

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

April 26, 2000  
CDER Advisory Committee Conference Room 1066  
5630 Fishers Lane  
Rockville, MD

**AGENDA**

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8:30	Call to Order/Chairman's Remarks	Vincent H. L. Lee, Ph.D.
8:40	Introduction and Objectives	Eric Sheinin, Ph.D.
	<b>Chemistry, Manufacturing and Controls: Content Uniformity</b>	
8:55	Current FDA Practices for NDAs	Guirag Poochikian, Ph.D.
9:10	Alternative Statistical Approaches	Walter W. Hauck, Ph.D.
9:30	Subcommittee Discussion	
1:00	<b>Break</b>	
	<b>Bioavailability (BA) and Bioequivalence (BE)</b>	
10:15	Current FDA BA/BE Background and Issues	Wallace P. Adams, Ph. D.
	<b>In Vitro BA and BE Testing</b>	
10:30	Profile Analysis of Cascade Impactor Data: Proposed FDA Approach	Yi Tsong, Ph.D.
11:00	Profile Analysis of Cascade Impactor Data: An Alternative View	Andrew R. Clark, Ph.D.
11:30	DPIs: In Vitro Tests for Performance and Comparability	David Ganderton, Ph.D.
12:00	Subcommittee Discussion	
12:30	<b>Lunch</b>	
1:30	<b>Open Public Hearing</b>	
	Data related to BE testing of Nasal Sprays, and Comments on the BE Studies of Nasal Sprays for Systemic Action	Abdul Zahir, Ph.D. Clay-Park Labs, Inc.

Uniqueness of Lingual Spray Delivery

Harry Dugger, Ph.D.  
Flemington Pharmaceutical

**AAPS Inhalation Technology Focus Group(ITFG)/ International Pharmaceutical  
Aerosol Consortium (IPAC) Collaboration Technical Teams:**

Overview of the ITFG/IPAC Collaboration

R. Harris Cummings, Ph.D.  
Magellan Laboratories

Presentation on the Work of the BA/BE Team

Stephen J. Farr, Ph.D.  
Aradigm Corporaton

Presentation on the Work of the Specifications  
Team (Dose Content Uniformity/ Particle Size  
Distribution)

Bo Olsson, Ph.D.  
AstraZeneca

Presentation on the Work of the Tests and  
Methods Team

Carole Evans, Ph.D.  
Magellan Laboratories

Presentation on the Work of the Supplier  
Quality Control Team

Gordon Hansen  
Boehringer Ingelheim

Presentation on the Work of the Leachables  
and Extractables Team

Kaushik J. Dave, R.Ph.,  
M.R.P.S., Ph.D.  
Schering-Plough Research Institute

Concluding Presentation on ITFG/IPAC  
Collaboration

Cynthia Flynn, Ph.D.  
Aventis

CMC Issues

Kenneth B. Neugebauer  
Solvay Fluorides, Inc.

Growth Effects of Nasal Steroids in Children  
and Differences among the steroid preparations

Eric J. Schenkel, M.D.  
Valley Clinical Research  
Center

**In Vivo BA and BE**

**2:30**

Clinical Studies for Local Delivery of  
Nasal Aerosols and Sprays

Izabela Roman, M.D., Ph.D.

**2:50**

Clinical Studies for Local Delivery of  
Orally Inhaled Corticosteroids

Richard C. Ahrens, M.D.

**3:10**

**Break**

**3:25**

Subcommittee Discussion

**:50**

PK and PD Studies for Systemic Exposure of Locally Acting Drugs

3:50	Current FDA PK Practices	Venkata R. S. Uppoor, Ph.D.
4:00	Industry View	Lester I. Harrison, Ph.D.
4:20	Academic View	Hartmut Derendorf, Ph.D.
4:40	Subcommittee Discussion	
	<b>Adjourn</b>	

1 committee to understand, there was an effect on HPI axis.

2           So I think that this clearly shows that there are  
3 differences between these particular nasal corticosteroids.  
4 Can we translate this into other nasal corticosteroids? I  
5 believe we can based on bioavailability data. I think that  
6 if the committee is to consider other types of nasal  
7 corticosteroids, that they should all go through the  
8 rigorous growth studies as the currently available models  
9 have been done.

10           Thank you.

11           DR. LEE: Thank you very much.

12           I would like to thank all the speakers in the open  
13 public speaking session for being on time and informative.

14           Now we are going back to the form agenda which is  
15 a discussion on the in vivo BA/BE.

16           The first speaker in this session is Dr. Roman on  
17 clinical studies for local of nasal aerosols and sprays.

