone. This
22 variation, by the way, was somewhat similar to what was
23 presented earlier by Dr. Derendorf or nasal fluticasone.

24 [Slide.]

25 Here, budesonide. Again, very similar. These are

1 standard errors but, again, it is coming out to be 40 to
2 50 percent variability that you are encountering in plasma
3 levels.

4 [Slide.]

5 This is oral fluticasone. Again, you can see the
6 range that you get in the plasma levels in these twelve
7 individuals. So they vary broadly, but the curve pretty
8 much is established by the mean. It is something I think
9 that we can live with. We can reduce variability. There
10 are various possibilities.

11 Replicate study designs is an interesting
12 possibility that I have not seen anybody, at least approach
13 in the literature. It is something that could be
14 investigated.

15 [Slide.]

16 What people have looked at, what we have looked
17 at, is increasing the subject number. With the nasal route,
18 you may need to reduce the dose.

19 What we have looked at for oral inhalation is
20 training the individuals to use proper technique. A
21 criticism there; it is not the real world and there are
22 actually even little computer machines that could teach a
23 person exactly how to inhale the product properly.
24 Certainly, we have used that in the past and with good
25 results as well.

1 [Slide.]

2 So what are the limitations of, then, doing
3 pharmacokinetics? There really is no correlation with
4 efficacy right now. That has been seen. I will show you
5 some examples of that for the corticosteroids. And it does
6 represent only a fraction of the dose, usually less than
7 30 percent.

8 As we talked about for nasal, it could be just a
9 few percent. Again, if you compare the nasal PK, you may be
10 working hard to get equivalence of an extremely small part
11 of the real dose and what is being positive in the nose,
12 where your efficacy is, may be completely different than
13 what you are focussing on.

14 Again, there are even concerns with the fine-
15 particle fraction. That is debatable. What are the right
16 ranges? So there is still some confusion there. That is,
17 again, a limitation of how you interpret it.

18 Really, when you look at it, PK is the summary
19 parameter. It represents absorption through many different
20 routes; the mouth, the GI tract and, on first pass, going to
21 the liver, the lungs. Actually, the appearances really have
22 different rates into the blood. We have seen some
23 sensitivities there. In terms of depending on how much goes
24 in the mouth versus the lungs, you actually can get some
25 confusion in your datasets.

1 [Slide.]

2 Here is an example of what I want to get at now is
3 that there is no good relationship between efficacy and
4 blood levels. This is a study with fluticasone given
5 nasally. C1 represents the concentration at one hour and
6 the symptom score represents your efficacy.

7 What you see here is that, for the oral products
8 and the placebo, you saw no difference in the symptom score
9 but the nasal administration, you did whereas, in the blood
10 levels, you had detectable levels only orally but not
11 nasally. So, again, they were separated. Blood levels were
12 seen orally. Efficacy was only seen nasally.

13 [Slide.]

14 The same thing was done through the oral-
15 inhalation route, again with fluticasone. Again, what you
16 are seeing is a very similar type of design where now you
17 are looking at your efficacy parameters, AM FEV1 and symptom
18 score and you are seeing activity with the inhaled route but
19 not the oral route.

20 Then, if you look at the Cmax and AUC as your
21 pharmacokinetic parameters, what you are seeing there are
22 your highest levels orally. They are easily twice that of
23 what is seen by your higher inhaled dose and yet you are not
24 seeing any activity associated with that.

25 So, once again, what you have is really a

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1 dissociation between pharmacokinetics and efficacy. So that
2 is a limitation as well.

3 [Slide.]

4 The conclusions are that PK is useful to establish
5 systemic absorption. It really is not a surrogate for local
6 efficacy but it is doable. Right now, the assays are out
7 there. You can measure the levels, even nasally, and you
8 can reduce the variability to make it worthwhile and doable.

9 The next question to ask is can you actually do
10 systemic bioequivalence.

11 [Slide.]

12 We have got some examples there. We have done a
13 lot of work with BDP. What I want to talk about first, when
14 we are comparing two formulations. Formulations; we will
15 call them MDI-A, MDI-B. The study designs that we used were
16 single dose but multiple inhalations. They were asthmatics
17 with a crossover design and good inhalation technique.

18 So that will be common to the studies.

19 [Slide.]

20 In terms of the devices, if you look at the draft
21 nasal bioequivalence guidance, what you could say is Q1 and
22 Q2 were the same and identical, those two devices. The
23 particle-size distribution, the spray pattern, would meet
24 the criteria were essentially similar. The route size was
25 the same and the actuator, again, dimensions were

1 essentially the same.

