

1 FOOD AND DRUG ADMINISTRATION CENTER FOR
2 BIOLOGICS AND RESEARCH

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9 ALLERGENIC PRODUCTS ADVISORY COMMITTEE

10 TELECONFERENCE

11 (Open Session)

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18 8800 Rockville Pike

19 Bethesda, Maryland

20 March 24, 1998

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1 PARTICIPANTS:

2 JOHN W. YUNGINGER, M.D.

3 WILLIAM FREAS, Ph.D.

4 NANCY SANDER

5 TE PIAO KING, Ph.D.

6 DENNIS OWNBY, M.D.

7 BETTY WRAY, M.D.

8 HENRY N. CLAMAN, M.D.

9 ANDREW SAXON, M.D.

10 CAROLYN HARDEGREE, M.D.

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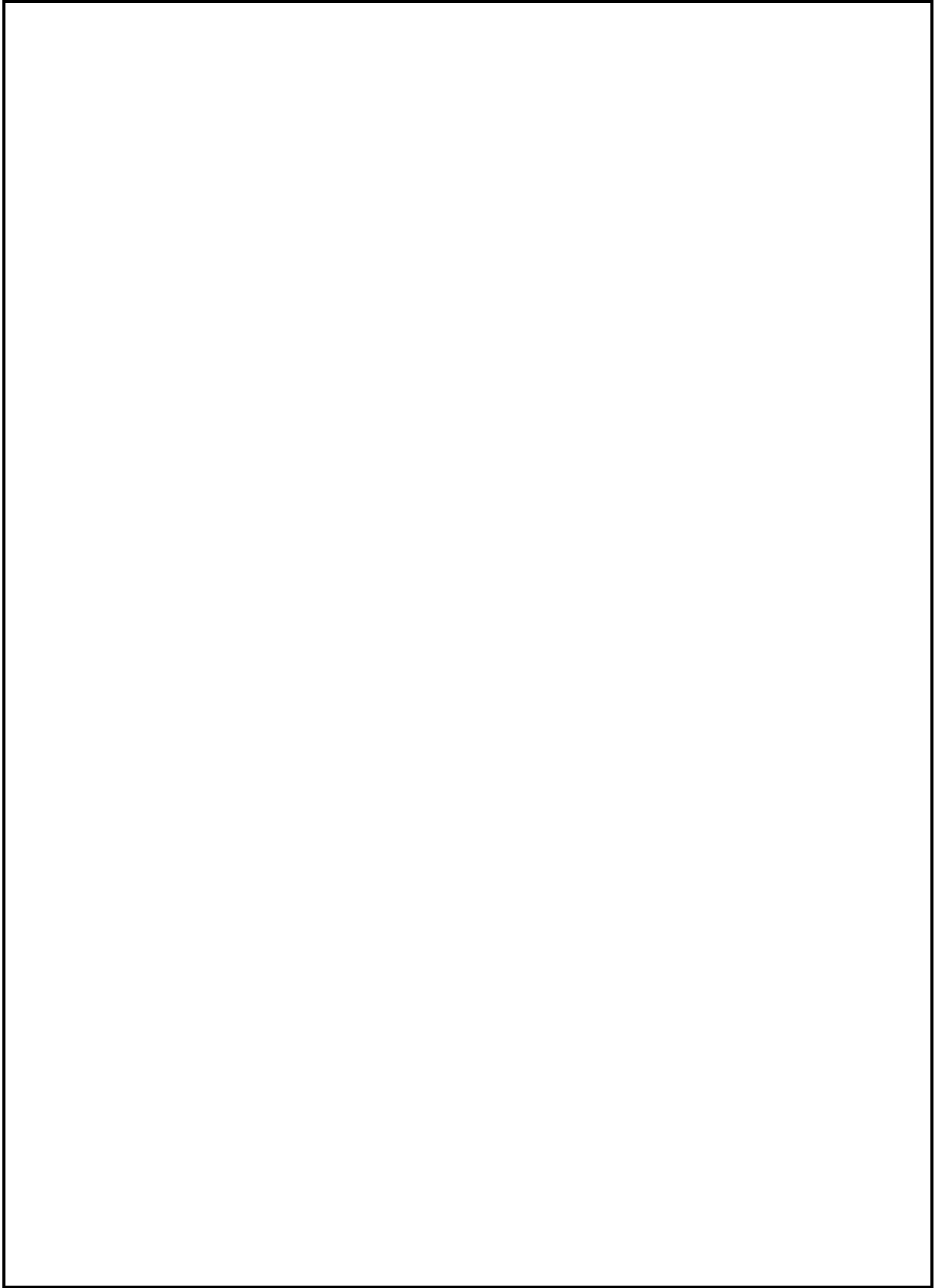
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1 P R O C E E D I N G S

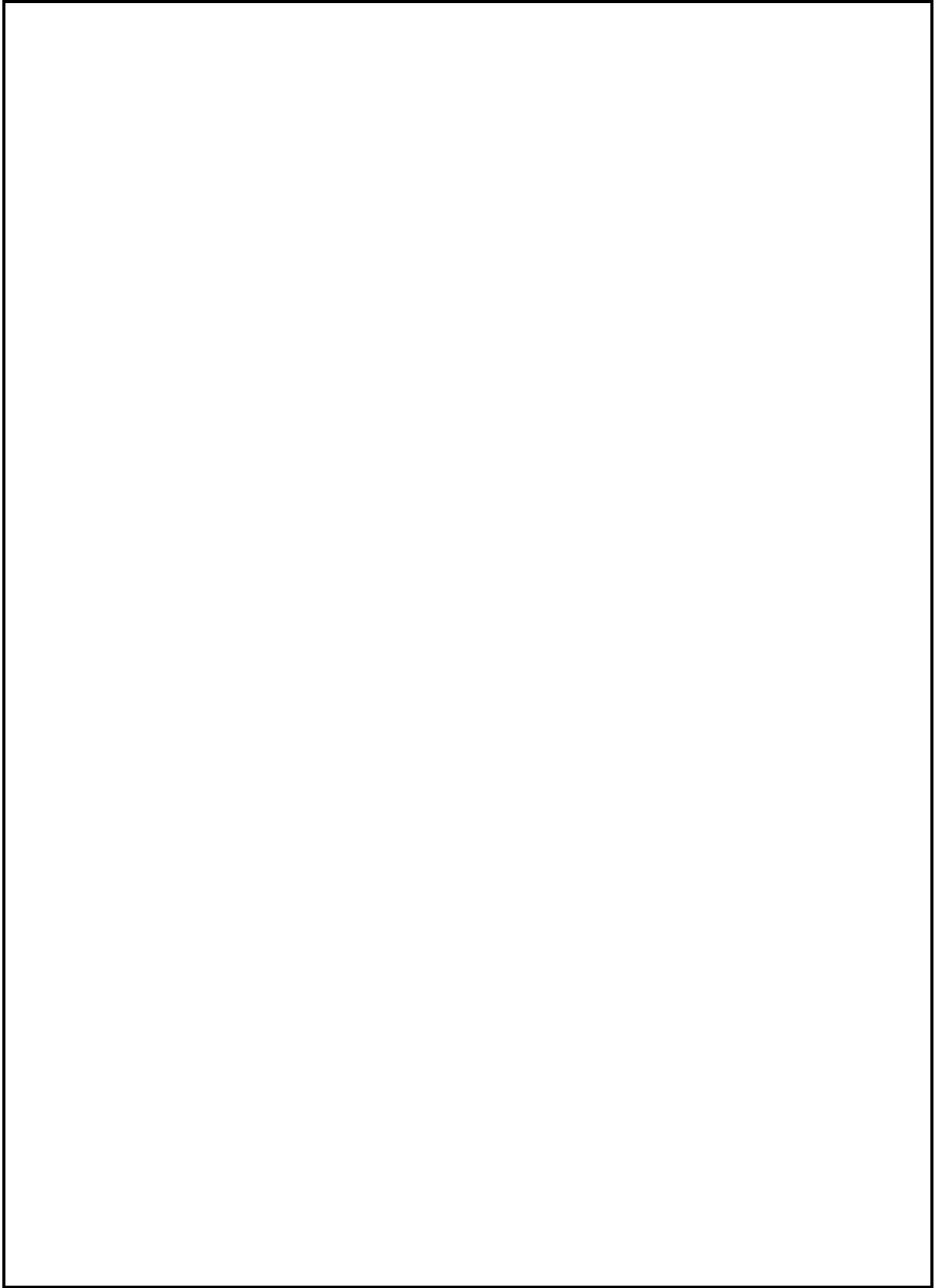
2 MR. FREAS: We welcome all of you
3 to our 14th meeting of the Advisory
4 Committee. There is a speaker phone provided
5 in this room, Conference Room 121 of
6 Building 29 on the NIH Campus for
7 participation.

8 The public is more than welcome to
9 participate in the first session of today's
10 meeting.

11 After the first session, we will go
12 into closed session, as announced in the
13 Federal Register Notice of February 27, 1998,
14 at which time the public, of course, will
15 have to be asked to leave.

16 Should one of our Committee members
17 get dropped from the line, I think you all
18 should have the number by now.

19 It's 1-800-545-4387, ask for I.D.
20 No. R61763 to be reconnected, and they will
21 reconnect you. We definitely want you on
22 this line if at all possible.



1 Two of our members, Dr. Saxton and
2 Nancy Sander, are soon going to join us.

3 At this time, I would like to go
4 around and introduce the members who are on
5 the line and then I'll try to give you a
6 brief description of what's going on in this
7 room right now.

8 Our Chairman is on the line,
9 Dr. John Yunginger, Professor of Pediatrics,
10 Mayo Clinic.

11 DR. YUNGINGER: Present.

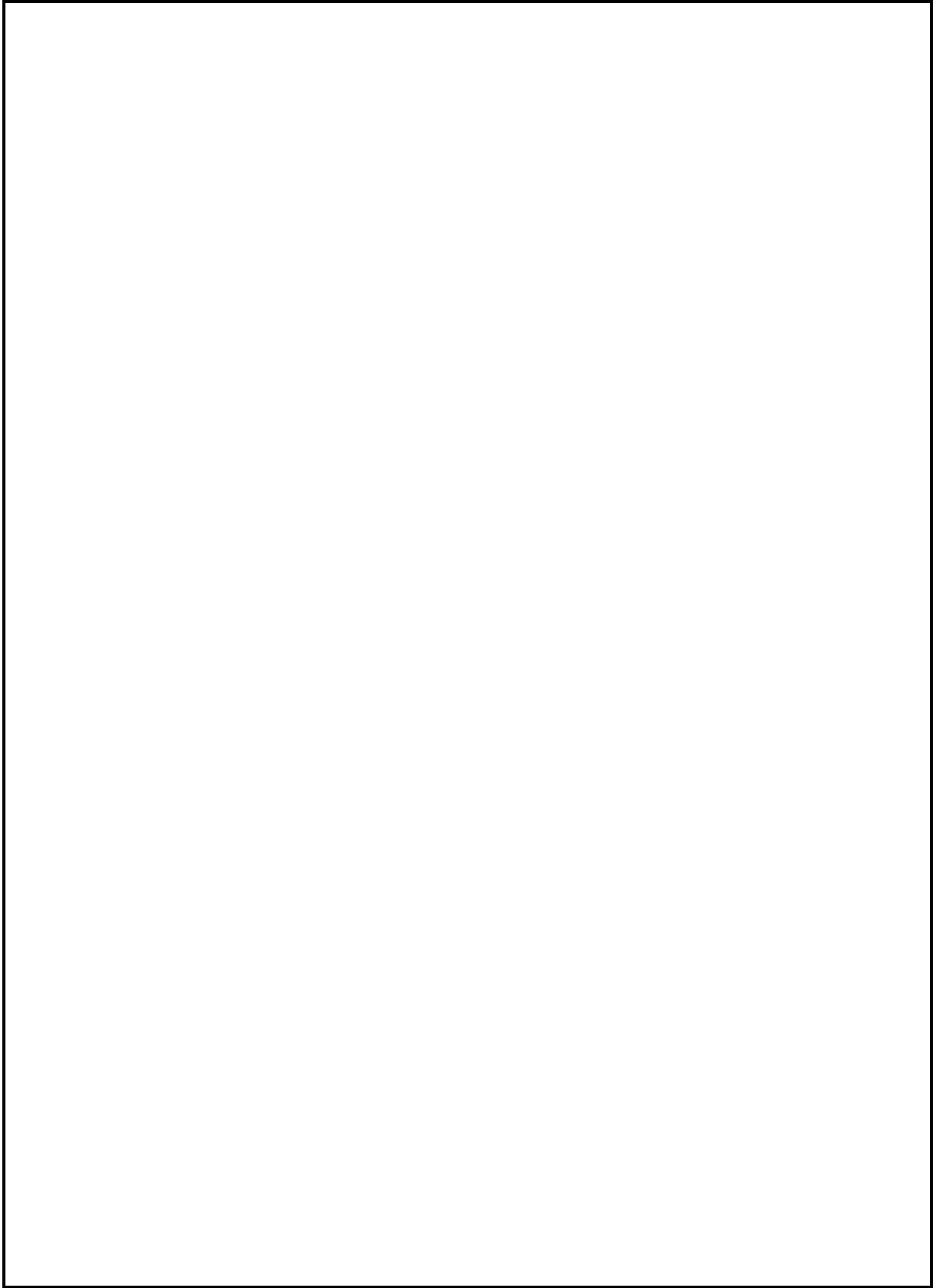
12 MR. FREAS: If the members would
13 say present, I'd appreciate it. Next on the
14 line we have Dr. Te Piao King, Associate
15 Professor, Rockefeller University.

16 DR. KING: Present.

17 MR. FREAS: We have Dr. Dennis
18 Ownby, Professor of Pediatrics,
19 Allergy-Immunology Section, Medical College
20 of Georgia.

21 DR. OWNBY: Present.

22 MR. FREAS: We have Dr. Betty Wray,



1 Professor of Pediatrics and Medicine,
2 Departments of Pediatrics and Medicine,
3 Medical College of Georgia.

4 DR. WRAY: Present.

5 MR. FREAS: Dr. Henry Claman,
6 distinguished Professor of Medicine and
7 Immunology, Division of Clinical Immunology,
8 University of Colorado.

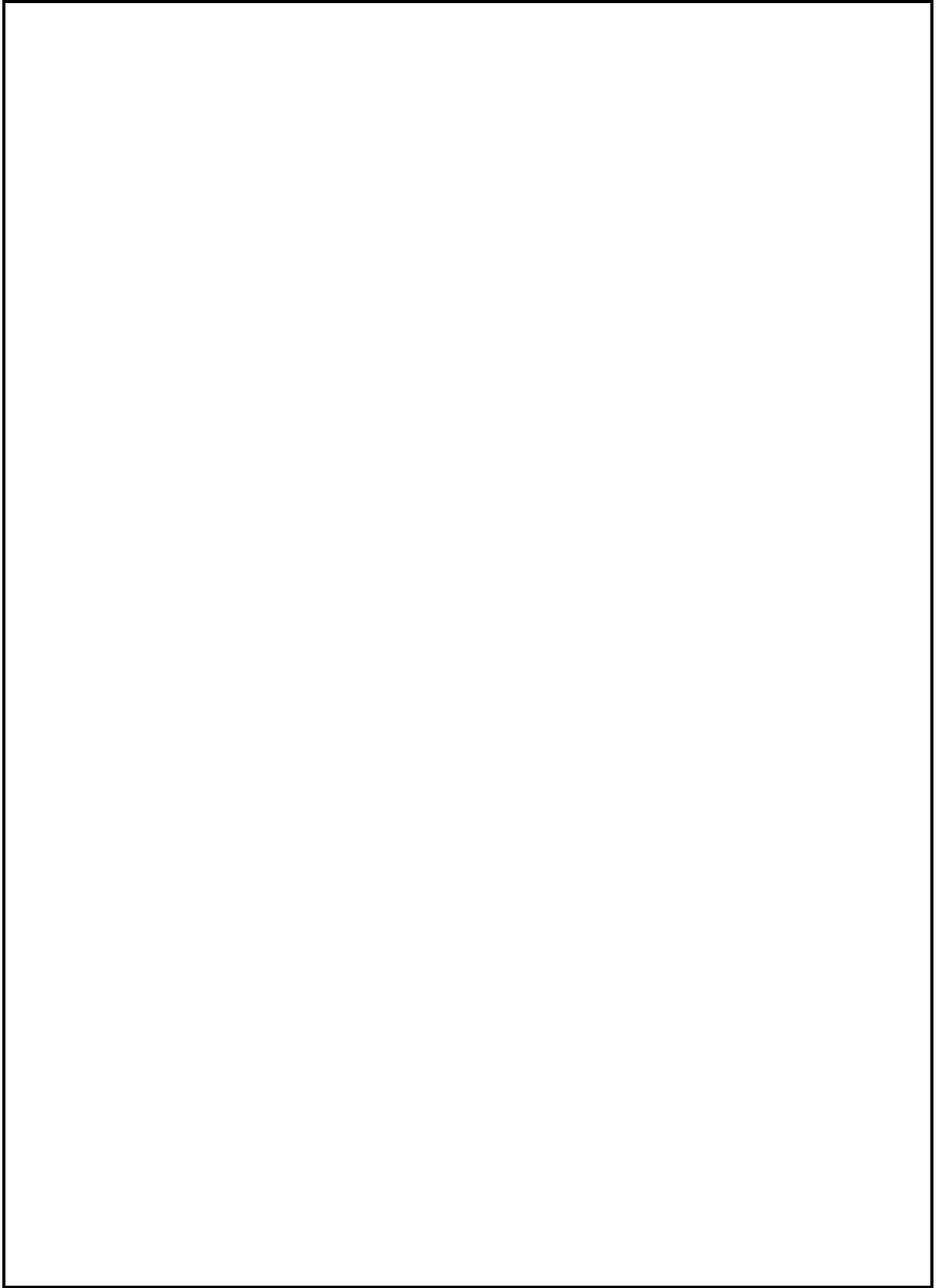
9 DR. CLAMAN: Present.

10 MR. FREAS: As I say, very shortly
11 Dr. Saxon is going to phone in and join us we
12 hope, and also Nancy Sander.

13 I would like to make the
14 announcement that Dr. Claman and Dr. Saxon
15 are two new members of this Advisory
16 Committee, and on behalf of FDA, I would
17 really like to welcome you at least now,
18 Dr. Claman, for joining this Committee.
19 Thank you very much.

20 DR. CLAMAN: Thank you.

21 MR. FREAS: When I hear that tone,
22 that should mean somebody just joined us.



1 MS. SANDER: Yes, Nancy Sander.

2 MR. FREAS: Nancy, thank you very
3 much for joining us. We are just starting.
4 There are two Committee members, and
5 hopefully only two Committee members, that
6 could not participate.

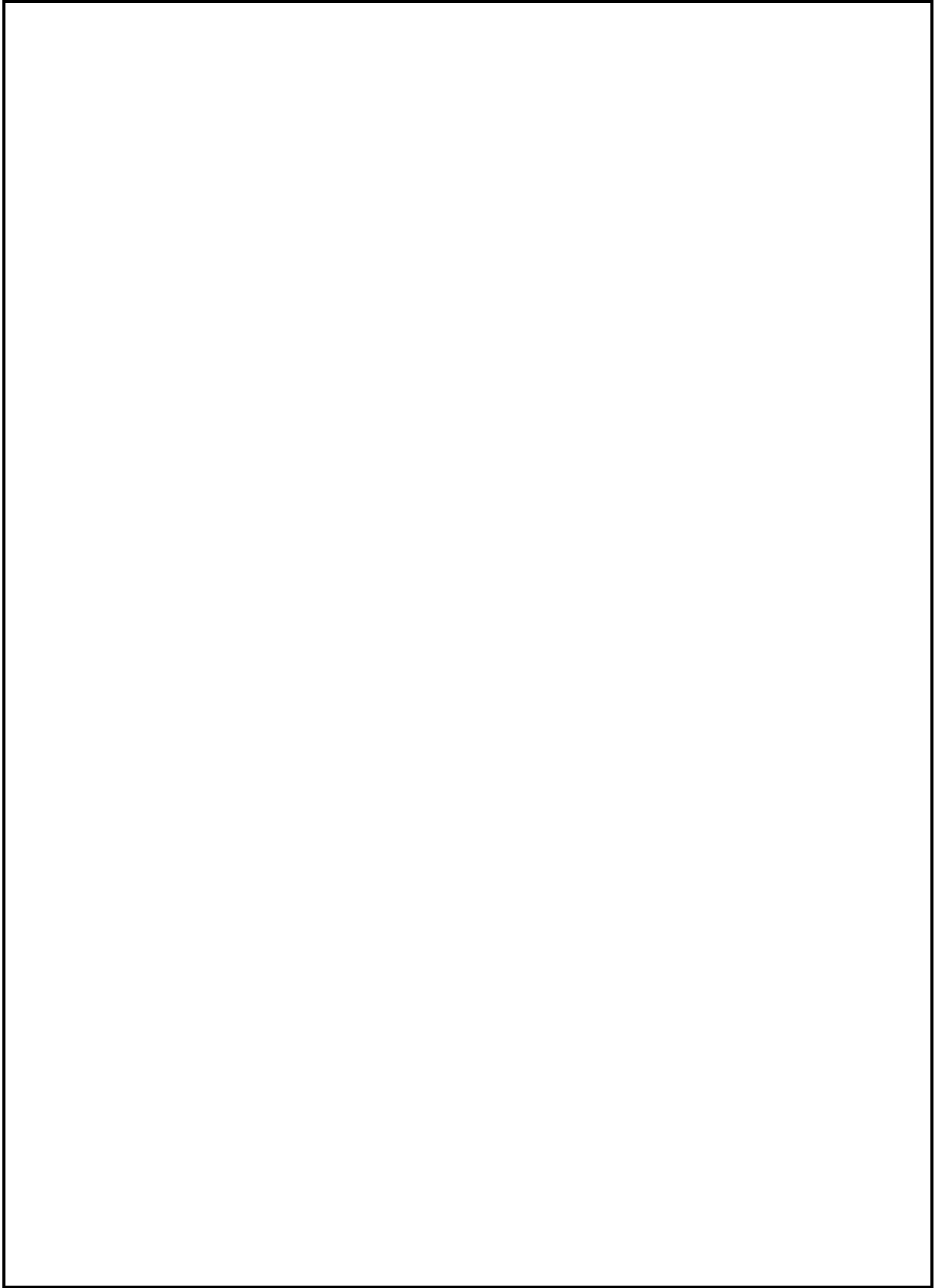
7 They are Dr. Daniel Ein from George
8 Washington University and Dr. Gail Shapiro
9 from Northwest Allergy Center.

10 Now, I'm going to attempt to
11 describe some of the key players in this
12 room. There are approximately 15 people in
13 this room.

14 I hope there are some members of
15 the public, but right now, it looks like it
16 is mainly FDA members sitting at the table.

17 Dr. Carolyn Hardegree, the Director
18 of the Office of Vaccines Research and Review
19 is here with us. Her Deputy, Dr. William
20 Egan, from the Office of Vaccines Research
21 and Review is here.

22 The Associate Director for Palsy



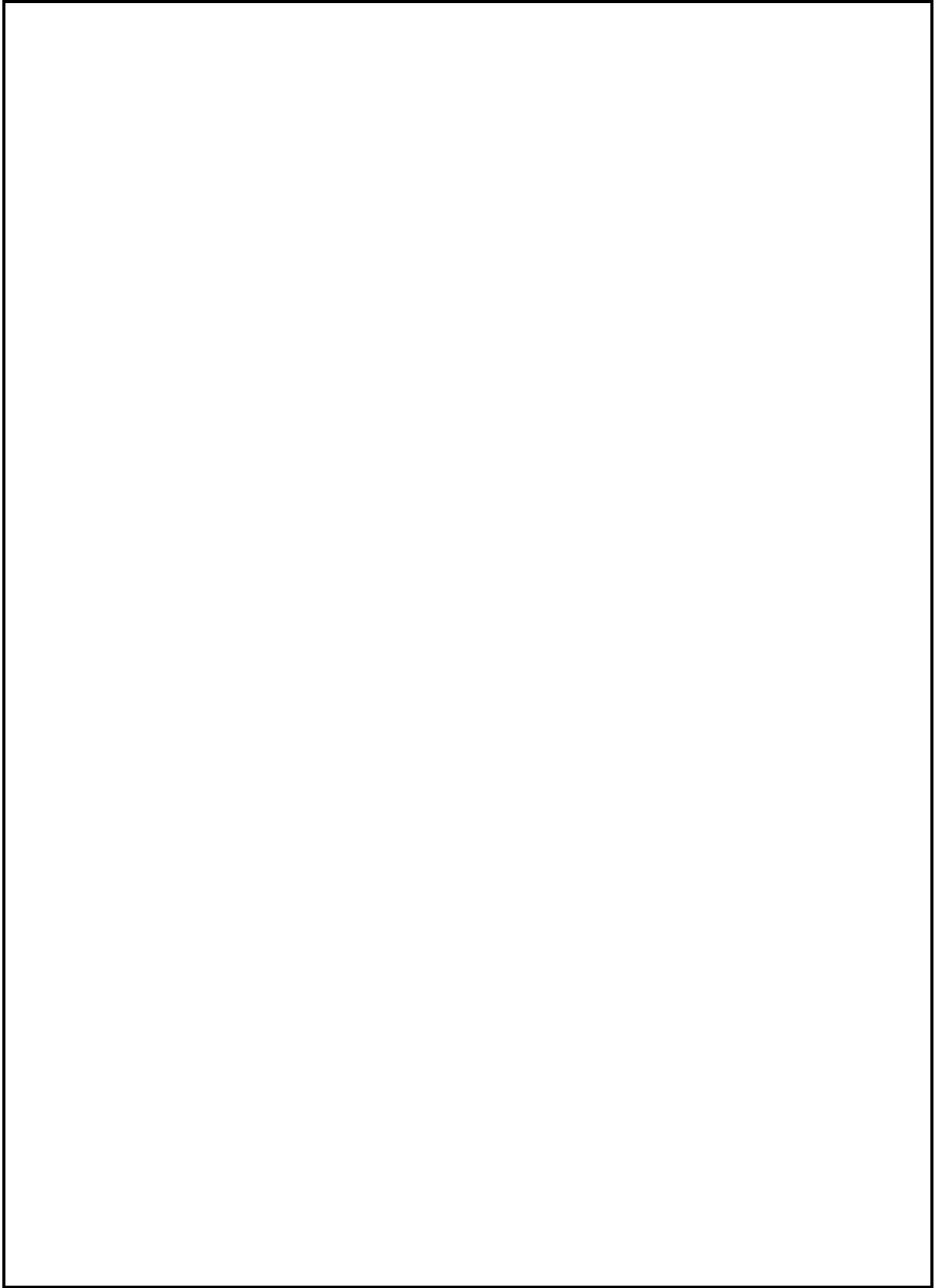
1 and Vaccines, Dr. Normal Baylor, is here.
2 Dr. Thomas Hoffman, who is the Acting
3 Director, Division of Allergenic Products and
4 Parasitology is here.

5 Ms. Jennifer Bridgewater, Consumer
6 Safety Officer, one of the presenters today,
7 is here. Dr. Paul Turkeltaub, head of the
8 Allergenic Clinical Program is here, and
9 Dr. Ira Berkower, Chief, Laboratory of
10 Immunoregulation, is also here.

11 I ask that all of our Committee
12 members and the staff who are
13 participating -- I do realize I left off some
14 key players, I'm afraid. Dr. Richman is also
15 here.

16 Others will be announcing
17 themselves as they go to speak during today's
18 meeting. I apologize to anybody who I did
19 leave off my list. They will introduce
20 themselves as they feel the need to present
21 today.

22 I ask the Committee members that



1 are on the line, we have a transcriber in the
2 room and she's trying to transcribe and
3 attribute all the comments to the appropriate
4 speaker.

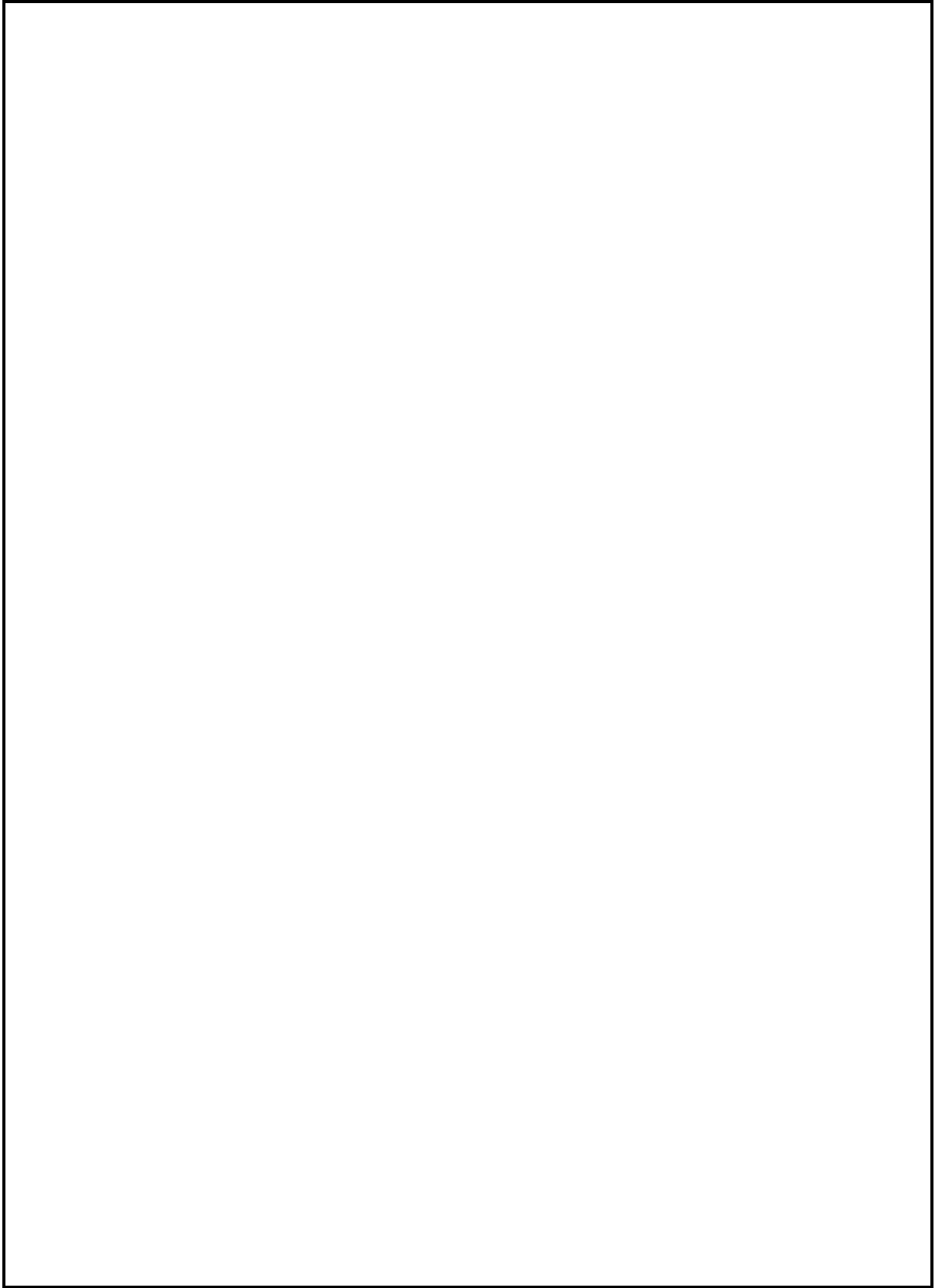
5 We ask if you do speak, please give
6 your name, so the transcriber can attribute
7 the comments to the proper individual.

