

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 [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.

at

268

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

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

at

272

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

at

278

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

at

281

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

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

3 adjourned.]

4

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

ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

VOLUME I

Wednesday November 15, 2000

8:30 a.m.

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  
10 establishing in vivo BE.

11           On the in vivo side we have the following wording,  
12 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 dearlly  
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  
10 analyzing data to test our position statements for these  
11 tests.

12 For further tests we have simply drafted comments  
13 on the requirements for MDIs, such as those for impurities  
14 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.

**JULY 2001**  
**STATEMENT TO ADVISORY COMMITTEE FOR**  
**PHARMACEUTICAL SCIENCE**  
**AND OINDP SUBCOMMITTEE**

*On the Work of the ITFG/IPAC-RS Collaboration  
Regarding Chemistry, Manufacturing, and Controls and  
In Vitro and In Vivo Bioavailability/Bioequivalence Issues in  
Draft Guidance Documents for Orally Inhaled and Nasal Drug Products*

**Submitted by:**

INHALATION TECHNOLOGY FOCUS GROUP OF THE AAPS  
INTERNATIONAL PHARMACEUTICAL AEROSOL CONSORTIUM ON REGULATION AND SCIENCE

10 July 2001

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# TABLE OF CONTENTS

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<b>INTRODUCTION</b> .....	3
<b>EXECUTIVE SUMMARY</b> .....	4
<b>SUMMARY OF RECOMMENDATIONS</b> .....	5
<b>REVIEW OF ITFG/IPAC-RS WORK AND PROPOSALS</b> .....	7
<b>I. In Vitro and In Vivo Tests for Bioequivalence Studies</b> .....	7
<b>II. Dose Content Uniformity Specifications</b> .....	12
<b>III. Particle Size Distribution Tests and Specifications</b> .....	14
A. PSD CMC Specifications .....	14
B. PSD as In Vitro Test for Bioequivalence Studies .....	15
<b>IV. Leachables and Extractables Testing</b> .....	17
<b>V. Supplier Quality Control</b> .....	19
<b>VI. Tests and Methods for Control of Product Quality</b> .....	20
<b>CONCLUSION</b> .....	22
<b>NOTES</b> .....	23

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## INTRODUCTION

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This statement is submitted to the OINDP Subcommittee and the Advisory Committee for Pharmaceutical Science in connection with their meetings on 17 and 19 July 2001, respectively.

The agenda for these meetings includes a consideration of the issue of dose-response of locally acting nasal drug products, with particular application to bioequivalence studies. The ITFG/IPAC-RS Bioequivalence and Bioavailability Technical Team offers their views on this topic in section **I.2.a** (page 7) of this report. Specifically, the Team reviews its findings on this issue, submitted to the Agency in August 2000, and presents its positions developed since the August submission.

We also provide an update on the work of the other Technical Teams of the ITFG/IPAC-RS Collaboration to inform the committee members of the progress made since the last meetings of these committees in 2000, to outline the full scope of our concerns with the draft Guidances for OINDP, and to highlight areas where additional research has been undertaken or proposed by the industry.

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## EXECUTIVE SUMMARY

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- In January 2000, the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) and scientists of the Inhalation Technology Focus Group (ITFG) of the AAPS initiated an extensive scientific collaboration to address important issues in the FDA's draft Guidance documents for orally inhaled and nasal drug products (OINDP).<sup>1</sup>
- Over 100 individuals from more than 25 companies and institutions are participating in the ITFG/IPAC-RS Collaboration.<sup>2</sup> The Collaboration involves several Technical Teams and Working Groups, addressing the issues of *in vitro* and *in vivo* tests for bioavailability and bioequivalence (BA/BE) studies, dose content uniformity (DCU) specifications, particle size distribution (PSD) tests and specifications, tests and methods used for control of product quality, leachables and extractables testing, and supplier quality control for orally inhaled and nasal drug products.
- ITFG and IPAC-RS are interested in data-based, scientifically justified Guidances for the development and registration of OINDP. In order to contribute constructively to the development of such Guidances, the ITFG/IPAC-RS Collaboration collected and analyzed relevant data and proposed modifications to the FDA draft Guidance documents.
- Since its inception, the ITFG/IPAC-RS Collaboration prepared and submitted seven scientific reports to the FDA and members of the OINDP Subcommittee and the Advisory Committee for Pharmaceutical Science, attended two meetings with the Agency regarding the findings and recommendations contained in the DCU and BA/BE reports, and made public presentations during the April 2000 meeting of the OINDP Subcommittee and the November 2000 meeting of the Advisory Committee. Copies of the reports submitted by the ITFG/IPAC-RS Collaboration are publicly available through the FDA dockets and are also posted at <http://www.ipacrs.com/submissions.html>. We respectfully request that the OINDP Subcommittee and the Advisory Committee for Pharmaceutical Science consider conclusions, recommendations and proposals presented in these reports.
- We are grateful for the time and attention the Agency has accorded to the consideration of the BA/BE and CMC issues for OINDP and we commend the Office of Pharmaceutical Science for its continuing interest in and support of this process. We are hopeful that through the meetings of the OINDP Subcommittee, Advisory Committee for Pharmaceutical Science, the Product Quality Research Institute (PQRI), and other appropriate fora, the work of the ITFG/IPAC-RS Collaboration will be carefully considered and taken into account by the Agency during its revision of the draft Guidances. If this happens, we believe that both the FDA and the pharmaceutical industry will be better able to respond to the needs of patients by expediting the availability of new OINDP products while maintaining appropriate standards of safety, efficacy and quality.

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## SUMMARY OF RECOMMENDATIONS

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As demonstrated in the following sections, the ITFG/IPAC-RS Collaboration has investigated a number of open CMC and BA/BE issues in the draft Guidances and looks forward to a careful discussion of its findings by the Agency and other appropriate bodies, such as PQRI, the OINDP Subcommittee, and the Advisory Committee for Pharmaceutical Science. The Collaboration is grateful for the Agency's consideration of its work and proposals. We summarize our general positions below.