2 So there wasn't a lot of difference between the
3 two.

4 [Slide.]

5 When we did the first study, it was in 18
6 asthmatics. The objective was comparability. What we found
7 was that we came close to matching confidence intervals but
8 we did not make it. You can see Cmax was on the low side of
9 the accepted 0.1 to 1.25. AUC was on the high side.

10 Coefficients of variability, about 50 percent for
11 Cmax, again, similar to what was seen in the earlier slides
12 I showed you with others. AUC also was variable.

13 [Slide.]

14 Another study was done, again with the exact same
15 MDIs, MDI-A, MDI-B. Here, the objective was systemic
16 bioequivalence. So, what we did is we increased in N number
17 to 45 and we actually looked at two doses, a low dose and a
18 high dose in this study.

19 [Slide.]

20 You can see here coefficients of variation were
21 reduced for the most part with a higher N number and now,
22 essentially, all the parameters did actually meet strict
23 bioequivalence criteria.

24 So we concluded from this that we could actually
25 show systemic equivalence but we also did local delivery

1 studies for efficacy. We did not stop there.

2 [Slide.]

3 Another example we have got is now looking at MDI-
4 C versus MDI-D. In this case, we actually had just
5 different strength products. So, it is the same dose. The
6 only thing different here to give the same dose is different
7 numbers of puffs because you had a different valve size.

8 So one MDI may require twice as much as the other
9 to get the same dose delivered. The study designs that we
10 looked at to analyze C versus D again were single-dose
11 asthmatics, crossover, and a good inhalation technique.
12 Similar to what we found in the previous examples, you have
13 everything matched identical in this case except for the
14 valve size.

15 So, again it was very similar, such as the same
16 formulation but different valve sizes and we did a study
17 with that. We are looking at systemic comparability here in
18 18 asthmatics and we came very close to getting
19 bioequivalence with an N of 18. It was just outside, 7.6
20 for Cmax. If you want to use a more liberal criteria of
21 7.5, it actually would make it.

22 CV wasn't that great in this case.

23 [Slide.]

24 If you look at the next study, when we went to 30,
25 we actually met the criteria. We could include equivalence

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1 as the conclusion, therefore. We, again, had equivalence,
2 in this case with a reduced N number but we did run a local
3 delivery study to demonstrate efficacy as well. We did not
4 stop there.

5 [Slide.]

6 Looking at other PK options, we have talked about
7 charcoal block. It certainly allows differentiation of the
8 pulmonary or non-pulmonary absorbed drug. It has got a lot
9 of appeal there. The nice thing is it utilizes the same
10 drug assays and metrics so there is little added time or
11 cost. You really don't have to alter the reference or the
12 test formulations as you would have to do for, like, gamma
13 scintigraphy. So it has got a certain appeal to it.

14 [Slide.]

15 However, the limitations that I see with the
16 charcoal block is that there is no evidence that pulmonary
17 absorbed drug correlates, again, with efficacy. It is true,
18 it gets into lungs, but that is where the real correlation
19 stops. And it does not discriminate potentially important
20 product differences such as oropharyngeal deposition or
21 regional lung deposition.

22 I look at it as a very useful laboratory tool to
23 get at the pulmonary drug absorbed but I don't see it,
24 really as adding very much more to PK. It could be looked
25 at as a potential surrogate for local delivery, again if we

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1 can establish that link between what is put in the lungs and
2 absorbed versus efficacy.

3 [Slide.]

4 Another option is urinary excretion. Supposedly,
5 when PK is not doable, that is a possibility. There are
6 examples of that in the literature. It has been reported
7 for the various products up there. There are references for
8 each one of them.

9 [Slide.]

10 Here is one, for instance, in nasal ipratropium.
11 It is highly variable. You can see the CV was 84 percent
12 and the dose excreted also was 89 percent. So, although
13 you can do it, it really doesn't seem to have a lot of added
14 value. So I look at it--it has got high variability. It
15 has got low sensitivity. And, therefore, it is unlikely to
16 be a reliable surrogate of what we are trying to do here.

17 [Slide.]

18 PD has been suggested as a surrogate when PK is
19 not doable. Now, the PD that I am considering is only
20 systemic PD. So you are looking at cortisol, markers of
21 bone growth, of demineralization, things like that. I am
22 not talking about FEV1s at all here. And, again, that
23 requires an appropriate study design.

24 You usually need a dose-response curve to show
25 that your PD measures are sensitive. It requires repeat

1 administration.

