

ajh  
RC

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

DERMATOLOGIC AND OPHTHALMIC DRUGS  
ADVISORY COMMITTEE 49th MEETING  
OPEN SESSION  
Volume I

1004 98 APR 27 10:58

Thursday, March 19, 1998  
8:30 a.m.

This transcript has not been edited or corrected,  
but appears as received from the commercial  
transcribing service; the Food and Drug  
Administration makes no representation as to its  
accuracy.

Holiday Inn  
Walker Room  
2 Montgomery Village Avenue  
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.  
507 C Street, N.E.  
Washington, D.C. 20002  
(202) 546 6666

## PARTICIPANTS

Joseph McGuire, Jr., M.D., Chairman  
Tracy Riley, Executive Secretary

## MEMBERS

Joel Mindel, M.D.  
William Rosenberg, M.D.  
S. James Kilpatrick, Jr., Ph.D.  
Lynn Drake, M.D.  
Eva F. Simmons-O'Brien, M.D.  
O. Fred Miller, III, M.D.  
Henry W. Lim, M.D.

## FDA

Roger Williams, M.D.  
Michael Weintraub, M.D.  
Jonathan Wilkin, M.D.  
Vinod Shah, Ph.D.

Special Government Employees, Consultants, Guest  
Speakers

Professor Hans Schaefer  
Kathleen R. Lamborn, M.D.  
Eduardo Tschen, M.D.  
Dr. Gayle A. Brazeau  
Dr. Gordon Flynn

ajh

C O N T E N T S

Page No.

Call to Order and Welcome Joseph McGuire, Jr., M.D., Chairman	4
Conflict of Interest Statement Tracy Riley, Executive Secretary	4
Overview of the Issues and CDER/OPS Perspectives Roger Williams, M.D.	5
Approaches for BA/BE: Dermatopharmacokinetics Vinod P. Shah, Ph.D.	18
Division of Dermatologic and Dental Drugs Perspectives Jonathan Wilkin, M.D.	29
DPK and Follicular Pathways Hans Schaefer, Ph.D.	36
Principles of Topical Drugs Gordon Flynn, Ph.D.	47
Open Public Hearing Louise Latriano, Ph.D. Dr. Auraham Yacobi	61 72
Comments Vinod P. Shah, Ph.D. Jonathan Wilkin, M.D.	78 84
Committee Discussion	92

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

2                   **Call to Order and Welcome**

3                   DR. MCGUIRE: Good morning. This is the  
4 Bioequivalence of Topical Dermatological Drug Products and  
5 Questions Regarding Clinical Trials for Stable Plaque  
6 Psoriasis. This is the 49th meeting of the Dermatologic and  
7 Ophthalmic Drugs Advisory Committee.

8                   The format will be as your printed program,  
9 however, it is not going to be as interactive as it usually  
10 is because we only have one working microphone. What I  
11 would like to do is have Tracy Riley, who is the Executive  
12 Secretary, read the Conflict of Interest Statement and then  
13 after Ms. Riley finishes, then, Roger Williams will  
14 introduce the speakers for the remainder of the program up  
15 until 10 o'clock this morning.

16                   When we have microphones, then, we will do the  
17 traditional walking around the table, introducing all the  
18 members of the advisory committee.

19                   Tracy.

20                   **Conflict of Interest Statement**

21                   MS. RILEY: Good morning. The following  
22 announcement addresses the issue of conflict of interest  
23 with regard to this meeting and is made a part of the record  
24 to preclude even the appearance of such at this meeting.

25                   Based on the submitted agenda for the meeting and

1 all financial interests reported by the committee  
2 participants, it has been determined that since the issues  
3 to be discussed by the committee will not have a unique  
4 impact on any particular firm or product, but rather may  
5 have widespread implications to all similar products, in  
6 accordance with 18 U.S. Code 208(b), general matters waivers  
7 have been granted to the members and consultants  
8 participating in today's meeting.

9 A copy of these waiver statements may be obtained  
10 by submitting a written request to the FDA's Freedom of  
11 Information Office, Room 12A-30 of the Parklawn Building.

12 In the event that the discussions involve any  
13 other products or firms not already on the agenda for which  
14 an FDA participant has a financial interest, the  
15 participants are aware of the need to exclude themselves  
16 from such involvement, and their exclusion will be noted for  
17 the record.

18 With respect to all other participants, we ask in  
19 the interest of fairness that they address any current or  
20 previous financial involvement with any firm whose products  
21 they may wish to comment upon.

22 Thank you.

23 **Overview of the Issues and CDER/OPS Perspectives**

24 DR. WILLIAMS: My name is Roger Williams. I am  
25 Deputy Center Director in the Center for Drug Evaluation and

1 Research, and I would like to thank the members of both  
2 committees for the opportunity to speak to you today on an  
3 interesting topic which relates to the quality of  
4 dermatologic drug products.

5 [Slide.]

6 Our goal in the next several minutes is to  
7 introduce the topic for you and to be done with the  
8 presentations by 10 o'clock. The Chair has asked me, both  
9 for myself and all the other speakers, to adhere to the time  
10 schedule and not go over.

11 My goal in presenting to the committee is to frame  
12 the debate and indicate where we are coming from  
13 organizationally in the Center relative to the particular  
14 topic.

15 Now, this, I apologize, it is not really meant to  
16 be read, but it is a picture of the Center for Drug  
17 Evaluation and Research. On the left, you will see a series  
18 of six organizational units, six boxes, under the Office for  
19 Review Management, which is headed by Dr. Mac Lumpkin.

20 That particular segment of the center focuses on  
21 the new drug approval process and particularly focuses, I  
22 would argue, on the safety and efficacy of the active  
23 moiety. These are, of course, the challenging public health  
24 questions that lead to a an approval and lead to the bulk of  
25 the labeling about an approved drug product.

1           In the middle are some organizational management  
2 units, four boxes that I won't talk about, and then over on  
3 the right you see the Office of Pharmaceutical Science where  
4 I have responsibility. Included in that unit you have the  
5 Office of Generic Drugs, and Office of New Drug Chemistry,  
6 Office of Research and Testing, and also an Office of  
7 Clinical Pharmacology and Biopharmaceutics.

8           This part of the center focuses on many things,  
9 but the particular topic that we will talk about today  
10 focuses on product quality. Product quality, I would say,  
11 is a key part of what the Agency tries to assure, working  
12 with its pharmaceutical sponsors and applicants, as it  
13 allows products to get into the marketplace and also to stay  
14 in the marketplace.

15           [Slide.]

16           One of the ways the center works to build good  
17 policy, good cross-cutting policy, is via a series of  
18 coordinating committees which have been established in the  
19 center over the last several years. You can see there are  
20 many of them now.

21           The top ones that are colored--this is my Easter  
22 overhead--focuses on the scientific disciplines in the  
23 center that lead to our policy. The way to think about  
24 these coordinating committees is to think of them generating  
25 policy that is designed to help pharmaceutical sponsors and

1 applicants as they submit information to the Agency.

2           Now, the particular coordinating committee that I  
3 will be talking about, the perspective in my talk this  
4 morning, and that you will hear later on in the course of  
5 the presentations is the orange one over there, the  
6 Biopharmaceutics Coordinating Committee, which focuses on a  
7 quality aspect that I will talk about that relates to the  
8 release of the drug substance from the drug product, and I  
9 will come back to that point in just a minute.

10           We could talk a long time about these coordinating  
11 committees, but I hope you get a sense that they focus on  
12 the disciplines that lead to recommendations from the Agency  
13 that helps sponsors submit information.

14           [Slide.]

15           I am speaking to you really on behalf of the  
16 Biopharmaceutics Coordinating Committee and I am the Chair  
17 of that committee. One of the things we deal with in the  
18 committee and that relate specifically to the concept of  
19 product quality refers to this slide.

20           Now, this slide has some very significant legal  
21 and regulatory meanings that I will try to walk through with  
22 you. On the horizontal axis, there is the concept of time  
23 that relates during the preapproval period to the generation  
24 of safety and efficacy information that rests in  
25 relationship to the quality of a product.

1           The quality refers both to the active moiety,  
2 active ingredient, as well as to its excipients in its  
3 packaging. The Agency via regulations that were published  
4 in 1977 and that have been refined and evolved since that  
5 time tries to establish the bioavailability of the drug  
6 product during this period, the IND period prior to  
7 approval.

8           After approval there is a period of time in the  
9 marketplace where our society has determined that the  
10 pioneer or innovator manufacturer will have a period of  
11 protection from competition. This protection arises either  
12 via patent or exclusivity provisions of our federal statute  
13 and regulations.

14           Then, at a certain point in time, that protection  
15 ends, and at that point in time, when patent and exclusivity  
16 protection ends, we can have multiple manufacturers for the  
17 same drug product.

18           That drug product at that point in time becomes  
19 the listed drug to which the generic or multi-source  
20 manufacturers must be equivalent to in order to get into and  
21 remain in the marketplace.

22           Now, embodied in this general approach, which I  
23 would say is a very evolved, very well-established approach  
24 in the United States, is the concept of equivalence.  
25 Sometimes we use the word sameness, sometimes we use

1 comparability, sometimes we use the word "identity," but  
2 in all circumstances, we are asking that both the pioneer  
3 manufacturers and the generic equivalent stay the same  
4 relative to the pivotal clinical trial material, if you  
5 will, on which the safety and efficacy data were based.

6           Now, that is a very important concept and I would  
7 also argue that it is a very technically challenging concept  
8 because we are asking stability in product performance  
9 characteristics over many, many years. I would argue the  
10 years could be 100 or more for a very good product. We have  
11 products now that have been in the marketplace for 75 years,  
12 and I would expect them as good products to remain in the  
13 marketplace indefinitely.

14           So, time on the horizontal axis is a long period  
15 of time, and there is also the concept of time related to  
16 shelf life, so we also expect that these products maintain  
17 their quality characteristics during the time on the shelf  
18 prior to sale and use by the patient or consumer.

19           Now, the concept of sameness is a critical issue  
20 both for chemistry and manufacturing controls in terms of  
21 product quality and also in terms of performance, and when I  
22 talk about performance relative to product quality, I talk  
23 about bioavailability.

24           Bioavailability relates to the release of the drug  
25 substance from the drug product, and in our society, we

1 express that in terms of the rate and extent of absorption,  
2 and that is in our statute.