8 I now would like to read from the
9 public record the conflict of interest
10 statement required to be read for this
11 meeting.

12 The following announcement is made
13 part of the public record to include even the
14 appearance of a conflict of interest at this
15 meeting.

16 All members were screened for their
17 interest with firms that could be affected by
18 today's discussion. The following interests
19 are being disclosed to avoid even the
20 appearance of a conflict of interest.

21 Dr. King reported that he consulted
22 in the past on an unrelated issue with a firm



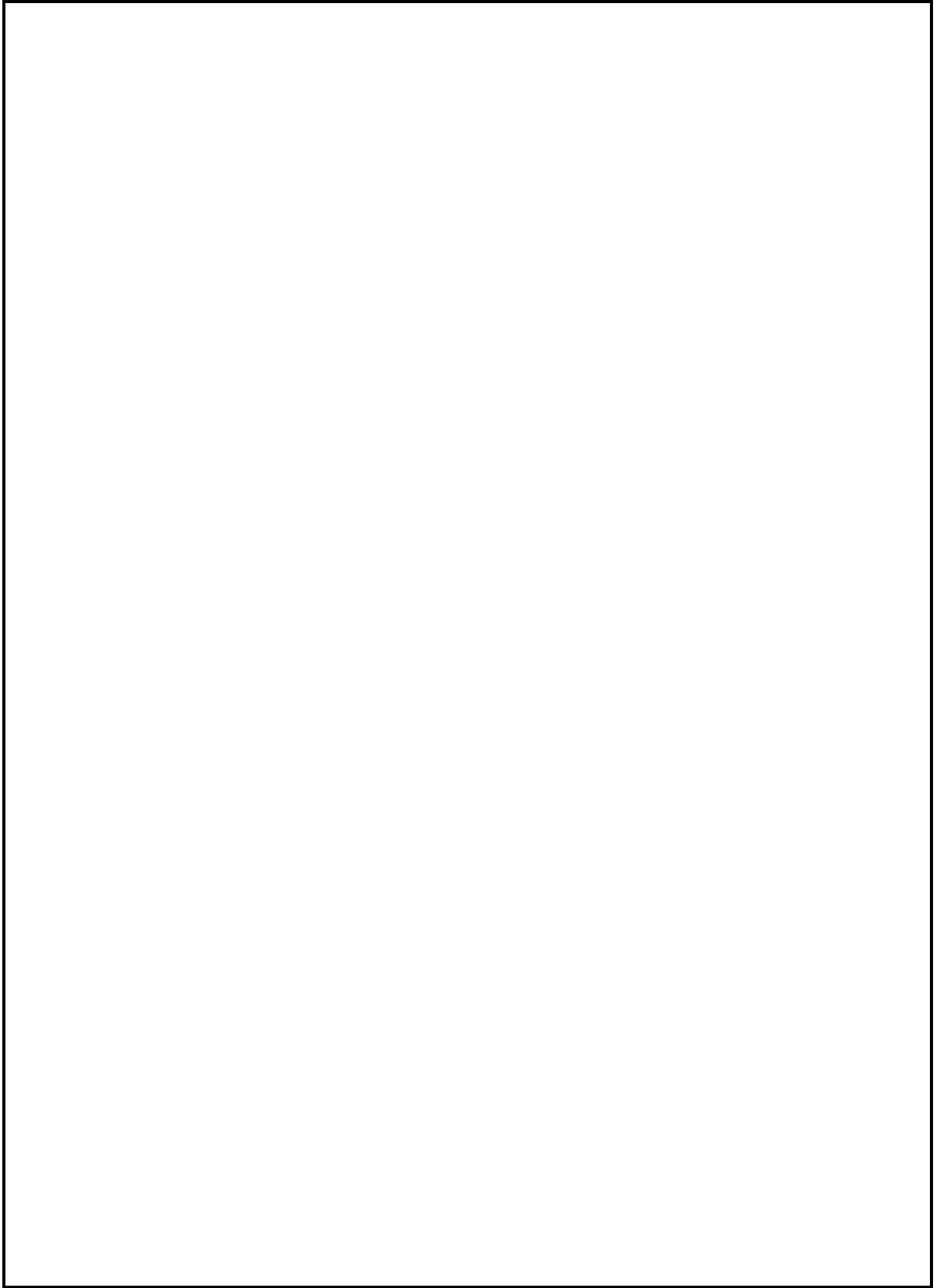
1 that could be affected by the discussion
2 today on candidate allergens. He received a
3 fee for his services.

4 Dr. Dennis Ownby reported that he
5 attended a meeting in the past on an
6 unrelated issue supported by a regular firm
7 that could be affected by the discussion on
8 candidate allergens. He received travel
9 reimbursement only.

10 Ms. Nancy Sander reported that her
11 employer received an unrelated grant in the
12 past from a firm that could be affected by
13 discussions on candidate allergens.

14 Drs. Claman, Saxon, Wray, Yunginger
15 had no financial interests to report.

16 In the event that the discussions
17 involve other products or firms not already
18 on the agenda for which FDA participants have
19 a financial interest, the participants are
20 aware of the need to exclude themselves from
21 such discussion and their full exclusion will
22 be noted in the public record.



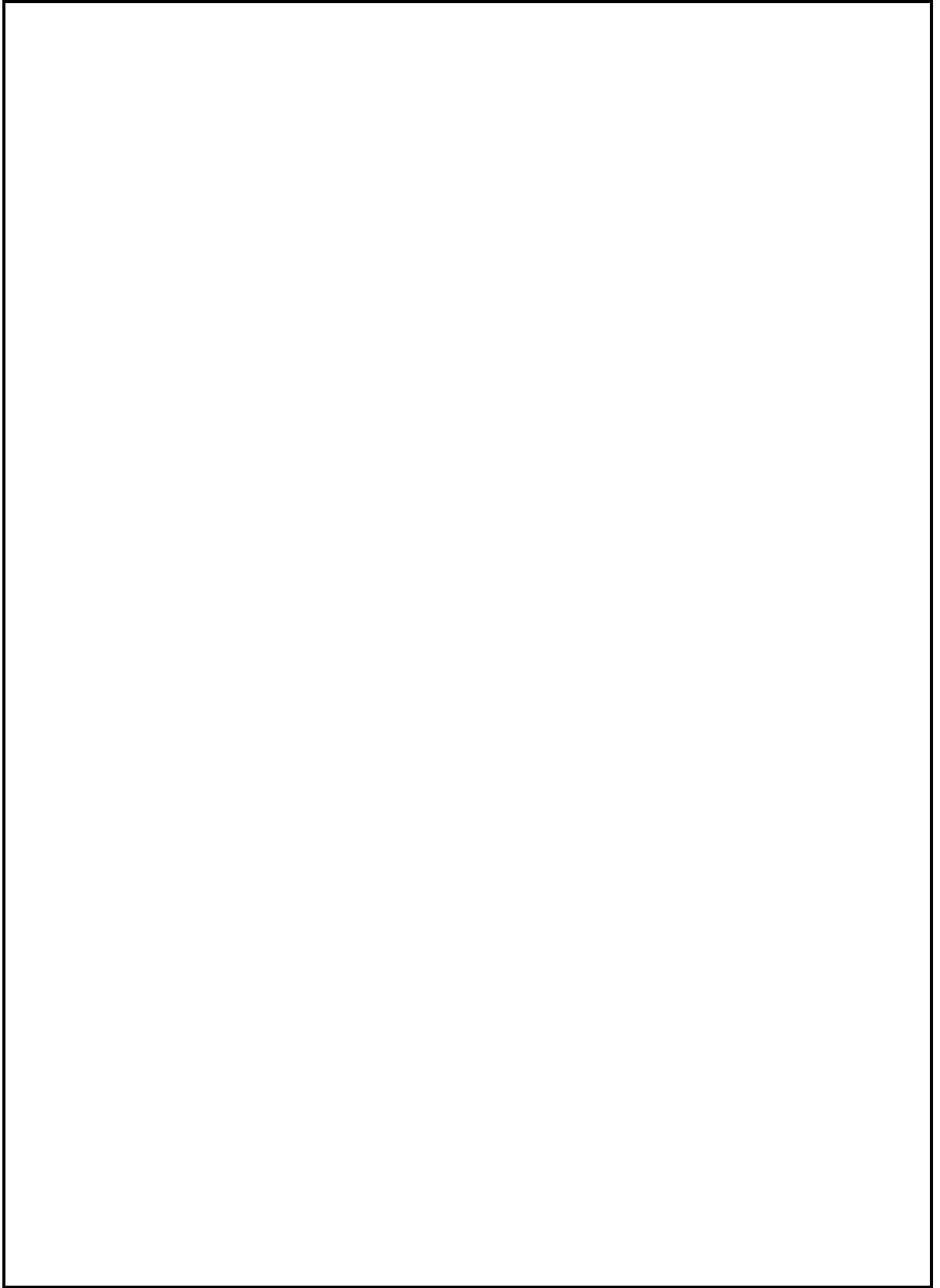
1 With respect to all other meeting
2 participants, we ask in the interest of
3 fairness that they address any current or
4 previous financial involvement with any firm
5 whose product they may have wished to comment
6 upon.

7 So ends the reading of the conflict
8 of interest statement. Dr. Yunginger, I turn
9 the meeting over to you.

10 DR. YUNGINGER: Thank you,
11 Mr. Freas. I think I would like to begin by
12 welcoming our two new committee members,
13 Dr. Henry Claman and Dr. Andrew Saxon, and
14 hopefully Dr. Saxon will be joining us
15 shortly.

16 We have very distinguished people
17 here that are obviously good folks and I
18 encourage everyone to join in the discussion
19 today.

20 Bill, will you make the appropriate
21 announcements about the first item on our
22 agenda for the open session, please?



1 MR. FREAS: With pleasure. As part
2 of the FDA Advisory Committee meeting
3 procedure, we are required to hold an open
4 public hearing for those members of the
5 public who are not on the agenda and would
6 like to make a statement concerning matters
7 pending before the committee.

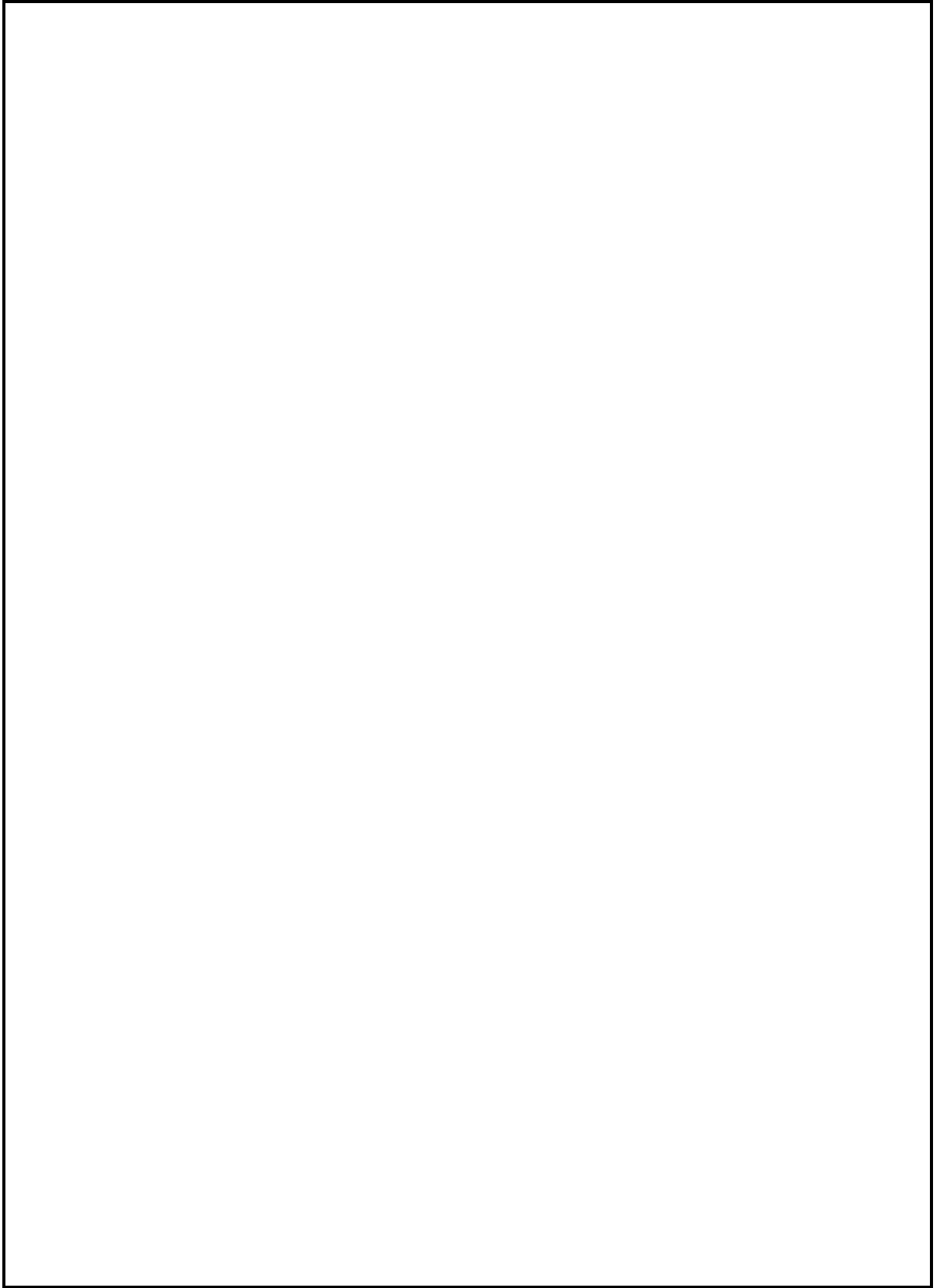
8 I have not received any requests in
9 response to our F.R. notice at this time.

10 Is there anyone in the room who
11 would like to address the committee?

12 Dr. Yunginger, at this time, there
13 appears to be no one in the room interested
14 in addressing the committee at this time.
15 I'll let you know if anything has changed
16 during the course of the proceedings.

17 DR. YUNGINGER: Okay. Mr. Freas,
18 are we required to maintain a certain minimum
19 period for the open portion of the committee,
20 in case there are latecomers?

21 MR. FREAS: There is no minimum
22 period. There's a maximum period of at least



1 an hour. We do our best to accommodate the
2 participants, participation of the public.

3 If somebody does come before we go
4 into closed session, I would let you be aware
5 of it and if at all possible, we would like
6 to have them make a short presentation.

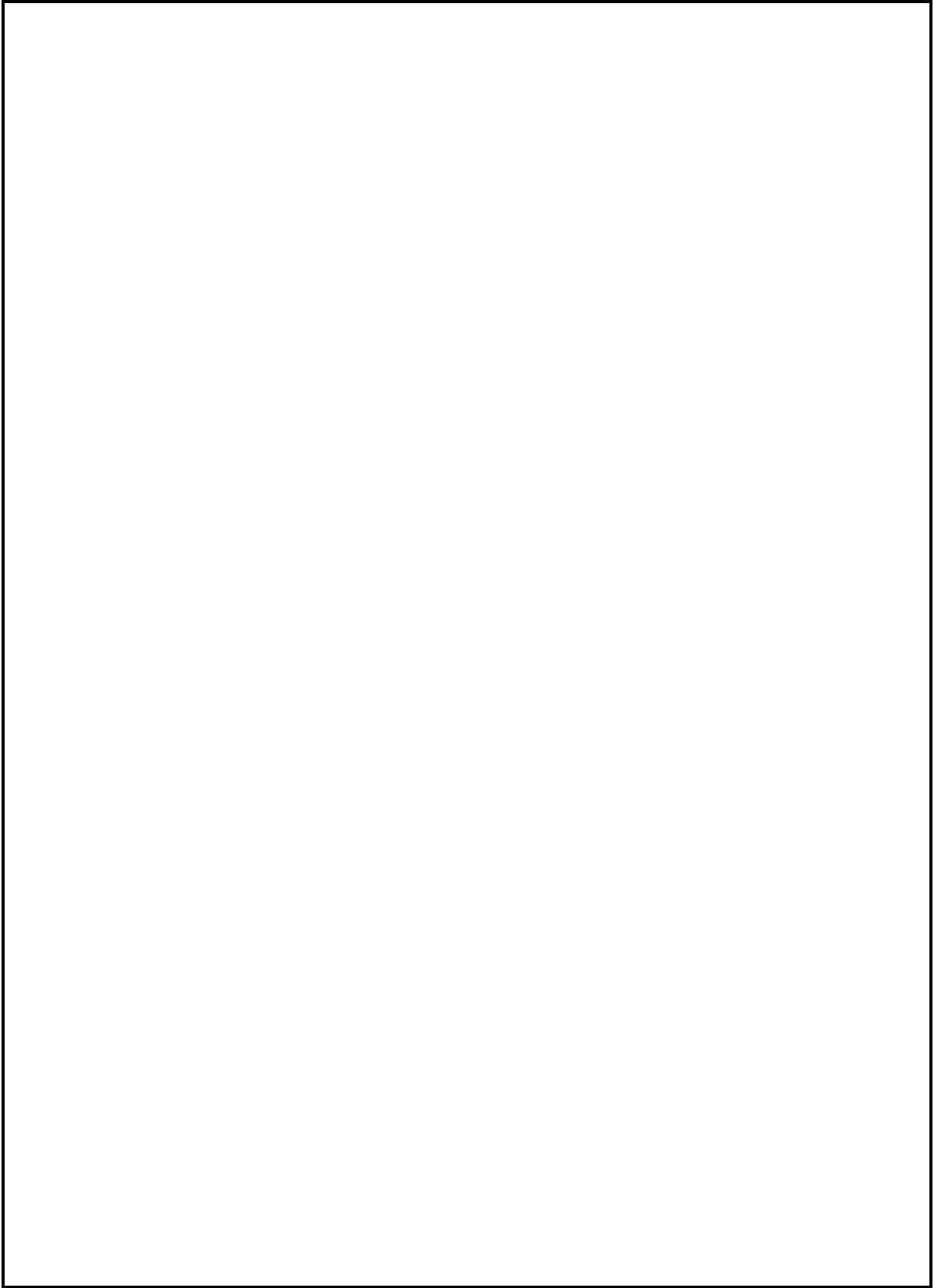
7 DR. YUNGINGER: Very good.

8 MR. FREAS: For our committee
9 members, I do believe we are hooked up.
10 There is a microphone in here which I believe
11 is broadcasting this meeting to paid
12 subscribers.

13 I want our committee members to be
14 aware that during the open public hearing, it
15 is going to beyond just FDA at this time.

16 DR. YUNGINGER: Thank you,
17 Mr. Freas. We have next some presentations
18 by the FDA personnel. Our first speaker is
19 Dr. Thomas Hoffman, Acting Director, Division
20 of Allergenic Products and Parasitology.
21 Dr. Hoffman?

22 DR. HOFFMAN: Thank you very much.

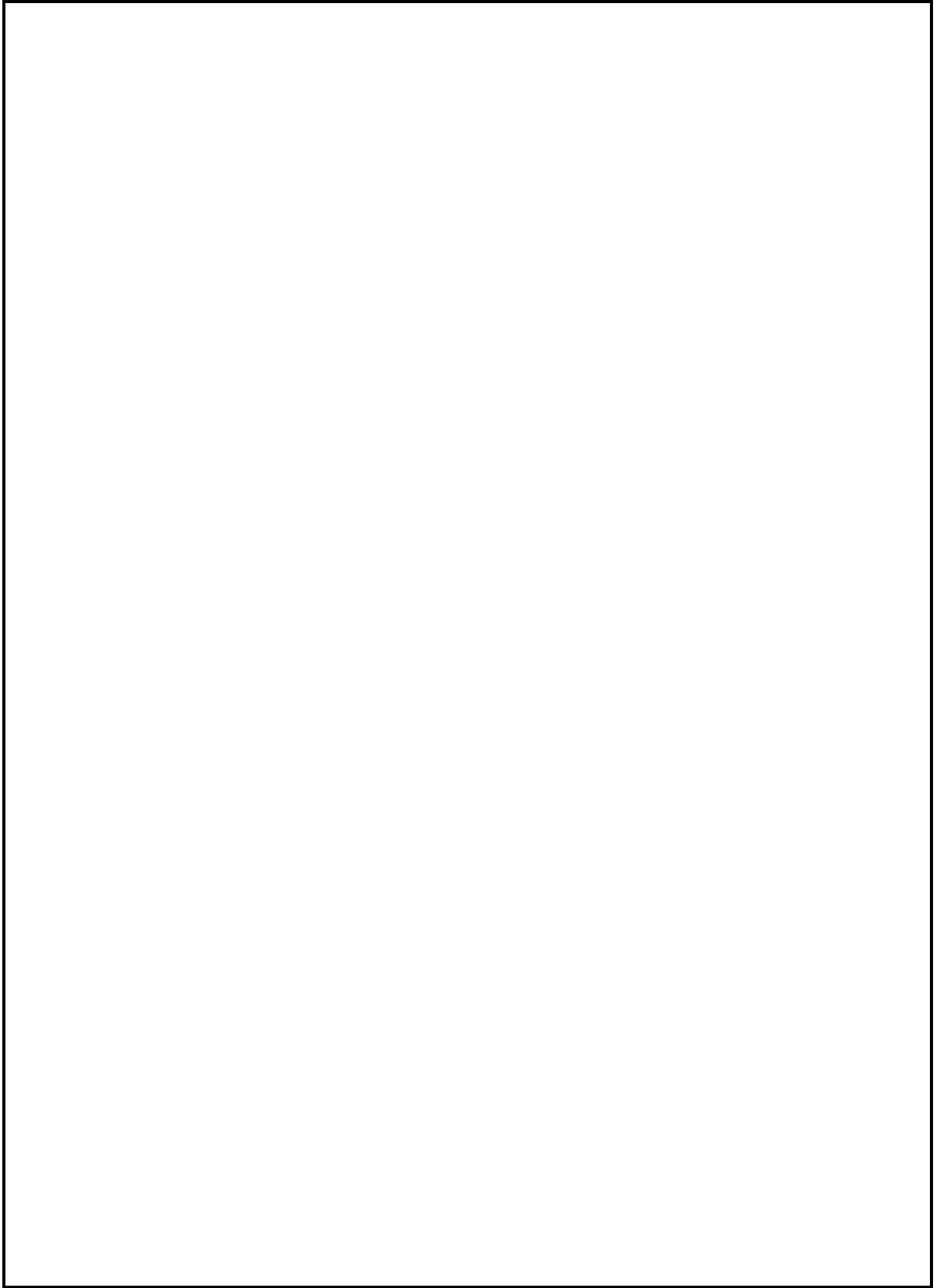


1 It's a pleasure to participate in this
2 meeting today. The principal items have been
3 conveyed to you on the agenda and materials
4 that you received. I hope you found them
5 helpful.

6 The principal goal of today's
7 session is to both update you on recent
8 progress in our standardization program for
9 allergens in general and grasses in
10 particular, and also to make you acquainted
11 with some of the changing staff and personnel
12 that are participating in the program here at
13 the FDA, that might have some implications
14 for the way we proceed in the future.

15 I think we will go directly into
16 our first presentation, which will be offered
17 by Ms. Jennifer Bridgewater, who is the
18 Regulatory Coordinator in our division.

19 MS. BRIDGEWATER: Good afternoon.
20 Let me start the meeting off on a positive
21 note. My purpose today is to give you an
22 update on the standardization program.



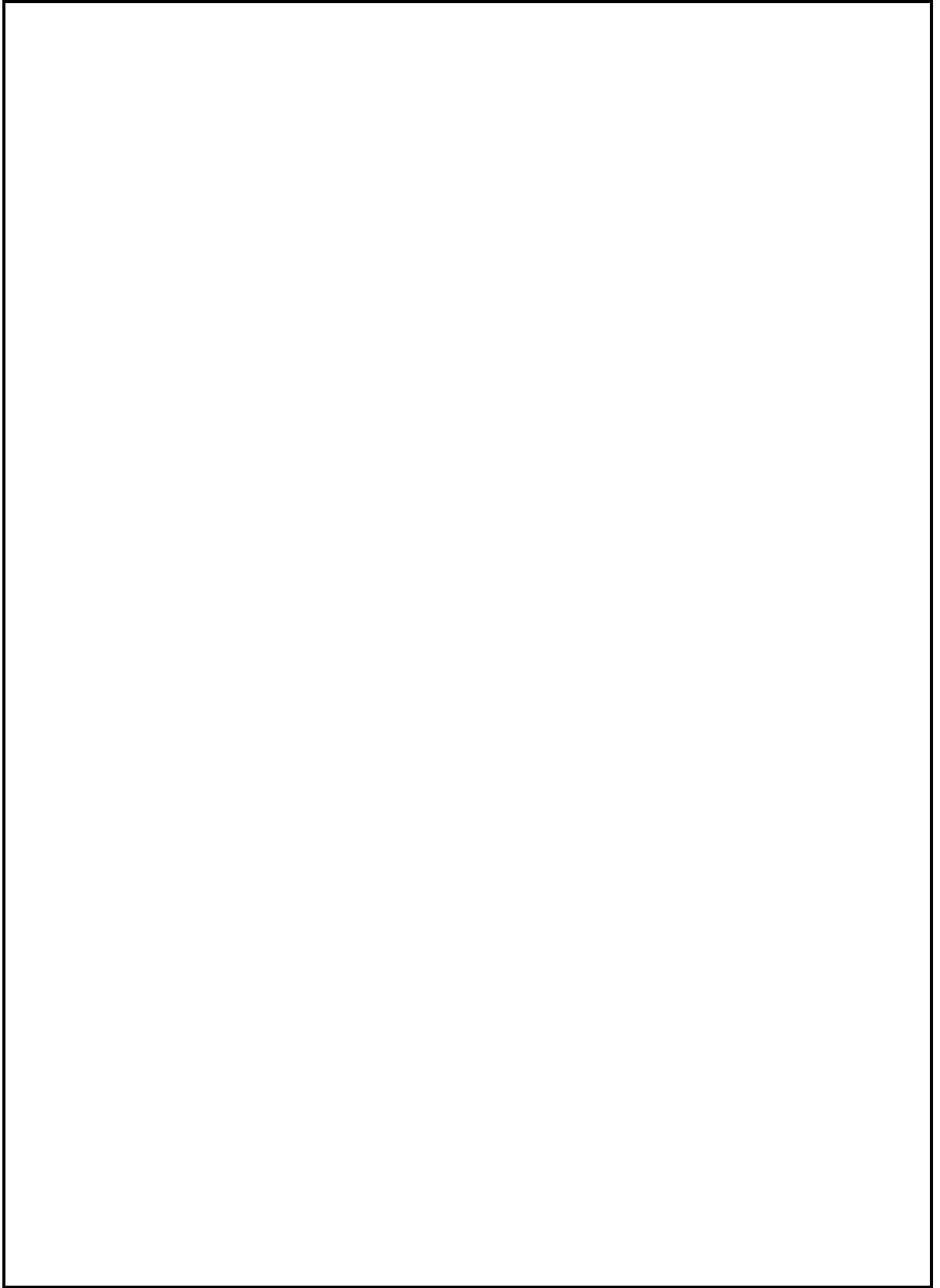
1 At this time, CBER has successfully
2 completed the grass standardization program.
3 As of February, all allergenic extract
4 manufacturers have been approved for most of
5 the standardized grass pollen extracts.

6 However, in response to requests
7 from the Allergen Products Manufacturing
8 Association, physicians and the American
9 Academy of Allergy, Asthma and Immunology,
10 the deadline has been extended an additional
11 six months until July 8, 1998.

12 As the previous January 8th
13 deadline approached, CBER received requests
14 from both the APMA and the AAAAI that the
15 deadline be extended.

16 Both the APMA and the AAAAI raised
17 concerns that the January 8, 1998 deadline
18 for succession of manufacture and
19 distribution of non-standardized extracts may
20 result in an inadequate supply of
21 standardized grass pollen extracts.

22 Specifically, on July 1, 1997, the



1 APMA submitted a petition for stay action
2 requesting that FDA stay the effective date
3 of all requirements pertaining to
4 standardization of grass pollen extracts, and
5 this action is currently under review by the
6 agency.