2 [Slide.]

3 Frankly, it is highly variable. It has got low
4 sensitivity. It requires, again, multiple dose levels. I
5 don't see that as being very valuable. If you can't do
6 pharmacokinetics, the likelihood of doing PD is very low.
7 If you are looking at, say, what is out there published with
8 nasal products, if you cannot do pharmacokinetics, I don't
9 know how you are going to deal with, say, urinary cortisol
10 or 24-hour cortisols. It just doesn't have the same
11 sensitivity.

12 You get the best results when you can do PK as
13 well so, therefore, I don't see that as a great surrogate
14 either.

15 [Slide.]

16 PK/PD. That is a very nice thing. There has been
17 a lot of work done there. It, again, allows correlation of
18 PK with PD. PK is linear. PD has got a dose-response
19 curve. It certainly offers increased understanding of what
20 is happening for systemic exposure and safety.

21 So it has got, again, a lot of appeal in helping
22 the understanding.

23 [Slide.]

24 It is sophisticated work, though. It requires
25 several dose levels, additional analyses and I don't think

1 it really increases the ability to discriminate which is the
2 bottom line for doing bioequivalence. So I look at as a
3 very useful laboratory tool but I don't see it as needed for
4 bioequivalence either.

5 [Slide.]

6 So, in summary, systemic PK assessment really is
7 what is needed to assure systemic safety and it really is
8 doable for most drugs. The state of the art is you can do
9 it, even nasally.

10 The other possibilities, PD, urine levels, are not
11 likely surrogates. Charcoal block and PK/PD, again, are
12 nice development tools but I don't really see them making
13 the leap, either.

14 [Slide.]

15 So my input into the last question, are there
16 situations where in vitro data plus PK, and, again, even PD,
17 can be relied upon to show assure local efficacy, they can
18 be relied on is the key thing. It really does imply
19 predictability and the list of drugs. It has not been
20 established, really, for any of them.

21 Certainly, there are a lot of questions there.
22 Until we can get better information, I think we need to have
23 caution and err on the side of caution and not really look
24 for situations where you can just do PK without having some
25 type of local delivery component.

1 DR. LEE: Thank you, Lester.

2 Subcommittee Discussion

3 DR. LEE: Wally, would you like to provide some
4 background for your question?

5 DR. ADAMS: Yes. I would like to ask Lester a
6 question concerning his last slide. Lester, you were
7 talking about in vitro data plus PK plus systemic absorption
8 PD in that case.

9 DR. HARRISON: Yes; that is correct.

10 DR. ADAMS: Our question was a general one related
11 to whether in vitro data plus PK data would be able to
12 assure bioequivalence. Lester, you are saying no; that is
13 your answer to this question?

14 DR. HARRISON: That's correct.

15 DR. ADAMS: Yet there are cases where you are
16 indicating if PK data are not doable, then you feel that the
17 PD is not going to contribute.

18 DR. HARRISON: That is my position. Based on what
19 I have experienced in the literature, I have never been
20 convinced that, if you can't do one, you can do the other.
21 It is a nice objective but, in reality, I have not seen it
22 done.

23 DR. ADAMS: You could have situations where
24 neither a test product nor a reference product may inhibit
25 the adrenal axis.

1 DR. HARRISON: Exactly; that is more likely to
2 happen. That is why going up in doses may be an absolute
3 necessity in cases like that. But, even for fluticasone,
4 you can do nasal fluticasone now and the assays are so good
5 that I think that it is getting to the point where we can
6 measure almost anything.

7 DR. LEE: Are there members of the committee who
8 can shed some light on this question?

9 DR. LI: I think, from the standpoint of orally
10 inhaled drugs, that are sufficient variables in regional
11 lung deposition, particle-size distribution, that the sort
12 of in vitro assessment along with pharmacokinetic data
13 without any clinical types of evaluation is probably not
14 going to be enough.

15 I would say that the orally inhaled products
16 should have an in vivo assessment.

17 If we kind of look back to some of the cascade
18 data that we saw and our attempts to use the chi square to
19 get a numerical handle on comparability, chances are that
20 any in vitro assessment for a new product is not going to be
21 exactly the same as the reference product. There are going
22 to be some differences, and the differences may be at
23 various stages of cascade or may be differences in particle
24 size and different ranges.

25 So it is going to be really impossible to predict

1 precisely the biological activity of that orally inhaled
2 product. So I, basically, would agree, at least certainly
3 in the area of orally inhaled products, that in vitro
4 assessment is important but not sufficient. Pharmacokinetic
5 data is also important but not sufficient. Some in vivo
6 assessment would be necessary.