3           Sometimes we ask the question of relative  
4 bioavailability in which case we are talking about  
5 bioequivalence, so it becomes a comparative test where we  
6 are comparing the rate and extent of absorption of one  
7 product relative to another.

8           Now, before I leave this slide, I would like to  
9 emphasize that sometimes we talk about bioequivalence and  
10 sameness in performance as though it were a generic versus  
11 pioneer issue, but the reality is that it is not the case.  
12 It affects both pioneer innovator manufacturers, as well as  
13 generic manufacturers, during the period of post-approval  
14 change.

15           We all recognize that manufacturers frequently  
16 change their manufacturing after approval, and this is true  
17 both for pioneer manufacturers, as well as generic  
18 manufacturers, so the concepts that we are going to be  
19 talking about in the course in the morning apply both to  
20 pioneer and generic manufacturers when a question arises of  
21 sufficient magnitude and change in manufacturing, such that  
22 you ask does bioequivalence need to be reestablished.

23           Now, I have talked about a very complicated  
24 system, but I hope in the overview, you get the sense of the  
25 science and technology challenge, and I would argue that it

1 is not an easy one for us and it is one that the Agency  
2 struggles with on many occasions.

3 [Slide.]

4 Now, as we talk about bioavailability and  
5 bioequivalence--and I am not going to focus primarily about  
6 bioavailability/bioequivalence recognizing that there are  
7 other product quality attributes that we can pay attention  
8 to--there are three questions that I frequently pose not  
9 only for myself but for the audience when I speak.

10 These are the three questions: What is the  
11 question, what do we want to know? What assumptions are we  
12 willing to make? How sure do we want to be?

13 Now, we have advisers that speak to us, and the  
14 adviser generally says if you can answer these questions  
15 pretty well, then, the rest of the approach in terms of the  
16 study design and analysis becomes a topic for technicians,  
17 so these are the critical questions, and I would argue and I  
18 have said already in the presentation that when we talk  
19 about bioavailability and bioequivalence, we are focusing on  
20 the release of the drug substance from the drug product.

21 Now, that is a very different question from the  
22 question of safety and efficacy, which I might argue is what  
23 we usually deal with and certainly the center deals with in  
24 the Office of New Drug Management.

25 The next question relates to what assumptions are

1 we willing to make, and I would argue that before the  
2 committees this morning, that will be the key question. The  
3 assumptions that we make are frequently related to the  
4 question of surrogacy - do we want to rely on a surrogate  
5 marker to address our question.

6           Now, I don't have to tell the members of the  
7 committee that the issue of surrogacy appears all the time  
8 in the new drug development process, and as you can see and  
9 as I will emphasize in the next few words, it also is a  
10 critical issue for when we talk about bioavailability and  
11 bioequivalence.

12           To expand on that thought for a minute, let me  
13 tell you that in most instances, we can rely on  
14 pharmacokinetics as a measure of release of drug substance  
15 from the drug product, and it is in that context that our  
16 statute speaks to us in terms of the rate and extent of  
17 absorption.

18           If you think about it, pharmacokinetics itself is  
19 a surrogate for what we really care about, which of course  
20 is comparable safety and efficacy, so we are highly used to  
21 relying on pharmacokinetic parameters, for example, area  
22 under the concentration time curve, peak concentration as a  
23 surrogate for comparing two products in terms of their  
24 bioavailability or their relative bioavailability and  
25 bioequivalence.

1           In the course of the discussion this morning, you  
2 will hear proposals that we would like to rely on instead on  
3 another surrogate which is the dermatopharmacokinetic  
4 approach that you will hear about presented by a subsequent  
5 speaker, I believe Dr. Shah.

6           How sure do we want to be is another topic that I  
7 would say is highly interesting. It relates to topics that  
8 I call confidence intervals and goalposts, and since we just  
9 spent a three-day meeting earlier this week on that topic, I  
10 won't spend any time on it this morning with the committee,  
11 but I will certainly be prepared to answer questions.

12           That, too, is an extremely exciting question, and  
13 we are continuing to struggle with that in various new and  
14 interesting ways.

15           [Slide.]

16           Now, having said that the topic doesn't devolve  
17 entirely on the generic versus pioneer issue, I would like  
18 to focus for a bit on the generic issue in the United  
19 States.

20           When I explained how we allow multi-source  
21 products into the United States market, I have already  
22 mentioned to you that there is the concept of the listed  
23 drug. Before we can receive an abbreviated application in  
24 the United States, the sponsor of the abbreviated  
25 manufacturer must cite the reference listed drug, in other

1 words, what product that is already in the marketplace do  
2 they want to be interchangeable with.

3 Without that, we cannot receive the application.  
4 Having gotten over that hurdle, the next question for--I am  
5 used to coping with presentational disasters, so this  
6 doesn't bother me, but I don't know if the committee can  
7 hear--

8 DR. MCGUIRE: Carry on.

9 DR. WILLIAMS: Carry on? Okay.

10 [Sound system malfunction.]

11 While that is getting repaired, I will continue on  
12 with the generic story. I apologize for that delay to the  
13 committee, and I think I can finish up in just a few  
14 minutes.

15 The first hurdle is you must have a listed drug to  
16 receive a generic application. The second hurdle is the  
17 hurdle of pharmaceutical equivalence. This is a very  
18 complicated question sometimes and relates to whether we can  
19 say the multi-source active moiety is the same as the active  
20 moiety of the listed drug, however, I would say for most  
21 dermatologic products, this is not a difficult decision.

22 Finally, we get to the next hurdle, which is  
23 bioequivalence, which I have already talked about, and you  
24 can see from this particular overhead that our statute and  
25 regulations allow us several modalities to document

1 bioavailability and bioequivalence.

2           Now, this gets to the issue of surrogacy that I  
3 have already alluded to, but you can see that we have  
4 pharmacokinetic measurements, we have pharmacodynamic  
5 measurements, we have in vivo clinical comparisons, and we  
6 also have in vitro comparisons, and all of these in one way  
7 or another I would say are actively used for the category of  
8 locally acting drug products to document release of the drug  
9 substance from the drug product.

10           Now, if all those hurdles are met, then, we can  
11 declare therapeutic equivalence, we allow the product in the  
12 marketplace, and, as you know, it receives the very  
13 important rating from the Orange Book that allows  
14 interchangeability in the U.S. marketplace.

15           [Slide.]

16           Now, this is a particular overview of the working  
17 groups of the Biopharmaceutics Coordinating Committee, and I  
18 won't talk about the left and right set of units and working  
19 groups, but I will ask the committees to focus on the bottom  
20 group, the Locally Acting Drug Products.

21           I would argue that this is a challenging group of  
22 drug products when it comes to documentation of  
23 bioavailability and bioequivalence. The reason for that  
24 challenge arises from the fact that we cannot rely on blood  
25 levels as our surrogate for release or safety and efficacy,

1 and we have to turn to some other, more complicated  
2 approaches that include pharmacodynamics,  
3 dermatopharmacokinetics, in vitro approaches, and sometimes  
4 comparative clinical trials as a way of documenting  
5 comparability in terms of performance.

6           If you go on to the next overhead--and this my  
7 last one I believe--

8           [Slide.]

9           Right now the Biopharmaceutics Coordinating  
10 Committee is working on a series of three guidances that  
11 will provide recommendations to sponsors in the general area  
12 of biopharmaceutics, bioavailability, and bioequivalence.

13           The panel on the left refers to a general guidance  
14 that will amplify our statute and regulations in the matter  
15 for drugs that can generally rely on pharmacokinetic  
16 measures.

17           The panel on the right deals with another very  
18 difficult group of drugs for us, the oral inhalation and  
19 nasally administered drug products, which are also  
20 considered locally acting in our approaches, and then the  
21 one I would like the committees to focus on is the central  
22 panel, which is the locally acting drug products for topical  
23 dermatologic drug products.

24           You can see here that we are working on a  
25 guidance, and if you go under IV.B., you will see that we

1 are now going to hear the approach called  
2 dermatopharmacokinetics, which we think could be a  
3 reasonable approach to document release of the drug  
4 substance from the drug product.

5 That concludes my presentation. I will turn it  
6 over now to Dr. Shah, who will describe that approach and  
7 provide further information about it for the committee.

8 Thank you very much.

9 **Approaches for BA/BE: Dermatopharmacokinetics**

10 DR. SHAH: Thank you, Dr. Williams.

11 I will be making the presentation on an approach  
12 called the dermatopharmacokinetics for the measurements of  
13 bioavailability and bioequivalence.

14 [Slide.]

15 Before I go into describing as to what is the DPK,  
16 I would like to focus two questions to the committee, the  
17 two questions being: Can dermatopharmacokinetic methodology  
18 be used for the bioequivalence determination of  
19 dermatological drug products, such as antiviral, antifungal,  
20 antibacterial, glucocorticoids, and retinoids, and the  
21 follow-up question is, if we cannot use the  
22 dermatopharmacokinetic approaches, then for what classes it  
23 can be used and why not.

24 The second question I would like to focus, which  
25 is a minor question I would say, is can in-vitro drug

1 release be used for granting bio-waivers for the lower  
2 strength of the generic topical product after the higher  
3 strength is approved as bioequivalent, and the only change  
4 is in the amount of the active ingredient.

5 [Slide.]

6 As Dr. Williams pointed out earlier, at least  
7 there are four different ways we can determine the  
8 bioequivalency of the dermatological drug product, they  
9 being the clinical, which in general, it is difficult to do  
10 because you are doing the comparative clinical trials, it is  
11 expensive, and at times it is insensitive to really see if  
12 there are differences between the two formulations or not.

13 The other approach is the pharmacodynamic  
14 approach, which is right now applicable only to one class of  
15 the drug products, the glucocorticoids.

16 The other approach which I would like to focus on  
17 is the dermatopharmacokinetic approach, which is feasible,  
18 it is logical, and we think it is generally applicable to  
19 most of the topical dermatological drug products, and the in  
20 vitro method is generally used as a signal for the possible  
21 bioinequivalency of the product.

22 [Slide.]

23 So, the most important approach we thought which  
24 is feasible is the dermatopharmacokinetic approach and that  
25 that was a basis for a workshop we had in September 1996,

1 which was attended by about 250-plus scientists from around  
2 the world, and the report of that has been just published  
3 now, and everyone has a copy in the form of the handout,  
4 which was a prepublication report.

5           There were three principal things which came out  
6 from the workshop report for this particular issue, and they  
7 are that DPK is a viable method for the bioequivalence  
8 evaluation of topical dermatological drug products.