18                           **In Vivo BA and BE**

19                                   **Clinical Studies for Local Delivery**

20                                           **of Nasal Aerosols and Sprays**

21           DR. ROMAN: Good afternoon. However, it feels  
22 more like "good evening" to me. My name is Izabela Roman  
23 and I am Medical Director and Founder of a contracting  
24 organization specializing in nasal study. I was involved in  
25 developing new drugs and studying generic products in nasal

1 allergy now for over twenty years, close to twenty years.

2 I would like to thank you very much for inviting  
3 me to help you with selection of a proper model of nasal  
4 study for the advisory board of FDA. I hope I will not  
5 disappoint you, that I will not present to you a novel,  
6 revolutionary model which will answer all the questions.  
7 We, as researchers of nasal allergy, are still struggling  
8 with the selection of the proper efficacy endpoints since we  
9 are still relying mostly on patients' reported symptoms and  
10 signs of nasal allergy which are very a variable and not  
11 very well standardized endpoint..

12 So, instead of presenting a completely new model,  
13 I will review the three proposed models in the draft  
14 guidance vis-a-vis their strengths, weaknesses and potential  
15 for bioequivalence studies.

16 [Slide.]

17 So, as you are all familiar, there are three well-  
18 studied models in nasal allergy; the so-called "park" study,  
19 the environment unit and traditional clinical study of  
20 seasonal allergic rhinitis. Each of them has their  
21 weaknesses and strengths and I will not go over, first of  
22 all, the detailed description of the basic principles that  
23 they can all be done double-blind, placebo-controlled, most  
24 of them parallel. That is all well known.

25 I also will not repeat the presentation of Dr.

1 Mary Fanning who did this overview in the June presentation  
2 to you in 1999. Again, I would like to present my opinion  
3 on the strengths and weaknesses.

4 [Slide.]

5 So the park study, so-called, which usually  
6 involves one or two days. It is a short duration of study  
7 which, of course, implies less weather variability and  
8 potentially better control evaluation of symptomatology and  
9 severity of symptoms over two days. However, of course, it  
10 does not allow us to study drugs with longer duration of  
11 action and drugs which will require, for a steady state,  
12 longer treatment than one or two doses.

13 It allows cohort enrollment, again potentially  
14 dealing with less environment variability and patient-to-  
15 patient variability since they are all exposed to the same  
16 concentration of allergens. Nonetheless, I believe this is  
17 not an easy way to deal when you talk about bioequivalence.  
18 It is too short a study.

19 Of course, it offers more control compliance. The  
20 drug is delivered by the medical staff, mostly by nurses or  
21 research associates, so we know how the patient took the  
22 drug, how it was delivered to the nose. It offers better  
23 compliance. It has a great potential for, of course,  
24 obtaining a greater number of time points for subjective and  
25 objective data, subjective, again, evaluation of symptoms of

1 patients' objective, potentially waiving the nasal tissues,  
2 collecting nasal washings, et cetera.

3 [Slide.]

4 However, it has a whole list of weaknesses.  
5 Again, it is restricted to seasons. Therefore, there are  
6 only three opportunities of conducting such trials in this  
7 country, at least; spring season, fall season and so-called  
8 cedar season in Texas.

9 I get mixed up a little bit, not looking at my  
10 slides. That is actually a weakness and I presented it  
11 previously as a strength that the drug does not reach  
12 effect. There is a weather risk. Frequently, it takes a  
13 long preparation to set up the studies, selection of  
14 patients and so on and so forth, and then rainy weather or  
15 stagnant weather does not permit you to conduct these  
16 trials.

17 There is a lack of site and population diversity.  
18 Again, it is done usually by one site--the other ones were  
19 done by two investigators--so it is less representative of  
20 geography and other sites in the United States. It is  
21 susceptible to single-investigator influence. Obviously  
22 systemic error done by one investigator carries through the  
23 whole study.

24 There is lower variability than the traditional  
25 study model--I'm sorry; that belongs to the strengths.

1 However, the next one is the potential for high incidence of  
 2 sedation. It is a boring type study and if we study drugs  
 3 which have a sedation potential, they are reporting in this  
 4 type of study a lot of sedation.

5 Then it is not, of course, good for overall safety  
 6 information.

7 [Slide.]

8 The type of study is most frequently used for  
 9 pilot efficacy of new drugs, for onset of action, for dose-  
 10 response or at least the approach of dose-response studies,  
 11 and duration of the effect for single dose.

12 [Slide.]

13 In my opinion, as far as the bioequivalence  
 14 potential of this, it is not very high particularly for the  
 15 drugs which take more than two days to reach maximum effect.  
 16 Usually, because of less variability in weather and between  
 17 subjects, the treatment sizes are smaller than the  
 18 traditional study, up to 50 to 100 patients per treatment  
 19 group. 100 is pretty big in this model. And it is not  
 20 inexpensive.