### Regarding the BA/BE draft Guidance:

- Pertinent data should be gathered and evaluated to address the potential risks in the proposal that *in vitro* tests alone would be adequate to demonstrate the bioequivalence of generic nasal solutions for local nasal therapy.
- Further investigation of PSD profile comparison methods should be undertaken in order to identify appropriate means to compare Reference and Test products and to evaluate what test metrics have clinical relevance for nasal and inhaled delivery.

### Regarding the CMC draft Guidances:

- The parametric tolerance interval DCU test developed by IPAC-RS in collaboration with ITFG scientists should be considered by the Agency as a replacement for the approach to DCU specifications in the current draft Guidances for OINDP.
- The mass balance specification requirement should be removed from the CMC Guidances for OINDP. If appropriate, additional dialogue on PSD specifications and the utility of mass balance should take place as part of the process of revising the draft Guidances.
- The revised CMC Guidances for OINDP should include a leachables qualification program, including reporting and toxicological qualification thresholds for leachables. Further, the approach to establishing reporting and qualification thresholds and the thresholds proposed by the Collaboration should be evaluated and carefully considered by toxicologists and chemists from the FDA, industry, and other interested parties.
- The revised CMC Guidances for OINDP should include a statement recognizing the value of a cGMP guideline for component suppliers, and acknowledging that if sufficient supplier control mechanisms are in place, appropriate reductions in testing of the finished product will be considered.

- The revised CMC Guidances for OINDP should avoid requiring redundant or irrelevant routine testing of finished products. The Guidances should recognize that most appropriate tests for the quality control of commercial products should be selected based on the product development data.

We believe that through additional work in the identified areas, the draft Guidances for OINDP could be significantly improved, which would offer a win/win/win solution for the Agency, industry and patients.

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# REVIEW OF ITFG/IPAC-RS WORK AND PROPOSALS

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At the 26 April 2000 meeting of the OINDP Subcommittee, the ITFG/IPAC-RS Collaboration presented<sup>3</sup> its concerns regarding a number of CMC and BA/BE issues in the FDA draft Guidances and made a commitment to collect and analyze relevant data in order to contribute constructively to the revision of the draft Guidances. A comprehensive review of the ITFG/IPAC-RS work carried out through November 2000 was presented to the Advisory Committee for Pharmaceutical Science on 15 November 2000.<sup>4</sup> Following is a brief update on the work and progress of the Collaboration since these meetings. Copies of the scientific reports prepared by the ITFG/IPAC-RS Collaboration are posted at <http://www.ipacrs.com/submissions.html>, and are also available through the FDA dockets for the draft Guidances.

## I. IN VITRO AND IN VIVO TESTS FOR BIOEQUIVALENCE STUDIES

### 1. Key Concerns with Draft BA/BE Guidance

The BA/BE Technical Team of the ITFG/IPAC-RS Collaboration reviewed the draft Guidance for Industry: *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, reviewed and analyzed available literature and data, and has prepared and submitted to the FDA three technical papers.<sup>5</sup> The papers outline the key concerns with the draft BA/BE Guidance and propose possible approaches for the way forward.

### 2. BA/BE Work to Date

#### 2.a. Dose-Response and Transfer of Indications for Locally Acting Nasal Drug Products

In the paper entitled *Technical Paper on FDA's Bioavailability and Bioequivalence Questions Presented at 26 April 2000 OINDP Advisory Subcommittee Meeting*, submitted to the Agency in August 2000, the Team addressed the Agency's questions regarding clinical studies for locally acting nasal drugs.<sup>6</sup> Based on the review of published data, the Team arrived at the following conclusions:

- The approach to collection and presentation of data, and selection of primary and secondary endpoints described in the draft *Guidance for Industry Allergic Rhinitis: Clinical Development Programs for Drug Products* (April 2000)<sup>7</sup> may be an appropriate model for differentiating between several doses of Test/Reference product in a 2 week clinical study using endpoint comparisons including onset of action, and mean change from baseline for

patient-rated total nasal symptom score over the entire double-blind period. Replication or substantiation of these results in either an Environmental Exposure Unit or Days-In-The-Park study may be appropriate. The products should be equivalent at all pre-defined timepoints. The standards used to establish statistical equivalence must have been shown to be of some clinical relevance.

- At present, the studies proposed in the draft BA/BE Guidance for nasal aerosols and nasal sprays describe studies that are useful for determining the comparability of products. However, their value for establishing clinical equivalence and substitutability is unproven. The traditional treatment study offers the most appropriate study design for assessing nasal drug products intended for local delivery. There is a need for the draft BA/BE Guidance to further develop the statistical requirements for this study if it is to be used for equivalence testing and link appropriately to the guidance on Allergic Rhinitis referenced above, without confusing the issues of equivalence and comparability. At present the Team is not aware of an alternative method that can be relied upon to establish equivalent local delivery.
- A pre-existing indication for Perennial Allergic Rhinitis, Perennial Non-allergic Rhinitis or nasal polyps at the same dose should be transferable from the Reference product to the Test product if the Q1, Q2 and container-closure standards are met and bioequivalent performance in terms of efficacy, onset of effect, duration of action, systemic and local safety have been clearly demonstrated in SAR. In order to transfer a pre-existing indication for use in children from Reference to Test product, care should be taken to ensure that the studies conducted to assess systemic safety are predictive of all potential patient subgroups.

Since the last Advisory Committee meeting, the BA/BE Team has sought additional information to answer the questions posed in connection with dose response studies, *in vivo* study waivers for locally acting nasal products, and test metrics for *in vitro* as well as *in vivo* comparisons. This effort continues to reinforce the earlier findings that the development of robust clinical protocols, the availability of reliable metrics, and the establishment of relevant *in vitro* test platforms are lagging behind present regulatory needs.

Because of this lack of firm information upon which to base sound regulatory policies, the BA/BE Team has analyzed the problem from the standpoint of risk management. The idea is to focus thinking and scientific investigation toward those critical elements whose uncertainty should be given priority as the development of guidances progresses. This analysis has brought forward three risk areas that are present with locally acting nasal sprays in the context of dose response and clinical equivalence:

- primary local effect;
- local side effects; and
- systemic side effects resulting from absorption of a fraction of the locally applied preparation.