7 MR. FREAS: Is that Dr. Saxon?

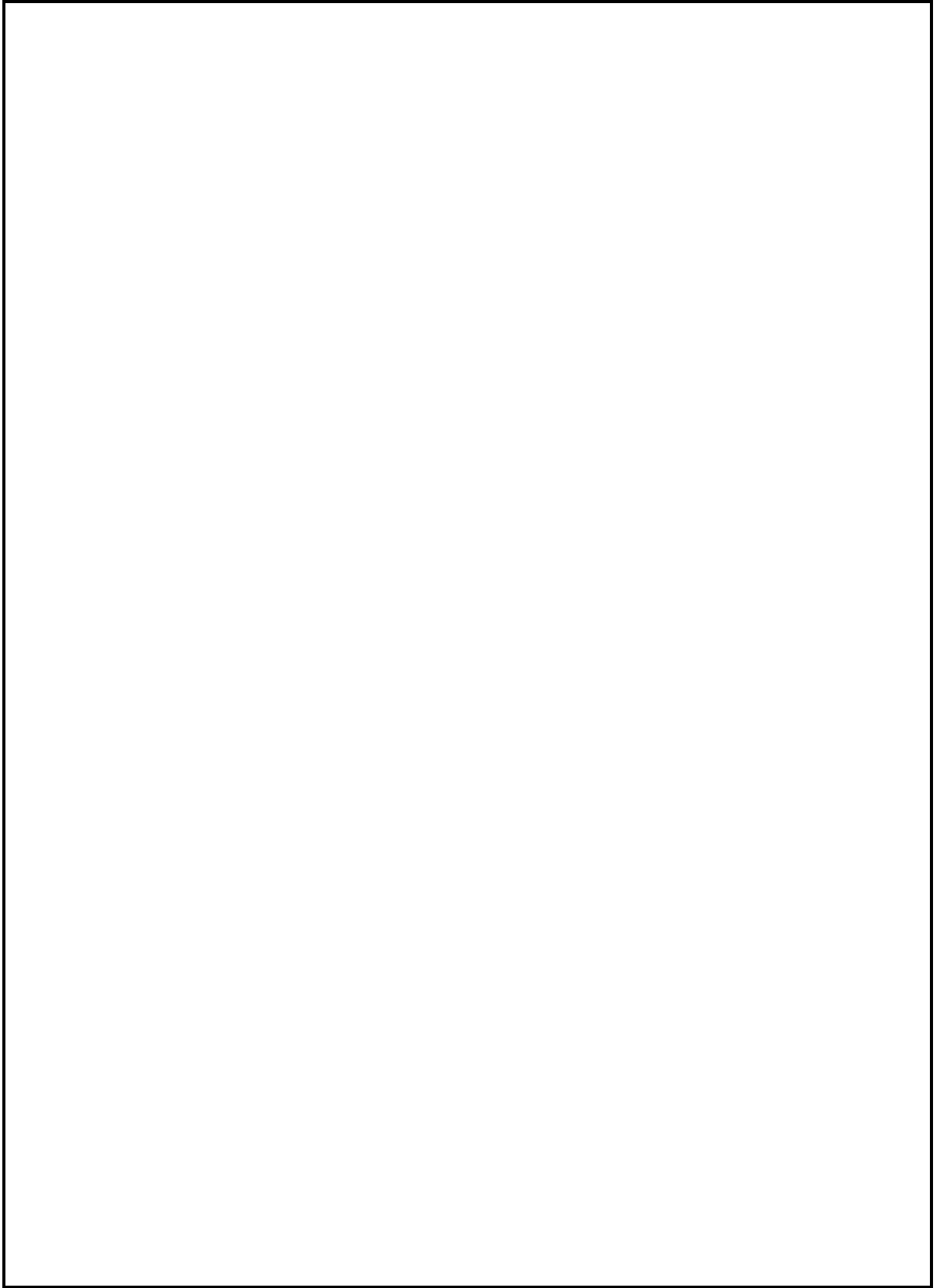
8 DR. SAXON: Yes. I have been
9 trying to reach you for over 15 minutes.
10 Unfortunately, the conference operators are
11 busy and would not accept calls for the
12 last 15 minutes.

13 MR. FREAS: Dr. Saxon, we are very
14 delighted to have you. Unfortunately, we did
15 begin without you.

16 DR. SAXON: I don't blame you.

17 MR. FREAS: We are going to go
18 ahead and proceed where we left off, but
19 welcome. Dr. Yunginger, would you like to
20 say anything to Dr. Saxon, as long as I've
21 interrupted everybody?

22 DR. YUNGINGER: This is



1 Dr. Yunginger. As chair of the committee, I
2 am pleased to have you on the committee,
3 Andy. Welcome aboard.

4 DR. SAXON: Thank you, and I'll try
5 to get on earlier next time.

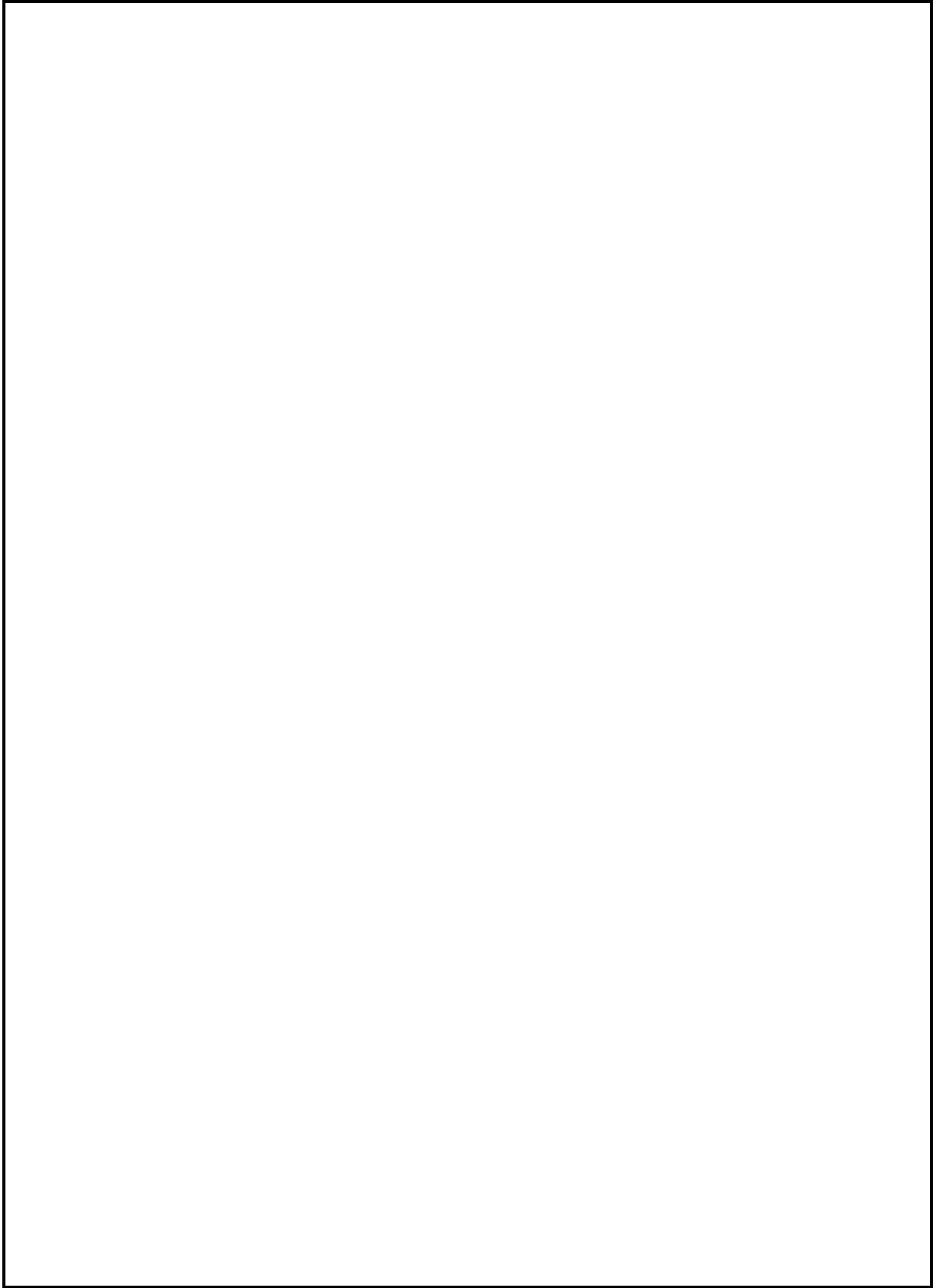
6 MR. FREAS: Next time, we'll call
7 you. Don't worry, Dr. Saxon. We will take
8 care of it. It was our fault. Thank you.

9 DR. SAXON: Fine.

10 MS. BRIDGEWATER: On
11 December 5, 1997, members of the AAAAI met
12 with CBER and urged that the January 8th
13 deadline be extended, later formalizing their
14 comments in a letter to the agency.

15 The AAAAI requested an extension of
16 the deadline to allow for a transition period
17 in which standardized and non- standardized
18 extracts could be jointly distributed, so
19 that patients receiving immunotherapy could
20 be converted and that physicians could be
21 educated.

22 AAAAI further requested CBER's



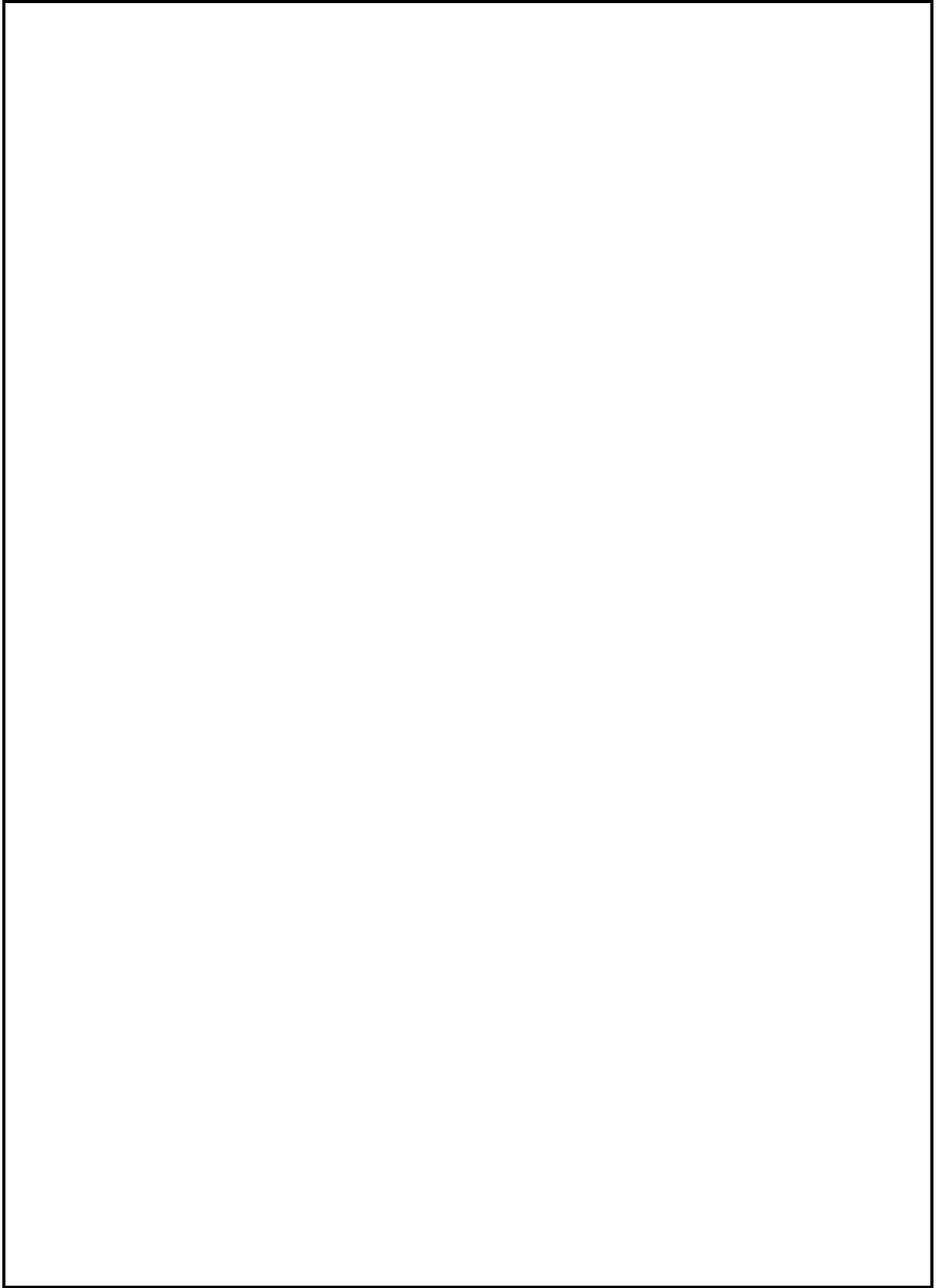
1 assistance in the physician education
2 process.

3 After consideration of these
4 requests, CBER extended the deadline an
5 additional six months to allow for patient
6 conversion and physician education.

7 CBER has placed information
8 regarding standardized grass pollen extracts
9 on the external CBER Web Page, and the
10 address should be in your packet.

11 Currently, the letter sent to
12 licensed manufacturers of allergenic extracts
13 regarding the extension of the deadline and
14 the listing of standardized grass pollen
15 extract product approvals by date and by
16 manufacturer on available on this site.

17 Finally, licensed manufacturers
18 were required to send a "Dear Doctor" letter
19 regarding the use of these products to all
20 their customers as a condition of license
21 approval. These letters should further
22 educate physicians on the use of these



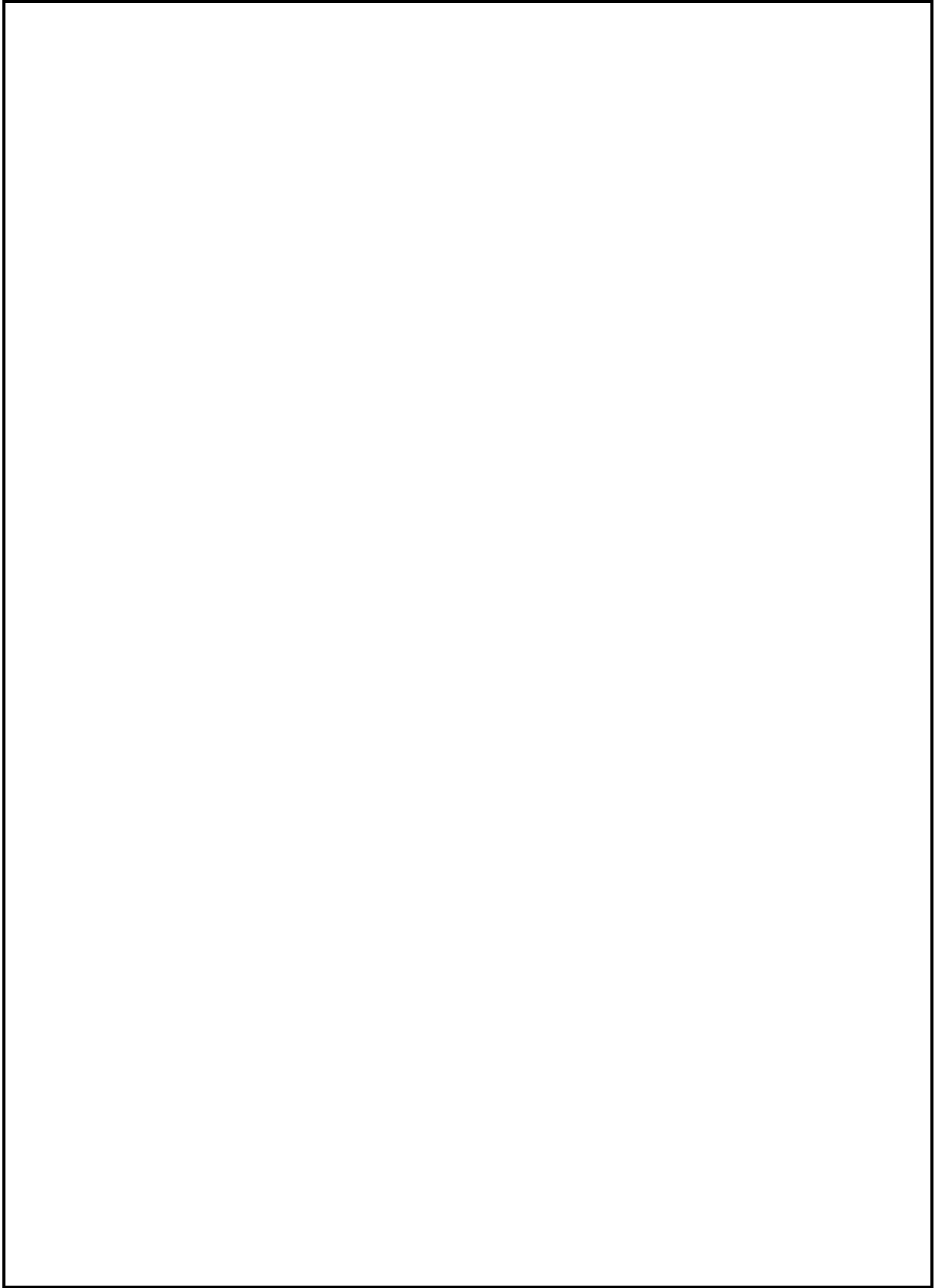
1 products.

2 That concludes my presentation.

3 MR. FREAS: Dr. Yunginger, the next
4 speaker on the agenda is Dr. Hoffman. I'm
5 sorry. Are there any questions from the
6 committee members on the previous topic?

7 DR. YUNGINGER: In the letter from
8 manufacturers to the purchasers of the
9 extracts, will these have available the
10 previous weight and volume or protein
11 nitrogen unit concentrations and their
12 approximate equivalence in BAU's for that
13 particular manufacturer's product to assist
14 the users of these new standardized extracts
15 to make the conversion?

16 DR. TURKELTAUB: They make
17 reference to that information which is in the
18 package insert for each of the companies with
19 respect to the relative potency. In a number
20 of sample lots that were previously
21 distributed, they were not standardized
22 compared to the standardized extracts.



1 In addition, some of the companies
2 have asked for and have been given permission
3 to indicate to their end users what the
4 potency is of the products that the customer
5 is currently using, in addition to, to
6 facilitate the transfer. Both options, both
7 written and verbal, are available.

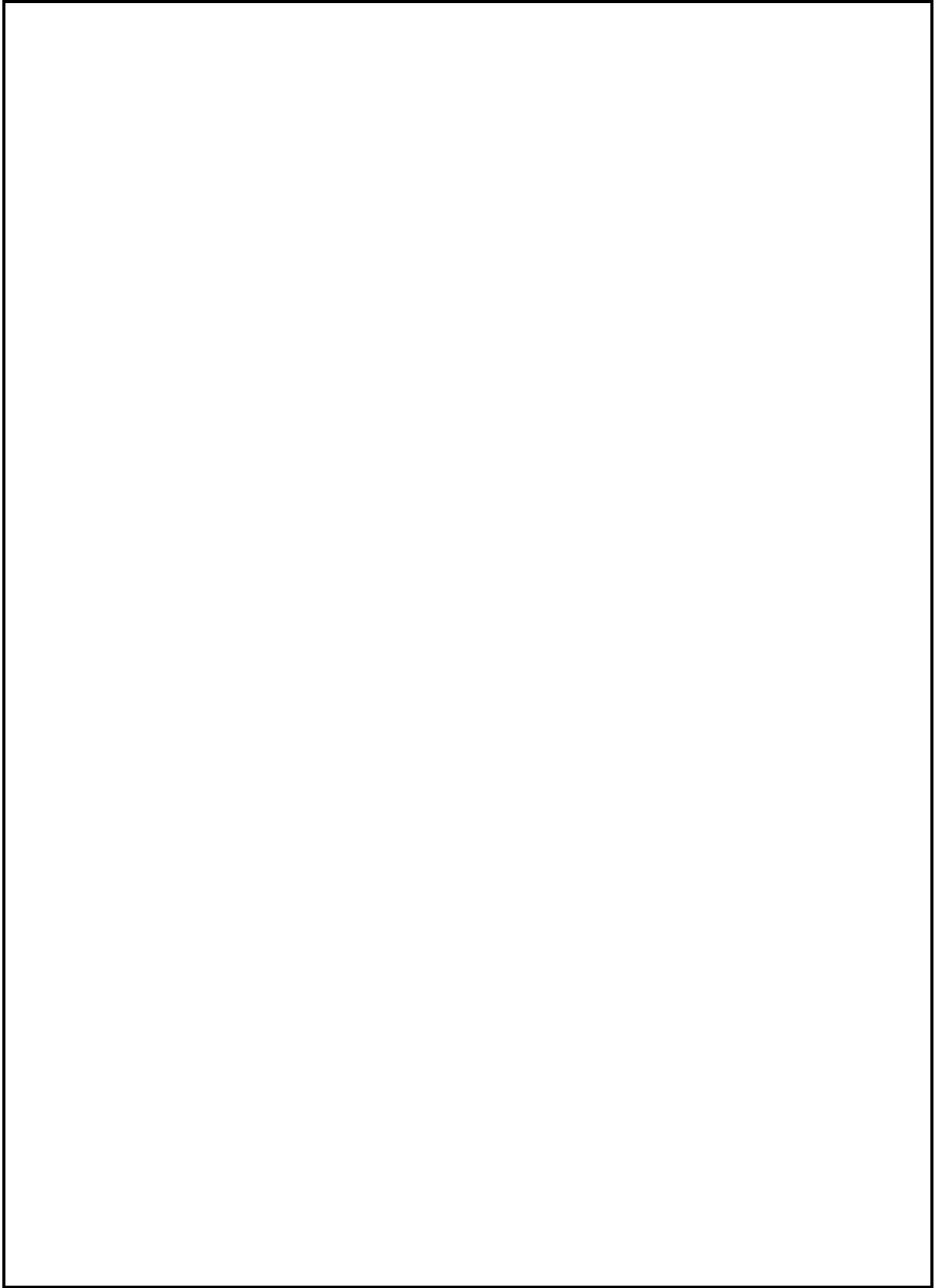
8 DR. YUNGINGER: I think that's a
9 wonderful idea. I know some discussion came
10 up with previous standardized extracts.
11 There was a reluctance to have double
12 labeling or triple labeling on the actual
13 product itself.

14 I'm pleased that the package insert
15 or the accompanying letter from manufacturers
16 will have this information.

17 It is going to be a very traumatic
18 time for the users of the grass extracts, and
19 I think this will help ease the pain.

20 MS. SANDER: I have a question and
21 that is what will be different for patients?

22 DR. TURKELTAUB: I think there are



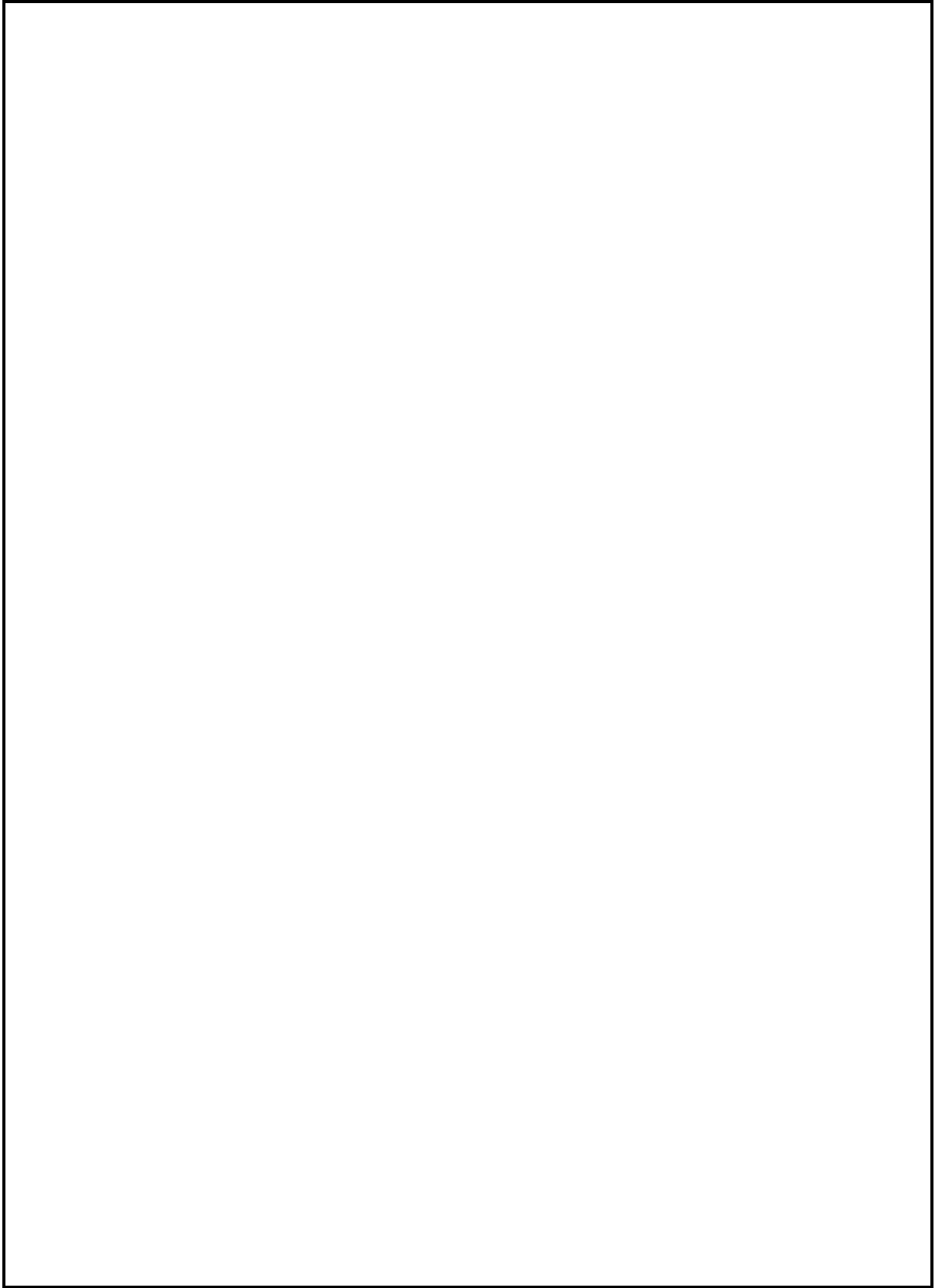
1 a couple of things. One, that these products
2 meet standards of potency whereas the
3 previous non-standardized products by
4 definition don't.

5 They in fact state no U.S. standard
6 of potency. There will be consistency from
7 lot to lot over time.

8 There will also be an unit, a
9 common unit on these preparations, in terms
10 of BAU's. When the patient is seen by the
11 physician, they will know how many units they
12 are getting of that particular standardized
13 product.

14 Therefore, there will be some
15 accountability. If the nurse is supposed to
16 give them 100 units and the patient asks, how
17 many units am I getting, and the person
18 says 10 or 1,000, they will be able to check
19 in terms of their dose.

20 With the managed care situation, if
21 a company can't provide the particular BAU's,
22 the physician and the patient will have the

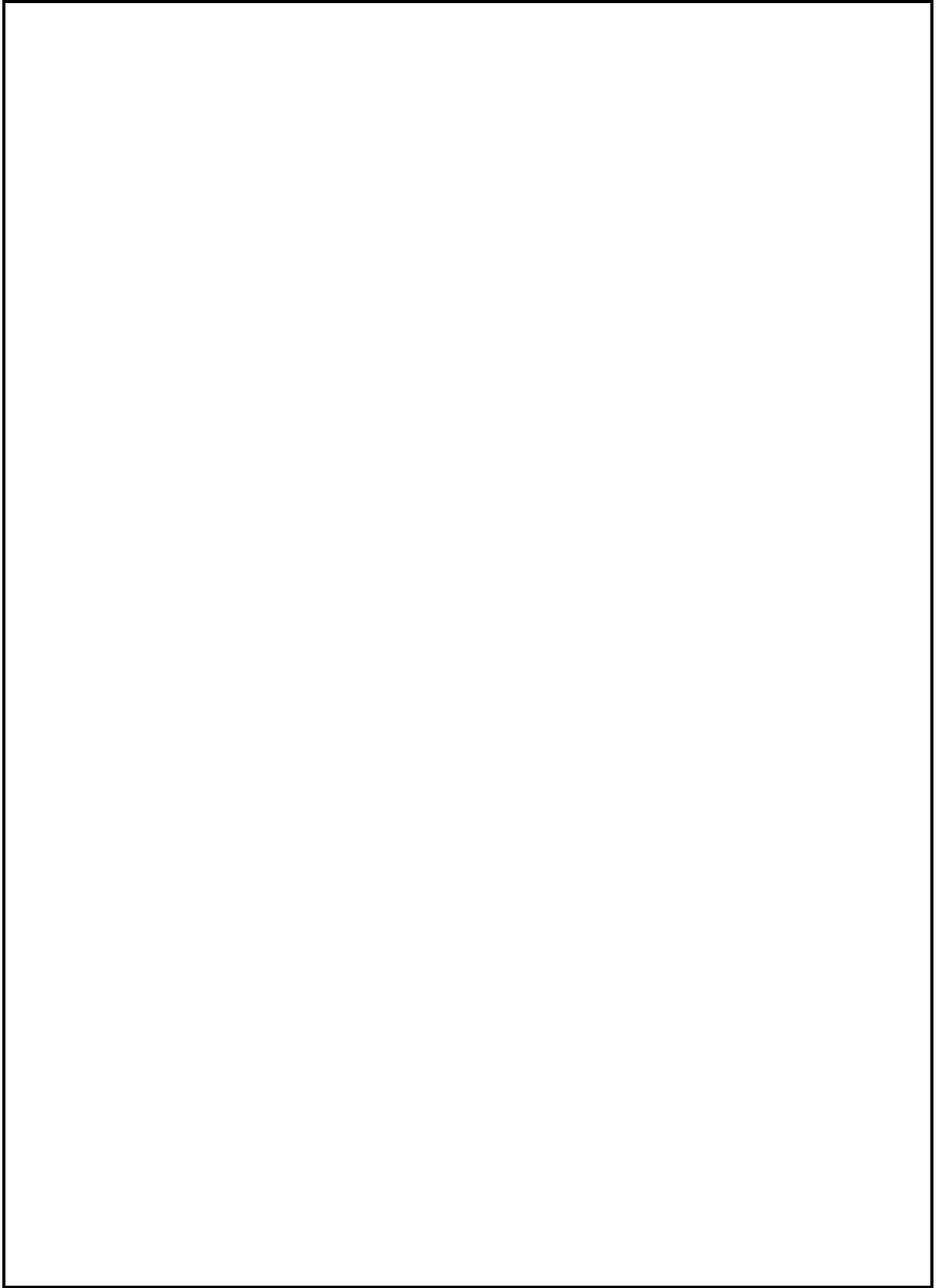


1 ease of going to another manufacturer and
2 ordering the same 100 or 1,000 BAU's that the
3 previous manufacturer used or provided.

4 This will make it very easy for
5 patients who need to switch because of
6 managed care kinds of considerations to do
7 that without having to be re-tested or
8 re-titrated.

9 There is tremendous value of the
10 information that will be available with
11 respect to these products in terms of a
12 common unit.

13 In addition, in terms of the cost
14 of care, it should have an downward pressure
15 on the cost of care, because patients and
16 physicians can purchase these extracts based
17 on the cost per BAU, which in a free market
18 should have a downward pressure on pricing
19 and make these products more accessible to
20 folks who may be at the margins in terms of
21 economics, and should provide more
22 availability.