9           The skin stripping method, which I will describe  
10 in a few minutes, is a specific dermatopharmacokinetic  
11 method that assesses the drug concentration in the stratum  
12 corneum as a function of time.

13           The drug uptake and elimination phases of the  
14 dermatopharmacokinetic profiles should always be evaluated  
15 when we are using this approach for the bioequivalency  
16 determinations.

17           [Slide.]

18           With this as a background, let's just find out  
19 what is the main hypothesis for this. The hypothesis is  
20 that the bioavailability and the bioequivalency can be  
21 determined as the amount of the drug in the skin target site  
22 after the topical drug application.

23           [Slide.]

24           This also allows us the measurement of the drug  
25 uptake in the skin and elimination of drug from the skin.

1 It may provide the dermatopharmacokinetic means of assessing  
2 the bioequivalence of two topical products.

3           The two formulations that produce comparable drug  
4 concentrations in the skin--here, I mean the skin is the  
5 stratum corneum--time curves may be bioequivalent, just as  
6 two oral formulations are judged bioequivalent, if they  
7 provide comparable plasma concentration/time curves.

8           [Slide.]

9           This is depicted in the slide here. This is the  
10 normal way how we compare the oral drug administration, the  
11 skin and the blood samples taken after the oral drug  
12 administration. This forms the absorption phase and the  
13 elimination phase. We think that a similar approach could  
14 be done for the stratum corneum drug uptake and drug  
15 elimination after the topical drug administration.

16           [Slide.]

17           Now, how exactly to do that, how do we take the  
18 skin samples? It must sound very difficult, but it is a  
19 very simple, almost non-invasive technique, and also it  
20 allows us the application of the test and the reference  
21 product, the reference product being the reference listed  
22 drug as it was pointed out earlier by Dr. Williams, and the  
23 test product is the generic product, so this particular  
24 principle allows us the application of the test and the  
25 reference product concurrently to the multiple sites in a

1 single subject, with each site yielding a single drug  
2 concentration in the skin.

3 For drug uptake, for example, in the skin--meaning  
4 again the stratum corneum--is maybe 15 minutes, half an  
5 hour, 1, 2, 4 hours. By that I mean we apply the drug  
6 concentrations on the forearm at multiple sites, and the  
7 same thing we do for the drug elimination at different time  
8 intervals after the drug is removed, which is, for example,  
9 4, 6, 8, 10, and 24 hours.

10 [Slide.]

11 To describe the procedure in very brief, we  
12 applied the product. After certain time interval, we clean  
13 the area at least three times lightly with tissue, and now  
14 we have some more evidence that maybe if you are dealing  
15 with an ointment, we may have to clean it with a very mild  
16 soap and gently remove the stuff which is still sticking on  
17 the skin.

18 Apply the adhesive tape, which is something like a  
19 Scotch tape, but the two special brands which we have used  
20 are the Transpore or the Cuderm's, with uniform pressure,  
21 remove and discard the first stripping, because this  
22 represents the amount of the drug that has not penetrated in  
23 the stratum corneum.

24 At the same site, we apply at least 10 more times,  
25 we remove the tape, extract it, and do the analysis using

1 the standard HPLC method, and express the results as the  
2 amount per surface area, such as nanogram/square centimeter.

3 [Slide.]

4 Now, in one of the other slides I showed that  
5 maybe we would like to make a comparison between the test  
6 and the reference product. If the test product is  
7 significantly different from the reference product, we feel  
8 that this technique, the dermatopharmacokinetic technique,  
9 can be an initial indicator that there is a difference  
10 between the two formulations even before the pharmacodynamic  
11 or even before the clinical activity can be seen.

12 For example, these two products, which show the  
13 steady-state concentration in the stratum corneum, they are  
14 significantly different in terms of the  
15 dermatopharmacokinetic activity, but they are not different  
16 in terms of the clinical efficacy, so this DPK technique  
17 could be really working to give you an indication that the  
18 products may be different.

19 That is what is shown here, two different products  
20 having completely different drug concentrations in the  
21 stratum corneum at a steady-state level, and if you take  
22 each strip and try to do the analysis, it gives you a  
23 classical pharmacokinetic type of the line or the profiles.  
24 Again, the same thing is being followed here.

25 This work, I should indicate here, was done under

1 the guidance and leadership and direction of Professor Hans  
2 Schaefer, who will be providing more detailed information on  
3 some of these principles and the other principles.

4 That was the example of a glucocorticoid  
5 hydrocortisone.

6 [Slide.]

7 This is an example of tretinoin. One of the  
8 things we always want to make sure is that when you take a  
9 method, it is going to be linear, it should be able to  
10 detect any differences there may be between the two  
11 concentrations or any differences that may be existing  
12 between the bioavailability or the bioequivalency of the two  
13 products.

14 This is an example which shows that. The three  
15 different concentrations of Retin A, when applied, and its  
16 concentrations measured in the stratum corneum, shows a nice  
17 linear relationship between the drug concentration and the  
18 formulation, and between the pharmacokinetic or the  
19 dermatopharmacokinetic profiles. This is the example of the  
20 retinoids.

21 [Slide.]

22 Similarly, this is an example of an important  
23 glucocorticoid, betamethasone dipropionate. Again, you can  
24 see here the drug uptake and the steady-state level, and on  
25 the other side you see the drug elimination phase.

1           This piece of work was done under the FDA contract  
2 at University of Utah by Professor Lynn Pershing. This is  
3 all the stratum corneum levels. All the data in the DPK  
4 translate into the stratum corneum levels, not in the skin.

5           [Slide.]

6           When I take the previous slide and put the two  
7 data together, it gives us the information that you see, the  
8 drug uptake and then the drug elimination, with the  
9 simulations, if you do the studies again, we will expect the  
10 data which will be following a path which is similar to  
11 this. For some reason, we had a much higher concentration  
12 here, and that is why you see the earlier data point.

13           So, again, this is an example showing that the  
14 dermatopharmacokinetic principles could be used for the  
15 glucocorticoids.

16           [Slide.]

17           In brief, because of the time constraints, we have  
18 the data which shows that the DPK principles could be used  
19 for almost all the glucocorticoids. For the antifungal  
20 agents, we have the data, and Professor Pershing has  
21 published some information on this with the antifungals  
22 miconazole, ketoconazole.

23           I showed you the data on the antiacne, the  
24 tretinoins. We also have the data unpublished that similar  
25 work could be also done for the antiviral acyclovirs, and

1 the antibiotics.

2 [Slide.]

3 With this in mind, what the guidance would be  
4 describing principally is that we need to do at least two  
5 studies for each product. One, we call a pilot study, and  
6 the second, pivotal bioequivalency study.

7 The pilot study should take care of the following  
8 principles: the validation of the analytical method, which  
9 includes the accuracy, precision, sensitivity, specificity,  
10 and the reproducibility; also, the validation of the skin  
11 stripping technique because this is a new technique which is  
12 very sensitive from one clinician to the other clinician, or  
13 one investigator to the other investigator, and how exactly  
14 you do that.

15 So, we need to have a good handle on the  
16 validation of the skin stripping technique, plus we should  
17 have a good handle on the intersubject and intrasubject  
18 variability on the arm primarily because that is where we  
19 have most of the studies done because of ease of operation.

20 We should establish the dose-response  
21 relationship, as I showed you the example of the tretinoin,  
22 and the selection of the sampling time, which will generate  
23 the concentration/time profile.

24 This is important because it is directly dependent  
25 on the product itself, the type of the product, the nature

1 of the product, the nature of the active ingredient. So,  
2 all these parameters should be determined using the pilot  
3 study program.

4           Following that, once you have the time schedules  
5 and all, a full bioequivalency study should be done using  
6 the sampling time points and the figures determined in the  
7 pilot study to come to the conclusion of the bioequivalency  
8 study.

9           [Slide.]

10           So, again, this is the same question I had in my  
11 other slide, the first slide, is can the  
12 dermatopharmacokinetic methodology be used for the  
13 bioequivalence determination of the dermatological drug  
14 products. The following are the drug products.

15           [Slide.]

16           Also, we would like to acknowledge the fact that  
17 under certain circumstances, this may not be enough  
18 information, but is it or not. So, to answer some of the  
19 questions, such as under what circumstances a follicular  
20 pathway is an important consideration in the bioequivalence  
21 determination of dermatological drug products, because the  
22 question has been raised by the different scientists that  
23 maybe we need to take into consideration the follicular  
24 pathways, what might be happening.

25           The second question we would like to answer is

1 what factors influence a follicular pathway, and what tests  
2 may provide information to bypass the follicular pathway  
3 measurements.

4           Some of these things with respect to the  
5 dermatopharmacokinetics and the follicular measurements will  
6 be addressed by Professor Hans Schaefer within a few  
7 minutes.

8           The last issue or point here is can a  
9 dermatopharmacokinetic data, along with the particle size  
10 distribution, and along with in vitro drug release provide  
11 us sufficient information to make the final determination of  
12 the bioequivalency of the topical drug product. That is the  
13 final issue.

14           [Slide.]

15           This is just a slide to indicate that this is not  
16 the first time we are discussing the dermatopharmacokinetic  
17 aspects or the principles. There have been a series of  
18 workshops and open public discussions both in this country,  
19 as well as in Europe and other places, where the  
20 dermatopharmacokinetic principles have been discussed  
21 extensively, and it has been also discussed twice in our  
22 initially called the Generic Drug Advisory Committee meeting  
23 in 1992, and now in our advisory committee called the  
24 Pharmaceutical Sciences in December of 1997, the same two  
25 questions, and now we are presenting it to you people to

1 have your scientific input, so that we can proceed further.

2 All this work, we have been getting it out for  
3 about the last 12 to 14 years, in France under Professor  
4 Hans Schaefer, in Utah under Professor Lynn Pershing, with  
5 our consultant Professor Tom Franz, and also in California  
6 with Professor Howard Maibach. Just to acknowledge the  
7 contributions of these scientists in this area.

8 I think this is my last slide. With this, we will  
9 hear the comments from Dr. Jonathan Wilkin on this area.

10 **Division of Dermatologic and Dental**

11 **Drugs Perspectives**

12 DR. WILKIN: I am Jonathan Wilkin from the  
13 Division of Dermatologic and Dental Drug Products.

14 One of the values that we discuss within the  
15 division is the notion of elegance and when we think of  
16 this, we think in terms of the use of the word "elegance"  
17 that the mathematicians use. They talk about an elegant  
18 mathematical proof being one that has the fewest number of  
19 steps to get to the conclusion, in the same way organic  
20 chemists talk about elegance in terms of pathways to the  
21 product, it's the fewest number of synthetic steps that  
22 ultimately would lead to the product in order to have the  
23 highest yield.