While the first two risk areas can possibly be grouped together and dealt with in a single trial, the third must be treated independently. In fact, the types of clinical trials needed to address each risk area may be very different in nature and construction. It cannot, therefore, be presumed that an *in vitro* test that correctly correlates with the local actions will also be predictive of the systemic outcome.

Although the Team agrees that development and validation of an appropriate model for assessing dose-response as a model of *in vivo* equivalence (in terms of local efficacy and local side effects) is an important element in development of equivalence standards for this group of products, the BA/BE Team believes that the highest risk area in the establishment of product equivalence is the systemic absorption component. We suggest that the design of studies to assess systemic availability and equivalence between nasal solutions for local action deserves the highest level of attention.

## **2.b. Role of In Vivo and Vitro Tests for Bioequivalence Studies**

In the paper entitled *Review of In Vivo and In Vitro Tests in FDA's Draft Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action and Anticipated Forthcoming Guidance for Orally Inhaled Drugs*, the Team described and supported its two general position statements that (i) *in vitro* testing is essential for pharmaceutical product equivalence and should be included as part of the BA/BE Guidance for all nasal and oral inhalation products, but is not currently sufficient for BE approval without establishing *in vivo* BE; and (ii) for BE approval, BA/BE Guidance documents for nasal and oral inhalation drug products for local action should require use of validated human models for *in vivo* testing for local and systemic exposure, efficacy and safety.

One of the Team's hypotheses expressed in that paper is that:

*the assumption that in vitro studies alone are sufficient for BE of solutions is unfounded. The draft BA/BE Guidance should not distinguish between nasal suspensions and solutions for in vivo BE.*

Following the submission of the paper, the Agency requested that this position be substantiated with additional data. In response to this request, the Team conducted further research to supplement its previous survey of the scientific literature in regard to this position. This investigation is described in the Team's third paper, *On the Risks of Eliminating In Vivo Studies for Nasal Solutions for Local Action*, which was submitted to the Agency in April 2001.

The scope of the survey was expanded to include opinions of international regulators and examples from orally inhaled systems, since many of the underlying concepts, design requirements and performance attributes of drug/device combinations for orally inhaled products parallel closely those demanded of nasal solutions and nasal suspensions. Unfortunately, even after this thorough evaluation of the available literature and information, the Team was unable to identify references that could provide an unequivocal foundation for either the Team's or the Agency's positions in regard to the bioequivalence of nasal solutions.

The Team has found, however, that there is a lack of documentation from well-controlled, replicate trials that demonstrate (i) the correspondence between the proposed *in vitro* tests and *in vivo* measures of safety and efficacy; (ii) the discriminatory capability and reliability of the proposed *in vitro* tests as surrogate markers for clinical safety and efficacy parameters; and (iii) that the *in vitro* tests uniformly apply to all classes of drugs under review, *i.e.*, nasal solutions and suspensions for administration via spray or aerosol for local action.

Furthermore, there is clear evidence of a lack of agreement among regulators, as reflected in the current draft CPMP guidance on bioavailability and bioequivalence. This EU guidance proposal does not differentiate between nasal solutions and nasal suspensions for local use (section 5.1.8 (a) of CPMP/EWP/QWP/1401/98). Moreover, it requires pharmacodynamic or comparative clinical studies for locally acting nasal products. Additionally, there is general acknowledgement among scientific and clinical experts regarding the need for more work before the *in vitro-in vivo* correlations necessary to support waivers of clinical testing for this group of drug/device products can be made.

Because there is not sufficient data to show that *in vitro* testing methodologies are an adequate substitute for *in vivo* studies, the Team believes that the Agency should reconsider the draft Guidance's biowaiver provision for nasal solutions for local delivery. In addition, more specific and relevant data must be generated in order to ensure that the final guidance reflects best practices in regulatory science.

### **2.c. Development of Risk Management Framework**

The BA/BE Team believes that the current lack of definitive information and expert consensus regarding the validity of current *in vitro* testing as a guarantee of *in vivo* outcome is a risk situation, with unknown clinical efficacy or safety consequences, to the users of nasal pharmaceutical products. However, the current draft Guidance does not acknowledge this risk, and does not, therefore, fall within the risk management framework elaborated in the 1999 Report from the Task Force on Risk Management to the Commissioner.<sup>8</sup>

The Team has outlined three possible risk management approaches (*i.e.*, risk avoidance, risk stratification, and risk comparison) that may be incorporated into the Guidance until relevant data on the sufficiency (or insufficiency) of *in vitro* testing to demonstrate bioequivalence of nasal solutions is generated.

The Team is a committed stakeholder in this process and is interested in exploring with the Agency the manner in which the appropriate risk analysis and risk assessment can be brought into the text of the draft Guidance. The Team is interested in collaborating with the Agency to define appropriate measurement systems and reliable test conditions which could be adopted to address the risk factors objectively.

Furthermore, correct methods of numerical analysis and valid comparison metrics should be developed, which will ensure that a uniform state of minimized risk is maintained. In the meantime, the Team strongly recommends that any consumer risk should be avoided by

requiring that all nasal solution, as well as suspension, products meet both the *in vitro* and *in vivo* BE criteria suggested in the draft Guidance.

### **3. Team's Current Activities**

In light of the current lack of data regarding appropriate *in vitro* tests to establish equivalence of nasal solutions, the Team will propose to explore the following hypothesis through PQRI:

*sole reliance on the in vitro tests outlined in the draft BA/BE Guidance may not be sufficient to establish bioequivalence, including equivalent systemic absorption (for safety purposes) between two Q1/Q2-equivalent nasal solution products which exert their efficacy through local action.*

In parallel, the BA/BE Team will also develop a risk management framework for addressing risks of elimination of *in vivo* studies for nasal solutions.

### **4. Next Steps Regarding In Vitro and In Vivo Tests in draft BA/BE Guidance**

The Team is grateful that the Agency has recognized the value of gathering and evaluating relevant data through PQRI and addressing the risks inherent in FDA's biowaiver provision for nasal solutions for local delivery.