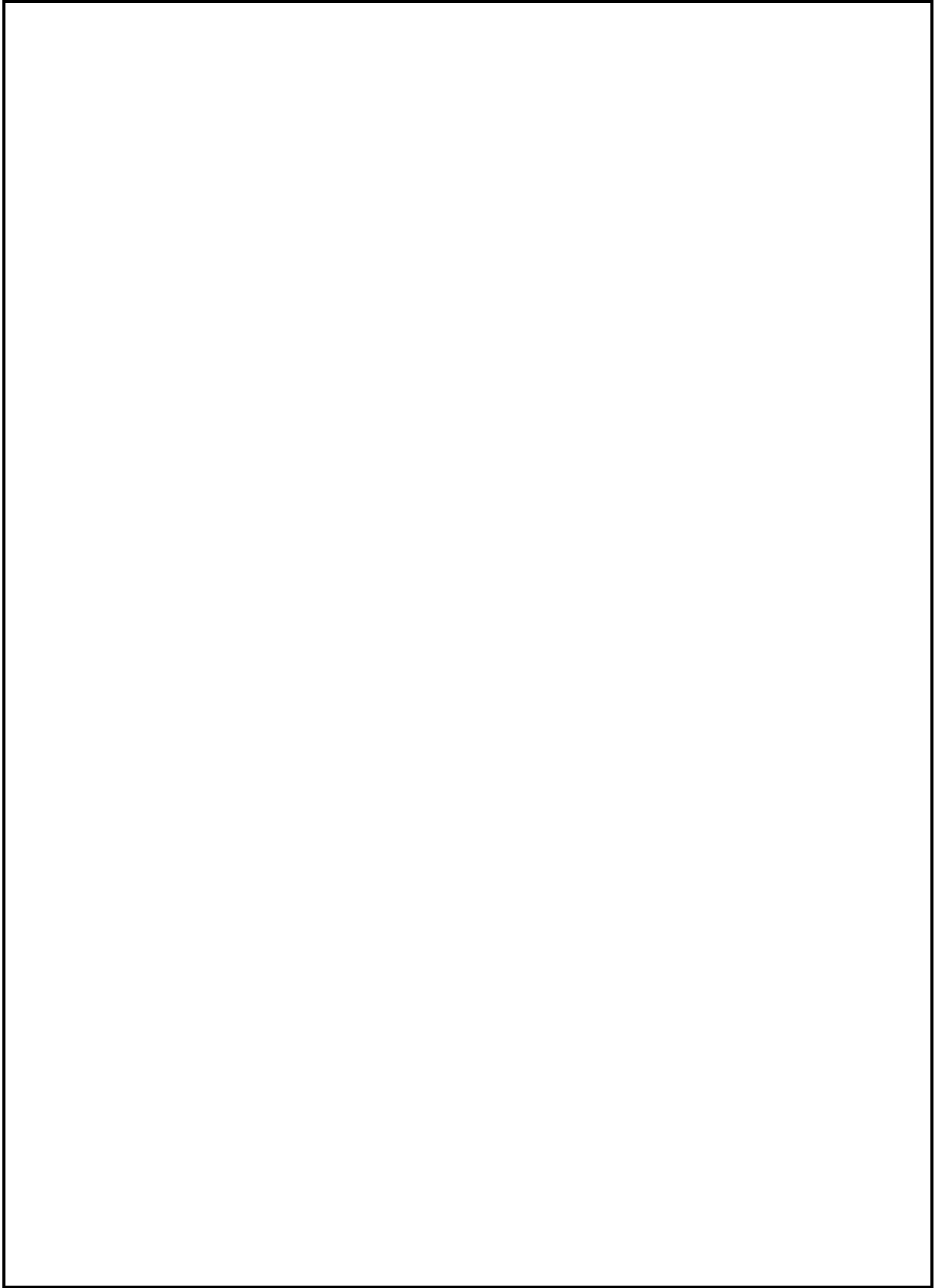
1 High quality products, number one.
2 Number two, increased value of information
3 related to a common unit and a common
4 standard.

5 MS. SANDER: Will people who are on
6 non- standardized extracts now need to be
7 re-tested or will that just start their cycle
8 again when they are transferred over to the
9 standardized or is it seamless?

10 DR. TURKELTAUB: It should be
11 seamless and much easier than the current
12 products where there is no standard. How
13 does the doctor know today when he gets one
14 lot of the same material from the same
15 manufacturer whether it has a million units
16 of potency or zero units of potency?

17 The new products will have an
18 uniform defined unit of potency. It is going
19 to be much more safe and more effective to be
20 switched to these products than the current
21 state of affairs, which is chaotic.

22 DR. SAXON: But there will be --



1 prudence will dictate. There will be some
2 slight increased activity related to the
3 transition.

4 DR. TURKELTAUB: Andy, I don't know
5 if you heard John Yunginger's question, will
6 there be information available about the
7 potency of these non-standardized materials
8 the patients were previously on, and I
9 indicated the package insert will have --

10 DR. SAXON: I understand.

11 DR. TURKELTAUB: And the companies
12 will be able --

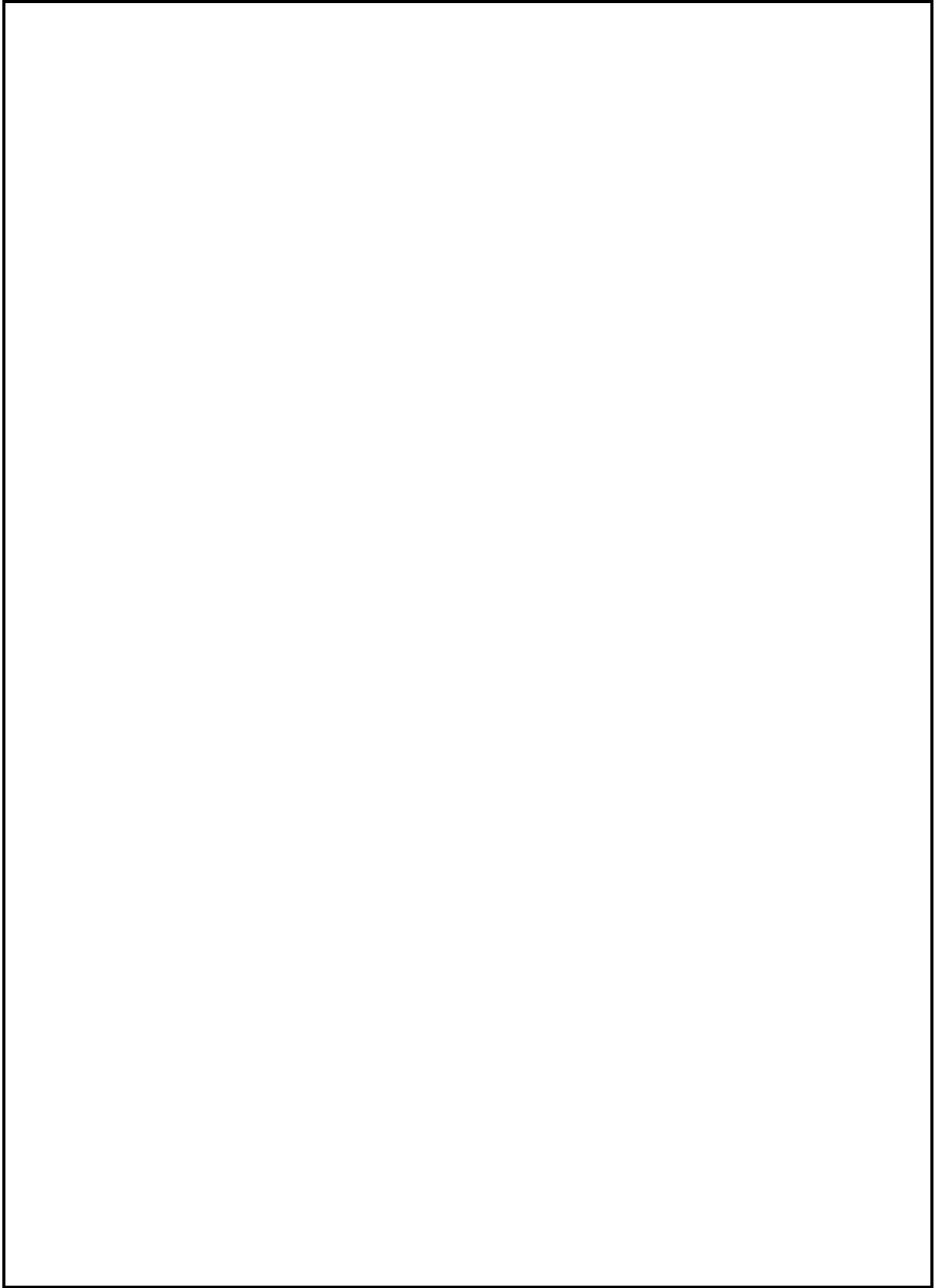
13 DR. SAXON: It's a very small
14 thing.

15 DR. TURKELTAUB: Right. The insert
16 indicates dropping back is appropriate, side
17 by side skin testing is appropriate. It does
18 not require re-titration or re-testing.

19 DR. SAXON: It is very small.

20 DR. TURKELTAUB: Exactly.

21 DR. WRAY: Even with labeling of
22 BAU's, there is still considerable



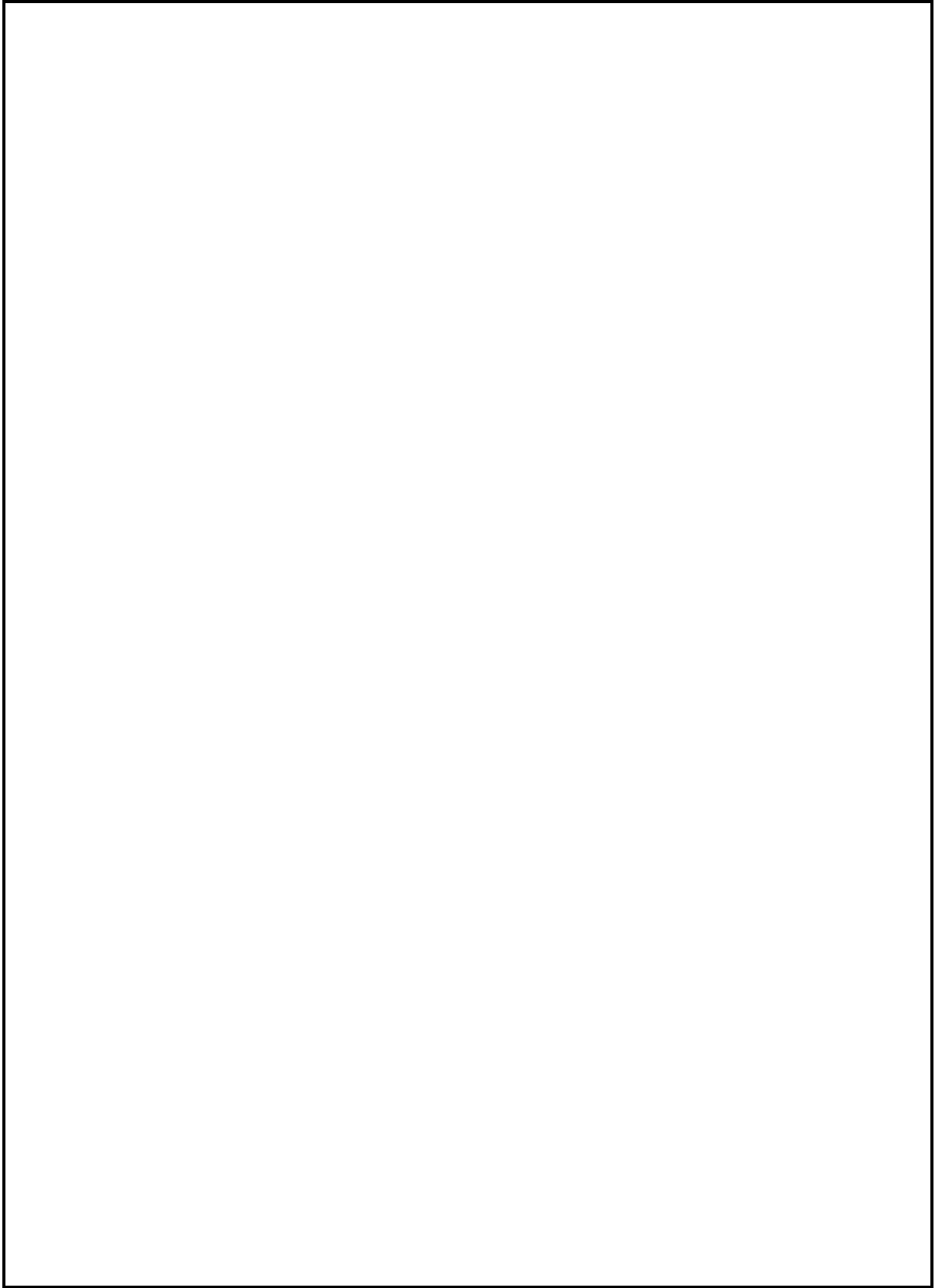
1 variations. We could get a label of 100,000
2 BAU's from one company and it's going to be
3 easily transferable, in other words, you
4 could use that from another company
5 without --

6 DR. TURKELTAUB: They both meet the
7 same potency test. We are not saying that
8 the products are identical but that's true
9 from lot to lot, you know, these are
10 complicated products in terms of their
11 composition, their protein and allergen
12 composition.

13 Within the confines of the test,
14 the variability is not particularly great
15 compared to non-standardized products, which
16 have infinite variability. These only have
17 three to fourfold variability.

18 That's the best we can do right
19 now. I don't know if anybody does any better
20 around the world.

21 DR. WRAY: The variation is three
22 to fourfold?



1 DR. TURKELTAUB: Yes, and the
2 advice in the package insert is when you
3 switch from one lot of the same material to
4 the next lot, to reduce the dose 75 percent
5 to account for that three to fourfold
6 variability.

7 Has any of the members on the
8 Advisory Committee received the letter
9 related to grass standardization from a
10 company they might deal with?

11 DR. WRAY: I'm not sure what letter
12 you are referring to. We have had several
13 communications.

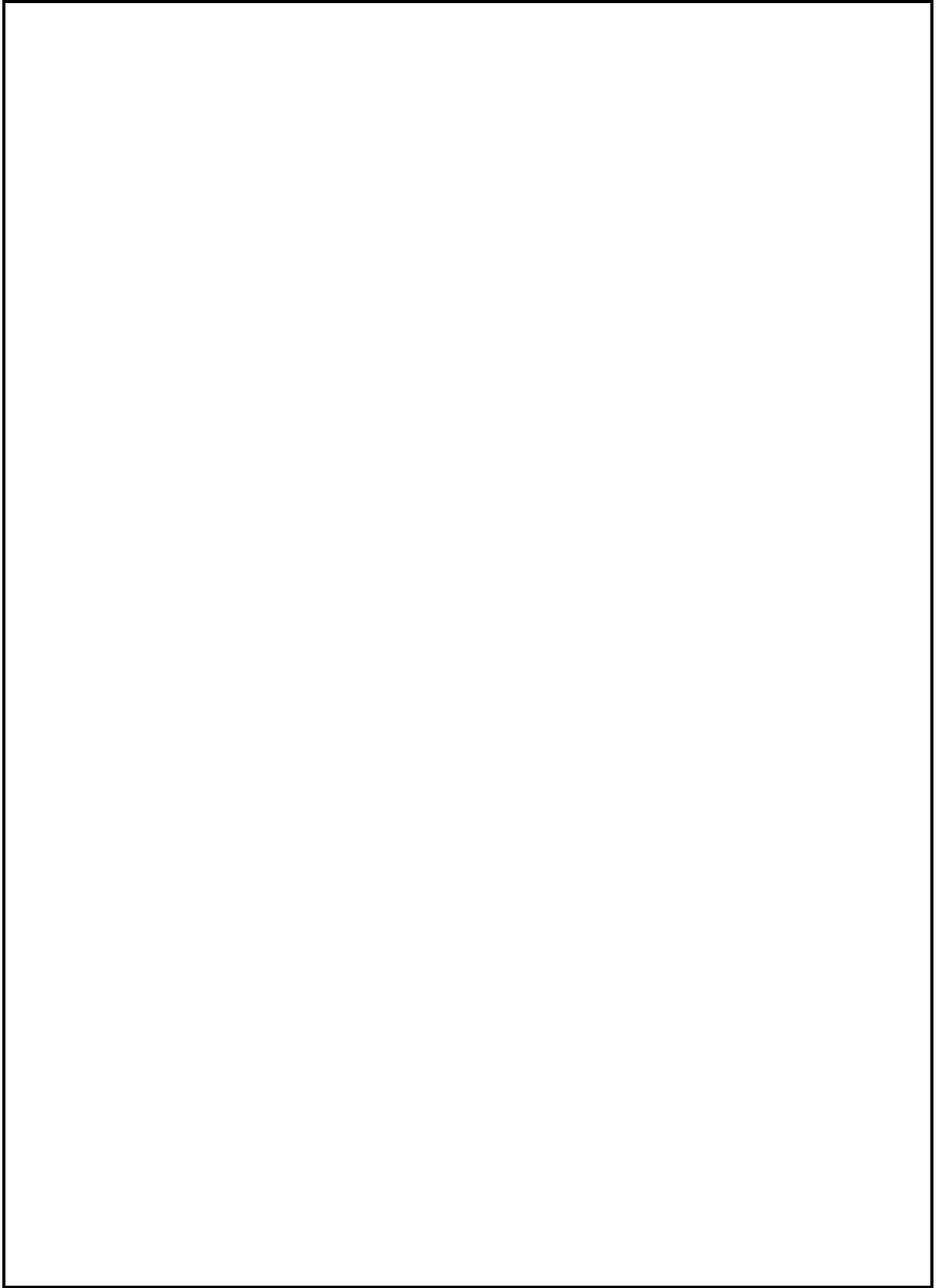
14 MR. FREAS: Dr. Wray, if that was
15 you, please identify yourself for the
16 transcriber.

17 DR. WRAY: I'm sorry.

18 MR. FREAS: Thank you.

19 DR. WRAY: Wray. We have had
20 several communications but I'm not sure
21 exactly which letter you are referring to.

22 DR. TURKELTAUB: Is the letter

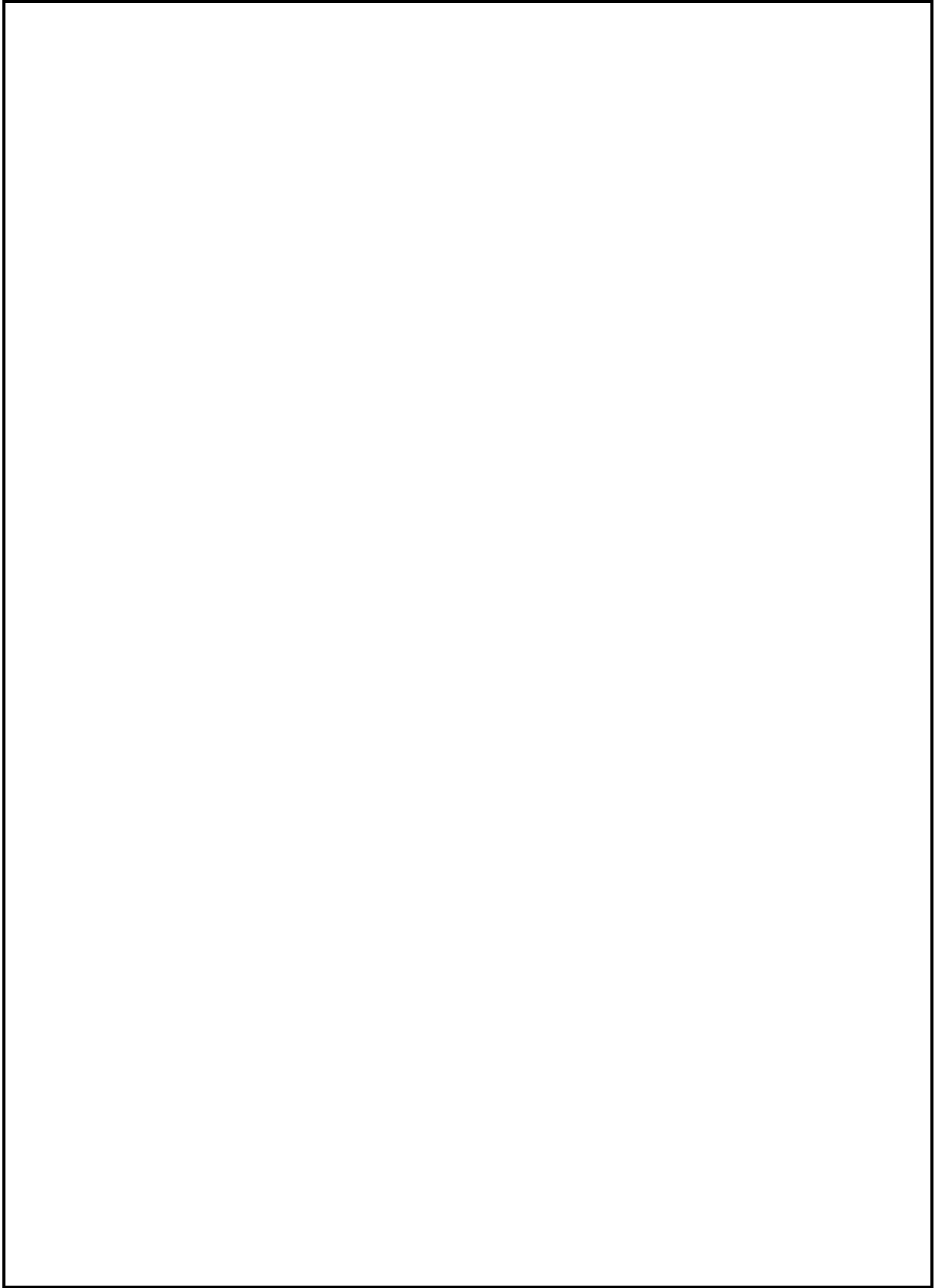


1 related to the availability of the
2 standardized grass products with some of the
3 cautions and information related to
4 switching, et cetera?

5 DR. CLAMAN: Henry Claman. I have
6 received a letter from ALK, one page, telling
7 me about the availability of the grass
8 extracts and 10,000 and 100,000 BAU's and
9 telling me that more information is on the
10 way.

11 DR. TURKELTAUB: Well, maybe the
12 fact that the deadline was postponed, they
13 are holding back on sending out some of that
14 communication in terms of that which we have
15 approved. We don't define when they send
16 these out and maybe they are waiting later,
17 until the very bitter end.

18 DR. YUNGINGER: The letters that I
19 have seen have been just general letters of
20 announcing availability. I received the same
21 letter that Dr. Claman has. I have not seen
22 any letters from manufacturers as yet



1 advising me of how their old and new
2 standardized product compares with respect to
3 potency.

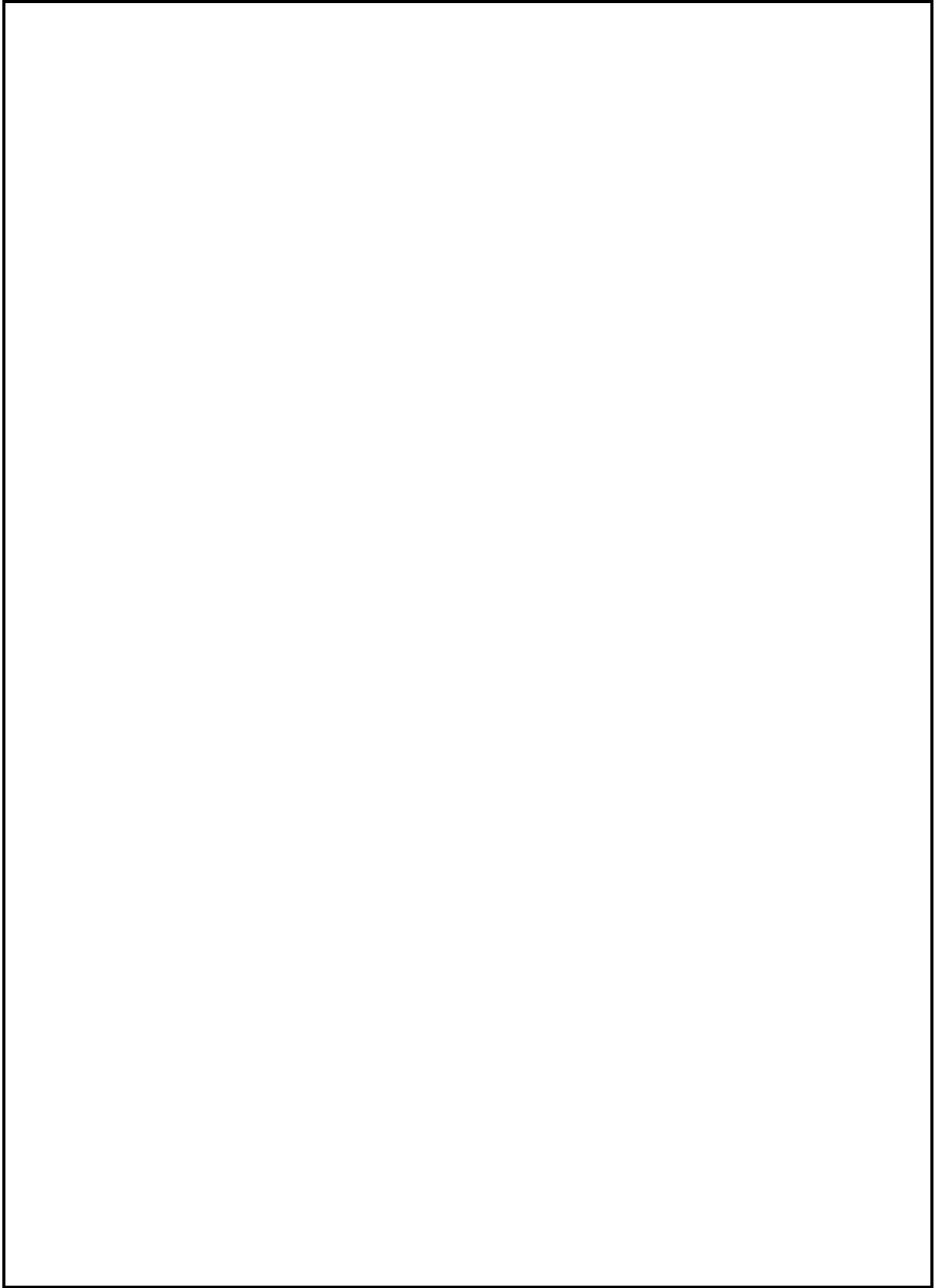
4 DR. TURKELTAUB: Well, again, that
5 information will be in the inserts. I
6 thought some of the companies would be
7 attaching the insert along with the "Dear
8 Doctor" letter. Maybe they haven't.

9 DR. YUNGINGER: It might be prudent
10 for us to check with our nurses, the persons
11 who actually are working with this on a day
12 to day basis. I'm sure the physicians would
13 probably be the last people to be aware of
14 this.

15 DR. BERKOWER: Dr. Yunginger, I'd
16 like to make one other comment.

17 DR. YUNGINGER: Yes.

18 DR. BERKOWER: The standardized
19 products have been tested for stability, so
20 they have real time stability studies showing
21 that they still fall within their specs
22 during a real time dating period, and that's



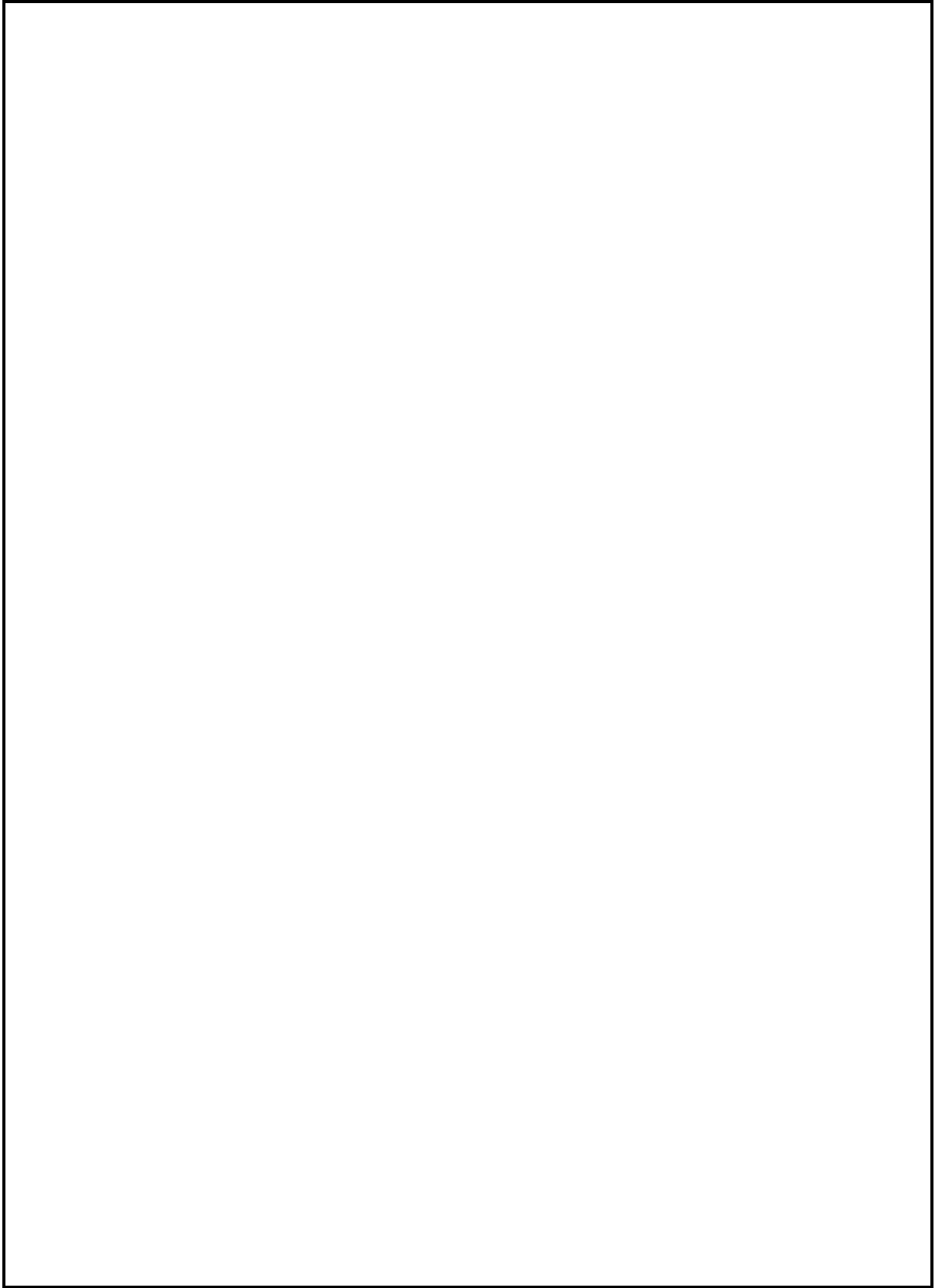
1 another advantage of the standardized
2 materials, that it is going to be potent
3 right up to the time that it gets into the
4 needle.

5 DR. YUNGINGER: Just one other
6 observation. I think this has been a tough
7 extract to standardize and put into clinical
8 use, simply because it tends to be one that's
9 very widespread.

10 There was a similar dislocation
11 when the cat allergen materials were
12 re-labeled and standardized several years
13 ago, but I sense a good spirit of cooperation
14 between the agency, the consumer and the
15 manufacturers here to get this on board with
16 as much good data as we can and hopefully
17 with a minimum amount of dislocation.