24 We think of the notion of regulatory elegance  
25 being the same sort of notion, that we want just the right

1 kind of information from the sponsor and really nothing in  
2 excess of that.

3           It is not a passive sort of thing. We believe  
4 that to really fulfill the notion of regulatory elegance,  
5 that we should be actively thinking about it at all times.

6           One of the first things we do is when an  
7 application comes in or a briefing package and we are  
8 talking with sponsors, our first goal is to look over the  
9 tests that are often done and see if we can't reduce the  
10 number or extensiveness of the required tests.

11           The second is refinement. Sometimes we can  
12 optimize a test, suggest a way that different tests can be  
13 combined, for example, contact irritation, contact  
14 sensitivity can sometimes save resources.

15           The final one, which is the one that Dr. Shah is  
16 talking about today, is replacement, and that is  
17 substitution of a simpler, cheaper, more informative test.  
18 Right now the generic companies, to get a dermatologic  
19 topical often need to have a clinical study, and what Dr.  
20 Shah and his group are vigorously working on is a simpler  
21 methodology.

22           [Slide.]

23           Rather than conclusions, maybe this would be  
24 axioms. Regulatory elegance is our goal. Replacement of a  
25 current test method with simpler, cheaper, more informative

1 test methods furthers regulatory elegance, and alternative  
2 test methods can replace current test methodology if peer  
3 review finds--and this, of course, would mean that Dr. Shah  
4 and his group might come back and present the data at some  
5 point, I think we have the need--that validation is complete  
6 and documented, and that the results of  
7 dermatopharmacokinetics are at least equivalent to the  
8 current methodology. Certainly, we think they would be less  
9 expensive.

10 [Slide.]

11 The Hatch-Waxman law, which provides for generics,  
12 one of the key underlying premises is that bioequivalent  
13 products are therapeutically equivalent and therefore  
14 interchangeable, that they would be predicted to have the  
15 same efficacy and the same safety.

16 [Slide.]

17 Bioequivalent products should show comparable  
18 bioavailability when studied under similar conditions.  
19 That, I think is the essence of what we are talking about  
20 this morning - can DPK actually do this.

21 [Slide.]

22 Bioavailability is the rate and extent to which  
23 the active ingredient is absorbed from a drug product and  
24 becomes available at the site of action.

25 [Slide.]

1           So, the question is can dermatopharmacokinetics,  
2 as described, lead to bioequivalence estimates.

3           [Slide.]

4           Well, there were a couple of concerns that emerged  
5 from the division that we have shared with Dr. Shah, and I  
6 have to say that his group has been modifying and rethinking  
7 and improving upon their methodology and description over  
8 the many months, and that resonates very well with our  
9 group. I mean we believe that this is the direct way to go,  
10 but there are still some concerns.

11           The first concern is that, as presented, it seems  
12 that the layers somehow are meaningful, and I would point  
13 out that stratum corneum is not baklava. It does not come  
14 as discrete layers. Instead, there is tape stripping of the  
15 human stratum corneum that yields cell layers that originate  
16 from various depths, because there are furrows and twists in  
17 the surface.

18           [Slide.]

19           The second issue that we have brought to his  
20 group's attention is that really there are two pathways to  
21 the biophase, the important targets for drugs in the skin.  
22 There is the transepidermal pathway, which is the focus of  
23 dermatopharmacokinetics, and then there is the  
24 transfollicular or, in Dr. Schaefer's work, often referred  
25 to as shunt pathway, and it would be important we think to

1 assess that shunt.

2 [Slide.]

3 In one study it was shown that adapalene 0.1  
4 percent was found in the follicle as early as five minutes  
5 after topical application, and then after two hours it was  
6 found at a depth of 400 micrometers in the follicle, and  
7 they suggested in this paper that it would be very useful  
8 for the treatment of microcomedones because it seemed to  
9 preferentially go right to that site.

10 [Slide.]

11 These are some points taken from one of Dr.  
12 Schaefer's papers, concentration of topical drugs into the  
13 pilo-sebaceous and perifollicular regions. He quoted some  
14 papers that identified that.

15 Also, drugs can be delivered selectively to skin  
16 appendages, and he ended up in his conclusion section with  
17 the need to quantitate the contribution of the shunt  
18 pathway, and this should be percutaneous penetration, and I  
19 think that really is a good conclusion.

20 It would be important to quantify how much is  
21 going through the transfollicular pathway relative to the  
22 transepidermal pathway before we can really use DPK as the  
23 surrogate.

24 [Slide.]

25 Now, there has been an allusion to the plasma

1 time/concentration curves. When one gives an oral drug and  
2 you look at that showing up in the plasma, and then watch it  
3 gradually disappear, you can look at that area under the  
4 curve, and you can describe drug in the stratum corneum in a  
5 way that is going to graph out with that same kind of slope  
6 up and then gradual slope down.

7           It probably would look very much like the Sandia  
8 mountains from Albuquerque, but you wouldn't ascribe  
9 anything to the outline of the mountains, and I am not sure  
10 that the stratum corneum profile should really tell us its  
11 bioequivalence unless we can make the connection that there  
12 is equilibrium between the stratum corneum and the target  
13 site.

14           The key thing about why the plasma is so useful,  
15 the plasma time/concentration curve, is that the drug in the  
16 plasma is in equilibrium with the organs that are the site  
17 of the activity of the drug.

18           [Slide.]

19           The final item that is in Dr. Shah's that I would  
20 lift out is that this is going to be explored on healthy  
21 skin, and we know, for example, that the percutaneous  
22 penetration of hydrocortisone is increased with severity of  
23 atopic dermatitis and also there is an enhanced percutaneous  
24 penetration of several drugs in psoriatic skin versus  
25 uninvolved skin in the same subject.

1           So, one of the concerns is if you are only looking  
2 at healthy skin, are you really able to extrapolate to  
3 diseased skin, that perhaps in diseased skin, one might be  
4 able to discriminate better between something that is very  
5 efficacious and something that is less so, but the  
6 constraints with healthy stratum corneum where the  
7 percutaneous penetration will be much less, one might not  
8 see that difference, so healthy versus diseased skin.

9           [Slide.]

10           I will just go over the brief list again for DPK,  
11 dermatopharmacokinetics. The interfollicular stratum  
12 corneum, I think we saw several slides of Dr. Shah's, where  
13 it was referred to as skin. I think we always need to  
14 remember that we are talking about stratum corneum. We are  
15 really not talking about skin uptake and skin elimination,  
16 we are talking about stratum corneum.

17           This methodology will not tell us about the  
18 follicular path. There are many skin targets. Some are at  
19 the bottom level of the stratum corneum. That would be  
20 where the dermatophytes would be. But others are the blood  
21 vessels in the superficial dermis and at different sites  
22 throughout the skin. The skin is more complex.

23           The analogy to plasma bioequivalence, again, there  
24 is no equilibrium that has been demonstrated for DPK, so I  
25 think that undermines its utility, and the percutaneous

1 penetration in disease might not be exactly modeled by  
2 looking at DPK in healthy skin.

3 We think the approach is an important approach,  
4 and many of these kinds of questions could be answered in a  
5 laboratory setting. So, in the end, there could be very  
6 satisfactory answers, and this could be a very useful  
7 methodology.

8 I would like to defer talking about lower  
9 strengths by ratio of release rates because that is yet to  
10 be presented by Dr. Shah.

11 The next speaker is Dr. Hans Schaefer.

12 **DPK and Follicular Pathways**

13 DR. SCHAEFER: I will try to focus on those  
14 critical points which have been mentioned by Jonathan  
15 Wilkin, and this in three respects.

16 [Slide.]

17 First of all, the applicability of the stripping  
18 method; secondly, the precision of the stripping method;  
19 thirdly, of the power of discerning between different  
20 situations of the stripping technique, and this specifically  
21 addressing the problem of follicular penetration.

22 Here is the principle, as Dr. Wilkin said, there  
23 is interfollicular penetration that is in the space in  
24 between follicles, the transepidermal penetration, and the  
25 follicular penetration, that is, the entrance into the

1 follicle.

2           The point which we will have to address is under  
3 the premise of sameness, of bioequivalence, that is, the  
4 same compound, a similar formulation, same physical/chemical  
5 conditions.

6           [Slide.]

7           Can follicular penetration bear on the validity of  
8 the stripping method for the assessment of dermal  
9 bioequivalence? The question is not do we see differences  
10 with different substances, though I will show them to you.

11          [Slide.]

12          In other words, could the stratum corneum  
13 reservoir--and please keep in mind the term reservoir, it's  
14 hardly ever mentioned, and it's the key issue in discussion  
15 of dermatopharmacokinetics related to the stripping  
16 technique, related to normal skin--could the stratum corneum  
17 reservoir, as determined by the stripping method, remain the  
18 same for two formulations even when the ratio between what  
19 enters into the follicle versus what enters  
20 interfollicularly into the epidermis changes? This is the  
21 key question which I have tried to address.

22          I repeat even when there are minor changes which  
23 favor the follicular penetration in respect to another  
24 preparation, can we see the difference, can we expect to see  
25 the difference, or will it disappear?

1 [Slide.]

2 So, we are dealing with the same compound, same  
3 concentration, similar vehicle, same physical/chemical  
4 properties, same compound, is either dissolved or it occurs  
5 in same particles, particle size, and the distribution  
6 should be the same, and no polymorphism, very generally  
7 speaking.

8 [Slide.]

9 Under which conditions could such a shift in the  
10 ratio between what enters through the follicles and what  
11 enters transepidermally occur?

12 If you ask me, there are only two conditions which  
13 I encountered, the one is follicular targeting--this has  
14 been mentioned by Dr. Wilkin--when you on purpose formulate  
15 in a way that the reservoir is not filled up because of the  
16 particle size, and the particle size is very discriminatory.  
17 I will show you examples of that.

18 The second is potent penetration enhancers.  
19 Potent penetration enhancers do favor the transepidermal  
20 penetration such that the transfollicular penetration is  
21 diminished. These are the two conditions which I personally  
22 encountered.

23 [Slide.]

24 In other words, could such a shift stay below the  
25 level of detection, however, have a significant impact on

1 therapeutic efficacy? That is the key question.