## II. DOSE CONTENT UNIFORMITY (DCU) SPECIFICATIONS

### 1. Overview of Key Concerns with DCU Specifications in FDA Draft Guidances

At the 26 April 2000 meeting of the OINDP Subcommittee, the DCU Working Group committed to examine the suitability of the DCU specifications recommended by the FDA Guidances and to explore alternate approaches to setting DCU specifications that would ensure consistent and uniform dosing for each drug product. As a first step in these investigations, the Working Group committed to collect industry data and to evaluate the following hypothesis:

*The current state of OINDP technology may not allow general compliance with the dose content uniformity specifications in the draft FDA CMC Guidances.*

FDA has also acknowledged that the current approach to DCU specifications in the draft CMC Guidances may need to be re-evaluated. At the April meeting, the Agency posed the following questions<sup>6</sup>:

*Should there be a single content uniformity standard for all orally inhaled and nasal drug products? Should the FDA continue development of the proposed statistical approach to evaluating content uniformity?*

### 2. DCU Work to Date

In the spring of 2000, the DCU Working Group conducted an industry-wide survey of DCU data. The initial analysis of the collected data was presented in a technical paper submitted to the Agency and the members of the OINDP Subcommittee on 31 July 2000.<sup>9</sup> In the paper, the Working Group concluded that the database indicates that orally inhaled products do not in general comply with the DCU specification in the FDA's draft Guidances and that the relatively large differences between products and between product types suggest that a single content uniformity specification for all inhaled and intranasal drug products is not suitable. These findings were reported at the November 2000 meeting of the Advisory Committee for Pharmaceutical Science<sup>4</sup>.

Since the fall of 2000, the DCU Working Group has been exploring alternate approaches to DCU specifications and has developed a new DCU test, which is grounded in general statistical considerations, quality standards set by the draft Guidances, and the capabilities of modern inhalation technology. The new test follows the parametric tolerance interval approach propounded by Dr. Walter Hauck. The test also builds upon certain aspects of the approach put forth by the Pharmacopeial Discussion Group of ICH. The main features of the test developed by the Working Group can be summarized as follows:

- The new DCU test is based on a parametric tolerance interval approach, which uses information contained in a sample more efficiently than the DCU tests in the FDA draft Guidances. This increased efficiency allows the test to provide an improved level of consumer protection (in the statistical sense), while at the same time mitigating the producer risk compared to the FDA draft Guidance tests.

- Quality is defined in terms of the proportion of doses in the batch that fall within a specified target interval.
- To ensure the pre-defined batch quality, the new test uses three acceptance criteria: for the sample mean, sample standard deviation, and the so-called acceptance value. These acceptance criteria ensure that the mean dose is close to the label claim, that dose variability is controlled and that the frequency of outliers is limited.
- Control of through-life trends is achieved through a stratified sampling plan that allows simultaneous evaluation of both between-container and through-container-life uniformity of multi-dose products using a single test.
- The test establishes a uniform minimal quality standard regardless of the dosage form (*e.g.*, MDI, DPI, multi-dose, unit-dose, sprays), yet allows the producer to select the testing schedule most appropriate for their product.
- The improvements accomplished by this test are due to the use of a parametric approach (rather than the non-parametric approach of the draft Guidances) and an increased sample size.

### **3. Current Activities**

The IPAC-RS companies and the DCU Working Group under the leadership of prominent industry experts have undertaken an unprecedented effort to develop a test that could replace the DCU tests in the draft CMC Guidances. In this process, the DCU Working Group has consulted with ITFG scientists, academicians and representatives of the Agency.

The Working Group expects to submit a written proposal on the alternative DCU test to the Agency in the fall of 2001. The Working Group believes that the proposed test will benefit the Agency, the industry and patients by establishing a long-term solution to the control of DCU in OINDP, by ensuring consistent quality standards for such products, and by facilitating the development and CMC approval of new orally inhaled and nasal medicines.

### **4. Next Steps Regarding DCU Specifications**

We acknowledge and appreciate the Agency's attention to the critical issue of DCU. We encourage members of the OINDP Subcommittee and Advisory Committee for Pharmaceutical Science to consider our forthcoming DCU proposal for an alternative approach to DCU testing. To facilitate the evaluation of the new test by the Agency and other relevant parties, we encourage a broad scientific discussion of the merits of the proposed test. In this spirit, the IPAC-RS proposes to hold, in coordination with all interested parties, a public workshop on the newly developed test, once the written proposal of the DCU Working Group is submitted to the FDA docket.

### III. PARTICLE SIZE DISTRIBUTION (PSD) TESTS AND SPECIFICATIONS

#### A. PSD CMC Specifications

##### 1. Overview of Key Concerns with PSD in FDA Draft CMC Guidances

The PSD Working Group's key concerns regarding the current draft CMC Guidances for OINDP are related to the requirement that:

*the total mass of drug collected on all stages and accessories is recommended to be between 85 and 115 percent of label claim on a per actuation basis.*

The PSD Working Group strongly objects to the inclusion of the mass balance specification in the CMC Guidances because:

- As a specification for the finished product, the mass balance specification requirement uses PSD mass balance as a measurement of emitted dose rather than a characteristic of the particle size distribution;
- Control of emitted dose is accomplished through a separate test (dose content uniformity);
- The use of mass balance may be valuable as a control of system suitability, but is not justified as a drug product specification;
- The limits on mass balance used for control of system suitability should be established in validation studies and not arbitrarily set by a CMC Guidance;
- The definition of mass balance should not be based on the label claim (LC) because the label claim is not necessarily defined by the total mass of drug collected on all stages and accessories. For example, LC for DPIs that use pre-metered blisters or capsules can be based on the amount in the blister or capsule rather than the amount emitted by the device. Since capsule/blister residual is not quantitated during particle size determinations, obtaining 100% LC mass balance is not possible; and
- The initial analysis of the industry data has demonstrated that general compliance with the requirement as given in the draft CMC Guidances may not be feasible.