18 Are there any other comments with
19 respect to the standardized grass extracts at
20 this time?

21 DR. HOFFMAN: Yes, this is Thomas
22 Hoffman. We are pursuing educational efforts

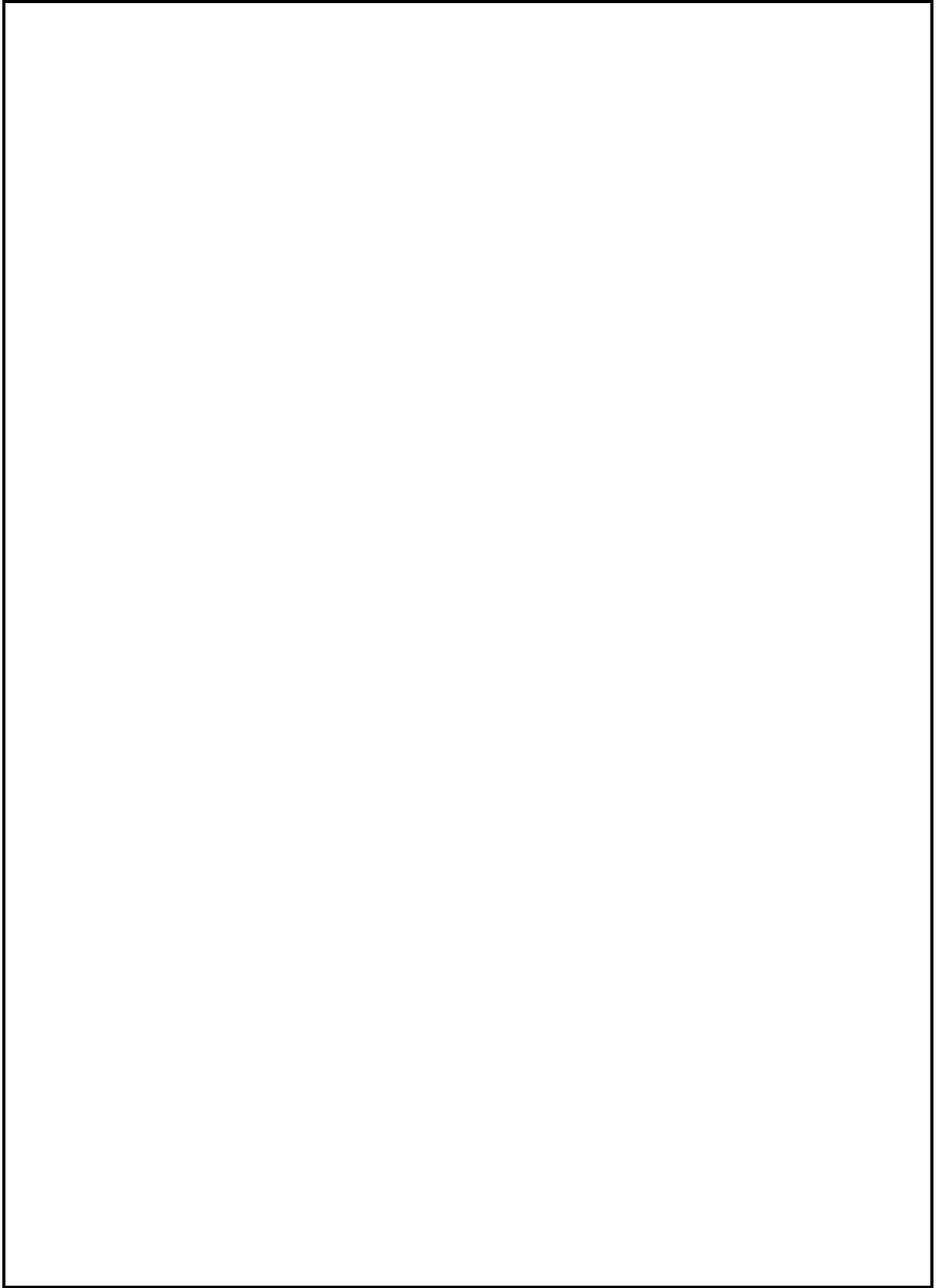


1 from our end as well. We have formulated our
2 own "Dear Doctor" letter which is in the
3 final phases of approval within the
4 Commissioner's Office, and that will be going
5 out shortly, and a companion piece containing
6 much similar information will be published in
7 FDA Bulletin quite soon.

8 I can't give you the exact dates
9 for that, but I believe those are eminent.

10 DR. HARDEGREE: This is Carolyn
11 Hardegree. It's my understanding that the
12 letters that will go to the "Dear Colleagues"
13 will go primarily to the various medical
14 groups as opposed to individual physicians,
15 and will be dependent upon those medical
16 groups to see that their constituents receive
17 the information.

18 MS. BRIDGEWATER: This is Jennifer
19 Bridgewater. Once that letter is completed,
20 we will also post that on the Web Page, so
21 that it will be available to anyone who wants
22 to look at it.



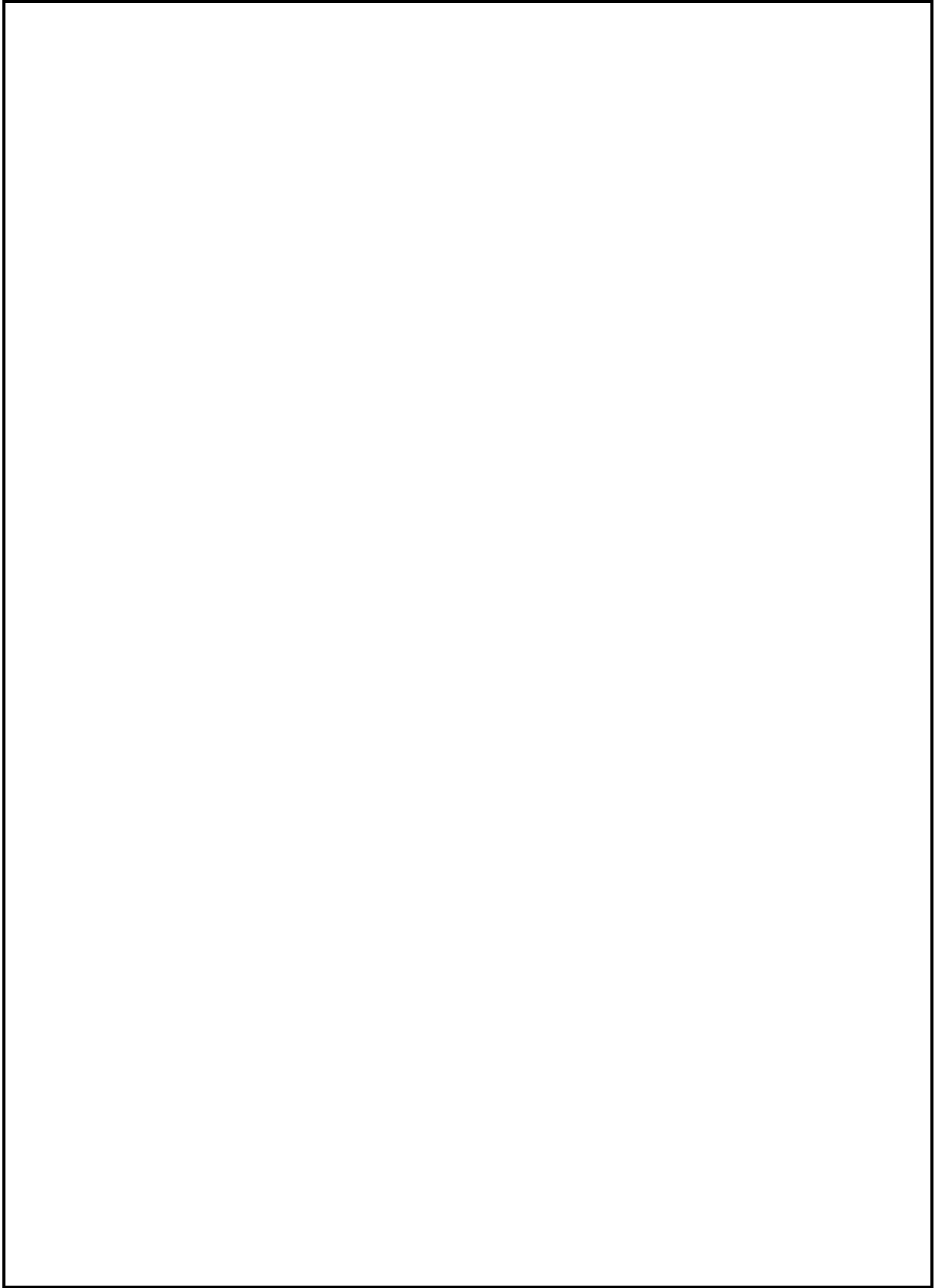
1 DR. YUNGINGER: Is there any
2 further announcement that you could give us
3 concerning the APMA petition for stay of
4 action.

5 The manufacturers are seemingly all
6 on board here with respect to standardized
7 grass extracts and have them available. Is
8 the petition still pending for stay of action
9 or has it been withdrawn?

10 DR. HOFFMAN: This is Thomas
11 Hoffman again. We are in a position that we
12 can but acknowledge the existence of this
13 petition and we really can't comment further
14 on any of its details. The petition is
15 before the agency.

16 DR. YUNGINGER: When that matter is
17 resolved, how will the resolution be
18 publicized?

19 DR. HOFFMAN: I presume the APMA
20 will publicize it. I think it's really out
21 of our hands. I mean it just will be
22 resolved in that fashion.



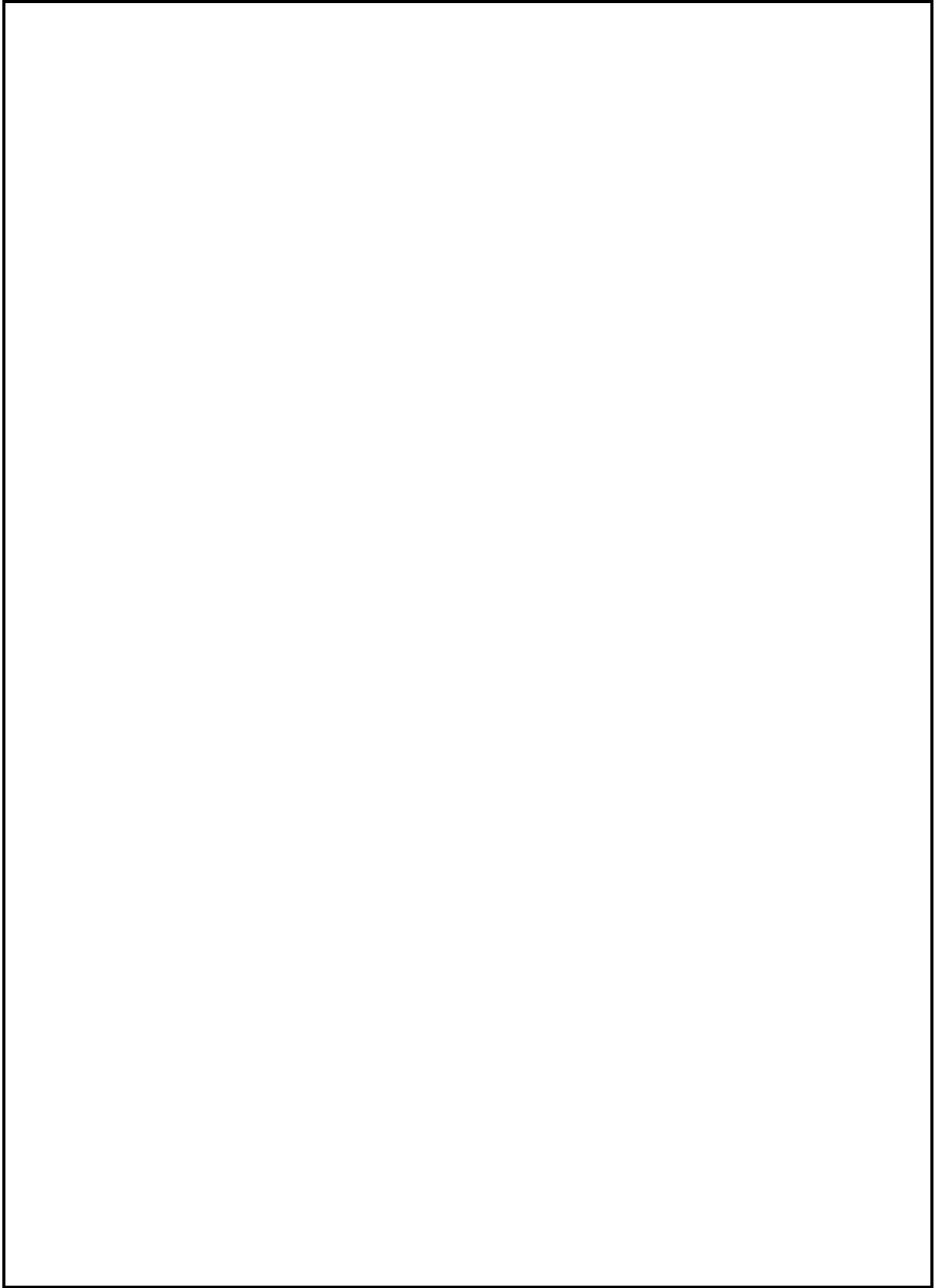
1 DR. HARDEGREE: Dr. Yunginger and
2 committee, this is Carolyn Hardegree again.
3 There are administrative procedures that FDA
4 will follow to have to deal with this
5 petition, so we will follow through those
6 processes. Once it's done, then we will see
7 how widespread any response can be made.

8 DR. YUNGINGER: Thank you,
9 Dr. Hardegree. Are there any other comments
10 regarding the grass standardization?

11 DR. HOFFMAN: I'd just like to say
12 the approvals are on the Web site but nine
13 manufacturers have been approved for the
14 grasses, without listing them here, but they
15 are on the Web site. I think we can say that
16 all have been approved.

17 DR. YUNGINGER: Mr. Freas, are
18 there any members of the public with us that
19 weren't there before that wish to make any
20 comments, before we move onto the next item?

21 MR. FREAS: We did one member of
22 the public but she does not wish to



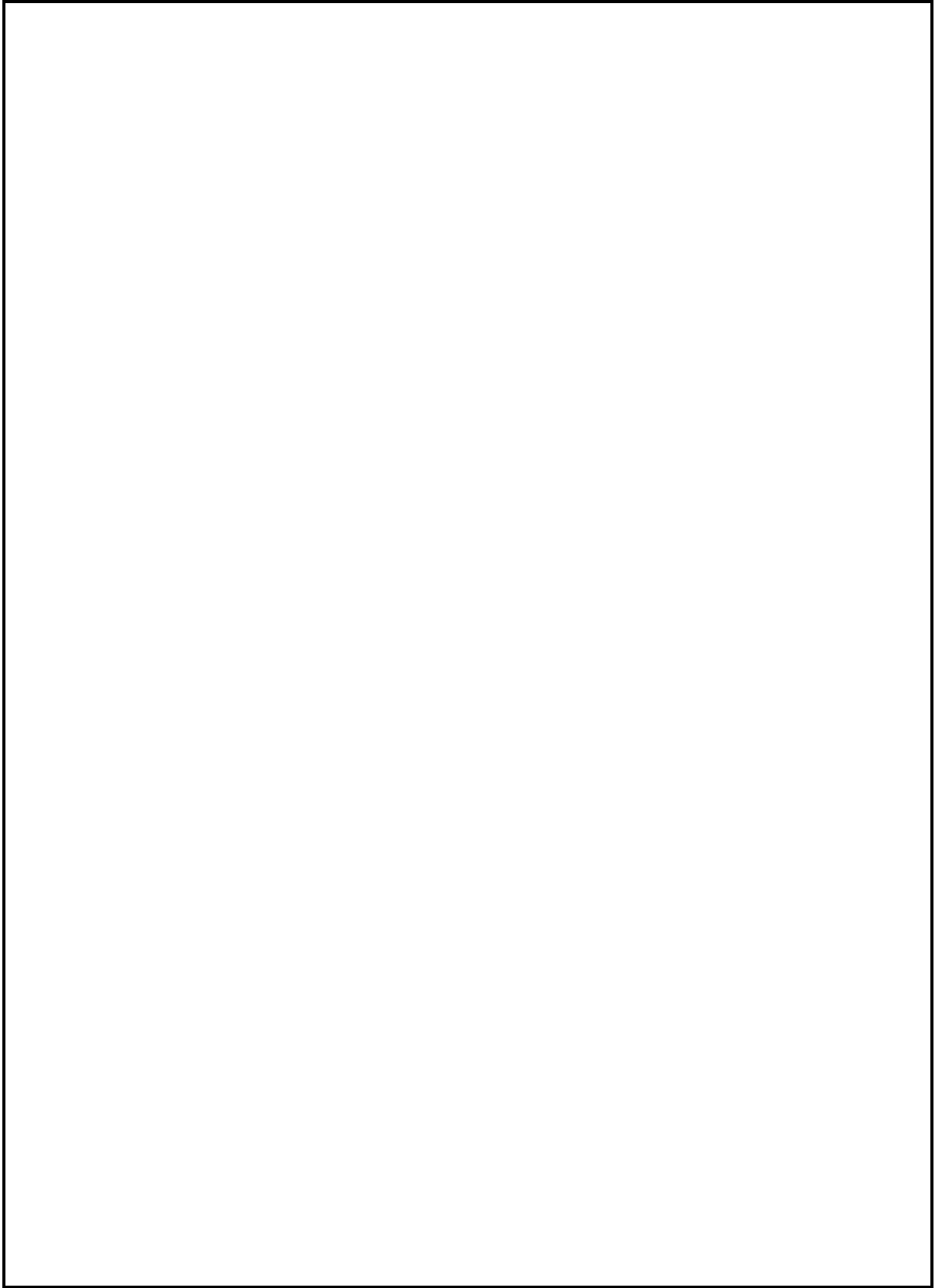
1 participate at this time. It's good to have
2 public representation here. We are ready to
3 move on.

4 DR. YUNGINGER: The next item on my
5 list has to do with future standardization
6 efforts. Does someone from the agency wish
7 to introduce this subject?

8 DR. HOFFMAN: Yes, this is Thomas
9 Hoffman again. I will be giving an entree to
10 any discussion that we have, and I thought
11 that I would take the opportunity to make the
12 committee members aware of some of the
13 changes that have taken place, and some of
14 the personnel that are participating in this
15 effort, and some background information prior
16 to the discussion.

17 In the first page of the handout
18 that you received, I've listed one component
19 of the Division of Allergenic Products and
20 Parasitology, which is the Laboratory of
21 Immunobiochemistry.

22 Approximately six weeks ago,



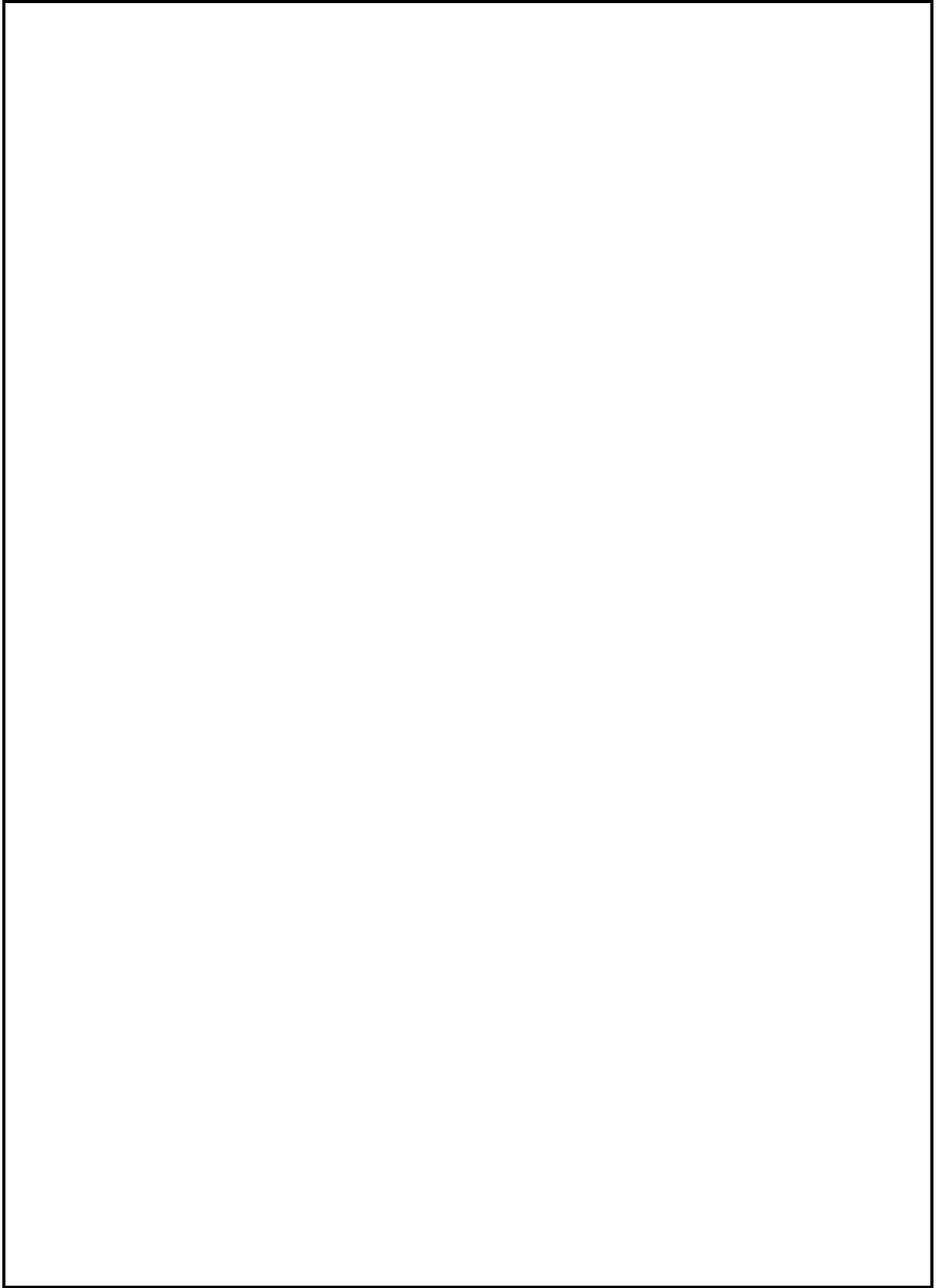
1 Dr. Richard Pastor, who is present, has
2 consented to act as the chief of that
3 laboratory.

4 Dr. Pastor has taken over the
5 responsibilities of that laboratory which
6 include the allergenic product testing, lot
7 release, and standard maintenance and
8 characterization.

9 He has been joined by a number of
10 personnel who are listed in the paragraph
11 below. There are four technical personnel
12 who are actively involved in our testing
13 program and are carrying out a thorough
14 re-evaluation of some of the laboratory
15 procedures that are involved.

16 In addition, there is research
17 ongoing in that laboratory pertaining to
18 allergenics characterization by molecular
19 biological techniques, and this effort is
20 being headed by Dr. Totobo.

21 In addition, although it is not
22 listed on your form, many other personnel



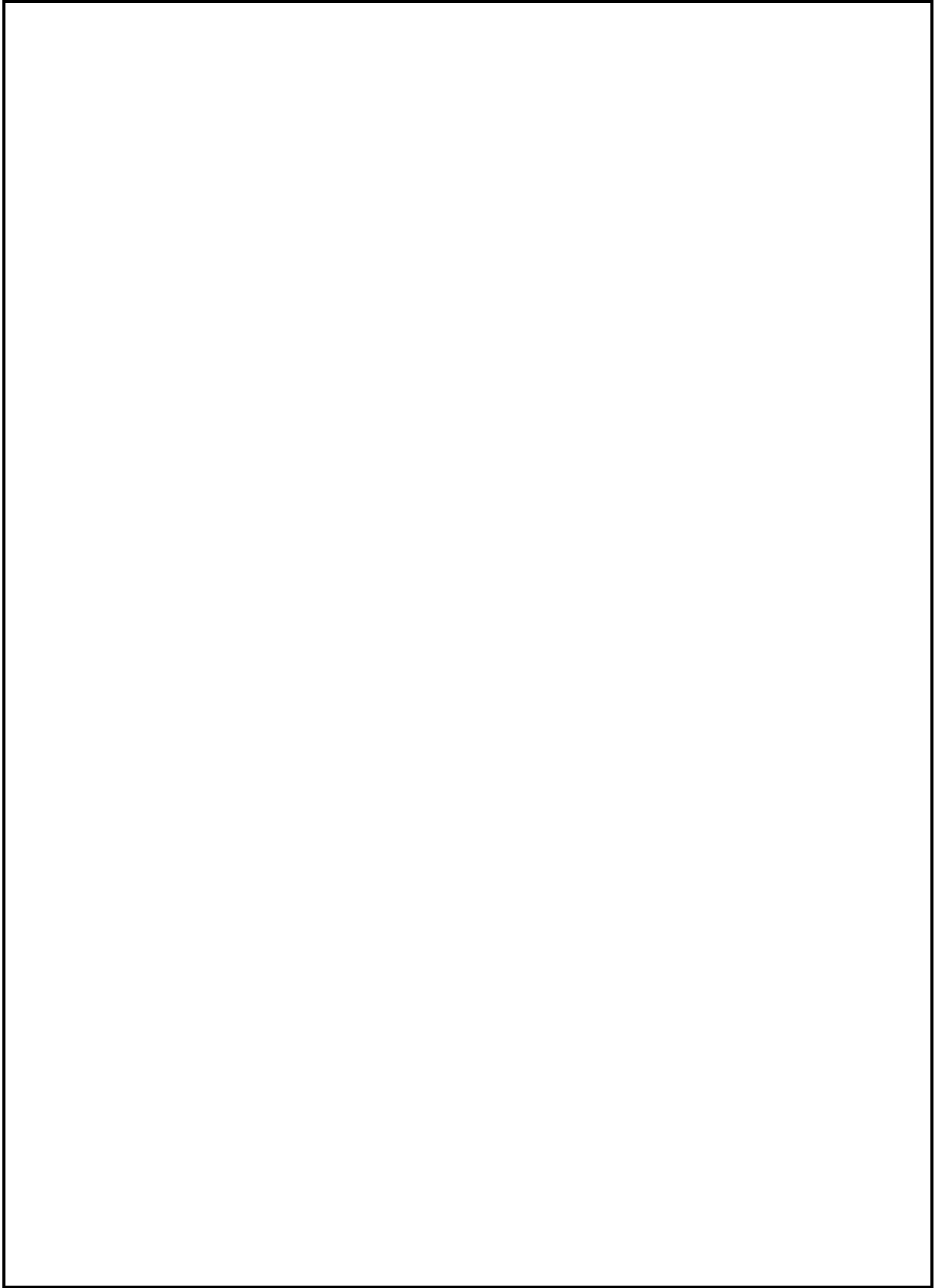
1 from the other laboratories, you will hear
2 from Dr. Berkower, who is the head of the
3 laboratory of immunoregulation, is also
4 participating in this effort, and personnel
5 from the laboratory of parasitology are also
6 assisting in standardization efforts.

7 It's an umbrella effort on the part
8 of virtually all components of the division.

9 You have interacted in the past
10 with Dr. Turkeltaub, the Associate Director
11 of the Division, who really has almost
12 single-handedly fostered the clinical program
13 within the Division.

14 In an attempt to assist him and
15 shore up this effort, we have instituted an
16 ad hoc clinical program or working group
17 consisting of Dr. Berkower and myself.

18 Dr. Berkower, as you may know, is a
19 Board certified allergist. I am a clinical
20 immunologist. Dr. Weiss and Dr. Kenny, who
21 are members of other laboratories within the
22 Division have also been recruited to



1 participate in this effort.

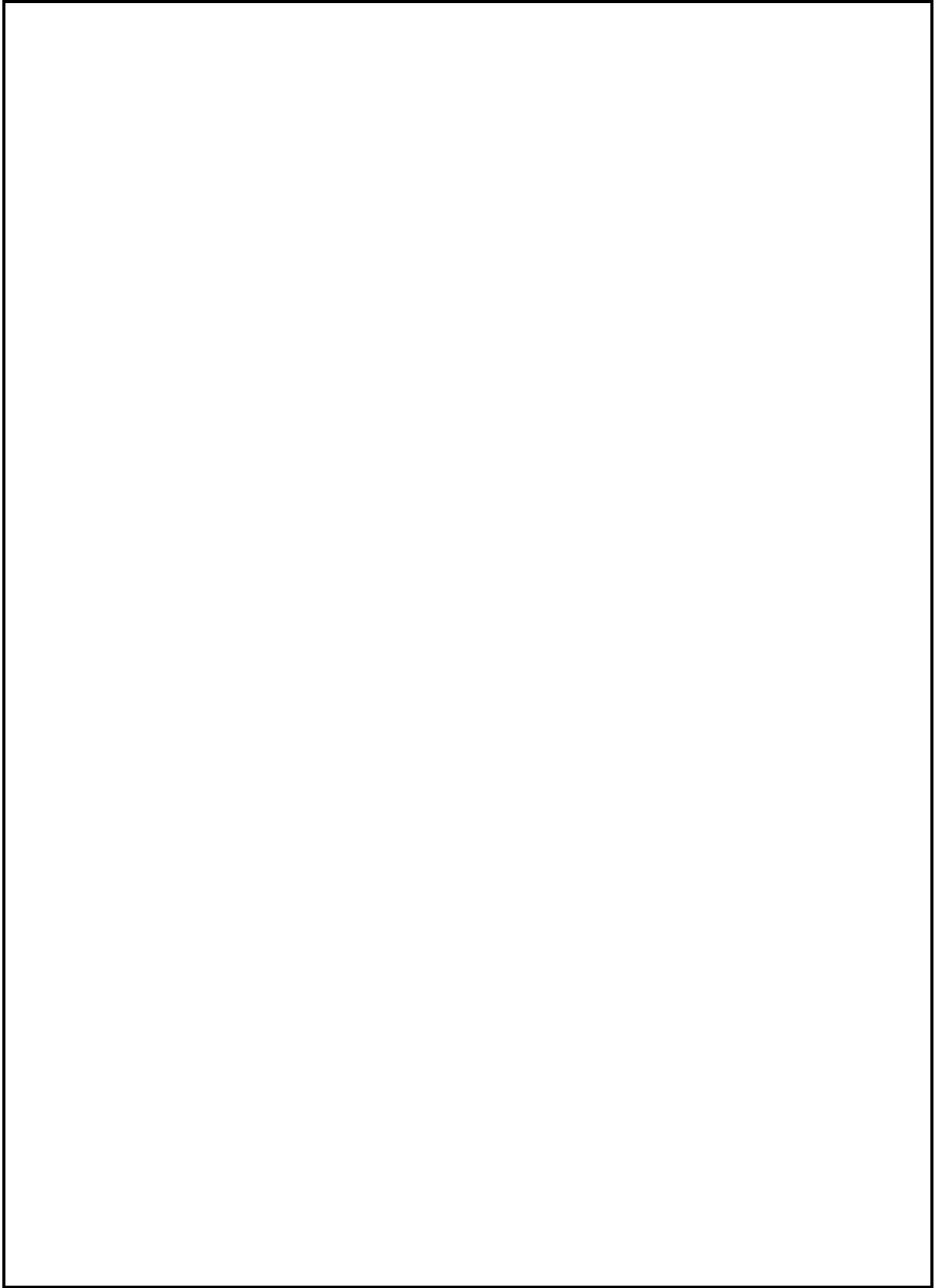
2 Hopefully, we will have our bases
3 covered a little bit more solidly in that
4 regard, too.