2 [Slide.]

3 Now, the quantitative link between the horny layer  
4 reservoir, as measured by the stripping technique, and the  
5 subsequent penetration into and permeation through the skin  
6 has been clearly demonstrated. We started to work on this  
7 in the late seventies and the early eighties, and I will  
8 give you some examples.

9 [Slide.]

10 Only to show you that there are four conditions,  
11 different compounds. Here are different compounds at  
12 different concentrations. Here are different vehicles.  
13 These are 1, 2, 3 are animals where we compared the  
14 stripping, the material in the horny layer reservoir with  
15 the total balance, that is, what happens in an animal during  
16 four days complete analysis of excretion and retention in  
17 the body, and so on, 100 percent recovery.

18 This is, together with Howard Maibach and his  
19 team, the same technique in humans related to the data he  
20 had already related to radioactivity. Again, 100 percent  
21 balance, and we investigated the correlation between  
22 stripping technique and the uptake in the body of  
23 radioactive material.

24 We can skip the next four because you have seen  
25 them already in order to accelerate a bit.

1 [Slide.]

2 This is the data in humans. You see it again,  
3 four different compounds, acetylsalicylic acid, benzoic  
4 acid, caffeine, and sodium salt of benzoic acid, and you see  
5 the slope. The  $r$  is very, very close to 1.

6 Now, this, I have to emphasize is under  
7 standardized conditions. The technique is very sensitive to  
8 standardization. Standardization means removal of the  
9 surplus and disregarding the first two strips, accounting  
10 for them in terms of the balance, but not including them  
11 into the kinetics because it is from there where uncertainty  
12 and variation comes.

13 [Slide.]

14 You have seen this. Vinod Shah showed you the  
15 other curves. This is the study he mentioned where we have  
16 seen the minor differences in pharmacodynamics are clearly  
17 depicted in the pharmacokinetic measurements. I won't go  
18 into the details.

19 [Slide.]

20 Now, here comes the point we want to discuss  
21 today. Imagine that this follicle would be absent, what  
22 would happen in terms of the pharmacokinetics, is there a  
23 difference between presence and absence wherein material is  
24 applied to the skin surface, enters into the reservoir, and  
25 is left on the skin for a certain time.

1           The next slides are to show you that, yes, there  
2 is a dramatic difference. Now, I must say the model we are  
3 talking here is exaggerating the situation. It is hairy  
4 skin of rats, and when you create a scar on red skin, it is  
5 devoid of follicles, so one rat, on one side with follicles,  
6 on the other side without follicles, you now can compare the  
7 situation, presence or absence of follicles for the same  
8 compound, and look into what happens in the deep  
9 compartments of the skin and later on to stripping  
10 technique.

11           [Slide.]

12           Now, here, you see clearly scar skin, only  
13 fractions of what is entering into the normal skin, which is  
14 telling that, yes, the follicle of the shunt pathway is of  
15 great importance for lipophilic compounds, for progesterone,  
16 estradiol, and the next, please.

17           [Slide.]

18           Progesterone, more details in terms of timing, and  
19 you see the kinetics are clear, and again clear-cut  
20 differences between normal and scar skin.

21           [Slide.]

22           Estradiol, same. Clear-cut differences in terms  
23 of the kinetics between normal and scar skin, and you always  
24 see that in scar skin, the concentrations are higher because  
25 the diffusion into the follicles is lower. It is quite

1 logical.

2 [Slide.]

3 Now, here comes the critical question. Are these  
4 relations, are these differences seen in the stripping  
5 technique? The answer is yes, we see clearly normal skin,  
6 scar skin more in the horny layer in the scar skin relative  
7 to normal skin, that is, hairy skin, and again, the kinetics  
8 are clearly seen with the exception of six hours. This is a  
9 detail which we can discuss in the discussion, but anyway,  
10 the stripping technique clearly depicts these differences.

11 [Slide.]

12 Here you see the kinetics of hydrocortisone,  
13 normal skin versus scar skin. As you see with the time  
14 passing by, things shift.

15 [Slide.]

16 Thirty minutes. Higher concentrations in the  
17 normal skin compared to the scar skin depending on the  
18 depth. Here we are looking at the depth of the skin, of the  
19 concentrations in deeper layers.

20 [Slide.]

21 Same after two hours.

22 [Slide.]

23 After six hours. Again, we have to say there are  
24 clear-cut differences, follicular pathway versus absence of  
25 follicular pathway.

1 [Slide.]

2 Here is the kinetics again. You see a clear-cut  
3 difference in terms of peak and of the whole kinetic in  
4 respect to timing.

5 [Slide.]

6 The stripping. Again, we clearly can see the same  
7 differences in the stripping technique, normal versus scar  
8 skin. Again, the same ratio, which is logical. In scar  
9 skin, we find more in the stratum corneum because less is  
10 taken up by the follicles rather than normal, that is, very  
11 hairy skin in animals.

12 I have to emphasize that the difference between  
13 the normal and scar skin in humans has been investigated in  
14 my place. The differences are smaller. They are smaller  
15 because there are less follicles, and the structure of the  
16 follicles is different compared to animal skin, but it is  
17 there.

18 [Slide.]

19 Now, here I show you something which is not  
20 directly related, but which is very telling. We looked into  
21 particles, 5 micrometer diameter spheres can be found on the  
22 market, can be incorporated into the preparations and  
23 applied to the skin, and we do know that these particles do  
24 not enter into the living layers of the skin. They don't  
25 enter into the keratinocytes or into the fibroblasts, they

1 don't enter into the skin at all. They stay in the horny  
2 layer or in the follicle.

3 Can we detect differences in terms of time  
4 kinetics as to the fate of microbeads in the horny layer?  
5 Again, the answer is yes, and you can go one step further.

6 [Slide.]

7 Here, you see the difference--sorry for the  
8 French--here you see the difference between skin where the  
9 surface is normal and skin where prior to application, the  
10 horny layer has been removed, and these are orders of  
11 magnitude of difference, which show clearly that yes, you  
12 can follow the fate, and secondly, they don't enter into the  
13 normal skin. So, in other words, this technique is very,  
14 very sensitive.

15 [Slide.]

16 We can skip that because it only shows the same  
17 relationship.

18 [Slide.]

19 You can see that even in terms of kinetics, we  
20 clearly can distinguish between different situations in  
21 respect to solid material, which is not dissolved. These  
22 are glass particles.

23 [Slide.]

24 This is a special gift to you. I got this the day  
25 before yesterday on my desk. What is it? A completely

1 different question. We investigated the fate of titanium  
2 dioxide nanoparticles, and wanted to know do they enter into  
3 the skin; if yes, where, or don't they, and how can you  
4 prove it?

5           For this purpose we looked into different brands  
6 and different coating of titanium dioxide. In essence, we  
7 expected to find no difference between the different kind of  
8 coating. We found it, different coated titanium dioxide  
9 behaves different in respect to the distribution within the  
10 horny layer.

11           [Slide.]

12           So, in other words, again, the technique is  
13 extremely sensitive even in respect to compounds and to  
14 material which has the same particle size, but which has  
15 different, slightly different physical/chemical properties,  
16 the one being coated with magnesium stearate and the other  
17 one being coated with aluminum oxide, and we see a clear-cut  
18 difference between these situations.

19           [Slide.]

20           So, I hope I could show you the difference for  
21 different substances are clearly detected by the technique.  
22 The differences in vehicles are clearly detected, that  
23 kinetic differences are clearly detected, that differences  
24 in follicular penetration are clearly discernible.

25           [Slide.]

1           In our book, the stripping technique is sensitive  
2 to arithmetic differences in dosage, that is, 0.1, 0.15,  
3 0.2, and so on, can be clearly distinguished in terms of  
4 concentrations in the reservoir, whereas, as all of you  
5 know, in clinical investigations of topical drugs, the  
6 differences you can distinguish is 0.1 to 0.3 to 1.0 to 3.0,  
7 not in between.

8           [Slide.]

9           In other words, such a shift would be detected by  
10 the stripping technique before it becomes clinically  
11 relevant, because the stripping technique is just so much  
12 more sensitive.

13           Now, in this respect, I said reservoir. I have to  
14 reemphasize reservoir because in my book, the reservoir  
15 resembles the plasma compartment in that from both cases,  
16 material is delivered from the compartment to the target  
17 tissue, from the plasma to the tissue in the body, from the  
18 horny layer reservoir to the skin.

19           [Slide.]

20           Thus, changes in follicular penetration will not  
21 escape attention. Please keep in mind again the initial  
22 question was same compound, similar preparations, can there  
23 be a shift from transepidermal versus transfollicular, which  
24 remains undetected, and from what I know, I would say no  
25 way. You will see them earlier than ever you could prove

1 them in clinical assays.

2 Thank you for your attention.

3 DR. MCGUIRE: The next speaker is Dr. Gordon  
4 Flynn.

5 **Principles of Topical Drugs**

6 DR. FLYNN: You can see that I have changed the  
7 title to Theoretical Odds and Ends: pharmacokinetic  
8 analysis related to the release test, as well, and I have  
9 just a couple of points that I want to make.

10 We are speaking this morning about surrogacy and  
11 substituting an in-vitro procedure perhaps for a clinical  
12 study. Under the circumstances, it appears to me the in-  
13 vitro procedure might, in fact, be more telling and more  
14 discriminating between formulations than you can actually  
15 get discrimination with a clinical study.

16 We have had the [Beclevelian] uncertainty  
17 principle introduced, and there are some serious concerns  
18 about method and in alkability and follicular pathways, and  
19 all, and I think some of the things I will say in the  
20 theoretical area should allay some of those concerns if I  
21 had enough time to make the points well enough, and I am not  
22 sure I have that.

23 What we really are concerned about I think  
24 collectively, all of us, is the confidence we can have in  
25 the data and the extent to which, if you are going to use a

1 them in clinical assays.

2 Thank you for your attention.

3 DR. MCGUIRE: The next speaker is Dr. Gordon  
4 Flynn.

5 **Principles of Topical Drugs**

6 DR. FLYNN: You can see that I have changed the  
7 title to Theoretical Odds and Ends: pharmacokinetic  
8 analysis related to the release test, as well, and I have  
9 just a couple of points that I want to make.

10 We are speaking this morning about surrogacy and  
11 substituting an in-vitro procedure perhaps for a clinical  
12 study. Under the circumstances, it appears to me the in-  
13 vitro procedure might, in fact, be more telling and more  
14 discriminating between formulations than you can actually  
15 get discrimination with a clinical study.