##### 2. Work to Date on PSD issues in CMC Draft Guidances

At the 26 April 2000 meeting of the Subcommittee, the PSD Working Group committed to collect industry PSD data to investigate the suitability of the mass balance requirement. In a paper<sup>10</sup> that was subsequently submitted to the FDA and the members of the OINDP Subcommittee, the Working Group concluded that:

*the initial assessment of the database indicates that orally inhaled products do not in general comply with the proposed mass balance requirement in the draft CMC Guidances (85-115% LC) and that the proposed requirement is not suitable as a drug product specification but could be appropriate as a system suitability test defined on a case by case basis.*

The Working Group also used the collected database to carry out an initial investigation of the utility of the requirement in the draft CMC Guidances that 3 to 4 stage groupings be used for PSD specification.

### **3. Current Activities**

The PSD Working Group would like to receive clarification from the Agency on the intention of the mass balance requirement and to explore alternate ways to address the Agency's concerns. The Working Group has prepared a proposal for PQRI to investigate this issue and to make a data-based recommendation for the CMC Guidances.

### **4. Next Steps Regarding PSD CMC Specifications**

We respectfully request that the OINDP Subcommittee and the Advisory Committee consider the PSD Working Group's previous submission<sup>10</sup> in support of the recommendation that the mass balance specification requirement be removed from the CMC Guidances. If appropriate, additional dialogue on PSD specifications and the utility of mass balance should take place, possibly through PQRI.

## **B. PSD as In Vitro Test for Bioequivalence Studies**

### **1. Key Concerns with PSD in Draft BA/BE Guidance**

The draft BA/BE Guidance recommends that in order to establish bioequivalence, the Test and Reference products have to demonstrate equivalent PSD profiles. The method for profile comparisons recommended by the draft BA/BE Guidance is based on chi-square differences. However, this method has a number of limitations, as reflected in the Agency's question to the OINDP Subcommittee in April 2000 regarding the appropriateness of the chi-square comparative approach.<sup>6</sup>

Some of the limitations of the chi-square method are the following:

- In the chi-square method recommended by the draft BA/BE Guidance, cascade impactor or multistage liquid impinger data is used to calculate chi-square differences between Test and Reference profiles. The use of alternate methods of particle sizing is precluded by this approach.

- A decision regarding equivalence or inequivalence of profiles is made based on the comparison of chi-square ratios to a pre-defined critical equivalence limit. The selection of this equivalence limit at present is arbitrary.

## **2. Work to Date on PSD Issues in BA/BE Draft Guidance**

Using industry data, the PSD Working Group carried out an initial investigation of alternate analytical techniques, such as that based on bootstrapping, that may improve the discriminating ability of profile comparisons, and provide consistency in the approach used for various products and measuring devices. The Working Group also believes that methods using different metrics, or weighting factors, should be investigated, as they may better reflect the clinical relevance of different portions of the particle size profile when making a decision regarding bioequivalence of two products.

## **3. Current Activities**

The PSD Working Group prepared a proposal for investigating through PQRI the following hypothesis:

*A method for comparing particle size distributions of the Test and Reference product may be developed such that it does not depend on particular product type or particle sizing equipment, and may include metrics that relate to clinical relevance of various particle sizes.*

## **4. Next Steps Regarding PSD BE Issues**

The PSD Working Group recommends that further investigation of the profile comparison methods be undertaken in order to identify appropriate means to compare Reference and Test products and to evaluate what test metrics have clinical relevance.

#### IV. LEACHABLES AND EXTRACTABLES TESTING

##### 1. Overview of Key Concerns with Leachables and Extractables in CMC Draft Guidance

At the April 2000 OINDP Subcommittee meeting and at the November 2000 meeting of the Advisory Committee for Pharmaceutical Science, the Leachables and Extractables Team committed to preparing a data-based technical report and recommendations on leachables and extractables. In March 2001, the Team submitted its paper entitled *Leachables and Extractables Testing: Points to Consider*<sup>11</sup> to the Agency and the members of the OINDP Subcommittee and the Advisory Committee for Pharmaceutical Science. In this technical paper, the Team identified several areas of the draft CMC Guidances regarding leachables and extractables that could benefit from clarification or further development, and made recommendations regarding these areas.

##### 2. Leachables and Extractables Team Work to Date

To address key areas of concern in the draft CMC Guidances, the Team conducted industry-wide surveys of current practices utilized by pharmaceutical companies as well as suppliers of components for finished drug products. The Team also collected leachables and extractables data and conducted literature reviews, where appropriate. In its work, the Team drew on the collected data and the expertise of leading analytical chemists, product development scientists and toxicologists. The recommendations contained in the *Points to Consider* paper are based upon relevant data and best industry practices. In particular, the Team recommended that the CMC Guidances should:

- state that toxicological qualification be performed only on leachables.
- include reporting and qualification thresholds for leachables. These thresholds should be based on relevant data and best industry practices. *Points to Consider* recommends that toxicological evaluation should only be performed on those leachables that exist above a data-supported threshold. The paper proposes a reporting threshold of 0.2 µg/day and a qualification threshold of 5 µg/day, and provides support and justification for these thresholds.<sup>12</sup>
- provide a definition of *correlation*. The Team suggests that a *correlation* is established when each leachable in the drug product can be assigned qualitatively, directly or indirectly, to an extractable.
- clarify which *critical components* should be tested in control extraction studies. The Team recommends that *critical components* include only those device components that are in contact with the formulation or the patient's mouth or nasal mucosa.

- include a description of the toxicological evaluation process. The Team proposes a complete toxicological evaluation process (including reporting and qualification thresholds for leachables) in *Points to Consider*.
- clarify the process for extractables and leachables testing. The Team offers alternate language and flowcharts, for possible inclusion in the draft CMC Guidances, that provide clarification of this process.

### **3. Current Activities**

The Team will submit to PQRI a proposal to investigate the Team's recommendations, and in particular the development of reporting and qualification thresholds for leachables.

### **4. Next Steps Regarding Leachables and Extractables**

The Leachables and Extractables Team recommends that the Guidances for OINDP incorporate a leachables qualification program, including reporting and toxicological qualification thresholds for leachables. Further, the Team strongly recommends that the approach to establishing reporting and qualification thresholds, and the thresholds proposed by the ITFG/IPAC-RS Collaboration be evaluated and carefully considered by toxicologists and chemists from the FDA, industry, and academia. The Team looks forward to such considerations through the PQRI process.