5 On the next page of your handout, I
6 thought it would be instructive and useful to
7 go over what it takes to carry out the
8 allergenic standardization program. You may
9 think of this as maybe the denominator of the
10 effort.

11 I've categorized a number of areas
12 where I believe we are trying quite earnestly
13 to have as complete expertise and knowledge
14 as we can muster.

15 Obviously, we all feel that a
16 fundamental knowledge of allergy and
17 immunology is crucial, both for understanding
18 the normal immune response and the aberrant
19 immune response which takes place during an
20 allergic reaction.

21 Hopefully, the expertise that you
22 have heard about from the personnel that I



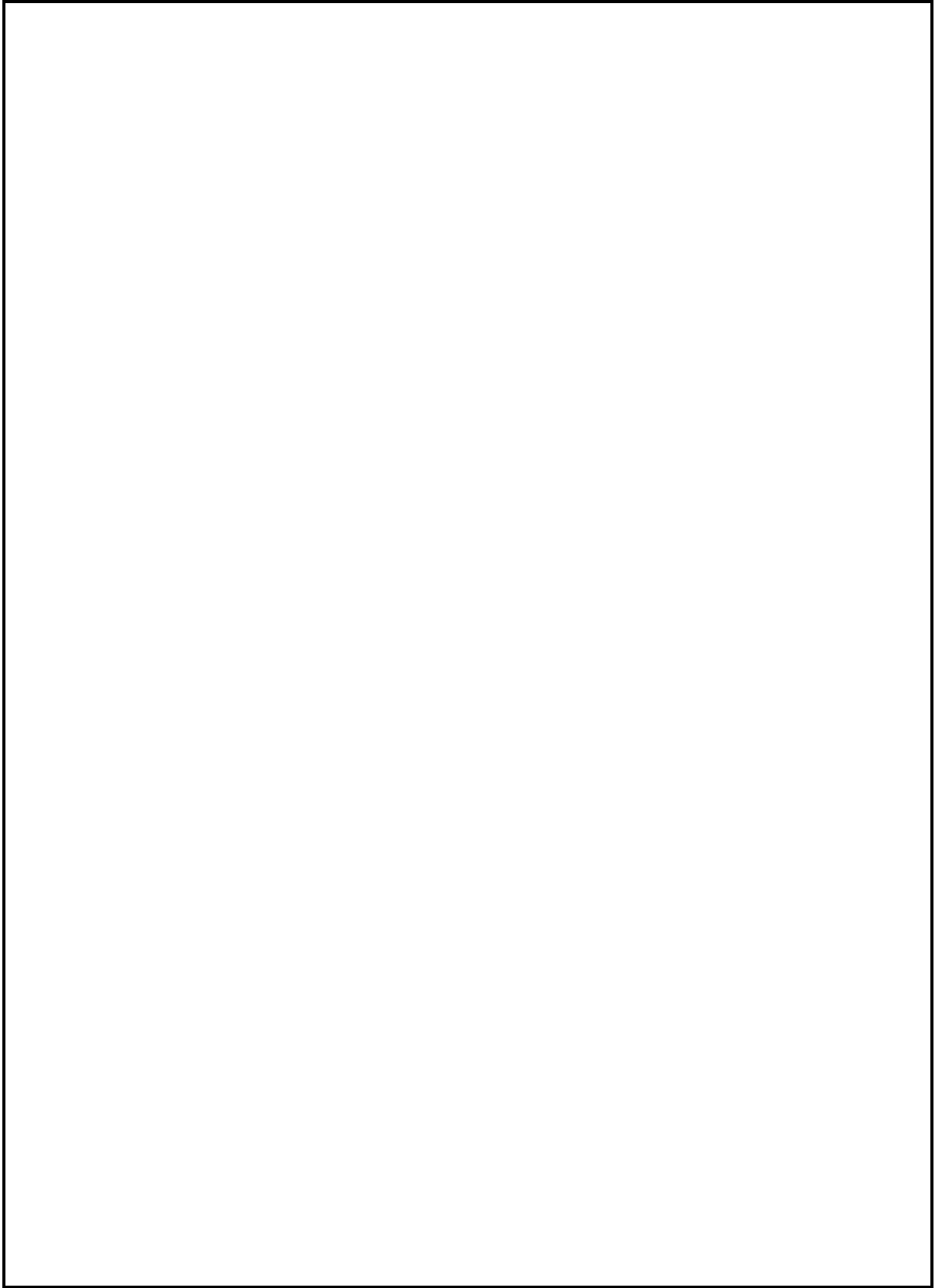
1 mentioned begins to make some effort at
2 having this area covered.

3 Obviously, this is a very important
4 regulatory issue and issues related to the
5 compliance program in terms of the way that
6 the allergenic products are manufactured.

7 And the appropriateness of their
8 ability to comply with the various
9 regulations for safety of allergenic products
10 is a complicated matter.

11 We are fortunate to have
12 Ms. Bridgewater who has both laboratory
13 knowledge and a long history of expertise in
14 this area.

15 The clinical program that was
16 instituted by first Dr. Bayer along with
17 Dr. Turkeltaub, consists of, as you well
18 know, the basic skin testing and epidemiology
19 of allergy in the United States, and entails
20 an important effort in keeping track of the
21 appropriate patients, the appropriate
22 allergic populations in which to test our



1 products, and to establish standards.

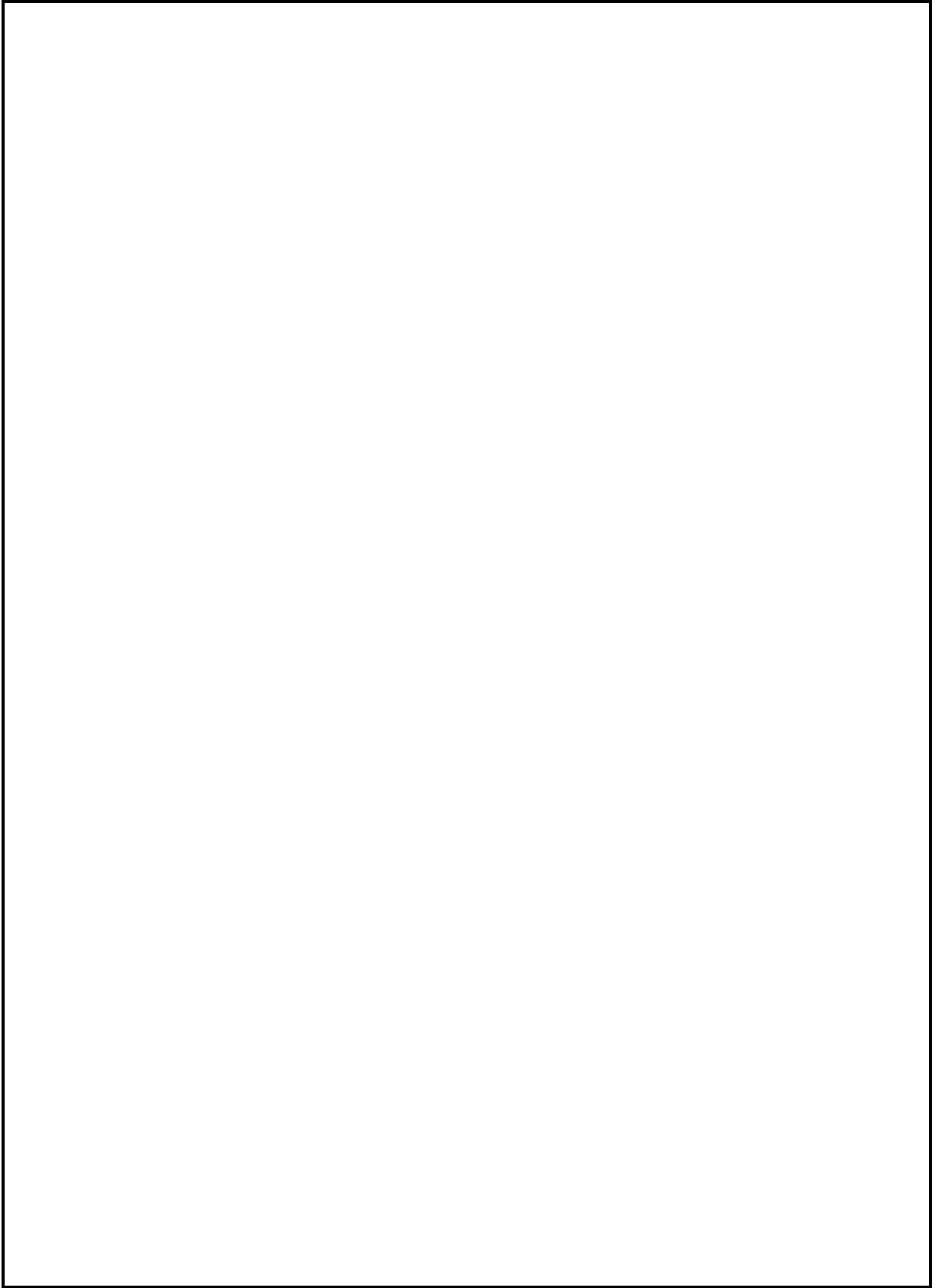
2 This requires both expertise in
3 database management, database maintenance,
4 patient management and patient accrual.

5 In addition, we must keep track of
6 a wide variety and type, a differing number
7 of types of sera from our patients, storing
8 them appropriately, making sure that they
9 meet the standards they are supposed to
10 represent.

11 One of the areas that we are
12 particularly fortunate to have wide and deep
13 expertise in is in the area of biochemistry
14 and biophysics.

15 The laboratory of biophysics has
16 expertise in a wide variety of computational
17 and analytical methods that are becoming more
18 and more vital as we pursue allergenic
19 standardization for many aspects, both in
20 terms of the clinical response as well as the
21 chemical response.

22 We are quite expert in protein



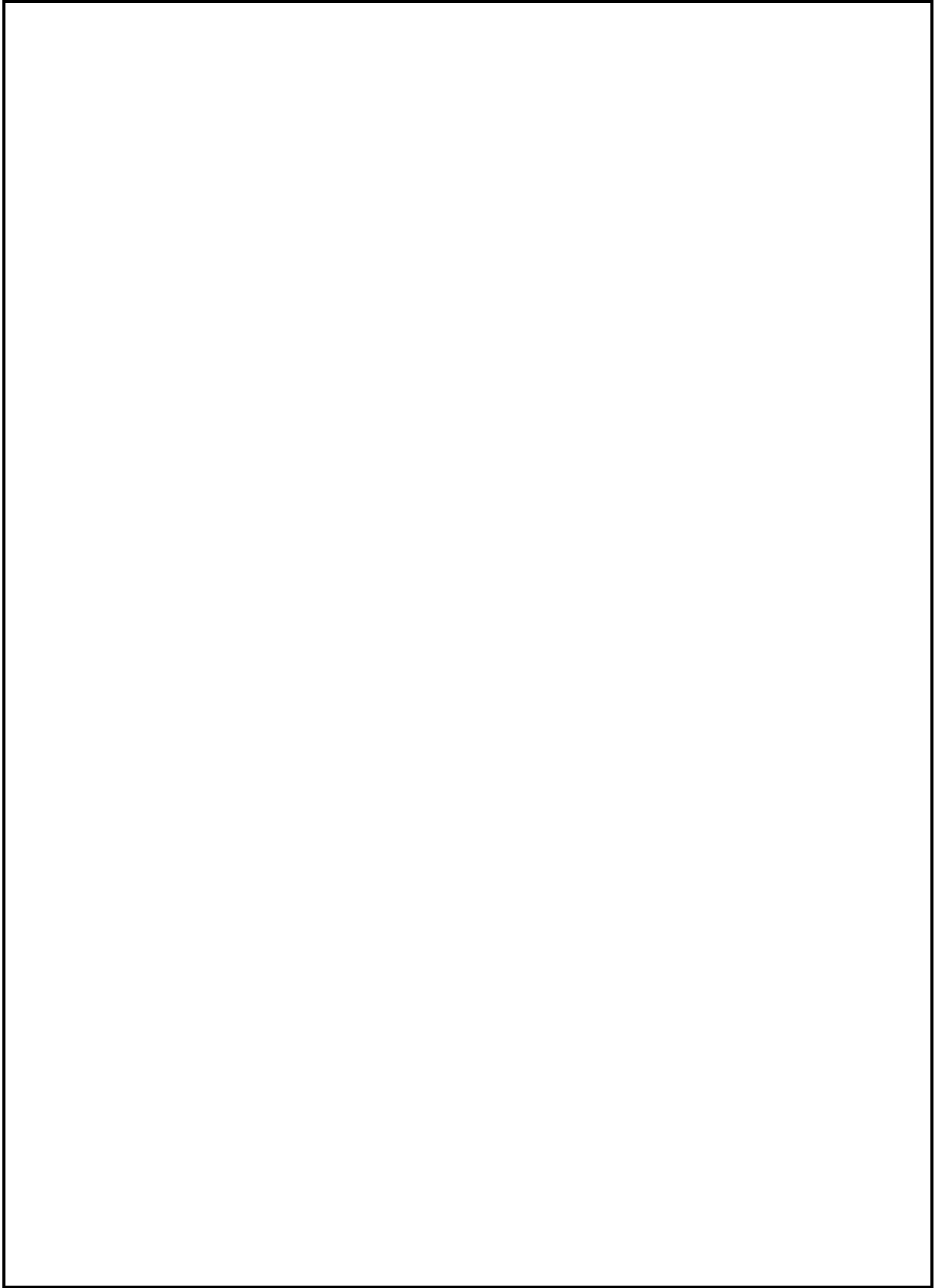
1 chemistry and specifically immunochemistry,
2 and we are trying very hard to maintain a
3 high level of analytical knowledge that
4 includes statistical knowledge, quality
5 assurance and quality control.

6 As you see, we have had to draw on
7 resources from outside the laboratory,
8 including those within the Division, and
9 other areas of the Center.

10 Although this is sometimes
11 overlooked, the management of this issue, in
12 communicating, we talked about the issues of
13 education of physicians, interacting with the
14 public on these very important issues is
15 something that we are making a particular
16 effort on today.

17 On the next page, I tried to
18 outline some of our thinking pertaining to
19 the major topic that we are discussing today,
20 on which allergenics we might standardize.

21 I think that the standardization of
22 the grass is a yeoman effort. I hesitate to



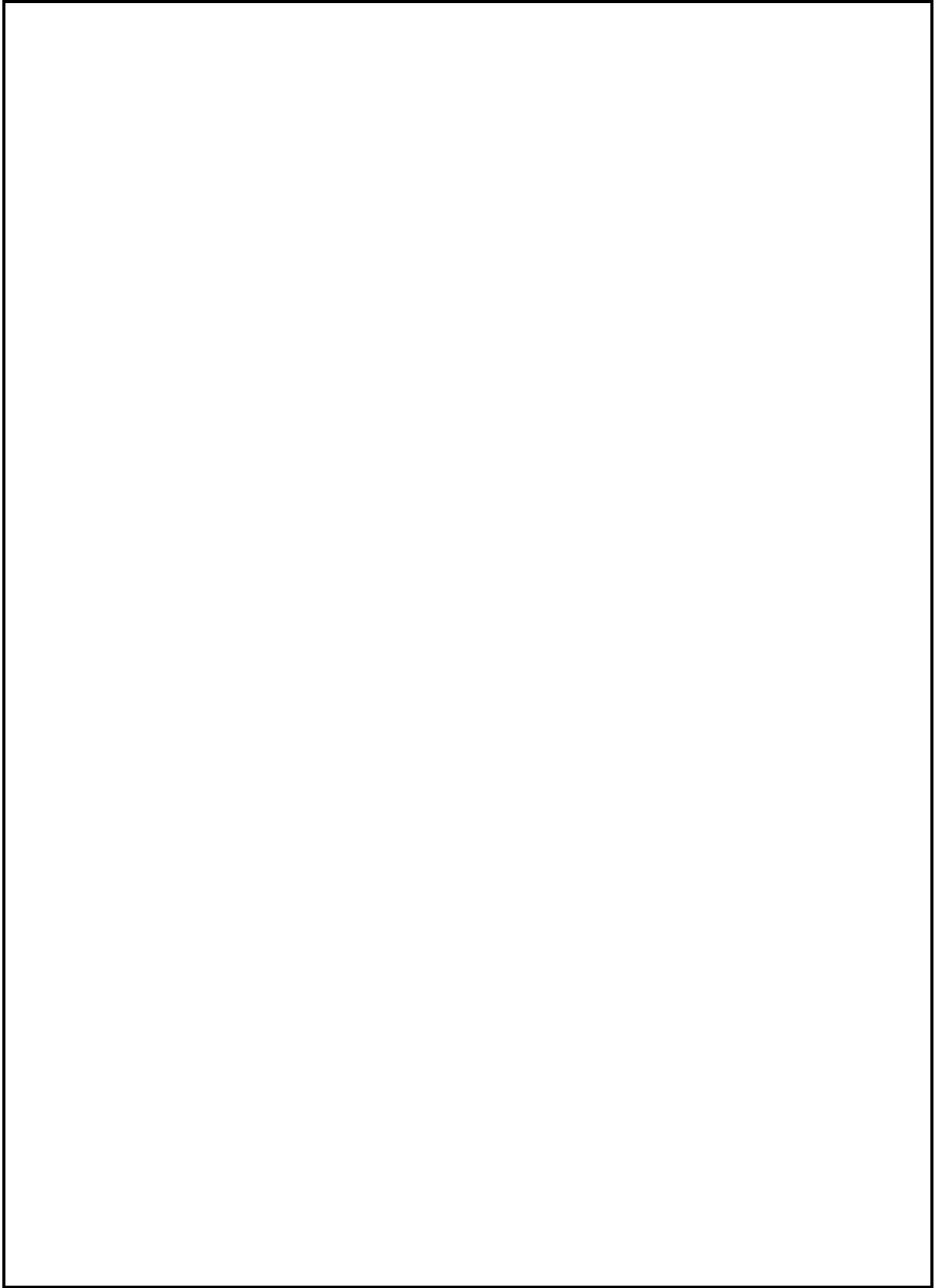
1 use the word "Titanic," but it has been on a
2 scale, considering the resources that have
3 been available, something that's really
4 amazing.

5 I was not originally involved in
6 this process but it is really remarkable, the
7 team work and cooperation that went into this
8 effort, and kudos are extended to all the
9 people at the FDA who did so.

10 Well, we are not ones to rest on
11 our laurels. We have thought about other
12 areas and I have listed them in part as a
13 basis for discussion.

14 Certainly, a wide spectrum of the
15 population is allergic to tree pollens. This
16 is one area in which standardization could
17 conceivably have an impact, at least on the
18 scale of grasses.

19 The matter of latex has come up
20 before as obviously pervasive, given the
21 biomedical uses to which latex is given and
22 its wide pervasiveness in a variety of



1 products to which the public at large is
2 exposed as well.

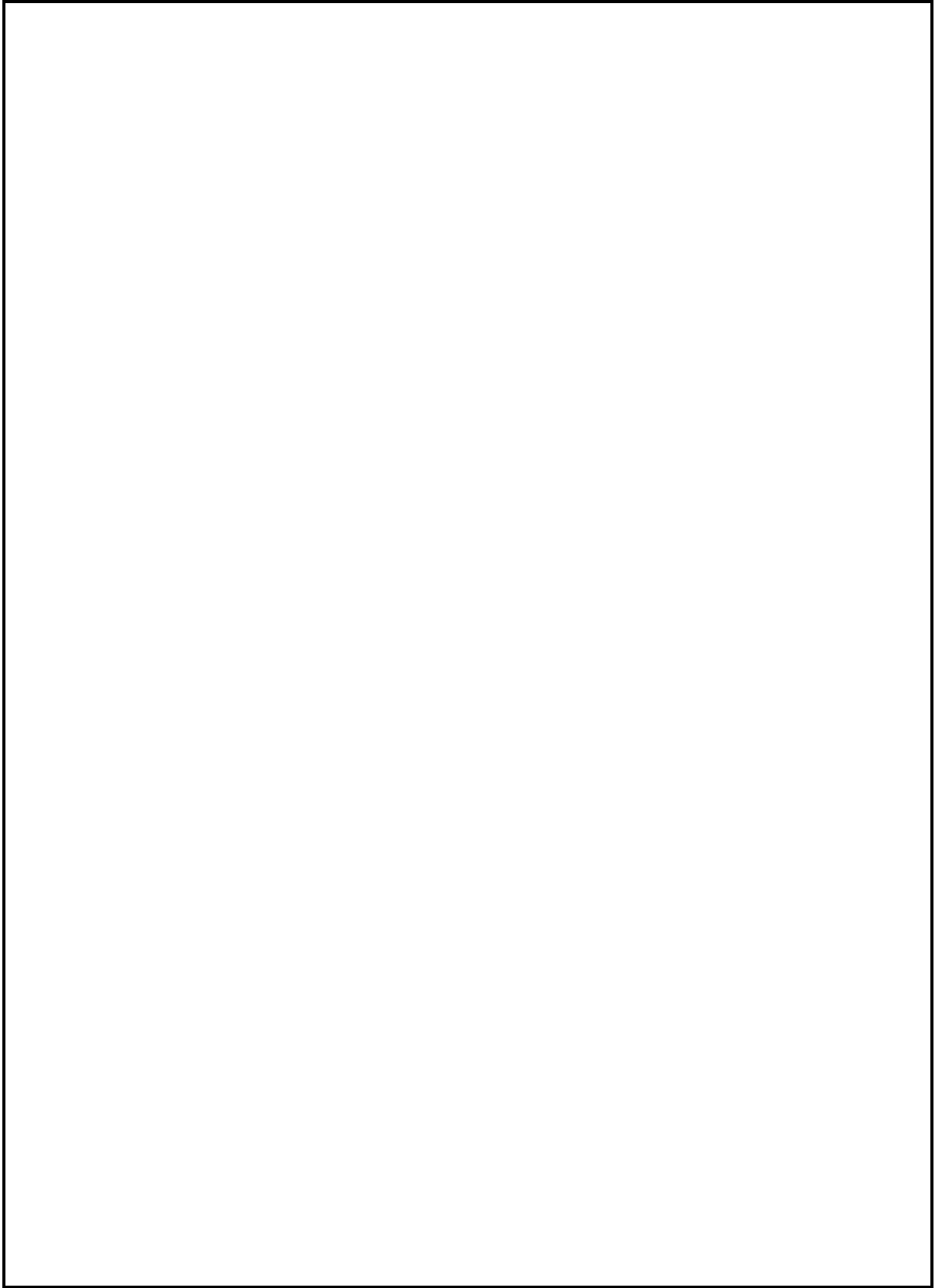
3 I've broken the food allergens into
4 two areas, mainly for interest, and as you
5 all know, there is a high prevalence of food
6 allergy amongst people in the United States.

7 Peanuts is just an example that I
8 have given for this, and finding out which of
9 the component peptides or components of foods
10 are important is one area that we could go.

11 It has also come before the agency
12 now that as molecular biology and molecular
13 engineering are being introduced in more
14 widespread use in the food industry, it is
15 possible that new or old allergens in new
16 forms could potentially be introduced to
17 allergic subjects.

18 There are some recent papers in the
19 New England Journal pertaining to Brazil nut
20 allergy testifying to this, so we are aware
21 of it.

22 The molds also represent a complex



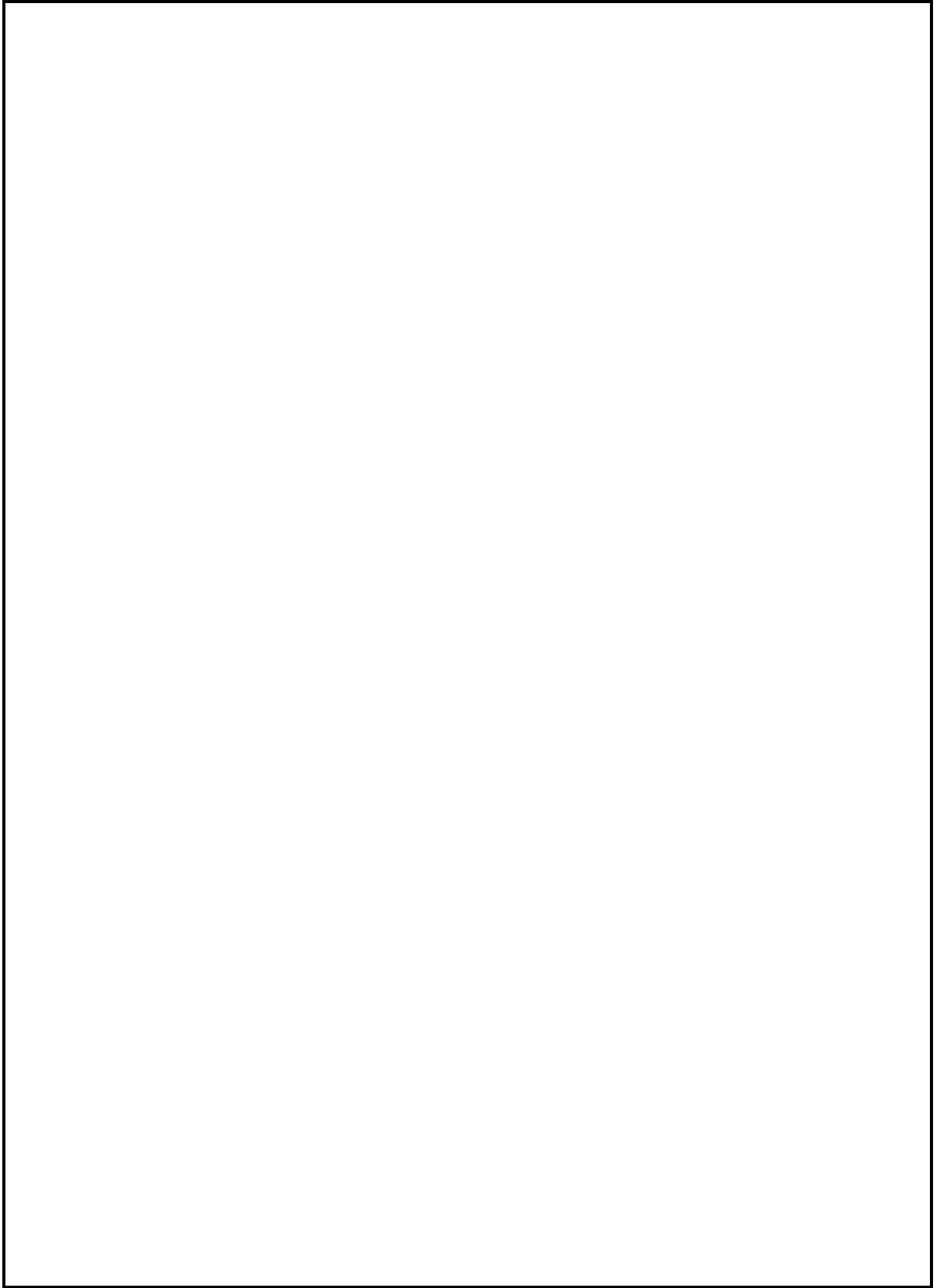
1 problem. There are some that have been
2 identified as an area that we could
3 conceivably invest resources in
4 standardization to.

5 The cockroach problem, particularly
6 in its effect on inner city children, has
7 received attention and is close to our
8 attention.

9 Obviously, although there exists
10 good standardization efforts for various
11 insect venoms, certainly not all have been
12 standardized so far, and we could include
13 some of the other animal allergens, as
14 mentioned by Ms. Bridgewater in her handout
15 as potential candidates.

16 This list reflects in not exactly
17 any order, except for the purposes of
18 presentation, some of the thoughts that we
19 had in recent months about where to take
20 allergenic standardization.

21 So therefore, we posed to the
22 committee for discussion today, to obtain



1 your thoughts for how you would approach
2 prioritization of standardizing any of the
3 above allergens or allergens that you'd like
4 to introduce into the discussion as well.

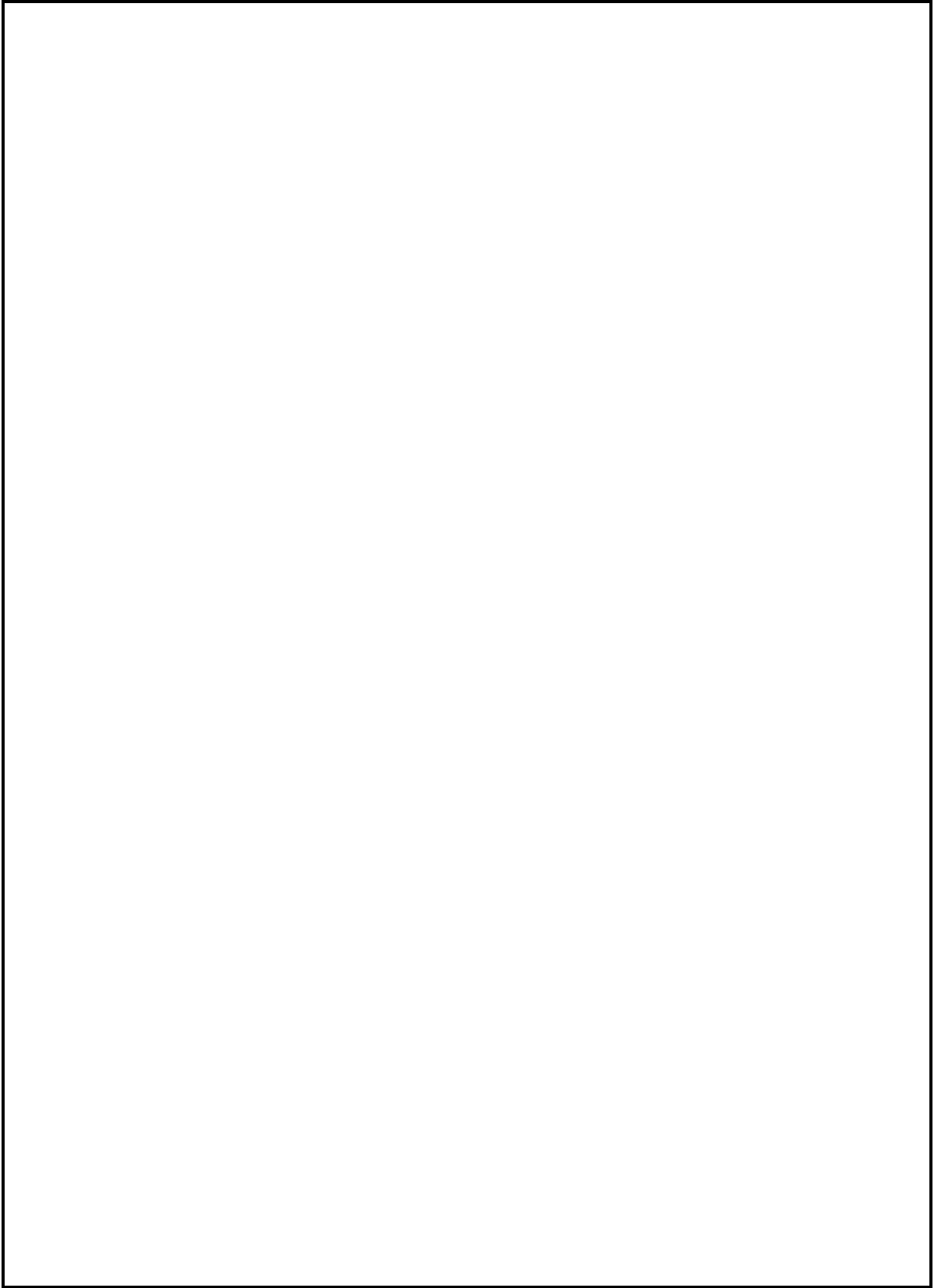
5 An under current of this is that we
6 do have to prioritize based on budgetary,
7 resource, planning, strategizing issues.

