



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

14 SEP 1978

OFFICE OF TOXIC SUBSTANCES

Dear Registrant,

Since our request that registrants perform an audit of studies performed at Industrial Biotech Laboratories Inc., many registrants have contacted both EPA and Canada's Health Protection Branch (HPB) with questions regarding the actual performance of such an audit. In addition, several audit reports have been submitted which are unacceptable.

In order to assist registrants in the validation process, EPA and HPB have scheduled a meeting which will give you an opportunity to ask questions as well as discuss common or unique problems. The meeting will be held on Tuesday, October 3, 1978 at Howard Johnson's Airport Hotel, 2650 Jefferson Davis Highway, Arlington, Virginia 22202 from 9:30 a.m. to 5:00 p.m. It is requested that each registrant send no more than two representatives to the meeting.

EPA and HPB have developed a manual in response to inquiries received from a number of registrants concerning the approach to be taken in auditing and validating IBT studies. This manual will be sent to you under separate cover prior to the meeting.

If you have any further questions regarding the meeting, please contact Fred Arnold or Ann Dizard at 202-755-8026. We appreciate your continuing cooperation in this matter.

Sincerely yours,

Robert W. Brown for

William A. Wells
Acting Director
Special Pesticide Reviews Division

1 U. S. ENVIRONMENTAL PROTECTION AGENCY
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4
5
67 Arlington, Virginia
8 Tuesday, October 3, 19789 INDUSTRIAL BIO-TEST LABORATORIES, INC.
10 AUDIT MEETING11 The proceedings in the above-entitled matter was held
12 at the Howard Johnson Motor Inn, Banquet Room, 2650 Jefferson-
13 Davis Highway, Arlington, Virginia, commencing at 9:45 o'clock,
14 a.m.

15 PANEL MEMBERS:

16 FRED T. ARNOLD
17 Acting Branch ~~Chief~~ Chief
18 Regulatory Analysis & Lab Audits
Special Pesticide Review Division
U. S. Environmental Protection Agency19 DAVID CLEGG
20 Head, Pesticide Section
Foods Directorate
21 Health Protection Branch
Health and Welfare, Canada
22

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1 DR. ARTHUR PALLOTTA
Consultant
2 Special Pesticide Review Division
Office of Pesticide Programs
3 U. S. Environmental Protection Agency

4 DR. LAMAR B. DALE
Acting Chief
5 Toxicology Branch
Hazard Evaluation Division
6 Office of Pesticide Programs
U. S. Environmental Protection Agency

7 FRANK SANDERS
Product Manager
8 Registration Division
9 Office of Pesticide Programs
U. S. Environmental Protection Agency

10 JOHN ULFELDER, ESQ.
Attorney
11 Office of Enforcement
12 U. S. Environmental Protection Agency

13 MITCHELL BERNSTEIN, ESQ.
Attorney
14 Office of General Counsel
15 U. S. Environmental Protection Agency

P R O C E E D I N G S .

1
2 MR. ARNOLD: Good morning. I guess we might as well
3 get started. We are still missing one of our panel members and
4 I expect that people will come wandering in here for the next
5 few minutes, but we've got some introductory comments to make
6 and some discussions that are sort of general to cut across all
7 the issues that are related to the IBT validation effort.

8 My name is Fred Arnold. I'm the Acting Branch Chief
9 for the Regulatory Analysis and Lab Audits in the Office of
10 Pesticide Programs and I got involved in the Lab Audit Programs
11 several years ago.

12 We intend to deal with questions relating to Industrial
13 Bio-Test as a separate issue from the rest of the joint audit
14 programs which are being carried on cooperatively with the Food
15 and Drug Administration.

16 Ed Johnson, the Deputy Assistant Administrator of
17 Pesticides and Steve (Jolnick), Assistant Administrator, both
18 asked me to extend their welcome to all individuals who are
19 attending this conference. They have taken a very active role
20 in our Lab Audit Program and, particularly, in questions dealing
21 with Industrial Bio-Test.

22 As you are no doubt aware, the questions which were

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1 raised by findings of the Food and Drug Administration, when
2 they performed the first audit at Industrial Bio-Test, raised
3 extremely serious questions for the pesticide regulation process
4 because we do have a rather large number of Industrial Bio-Test
5 studies in our data base.

6 This is particularly important now since the Agency
7 is finally beginning to move forward on the re-registration
8 effort and, since there are 4,500 tests in our files from IBT,
9 all of which are subject to some scrutiny and question right
10 now, it's an extremely critical piece of information in that
11 process.

12 For that reason, we have devoted a substantial amount
13 of resources to, first, try and determine in our own minds the
14 kinds of problems that may have been encountered in testing per-
15 formance at IBT and whether those problems create any kind of a
16 significant question for us in a regulatory vein.

17 We have determined that they are serious based upon
18 approximately 12 detailed study audits which we completed at
19 Industrial Bio-Test and from the continuing findings that we
20 get as registrants submit validations to us. It's, I am sure,
21 a very serious question and issue from the point of view of
22 sponsors of other studies and registrants who have submitted

1 IBT data to EPA or its predecessor agency.

2 At one time, we discussed what the options of the
3 Agency were. The most extreme would have been to purge our
4 files of all IBT data and either impose a data requirement on
5 the registrants or initiate a more extreme action in the case
6 when the entire toxicological data base was essentially des-
7 troyed by that action.

8 We determined that that was neither in EPA's interest
9 or the public interest or the registrants' interest because a
10 large number of studies, which were performed at IBT, were per-
11 formed satisfactorily. Our experience has indicated that. I
12 think the experience of most of the registrants to date has
13 indicated that.

14 There is another subset of tests which, although may
15 not have been completed in the manner in which the report was
16 written and the manner in which the sponsors anticipated the
17 tests were carried out, nevertheless, do provide useful, sig-
18 nificant toxicological information upon which we can make
19 findings of safety and upon which registrants can audit their
20 compounds.

21 There is another subpopulation of the test which we
22 have found are entirely invalid for any purposes, either for

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1 regulatory purposes or for trying to determine the toxicological
2 significance of the compound.

3 Without a detailed audit to determine where the tests
4 lie, there is no reasonable way that the Agency can proceed,
5 either in re-registration efforts or in making regulatory de-
6 cisions on the safety of the compound.

7 So I would like to stress the importance of the effort,
8 although it may appear to be another data requirement which
9 EPA, as ^{part} ~~one~~ of ^{the} ~~a~~ Federal regulatory body, has imposed upon
10 this private sector.

11 We'don't see any way to conceivably proceed, in a
12 timely fashion, without doing this because, if the registrants
13 chose not to audit the studies, we would either purchase, buy
14 or we would have to devote resources to ourself and that would
15 tie us up for years and also tie up the re-registration process.

16 To underscore the seriousness of it, we have had a
17 number of discussions with representatives of other Governments.
18 They say they have attempted to understand the significance of
19 IBT and to evaluate whether or not EPA is proceeding in a
20 fashion that will provide sound information for their regula-
21 tory decisions.

22 In two instances, the representatives of other

1 governments came to Washington with the expectation that they
2 would go home and recommend to their administrators that they can-
3 cel tolerances and cancel registrations in their countries which
4 relied, in a significant way, on IBT data.

5 After reviewing our procedures and after understanding
6 a bit more the concept problems and the ability to determine the
7 problems, they both chose to await the results of the validation
8 effort and make their judgments based upon the best available
9 information on each study.

10 In another instance, we have formed an agreement with
11 the Government of Canada to jointly review all IBT data which
12 either Canada or the U.S. feels are significant, and that is
13 certainly a very small number of the total tests done by IBT.

14 We are splitting the workload around Canada to re-
15 view a portion of the tests, the U. S. to review a portion of
16 tests and we will adopt each others conclusions. That doesn't
17 mean that we will adopt each others regulatory recommendations,
18 but we will adopt some of the conclusions and we don't intend
19 to redo each other's work.

20 The reason that we initiated this conference was to
21 provide some uniformity to the validation effort. We think
22 that we have a perspective on the types of testing procedures

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1 and other problems that you will come across as you review
2 your individual test data and, rather than attempt to answer
3 individual questions as they come up, which would slow you down
4 and it would certainly slow down the process of determining the
5 acceptable and the unacceptable tests, we prepared a manual.
6 It's kind of a guide to, first, how do you perform an audit,
7 and, secondly, what exactly would the records look like and how
8 the records are reviewed in an orderly fashion. It's not man-
9 datory. It's meant just as a working guide to assist regis-
10 trants or consultants as they review their individual data.

11 We have also prepared -- and I think it was distri-
12 buted this morning -- an outline for submitting a validation
13 report. Again, that's certainly not mandatory. It's a format
14 which we have found extremely useful in preparing our own re-
15 ports as well as useful in reviewing the work of others. It's
16 one that has been used by a number of sponsors and they have
17 found it an acceptable method to report their findings.

18 We met last evening with representatives from Indus-
19 trial Bio-Test to discuss the current status of their Valida-
20 tion Assessment Team, the current status of their microfiche
21 efforts, and they asked me to pass on several general comments
22 that are going to be of interest to everyone, and requested

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1 that any questions that you may wish to pose to them, that you
2 do it individually, either during a break or after the meeting.
3 They will be available this evening after the conference.

4 They have requested that to avoid any possibility of
5 making a general comment or a specific comment to one question
6 and having it interpreted as a general policy.

7 The first point that I would like to bring up regards
8 the status of the microfiche effort at IBT. They have completed
9 the microfiche of all product studies which were completed and
10 mailed out to sponsors as of January, 1978. Chronic studies
11 include all studies 90 days and longer. The only exception to
12 that are about ten studies which are currently being completed
13 in a file which they have characterized as a bits-and-pieces
14 file.

15 That file will contain individual pages or a very
16 small number of pages that had no major data base within their
17 files. The bits and pieces were correlated with the idea that,
18 after all the studies were copied and sent to registrants, the
19 bits and pieces could be merged into those studies or, to the
20 extent that nothing was related, nothing was available except
21 the bits and pieces file, they would be sent on to the regis-
22 trants.

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1 The bits-and-pieces file, by itself, is not sufficient
2 to carry out an audit. It is not a major data base. Therefore,
3 if you haven't received microfiche copies of the studies, to
4 date, in all likelihood you will not receive a large body of
5 data upon which to prepare a validation report.

6 If there are studies you are interested in and they
7 fall within the chronic classification, and you haven't received
8 them, I suggest that you take action on your part to contact
9 Industrial Bio-Test, because addresses have changed over the
10 years, mail delivery is variable, there is a possibility that
11 the studies have been microfiched and you have just not received
12 them but, if you determine that they have not been sent to you
13 and all that remains is bits and pieces, I suggest that you
14 don't exert any resources towards attempting to validate that
15 study because there won't be any data base upon which to do that.

16 They have commented upon time records which are avai-
17 lable at Industrial Bio-Test. These records, we have found, are
18 useful in terms of determining starting and ending dates on some
19 studies for which the records are incomplete; for determining
20 the individuals who are responsible for carrying out the studies.

21 Prior to 1972, there is difficulty in going back to
22 the time records because they are on individual time and

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1 accounting sheets. Post-'72, they have been computerized. So
2 to recall them will be much easier.

3 Again, this is an issue that, as you visit IBT, if
4 you determine that it is important to substantiate the beginning
5 or the ending or determine who is involved in a study, you can
6 deal individually with them. Prior to 1972, there will be some
7 difficulty.

8 We have suggested a review of animal ordering receipt
9 records. IBT informs me that, in many cases, animals were
10 received or ordered, not for an individual study, but for en
11 masse to service a number of studies which were going on at the
12 same time. So that, by itself, may not determine your popula-
13 tion size if the records are incomplete in that area. It's a
14 possibility, but it's not something that is always going to
15 provide the information that you may want.

16 The records on the receipt of test material are
17 available at IBT. In most cases, a substantially larger amount
18 of material was sent by sponsors than was actually necessary to
19 complete the studies at Bio-Test.

20 Certainly, if you determine that less material was
21 actually sent to IBT than was necessary to complete the protocol,
22 that ought to be a flag of a problem, but the fact that more

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1 was sent is of no particular concern to us, nor should it be
2 of any particular concern to you.

3 For those of you who haven't dealt personally with
4 Industrial Bio-Test in the validation effort, we have received
5 copies of their Validation Assessment Team procedures and guide-
6 lines. We have, I believe, made some copies of those and they
7 are available this morning, and they will define the relation-
8 ship between sponsors and IBT as they, again, attempt to work
9 together to resolve questions which cannot be resolved through
10 review of the microfiche alone.

11 I would like to point out that Industrial Bio-Test
12 has been willing and continued to operate in this effort. How-
13 ever, they are not providing the resources to perform the audit
14 for sponsors. Their resources are there to resolve unanswered
15 questions, to provide guidance to individuals, and may be con-
16 tacted to shed some light on a particular phase of a study, and
17 to provide assistance in reviewing the records at IBT, but
18 they will not initiate validation efforts on their own, nor do
19 they expect to take a substantial part in defining areas for
20 validation which the sponsors have not initiated on their own.

21 IBT does have the pathology material under the same
22 storage system which they have utilized in the past. It's a

1 private subcontractor who maintains all the slides, tissue box
2 -- that material. In the instances when we have attempted to
3 look at pathology material, it has been available. We are
4 satisfied that the current method of handling and storing that
5 material is satisfactory.

6 I am aware that some questions have arisen regarding
7 the ultimate ownership of pathology material -- whether it be-
8 longs to the sponsors or whether it belongs to IBT. Bio-Test
9 has taken the position that they will remain in the custodial
10 role and that they will make that material available to regis-
11 trants and sponsors on an as-needed basis. Their facilities
12 will be available; their lab facilities. However, they will
13 not provide the technician's support nor the pathology support.
14 You either reread or prepare new pathology material.

15 In several instances, registrants have employed con-
16 sultants to carry out this validation effort. Bio-Test has
17 requested that we point out that the consultants must have a
18 written authorization from the sponsor before they can release
19 the records and material to the consultants. Upon receipt of
20 that authorization, they will cooperate with the consultants
21 in the same way that they have attempted to cooperate with us
22 and the sponsors.

1 That also goes to the situation where the original
2 sponsor of a study has subsequently either sold the registra-
3 tion rights or the data to a second registrant. In that instance,
4 they would need authorization from the original sponsor to pro-
5 vide access to the subsequent owner.

6 Any questions dealing with any study which has been
7 closed out at IBT, where the final report has been prepared
8 and mailed, should be referred to Fred Current or a member of
9 the Validation Assessment Team, and that goes whether it deals
10 with a validation effort or any other inquiry on an IBT study.

11 They are continuing negotiations with several indi-
12 viduals on the sale of the assets of IBT. That does not in-
13 clude any of the past records or their validation effort. IBT
14 will, regardless of the subsequent sale of the assets, remain
15 a corporation for the purpose of assisting in the validation
16 effort and for retaining and managing the records of all prior
17 studies.

18 We have had the opportunity to review a number of
19 validation reports and, when I say "we," that goes for Canada
20 and the U.S.

21 Dave Clegg has completed 45 audits of all types of
22 studies carried on at different times. This certainly is not

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1 an exhaustive nor a statistical sample, but his results, to
2 date, are that 16 of the studies are completely invalid for any
3 purpose for which they were originally intended. Five or six
4 of the studies, although they are deficient in significant
5 areas, do provide a substantial body of information upon which
6 we, as regulatory bodies, feel we can make decisions. The
7 remainder of the studies appear to be completely valid for all
8 the purposes for which they were originally submitted and will
9 continue to be valid for registration in pesticide matters.

10 The major problem areas have been in the chronic
11 studies. That's been Mr. Clegg's experience and that has cer-
12 tainly been our experience. I would say that our experience
13 has been similar to this and, in addition, the early validation
14 reports which we have received, our policy has been to review
15 the entire microfiche data base, to gather an understanding of
16 how the registrants are proceeding with the validation and to
17 assure ourselves that we are making consistent decisions with
18 our colleagues in Canada.

19 We haven't found a single study, to date, where the
20 microfiche is fully consistent with the validation report. The
21 kinds of problems that we are seeing are, I think, random errors
22 in reviewing records, transcribing tables and reperforming

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1 certain kinds of numerical, statistical analyses. I would
2 suggest that it's going to be much more efficient if the origi-
3 nal effort on the validation is a rather intensive effort,
4 rather than having to bounce back and forth a number of times.

