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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING OF
THE ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE

8:32 a.m.

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Ballroom
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2 Montgomery Village Avenue
Gaithersburg, Maryland

C O N T E N T S

AGENDA ITEM	PAGE
CONFLICT OF INTEREST STATEMENT by Ms. Kimberly Topper	7
SUPAC-IR: UPDATE OF GUIDANCE	
Introduction - by Dr. Eric Sheinin	9
Issues and Strategies - by Dr. Ajaz Hussain	20
PQRI Research: Drug Product Technical Committee - by Dr. Larry Augsburger	30
Industry Perspective/PhRMA - by Mr. Thomas White	42
Industry Perspective/IGPA - by Mr. Roger Schwede	46
Open Public Hearing	54
Committee Discussion	63
COMPLEX DRUG SUBSTANCES	
Overview - by Dr. Roger L. Williams	104
Complex Drug Substances Coordinating Committee - by Dr. Yuan-Yuan Chiu	108
CBER Perspective - by Dr. David Finbloom	119
Clinical Perspective - by Dr. Bruce Schneider	125
Industry Perspective - by Dr. Ken Seamon	139
Open Public Hearing	156
Committee Discussion	156

1 necessary.

2 In conclusion, we would like to have the
3 advisory committee discuss the concept of this coordinating
4 committee, also give us recommendations whether we are on
5 the right track in terms of the structure of this
6 coordinating committee, and also what you see in the future
7 what we need to do.

8 DR. WILLIAMS: Our next speaker is a
9 representative from CBER, Dr. David Finbloom, who we're
10 delighted to have with us today. I think the committee can
11 see how important it is that we stay in tune with CBER on
12 these topics.

13 DR. FINBLOOM: I just want to give some
14 information on the comparability document which was
15 published in April of 1996 and go into some of the issues
16 that have come up with this document and how we use this
17 document when companies who have licensed products or
18 products that are coming near to licensing are going to
19 change that product in one way or another.

20 This just points out there's again a
21 comparability document. I just want to point out that it
22 is for the same product. In other words, it is for the
23 product within one company, and it's a change for that
24 product or within that product.

25 I want to briefly, at the end of the talk, talk

1 about different products, in other words, one product
2 compared to another product, which is sort of the worry
3 that we don't talk about very much over at CBER, which is
4 generic.

5 The reason that the comparability document was
6 important to get out was that this is a process-dependent
7 change. In other words, the change that we're talking
8 about with a product depends upon how that product is made.
9 In other words, the extent to which fermentation, the cell
10 bank, and things like that are formed will depend on how
11 that change is implemented.

12 The other thing that's very important in this
13 document is when the change is made. If it's pre-phase
14 III, this is a very important concept because if it's
15 within a phase I-II type study and if it's before the time
16 that you're implementing a pivotal phase III trial that
17 you're using to base the information that you're going to
18 be using for your licensure, then changes can be made. If
19 it's a post-phase III change, then the changes that are
20 made have to be shown to be similar to the changes made
21 during the pivotal phase III trial, and that's what's
22 critical. The component used during the pivotal phase III
23 trial has to be shown to be equivalent to the marketing
24 product.

25 The changes can be instituted during any part

1 of the manufacturing process, including very early in the
2 molecular biology, in the DNA, in the master cell bank,
3 fermentation, purification, specification, et cetera.

4 Once you initiate any of these changes, then
5 you've got to ask yourselves, are the products comparable?
6 Is the old product comparable to the new product? When
7 you're going to ask yourself that question, then you're
8 going to through a number of tests at certain stages of the
9 whole process. What that means is it's going to depend in
10 part on where those changes are being made. At many of the
11 steps during the process, you may have to go through the
12 whole cycle of tests here to show that these products
13 indeed are comparable. However, there are changes that can
14 be made where you don't have to do many of these tests.

15 Physical-chemical type tests can occur early in
16 the process, such as in molecular biology and the cell
17 bank, fermentation, purification. They may not be needed
18 for changes in formulation. It's just for changes prior to
19 formulation and drug substance. These are a number of
20 tests that would probably be necessary, reverse phase HPLC,
21 size exclusion chromatography, anion exchange
22 chromatography, chromatography zone, electrophoresis, a
23 number of different tests to show that there are no
24 differences between the old substance and the new
25 substance.

1 Viral clearance was already mentioned. I guess
2 you can call it an impurity, but it's going to be very
3 important to show that when you induce changes, especially
4 in column purification and in filtration, that things like
5 viral clearance and MCB validation, there have been no
6 changes between your old product and your new product.