8 It would be very easy to say by all
9 means, let's do them all, but I think we have
10 to at the very least approach them with some
11 sort of priority.

12 That concludes my remarks by way of
13 introduction. If anyone has a comment, we'd
14 be pleased to listen.

15 DR. YUNGINGER: I think what I'd
16 like to do is have the individual panel
17 members respond to Dr. Hoffman and the
18 agency's listing of potential standardized
19 material here and perhaps give their
20 individual thoughts on where they think the
21 priorities should be.

22 Dr. King, do you want to start off



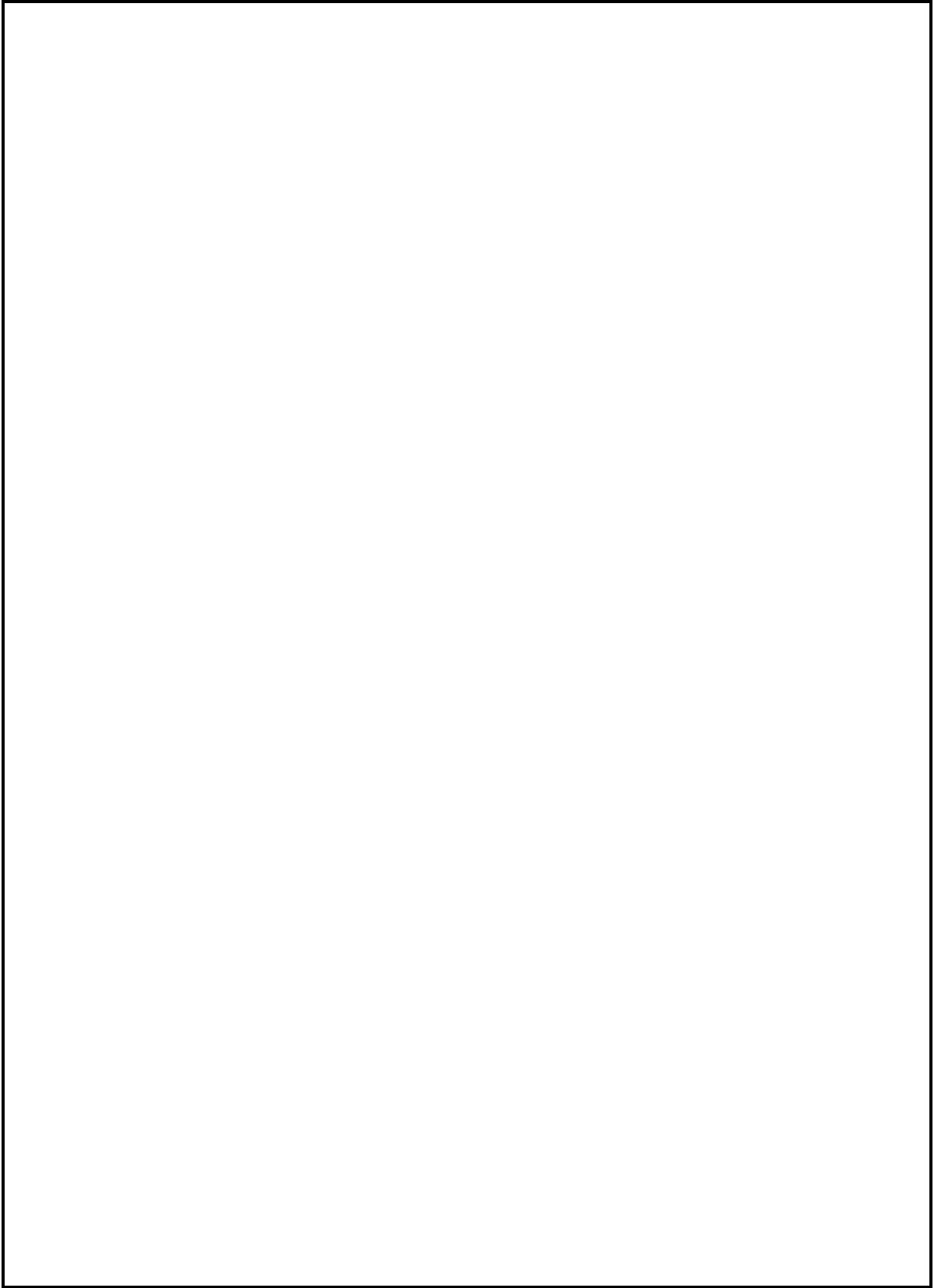
1 for us, please?

2 DR. KING: Yes. I think the next
3 one that should be done is tree pollen. I'd
4 like to come back to the grass pollen. The
5 standardization is based on BAU's; is that
6 right?

7 People respond different to grass
8 pollen. I'm wondering how can you establish
9 this, let's say, to rye grass pollen, do you
10 test only rye grass pollen? You are testing
11 a mixture of patients who may be really
12 sensitive to -- this is really my question.

13 I believe that pollens should be
14 standardized on the basis of their protein by
15 using animal sera.

16 Then we can measure exactly so we
17 would have a standard antibody preparation to
18 measure an unknown pollen extract, while the
19 current way to do the grass pollen is to
20 measure unknown pollen extract on an unknown
21 population of patients with variable
22 sensitivities to different pollens.



1 That's my comment.

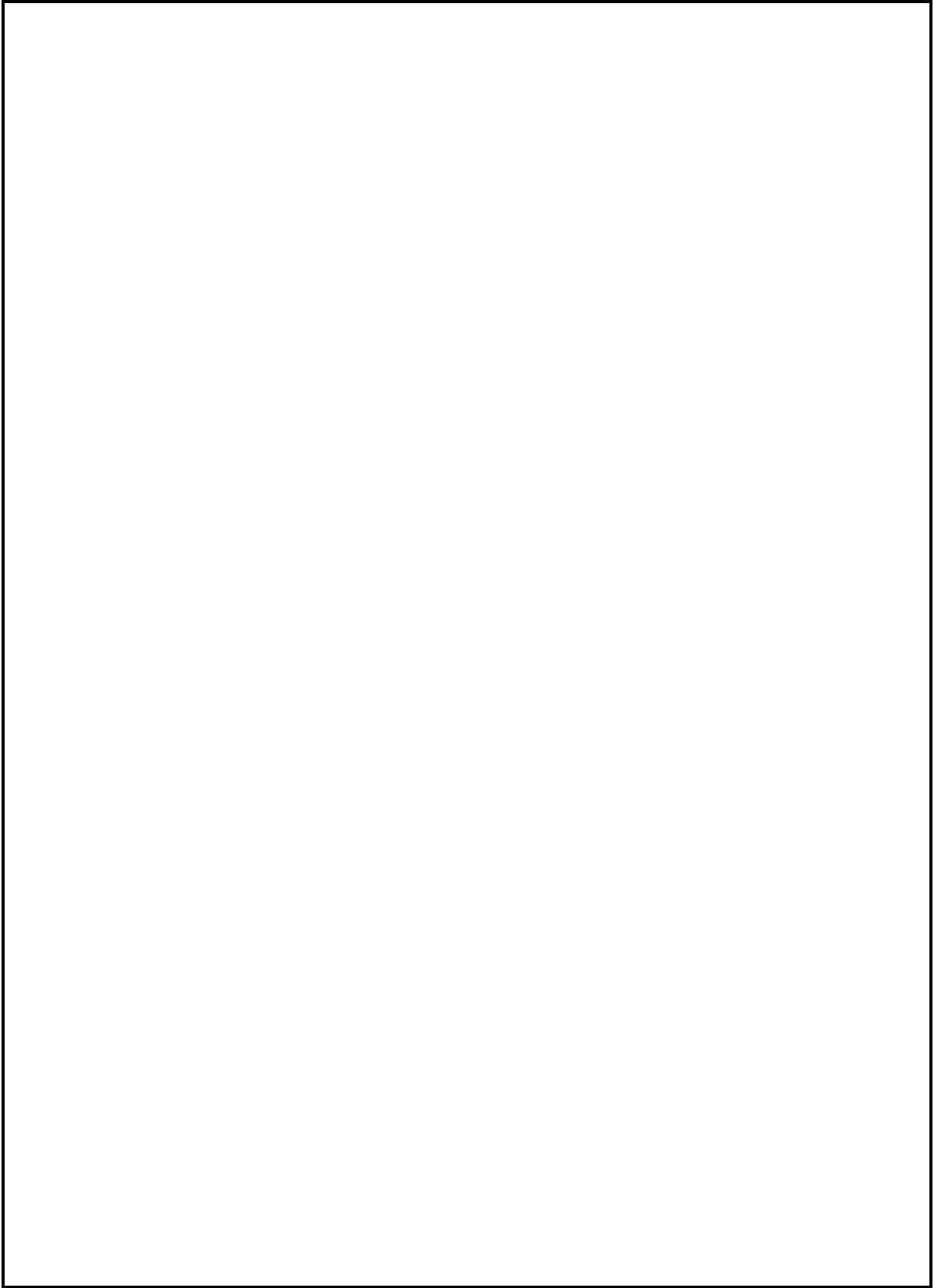
2 DR. YUNGINGER: Thank you,
3 Dr. King. Ms. Sander, do you want to comment
4 on the list of potential allergens for
5 standardization?

6 MS. SANDER: Well, I agree that
7 tree pollen is probably the most common
8 second one on the list, but then I also
9 looked down the list and I think of how
10 important it is that we understand the latex
11 more and look towards development in that
12 area as well as in cockroach allergens,
13 extracts.

14 DR. YUNGINGER: Thank you.
15 Dr. Wray?

16 DR. WRAY: I agree with Nancy as to
17 latex. I think it is extremely important in
18 that this is a potential life threatening
19 allergy.

20 We are seeing it certainly in the
21 patients being referred more and more
22 urgently. A standardized skin testing



1 extract would be very useful to us in
2 clinical practice. That would be my number
3 one.

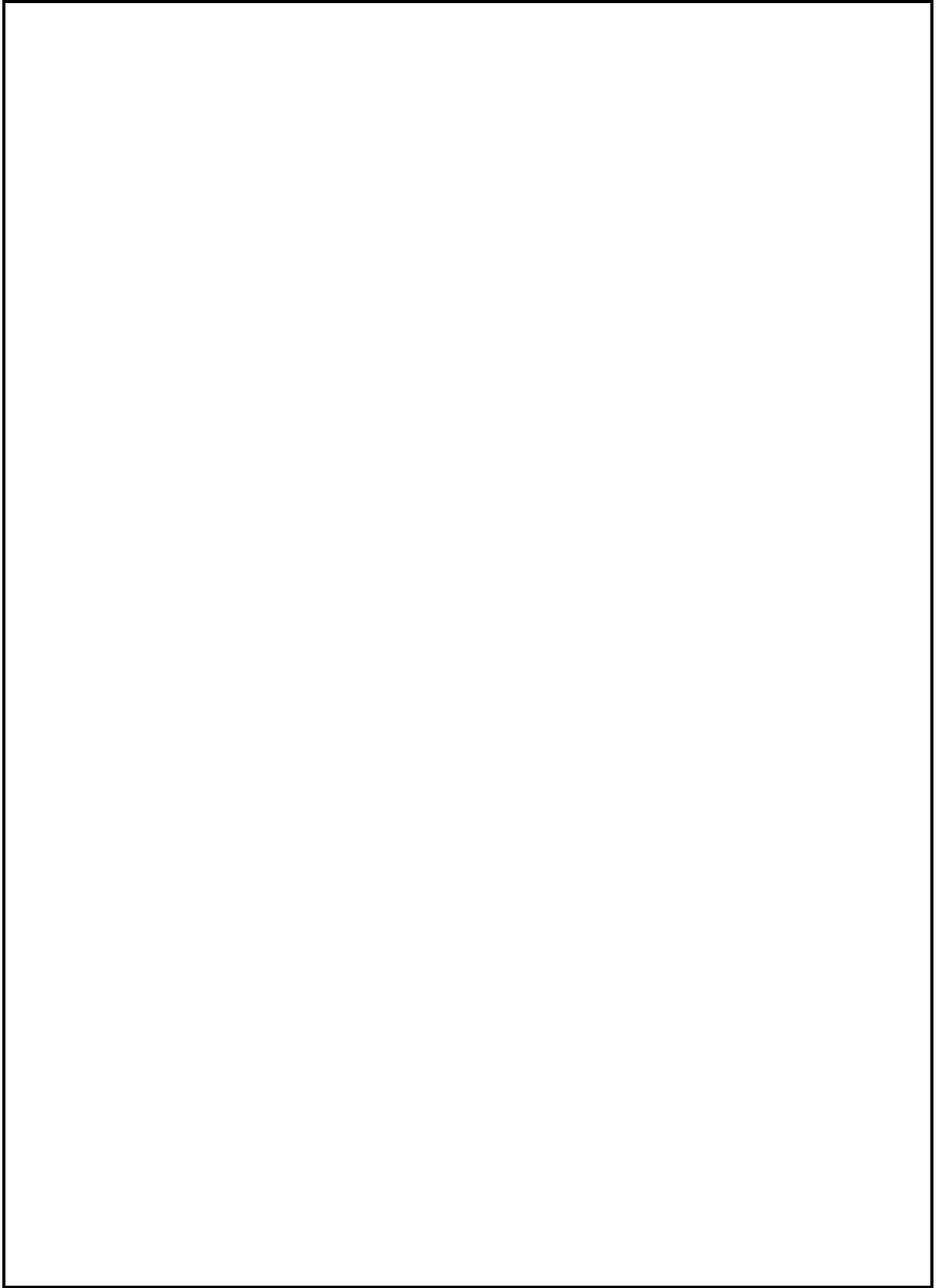
4 After that, I don't have a strong
5 preference for the others.

6 DR. YUNGINGER: Thank you.
7 Dr. Ownby?

8 DR. OWNBY: I would have to agree
9 with Dr. Wray that I think in terms of
10 importance to the population and the
11 available science, that latex leads the list
12 here on being a very good candidate for
13 standardization.

14 Certainly, I would agree with
15 Dr. King that tree pollens are also important
16 allergens that could be standardized,
17 although on that list after latex.

18 I would choose molds as having a
19 bigger impact clinically on so many people
20 and where standardization really would be
21 much more important than it would be in the
22 tree pollen group.



1 DR. YUNGINGER: Thank you.

2 Dr. Claman?

3 DR. CLAMAN: I would vote for latex
4 as being important, as already mentioned,
5 that we are really only looking for a skin
6 test reagent, not for therapeutic reasons.

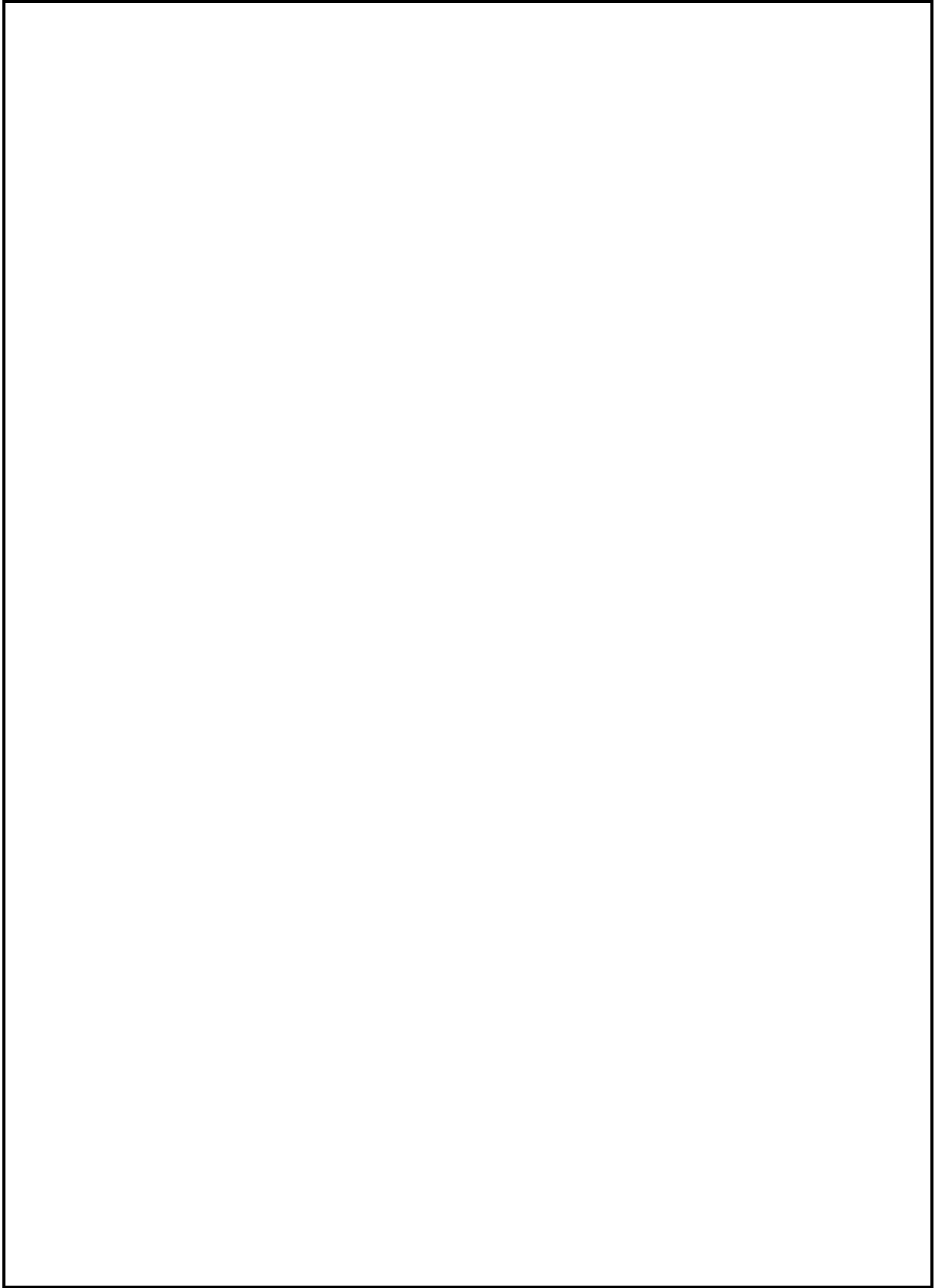
7 I think peanuts, because of the
8 severity of the reaction and frequency, it is
9 important. Cockroach is, not so much where I
10 live, but in other parts of the country, and
11 I think indoor allergens are important and
12 would like to question the morass that we
13 have with dog allergens. I find the current
14 situation very unsatisfactory.

15 DR. YUNGINGER: Thank you.

16 Dr. Saxon?

17 DR. SAXON: Let me clarify one
18 thing, since this is new to me. Are we
19 speaking about with standardization both for
20 diagnostics and/or therapeutics? Do we
21 discuss both areas?

22 DR. HOFFMAN: Yes. We are speaking



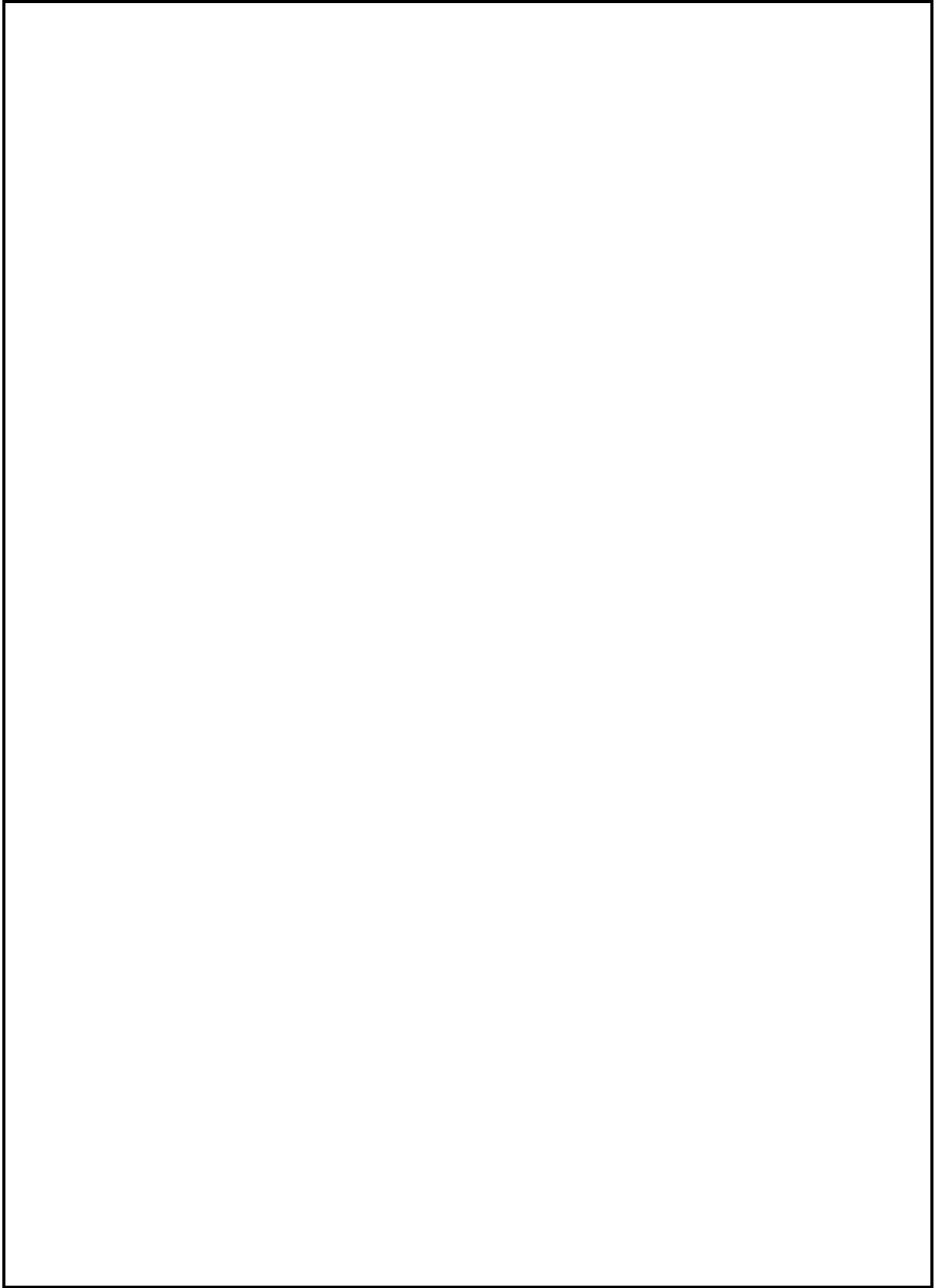
1 of both.

2 DR. SAXON: Good, I just wanted to
3 be sure. I would say that I think getting
4 the latex standardization for diagnostics is
5 very important and science is at a point
6 where it should not be difficult.

7 After that, the others all have
8 major -- it's difficult, trees, mold,
9 cockroach. I would think standardization of
10 a diagnostic reagent for cockroach would be
11 very important.

12 DR. YUNGINGER: One of the
13 advantages of being the chair is you get to
14 go last. I would put in my vote for latex,
15 mainly because it's a major central
16 importance with respect to healthcare workers
17 and again, as Dr. Wray pointed out, the
18 reactions to this can be fatal.

19 Peanuts, I would have put higher on
20 the list a year or two ago, but they have
21 some very good workers hard at work working
22 on the peanut problem with respect to the



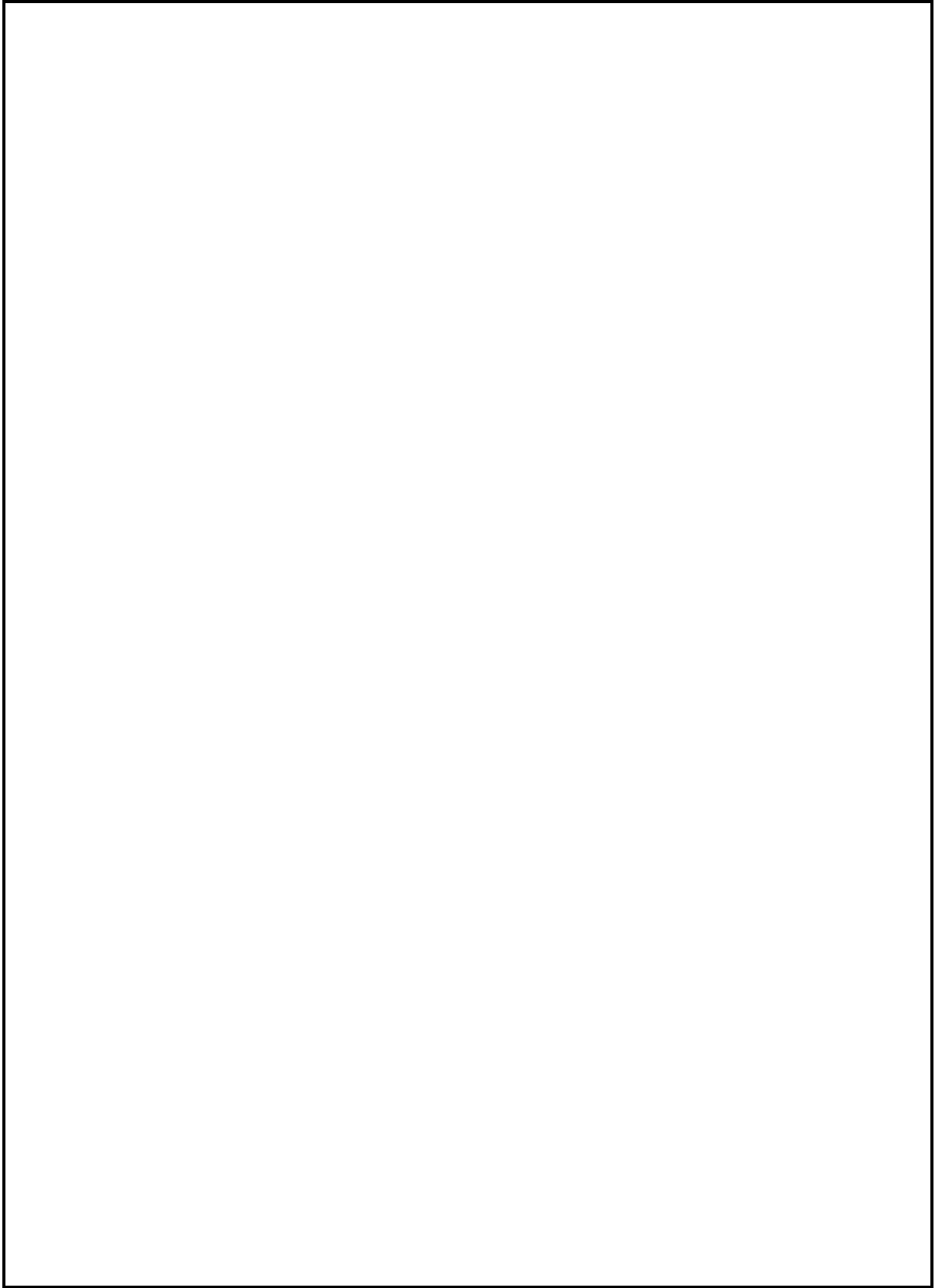
1 allergen isolation characterization and
2 epitope mapping.

3 I think they might be better to put
4 their efforts into other areas and let the
5 peanut people keep working for a bit if they
6 are making good progress.

7 As a former mold researcher, I can
8 attest to the difficulty of trying to deal
9 with molds. There is no doubt they affect a
10 large number of people. This is a very
11 difficult area to work in.

12 Since Dr. King is on the conference
13 call, I can tell him what I always assure our
14 lab technicians, if mold allergy would be
15 easy, King and Norman would have written
16 about alternaria and not antigen E some 20
17 or 30 years ago.