## **V. SUPPLIER QUALITY CONTROL**

### **1. Overview of Key Concerns with Supplier Quality Control in CMC Draft Guidance**

The current draft CMC Guidance documents in several instances require excessive testing of the finished product in an attempt to control changes in the supply chain. The Supplier Quality Control Team of the ITFG/IPAC-RS Collaboration believes that the appropriate way to control quality of incoming components is through a comprehensive system of supplier quality control.

### **2. Work to Date on Supplier Quality Control**

As reported at the April 2000 meeting of the OINDP Subcommittee and the November 2000 Advisory Committee meeting, the Supplier Quality Control Team, which includes representatives of pharmaceutical as well as supplier companies, conducted a survey of current cGMP practices among the suppliers of pharmaceutical device components. The survey identified existing practices that could be used as a standard for the supplier industry and areas that would benefit from the development of comprehensive cGMP guidelines.

### **3. Current Activities**

The Team is exploring the feasibility of an industry-wide initiative to undertake the development of a cGMP guideline for suppliers of pharmaceutical device components.

### **4. Next Steps Regarding Supplier Quality Control**

The Team encourages the OINDP Subcommittee and the Advisory Committee for Pharmaceutical Science to recommend that the Agency consider inserting into the revised CMC Guidance documents a statement that recognizes the value of a cGMP guideline for component suppliers, and acknowledges that if sufficient supplier control mechanisms are in place, appropriate reductions in testing will be considered.

## VI. TESTS AND METHODS FOR CONTROL OF PRODUCT QUALITY

### 1. Overview of Key Concerns with Tests and Methods in CMC Draft Guidance

The draft CMC Guidances require a large number of tests on the finished drug product, some of which are redundant or add little value to the assurance of product quality. The Tests and Methods Technical Team of the ITFG/IPAC-RS Collaboration outlined its concerns at the April 2000 OINDP Subcommittee meeting and the November 2000 meeting of the Advisory Committee for Pharmaceutical Science.<sup>3,4</sup>

### 2. Tests and Methods Team Work To Date

In 2000, the Team committed to collect industry data on key tests recommended by the draft CMC Guidances and to prepare and submit a technical report to the FDA containing the Team's findings and recommendations. In May 2001, the Team completed its work on the MDI tests of greatest concern to the Team and submitted a paper entitled *Recommendations for Tests and Methods*<sup>5,3</sup> to the Agency. The paper focused on the following tests: water content, shot weight, plume geometry, pressure, spray pattern, particle size distribution, dose content uniformity, and impurities and degradants. The paper provided a critical assessment of the value that these individual tests add to the development and control of a new product.

In general, the Team recommended that a fixed list of control tests may not be appropriate for all products. Furthermore, the Team proposed that the draft CMC MDI/DPI Guidance:

- should support the concept of characterizing a new product in development and applying that information to select appropriate control tests for the commercial product; and
- should eliminate redundant control tests which do not add meaningful information about product quality.

Through scientific evaluation of industry and literature data, the Team made specific assessments regarding the relative value and usefulness of the investigated tests. For example:

- **Some tests provide little or no value in the development phase or as tests for control of product quality, e.g.,** spray pattern, plume geometry, pressure (propellant/co-solvent formulations only).
- **Some tests are useful for product characterization during the development phase, but for certain products may be irrelevant for control of product quality, e.g.,** water content, control of relative humidity and temperature on particle size distribution.
- **Some tests may be useful for control of product quality:** water content (if development studies demonstrate product sensitivity to moisture); shot

weight (only to verify quality of incoming components, and as a diagnostic tool).

The Team is therefore assessing tests in such a way that they are able to offer recommendations on *how* to select tests needed to characterize a new product and to control a finished manufactured product. The overall goal is to maximize the value of characterization and control testing, and minimize redundant testing and testing that does not provide meaningful information about product quality.

### **3. Current Activities**

The Team is considering development of proposals that could be submitted to PQRI based on the concepts and the findings in *Recommendations for Tests and Methods*.

### **4. Next Steps Regarding Tests and Methods**

The Team encourages the Agency, the OINDP Subcommittee and the Advisory Committee for Pharmaceutical Science to consider the conclusions in *Recommendations for Tests and Methods*. This paper confirms the Team's belief that the revised CMC Guidance should reflect the concept that appropriate control tests for the commercial product should be selected based on the product development data. The Team is hopeful that its findings will assist the Agency in eliminating redundant or unnecessary testing recommendations in the draft CMC Guidance documents.

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## CONCLUSION

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IPAC-RS and ITFG strongly support the Agency's development of draft Guidance documents for orally inhaled and intranasal drug products. We recognize the value of Guidance documents in facilitating the development and approval of new products. We are encouraged by the Agency's effort to address open CMC and BA/BE issues in developing the Guidances for nasal and orally inhaled medications.

We agree that development and validation of an appropriate dose-response model of *in vivo* equivalence (in terms of local efficacy and local side effects) is an important element in development of equivalence standards for this group of products but note that in order to manage the potential risk for systemic side effects, there is also a need to establish clear protocols for assessing equivalence of systemic absorption. We commend the Agency on ensuring that pertinent data are evaluated to address the potential risks associated with selecting particular *in vitro* and *in vivo* models to demonstrate the bioequivalence of nasal solutions and suspensions for local nasal therapy.

We hope that the Agency continues to work toward resolving all of these important CMC and BA/BE regulatory science issues by utilizing existing avenues for interactive, scientific dialogues, including, as appropriate, the OINDP Subcommittee, the Advisory Committee for Pharmaceutical Science, PQRI, an FDA/USP/AAPS workshop on OINDP regulatory issues, or meetings with representatives of the ITFG and IPAC-RS. Further discussion will ensure that the OINDP Guidances bring maximum value to regulators and industry, and most of all, to patients and physicians.