16 We have had the [Beclevelian] uncertainty  
17 principle introduced, and there are some serious concerns  
18 about method and in alkability and follicular pathways, and  
19 all, and I think some of the things I will say in the  
20 theoretical area should allay some of those concerns if I  
21 had enough time to make the points well enough, and I am not  
22 sure I have that.

23 What we really are concerned about I think  
24 collectively, all of us, is the confidence we can have in  
25 the data and the extent to which, if you are going to use a

1 surrogate, that it is telling you what you want to know or  
2 that it may be misleading you.

3           There are alpha and beta errors, and we are  
4 depending on a good batting average or, in statistical  
5 terms, a good probability of reaching a fair conclusion  
6 about something, and I think most of us are most concerned  
7 with this situation here in terms of alpha or that is a  
8 situation where products are different, but they test the  
9 same, and I think if we looked into the things that Hans  
10 Schaefer just said, I think one of his main messages is that  
11 is not likely to happen, and I personally believe that is  
12 also true.

13           So, ladies and gentlemen, friends, and I am sure  
14 some adversaries, let me start and have the first slide,  
15 please.

16           [Slide.]

17           I have written out things and I plan to go through  
18 some transparencies with written information on them  
19 relatively quickly. I am certainly not going to read them  
20 to you.

21           But we see and have heard about the fact that  
22 experimental data from several laboratories that point to a  
23 procedure that may be used as a surrogate or actual  
24 bioequivalency testing in an area where it is almost  
25 impossible to do a true bioequivalency test,

1 dermatologicals.

2           The point made about not having the equivalent of  
3 serum blood levels is a fair point, is an important point.  
4 We don't have 10 angstrom scientists that can go into the  
5 skin and actually measure the levels where the drugs are  
6 active, and so this makes this an extremely difficult  
7 assessment from the laboratory standpoint.

8           A method is proposed which is relative to the  
9 alternatives, fairly simple, straightforward. I am not  
10 saying that you don't have to be skilled in the method, but  
11 it is not as sensitive as many of the alternatives in terms  
12 of the skill of the laboratory people and running it  
13 effectively. It's pseudoclinical. It is run in a situation  
14 where the subject, him or herself, is the control, as well,  
15 at the same time, with the same formulations, and this is  
16 the thing that helps build statistical confidence in  
17 results.

18           The so-called \$64,000 question about the test is  
19 why should it work, why might it work, and that is where I  
20 would like to bring in a few theoretical principles.

21           [Slide.]

22           There are fundamental parallels between what is  
23 being proposed within the release test and regular transport  
24 theory. What I have got in front of you are some equations  
25 that I don't really expect you to assimilate in the very

1 short period of time they are going to be in front of you.

2           They are drawn for a simple membrane isotropic  
3 uniform in all its properties. I should add that the  
4 principles underlying these equations, however, apply to  
5 very complex membranes like the skin.

6           The equations are written under circumstances  
7 where we set up a steady state of diffusion, and so we have  
8 to have boundary conditions and initial conditions which  
9 will accomplish that. I put that all down on the slide.

10           We wind up with a fairly complex equation down at  
11 the bottom of the slide, which describes the concentration  
12 in the membrane as a function of depth and time, and so a  
13 position in the membrane.

14           [Slide.]

15           That particular equation leads you through three  
16 further steps to the second complex equation at the top of  
17 this transparency, which says that the amount which has  
18 penetrated the membrane has a mathematical relationship, and  
19 if you will let time pass and mathematically say let time  
20 approach infinity, but, in fact, a limited amount of time  
21 leads to the collapse of the righthand most term in that  
22 equation, and you wind up with a simple equation which most  
23 people in the diffusion business are familiar with, in the  
24 middle of this transparency.

25           The point I want to make about this equation is

1 that the penetration of the membrane depends on diffusion  
2 coefficient  $D$ , partition coefficient into the membrane  $K$ ,  
3 concentration in the vehicle  $C_0$  and the thickness of the  
4 membrane, reciprocal thickness of the membrane are  $1/h$ , and  
5 there is a period of time it takes for the gradient to be  
6 established in the membrane, and so, in fact, you have  $t$ -  
7  $A^2/60$ , and if you solve this equation for the intercept of  
8 this line, on the  $x$  axis you wind up with what we call the  
9 diffusion lag time which allows you to calculate the effect  
10 of diffusion coefficient.

11           This works out beautifully for a simple isotropic  
12 membrane. We wind up with relatively useful numbers, but  
13 with no absolute meaning in terms of true diffusion  
14 coefficients and true partition coefficients and all when we  
15 are dealing with complex membranes of the skin, but the  
16 principles underlying this equation apply to transdermal  
17 delivery and skin penetration and gastrointestinal  
18 absorption even as they do to an isotropic membrane.

19           [Slide.]

20           Now, in the case of the procedure that is being  
21 considered here, we are dealing with what is known as the  
22 non-stationary state portion of the diffusion curve. As  
23 many as 75 years ago, a theorist took the master equation on  
24 the previous slide and resolved that by a Fourier  
25 transformation and then reintegration to come up with an

1 equation now sitting on this slide for the dependency of the  
2 permeation process in the non-stationary state.

3           The only reason I put this in front of you--and  
4 there is some more information on this--but the reason I put  
5 this in front of you is that dependency changes in terms of  
6 the order of magnitudes of the variables, but the variables  
7 are exactly the same - time, concentration, partition  
8 coefficient, thickness of the membrane.

9           By that type of analogy, we can expect a  
10 deposition test to share properties and outcomes with a  
11 throughput test or the steady state and the non-stationary  
12 state have a strong relationship to one another in terms of  
13 the underlying fundamental properties which drive the  
14 processes.

15           [Slide.]

16           My second point is the second question. You can  
17 see that each one of these is probably an hour or so worth  
18 of further discussion, and we don't have time for that.

19           What is the relationship, if any, between topical  
20 drug delivery and the so-called release test? That is now  
21 part of SUPAC-SS. There is two levels of answering this  
22 question, and I want to make sure I don't create a confusion  
23 about the second level by starting now right off the top  
24 saying I am talking about in an absolute sense. I mean  
25 talking about the bioavailability/bioequivalence and

1   equivalency in release of two formulations, an innovator and  
2   a generic product.

3           I am not talking about relative strengths or  
4   lesser strengths issue, which is different. When we look at  
5   this in the absolute sense, we built SUPAC-SS around a  
6   release test, and then it has been suggested by some of our  
7   family of scientists that this test itself might serve as a  
8   surrogate for bioequivalency, what might we have to say  
9   about that.

10           So, answering this question is a matter of  
11   answering the sameness and the dissimilarity of the expected  
12   outcomes in the process and underlying principles.

13           I have written in the clinical situation a topical  
14   formulation is applied to a membrane--obviously, the skin  
15   surface--and diffusion of the drug it contains out of the  
16   formulation and into and through the membrane, the stratum  
17   corneum for the most part, from the formulation is driven by  
18   natural forces.

19           We are talking about activity, thermodynamic  
20   activity, we get down to the nit of it, and diffusion,  
21   point-to-point movement of molecules and diffusion space. In  
22   release testing, a topical formulation is applied to a  
23   membrane, here is a synthetic membrane, and diffusion of the  
24   drug it contains is through the membrane and also driven by  
25   natural forces. So, to this point, these processes are the

1 same.

2 [Slide.]

3 That is where the sameness ends. In the clinical  
4 situation, a formulation is typically applied in amounts  
5 between 1 mg/cm<sup>2</sup> and 3 mg/cm<sup>2</sup>, but in the clinic you have no  
6 real control over this. People have a tube in their hand  
7 and they spread these things liberally or not liberally  
8 depending on their inclinations, and so these are just  
9 middle numbers and the range can be much greater than this.

10 One attempts to perform the release test using a  
11 functionally infinitely thick application. That is a major  
12 difference. In "diffusion-speak," as I put it here, release  
13 is from a semi-infinite medium. In the clinical situation,  
14 the applications are more often than not open, meaning that  
15 volatile components of the formulations are quickly lost.

16 Thus, formulations undergo substantial  
17 compositional adjustments over the course of their delivery  
18 performance and the drug's thermodynamic activity is  
19 continuously changing while the formulation is on the skin.

20 We set up a release test, so that the formulation  
21 doesn't change. We deliberately do that. We use occluded  
22 conditions. We put very thick layers over the membrane, a  
23 major departure.

24 In the clinical situation, the membrane,  
25 especially the stratum corneum covering of the skin, is

1 extremely resistant. It is a highly resistant membrane.  
2 The membrane exerts the principal barrier in the transport  
3 process.

4 In the release test, we deliberately pick a  
5 membrane of the lowest conceivable possible attainable  
6 diffusional resistance. We pick it that way because we want  
7 the release test to reveal the diffusion process as it is  
8 occurring in the vehicle, not through the membrane. We want  
9 the membrane's interference with the curve to be very  
10 transient, and we want to get into the period of dependency  
11 of release from the vehicle very quickly.

12 That is exactly what we do, and we are successful  
13 in doing that. In the clinical situation, with some  
14 formulations, you may, in fact, have something like a zero  
15 order of delivery, particularly from a suspension.

16 In the release test, you are looking for a square  
17 root dependency of delivery on time. Major differences.

18 [Slide.]

19 The bottom line to the previous question is these  
20 are so different in an absolute sense that the release test  
21 is not in fundamental ways suitable as a test of itself for  
22 bioequivalency, it just is not.

23 Now, Dr. Shah is going to tell you about using  
24 release testing after equivalency established at a high  
25 strength for lower strength, and I believe that, in fact, is

1 rational, and that is a different position.

2           So, how useful is the release test? I just want  
3 to fly through a couple of things, and this represents data  
4 from our laboratory.

5           [Slide.]

6           This is our formulation in a schematic way. We  
7 have a vanishing cream. They are emulsified and solidified  
8 droplets of stearic acid mixed with stearic alcohol, acetyl  
9 alcohol. A great deal of the stearic acid is converted to  
10 potassium stearate, the way we make this formula, and  
11 therefore, that is a soap, a surfactant. We have a lot of  
12 micella structure. There are individual micelles, they are  
13 3-dimensional micella networks, which are actually  
14 solidified, and that is what makes vanishing cream semi-  
15 solid. It is the micella structure that does that.

16           We have crystals of different size and then we  
17 have drug in solution, a fairly complex system from what  
18 seems to be a very simple formula.