18 My second vote after the latex
19 would be for cockroach. As Dr. Claman
20 mentioned, there are some parts of the
21 country where the Chamber of Commerce does
22 not permit cockroaches, Rochester being one,

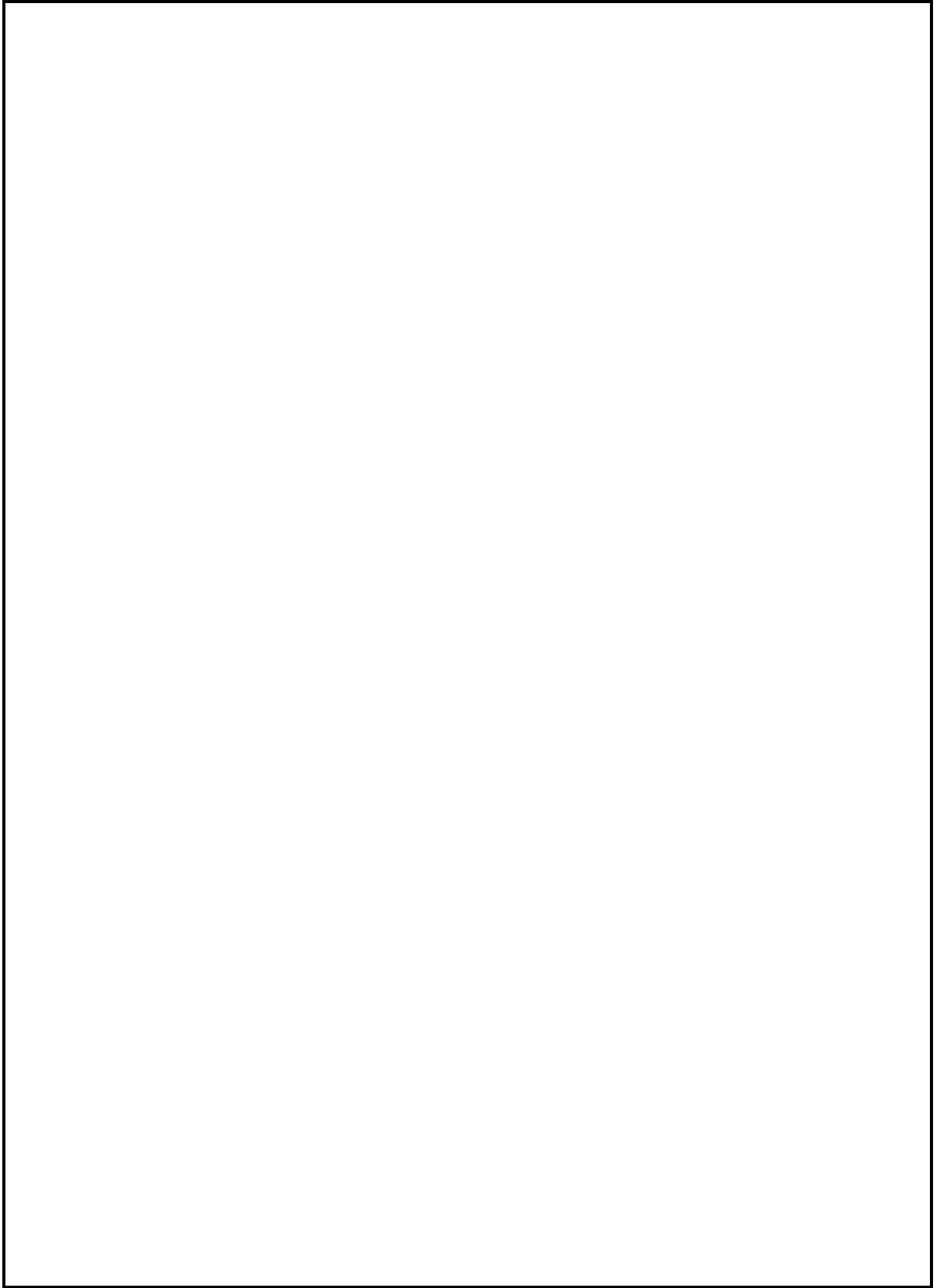


1 but I came away from the recent Academy of
2 Allergies' meeting in Washington with respect
3 to the ubiquitous nature of allergens and the
4 fact that preventing exposure eradication is
5 impossible.

6 Although I don't think this is one
7 that has a potentially fatal effect on folks
8 to the extent that perhaps latex or peanuts
9 do, it's one that is a very important
10 allergen in the inner city areas and in the
11 southern parts of the country, it is so
12 ubiquitous that there is no correlation
13 between the exposure and socioeconomic
14 status.

15 Since the eradication efforts are
16 so dismal, I would expect that perhaps this
17 might be an allergen for which conventional
18 or newer forms of immunotherapy might be
19 reasonably and predictably used in the
20 upcoming years.

21 That would be my second vote. Does
22 anybody have any other comment on the list



1 here or wish to add other?

2 DR. KING: May I come back again?

3 DR. YUNGINGER: Yes.

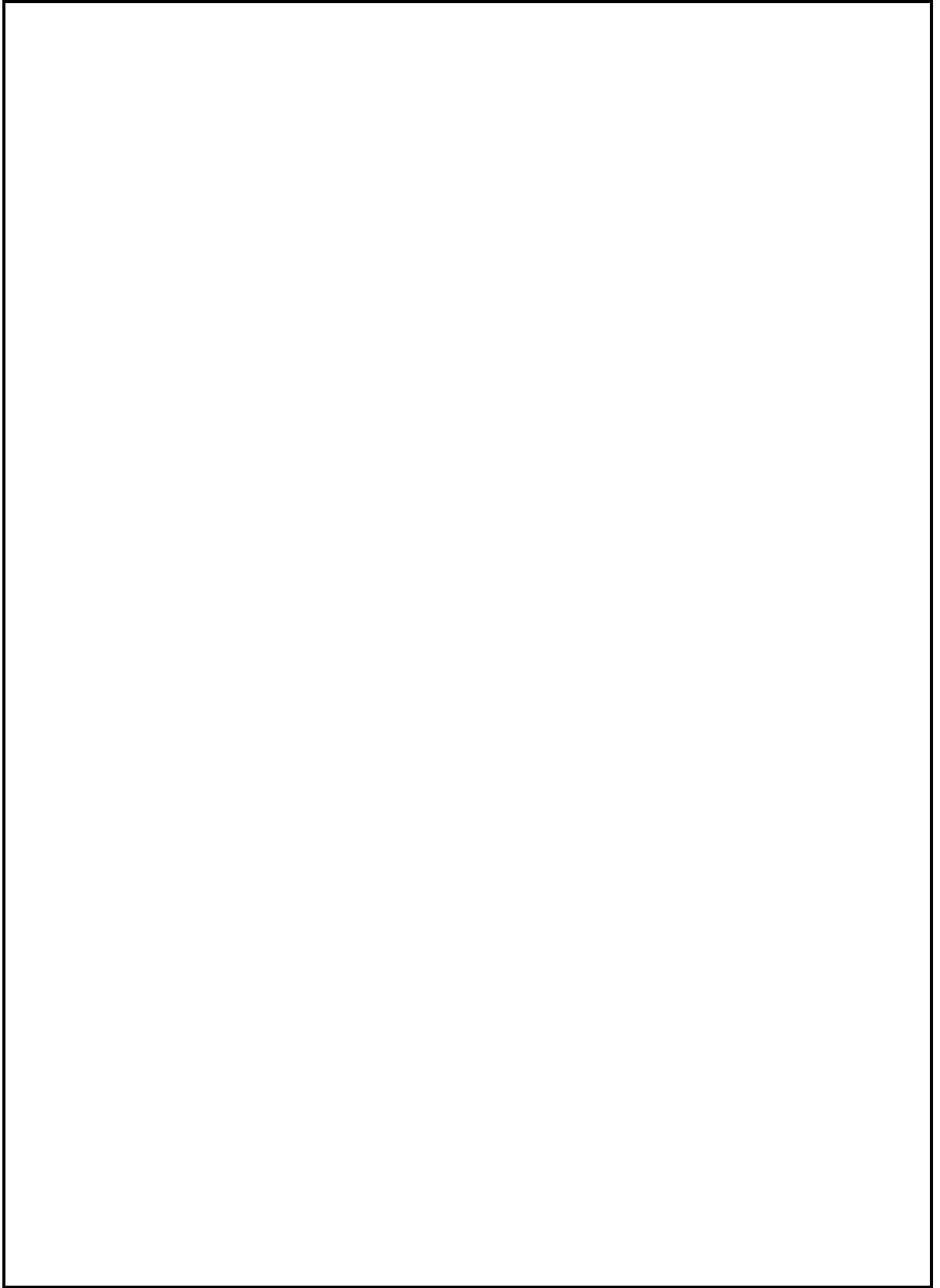
4 DR. KING: I started promoting tree
5 pollens for standardization first because the
6 allergen of tree pollen is very well
7 characterized, but it can be easily done.

8 I recognize the clinical importance
9 of latex. As you well know, latex has so
10 many allergens, it's very hard to pinpoint
11 which ones are the important ones. Maybe you
12 know more. Maybe you can comment more, John.

13 DR. YUNGINGER: I don't have too
14 much to add. The last time I looked at the
15 list, I believe they were up to seven or
16 eight.

17 DR. KING: That's right.

18 DR. YUNGINGER: Identified
19 allergens. Again, they have very good groups
20 that are hard at work on that. I think the
21 situation with latex is that unfortunately,
22 it's not like cat, where you have a single



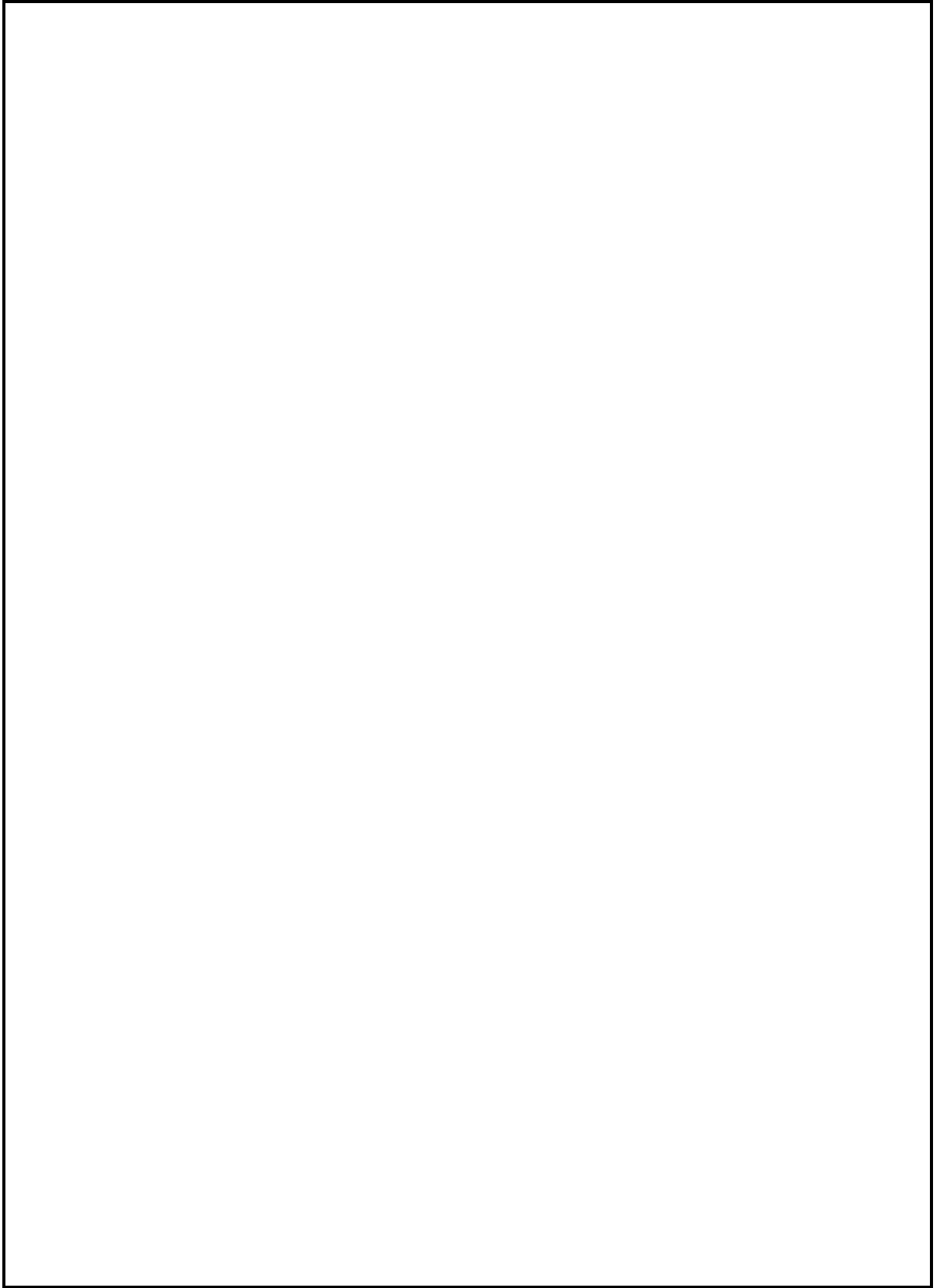
1 predominant major allergen to which 80 or 90
2 percent of the people are reactive, the latex
3 seems to be a bit more heterogeneous.

4 DR. SAXON: I think I can clarify
5 it a little more. They are now up to 12,
6 there are 12 cloned recognized antigens. It
7 turns out using them, it may turn out there
8 are only three or four that may be the major
9 allergens like in peanut.

10 It may turn out that that you
11 cover 90-X percent of the clinically reactive
12 people with a small number, and since they
13 are all known and I think monoclonal
14 antibodies are not far away for many of them,
15 it may not be that hard to standardize.

16 The numbers are very large on
17 protein. There was a paper by a group, of
18 the Malaysian groups, testing people with
19 purified Held 1 through 6 or 7. It may not
20 be that complex. It may not cover
21 everything.

22 DR. KING: It's probably a good



1 idea to standardize, whether pollen or
2 several allergens.

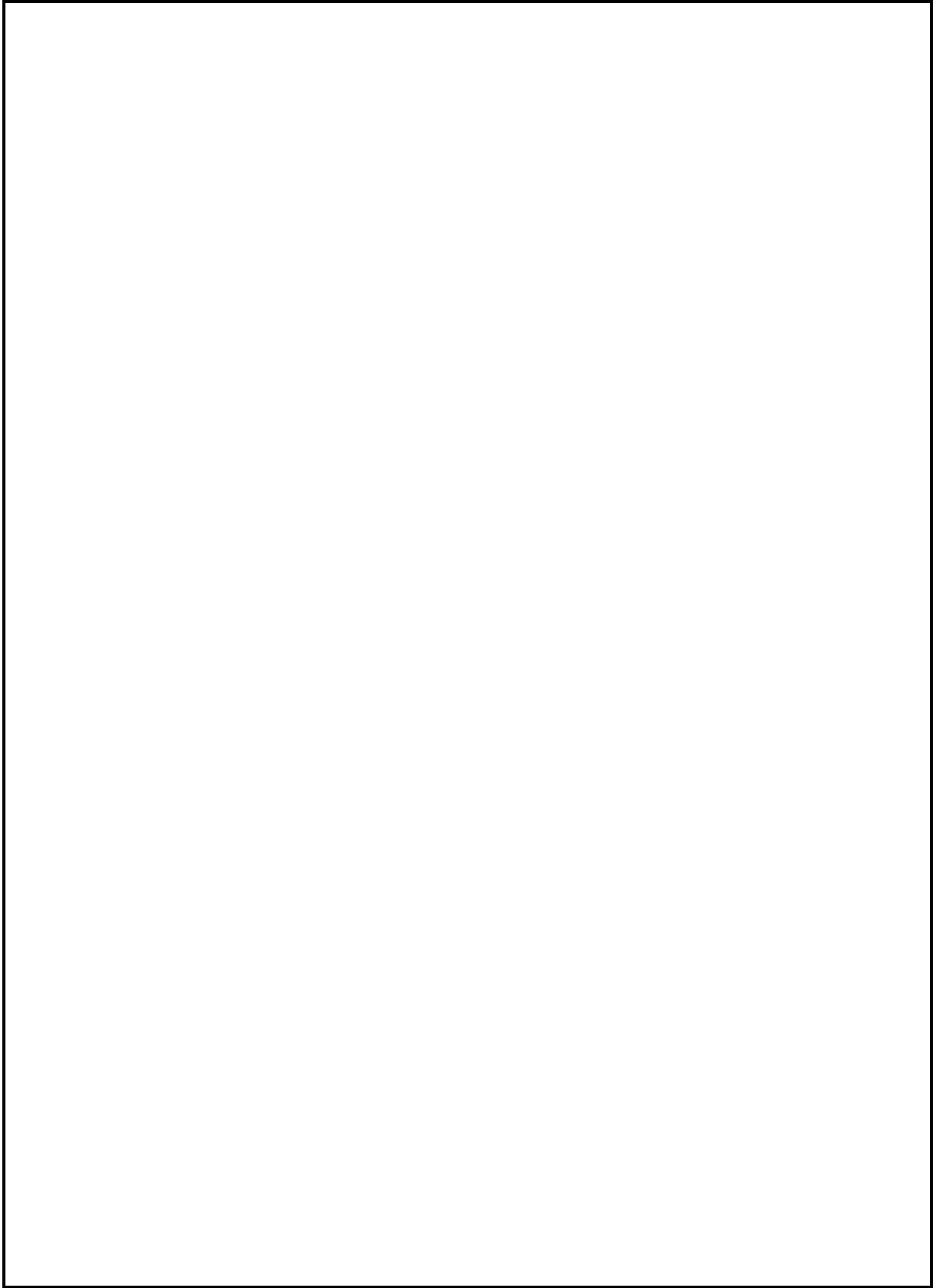
3 DR. SAXON: Six might cover the
4 vast majority.

5 DR. YUNGINGER: If there are no
6 other specific questions regarding the list
7 of allergens, Dr. Hoffman, do you have some
8 other questions for deliberation for us?

9 DR. HOFFMAN: No. I think given
10 the agenda that has been forwarded to you, we
11 will restrict the discussion to today's
12 comments that have already been made. We
13 appreciate them greatly.

14 I think what this bodes for us is a
15 discussion with you some time in the very
16 near future, how to approach this problem,
17 both from a scientific perspective and
18 possibly greater depth.

19 And invariably from a resource
20 perspective, and to discuss with you at a
21 later date, some time quite soon, your
22 perspective on the resources that would be



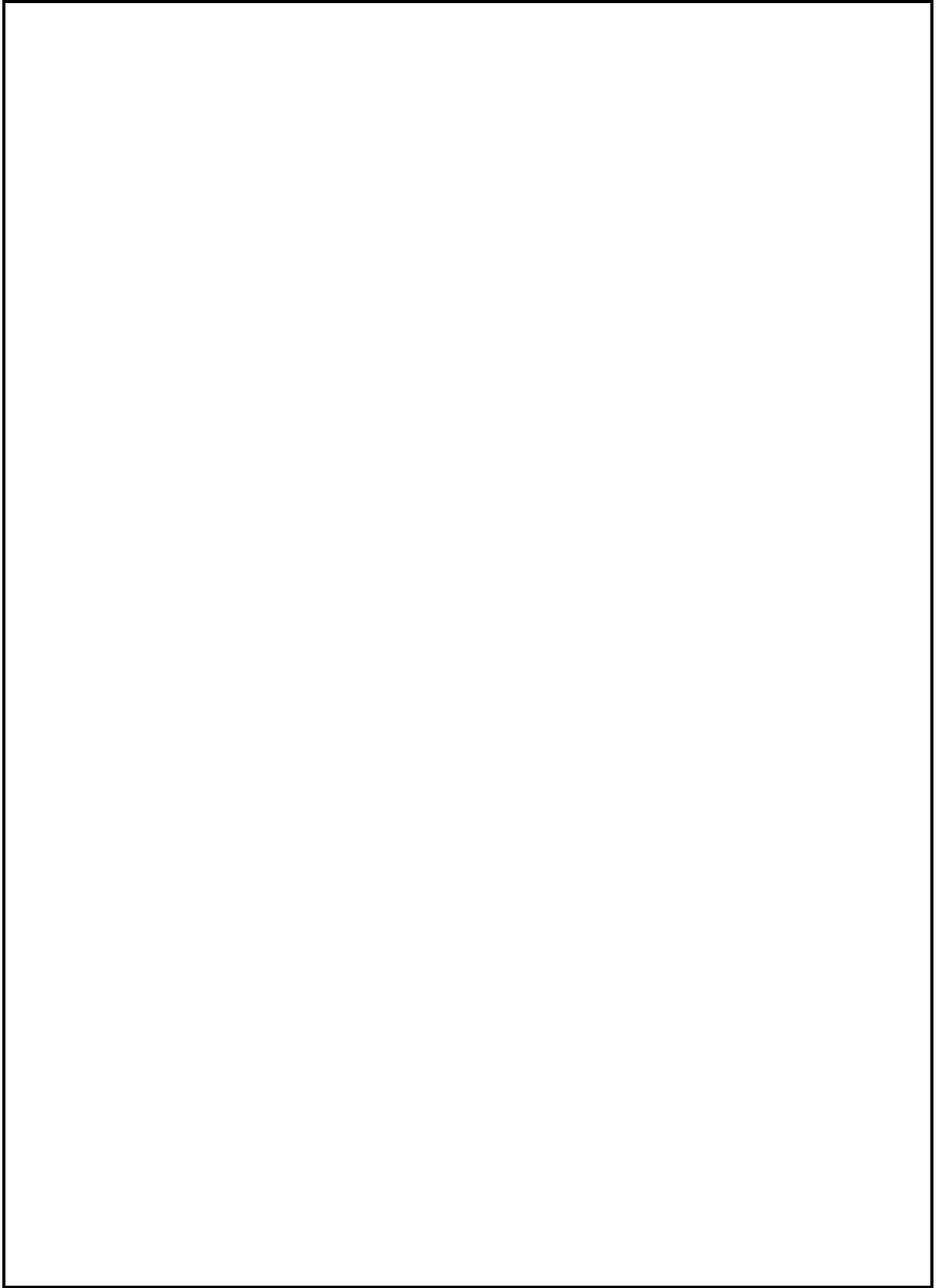
1 necessary to tackle any of these problems or
2 any or all of these problems.

3 DR. YUNGINGER: Thank you,
4 Dr. Hoffman.

5 DR. HARDEGREE: I wonder,
6 Dr. Yunginger, whether you could summarize
7 then what you thought the sense of the
8 committee was based on today's discussion of
9 where you thought we should be putting our
10 next immediate efforts until we can have a
11 further discussion on various tools and
12 approaches and such that you may want to
13 recommend to us.

14 DR. YUNGINGER: I was taking notes
15 of the various panel members who were
16 speaking and according to my listing here, I
17 heard six people, Ms. Sander and Drs. Wray,
18 Ownby, Claman, Saxon and Yunginger speaking
19 for latex standardization.

20 I heard four folks speak in terms
21 of cockroach, Ms. Sander, Drs. Claman, Saxon
22 and Yunginger. In addition, two folks,



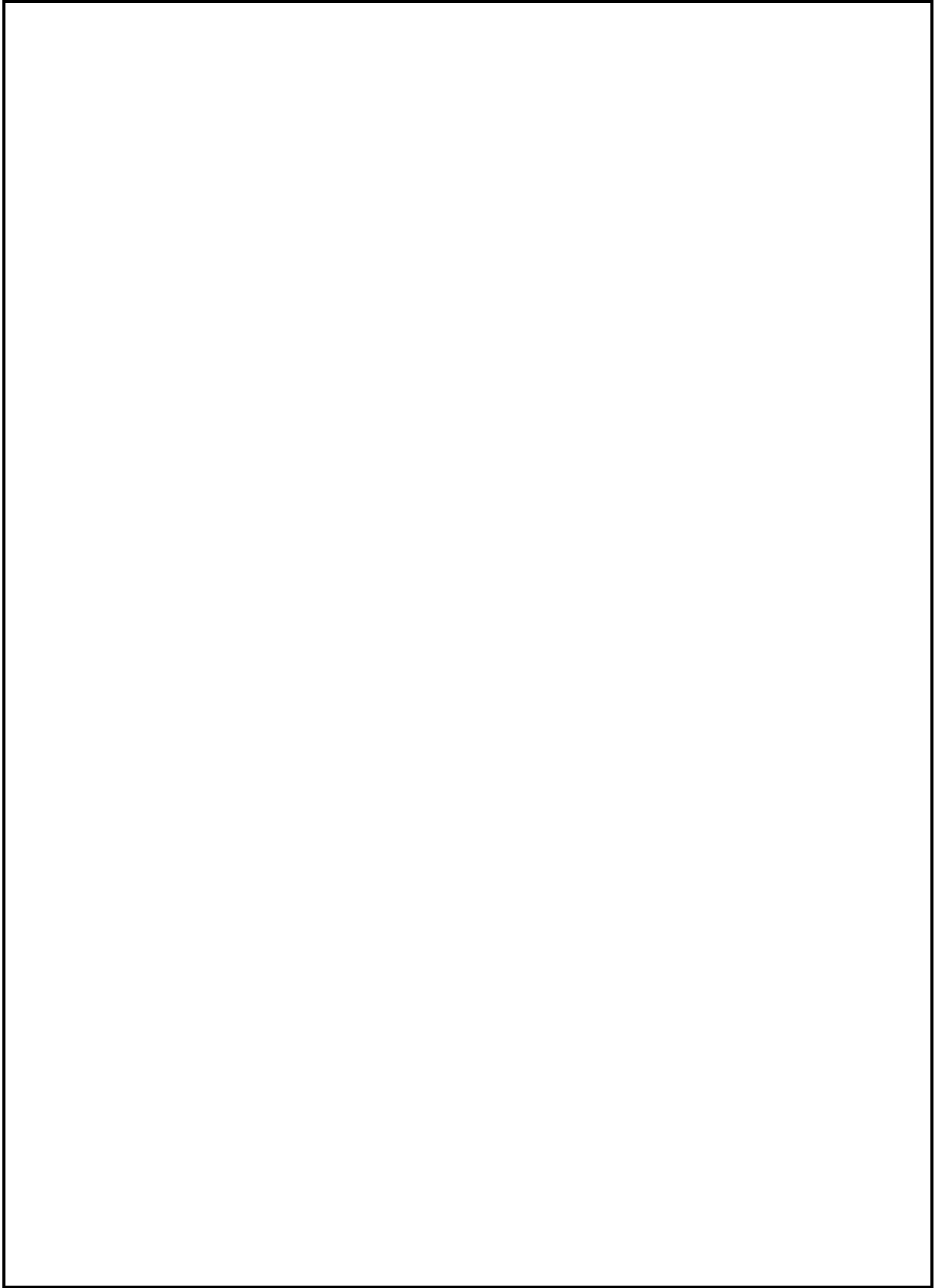
1 Dr. King and Ms. Sander spoke in favor of
2 tree pollens, and then Dr. Ownby, molds;
3 Dr. Claman, dog, and Dr. Claman, peanut.

4 Speaking just for myself, the
5 reason I was swayed toward the latex and the
6 cockroach was that these are two antigens
7 where there are a number of the allergenic
8 proteins that have already been cloned and
9 their structure delineated.

10 It would be a little bit less of a
11 black box and in terms of strict R&D work
12 than perhaps Brazil nuts or some of the
13 molds, particularly non-alternaria molds.

14 There has been some work done with
15 alternaria, some work with dog allergens, and
16 several of the trees, as Dr. King has noted.
17 There has been some similar work.

18 I think we need to balance the
19 importance of these, not just by the number
20 of people that are affected, but also by what
21 types of reactions are being caused, perhaps
22 also on the basis of whether they are just



1 diagnostic products only or whether they are
2 potential products for diagnosis and therapy,
3 and lastly, whether there are other
4 alternatives for handling exposure to some of
5 the allergens.

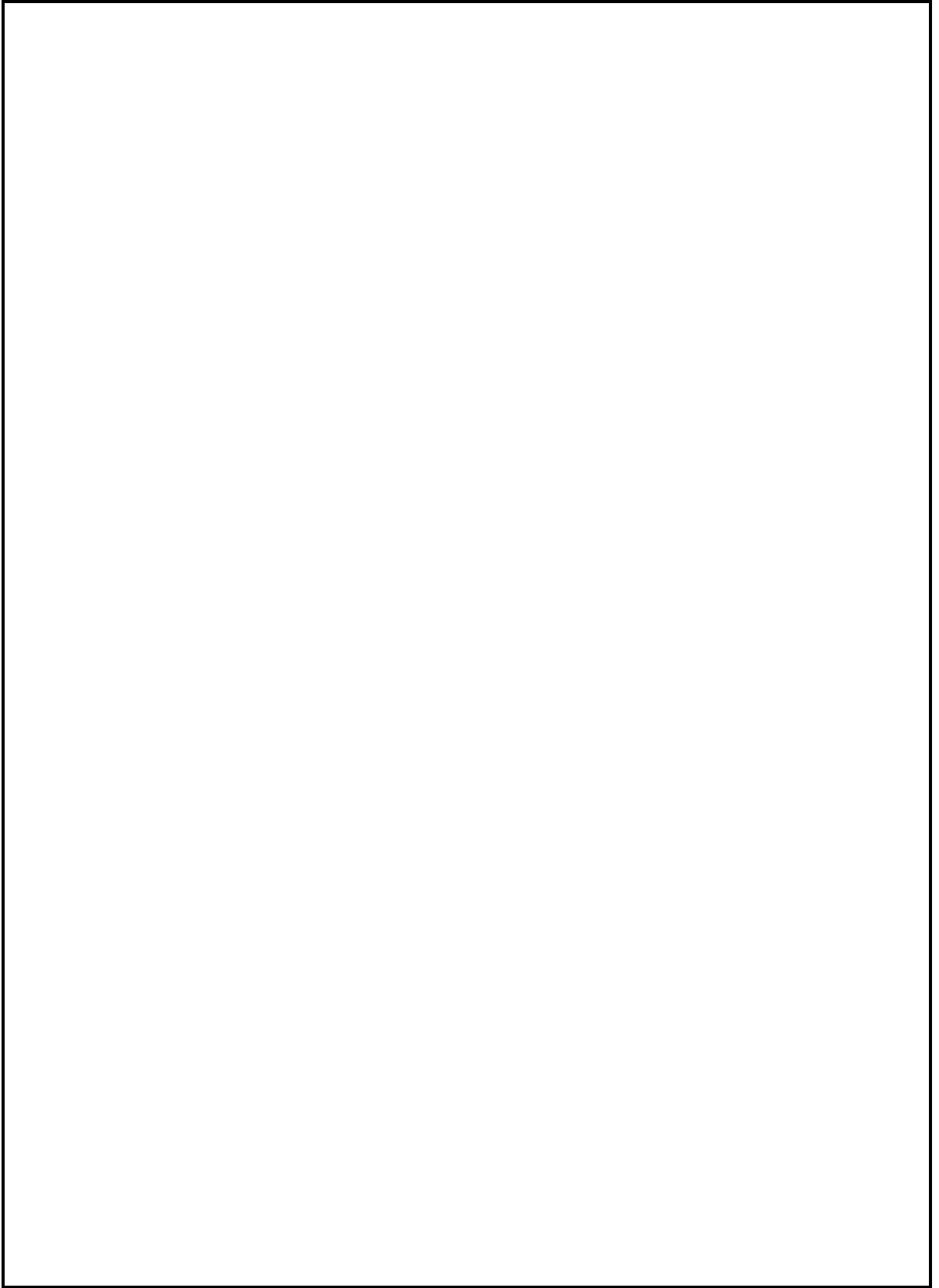
6 As I mentioned for the cockroach,
7 I've been impressed by how dismal the
8 prospect is for any environmental control
9 measures there.

10 I think geographic considerations
11 are very important here as well. Some of
12 these molds are much more important in some
13 areas of the country than in others.

14 I'm sure geographical and political
15 considerations come into the prioritization
16 process that the agency uses. I leave those
17 to other people.

18 DR. HOFFMAN: Thank you very much,
19 Dr. Yunginger.

20 DR. YUNGINGER: Mr. Freas, are
21 there any other items for the open session of
22 our panel meeting today?



1 MR. FREAS: I am unaware of any
2 other discussion in open session. Is there
3 someone in this room at this current time who
4 would like to address the committee in open
5 session?

6 I see no takers on that offer.

7 DR. YUNGINGER: Hearing none, could
8 I propose that we take a five minute recess
9 and then begin the closed session?

10 MR. FREAS: That would be perfect.
11 We need a little time to check the lines and
12 we will -- please don't hang up.

13 You can put us on hold, if you just
14 put your phone on mute or just leave your
15 phone the way it is, we will resume in five
16 minutes.

17 Thank you.

18 (Whereupon, the PROCEEDINGS were
19 concluded.)

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