5 We will continue to review all the microfiche data
6 until we feel we have learned enough to establish a reasonable
7 kind of sampling process. So that we can sample for key assump-
8 tions and conclusions and satisfy ourselves that the validation
9 report is truly reflective of the raw data and should stand by
10 itself in our registration files.

11 We have attempted to consider large aggregates of the
12 raw data, which are available at IBT, to determine the bare
13 minimum data requirements beyond which we don't feel the vali-
14 dation is going to be fruitful.

15 If you will refer to the proposed outline, which you
16 were provided with this morning, if there is no material, no
17 data, that relates to test material in dosage levels, that's
18 been a key problem that we have observed in IBT studies. Lack
19 of control on the way diets were prepared, the way test material
20 was administered. If there is no material on that, our sugges-
21 tion would be do not proceed with your validation effort. It's
22 a fundamental piece of information. If it's not available, all

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1 the remaining conclusions are very hard to construct.

2 The same goes for information on body weights. If
3 all you have got relating to body weight is whatever is in the
4 report which you received and subsequently transmitted to EPA
5 or the Food and Drug Administration, we suggest you not proceed
6 with the validation of that study.

7 In the case of a pathology study, if you have no in-
8 formation on the mating procedures which were utilized, again,
9 that study probably is not going to be one which can be vali-
10 dated or one which we would accept as a sound basis for making
11 our determination on that test.

12 Gross autopsy sheets or records must be available on
13 all animals for which histopathological material was taken.
14 If that information is not available, we suggest that you not
15 attempt to proceed with the validation of that study.

16 Also, as kind of a guideline, about 75 percent of
17 the gross autopsy sheets are to be available on all animals in
18 the test, regardless of whether there has been pathology or not.
19 That's kind of a guideline, but we found a number of instances
20 where observations were made at the time of gross autopsy and
21 were never followed through in histopath. So tissue mass was
22 never commented on later. It has been a significant enough

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1 problem that we have identified this as being a fundamental
2 piece of information which we will require.

3 Certainly, all the records relating to histopathology
4 must be available.

5 In the area of animal accountability, the guideline
6 which we have used and will continue to use is that any animals
7 which are unaccounted for -- the raw data -- should not be used
8 to form conclusions or findings which are submitted in the
9 validation report.

10 If the protocol calls for 25 animals, per sex, per
11 group, and only 15 animals can be accounted for from the time
12 they went on test material until the time they went into patho-
13 logy, then that's the population you ought to deal with in the
14 validation report and ignore any conclusions on the other ten
15 animals which may have been introduced midstream in the study
16 or for which various cryptic notations will be found in the raw
17 data.

18 That pretty much covers the introductory comments
19 that I want to make. I will say that the stenographer is here
20 at the request of Industrial Bio-Test to maintain a record of
21 this meeting for purposes of assisting in later validation
22 assessments. They have informed that, if anyone wants a copy

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1 of the transcript, they ought to contact the stenographic ser-
2 vice directly. The firm is here in Washington. It's Stewart,
3 Poe & Oglesby, 711 - 14th Street, Northwest, Washington, D. C.
4 20005, and you can contact Ann Tipton, who is the stenographer
5 today.

6 I would like to introduce the members of the panel
7 here, and take this opportunity to thank them for their coopera-
8 tion that they have provided to myself and others who have had
9 to attempt to steer the course and where we are going with IBT.

10 This is a corps of people upon which all major deci-
11 sions are discussed and they represent various views, both of
12 EPA as well as Canada.

13 On my extreme left is Mich Bernstein who is with the
14 Office of General Counsel. He has advised us on data require-
15 ments under (PIFRA) as well as certain regulatory positions
16 that we have discussed in the past.

17 On his right is John Ulfelder with our Office of
18 Enforcement. The Enforcement individuals get involved in Lab
19 Audits when questions of the nature raised by IBT become appa-
20 rent because they have legal as well as scientific issues re-
21 lated to them.

22 On my extreme right is Frank Sanders who has been

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1 attempting to coordinate the efforts of the Registration Divi-
2 sion in their ongoing registration process with the procedures
3 and guidelines which we have been developing to review the IBT
4 data.

5 I know a number of you, your first contact with us
6 may have been not because of a prior test which was performed
7 but because of an ongoing registration action where IBT data
8 was cited as the basis for an amended use or as a tolerance.

9 Frank will be available to discuss the current operating
10 procedures and guidelines within the Registration Division. I
11 will request that we take any issues dealing with the registra-
12 tion status first and then deal with the more general questions
13 of validation after Frank has had a chance to respond and, that
14 way, we won't tie up his valuable time all day long.

15 Lamar Dale is the Chief of the Toxicology Branch of
16 the Hazard Evaluation Division. He represents a major scientific
17 resource which I have at my disposal to review the IBT data as
18 well as to determine the significance of the anomalies which are
19 uncovered.

20 Actually, there are very few tests ever performed --
21 long term tests -- that are done exactly as the protocol might
22 have originally stated. The variability in animals is enough

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1 to account for that and we've relied upon L.D. and his staff
2 to guide us in the significant questions of validity and attempt
3 to ignore those which are just due to random fluctuations that
4 might be expected at any time in any facility.

5 Art Pallotta many of you may know. He is a consul-
6 tant who works full time with me on IBT. He offers perspective
7 not only of toxicology but also of administering Bionetics
8 prior to Litton's purchase of Bionetics. So he is familiar
9 with the kinds of problems that are encountered in testing as
10 well as the test procedures which were the state of the art at
11 various times in the past because, in the validation effort, we
12 judge the quality of the study against the standards of the
13 time. Not against the standards which are proposed today or
14 may be proposed two years from now.

15 Dave Clegg is with the Health Protection Board in
16 Canada. He has the same function that we do to determine which
17 tests are valid, for pursuing scientific questions and regula-
18 tory decisions.

19 The procedures which they have suggested to us for
20 cooperation have proved extremely satisfactory to date and we
21 certainly anticipate that it is going to save resources for our
22 individual governments as well as reduce the amount of time

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1 which will be required to review all of the IBT data which we
2 have identified as being critical to our decision-making.

3 John Ulfelder has several comments that he would like
4 to make to provide a bit of a background for the Enforcement
5 Division's perspective at this time.

6 MR. ULFELDER: I am going to be brief and to the
7 point. I am here in a sense, I guess, to represent the heavy
8 hand of enforcement, but, basically, this is a scientific work-
9 shop to outline the procedures that you all will have to follow
10 in auditing and validating IBT studies.

11 It's not a fishing expedition by the Agency. As you
12 know, the Government has to major responsibilities here. One
13 is we have to make a series of regulatory decisions about pro-
14 ducts that are on the market and questions that may have been
15 raised about their safety or the hazards they pose.

16 Validation procedure that IBT is assisting us with
17 and that you all will be principally responsible for is designed
18 to try to raise some of the questions on these individual studies
19 relating to specific products and chemicals and to give the
20 Government some base for making further decisions about what may
21 or may not have to be done on a product-by-product basis.

22 The second area that we are concerned with is in areas

1 where problems have been pinpointed. What kind of responsi-
2 bility is there? Where do the problems come from? How do they
3 arise?

4 I would just like to urge that, in the course of con-
5 ducting your own audits and validations, if you come across in-
6 formation which you have reason to believe is important informa-
7 tion that the Government or EPA should know about how a particu-
8 lar study was conducted, we would expect you to focus in on that
9 information and inform us what you may have found. This is
10 aside from -- obviously, the basic job here is to determine
11 whether a particular study is valid or invalid.

12 We are also concerned about possible reasons for the
13 invalidity of particular studies.

14 I would just like to point out, also, in conducting
15 your own validations, on page 77 of the Manual, there is a form
16 -- Certification Form -- which is expected to be filed with
17 your validation report and that Certification Form makes it
18 absolutely clear that the Government expects the validation
19 to be completely accurate -- as accurate as possible -- and
20 certainly not falsified in any respect.

21 These forms will be signed by responsible representa-
22 tives of the individual firms undertaking the validation.

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1 This meeting, as I say, is principally to answer your
2 questions about how you can go forward and conduct an audit and
3 validate a study, and how you can, from the scientific point of
4 view, come up with the answers to the question of whether the
5 study is valid or invalid, and that should be the focus of this
6 meeting.

7 I am just here to be responsive to any questions that
8 may arise that relate to aspects of this process that relate
9 to EPA's enforcement responsibilities, but we have a group of
10 people here, who have been working hard on the problems and
11 questions that are involved here, and are prepared to try to
12 give you the best guidance they can, so that the documents you
13 prepare are the best we can possible do under the circumstances.

14 MR. ARNOLD: Thank you, John. I'm going to ask Art
15 Pallotta to quickly review the concepts and the experiences
16 which he utilized in his preparation of the guide for valida-
17 tions. Art was the principal architect of this.

18 Certainly a number of people reviewed it and contri-
19 buted towards it but, basically, Art felt that it was an impor-
20 tant piece of information which should be shared with registrants
21 and which would substantially reduce the effort and resources
22 that would be involved in this.

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1 I would like to make on additional point. In instances
2 when you come across a study which either because of the data
3 which indicates it is invalid or lack of data upon which to per-
4 form a validation, you, in your own interest, probably should
5 begin either submitting an additional study, which you may know
6 of or which you may have in your files which was not referenced
7 in the original submission, or originate new testing in that
8 area. New tests certainly ought to be carried out in conformity
9 with the guidelines today, whether it is attempting to redo a
10 test as it was done eight or ten or five years ago, rather than
11 wait for the Agency to notify you of a data gap, which could
12 come up either in the reregistration process or, in the event
13 that it is a more significant concern of the Agency, we may
14 contact you upon our determination that the study is invalid,
15 to attempt to spread out the testing requirements which, cer-
16 tainly, are becoming large to the Office of Pesticides Programs
17 in toxics and a number of other external factors.

18 In the case of an invalid study, if it is a require-
19 ment of registration, you won't be wasting your time to initiate
20 a study at this point.

21 DR. PALLOTTA: I think, first of all, we should pro-
22 bably say why we drew up the guide and also why the meeting.

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1 A number of validations were coming into the Agency
2 which were simplified statements, such as the raw underlying
3 data that, for this study, was reviewed and supports the report
4 submitted to the EPA.

5 In our experience, in the auditing of these 12 or
6 more reports at EPA, plus the validations that have been coming
7 in that were more complete, it certainly indicated that there
8 were few studies that did not have discrepancies, errors and
9 omissions.

10 This is a guide that is not mandatory, as Fred Arnold
11 indicated. It is a technique that our team used when we went
12 out to the Decatur facilities and we found it very useful. I
13 hope all of you received the guide before the meeting and had
14 an opportunity to review it.

15 Basically, in going through it, we found the first
16 and most important thing to do was to review the correspondence
17 files. This gave a very good understanding as to what the in-
18 tent of the sponsor was and what IBT personnel's response to
19 their inquiries were.

20 The major point was reviewing all of the data and
21 trailing every single animal in the raw data and eliminating
22 those animals which could not be trailed from their receipt

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1 to the laboratory to their death.

2 Now, in the case of the types of report, we would like
3 to see you take the reports, that you submitted to the Agency
4 itself, and highlight those discrepancies where, say, for example,
5 body weights were different for a particular animal, and a single
6 line drawn through the erroneous data and corrected data replacing
7 it.

8 When all the trail is done -- that is, to the end of
9 the study -- if a significant number of animals are missing,
10 and I think, in the vast majority of cases, you are going to
11 find this, then statistical analyses are going to have to be re-
12 done to come to some conclusions.

13 In your validation reports, also, we would like, as
14 indicated in the guide, in coming to the conclusions of valid
15 or invalid, steps that could be taken to salvage a borderline
16 report.

17 I think that there is a large number of you in the
18 audience who are certainly familiar, or who have become familiar
19 at least, with the IBT situation, that are experts in the
20 auditing of data. I would like to have some idea of those who
21 would want to go into actual details of the guide versus -- I
22 mean, do you want to go page by page?

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1 The intent was only to give examples of both forms
2 and some of the discrepancies. We have additional discrepancies.
3 This by no means represents all the kinds of discrepancies that
4 were counted. It is only to just give you some ideas of the
5 things that you should be expecting to do in the validations.

6 Would you rather do it page by page or just open it
7 up to questions and answers? All those in favor of just going
8 right into questions and answers just throw up your hands.

9 Why don't we go into some of the additional problems?
10 It looks about fifty-fifty.

11 I think the problems in the manual itself are self
12 evident. We are trying to use IBT forms. We changed, obviously,
13 the project numbers. All compounds are blacked out and so are
14 sponsors.

15 Some of the additional types of problems that were
16 encountered -- a very common problem was this problem of the
17 extra animals.

18 There seemed to be at least three and maybe four dif-
19 ferent types of extra animals that were used. The first group
20 of extra animals were those which were a common practice in the
21 years past, and that is, when the study was initiated, a few
22 extra animals per group were ordered to replace those animals

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1 which would not adapt to the caging or the watering systems
2 that were being used. Then after several weeks -- maybe three
3 to six weeks -- they would be discarded.

4 The second group of animals were these animals that
5 went on a diet at the beginning of the study and they were
6 gang-caged within a room and not identified except as to the
7 level of test material being given to them. As an animal died,
8 the individually caged animals, they were replaced by one of
9 the animals that was receiving the test material.

10 A third group of extra animals were those animals
11 which were actually control animals. That is, not receiving
12 any test material, and were used to replace animals that died
13 during the study.

14 Now, in the audit trail, it was very difficult to find
15 all of these and, certainly, the latter was probably the most
16 difficult because of the lack of recordkeeping on any of the
17 extra animals.

18 These extra animals in the second category, for example,
19 although they were receiving test material, were not animals
20 that had any body weights taken or were, for example, used for
21 hematology or certain chemistries.

22 We gave some examples on how we audit trail and

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1 found these extra animals. Sometimes, it was very overt -- that
2 is, the 50-plus-extra group was crossed out and 80 animals were
3 indicated in the protocol.

4 In other cases, the receipt of animals indicated a
5 very large number of animals were being ordered by a study num-
6 ber but, as Fred indicated, we have subsequently found out that
7 the receipt of animals was not always indicated by project num-
8 ber and, therefore, an audit trail by that technique may be not
9 so helpful.

10 The final area, where we were able to definitely get
11 extra animals identified, was in the histopathology laboratories
12 because autopsy sheets were either marked GC, EX, Extra -- that
13 type of notation. I'm sure for many of you who have reviewed
14 some of the audit studies, you have encountered many of these
15 types of things that were in the upper righthand corner of the
16 gross autopsy area.

17 The actual starting dates and termination dates. We
18 have encountered many studies that, although they may have been
19 started as two-year rat studies, for example, actual termina-
20 tion occurred after 18 months. Even in that type of study, we
21 have actually encountered animals that have continued on past
22 the 24 month period, and that's why it is absolutely important

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1 that every individual animal be accounted for. The statistics
2 we performed gave us a great deal of difficulty because of the
3 lack of standard deviations.

4 That means that, unless you get into the raw data,
5 you could not see the actual standard deviations. So, there-
6 fore, in a very large percentage of the test studies, it is
7 going to be necessary that you reanalyze the data by your own
8 statistical methods.

9 One of the biggest problems we did encounter were the
10 reports where there was no adverse effect. Body weight gain
11 certainly becomes very important at that point because, as you
12 all know, so many times only body weight is effected in histo-
13 pathology and that does not account for the lack or gaining of
14 any body weight.

15 Certain additional data, as you are trailing animals,
16 would probably lead to the fact that an animal was substituted
17 in the study itself. For example, if you are following an
18 animal by body weight that would suddenly go from 350, in one
19 month or one week, say, down to 250, it would certainly raise
20 your eyebrows, when the animal is in good health with no other
21 clinical signs of illness, that it was most likely a substitu-
22 tion. You should pay close attention to that type of thing,

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1 because we really want to end up only with those animals that
2 we feel secure or have received the animals during the entire
3 test period.

4 I think Dave had a few examples that he would like
5 to bring up.

6 MR. CLEGG: Art is being a little unfair on this. He
7 has written down most of my examples and he has used them.

8 There are one or two which, perhaps, I should mention.
9 One of them relates to the timing of studies in terms of how
10 long was the study performed, as Art pointed out, and, also, the
11 availability of the test material when the study started.

12 Now, we have come across the 90-day study where the
13 study started on, let's say, the 1st of June. The invoice for
14 shipment of the test material from the firm was the 9th of
15 June, and the diet preparation sheets are for the 12th of June.