19           [Slide.]

20           In the release test--and there is no background, I  
21 am just showing you data--when you change the concentration  
22 of the drug in the medium under circumstances where we are  
23 dealing with all suspensions here--we know that now because  
24 we have an absolute measure of the solubility--even the  
25 lowest 0.25 percent strength is about 12 times the

1 solubility of hydrocortisone in the system.

2           We got a clear differentiation of release based on  
3 the concentration of the drug in the formula. Interesting,  
4 but none of you that are producing product are going to make  
5 the mistake of putting the wrong concentration in your  
6 formula and not first find that in quality control in a  
7 direct assay, so I am not suggesting that this is going to  
8 be useful in that sense.

9           [Slide.]

10           There is an actual dependency of those slopes on  
11 the square root of the total amount of drug in those  
12 formulations. That is all this transparency shows. This is  
13 a stepping stone to what Dr. Shah will show you in a few  
14 minutes.

15           [Slide.]

16           I think it becomes a little more interesting here  
17 when we change the amount of the potassium hydroxide we add,  
18 and we see a different release. This is, in fact, something  
19 that you might do in your production and not pick up in the  
20 course of ordinary quality assurance processing of a  
21 formulation, and these are rather substantial differences in  
22 slope.

23           [Slide.]

24           Here, I put one on where we have two manufacturing  
25 methods. I think this is the most interesting one of all.

1 The only difference here in these formulas is in one case we  
2 used a homogenizer, one or those rotostater type running at  
3 4,800 rpm, and the next time we ran it up at 6,400 rpm, it  
4 changes the release rate because it changes the fineness of  
5 the emulsion state, and that is something that clearly could  
6 happen if you took your production from New Jersey to Puerto  
7 Rico.

8 [Slide.]

9 Here are three particle sizes of hydrocortisone--  
10 that is the drug in all of these incidently--done by  
11 screening regular hydrocortisone, so we have coarser  
12 materials and finer materials here. The particle size of  
13 the drug is clearly differentiated in the release test.

14 That is it. From the standpoint of its mission in  
15 SUPAC, I more and more believe that this test is a very  
16 valuable addition to our repertoire of tests. It allows a  
17 manufacturer to keep control of the product in processing  
18 when certain level changes are made that are reasonable and  
19 rather the ordinary ones without having to first get  
20 approval from the FDA every time something is done to the  
21 product, and I don't recommend this test as a routine  
22 quality control issue test. I don't believe it is  
23 discriminating enough for that.

24 The point I have made several ways in several  
25 places, that when this test shows up a difference, that

1 doesn't necessarily mean the formulas are now clinically  
2 different, but is reason to be concerned about the fact that  
3 something has changed from the way you used to make the  
4 product, and that bears further looking into.

5           On that, I will close my thoughts. Thank you very  
6 much.

7           DR. McGUIRE: I think with the concurrence of the  
8 committee, we will have a break now. After the break we  
9 will have a public hearing. We are running a little bit  
10 behind. Is it likely that we are going to have sound after  
11 the break? Is that working, does anyone know? Without  
12 sound we can't have any discussion.

13           We are going to start at 10:35.

14           [Recess.]

15           DR. McGUIRE: Good morning again. We now have  
16 audio and I would like to start the remainder of the morning  
17 session, if people could be seated.

18           Before I introduce our next speaker, I would like  
19 for the members of the committee and the people sitting  
20 around the table to introduce themselves. There are some  
21 familiar faces and some new faces.

22           Roger, could we start with your end of the table  
23 and let's just go around.

24           DR. WILLIAMS: Roger Williams, Center for Drug  
25 Evaluation and Research.

1 DR. WEINTRAUB: Mike Weintraub, FDA.

2 DR. WILKIN: Jonathan Wilkin, Dermatologic and  
3 Dental Drug Products.

4 DR. SHAH: Vinod Shah, Office of Pharmaceutical  
5 Science.

6 DR. MINDEL: Joel Mindel, Departments of  
7 Ophthalmology and Pharmacology, Mt. Sinai Medical Center,  
8 New York.

9 DR. SIMMONS-O'BRIEN: Eva Simmons-O'Brien,  
10 Departments of Dermatology and Internal Medicine, Johns  
11 Hopkins, Baltimore, Maryland.

12 DR. FLYNN: Gordon Flynn, University of Michigan,  
13 College of Pharmacy.

14 DR. BRAZEAU: Gayle Brazeau, Department of  
15 Pharmaceutics, University of Florida, College of Pharmacy.

16 DR. KILPATRICK: Jim Kilpatrick, Biostatistics,  
17 Medical College of Virginia, Richmond Virginia.

18 MS. RILEY: Tracy Riley. I am the Executive  
19 Secretary to the committee.

20 DR. DRAKE: Lynn Drake, Departments of Dermatology  
21 at the University of Oklahoma Health Sciences Center and at  
22 Massachusetts General Hospital, Harvard Medical School.

23 DR. LIM: Henry Lim, Department of Dermatology,  
24 Henry Ford Hospital, Detroit, Michigan.

25 DR. ROSENBERG: Bill Rosenberg, Dermatology,

1 University of Tennessee, College of Medicine.

2 DR. TSCHEN: Eduardo Tschen, Department of  
3 Dermatology, University of New Mexico.

4 DR. SCHAEFER: Hans Schaefer, Research Management,  
5 Loreal, Paris.

6 DR. LAMBORN: Kathleen Lamborn, Neurological  
7 Surgery, University of California, San Francisco, but I am a  
8 biostatistician.

9 DR. MILLER: Fred Miller, Dermatologist, Geisinger  
10 Medical Center, Pennsylvania.

11 DR. McGUIRE: And that leaves me. I am Joe  
12 McGuire. I am in Dermatology and Pediatrics at Stanford.

13 The next speaker, speaking in the open public  
14 hearing, we will have only one presentation in the public  
15 hearing, she is Dr. Louise Latriano. She is the Manager of  
16 Drug Development and Pharmacokinetics at J & J.

17 Dr. Latriano.

18 **Open Public Hearing**

19 DR. LATRIANO: Thank you. Good morning. I am  
20 here to present to you today the results of studies done to  
21 explore some of the issues in the validation of the tape  
22 stripping methodology that you have heard about from the  
23 previous speakers.

24 This data was originally presented at the Workshop  
25 on Dermatopharmacokinetics and Bioequivalence that was held

1 in September of '86, however, these results were excluded  
2 from the consensus report of that workshop and therefore I  
3 am very glad to have this opportunity to present this  
4 information to the Advisory Committee here today.

5 We feel that the results of these studies are  
6 highly relevant in that they present some practical  
7 limitations to the implementation of what appears to be  
8 conceptually good methodology, and that is, the measurements  
9 of drug concentrations at the target sites.

10 [Slide.]

11 Now as Dr. Wilkin has already alluded to, the skin  
12 is a complex organ made of numerous layers of tissues and  
13 other appendages which may serve as target sites for various  
14 therapeutics. It is also well known that the penetration of  
15 drug into the skin, into the target site, is dependent on a  
16 variety of factors that are illustrated in this slide down  
17 here, and I won't go into those this morning.

18 [Slide.]

19 The results of the studies that I am going to show  
20 to you today indicate that there is a wide variability in  
21 the tape stripping assay related to the number of layers of  
22 stratum corneum removed during the removal of the  
23 application and removal of the tape.

24 This variability is manifested itself by  
25 variability in weight, in other words, the amount of skin

1 removed, variability in a biological measure of the  
2 epidermal barrier of the skin, and that is TEWL, trans-  
3 evaporation water loss, which is an accepted method to look  
4 at barrier function and the stratum corneum.

5 This variability is both intersubject variability,  
6 as well as intrasubject variability.

7 All of the studies that I am going to present to  
8 you were done using the following conditions. These were  
9 parameters that we sought to standardize right from the  
10 onset based on our extensive knowledge in adhesive  
11 technology in support of our Brand A brand, so I was lucky  
12 to have the opportunity of having the appropriate tools and  
13 the expertise to understand a little bit about what happens  
14 when you apply and you remove tape.

15 [Slide.]

16 All work was conducted in an environmentally-  
17 controlled room for temperature and humidity. The tapes  
18 that we selected were those most commonly used in the field,  
19 the D-Squame or Cuderm tape which comes as 22 mm discs or  
20 Transpore tape, which we were able to precision cut into  
21 one-inch squares.

22 We controlled the application and the removal  
23 process by using a constant force to apply, which is just a  
24 little roller of constant weight. We left it on the site  
25 for 10 seconds. This was templated sites. Usually, we used

1 a single person to do the application and removal process  
2 because experience tells us that this is an important  
3 parameter and that particularly in the removal, both the  
4 speed and the angle which you remove the tape makes a  
5 significant difference in how much skin gets removed.  
6 Anyone who has had a band-aid removed can probably  
7 appreciate that fact.

8           We took great care in the weighing of the samples,  
9 weighing small amounts. We always used an analytical  
10 balance, and we allowed the tapes to equilibrate overnight  
11 in the environmental room in order to have a consistent  
12 moisture content which can affect the ability of the  
13 adhesive to remove the skin.

14           [Slide.]

15           These are the results of these studies. It is a  
16 similar procedure throughout, so let me explain what we are  
17 looking at here.

18           On the y axis we have the amount of stratum  
19 corneum removed onto the tapes. We used up to 24 tapes, and  
20 the reason for that will become apparent in a moment. For  
21 sake of convenience we weighed those tapes in sets of four.

22           This is the data obtained with the Transpore tape  
23 and this is the data obtained with the D-Squame tape. As  
24 you can see, there is a large variability in the amount of  
25 skin removed both between subjects, and interestingly also

1 as you progress through the layers of the skin, there is not  
2 a consistent amount of tape that is removed.

3           With the D-Squame tape, we got some very unusual  
4 results in that we actually saw a net loss in the weight of  
5 the tape, which we attributed to the cohesive failure of the  
6 tape, in other words, when the tape was pulled off, the  
7 adhesive backing was left on the skin, resulting in the net  
8 loss of weight.

9           [Slide.]

10           Here is the same data, but presented now as the  
11 cumulative amount removed in the stratum corneum up through  
12 those 24 tape strips. It is a little easier here to see the  
13 intersubject variability in that subject 1 and subject 6,  
14 the amount of skin removed varies about 3-fold. Even  
15 plotting cumulative with the D-Squame we still came out with  
16 these negative values.