We appreciate the opportunity to submit this statement to the Agency and the members of the OINDP Subcommittee and the Advisory Committee for Pharmaceutical Science. We hope that this statement and our past and future submissions and interactions will assist the Agency, the Advisory Committee for Pharmaceutical Science and the OINDP Subcommittee in their work on these important documents based on all currently available scientific evidence.

## NOTES

- <sup>1</sup> 1) *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls (CMC) Documentation*;  
2) *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation*; and  
3) *Bioavailability and Bioequivalence (BA/BE) Studies for Nasal Aerosols and Nasal Sprays for Local Action*.  
These draft Guidances are available at <http://www.fda.gov/cder/guidance/index.htm>.
- <sup>2</sup> The IPAC-RS member companies include: Aradigm, AstraZeneca, Aventis, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Inhale Therapeutics Systems, IVAX, Kos Pharmaceuticals, Pfizer, and Schering-Plough. ITFG scientists from the following companies and institutions have contributed to the work of the ITFG/IPAC-RS Collaboration: Bepak, BI Roxane, Dura Pharmaceuticals, Inspire Pharmaceuticals, Lovelace Respiratory Institute, Magellan Laboratories, Microdrug Development, Pfeiffer, Presspart, Primedica, Sciarra Laboratories, RWJ-PRI, Trudell Medical, University of Rhode Island, Valois, 3M Pharmaceuticals.
- <sup>3</sup> ITFG/IPAC-RS presentations to the OINDP Subcommittee on 26 April 2000 are available at <http://www.fda.gov/ohrms/dockets/ac/00/slides/3609s1.htm>.
- <sup>4</sup> The ITFG/IPAC-RS presentation to the Advisory Committee for Pharmaceutical Science on 15 November 2000 is available at <http://www.fda.gov/ohrms/dockets/ac/00/slides/3657s1.htm>.
- <sup>5</sup> 1) *Review of In Vivo and In Vitro Tests in FDA's Draft Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action and Anticipated Forthcoming Guidance for Orally Inhaled Drugs* (August 2000),  
2) *Technical Paper on FDA's Bioavailability and Bioequivalence Questions Presented at 26 April 2000 OINDP Advisory Subcommittee Meeting* (August 2000), and  
3) *On the Risks of Eliminating In Vivo Studies for Nasal Solutions for Local Action* (April 2001).  
These papers are available at <http://www.ipacrs.com/bio.html>.
- <sup>6</sup> The list of questions presented to the OINDP Subcommittee on 26 April 2000 is available at <http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3609q1.pdf>
- <sup>7</sup> Draft Guidance for Industry *Allergic Rhinitis: Clinical Development Programs for Drug Products* (April 2000), available at <http://www.fda.gov/cder/guidance/2718dft.pdf>
- <sup>8</sup> *Managing the Risks from Medical Product Use: Creating a Risk Management Framework*. Report to the FDA Commissioner From the Task Force on Risk Management. (U.S. Department of Health and Human Services, FDA, May 1999).  
<http://www.fda.gov/oc/tfrm/riskmanagement.html>.

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- <sup>9</sup> *Initial Assessment of the ITFG/IPAC Dose Content Uniformity Database by the CMC Specifications Technical Team of the ITFG/IPAC Collaboration* (July 2000), available at [http://www.fda.gov/ohrms/dockets/ac/00/techrepro/3609\\_reports.htm](http://www.fda.gov/ohrms/dockets/ac/00/techrepro/3609_reports.htm).
- <sup>10</sup> *Initial Assessment of the ITFG/IPAC Aerodynamic Particle Size Distribution Database* (August 2000) available at [http://www.fda.gov/ohrms/dockets/ac/00/techrepro/3609\\_reports.htm](http://www.fda.gov/ohrms/dockets/ac/00/techrepro/3609_reports.htm).
- <sup>11</sup> *Leachables and Extractables Testing: Points to Consider* (March 2001) available at [http://www.fda.gov/ohrms/dockets/ac/00/reports/3657\\_reports.htm](http://www.fda.gov/ohrms/dockets/ac/00/reports/3657_reports.htm).
- <sup>12</sup> Note that for certain classes of potential leachable compounds with special toxicological concerns [*i.e.*, nitrosamines, polynuclear aromatics (PNAs), mercaptobenzthiazole, *etc.*] much lower reporting thresholds, and appropriate qualifications and risk assessments may be required.
- <sup>13</sup> *Recommendations for Tests and Methods and Appendices* (May 2001) are available at <http://www.ipacrs.com/tests.html>.

# Bioequivalence Studies and Other Recommendations for Orally Inhaled and Nasal Drug Products:

## Work of the ITFG/IPAC-RS Collaboration

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Presented by  
Cynthia Flynn, Ph. D. and  
Joel Sequeira, Ph. D.

Rockville, MD

17 July 2001

# Background

- ITFG and IPAC-RS formed a collaboration in 2000 to address CMC and BA/BE issues in FDA draft Guidances
- ITFG/IPAC-RS Technical Teams previously presented their concerns with regulatory science issues of OINDP and made commitments to gather and analyze relevant data and submit technical reports
  - 26 April 2000 (OINDP Subcommittee)
  - 15 November 2000 (Advisory Committee)

# Objective

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- Update committee members on work and proposals of ITFG/IPAC-RS CMC Technical Teams
- Present views of ITFG/IPAC-RS BA/BE Technical Team on dose-response studies

# CMC Issues Addressed by ITFG/IPAC-RS

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- Dose Content Uniformity
- Particle Size Distribution
- Tests and Methods
- Leachables and Extractables

# DCU Update

- Collected and analyzed DCU database
- Submitted report to FDA in July 2000

*Initial Assessment of the ITFG/IPAC-RS Dose Content Uniformity Database by the CMC Specifications Technical Team of the ITFG/IPAC-RS Collaboration*

- In November 2000, reported results to the Advisory Committee for Pharmaceutical Science: 68% of analyzed products do not comply with one of FDA test requirements
- Met with FDA in November 2000 and May 2001 to discuss findings and plans for future work
- Developed improved DCU test

# Foundation for New DCU Test

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- Parametric tolerance interval approach proposed by Dr. Hauck
- Test design concepts proposed by ICH
- Quality standards implied by FDA draft Guidances
- Capabilities of modern inhalation technology