16 In other words, by the time the diet was prepared,
17 according to the raw data, the study has been underway for 12
18 days for a 90-day study.

19 This does not necessarily invalidate the study, of
20 course. You can still get some information from it, but the
21 whole base line, which you are working from, has to be altered
22 to deal with an 88-day study or whatever length it is and

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1 conclusions have to be drawn on this sort of basis.

2 Another area where we have run into trouble is where
3 the raw data base is such that there are very marked changes
4 between the final report which was submitted and the raw data.
5 The type of thing I've got in mind here is perhaps relating to
6 (Coenstray's) determination where, on a number of occasions, we
7 found that the so-called no effect level from the raw data base
8 is lower than the no effect level that was calculated from the
9 final report. In other words, there is a change in the basis
10 for calculating your acceptable data for your test material.

11 This, of course, is going to have some reflection, or
12 bears the potential of having some reflection, on the regula-
13 tory stages of a compound. This is something we will probably
14 get into later on.

15 Art is happily pointing to one of his, now, giving
16 me something back. Since he is using the example, let him talk
17 about it. There are so many.

18 DR. PALLOTTA: There are so many. I am sure we will
19 never be able to cover all of the problems, actually. I don't
20 mean that to be accusatory, but really the large number of
21 studies that had to be reviewed -- and I'm sure you will start
22 finding many, many things that we didn't find, but we did

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1 encounter, for example, clinical chemistry or hematology results,
2 in one study, where, actually, the raw data indicated it was
3 entirely different dogs from another study. That type of thing
4 happened also.

5 MR. CLEGG: Fred, if I can just take the floor for a
6 moment, again. I'm not relating specifically to examples, but
7 one or two things that have been said previously.

8 For instance, John mentioned the certification form
9 which has to be forwarded. The example in the notebook, in fact,
10 is the one that is applicable to the United States. There is
11 also -- and I think anybody who is involved in IBT who had con-
12 tacted us has copies of this -- a form which is somewhat dif-
13 ferent which was sent out by the Canadian Government.

14 This is also required to be signed. We are finding,
15 in Canada, that, in some cases, what we are getting is the
16 American form which is completely useless from our point of view.

17 Certainly, we don't have the various rules and regula-
18 tions that are laid down in there. So it has no meaning at all.

19 We would appreciate it very much if you would make
20 sure that you send the correct form when you are submitting data
21 to Canada, rather than just copying exactly what is sent to EPA.
22 It saves us a lot of effort in having to go back to firms and

1 asking them to fill out the right form and then return them to
2 us.

3 Another point I would like to make as well, which
4 relates to some other comments that Fred Arnold made. He indi-
5 cated that a study could be considered to be invalid if certain
6 data was missing. However, I think it should be pointed out
7 that it is necessary, from the point of view of both our govern-
8 ments, that some form of validation should be done on these.
9 They can't just be dropped because data is missing. We must
10 have some sort of report indicating why there is no validation
11 and I think this is fairly important.

12 Similarly on those, if any adverse effects, which
13 would otherwise be missed, are picked up in the raw data which
14 have not been in the final report, then these should be indi-
15 cated to the government involved because, since the main func-
16 tion of both agencies dealing with this is the protection of
17 public health, if there is some adverse effect we are not aware
18 of, then we're not doing our job efficiently. So it is essen-
19 tially to have some sort of validation on all studies which
20 have been requested for validation even if it's only a few
21 lines indicating why a validation can't be done in any depth
22 or why a validation shows that the material is going to be

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1 invalid or the study is going to be invalid.

2 I'm pointing out that, if there are any adverse effects
3 which may appear from that raw data, even though they can't
4 necessarily be validated, they indicate this compound may have
5 (cross generic or inter generic) types of potentials, I think
6 this is essential to both our governments.

7 DR. PALLOTTA: I would like to reemphasize something
8 that Fred said, also, and that is that both we -- Canada and
9 the U.S. -- have decided we are going to review, not report by
10 report but by compound.

11 In other words, we would like to have all of the data
12 submitted on a compound before we initiate our actions.

13 I would also like to emphasize one last point, Fred,
14 and that is, in those studies which you have difficulty with
15 validating and feel they fall into the salvage possibility, that
16 you indicate in the report those steps that you feel would be
17 necessary to salvage. . . .

18 A VOICE: A point of clarification, Mr. Arnold. You
19 said, for example, if you don't have diet preparation sheets,
20 not attempt to proceed with the audit and I heard Mr. Clegg
21 state that you should continue with the audit with all possible
22 information. Could you clarify this point?

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1 MR. ARNOLD: When I discussed the bare minimum, our
2 conclusions would, in all likelihood, be -- and I'll state
3 parenthetically, certainly feel free to contact us if you feel
4 differently -- that there are fundamental pieces of information
5 that are listed that are critical for us to make a determination
6 that a study is valid; that it can stand alone; that it can re-
7 main as a basis for making regulatory decisions.

8 There is a great deal of other information that may
9 be in the reports which shed some light on the toxicity of the
10 compound or the various characteristics associated with the
11 compound. That's what Dave is talking about.

12 Review it and find out if there is, in fact, something
13 in that study which suggests a finding other than that origi-
14 nally tendered to either EPA or Canada, but in terms of anti-
15 cipating that you can prepare a validation report which is going
16 to suffice to meet our requirements, lacking that data, I think
17 it is highly unlikely.

18 A VOICE: Are you finding cases where diet prepara-
19 tion sheets and dosage feeding level forms are not available
20 for these studies?

21 MR. ARNOLD: I'll let Art and Dave answer that.

22 MR. CLEGG: Yes, we are finding quite a lot where the

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1 diet preparation sheets are either incomplete or, in fact, are
2 missing almost totally. However, the majority of cases we
3 do find the calculations which were the bases for determining
4 what amounts of the test compound should be added to the diet
5 for diet preparation. I don't say it is always there, but it
6 is frequently there.

7 We have also found, in at least one case, that these
8 calculations were inaccurate.

9 DR. PALLOTTA: Also, the timing for mixing has been
10 a problem in many of the cases that have been reviewed. Where
11 a large batch of mix had to be prepared, mixing only occurred
12 for, say, five minutes and it is indicated in the raw data.

13 One additional point which we overlooked, and I know
14 it is very important to a great number of you, and that is con-
15 trol animals. We are aware of the fact that common controls
16 were used in a very large number of these tests performed at
17 IBT. We have agreed on the policy of accepting common controls,
18 in spite of the fact that these common controls may have been
19 in another room.

20 I would like to put some caveat on that because we
21 are not fully aware of all of the problems that were associated
22 with common controls but I think, if you received raw data on

1 your test animals, and no control data, there is a very good
2 possibility that IBT, through the VAT program, may be able to
3 uncover this data, because the animals were in another room.

4 Now, obviously, timeframe is going to be extremely
5 important. We have encountered where these common control
6 animals were started at the same starting date as the test
7 animals; we've seen them starting just a few weeks prior to;
8 and, sometimes, towards the end; and, sometimes, not anywhere
9 during the study.

10 So, I think we are going to have to take each of these
11 cases case by case, but, when you have these interviews with
12 VAT, they will do everything they can to dig out the common
13 controls that were used on your study, both negative and posi-
14 tive.

15 A VOICE: (Inaudible.)

16 MR. ARNOLD: Let me repeat that question. Can you
17 use contemporary but historical control data to validate one
18 study when the control data relates perhaps to another study?

19 MR. CLEGG: This is what I was just about to add to
20 what Art said. As far as weight concern, we are trying to get
21 some sort of basis for a common control which would be appli-
22 cable to IBT studies on a year-by-year basis. As yet, we

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1 haven't been able to do this, because we haven't got enough
2 data.

3 I can't say that I am very happy about this on
4 scientific grounds, but we are trying to run this as a salvage
5 operation and, if we can come up with something which gives us
6 a reasonable base line for controls which may be applicable to
7 a number of studies, then, when controls are not available,
8 we'll compare them against those controls.

9 DR. PALLOTTA: I would like to emphasize, though, if
10 there are common controls, they should be used over the histo-
11 rical data.

12 A VOICE: Have validations for tests, such as bird
13 and fish tests, been offered? If they have, what has been the
14 experience as to whether most of these have been validated or
15 not validated?

16 MR. ARNOLD: Let me respond, first, and then I will
17 ask someone else to.

18 We have not requested that kind of data in our review
19 of the files. There have been cases when a pending action had
20 some acute data from Bio-Test which the Product Managers and
21 Registration Division have requested. I haven't seen a whole
22 list of such studies but perhaps Mr. Sanders would give an idea

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1 of what the experience has been to date.

2 MR. SANDERS: In the Registration Division, we have
3 not received that many new acute studies. From an administra-
4 tive standpoint, if we do receive acute studies, opinion appli-
5 cations, that study should be validated.

6 As to the disposition of that, perhaps we can deal
7 with that some other time.

8 MR. ARNOLD: We haven't, within the group that I work
9 with, looked at any acute data. I think Dave Clegg has had the
10 opportunity to review a small number but I don't believe it is,
11 representative. I don't know if he can base a conclusion on it
12 or not.

13 MR. CLEGG: Well, as far as we are concerned, we've
14 looked at one or two acute studies but only in relation to dermal
15 toxicity and interrelation of toxicity. We have not looked at
16 any wild life studies. The number we have looked at, I'm sorry,
17 I can't give you any indication. I think we've only looked at
18 about three in each category and it's insufficient to make any
19 statement.

20 A VOICE: I don't know that we will ever ask for
21 validation of those.

22 MR. ARNOLD: Our first priority is to review the tests

1 in support of tolerances.

2 A VOICE: There are so few instances in which they
3 have made that point.

4 MR. ARNOLD: It may have come up in the registration
5 process but it's not going to be a common question.

6 A VOICE: Our company has already been asked for a
7 validation revision of wildlife. We have been asked to submit
8 this.

9 MR. ARNOLD: Well, I did say, if you have a pending
10 registration action and if that is relying partially on IBT
11 data, they will ask for a validation but whether we will ever
12 get back into the files to review the 3,800 additional tests,
13 which we really haven't done anything about, is highly ques-
14 tionable, at this time.

15 A VOICE: But what happens to all the applications
16 for registration in the meantime? We have been asked to supply
17 this data.

18 MR. ARNOLD: The review of those test results will not
19 proceed until the validation is received. When the validation
20 is in, the validation plus the original submission goes for
21 review and they process it just like they would any other regis-
22 tration action, but they won't proceed with any valuation of

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1 that data absent validation.

2 We are trying to avoid creating additional issues and
3 problems for the future.

4 We've got one kind of a situation where, in the past,
5 we have accepted a large number of tests which now are ques-
6 tionable. Knowing that there is a potential for problems, we
7 would like to avoid that for the future, and there are a small
8 number of tests involved because, basically, they are ones that
9 have been completed in the very recent period for which audit-
10 able information ought to be available, but we won't proceed
11 without that.

12 A VOICE: I would like to ask Dr. Pallotta a question
13 concerning putting all your data on one (inaudible). It's an
14 impossibility in most cases. We have not received the micro-
15 fiche on several tests. The Registration Product Specialist
16 is asking us for some study, for instance, and we have that.
17 So we have submitted that.

18 I feel that it would be an ideal situation if you
19 could put all the tests in only one product, but it's not a
20 practice way of action.

21 DR. PALLOTTA: I think Fred addressed that problem
22 earlier and IBT has indicated that, at the end of the year --

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1 MR. ARNOLD: At this point, they have provided all
2 the data to sponsors on chronic studies which were completed,
3 mailed out as of January 1st, '78.

4 Now, if you haven't received a test that falls in
5 that category from any of the three IBT facilities, one of two
6 things has happened. Either, there is no raw data for you to
7 audit, or it's been sent to a wrong address or there has been
8 a mail mix-up. So I suggest that you contact IBT.

9 We've now been waiting about a year to proceed with
10 this validation effort and I recognize that the problem of cata-
11 logging and microfiching five million -- or some number like
12 that -- pages of records, correlating it and providing it to
13 sponsors for review takes a lot of time. A great deal more
14 time than anyone originally anticipated.

15 For that reason, we haven't taken any actions, but
16 I think the point to keep in mind is that we are not going to
17 begin with the review of a compound -- a historical compound.
18 One for which we noted a concern in our letter of correspondence
19 last July. We are not going to proceed with a review of one
20 study when another one is being audited. We'll wait until we
21 get the entire auditable data base and we'll review it at one
22 time to determine, first, are the studies valid and, to the

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1 extent they are not, what do we know of the toxicity of the
2 compound in question. C

3 Otherwise, it requires us to go back several time to
4 salvage bits and pieces of information from this study and that
5 study and it would slow you down and it would slow us down.

6 If you don't have the data base, obviously we can't
7 ask you to audit it, but we are pointing out that it is our
8 understanding that, if you don't have the data base now, in
9 all likelihood you are not going to get it.

10 DR. PALLOTTA: Just adding to that, if you have re-
11 ceived some of your validations, after you have met with some
12 of the IBT VAT effort, you still do not have any studies, then
13 you can assume that those studies are invalid because of lack
14 of raw data.

15 A VOICE: Well, it's more complicated than that be-
16 cause, before we got the microfiche, we went to make copies of
17 the raw data. So we know the raw data is there. But, every-
18 time we call IBT, it's another two months before that can be
19 sent. So we've waited, now, for about a year and it's just one
20 of those things.

21 MR. ARNOLD: I don't believe we have been exerting an
22 undue pressure on anyone to perform something that physically

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1 can't be done.

2 A VOICE: More than pressure is on us because, as a
3 registrant, we would like to continue registrations and yet you
4 can't do that without --

5 MR. ARNOLD: Because you are tied up by IBT data.
6 I suggest that you raise the question with Mr. Current, perhaps
7 during a break, but his information to us is that it has all
8 been sent out, absent a very small number of tests in the bits
9 and pieces file.

10 A VOICE: (Inaudible.)

11 MR. ARNOLD: We discussed that last night and I sus-
12 pect that the majority of the metabolism studies would not fall
13 within that 90-day and longer classification.

14 It doesn't mean that some of them might not have been
15 microfiched and sent but, at this time, they can't make a broad,
16 general statement about these studies less than 90 days, and
17 that's where the majority of the metabolism studies would fall.

18 A VOICE: Again, with that letter I'm referring to,
19 we received a letter from EPA saying these studies had to be
20 validated in one year. Now, again, you are telling me that
21 these studies will not be looked at until you have the entire
22 package is in. We sent the validation in six months ago and it

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1 apparently is sitting on somebody's desk. So this metabolism
2 work isn't done. We don't have this information. We may not
3 get it for quite a while and, when we do get it, it's going to
4 take time to validated it. So things will be held up.

5 MR. ARNOLD: We have proceeded on a piecemeal basis
6 to date, and we've decided that it's just not sufficient be-
7 cause of the number of issues that are raised in the validation
8 reports. We have to go back over the same information more
9 than once.

10 So we are going to not proceed with the entire review
11 of the chemical in question until we've got all of the IBT
12 validation effort in hand.

13 That's strictly from the point of view of efficiency
14 because we can't make a decision, in many cases, on pesticides
15 until we've had a chance to review all the data because of
16 fundamental errors in key studies and there is just no way
17 around it.

18 I know it creates a problem for you. I'm hoping IBT
19 is almost to the point now of being able to make a blanket
20 statement, "You've got it all. If you don't have it, there is
21 no more information," and everybody can kind of bite the bullet
22 and decide what they are going to do.

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1 It is extremely frustrating for me and everyone else
2 involved here, too. We're not attempting to sandbag you. It's
3 just that there are too many uncertainties for us to proceed
4 when you've got a significant problem with key studies.

5 A VOICE: (Inaudible.)

6 MR. ANROLD: No. Both Dave Clegg and I have attempted
7 to go from the total of all the IBT data down to ones where we
8 really have a concern and, basically, they are the ones upon
9 which we have based the public health hazard. Now, the fish
10 and wildlife, the acute studies and the precautionary statements
11 are another matter, but we're not going to hold up our review
12 on those. We've not even asked that they be audited. We're
13 dealing, now, just with the ones in support of tolerances.

14 MR. CLEGG: If I may, I would just like to cut in.
15 I'm not quite sure that this has come over very clearly from
16 the Canadian standpoint, anyway.

17 We are, in fact, looking at studies as they come in,
18 in terms of checking the audits and validations, and we are
19 going through the raw data on these.

20 What we are not doing -- I think this is what Fred is
21 talking about -- is going back to the companies until we have
22 the whole data base on that compound.