7 DR. ADAMS: Just for clarity, Dr. Li, you are
8 talking about efficacy.

9 DR. LI: That's correct; for orally inhaled
10 products.

11 DR. BEHL: Which could be a bridging study also as
12 opposed to a full-scale study.

13 DR. LEE: Is Steve Forrester here? He left?
14 Okay.

15 DR. ADAMS: Just to follow up further on this
16 question, Dr. Upoor, did you wish to ask the subcommittee
17 any question with regard to that last question?

18 DR. UPPOOR: I actually just want to find out,
19 even if you have an innovative product, for example, and
20 that has been shown to be clinically safe and efficacious
21 and you have done all these trials that have been approved,
22 and some minor, some type of change is made to that product
23 and it is the same product, you have a handle on what goes
24 on with that product, you have some understanding or,
25 hopefully, a reasonable understanding of the product, and

1 some minor changes are made, even in those cases, what I am
2 hearing is it doesn't matter what the change is, but if it
3 is an orally inhaled drug product, we would like some kind
4 of efficacy data in addition to in vitro and PK.

5 DR. LI: If you are addressing that question to
6 me, that would be a question that would, in my view, be
7 extremely focused. I did not, in fact, say that, in that
8 particular set of circumstances, one would necessarily need
9 to go through clinical studies and even to specify what kind
10 of in vitro studies would be necessary.

11 I think, in a very narrow sense, depending on what
12 those changes were, say, in the development of the product,
13 if they were such change where one might not expect any
14 significant, really, change in delivery, then probably I
15 would say how things are handled now, case-by-case, would be
16 the way to go.

17 If there are major changes in the formulation and
18 the production and changes in propellant, for example, that
19 would be an example. A change in propellant is probably
20 enough of a change that you would really need to do more
21 extensive testing.

22 DR. GORE: Just a comment from the perspective of
23 those of us in product quality that have a lot of experience
24 with cascade impactors, rather minor changes in the
25 formulation of the composition of the material can, in fact,

1 change what you are, in reality, measuring in the individual
2 stages of the cascade impactor.

3 So, because of formulation and what is deposited
4 on the cascade-impactor stage is a combination of excipients
5 as well as active ingredient. That is something that would
6 require a lot of validation if you were trying to make a
7 crossover between two different formulations.

8 DR. LEE: Are there any comments? I think we are
9 kind of supersaturated.

10 DR. LAGANIERE: I would just add that the
11 experience of Dr. Harrison concerning nasal drug
12 administration, he seems to be alluding to the fact that you
13 can increase the dose if you are not able to see it at the
14 small doses that are usually administered in therapeutics.

15 But, in the context of safety or exposure, I would
16 like to have maybe the opinion of physicians regarding the
17 relevance of using a so much higher dose that would be
18 usually higher than the recommended daily dose.

19 DR. HARRISON: Let me just clarify that before you
20 ask an opinion. I meant within the therapeutic dose range.
21 You increase the dose. As long as it is in the therapeutic
22 dose range, say up to four puffs per nostril, you can do
23 that much.

24 DR. LAGANIERE: Okay. So that would be a limit in
25 establishing whether a pre-case exposure study is feasible

1 or not.

2 DR. HARRISON: Yes. I went fast through my
3 slides, but what I did show is pharmacokinetically, you can
4 get a nice dose response with pharmacokinetics in the nose.
5 It has easily been shown by inhalation, but nasal as well.

6 DR. LEE: Wally, the short answer to your question
7 is that, apparently, nobody around this table has any
8 situations that would respond to your question.

9 DR. ADAMS: I hear that. Thank you, Vincent.

10 DR. LEE: Guirag and Wally, are there any other
11 questions for the committee before we adjourn the meeting?
12 Anybody else?

13 DR. GORE: May I ask more of a procedural question
14 because there was actually a comment made earlier about the
15 need for another meeting. I would like to say I think there
16 is a need for another meeting. There is a huge amount of
17 information, particularly in the CMC area, that was brought
18 forward in the afternoon that we did not have an opportunity
19 to discuss and also some proposals for ways to bring more
20 data into the discussion.

21 .. That is just my proposal. I think we need another
22 meeting.

23 DR. LEE: If there are no further comments, I
24 would like to thank everybody for participating openly. I
25 am surprised that I am still alive. I thank you for your

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1 input and have a safe journey home. Thank you.

2 [Whereupon, at 5:08 p.m., the meeting was
3 adjourned.]

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