# Parametric Tolerance Interval Test for Improved Control of DCU in OINDP

- Parametric tolerance interval approach
  - Increased efficiency in using sample information
  - Improved consumer protection (in statistical sense)
  - Improved producer protection
- Quality: proportion of doses in batch that fall within target interval
- Acceptance criteria on sample mean, sample standard deviation and acceptance value
- Consistent quality standard, flexible testing schedule
- Single test for control of within-unit and between-unit variability
- Sample size on average is increased

# DCU Next Steps

- Draft report currently under review.  
Anticipate submission to FDA in fall 2001
- Anticipate meeting with FDA to discuss new test  
Recommend that new test replace that in current draft  
Guidances

# Particle Size Distribution - Mass Balance

## Key Concern

- 85-115% LC mass balance is not appropriate as a drug product specification

## Update

- Collected and analyzed industry data
- Submitted report to FDA in August 2000:  
*Initial Assessment of the ITFG/IPAC-RS Aerodynamic Particle Size Distribution Database by the CMC Specifications Technical Team of the ITFG/IPAC-RS Collaboration*
- Compliance in general is not feasible

## Next Steps

- Submitted proposal to PQRI

# Particle Size Distribution as In Vitro BE Test

## Key Concern

- PSD Profile Comparisons based on chi-square differences of Test and Reference profiles may not be most appropriate method

## Update

- Carried out initial investigations of alternate approaches

## Next Steps

- Submitted proposal to PQRI

# Tests and Methods (1)

## Key Concern

- CMC QC tests for drug product should be selected based on development data, and should provide meaningful information about product quality

## Update

- Collected and analyzed industry data
- Submitted report to FDA in May 2001

*Recommendations for Tests and Methods*

# Tests and Methods (2)

## Recommendations for Tests and Methods Paper

- Water Content
- Shot Weight
- Spray Pattern
- Plume Geometry
- Pressure
- Particle Size Distribution
- Dose Content Uniformity
- Impurities and Degradants

## Next Steps

- Will consider submitting proposals to PQRI

# Leachables and Extractables (1)

## Key Concerns

- Appropriate reporting/identification/qualification thresholds for leachables and extractables
- Definition of *correlation*; *critical component*

## Update

- Collected and analyzed industry data
- Submitted report to FDA in March 2001

*Leachables and Extractables Testing: Points to Consider*

# Leachables and Extractables (2)

## Points to Consider Paper

- Toxicological qualification should be performed only on leachables
- Developed reporting and qualification thresholds for leachables, proposed justification
- Developed and proposed leachables qualification process
- Proposed clarifications for draft Guidances

## Next Steps

- Guidances should incorporate a leachables qualification program, including reporting and toxicological qualification thresholds for leachables
- Submitted proposal to PQRI

# Consideration of OINDP Issues

- The ITFG/IPAC-RS Collaboration plans to bring several proposals to PQRI, and continue discussions with the Agency regarding the new DCU proposal
- We hope that through the meetings of the OINDP Subcommittee, Advisory Committee for Pharmaceutical Science, PQRI, and other appropriate fora, the work of the ITFG/IPAC-RS Collaboration will be carefully considered
- We believe that FDA and industry will be better able to respond to the needs of patients by expediting the availability of new OINDP products while maintaining appropriate standards of safety, efficacy and quality
- We are grateful for the Agency's consideration of BA/BE and CMC issues for OINDP

# Bioequivalence Studies for Locally Acting Nasal Drugs

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Presented by  
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July 2001

# BA/BE Team's Work to Date

## FDA Presentations

- 26 April 2000 OINDP Subcommittee Meeting
- 15 November 2000 Advisory Committee for Pharmaceutical Science
- Agency Meeting 26 April 2001

## Reports Submitted to FDA

- 30 August 2000: *Technical Paper on FDA's BA/BE Questions Presented at 26 April 2000 OINDP Advisory Subcommittee Meeting*
- 30 August 2000: *Review of In Vivo and In Vitro Tests in FDA's Draft Guidance on BA/BE Studies for Nasal Aerosols and Nasal Sprays for Local Action and Forthcoming Guidance for Orally Inhaled Drugs*
- 5 April 2001: *On the Risks of Eliminating In Vivo Studies for Nasal Solutions for Local Action*

# Dose-Response of Locally Acting Nasal Drugs

- In vitro study designs in draft BA/BE Guidance: useful for determining comparability of products, but unproven value for establishing clinical equivalence and substitutability
- Support inclusion of at least two doses of the Reference and Test product in the clinical dose-ranging study, and at least one of these doses should be representative of the currently approved dosage regimen for the Reference product

# Traditional Treatment Study

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- Traditional treatment study (TTS) = most appropriate study design for nasal products for local delivery
- Weaknesses of TTS include dependence on seasons, measurable placebo effect
- 2 week duration is appropriate

# Further Work Needed

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Further work needed to:

- develop robust clinical protocols,
- identify reliable metrics,
- establish relevant *in vitro* test platforms

# Case study

## Design Issues with a 1999 BE traditional treatment study\*:

- hierarchy
- statistical power
- bias

\* Casale TB., Azzam SM., Miller RE et al., Demonstration of therapeutic equivalence of generic and innovator beclomethasone in seasonal allergic rhinitis. *Ann. Allergy Asthma Immunol* 1999; 82:435-41

# Steps to Confirming Correct Study Design

- The recommended study design should address the issue of substitutability and not confuse this with comparability
- Need to develop statistical requirements for this study design for use in equivalence testing

# Risk Management as a Tool

- Three risk areas are present with locally acting nasal products in the context of dose response and clinical equivalence:
  - primary local effect
  - local side effects
  - systemic side effects
- It cannot be presumed that an *in vitro* test that correctly correlates with the local actions will also be predictive of the systemic outcome

# Conclusion

- Development and validation of appropriate model for assessing dose-response as a model of *in vivo* equivalence (in terms of local efficacy and local side effects) is an important element in development of equivalence standards
- Systemic absorption is a high risk area in the establishment of product equivalence.  
Design of studies assessing systemic availability and equivalence deserves appropriate attention