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1 It doesn't mean to say that the data, which you have
2 submitted, is not looked at. It is being looked at. At least,
3 as far as we're concerned in Canada, but we can't go out on
4 individual studies and respond to them for the simple reason
5 we don't have the manpower to write all the letters which would
6 be required of us. It would be a horrendous task, from that
7 point of view.

8 What we are doing is auditing, validating and filing
9 our opinions on each study and, once we have done that, when we
10 have the complete data base, it will be re-reviewed and comments
11 will be sent out that these studies were considered valid and
12 these were considered invalid.

13 If there is any argument about that between your
14 consultants or yourselves or ourselves, then, we're not infallible,
15 we are quite prepared to sit down and talk about it and discuss
16 it and find out whether there is any difference that can be
17 reconciled, if necessary.

18 Then, finally, when we have dealt with this, we will
19 come up with a registration situation by looking at the total
20 data base, but we can't do anything about registrations or the
21 tolerances, per se, until we've looked at that total data base,
22 because we don't know what is going to be available.

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1 MR. ARNOLD: That is certainly an accurate reflection
2 of what we are doing and the reason I say we are not proceeding
3 on chemicals is because, oftentimes, any communication that we
4 get with regard to the registration status of the chemical, it
5 is that status that we are not proceeding with until we have
6 had a chance to examine all the studies.

7 A VOICE: What is the Agency's action going to be?
8 We write a letter saying we are unable to validate a two-year
9 chronic dietary study, but we have initiated another two-year
10 study under today's protocols which we feel is substantial.

11 MR. ARNOLD: In that instance, and I think we will
12 start with the assumption that that is a critical piece of
13 information, we would request that you provide us with interim
14 sacrifice records on the new test as it is carried out.

15 We would, in all probability, if it is a compound that
16 has a large number of tolerances and one where there is a fair
17 potential for exposure in food chains, reevaluate our prior
18 tolerance decision based perhaps on a 90-day test with -- I'm
19 not even clear on that. Dr. Dale will comment on how the 90-
20 day tests are used to make interim tolerance decisions in the
21 old context.

22 We would not proceed with registrations of significant

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1 new use patterns for the compound, nor would we proceed with
2 the tolerance actions until we had what we thought was an accep-
3 table data base.

4 As far as the "me too" kinds of registration decisions
5 on that compound, we would proceed regardless of whether it was
6 IBT data or not with the assumption that there is a certain
7 market for a pesticide and whether its put between ten or two
8 people doesn't really matter much and, if we essentially had
9 made the decision to have the chemical on the market, we don't
10 really care how many people are using it in a particular product.

11 A VOICE: (Inaudible.).

12 MR. ARNOLD: There is another point. If, in the
13 validation of a compound, we determine that, in fact, not only
14 did the study perhaps fail to adequately identify no effect
15 levels, we might demonstrate adverse effect and then the Agency
16 feels compelled to take an action on it. but, as you are all
17 aware, the cancellation and suspension actions talk about un-
18 reasonable adverse effects, and lack of a data base is un-
19 reasonable but it's not an adverse effect by itself.

20 So, in the extreme case, when the data base that the
21 registrant thought they submitted. turns out to be shot full of
22 holes and unusable, then we might have some additional information

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1 that causes you concern, we could proceed under a tolerance
2 provision or voluntarily work with the registrant, modifying
3 some use patterns against some additional data.

4 We are going to be very flexible. We've got to. It's
5 that kind of a situation.

6 A VOICE: I would like to ask Mr. Sanders a question.
7 In the event that we do have a registration being held up in
8 the absence of validation for fish and wildlife, since addi-
9 tional registration seems to be an actuality, is it possible
10 that registrations will be granted on a conditional basis that
11 validation occur or new studies be instituted if not validated?

12 MR. SANDERS: I assume you are talking about a new
13 use?

14 A VOICE: Not necessarily, no.

15 MR. SANDERS: In connection with conditional regis-
16 tration, suspect data has no bearing, generally speaking. We
17 are talking about similar or identical products.

18 In other words, if you make an application that is
19 similar or identical to a registrants product and we don't know,
20 based upon our data base, whether or not you have relied upon sus-
21 pect data or not, we would issue you a registration anyway and
22 this is, at this point, something that may be new to many of

1 you because we have not fully developed implementation of
2 conditional registration, as you know, but, tentatively, that
3 is the direction we'll go.

4 A VOICE: What you are saying is that, in this in-
5 stance, you may grant registration and make collection of this
6 other data a condition, is that correct?

7 MR. SANDERS: That's correct. This is not a new use.
8 We're talking about carrying a registered product. With res-
9 pect to new uses, it may be a little difficult because we may
10 require new data.

11 A VOICE: How could that be followed up, now, in an
12 instance where registration actually exists?

13 MR. SANDERS: In re-registration, suspect data, as I
14 understand it -- and Fred can talk more about that -- at that
15 point the references that were used to support that registra-
16 tion have to become apparent and, at that time, we would deter-
17 mine whether or not suspect data was or was not used.

18 A VOICE: Okay. Thank you.

19 MR. ARNOLD: In the process of re-registering a com-
20 pound, basically, the Agency takes everything it's got in its
21 files and dumps it on the table and tries to construct standards
22 from that. What do we know of the toxicity of the compound?

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1 I don't really think that this is going to be a prob-
2 lem that is going to come up in the re-registration process.
3 Hopefully, most of the compounds, we will already have the
4 critical tests either validated at that time or we're going to
5 know that there is nothing to validate. Somebody is probably
6 initiating another test because there is a data gap and they've
7 got a certain amount of time to complete that data gap, in which
8 time we have additional registration.

9 This fish and wildlife question which, I think, is
10 perhaps something that may have been raised in the current
11 registration matter, it's kind of a problem that is going to
12 peak and go away because there are very few tests coming out of
13 IBT, right now, that have been referenced by registrants for
14 new actions and those that are coming out, they have records
15 and they've gone through an IBT assurance program with IBT,
16 which was initiated prior to this whole validation concept.

17 So, records are available and our experience has been
18 that the studies can be reviewed very quickly.

19 A VOICE: (Inaudible.) The problem is, if we assume,
20 now, this microfiche data that we have is all we're going to
21 get and then there are instances where you have 100 (inaudible)
22 saying, "You don't have the microfiche," it really makes for a

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1 tough decision.

2 MR. ARNOLD: I realize that. I understand that that
3 is the reason why individuals have been reluctant to proceed
4 with the validation on part of the data base which, subsequently,
5 may become modified and augmented with additional data.

6 Right now, it is my understanding that, on the chronic
7 studies, if you don't have any data on it, you're not going to
8 get any data except for unrelated pieces of several pages in
9 this bits-and-pieces file.

10 I think you might begin working under that assumption
11 that, if it's not lost in the mail, you're not going to get it.

12 In cases where you've got a data base on a study and
13 it falls in this chronic classification, in all likelihood,
14 that's all you are going to get. You may get some pieces of
15 communication when they go to microfiche the bits-and-pieces
16 file, but that's not significant information and it's usually
17 not related to a study for which they have built a large data
18 base.

19 So, I think, at this point, for the majority of
20 studies, you've pretty much got what you are going to get and
21 you can proceed and, in the case where you may have gone into
22 Bio-Test -- I've known several instances where sponsors went

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1 into Bio-Test, prior to Bio-Test attempting to build their own
2 library and classification system, and copied data which has
3 subsequently not been microfiched and sent out.

4 I just don't have any wisdom to offer on that problem
5 other than talking with Bio-Test, because I find it a rather
6 peculiar situation myself.

7 DR. PALLOTTA: Let me try and see if I can give you
8 an example of this type of problem.

9 Let say there is a two-year rat study and all of the
10 hematology data is missing but you do have all of the rest of
11 the information and you can validate without this hematology.
12 It appears to us that, by relatively simple target organ type
13 studies, you can indicate bone marrow effects on a relatively
14 short-term basis which would be helpful to support that par-
15 ticular study.

16 That's an example of the type of salvage material we
17 will accept.

18 A VOICE: I'm not so concerned about the bits-and-
19 pieces file. I'm concerned where we actually have knowledge or
20 hard copy data and didn't receive any on the microfiche.

21 MR. ARNOLD: In that instance, I would certainly expect
22 that you would proceed with the validation on all the data that

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1 you have. If you've got hard copy that wasn't microfiched,
2 then, obviously, between the time you retrieved your own data
3 and the time subsequent microfiche were made, it got lost --
4 unaccounted for -- but certainly no longer available in micro-
5 fiche form. You should proceed with that.

6 I don't intend to limit our review of data to just
7 the records provided by IBT. I think that, oftentimes, sponsors
8 may have records or correspondence. Perhaps they have hard
9 copy or hematological reports which were submitted during the
10 course of the study.

11 Any information that relates to it ought to be used
12 to review and build a proper perspective on the study.

13 A VOICE: Shouldn't it be possible, at some stage,
14 to get a statement from IBT, rather than make an assumption
15 that they have supplied all the data?

16 MR. ARNOLD: Well, I certainly hope so. I've been
17 attempting to kind of get it nailed down, now, for a long time,
18 simply because I feel it reasonable to insist that registrants
19 pursue in the effort and it is one that has been very frustrating
20 when there is a possibility that there is additional data out
21 there.

22 I'll see if we can, perhaps, get some guidance from

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1 the managers of the Validation Team, and I pass on to you what
2 they have passed on to me and I interpret that as it is time for
3 everybody to kind of face reality and there is not going to be
4 a large body of data that's going to come to the surface in the
5 next month.

6 There is a possibility -- a very strong possibility --
7 of problems in being able to contact their prior clients because
8 of people moving, people selling rights to data, changing com-
9 pany names. For a number of reasons, they have difficulty
10 trying to provide the records that they have to the sponsor who
11 is likely to be the one who wants it.

12 MR. ULFELDER: One point about the question of hard
13 copy. I think, in submitting a validation report, it is essen-
14 tial that you indicate whether you are using a copy you obtained
15 previously, or either contemporaneous to the delivery of the
16 study report, or whatever, or however you obtained it, as
17 opposed to microfiche data which you have been given by IBT as
18 part of the microfiche process that took place over the last
19 year.

20 For our purposes, in reviewing the validation reports,
21 we would like it noted as to what the source of the data was,
22 whether it was microfiche or some other source.

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1 MR. ARNOLD: I wonder if we could take about a ten
2 minute break, right now.

3 (Whereupon, a short recess was taken.)

4 MR. ARNOLD: Perhaps we can reconvene for about 45
5 minutes and then we will take a luncheon recess.

6 Let me just provide some additional comments upon
7 availability of microfiche.

8 Again, the representatives of Bio-Test urge each
9 sponsor to contact them individually about the status of what's
10 been sent, what records are available, what records might be
11 available in the future and they will provide an oral assess-
12 ment to you of what's been sent and what's the likelihood of
13 anything else being made available.

14 They will follow that up with a written confirmation
15 that you can proceed on, but they suggest that the oral assess-
16 ment would be enough for you to proceed, and I would certainly
17 expect then, given an oral report for them of what is available,
18 that you could proceed on this validation for which there is
19 data and begin to make any assessment of those studies for
20 which there is no data to determine whether or not you might
21 be able to reference and support additional studies to the
22 Agency in the case of data gaps we're beginning to test.

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1 We'll continue to be flexible. I think we have in
2 the past and, if we haven't been, I would appreciate it if you
3 would bring that to my attention, if we have constructed a sys-
4 tem of constraints where there is no feasible solution to the
5 problem: not feasible

6 Several points were brought up to me during the inter-
7 mission that I told you I was not making clear. Conclusions
8 reached on your part or on our part that a critical study is
9 in doubt, our process will be to examine the entire data base
10 which we have, whether it includes tests other than IBT tests.
11 Perhaps tests which were not referenced to any particular
12 tolerance petition but that do bear on questions of human safety.
13 We'll look at all available information to construct as much
14 of a data base as possible concerning the toxicology of the
15 chemical.

16 In the instances where you are aware of other tests
17 which you feel are relevant in the light of certain missing
18 data which, at one time, you assumed was satisfactory, please
19 point that out to us. The last letter from Ed Johnson made that
20 request in addition to a number of others.

21 Basically, what we were requesting was that, in the
22 event you determine that your toxicological data base is not

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1 as was originally presented, what do you suggest we do about
2 it? Do you have additional data that suggests the chemical is
3 safe and, therefore, there is nothing to be worried and tests
4 are underway, or are there tests which have been completed in
5 the public domain by NCI or by whoever that bear on your com-
6 pound and that you think support the continued registration and
7 continued use patterns? Certainly, provide us with any informa-
8 tion that you know of in those circumstances where, by your own
9 assessment, the data base just doesn't support the prior con-
10 clusions.

11 There is one additional point. Apparently, addendums
12 were often prepared for IBT reports -- addendums dealing with
13 one phase of the work -- and the individuals involved in the
14 validation assessment work have found, at times, in going through
15 file cabinets, items which may have been prepared after the
16 original report was completed, but they do supply more insight.

17 They are stand-alone kinds of documents. They have
18 been sent on to the recipients of the original data and, again,
19 a communication directly to Bio-Test can provide you any informa-
20 tion that they might have on these addendums -- these stand-
21 alone pieces -- that are cropping up, inadvertently, but they
22 are cropping up.

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1 I guess the best thing to do is to continue with
2 trying to answer your questions. It seems like the questions
3 are certainly good.

4 DR. PALLOTTA: One other comment was made during the
5 intermission and that is, especially among the larger companies,
6 you might find an awful lot of the missing data in your own
7 files.

8 If you are anything like EPA, the data tends to get
9 lost in the archives that you may have in your own companies.

10 I think we also want to make some comments about on-
11 going studies. As all of you are aware, a good number of the
12 scientific staff at IBT have left and many of you have studies
13 that are ongoing. We would strongly urge that you provide some
14 supervision in work until its completion.

15 MR. ARNOLD: I guess one additional point to be
16 brought up there. If you are not aware -- you soon will be,
17 if you have an ongoing test -- it is now a Bio-Test policy not
18 to sign the reports and the reason for not doing this -- and
19 I'll give you the reason they gave me and you can pursue it
20 individually with them if you would like to -- is that the
21 current management was not in charge of a number of these
22 tests at the time they were started or at times during the

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1. conduct of the test.

2 A number of scientists, who may have been involved in
3 the early states of a test, are no longer there and nobody can
4 state, categorically, that everything reflected in the report,
5 in fact, is borne out by the raw data. In the sense we are re-
6 quiring all tests be validated, the validation will be the proof
7 of the pudding. Either the data supports the conclusions or it
8 doesn't.

9 We have Reto Engler, who is Dr. Dale's Branch Chief,
10 who has developed a policy and transmitted it to more and more
11 registrants that unsigned reports would not be acceptable. That
12 is not the policy of the Agency. We discussed it last night
13 with Ed Johnson and we reviewed the prior registration revision
14 practices and, at times, tests have come in that were not
15 signed.

16 We have not, in the past, insisted upon that, although
17 it is certainly expected, and we are not going to create a
18 double standard now.

19 I might point out that, in reviewing the results of
20 an IBT test, when current management is unable to sign the re-
21 port and reflect that this report is fully accurate, it cer-
22 tainly raises questions in my mind and I think it ought to raise

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1 questions in anybody's mind, given the circumstances that there
2 is no affirmation that, in fact, everything happened as stated,
3 but our policy will be that the validators are going to speak
4 for themselves and, if IBT feels compelled, because of a cor-
5 porate point of view -- I don't believe it is because of a basic
6 scientific inadequacy. My understanding is that they don't
7 necessarily question it but they have no way to prove to them-
8 selves that everything is entirely supportable.

9 Given that -- their requirement -- we will accept un-
10 signed reports along with the validations and we will review
11 those just the same as we do any other test.

12 A VOICE: You stated that acute studies are not being
13 requested by your group. However, they are being requested by
14 other groups in EPA. Now, acute studies have some problems
15 because all the guidance that I've received to date refers to
16 long-term and they point out the importance of protocol and the
17 importance of receipt of animals. (Inaudible.)

18 Now, I'm getting consultants coming back and saying,
19 "I can't validate your study because, one, there is no protocol,
20 and, two, there is no receipt of six animals or 50 animals ever
21 being used." Would you elaborate on the importance of those
22 two items for an acute study?

1 MR. ARNOLD: I will attempt, and then I will pass
2 this burning issue on to Dave Clegg.

3 Actually, in discussing it, we don't know how to audit
4 an acute oral study and we really haven't asked for very many
5 of them. The only ones we've had are the ones that have come
6 up in a registration procedure.