21 [Slide.]

22 The other proposed model is the environment unit.  
 23 The strengths are very similar to the park model. Again, it  
 24 is of very short duration so it is easy to conduct. It  
 25 controls the environment. There is no environmental

1 variability. The concentration of allergen is controlled.  
2 It can be done all year around. It does not require  
3 seasons. It is also a good model for non-seasonal allergens  
4 such as cat dandruff.

5 [Slide.]

6 It is the farthest from reality. Of course, it is  
7 something completely artificial. It has a very limited  
8 number of center available. There are just a few in this  
9 country. The most well-known, actually, is Dr. Day in  
10 Canada. The whole duration is one day. The observations  
11 are over eight hours so it is just a single-dose type model.

12 The protocol is pretty complex. It requires  
13 priming of the patients for establishing baseline and  
14 severity of patients. Safety information is pretty limited  
15 from it.

16 [Slide.]

17 Again, it is more frequently used for onset of  
18 action, for pilot efficacy and for single-dose studies.  
19 However, this particular one offers a potential for the  
20 crossover studies. For short-acting drugs, which for  
21 bioequivalence purposes could be studied in crossover  
22 design, this is a model which potentially offers such a  
23 possibility for other drugs such as intranasal steroids  
24 which would require long-term treatment for maximum effect.  
25 It has rather low bioequivalence potential for using this

1 model.

2 Again, the treatment groups are much smaller than  
3 traditional, about 30 patients, and the cost is sky high.

4 [Slide.]

5 Finally, we are coming to the traditional clinical  
6 study. It is closest to reality. There are numerous sites  
7 around this country available to conduct such studies. It  
8 is well tested and quite well validated. It offers  
9 geographic diversification and, again, offers longer  
10 duration of observation versus the other models so we can  
11 observe steady-state efficacy and long-term safety.

12 [Slide.]

13 The weaknesses of this model is that it has high  
14 variability across sites, greater variability within a site  
15 due to the non-cohort enrollment. Some patients are  
16 enrolled at the peak season, others at the tail of the  
17 season, with different concentrations of pollens around.  
18 There is a lower sensitivity for detecting differences  
19 between the doses or vehicle or placebo inactive.

20 It is very much season-dependent. However, there  
21 is also a perennial rhinitis which could be potentially  
22 studied for bioequivalence. I don't think it will be a  
23 successful approach. And then, in this particular model,  
24 there is almost lack of total control over compliance since  
25 these intranasal drugs are very much technique dependent,

1 not to the same extent, of course, as an orally-inhaled  
2 drug, but still technique dependent.

3           The compliance in the study is in the hands of the  
4 patient and, very much, evaluations of efficacy depend on  
5 patient diaries and interpretation of the measurement used  
6 there which is severity of symptom scores with the best  
7 definitions from absent to more severe. Still it is patient  
8 dependent, how they evaluate themselves.

9           [Slide.]

10           It is most frequently used for efficacy and  
11 safety, for dose response and comparative studies.

12           [Slide.]

13           All of this is, of course, relative. But between  
14 the three models, I would suggest that this is the best  
15 model of all of the three for bioequivalence type studies.

16           [Slide.]

17           The problem with them is that, because of the  
18 endpoint insensitivity and variability, it requires large  
19 patient population size for treatment. Nowadays, it is  
20 about 130 and over per treatment arm and the cost is also  
21 substantial.

22           [Slide.]

23           So, in general, problems with in vivo  
24 bioequivalence studies, I would sort of summarize as  
25 follows; there is limited or lack of dose response. I do

1 not want to say that there isn't a dose response for nasal  
2 steroids or intranasal antihistamines. I believe that the  
3 limited way we can measure efficacy and variability and lack  
4 of sensitivity of this method does not allow for clear  
5 discrimination between the doses.

6 We have great difficulty in blinding. Obviously,  
7 all these products are delivered in devices which are  
8 patented specifically to the company producing them. In  
9 order to blind them, they have to be covered with something  
10 and there are a lot of problems with blinding them. The  
11 best way we can do it sometimes is just to have evaluator-  
12 blinded, not double-blind.

13 Vehicle and placebo responses make it quite  
14 difficult to distinguish between treatments. I just would  
15 like to bring to your attention that vehicle which is  
16 frequently used as a placebo for intranasal studies is a  
17 very effective treatment. In studies which we conducted in  
18 our group, we can prove a dose response to vehicle. Once-a-  
19 day vehicle is less effective than a twice-a-day vehicle.