7 Most changes occurring in any process is going
8 to involve some biological assay which shows that there has
9 not been any change, whether it's early in the process or
10 late, including in formulation. These generally occur as a
11 bioassay, as in vivo ones, or in vitro. We have been
12 thinking at CBER about binding assays, including cellular
13 or noncellular, but it's more or less thinking about them.
14 Most of the assays that we have now are based on assays
15 that are cell based or animal based.

16 Toxicology again may occur at any change in the
17 process, even in formulation, such as changes from one
18 product going to another product without the use of albumin
19 as one example, but basically what I think one needs to do
20 here is to talk with a toxicologist and finalize the
21 studies that need to be done to verify comparability.

22 Now we get to sort of the harder aspects or
23 subject in here and that's PK/PD because we can go through
24 the other areas in a comparability study with the
25 pharmacokinetics, with the biologics, with the toxicology

1 | studies and may not really show any differences. But the
2 | question is could there be differences that we don't see
3 | without giving the product to an animal or to a human to
4 | pick up something that we're just not able to see on the
5 | types of studies that we're doing.

6 | So, these studies may not be done if all the
7 | physical-chemical, viral, biologic, and toxic studies show
8 | comparability between the products before and after the
9 | change for drug substance. This statement really has to be
10 | worked out with the center in terms of whether a PK study
11 | needs to be done. This is almost a one-on-one situation in
12 | terms of whether the company needs to go forward because
13 | sometimes just to show -- and this is especially for
14 | products that are mammalian cell line products that are CHO
15 | cell products and recombinant DNA products or monoclonal
16 | antibody products, and if we're talking about a scale-up
17 | with fermentation, whether there are changes in PK and
18 | whether there are changes in glycoprotein and how do
19 | glycoprotein changes make a difference in the product
20 | itself. So, this may be a subject that may need to be done
21 | even though it may not be obvious from the earlier studies
22 | that show no change in the comparability.

23 | Let me just say one more word on that.
24 | Sometimes it may not need to be done in humans. You may be
25 | able to pick up changes in animals that may need to be done

1 | in humans, but other times we have had examples where
2 | studies in animals have been negative, whereas studies in
3 | humans have not with basically normal comparability studies
4 | for the studies prior to that, in other words, PK and all
5 | the other ones.

6 | When must the PK/PD studies be performed?
7 | Obviously when there are differences in the physical-
8 | chemical, biologic, viral, and toxic studies, and then it
9 | must be carried out in a way approved by CBER that
10 | obviously will act as a bridging study between the two
11 | products. And this is clear. You don't want a study
12 | that's not going to be done in a way where you can't
13 | adequately judge the study. Generally we prefer a PK study
14 | and not a PD study.

15 | A clinical study is obviously required when the
16 | products are not comparable, and then a study is required
17 | to be done to show efficacy, safety, purity, and potency.
18 | If throughout the comparability study there are things that
19 | are clearly -- especially in a PK/PD study that shows a
20 | difference between the two products.

21 | If there are two different products, then why
22 | can't the comparability guidance be used in this situation?
23 | That sort of has come up frequently. It cannot be used
24 | because the change has to be basically in the same product.
25 | So, we need the change within the same product based upon

1 | the same process with a history regarding the manufacturing
2 | operation of that particular product. It is not comparing
3 | one product with another product with an unknown process
4 | for either one or both of those. Well, obviously, you
5 | won't know one, but for one of the other products.

6 | Basically it comes from regulations. I think
7 | this is from the introduction to the FOIA that there's no
8 | such thing as a me-too biologic. At CBER we are under
9 | regulations that say we have no generic drugs right now,
10 | and if we're going to have generic drugs, then something
11 | will have to be done to get us to that point.

12 | DR. WILLIAMS: David, thank you very much.

13 | Our next speaker is Dr. Bruce Schneider. Bruce
14 | is a physician from the Division of HFD-510, Metabolic and
15 | Endocrine Drug Products. Names change, so I'm not sure
16 | I've got quite the right name. Bruce can correct me. But
17 | Bruce is coming to give a clinical perspective from the
18 | Office of Review Management. Bruce, thanks very much.

19 | DR. SCHNEIDER: Thank you. I was asked to give
20 | a clinical perspective. I'm a clinical endocrinologist,
21 | and the examples that I'm going to be using will come from
22 | endocrinology but they have to do with recombinant and
23 | synthetic proteins. What I'm about to say in the next few
24 | minutes I believe can be and should be generalizable to
25 | other recombinant and synthetic proteins when used as