7 In the case of a protocol, I agree there is going to
8 be a unique protocol, especially if the study was reported to
9 be a certain type and there is some information to suggest it
10 was carried out that way, or there is going to be a small body
11 of information.

12 In the case of animal receipt, I think it is fairly
13 clear that animals for acute studies were not ordered individ-
14 dually. It's really not irrelevant. I mean, if you have in-
15 formation on it, that's fine, but it certainly would not be a
16 fundamental kind of information on an acute study.

17 The reason we have not issued any guidelines on how
18 to audit an oral acute is that we really don't know. For that
19 reason, we didn't ask for the vast majority of those studies to
20 be audited. We really have no basis for deciding whether there
21 is a problem in that area or not.

22 If there are individual instances when the registration

1 process has requested information of that nature, the basic in-
2 tent that we have in performing an audit is to provide substan-
3 tiation that the test is actually carried out in the manner re-
4 flected in the final report, and I think that goes across the
5 board, no matter what kind of a test you happen to be looking
6 at.

7 We are not so much concerned with whether the final
8 report was the best kind of a test to do or whether it meets
9 today's standards. It is, does the raw data support the con-
10 clusions in that final report that, at some time in the past,
11 we made decisions on and, if it does, and we made a bad deci-
12 sion, then we just didn't do a good job of protecting the public
13 health but, if we made a wrong decision because the report was
14 incorrect, those are the ones we want to find out and we want
15 to try and fix.

16 A VOICE: Essentially, you are saying, in acute, it
17 is more important to have an audit than a scientific validation?

18 MR. ARNOLD: Yes, I think that's what I'm saying.

19 MR. CLEGG: I'm not quite sure why it was passed to me,
20 but I do have a comment in relation to this.

21 As far as we're concerned, with acute oral studies,
22 we have not requested any validations, nor do we intend to.

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1 There are a number of reasons behind this which are, perhaps,
2 worth considering lightly,

3 First of all, the relative cost of obtaining the
4 information for an acute study, going through an audit and
5 validation procedure, this is probably just as great as re-
6 peating the study, particularly with acute oral studies.

7 My own reaction to this would be that, if there is
8 a necessity for an acute study to be verified, then the easiest
9 way to do it is to repeat it and not bother with audits and
10 validations. That's for acute orals.

11 Now, whether the same is true when you are dealing
12 with acute inhalation or acute dermal, I'm not quite so sure.
13 I think, in all probability, since you are assessing certain
14 specific time intervals, the irritation scores or this type of
15 thing in both those types of studies, then it may be worthwhile
16 getting the data and going through it and doing a validation
17 on it but, as far as acute orals are concerned, I think the
18 probability of a request for these is going to be low.

19 There may be an odd one which will crop up where a
20 compound is close to the cut-off point in terms of labeling or
21 various LD-50's that are used there and where we have some
22 doubts, if one is very close to that cut-off point, then we may

1 ask for a repeat, but I don't really believe we are going to
2 ask for validations on any acute orals.

3 MR. ARNOLD: I would also add that it is not now our
4 intention to ask that registrants go back and audit all those
5 kinds of studies that historically exist in our files.

6 As a general guideline, from the discussion that we
7 had with Mr. Johnson last night, in the case of acute studies
8 or subacute fish and wildlife, as a general rule, when it
9 appears to be reasonable, if we have asked for a validation,
10 that it should be validated unless, one, there is comparable
11 data elsewhere -- which means a similar study has been done in
12 a different facility. There is no sense in going back and
13 auditing a study which already exists and, by its mere presence,
14 it is sufficient.

15 Or, if the study can be reperformed quicker and less
16 costly in the case of, perhaps, an oral acute study, we suggest
17 that that might be the better way to proceed than attempt to
18 spend the resources in validating an acute study.

19 A VOICE: There is a big distinction. When you are
20 talking about studies that are being requested which, as I can
21 see, wouldn't be requested unless we submit something. (In-
22 audible.) Now, is Canada still taking that position that, if

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1 it's an IBT study that is submitted for new use, that it will
2 not have to be validated?

3 MR. CLEGG: At the present point in time -- in fact,
4 just before I came away -- a memorandum went up to our senior
5 executives to determine whether this stand should continue.

6 The feed-back I have got on it is not complete by any
7 stretch, at this point in time, but the general consensus of
8 opinion, as far as it has gone, is that this stand will no
9 longer be taken.

10 MR. ARNOLD: Since it is an issue that has surfaced
11 a number of times, I'll make the commitment to discuss, speci-
12 fically, the question of those tests which we don't ourselves
13 have any idea how they could be really audited or validated,
14 such as an oral acute study, and give you a guideline, because
15 I don't know how many times that has been caught in the regis-
16 tration, like the experimental use permit, new application kinds
17 of decisions. I'll try, the remainder of this week, to get an
18 idea of how many times it's happened.

19 My feeling is it is very infrequent. It sounds like
20 you may have been the major recipient of the problem. I will
21 see if we can get some guidance to ease some of your problems.
22 It sounds like this problem has created an unreasonable kind of

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1 a situation and one which probably should never have happened.

2 I'm going to talk to Mr. Johnson about it and I would
3 suggest for those of you who are in that kind of a problem, why
4 don't you give me a call about next Tuesday. My number is
5 Area Code 202-755-8026.

6 MR. CLEGG: I have one additional comment I would like
7 to make in this area. I don't know whether this is the case
8 that is being discussed. It may be.

9 On area where we have run into trouble with acute
10 studies are those which are being done as range-finding tests
11 for neurotoxicity studies and, under these sort of circumstances
12 where the dose which is given does not tally with the acute
13 LD-50 in the hand then, obviously, there is need for some sort
14 of validation or at least some comments back as to why they,
15 instead of using the LD-50 or half the LD-50, why they have
16 used the best level for a neurotoxicity test which is much
17 lower.

18 As far as I know, in the acute studies encountered,
19 that is the only situation where we have, in fact, raised any
20 queries. I may be incorrect.

21 If the gentleman who is asking the questions would
22 like to talk to me afterwards, I will try and sought this out

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1 for him.

2 A VOICE: One other question. Earlier, you indicated
3 that you were going to divide these up between the U.S. and
4 Canada. How do you intend to divide these?

5 MR. ARNOLD: I asked Dave to do them all. That was
6 the first provision.

7 MR. CLEGG: I refused.

8 MR. ARNOLD: Actually, to date, the division has
9 pretty much been one of very frequent communications between
10 us and chemicals that they had a greater interest in, perhaps,
11 because they had a pending decision and one in which they were
12 already into the data base, they've gone ahead and proceeded
13 with it, and we've done kind of a similar thing.

14 We're proceeding with several that were of interest
15 to us for other reasons and we were able to kind of move ahead.

16 We've also taken, from the schedules that we have
17 received from registrants which, although they are no longer
18 relevant in an absolute sense, since basically everything has
19 gone well beyond the original kind of concept of how long it
20 would take to get the data together, we do think it still re-
21 flects the relative way in which the registrants will submit
22 data, and we'll get all the studies on Compound X before we go

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1 on to Compound Y, and we've taken a cut at that so that we don't
2 get redundancy. We are attempting to kind of stay several
3 steps ahead of the receipt of the data.

4 We do both need copies of the microfiche simply be-
5 cause we have got to maintain the integrity of our files. I am
6 not sure that it would be of particular importance -- or maybe
7 it would be. Maybe you would prefer that one or the other re-
8 view your data.

9 I suppose we could share with the people at least our
10 tentative conclusions as far as who is going to do what. I
11 think the validation findings are going to be the same. We, so
12 far, have attempted to do several independent ones and we have
13 reached, basically, the same conclusions.

14 MR. CLEGG: It's just sort of up in the air.

15 MR. ARNOLD: If you have a question as to "Who is
16 looking at my data?" by all means ask us and we'll tell you.

17 MR. CLEGG: This, basically, is part of a discussion,
18 I think, between Mr. Arnold and myself. I have the feeling that
19 it would be far wiser, once a compound has been allocated to
20 one of the particular agencies, we notify the firm in question
21 that their compound is being looked at either by EPA or by HPB.

22 Then, if there are any further questions which arise,

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1 then at least they know who they are dealing with. If they
2 have come up with something which suddenly alters one of their
3 validations -- for instance, somebody in the coffee break was
4 telling me that they had an ongoing procedure and they had gone
5 back to the raw data and they had modified, as a result, some
6 of their original validations they had sent in.

7 If this type of thing happens it is, obviously, to the
8 advantage of the firm to get that to whichever country is dealing
9 with that particular compound as soon as possible. So, for
10 Canada, if it is agreeable with EPA, I will be quite prepared
11 to indicate which compounds we are actively dealing with and,
12 as they are allocated -- and I should say, now, that so far only
13 22 out of the 50 or 60 compounds involved have been allocated --
14 we will notify the firm whose compound it is. Does that sound
15 reasonable?

16 MR. ARNOLD: Certainly. It sounds like a very
17 reasonable way to proceed.

18 MR. CLEGG: This, incidentally, does not mean that
19 correspondence should only be directed to the one country.
20 Anything relating to either compound, for the sake of complete-
21 ness of the files, should be directed to both countries, but,
22 if it's an urgent situation and you want to contact us by

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1 telephone, then at least you know where to go to straight away.

2 A VOICE: Not sending microfiche of raw data, a lot of
3 the raw data could be in your own files. Now, that could cer-
4 tainly cause a problem. Now, is it allowable to send copies of
5 our own data to you instead of microfiche ones? The letter I
6 received said raw data should be microfiched.

7 MR. ARNOD: I would certainly prefer that we get the
8 microfiche. You just have no idea what we would have if every
9 registrant dumped all the raw data on the steps of the east
10 tower of EPA.

11 The microfiche we can slip into a study which has been
12 submitted and it becomes something that's fairly easy to keep
13 intact for the future.

14 All the raw data, on the other hand, would be very
15 difficult to deal with. If that's all you've got and you don't
16 want to microfiche it, by all means provide us with that data,
17 but I would certainly prefer that we deal with the microfiche
18 because of the large volume.

19 If that's not something that you find acceptable, give
20 us the raw data and I suppose that we will, at some time in
21 the future, microfiche it. It just increases the potential for
22 creating, perhaps, a very unmanagerable situation where we can't

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1 even tie the raw data back into the studies because the problems
2 that Bio-Test has had in trying to build this library are pro-
3 bably typical of the problems we might encounter if we started
4 the five million pages of records relating to our 123-some
5 compounds.

6 MR. CLEGG: If I may, Fred, one thing from the point
7 of view of contact between us. Fred gave you his telephone
8 number. It might be a good idea for those who have compounds
9 in Canada to give them mine. It's Area Code 613-996-3833.

10 A VOICE: Fred, you mentioned, more than once this
11 morning, declaring a study valid. We have religiously avoided
12 reaching positive conclusions of the study because of the wide
13 variety of definitions a valid study can have. (Inaudible.)
14 Would we basically try to point out what data appears to be
15 real in a study and which statements we cannot verify from the
16 raw data, rather than attempting to say the entire study is
17 valid or not valid. Would you comment on that concept?

18 MR. ARNOLD: Yes. The cut that we are making between
19 --the black and white cut between valid and invalid is, first,
20 if a study is valid, then it needn't be repeated. It stands
21 alone. It answers all the questions that it was originally
22 intended to answer and the raw data supports the conclusions

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1 in the report.

2 Now, there are certainly, perhaps, a large number of
3 studies that are going to fall in the middle where perhaps a
4 two-year chronic feeding study offers a great deal of informa-
5 tion about the toxicology of the chemical but is not appro-
6 priate for an assessment of cancer. In that case, the study
7 might have to be repeated, but many of the conclusions that can
8 be drawn in it are valid conclusions.

9 The reason that we have asked the sponsors to comment
10 upon the validity of a study is because it is a very difficult
11 conclusion to reach. There are no guidelines.. No one every
12 had to go through this kind of a process in the past and we
13 have limited resources.

14 Any additional scientific input that we can receive
15 from the registrants we would appreciate, and their comments
16 upon the validity or invalidity, with regards to whether the
17 study can stand alone for its original purposes, we are still
18 waiting to see.

19 It's a conclusion that we are going to have to dis-
20 cuss in many cases because it basically tries the decision of
21 whether or not a study needs to be repeated. That's a financial
22 and a time burden that will be imposed by the decision and it's

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1 not going to be made lightly.

2 So, whether you reach that conclusion in your original
3 submission to us, or whether we discuss it after we evaluate the
4 study, is going to have to be discussed.

5 In those cases where we determine that a study is in-
6 valid and must be repeated, I think, oftentimes, the validation
7 reports sort of speak to that issue because they note deficien-
8 cies in major areas, but then go on to what can be determined
9 from the study.

10 I think that the next step is to say, "We have ini-
11 tiated new studies because of the deficiencies. However, we
12 feel that the following scientific information can be used in
13 the regulatory decision process." That's what we're looking
14 for.

15 A VOICE: (Inaudible.)

16 MR. ARNOLD: The question is whether we can predict
17 a range of time between the receipt of the validation and the
18 regulatory decision.

19 No, I can't, because, in many cases, the validations
20 will be reviewed and, in the situations where the tests are
21 valid or perhaps where the test needs to be repeated but it's
22 not a burning kind of a question and we have additional

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1 information that kind of adds insight, the first formal response
2 from the Agency would come during the re-registration process
3 when the generic standard is constructed. That could be several
4 years.

5 The data will be reviewed because we will have to
6 separate those compounds from which we really don't feel any
7 desire to speed up the new testing if it's called for from those
8 compounds where we do have a major concern on data gaps.

9 I believe that Dave's goal, right now, is to complete
10 his review of the IBT data sometime in 1981. Is that correct?

11 MR. CLEGG: Well, at the present moment, the resources
12 which have been allocated for this by Canada should be available
13 until the 1st of April, '81. On this basis, we're hoping we
14 will have everything sorted out by that time, but this is so
15 dependent on, (a), when we get data and, (b), the volume of
16 data that we have to deal with.

17 At the moment, the rate of data flow for the last
18 three months has been extremely low and, as a result, we've
19 had some people who were diverted on to other work because
20 there hasn't been enough on the IBT coming through for us to
21 be able to keep a steady flow on it.

22 It is very difficult, therefore, to assess how long

1 things are going to take, because it is really dependent on
2 you people how fast you get it to us. Equally, it is going to
3 work the other way around because, if we get a sudden dollop of
4 it -- a tremendous amount of material -- then, obviously, it's
5 going to take us longer to deal with the individual studies in
6 that large a quantity coming in than if we are dealing with
7 them as a steady flow.

8 I know that this is something which is always a prob-
9 lem in any submission to the government and I don't know how
10 you deal with it. Again, we would hope to have decisions made
11 by April, '81, and, hopefully, if the data is in our hands,
12 we should have decisions prior to that date. I think that's
13 all one can say at this point in time.

14 MR. ARNOLD: As we review a compound, when we know
15 it is of significant concern, we certainly won't wait until the
16 re-registration process to bring it up.

17 On the average, an average compound that we have
18 raised questions on, has about five tests associated with it
19 and that's simply taking the number of pesticide active ingredi-
20 ents and dividing it into the tests that we've requested.

21 Our outside estimate on the review process, if we have
22 to get back into the entire data base because of significant

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1 anomalies and a determination that the major body of data is
2 not reliable, it takes several months to get in and look at
3 all the underlying data.

4 Now, I'm not sure that there is such a thing as an
5 average test. We have a number of compounds that have 20 or
6 more tests that we've questioned and then some that have only
7 one or two. So I'm not sure that the average makes sense, but,
8 for our budgetary purposes, we've looked at about two man months
9 to get back in and assess it and, if we reach conclusions that
10 have an impact upon your registration process, for those who
11 have registered compounds, we'll share those with you immediately.

12 Looking at the schedule that we have for the receipt
13 of data, I hope that we're going to have all the data in hand
14 during the next year and we're reviewing it as it comes in.

15 We've got three compounds that are under review right
16 now because we have all the data for them. In addition, we
17 have a number that come in where it is just a study or two, and
18 we've looked at that.

19 I believe, in all instances, we have communicated
20 back with the registrants because it has been a learning pro-
21 cess to try and understand what the validation process was that
22 they carried out and shared, with them, our conclusions, and I

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1 think we will try to continue to do that.