20 So a vehicle is in higher doses, if you wish, or  
21 more frequent application, the efficacy is up to 35 percent  
22 change from baseline, which we usually use as an endpoint.  
23 Then, again, we are struggling with limited and non-  
24 standardized scales for efficacy measurements. Even with  
25 the best script, the interpretation of these scales by

1 patients that we are dealing with, and, of course, the  
2 sophistication of patient and user of such a method very  
3 much influences the results of the measurement.

4 [Slide.]

5 So, with this in mind, I would say that we have a  
6 changing nature of disease. We have a very variable  
7 environmental and mental conditions. We have subjective  
8 efficacy measurements and the spray-dose form is very much  
9 user-technique dependent, as I stated. So we have high  
10 variability and rather low sensitivity models.

11 [Slide.]

12 How I would suggest to improve this traditional  
13 study model; Again, as I stated before, the dose response is  
14 something which is quite difficult to establish with,  
15 particularly, intranasal steroids. So the requirements of  
16 doing two different doses to test the sensitivity of  
17 discriminating two doses is pretty hard. So vehicle  
18 control, which I suggested, is really an effective treatment  
19 and is, in my opinion, one of the arm of the dose-response  
20 treatments.

21 So, maybe just to make this more doable, vehicle  
22 control should serve as this noneffective dose, noneffective  
23 not in terms of active component but effective in terms of  
24 efficacy.

25 There are frequent designs using run-in period

1 with vehicle or placebo control sort of run-in period. We  
2 learned that this really decreases the baseline severity so,  
3 without run-in vehicle, we are increasing baseline severity  
4 and ability to discern differences in treatment groups.  
5 However, for a well-established baseline evaluation of  
6 symptomatology, some kind of just a collection of diaries  
7 and screening run-in is recommended.

8 [Slide.]

9 The last slide, which I will present, is real  
10 data. We conducted a study for a company with a generic  
11 intranasal steroid. The design of the study was  
12 traditional. What was done was a one-week run-in vehicle  
13 control, two weeks treatment, two doses of a reference  
14 product, two doses of the test drug and collection of the  
15 diary. Patients were evaluating their nasal symptoms scores  
16 and non-nasal symptom scores in a very classical way on a  
17 scale of 0 to 4.

18 We compared the overall results for two weeks to  
19 the baseline. So, in this particular study, the total nasal  
20 signs and symptoms expresses a percent mean change from  
21 baseline for the two weeks of treatment, for the lowest dose  
22 of tested drug, showed 21 percent improvement over baseline.  
23 The reference product showed 22 percent improvement. The  
24 high dose was 33 percent versus almost 31 percent for the  
25 reference product.

1           Now, for any physician looking at this, it will be  
2 quite sort of intuitive to say that, obviously, they are  
3 exchangeable or substitutable products since the efficacy  
4 there is quite close, or very close to each other. If they  
5 would be any closer, I would suspect that the data was  
6 cooked up. So I think that, in real life, that is exactly  
7 what we see.

8           As you see, the differences were not too big.  
9 However, because of variation of the methodology and so on,  
10 we have quite a bit standard error.

11           Now we applied, as requested by the FDA, the  
12 standards of bioequivalence for PK studies. So it was a  
13 90 percent confidence interval as determined, and it is  
14 supposed to range 80 to 100 of target parameters, our  
15 normally distributed data.

16           [Slide.]

17           So, even with the therapeutic equivalence, the  
18 very close efficacy of this product, when compared, the  
19 confidence intervals were nicely distributed around 0, -8.3  
20 to 6.2, but the at the 20 percent plus or minus as expressed  
21 as the delta 0.2 times reference product, the product did  
22 not make exchangeability criteria.

23           So the decision resulting from such a study--by  
24 the way, both of the doses showed statistically significant  
25 differences compared to vehicle or placebo. There was no

1 significant difference between the doses for most of the  
2 parameters. Still, this product would not, in some way,  
3 meet the exchangeability criteria.

4 My last suggestion is that the bioequivalence  
5 standards for PK studies should not be straightforwardly  
6 applied to in vivo trials and there should be some  
7 deliberation on what kind of standards should be developed  
8 for the in vivo trials.

9 Thank you very much for your attention.

10 DR. LEE: Thank you very much. At this point, I  
11 would like to announce a change in the program. Dr. Hartmut  
12 Derendorf also has to take an early exit, but I don't think  
13 he is going to Lubbock. He is going to talk about PK and PD  
14 studies for systemic exposure of locally acting drugs and,  
15 of course, the academic view.

16 Hartmut, I would like you to remain for a few  
17 moments after your presentation since you probably won't be  
18 here to participate in the discussion.

19 **PK and PD Studies for Systemic Exposure**

20 **of Locally Acting Drugs**

21 **An Academic View**

22 DR. DERENDORF: Good afternoon.

23 [Slide.]

24 It is a pleasure for me that I have the  
25 opportunity this afternoon to address some methods or some