2 Certainly, if it is something that is going to im-
3 pede registrability or new decisions on a compound, we're going
4 to notify the registrant of that as soon as we make that deter-
5 mination.

6 A VOICE: Can you comment a little bit further about
7 your timing for receipt of information, especially noting some
8 of the larger companies (inaudible) and pinpoint dates and
9 flexibility?

10 MR. ARNOLD: Well, originally, we had hoped that we
11 would have all the validation reports within a year. We had
12 asked for a schedule showing when they would be submitted and
13 there were several exceptions to that schedule.

14 There were large companies that had been totally rely-
15 ing upon Bio-Test for their toxicology testing capability where
16 there were several hundred tests involved. It was just un-
17 reasonable to expect them to come in at a rate of one a day.

18 In those cases, we said that we would be flexible but
19 we did ask for a schedule of when we could expect to see those,
20 so that we could kind of plan our resource commitments around
21 that and try to be responsive. I think that is still a reasonable
22 request, if you take into the light of the ability to get the

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1 raw data from IBT.

2 If we could start, today, with the assumption that
3 all the data is available that you are going to get, I don't
4 see any reason at all that the majority of the registrants will
5 not be able to provide those validations within a year and for
6 us to be able to look at those and comment back.

7 It's really dependent upon when you can get the firm
8 commitment from Bio-Test that you have got all the data that
9 you are going to be able to work with and I, again, stress that
10 you ought to contact them, take their assessment of the situa-
11 tion today, and proceed with that because I think, in most
12 cases, the data which is available is out. It's just a little
13 depressing when you come up and there is just nothing there,
14 but I think that's a situation you have to face.

15 A VOICE: Is there a separate group set up to evaluate
16 the validations or is this going to interfere with the evaluation
17 of new submissions from a biological standpoint?

18 MR. ARNOLD: Yes. That's the juggling act that the
19 Pesticide Program has been in for a number of years, now. I
20 have resources in the budget to utilize consultants for IBT.
21 There will be people to review the validations as they come in,
22 spot check those against microfiche. Sort of the routine part

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1 of it.

2 The issues that are raised will be referred to senior
3 toxicologists, statisticians, that will be in a consulting capa-
4 city as well as Dr. Dale's staff. We don't intend to use the
5 senior people to do the routine work of checking the raw data
6 against the validation. We expect that to be raised up and,
7 therefore, reduce the drain on the Toxicology Branch, which is
8 currently in re-registration and RPAR -- you name it. So we
9 are trying not to pull those back into the fray.

10 The unavoidable part becomes we won't, and we haven't
11 in the past, asked consultants to make regulatory decisions for
12 us. In the event that a determination is made, through the vali-
13 dation process, that a data base be significantly modified, we
14 are going to have to have that reviewed by the Tox Branch people
15 who normally pass on compounds, but, hopefully, that will be a
16 very small number of compounds and the issues will be fairly
17 well articulated when we get to them. That's what we've done
18 in the past.

19 MR. CLEGG: May I answer that on the Canadian side.
20 We have, in fact, set up a separate group to look at the IBT
21 problems and we are doing, basically, what Fred has just said.
22 his consultants will be doing and, then, after that, they will

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1 go into normal patent submissions and be dealt with on this
2 basis, going through various committees that usually decide
3 what happens.

4 A VOICE: It takes a lot of time for industrial com-
5 panies to funnel the data. (Inaudible.)

6 MR. ARNOLD: Somebody else brought that point up and
7 I said, "What other sort of bombshells have you got hidden?"

8 Happily, we have almost completed the site business
9 at all testing facilities. There are half a dozen or a dozen
10 very small companies, on which we have toxicology data in our
11 files, that we haven't been to, but they are very, very small.

12 We've been to 70 or 75 testing facilities and, if
13 you haven't heard any comments about that testing facility, you
14 can pretty much conclude that we didn't see anything that caused
15 us to have a concern.

16 We have been, in general, satisfied in the way in
17 which tests were performed. It's an understanding kind of a
18 learning process. We learned that ten years ago people did
19 things differently than they do today. For me, I'm not a toxi-
20 cologist, so that's an enlightening thing for most people who
21 are concerned.

22 The vast majority of the labs we've looked at, the

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1 raw data records support the conclusions that were submitted
2 and that's all we can ask for, and that's all we expect.

3 There are several labs where we had questions, one
4 of which was IBT. So, obviously, we have dealt individually
5 with registrants where we had questions on that, because, to
6 our understanding, there is not another issue that cuts so
7 broadly across the chemical industry as Industrial Bio-Test has.

8 A VOICE: One more related question is every company
9 is developing data of their own. When are you going to start
10 checking on those studies?

11 MR. ARNOLD: You are questioning, now, the data
12 generated by the registrants. We have audited the registrants'
13 facilities that are identified as toxicology testing facilities.
14 There may well be resident labs -- fish and wildlife. We haven't
15 got into that level of review but, when we began the toxicology
16 data auditing program with the Food and Drug Administration,
17 our intent was to review all the laboratories which had sub-
18 mitted data to either EPA or its predecessors to form an evalua-
19 tion of how reliable the data base was for purposes of regis-
20 tration.

21 We didn't make a distinction between commercial labs,
22 company-owned labs and university labs. We've attempted to go

1 to all of them, but we started off with a laundry list of about
2 340 testing facilities and that's really cut down to about 90
3 that are still in business today and ones which, in fact, did
4 carry out testing or tests we were looking at.

5 We have been, as I said, very satisfied in the vast
6 majority of cases with the ability to square away the test with
7 the raw records. I suppose the reason that we haven't talked
8 about that is it is sort of like "no news is good news" when it
9 comes from us regarding lab audits. It's an internal kind of
10 validation. Our own ability to make decisions which was sug-
11 gested to us by the Congress. We've carried it out and we've
12 identified one or two situations where we want to take a harder
13 look. IBT is one. In the other cases, we don't intend to ask
14 for validations.

15 I guess that's a question that came up this morning.
16 When are we going to have to start validating our studies from
17 this lab and that lab? That's not going to be a standard prac-
18 tice for EPA.

19 A VOICE: (Inaudible.)

20 MR. ARNOLD: Those labs that we were trying to look at
21 with the Food and Drug Administration were good laboratory prac-
22 tice inspections.

1 A VOICE: Can I go back to the question on results of
2 validation studies on new submissions on a compound. Perhaps
3 there was a study that would not be valid but, in the overall
4 assessment, changed the profile of the compound and the compound
5 was up for new submission application. (Inaudible.)

6 MR. ARNOLD: The question, for those who didn't hear
7 it, deals with a study which could not be validated for whatever
8 reason -- either not enough data or the fact that it was deter-
9 mined that the study was really not appropriate for its pur-
10 pose -- and it is supported by a new submission and I think you
11 mean, there, perhaps a significant new use or a new tolerance.
12 Something other than a B-2 or a rather routine kind of action.
13 I'll let Dr. Dale speak to that.

14 DR. DALE: I'm not sure I got your question exactly.
15 The question was, as you put it, you've gone back over and have
16 found a study invalid but the total data didn't change your
17 toxicological profile of the product and you are coming in for
18 a new registration or a new use.

19 A VOICE: New use.

20 DR. DALE: Well, I would say, in my opinion, that it
21 would go under the new guidelines in that case and, if the study
22 was required, that you would do it again.

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1 MR. ARNOLD: I think, with the final passage of the
2 new law and the conditional registration and requirement the
3 administrators make of finding safety under the concept of
4 Commission (AUDI), that we really haven't sorted out how that
5 is going to fit in there.

6 The way you describe the problem, it sounds like you
7 could make a finding of safety because, basically, your entire
8 toxicological profile would be supported by other pieces of
9 information and you may, in fact, have a data gap, but the
10 registration process could proceed.

11 I think it's going to take a little bit of time to
12 sought out whether -- I don't think conditional registration
13 process is anything that is necessarily going to trip when IBT
14 comes up because the concept of conditional registration is that
15 you don't look at all the data base when you make the decision
16 on the conditionality.

17 There would be no way to identify the fact that there
18 is an IBT study in there. I'm just not sure how we are going
19 to try and fine tune that concept of conditionality with res-
20 pect to IBT.

21 A VOICE: The reason I brought up the question is
22 that, so far, (inaudible).

1 MR. ARNOLD: Well, I guess we cite a case in point.
2 that perhaps is analogous to your situation.

3 We have just reviewed the data base for a compound
4 that has pending registrations. The entire data base was
5 generated at IBT and the recommendations that have come from
6 the Toxicology Branch are that the registration action should
7 proceed in allowing the use of the compound, but that there are
8 data gaps that must be solved.

9 Basically, several of the chronic studies, we feel,
10 provided us with the majority of the information we needed con-
11 cerning the chronic toxicity, but they didn't meet the require-
12 ments to assess carcinogenicity.

13 So I think our policy is going to become involved
14 like that. If we're satisfied on the safety of the chemical,
15 we'll proceed, regardless of where the data comes from, but,
16 because it's an IBT test, it's going to be flagged and we're
17 going to take a harder look at the data base, but we have not
18 established the policy to hold it up merely because it's IBT.

19 In this re-registration process, we are going to come
20 up with a lot of reasons for data gaps and uncertainties that
21 are going to exist, and the concept was to try and proceed in
22 an orderly fashion and fill data gaps and not interfere with

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1 the ability to control pests and market pesticides.

2 A VOICE: I have a question that relates to the diet
3 stability studies that we've been asked to do. One can calcu-
4 late, with the protocol that has been suggested, that you could
5 end up doing several hundred or even a thousand analyses.

6 We're wondering if it would be acceptable to do a
7 "worst case" study first and then, if the chemical is stable
8 under those circumstances, to delete some of the other time
9 points and conditions of the protocol.

10 The worst case might be the maximum time -- I think
11 three weeks was the maximum time in the protocol. Two tempera-
12 tures -- pick the higher temperature, and go with that and
13 then, if the chemical is stable, not bother with the lower
14 temperature and the intervening time points that were recommended.

15 MR. ARNOLD: I would ask these gentlemen to comment
16 on that.

17 DR. PALLOTTA: Yes, It goes like from A to Z. Even
18 a chemist can tell you the compound's stability in many cases
19 and the other techniques might not be necessary but, in general,
20 if you have the raw data that indicates, for example, that the
21 protocol calling for a weekly separation, and the raw data in-
22 dicates as much as three or four weeks of supply before mixing,

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1 I think we need some type of data to support that the compound
2 was stable. I think it's a case-by-case condition we'll have
3 to look at.

4 DR. DALE: Here, again, it would be the compound in
5 question. If you questioned that the compound would, indeed,
6 be stable. If your data shows it was, say, a month or so be-
7 tween mixing and the very nature of the compound in question
8 -- the stability of it -- I would say do the minimum amount to
9 show that, in that period of time, it was stable.

10 A VOICE: (Inaudible.) Would you accept a statement
11 of the chemistry of the quality indicating it's stability or
12 submission of a residue data that we have that we actually used?

13 DR. PALLOTTA: I think the food components would be
14 absolutely necessary to do some analysis.

15 MR. ARNOLD: Stability in the diet that was fed. You
16 Oftentimes, we've found that the registrants had that informa-
17 tion because, in fact, they did work that led up to the test
18 protocol or that, as a result of doing similar kinds of tests
19 a number of times, they developed that background information
20 just to determine what the protocol ought to be.

21 If you have the information available that talks about
22 the stability of a compound in the test material, don't redo

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1 the test. If you have got it available already.

2 DR. DALE: Here, again, it would be case-by-case. If
3 you have data which implies stability, we can talk it over.

4 DR. PALLOTTA: The real concern about this came about
5 because of the large number of tests that did show that the
6 diet perhaps was not made weekly when the protocol called for
7 it.

8 A VOICE: Now, it's probably impossible to obtain the
9 actual diets. There were lots of diets that were used in these
10 studies. It seems to me that the difference between those lots
11 might be as great as the difference between a rat and a dog
12 kind of diet. So I'm just wondering if we can just go with one
13 diet. That's what makes sense to me.

14 DR. PALLOTTA: It seems reasonable.

15 MR. ARNOLD: I would think if the diet that was used
16 was not available or you can't reproduce that that, again, you
17 probably ought to air on the side of "worst case," whichever is
18 the diet which is least stable and utilize that because, if
19 that one provides total assurance that the test material was
20 stable in the compound, then I think everybody is satisfied.

21 MR. CLEGG: Can I pick up a comment on this, please.
22 I think, in general, the proposal you are making is reasonable,

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1 providing you know, in this particular instance, the fat con-
2 tent of the diet is similar in both cases. Otherwise I think,
3 particularly in relation to that, you may have to do both diets
4 or three diets or how ever many were used.

5 Again, of course, that's going to be on a case-by-case
6 basis depending on the type of compound. There, I can see a
7 complication.

8 MR. ARNOLD: It's getting about the lunch hour. How
9 about if we break until 1:30.

10 (Whereupon, a luncheon recess was
11 taken at 12:35 o'clock, p.m.)
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A F T E R N O O N S E S S I O N (2:00 p.m.)

MR. ARNOLD: I guess we might as well try and recon-
vene and push on with answering questions.

A couple of questions were asked during the lunch
break, one of which dealt with the microfiche and how it should
be submitted. I would prefer that we receive the microfiche as
the validation study comes in, rather than just a large bundle
of microfiche.

If you could submit the microfiche records attached
to the validation report, it certainly is the easiest way and
the least confusing. The least potential for getting pages
and data mixed up.

There is another point. I understand that it's diffi-
cult to make copies of the microfiche from the microfiche re-
cords that were provided to you by IBT. IBT has retained the
master copies from which copies can be made and they can do
that with a very quick turn-around. So, if you need copies of
it, you can contact, again, the Validation Assessment Group at
IBT rather than attempting to try to make copies from the micro-
fiche records you receive.

A VOICE: You mean copies of the microfiche or hard
copies of the microfiche?

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1 MR. ARNOLD: No. Copies of the microfiche.

2 A VOICE: Duplicates, in other words?

3 MR. ARNOLD: I'm not clear on the technology of how
4 you duplicate those but, apparently, it's very easy to do it
5 with the master copy retained by Bio-Test.

6 Are there additional questions or issues that may have
7 come up during lunch or areas that you would like us to elabo-
8 rate on from the manual?

9 A VOICE: Relating to your previous statement, in the
10 case of submitted validation audit reports which did not have
11 microfiche, can the microfiche come in as a bundle?

12 MR. ARNOLD: Yes. For any test that you have sub-
13 mitted, in those instances where we started going through the
14 validation reports and we haven't seen the microfiche, what
15 I've been doing is calling up the sponsors and finding out
16 whether it's available in many cases or, in some cases, the
17 registrants had the records prior to their production of the
18 microfiche and that was the basis for the validation and that's
19 why I think they came in absent the microfiche but, now, if the
20 validation has been submitted and you have the microfiche, I
21 would appreciate it if you could just send it in and we'll go
22 ahead and line it up and attach it to the appropriate study.

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1 Try and keep it in individual packages so that we
2 don't have to burn our eyes out trying to make them match.

3 A VOICE: Would you, or somebody on this panel, be
4 specific about the type of tests that you have validated now?
5 (Inaudible.) Could you tell us just which ones are validated?

6 MR. ARNOLD: In our first communication with the
7 registrants regarding IBT, we identified there were three
8 general aggregates of tests that we were potentially concerned
9 about.

10 The first were the tests in support of tolerance pe-
11 titions. The second, I believe, were studies submitted in
12 support of registrations for products with home uses; and the
13 third was everything else.

14 We are interested, now, in the tests which support
15 the tolerance petitions. The ones cited in the tolerance peti-
16 tion. I'm not sure this includes everyone, but it includes at
17 least chronic feeding, reproduction, teratogenicity, oncogeni-
18 city and metabolism studies, as well as all neurotoxicity
19 studies. Those are

20 Those are the only ones, at this time, we have re-
21 quested a validation on except for the questions that have come
22 up in the registration process which is anything dealing with

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1 IBT that is currently being put forward to the Agency.

2 At this time, we don't anticipate going into the
3 second and third categories as an all out request for valida-
4 tions. We may, in the registration process, pose individual
5 questions on data gap, but we're not asking for audit of all
6 those studies at this time.

7 MR. CLEGG: May I just pick that one up a minute.
8 We have a slightly different approach in this respect. Cer-
9 tainly the group of types of studies which Fred indicated are
10 required by Canada and, in addition to that, we are also in-
11 terested in those which relate to the environmental aspects of
12 the use of pesticides and, therefore, we have requested or re-
13 quired validation of some of the dermal and inhalation studies
14 specifically, so that we can get some feel for the potential
15 problems with operator exposure, applicator exposure, formulator
16 exposure, even manufacturing exposure.

17 So we have got a request out that dermal and inhala-
18 tion studies should be validated, whether they are IBT studies,
19 where there are no replacements available.

20 MR. ARNOLD: We have not been able to make as thorough
21 review of our records as Mr. Clegg has. He was able to go
22 through and identify these studies from Industrial Bio-Test

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1 which didn't have a correlated study from a different lab. So
2 he was able to do a better job of targeting the ones that were
3 of unique significance to him.

4 Our policy was to take a cut on the ones upon which
5 we made findings for -- safety findings in the tolerance area
6 and deal with any additional validations on an as needed basis
7 in the re-registration process which they don't have ongoing.

8 A VOICE: I'm asking this question because we received
9 all the reports which were to be validated. (Inaudible.)

10 MR. ARNOLD: This question came up a number of times
11 and I think we dealt with -- probably every registrant received
12 a letter because our records are not 100 percent accurate and,
13 at times, we referenced tests which, in fact, perhaps, a re-
14 gistrant had not been the sponsor. So we did not refer to tests
15 which were critical but which our records didn't make the link
16 between sponsor, an active ingredient and the laboratory, and
17 that's basically the mesh that we've got to do to identify in
18 problem areas.

19 I think, at the outside, our records are about 80
20 percent accurate in terms of being able to do a quick recall of
21 that -- a computer search -- without actually going through
22

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1 all the data within rifle range, which we haven't done.

2 It will happen at some point in the future, but I
3 don't intend to initiate anything like that right now.

4 A VOICE: Will it be necessary for the sponsor to
5 account for each and every animal on study in the form of wet
6 tissues and tissue blocks?

7 DR. PALLOTTA: Well, we understand that IBT does have,
8 or has near completion, the inventory on all the wet tissues and
9 slides and blocks.

10 A VOICE: Then EPA will accept that as the inventory
11 that exists and that could become a part of the validation,
12 then, for any particular study -- that inventory?

13 DR. PALLOTTA: Yes.

14 MR. ARNOLD: The only need to be able to identify the
15 length of tissue and blocks back to the individual animals
16 would be if the validation effort suggests the study by itself
17 is incomplete without reperforming certain pathology or recutting
18 new tissues which would provide more information, perhaps leading
19 to a valid study.

20 In that case, you would have to be able to make the
21 link but, unless you intend to pursue that additional work, we
22 don't intend to get into pathology.

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1 DR. PALLOTTA: The only concern we have, there, is
2 that, in a vast majority of the pathology reports we have re-
3 viewed, the pathologist failed to indicate that the tissue was
4 actually read as called for by the protocol and, in reviewing
5 slides against blocks, we had some difficulty in missing tissues.

6 ARVOICE: Unless you can validate that the animal
7 received a given concentration of diet, you can't correlate it
8 with the tissue.

9 MR. ARNOLD: That is precisely the reason that we
10 didn't suggest that everyone go to the level of examining patho-
11 logy material because, unless you first do the review of which
12 animals you can describe the circumstances and tests on, there
13 is no sense attempting to check pathology.

14 One of the problems that Art points out -- a problem
15 that you may encounter if you go to pathology -- is that -- I'll
16 state it as a layman and perhaps state it succinctly.

17 The the test protocol may have suggested that five
18 organs were going to be examined but that, in preparing the
19 blocks and slicing the tissues, some of the pieces of organs
20 were imbedded further in the paraffin and you only get three
21 organs on the slide. That's why it was impossible to ever
22 examine the other two organs which the protocol might have

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1 suggested and, in our review of the study five years ago, the
2 lack of a organ would probably have been determined as "no sig-
3 nificant finding" when, in fact, the truth of the matter is the
4 organ was never examined.

5 That's a problem that I think you will encounter and
6 that's the issue that we were raising on the concept of tissue
7 accountability.

8 Slides may suggest to you that, in fact, tissues
9 could not have possibly been examined because the blocks were
10 incorrectly prepared and we certainly need to know that. I
11 think that your review of the pathologist's notes, if you find
12 that the protocol calls for an examination of a particular
13 tissue and there are absolutely no notes relating to that
14 tissue, it may well be the tissue was never examined rather
15 than it was examined and nothing was noted.

16 DR. PALLOTTA: Again, I should reemphasize that should
17 only be done on those animals that you can account for in the
18 audit trail.

19 A VOICE: I suppose this brings up another question
20 in my own mind on the audit trail and that is, if, in a study
21 that was designed to determine the incidence of tumor from a
22 particular substance, you have specifically identified animals

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1 going into the study -- and let's just take the worst possible
2 case -- there is not information inbetween but, at the end,
3 these animals are, again, identified and there are tissues
4 identified with those specific animals.

5 Let's just say, for hypothetical purposes, that the
6 diet formulation was present in the raw data and that you could
7 be confident, to some extent, that the diet was mixed and ad-
8 ministered to the animals. So, in effect, what you have is
9 animals going in and tumors coming out or the lack of tumors,
10 whatever.

11 MR. ARNOLD: But no body weights, no observations in-
12 between?

13 A VOICE: No body weights. None of those kinds of
14 observations.

15 DR. PALLOTTA: Obviously, these are the extra animals
16 that we were referring to before.

17 MR. ARNOLD: The potential exists for the extra ani-
18 mals.

19 DR. PALLOTTA: If there is some evidence of these
20 animals having been fed the experimental compound, even though
21 they were gang caged and records were not kept as to say, for
22 example, body weight, but were used to replace animals that

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1 died during the study, and you are confident, by any type of
2 record, that this animal can be tracked as having received the
3 experimental diet, that animal we do want reported on.

4 MR. ARNOLD: Let me restate your situation. I think
5 you said the situation might be that you have evidence that the
6 study started with a certain amount of animals; you have evi-
7 dence that that diet was prepared; and you seem to think that
8 the diet was stable. Then the next thing you know about is
9 some histopath report and you have nothing inbetween. You just
10 know you started with some animals, you ended with some animals
11 -- about the right number in there -- and you don't know if
12 there was any switching around inbetween or what might have
13 happened inbetween. Now what's the answer?

14 DR. PALLOTTA: Frankly, I think that has to be a case-
15 by-case because, if you do have some records that indicate that
16 these animals were, indeed, fed the experimental compound --
17 if you don't, there's no audit trail; if you do, then you have
18 to state it as such.

19 The use of extra animals, per se, is not, in itself,
20 an invalidation of the study, as long as those animals are re-
21 ported out on. If you have data on them, report them out.

22 The problem is that in many of the IBT studies, they

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1 started with 80 animals and the reports came out with 50 ani-
2 mals and the implication was that they started with 50 animals
3 and ended with 50.

4 They used these extra animals and, if you could iden-
5 tify these animals and they were fed this material, then report
6 them out the way it should have been in the first place.

7 MR. ARNOLD: I think, in the situation you described,
8 you are basically saying you have no information on body weight,
9 no observations made of the animals over the term of the test,
10 no autopsy sheets, no information.

11 I think that, under the guidelines that we've kind of
12 developed, that, basically, is a study that is not going to be
13 -- you're not going to be able to validate that study and say
14 it serves and suffices. It may well provide information which
15 is useful in an interim kind of a thing but, fundamentally, the
16 kinds of information that we're are missing would be the ones
17 that are precisely associated with the problem we are most
18 concerned about -- the conditions of the test during the study.

19 MR. CLEGG: I think one of your major problems with
20 that is, if you started with 80 animals and the report indicates
21 50 all the way through. I'd love to see how you are going to
22 go about sorting out your mortality rate. You're going to find

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1 it exceedingly difficult. We are trying to do it and we can
2 get some sort of estimate but really how valid that is, I wouldn't
3 like to even guess at this point in time. So I think that's
4 going to be your stumbling block. Straightforward mortality
5 data as to what happened, how many died, where and when.

6 A VOICE: What would, in a situation like this, inter-
7 view with technicians who are running these studies have as to
8 whether or not 80 animals were started and 50 finished? Would
9 this have any usefulness in an audit report?

10 MR. ARNOLD: I think, if you had nothing else other
11 than some technicians report that that's what they did, that's
12 not going to suffice by itself.

13 MR. CLEGG: I'm not quite so sure as Fred is on that
14 one. I think, probably, if you got a notarized statement that
15 was sworn to that 80 animals were started on that by the tech-
16 nician, then I think we could ignore it.

17 MR. ARNOLD: I didn't suggest ignoring it, but don't
18 think, by itself, it is going to convert a study which is in-
19 valid in the sense of not being able to describe a number of
20 key parameters to one which is fully acceptable and doesn't
21 need to be repeated.

22 DR. PALLOTTA: If that could be used to support an

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1 assumption you are making, I think that would be very valuable.

2 A VOICE: I have read reports that never mentioned
3 extra animals being started. Toxicologists then admit that it's
4 common practice. Now, when you audited these 90 labs or 300
5 labs or whatever you ran, did that mean that you found no cases
6 where other labs used extra animals and didn't report it.

7 DR. REISA: (Inaudible.)

8 MR. ARNOLD: Let me summarize. It was a common prac-
9 tice to start extra animals because of the problem of acclima-
10 tion to cage conditions. So that, several weeks into a study,
11 if there was mortality, the animals could be replaced and the
12 chronic study was not compromised but, as Diana pointed out,
13 the distinction between what one lab did and another, in our
14 concern about IBT, is the fact that the animals stayed around
15 for a long time and were replacing dead animals, rather foreign
16 to the study, and then, in the instance of the replacement,
17 oftentimes, we didn't know whether the animal had been on the
18 test compound or not.

19 So, all of a sudden, you no longer have a regime of
20 animals which you know something about in terms of their ex-
21 posure to the test compound. We certainly did encounter the
22 practice of having extra animals to solve the problem because

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1 of problems with their acclimation to their test conditions.

2 MR. CLEGG: Under these circumstances, you usually
3 have a cut-off period in which those animals can be added into
4 the study and in a number of recent protocols that I have come
5 across, you find that this is usually around one month.

6 After one month, it is not normal practice to add
7 animals into a study. Up to that point, provided he is duly
8 recorded, then I think it is acceptable but, once you've gone
9 beyond that, normally, no.

10 A VOICE: In cases where you identify introduction
11 of extra animals, would these extra animals have the same number
12 as the original animal?

13 MR. ARNOLD: That depends on the animal numbering
14 techniques. I'll let Art answer that.

15 DR. PALLOTTA: We've seen all types. Where they just
16 use the same number as the animal which died. I think you will
17 come across all extremes, if you have enough tests to review.

18 MR. ARNOLD: One of the problems that you may run in
19 to is the fact that, either during some period or some particu-
20 lar research, a practice was followed of numbering the animals
21 after the test was completed. The animals were not identified
22 during the test. They were identified at the termination of

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1 the test in a first-in numbering kind of concept.

2 There is a cage identification and then a post-study
3 identification. Therefore, the presence of an animal during
4 the middle of a study doesn't necessarily jump out at you until
5 you examine all the records.

6 That's why I suggested it's a bit of a problem if you
7 happen to have a test where the numbering system was the one
8 that was created after the test rather than at the beginning
9 of the test.

10 A VOICE: I was wondering if the EPA or the health
11 protectors had found, in their audits, that the general health
12 of the animals, not related to the chemical treatment, would
13 invalidate any studies?

14 MR. CLEGG: I think the only answer you can give to
15 that is the one that Art just muttered. It probably came over
16 the microphone.

17 It depends on your survival rate at the end of the
18 study and also depends on the purpose of the study. Obviously,
19 if you only end up with five percent survivors, then it's very
20 likely to invalidate the study.

21 A VOICE: Has that been a problem in the studies which
22 you have received?

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1 MR. CLEGG: We have come across it in some of them,
2 yes. Particularly in the rat studies, as far as I'm concerned,
3 and the mouse -- in both.

4 A VOICE: Now the auditors will have to make some
5 judgment of their own, I presume, about the health of the
6 animals as to the validity of the study, but is there any
7 criteria which would -- do you care to comment on any criteria
8 about the health of the animals in terms of longevity, in terms
9 of how they survive the study, their general health?

10 MR. CLEGG: There are comments one could make on that
11 but I think the only way you could handle this is on a case-by-
12 case basis. I think to give a general comment would be asking
13 for trouble. Quite rightly, too.

14 DR. PALLOTTA: I think I can give you an example of the
15 difficulty you are going to have. In one two-year, 400 animal
16 study we did audit, there were 14 entries about health on the
17 400 animals for two years -- 14 entries.

18 MR. CLEGG: If we're talking about the same study,
19 about 65 percent mortality.

20 A VOICE: Pursuing that a little further, let's take
21 an instance where survival is good but we have an incidence of
22 CRD that's been 80 percent mortality -- an oncogenicity study

ON 2 5

1 or a toxicity study -- in your opinion, is that a validated
2 study, if you've got good survival, you've gone the duration,
3 you've got all the parameters you are supposed to be looking it,
4 and you've tested for oncogenicity?

5 MR. CLEGG: I'm not sure I quite follow what you are
6 getting at.

7 A VOICE: The idea of an endemic disease in validating
8 a study which is designed to test oncogenicity and climatisicity,
9 we go a certain period, let's say, in a rat two years, or 18
10 months in a mouse, and the fact that you have endemic disease
11 is indicated by pathology in the lines such as CRD, is that
12 going to be an overwhelming factor?

13 MR. CLEGG: I can only answer that for Canada, in this
14 point in time, because it is one of the things we haven't disc-
15 ussed jointly. My own reaction to that would be it would be
16 highly improbable it would be a validated study.

17 I can think of certain circumstances where it might
18 and that is where you chose lung. Usually, under those sort
19 of circumstances, I would think it would not but, on occasion,
20 you can get lesions in liver from endemic disease and in kidney,
21 which would tend to mask any toxic effects of the compound you
22 might be looking at.

1 Then, under those circumstances, you may possibly
2 run into trouble in having this study invalidated but this
3 would depend upon what was found in the target organ in the 90-day
4 studies which, presumably, would also be available. Do you
5 agree?

6 DR. PALLOTTA: Yes.

7 MR. ARNOLD: Are there additional questions or have
8 we answered everything sufficiently?

9 A VOICE: If a study has not been submitted yet -- say
10 a 90-day -- that would have to be validated in the normal course
11 of the terms. I break validation into two sections. One would
12 be an audit where you just turn raw data in before the valida-
13 tion or scientific validity of the study.

14 Now, if it's never been submitted, when it is sub-
15 mitted, it would have to be reviewed by EPA's toxicologists
16 anyway. Is there any sense in the registrant paying someone
17 to validate a study when it has to be validated again to be
18 acceptable? That could be a large amount of money.

19 MR. ARNOLD: Well, I think this concept of separating
20 an audit from a validation is kind of artificial because, basi-
21 cally, the validation relies upon the audit. You get the raw
22 records. Now, we don't normally do that, as you are aware, on

1 studies routinely submitted to the Registration Division.

2 In the case of new IBT studies, we have requested
3 that the registrants submit an audit report, which is the raw
4 data supporting the conclusions that are in the report. As far
5 as I know, IBT reports are still reaching scientific conclusions.
6 They are just not attested to by signature, but they are still
7 reaching conclusions.

8 We need to see the underlying data for that and we
9 request that the registrant provide that data in a manner in
10 which we can judge the validity of it.

11 So I'm not sure I can appreciate the distinction you
12 are making between validation and audit.

13 A VOICE: The problem is this, some of the toxicolo-
14 gists would audit a study and do a damned good job of it. He
15 could not, under what I've seen, validate that study because
16 he doesn't have the qualification.

17 Now, somebody would have to audit that. Would audit
18 a document and send it to EPA and they have to review it anyway
19 to see that it is scientifically sound. Yet, if it is something
20 that has already been submitted to EPA previously, it would
21 also have to be validated before it was sent in.

22 MR. ARNOLD: I now understand your distinction. Dave

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1 has pointed out that this concept of a doctorate and non-doc-
2 torate is not a key to whether somebody can validate, but I
3 still think the point is somebody who is qualified, regardless
4 of whether they are a doctor or through experience or whatever.

5 Diana has a comment to make and perhaps that would be
6 the most enlightening.

7 DR. REISA: (Inaudible.)

8 MR. ARNOLD: Let me repeat it. I think I caught about
9 50 percent of it but it sounded like a reasonable way to pro-
10 ceed.

11 The audit process basically defines how much raw data
12 there is and, if that audit process comes through with all the
13 data to support the conclusions that are in the report, that's
14 all we need and we will review that report just like we would
15 any other report, except we will have the confidence that,
16 in fact, it is reflective of what happened in the laboratory.

17 Now, if, in the audit, it turns out that the raw
18 data doesn't support the conclusions -- there are either dif-
19 ferent conclusions, different mathematical determinations, of
20 an effect level or an LD-50 or, if in fact, there are fewer
21 animals to reach conclusions on than might have been represented
22 in the report, -- at that stage, then, the registrant would have

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1 to proceed with reaching some new conclusions, and those con-
2 clusions ought to be reached by somebody who is qualified to
3 do it, just like you would with any other submission.

4 The submission should be based upon somebody's ability
5 to reach a conclusion. So, if all the raw data is there, you
6 send it into us and we can then proceed with our evaluation
7 of the data.

8 A VOICE: I have one. I understand, at the present
9 time, there are three levels of priority in relationship to
10 validations of IBT.

11 Those materials where petitions have already been
12 filed, materials of marketing products; those where the peti-
13 tion has been filed but is not a marketed product; and those
14 where a petition has not been filed.

15 Now, in order for us to move along with some of these
16 validations and audits and get assistance out of the Validation
17 Assessment Team, I would like to have some direction from you
18 to the people at IBT on how they move along with those materials
19 that are in categories two and three, where the petition has
20 been filed and it's not a marketed product, or the material has
21 not yet been filed and we are awaiting the petition.

22 MR. ARNOLD: Yes, sir. I think you have probably hit

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1 on an area where I think our basic interests are probably going
2 to drive us to a different set of priorities.

3 From our point of view, our primary concern is the
4 public health consequences of the decisions that we make. The
5 fact that we have a petition pending creates a problem in that
6 we are not going on with the registration of pesticides which
7 the law requires that we do but, by the same token, we haven't
8 created a public health question in the concept of exposure to
9 the pesticide.

10 On the other hand, those that we have made decisions
11 on and that are rather far-reaching decisions, our instinct is
12 to concentrate on those because there is a potential for a prob-
13 lem and, if there is, we would just as soon identify it early
14 and try to take some remedial action either by requesting new
15 tests or, in the event of a determination of an adverse effect,
16 some regulatory action.

17 I think probably, from the point of view of the regis-
18 trants, the ones on the market are going to rise or fall in the
19 long run on the basis of the data that comes out of the audit,
20 but the new ones where you have exerted research and development
21 efforts and money and aren't getting on the market, my impres-
22 sion is that that's where the registrants want to concentrate

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1 the validation efforts, first, so that they can get on with the
2 normal marketing of pesticides.

3 We haven't, as yet, given IBT a direction to concen-
4 trate on of one type or another simply because there was no way,
5 in their creation of the microfiche library, that they could
6 have proceeded other than just to do 100 percent of it. There
7 was no way to do a little bit here and a little bit there, and
8 that's why we have kind of all been standing around waiting
9 while they could finish that first task.

10 Now, in the meeting with the Validation Team to answer
11 the final questions, they have indicated that they will be
12 responsive to the needs of EPA and Canada. Our first response
13 is to deal with the chemicals where we have a major reliance on
14 IBT data in the past.

15 However, we have already gone through a data base for
16 a compound that has been sort of sitting and churning in the
17 registration process for some time now. Lacking a rather strong
18 and compelling argument from a registrant, we are continuing to
19 try and concentrate on those pesticides that are on the market
20 for which the major or the entirety of the data base has been
21 generated from IBT and we have requested that the registrants
22 use a similar kind -- I think, in the second letter that came

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1 from Ed Johnson, we gave you, basically, a description of the
2 kinds of factors we would use for creating a priority and sug-
3 gested that you do the same.

4 There is no way that we can demand it but, certainly,
5 our priorities are the high tolerance, high volume pesticides
6 where the entire data base is with IBT.

7 A VOICE: It doesn't solve the problem.

8 MR. ARNOLD: No, it doesn't. I said that's why I
9 think we have probably come to an impasse.

10 A VOICE: What I am suggesting is that perhaps, over
11 the next six months, you have the immediate problem of working
12 with the Validation Team on the marketed products -- public
13 health products -- and then, those (inaudible.) But it seems
14 to me, as time permits, they should then deal, particularly
15 where some of the issues are rather minor as in the case of
16 some of the newer products, that they try to get those out of
17 the way.

18 Let's say, for the purpose of the discussion, you
19 have a 90-day study and, for one reason or another, you don't
20 even have the requirement for a two-year study on that particu-
21 lar material, the issues are much smaller than if you are
22 looking for data on multigeneration or reproduction and the

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1 investment in time of the IBT personnel will also, corresponding-
2 ly, be rather small.

3 So, what I'm suggesting is that we do appreciate the
4 immediacy to get on with those products that are on the market
5 but you ought to, then, be in a position to have some direction from
6 you to the people at IBT, as time permits, to work some of
7 these others in.

8 MR. ARNOLD: Certainly. We've been assured, and I
9 think we are all convinced, of the sincerity of the fact that
10 IBT will continue to exist for as long as it is required to
11 complete the validation effort, regardless of what happens to
12 the sale of the assets.

13 If we weren't convinced of that, we would certainly
14 be suggesting to the registrants that they push an ownership
15 on that data and we might even be considering something to pro-
16 tect the integrity of our own decision-making process which,
17 at this time, pretty much relies upon all the underlying data.

18 We've had very good cooperation, I think, to date with
19 IBT and I think we recognize the problems they went into trying
20 to pull together some sense out of 20 years worth of record-
21 keeping, and I keep my fingers crossed.

22 I think we are very close, now, to the point of

1 saying, "This is as good a record system as you are going to
2 get." We might not be satisfied with them, but there is no
3 more, and we should get on with it and I'm convinced with their
4 sincerity in trying to resolve any unanswered questions and,
5 certainly, we will continue to try and provide some direction
6 to the registrants and particularly to Industrial Bio-Test as
7 they schedule visits.

8 Now, they are attempting to schedule visits on a
9 chemical in line with our requirement or our needs to review a
10 chemical rather than an individual test. So, when an audit is
11 scheduled, they requested that we keep in mind the data base for
12 a particular chemical and try to estimate the time required to
13 get through that body of tests, and each chemical is going to
14 be unique. So there might be several long-term tests that could
15 require a fair amount of discussion. Others could have a number
16 of less complicated tests and ones with, perhaps, a better data
17 base that can be reviewed rather quickly.

18 They have indicated their willingness to be flexible
19 and concentrate on this chemical rather than tests reviewed.

20 I think the registrants are in the same position as
21 us in trying to construct a data base for a chemical rather than
22

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1 for an individual test.

2 A VOICE: At the start of the meeting, you mentioned
3 that there were some 45 studies that the people in Canada had
4 audited. You gave kind of a percentage breakdown on how many
5 were valid and what kind of questions came up and those not
6 completely valid, and then you mentioned the concern of the EPA
7 was based on 12 studies which had been audited jointly by the
8 EPA and the FDA plus a build-up of information from registrants
9 as they had asked for validation of studies from the EPA.

10 Could you give us an idea of the number of studies
11 that would be and what the breakdown would be there in terms of
12 the data that has been reviewed by the EPA?

13 MR. ARNOLD: Let me state that the 12 studies that
14 were looked at were not a random cut of all the studies that
15 were done. We concentrated on the chronic studies and that just
16 happens to be the area that we think the greatest problem is
17 probably associated with.

18 So, if we make a statement that we looked at 12 studies
19 and we didn't find any that were entirely acceptable and we
20 found X number that were invalid, that is certainly not repre-
21 sentative of what might be out there.

22 I will let Art comment further, but keep that in mind

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1 that ours was not a random cut.

2 DR. PALLOTTA: I hope you understand that our audits
3 were audits that were performed at IBT that were intended only
4 to give us an idea of how severe the problems were and approxi-
5 mately in what areas, and so forth.

6 They were not to validate studies. They were to get
7 a better understanding of the problems and I think that ought
8 to be very clear. They were selected studies in that sense.

9 MR. ARNOLD: As far as the conclusions which we have
10 reached from reviewing registrants audits, I, unfortunately, am
11 a little derelict. I didn't do that kind of a head count that
12 Dave did before he came down and I just don't have the informa-
13 tion. I am attempting to assemble it now.

14 Part of the problem is our two-phase approach to it.
15 The one that we have asked specifically for audits and the other
16 ones that have been caught up in the Registration Division and
17 I'm having a hard time getting a count of exactly what is coming
18 into the Registration Division.

19 They are going to start, hopefully, keeping me informed
20 of what's going on. I don't want to get in the middle of it.
21 All I want to know is who has asked for what and what they have
22 received, so that we can make the most intelligent decisions on

1 this.

2 Dave just pointed out, I did mention that copies of
3 the IBT formal conference procedures are available at the back
4 desk. If you haven't received those, they outline the proce-
5 dures which IBT will be working under in assisting you in re-
6 solving unanswered questions after you have reviewed your micro-
7 fiche. So you might pick a copy of that up and begin to kind
8 of work within those guidelines because I think, at this time,
9 they don't have a lot of resources to expend and they are trying
10 to figure a way that will most satisfy the registrants plus will
11 allow them to do it in as timely a fashion as possible.

12 MR. CLEGG: I would just like to come back, if I may,
13 to the question with regard to the number of studies which have
14 been looked at.

15 I would emphasize, again, that the number we have
16 looked at is very small and, therefore, to put any sort of
17 statistical analysis or anything else on to the number we have
18 looked at, with regard to the number which may or may not be
19 found to be valid in the future, is not a very wise thing to do.

20 The idea, as far as we were concerned, was just to
21 find out approximately what percentage may be invalid and, at
22 the moment, we are running somewhere just over 80 percent, but

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1 that does not mean that this is going to continue to be the
2 case.

3 There was no particular selection of studies. We just
4 took them as they came in and looked at them and they are not
5 particularly going in any one particular direction. So, if you
6 are looking at chronic, as Fred indicates, I suspect that you
7 will find there is a higher incidence of invalid studies. ~~On~~How-
8 ever, if you are looking at, let's say, 90-day dog studies, then
9 the probability is you are not going to find many of those which
10 are invalid. In fact, I don't think we've found any so far,
11 but then we've only gone through four or five.

12 A VOICE: On these validation packages, how many, per-
13 centagewise, have been found unacceptable when they are sub-
14 mitted to be validated?

15 MR. ARNOLD: I can't really answer that question. Let
16 me explain what we have done to date.

17 Almost all of the validation packages that have come
18 in, individuals have brought them into the office and we've sat
19 down and we've started going through them and, in almost every
20 instance, we've offered some suggestions, they've offered some
21 comments and they've gone back.

22 So we have been receiving almost draft validation

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1 reports and only in a very limited number of cases have we re-
2 ceived final validation reports on those 640 tests that we asked
3 about a year ago.

4 The ones that we have received -- in fact, if I'm not
5 wrong, Arthur, I think we've been quite satisfied with the qua-
6 lity of the validation work. I mentioned earlier in the morning
7 that we found no validations that were entirely consistent with
8 the raw data and, also, that the errors are kind of random and
9 I don't know whether they are significant or not.

10 I only raised it because, when that happens, if we're
11 in a spot-checking kind of procedure, spot checking, calcula-
12 tion and looking at a diet prep, and we start to see errors in
13 there, they are just going to slow it up, even small errors.

14 Large errors, if we are spot checking, the errors are
15 going to cause eyebrows to raise and then we are going to have
16 to get into it a little deeper.

17 So, to avoid that, I just said that the first effort
18 ought to be as good an audit as you can make, recognizing these
19 things can really burn your eyes out and it's awfully difficult
20 to make these linkages, but to be as careful as possible.

21 We've been quite satisfied with the quality of the
22 validation reports we've been receiving.

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1 A VOICE: If the validation has not been reviewed by
2 EPA for any reason, you could go for a year and get 20 valida-
3 tions and then you are doing something wrong that you had no
4 idea you were doing wrong and you'd never be told. You would
5 have done all this work and then you would have to redo it.

6 MR. ARNOLD: I think that's the reason why most of
7 the registrants -- and I think we have met individually with
8 at least six or seven different people in the room to date to
9 review early on what they were doing, to see if they had answered
10 the questions we want answered and, in all cases, when we sug-
11 gested that we need more information and to put less reliance
12 on something, the suggestions were taken.

13 I think we have now got down to a point where we can
14 offer a format for a report that we think, one, is useful from
15 the registrants point of view, and useful from our point of
16 view. Six months ago we couldn't have done that.

17 We could have because I should say, often, EPA issues
18 kind of interim guidelines and regulations. We didn't want to.
19 We're still willing to work with registrants.

20 If you have questions on whether or not a procedure
21 appears to be an appropriate procedure, by all means come in and
22 ask us and we'll offer whatever guidance we can.

1 MR. CLEGG: Two things I would like to add to that
2 before the next question comes up.

3 First, in terms of the validations we have looked at,
4 as Fred said, we have found errors in them. I would like to
5 indicate, straight away, that the errors do run both ways. They
6 are not all errors in favor of the compound. Some were errors
7 which were against the compound.

8 The way we have dealt with these is to go to to raw
9 data and do our own validation and then compare them with the
10 industry validation. That's the routine we have been using to
11 date. Whether we will continue that way, I'm not sure.

12 Also, on some occasions, people who have done the in-
13 dustry validations have picked up some of the things we've
14 missed. So I think it is a case of genuine errors and nothing
15 other than that. I would like to make that point very clear.

16 The other thing, which relates to the receipt of vali-
17 dations and the possibility of having a 12-month time gap before
18 a validation is looked at, I think this morning there was a
19 little confusion over this and I'll try to clarify it by indi-
20 cating that, in fact, when we have the raw data and the valida-
21 tion, these studies will be looked at.

22 It is the overall assessment of the compound which

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1 will be delayed in time until we have the total data base.

2 So, if we find something which is completely unacceptable,
3 with regard to the format or what-have-you of the validation
4 coming in, I think the probability is that whoever submitted
5 that particular validation is going to hear about it in fairly
6 short order.

7 In fact, if I can exemplify this, we have one firm
8 who came in, who sent in some validations and they sent in some
9 microfiche within 48 hours. I phoned them and said, "Look,
10 these microfiche are completely illegible. They were rather
11 startled. They reply I got from them was, "God, we didn't ex-
12 pect you to ever look at that raw data."

13 DR. PALLOTTA: I would like to also comment once more
14 that, on that sample report format that was handed out, that is
15 one way in which you can speed up the process yourselves by
16 following that format.

17 There will be inconsistencies and it will help in the
18 task force, both in Canada and the U.S.A., to get the job done.

19 A VOICE: (Inaudible.)

20 MR. ARNOLD: Let me just repeat that. You are sug-
21 gesting an old study was submitted and now you have a one-page
22 correction to that old study. The question is, do you submit

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1 just a page or two pages?

2 MR. CLEGG: That's quite acceptable. We've agreed
3 because, in fact, some companies have submitted audits and
4 validations and then have received additional information from
5 IBT. So we will accept amendments and changes to audit valida-
6 tions and to the data base which is involved in this, if neces-
7 sary.

8 MR. ARNOLD: This is a case where there is a page
9 changed in the final report. Not additional data to support a
10 conclusion, is that right?

11 A VOICE: Yes.

12 MR. ARNOLD: Well, it looks like we have either ex-
13 hausted our ability to answer questions or your ability to ask
14 them.

15 I will continue to try and work on a one-on-one kind
16 of capacity with you and you have the assurance from IBT that
17 they will be responsive to your requests for the status of the
18 microfiche and if, again, it appears you are not getting an
19 answer or you can't quite understand the status of your micro-
20 fiche, I wish you would raise that with me, so I could perhaps
21 go back to Bio-Test and find out specifically, because we do
22 want to begin moving on with this and I think there is just a

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1 natural inclination on everyone's part to avoid approaching
2 those studies for which there is no data. So we should be in
3 a position to find that fairly soon.

4 Thank you.

5 (Whereupon, the foregoing hearing was
6 concluded at 2:45 o'clock, p.m.)
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I, Elizabeth Ann Tipton, do hereby certify that the foregoing proceedings were taken stenographically by me and, thereafter, reduced to typewriting by me; that said transcript is a true and accurate record of the proceedings to the best of my ability.

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