17           [Slide.]

18           Now as I mentioned, one of the other parameters we  
19 measured throughout the course of these experiments was  
20 TEWL, which is a measure of the integrity of the stratum  
21 corneum. This represents the difference in TEWL values from  
22 baseline after the subjects and the baseline values were  
23 allowed to equilibrate.

24           What is interesting here is that until you get to  
25 about 16 tape strips, you really don't see much perturbation

1 of the TEWL values, and we have interpreted this that you  
2 really have not gotten very far into the stratum corneum in  
3 those 16 tape strips.

4           Once you get past that, you see a dramatic change  
5 in the TEWL values, indicating you are actually getting a  
6 little bit deeper into the stratum corneum.

7           Convention is that when you get two values of 35,  
8 40, or 50, that you have probably gotten most of the stratum  
9 corneum removed and the skin will be glistening. One of the  
10 problems overall with the methodology is it is hard to  
11 confirm without histology exactly where you are in the  
12 stratum corneum when you are at tape number 16 or 24, and  
13 clearly that varies depending on the subject.

14           The D-Squame, even though we had negative weights,  
15 we did see a raise in TEWL indicating that we had removed  
16 some of the barrier of the skin, but even though there is a  
17 trend in TEWL values, there is not a good correlation  
18 between the TEWL value and the amount of skin removed, at  
19 least not a linear correlation.

20           [Slide.]

21           Now, in order to determine what was the source of  
22 this intersubject variability, we conducted the same  
23 experiment on the same subjects the following week, and  
24 these are the results, and most of the results I am going to  
25 talk about now use just the Transpore tape because of the

1 problem we had with the Cuderm.

2           As you can see, in subject number 1, there was a  
3 large difference between what we saw from week 1 to week 2,  
4 while in other subjects there wasn't a lot of difference.  
5 What we quickly realized, though is that this difference  
6 that we were seeing from week to week, there could be other  
7 sources for this and mainly because it is hard, actually  
8 impossible, in this technique to go back and resample the  
9 same site in a reasonable amount of time.

10           This slide shows areas--and it is a little light  
11 in here so it is hard to see very well--of skin that has  
12 been tape stripped, and as you can see, it leaves behind an  
13 area of inflammation which eventually turns into  
14 hyperpigmentation, and depending on the amount of skin lost,  
15 it can take quite a long time for that area to resolve. So,  
16 therefore, we cannot go back and resample. So, the week-to-  
17 week variation could really be due to the fact that we were  
18 sampling at a different site.

19           Now, I also want to point out here that even  
20 though tape stripping is relatively non-invasive, especially  
21 compared to a biopsy, relative to a needlestick, it is more  
22 invasive.

23           [Slide.]

24           For easier representation, the rest of the data is  
25 going to be presented in bar graphs with the cumulative

1 amounts of stratum corneum removed after the 24 tape strips.

2           Site 1 and site 2 represent the upper arm from the  
3 volar forearm. As you can see, in some subjects, there was  
4 not a lot of difference between sites, but in other  
5 subjects, that difference was great.

6           [Slide.]

7           The FDA protocol, at least the one that I have  
8 seen, calls for looking at the innovator versus the referent  
9 product on adjacent sites on the arm, in other words, the  
10 innovator and the test would be the same, and that was  
11 probably an effort to reduce the variability as you go up  
12 and down the arm.

13           However, our study showed that the adjacent sites  
14 had as much variability, at least in these six subjects, as  
15 whether you were taking it from the upper or lower arm. So,  
16 even if you do a side-by-side comparison, you are still  
17 going to have differences in the amount of skin removed onto  
18 the tape and recovered into your sample.

19           [Slide.]

20           From this data set we reached a number of  
21 conclusions, and that is that there is a lot of variability  
22 in the amounts of stratum corneum removed, and as I showed  
23 you, that variability is in weights and also in TEWL values.

24           Intersubject variability is 3-fold n the six  
25 subjects that we examined, and intrasubject variability

1 looked to be almost as great whether it was, as I said, side  
2 to side or upper and lower arm.

3 [Slide.]

4 Now, why is this issue of stratum corneum recovery  
5 and its variability important? For that, I draw an analogy  
6 to our case of oral bioequivalence where we have a technique  
7 where we collect 7 milliliters of whole blood, usually only  
8 analyze a portion of that--we like to save some in case we  
9 need a duplicate analysis.

10 Then, we take that value we have gotten and we are  
11 able to normalize that concentration for pharmacokinetic  
12 analysis, usually an amount per milliliter of blood, plasma,  
13 or serum. We can do that with confidence because we know  
14 that the concentrations in the blood are homogeneous, and we  
15 know that there is a linear relationship that exists between  
16 the amount and the volume. So, if we analyze a half of a ml  
17 of blood, we just double it to know what is in the whole ml.

18 With topical tape stripping, we have a very  
19 different scenario. We have a gradient of drug across the  
20 skin, usually with the outer layers having the highest  
21 concentration and also the highest variability, probably  
22 mainly related that it is very hard to distinguish what is  
23 sitting on top of the skin and in contact to be absorbed  
24 versus what has gotten into the crevices, so it is very hard  
25 in those first layers to really know when you have got that

1 first layer of stratum corneum, and you are not really just  
2 sampling excess drug.

3 In this technique, we blotted the skin, as is  
4 normal, and we discarded the first five tapes because as  
5 some speaker already alluded to, we know that that is highly  
6 variable and we basically can't deal with that in analyses.  
7 We still have a lot of variability. It gets lower as we get  
8 deeper into the stratum corneum.

9 So, therefore, in the stratum corneum sampling, as  
10 I indicated, we can collect vastly different amounts of  
11 tissues. We analyze the entire set of tape strips to  
12 determine the total amount, and then we have to normalize  
13 those concentrations, and this is the part that becomes  
14 difficult to find an appropriate way to deal with.

15 As I just showed you, the amounts of drug in the  
16 skin is not linear, it's a concentration gradient, so  
17 therefore, when you are measuring, say, the test product,  
18 you might get all of this in your tape strips, but on the  
19 other hand, you might only get this amount depending on the  
20 subject and the site, and you will never really know what  
21 your absolute recovery is unless you sample the entire  
22 stratum corneum, which is probably more than the 24 tape  
23 strips that I have shown you.

24 So, this sort of comes down to almost a classic  
25 recovery problem for pharmacokinetic analysis, and as I

1 said, it leads us to an inability to normalize the data.  
2 Now, the data you saw this morning was normalized based on  
3 area, but the area in these studies are kept constant, so  
4 that just falls out of the picture anyway, so we are left  
5 with a raw number that we really don't have a good idea what  
6 it means in relation to the total amount of drug in the  
7 skin.

8 [Slide.]

9 Now, what does this mean to our pharmacokinetic  
10 analysis? In this plot here, I have shown in the white  
11 line, basically, a theoretical pharmacokinetic plot, where  
12 if we don't have 100 percent recovery, we have at least  
13 consistent recovery, and for all bioequivalence we  
14 demonstrate that our recovery is consistent over the  
15 sampling period.

16 However, when you have the DPK data, if you don't  
17 know the recovery, your plot can get very distorted. Here,  
18 Cmax, it may be this, but it only may be 60 percent recovery  
19 of the full amount of drug in the skin, and it has a  
20 distorting effect on the shape of the profile, making it  
21 very difficult to get a true estimate of the absorption and  
22 elimination phase of the drug.

23 Without good analytical data which is precise and  
24 accurate, it makes it very difficult and severely restricts  
25 our ability to use this pharmacokinetic data to predict what

1 is going to happen in terms of safety and efficacy.

2           So, for those reasons we believe, and I go back to  
3 what we spoke about earlier, all the bioequivalence we need  
4 to show equivalent rate and extent of absorption of the  
5 active drug at the target site. In reality, we use plasma  
6 as a surrogate.

7           For topical bioequivalence, because of this  
8 inherent variability in the tissue sampling technique, it is  
9 hard to get meaningful information regarding the rate and  
10 extent of absorption of the test and reference products.

11           Thank you.

12           DR. MCGUIRE: Dr. Latriano, thank you very much  
13 for your presentation. We have one other presentation in  
14 the open public hearing, and if you don't mind, I think we  
15 will go on to that. Since we are now wired for sound, we  
16 can have discussion afterward.

17           The second speaker is Auraham Yacobi from Taro  
18 Pharmaceuticals.

19           DR. YACOBI: Could we have more light, please. I  
20 haven't prepared slides and I have not come here prepared to  
21 make this presentation.

22           First of all, I would like to thank you all to  
23 give me this time to talk about dermatopharmacokinetics.  
24 Since I was one of the organizers and I was actively  
25 involved in drafting the report, the consensus report of the

1 workshop, I think I ought to make a comment about that  
2 because the previous speaker suggested that we excluded her  
3 recommendations, and I would like to assure you that this is  
4 not the case.

5 Our committee--and if you would refer to the  
6 paper, and I am positive that you will read the paper which  
7 is on your handout--you will find out that the committee who  
8 dealt with drafting the workshop report included seven  
9 regulatory people including Dr. Williams and Dr. Wilkin.

10 We had five university professors, some of whom  
11 are here, Dr. Pershing, Dr. Flynn, Dr. Schaefer, Dr.  
12 Maibach, and Dr. Marty. Also, there were four people from  
13 the industry, two from the brand industry, Dr. Joel Sequeira  
14 from Schering, and the previous speaker who I believe she  
15 dropped out or she withdrew because she did not agree with  
16 the consensus report, and the committee fully honored that  
17 request and respected that request.

18 The two people from the generic company were Dr.  
19 Kaplan from Pharma, and myself from Taro Pharmaceuticals.  
20 Taro Pharmaceuticals is involved in developing generic  
21 products, as well as novel products.

22 We are a research-based company and I do not like  
23 to really just to say that I am representing a generic  
24 company, I would like to be branded as a person who  
25 represents science, and I would like to go--I think those

1 people who know me, they know that I am quite interested and  
2 excited about finding new methodologies to evaluate  
3 products.

4           In this particular case for dermal products, I  
5 believe unless we will use our science, we will not be able  
6 to offer alternative products to the consumer, alternative  
7 products which are in quality, they are as good as the  
8 brand, but in price, is significantly less. I believe the  
9 consumer should have that luxury to choose, and the  
10 physician has to choose.

11           Now, about the workshop, Dr. Williams just  
12 mentioned to you that we had three days of extensive  
13 discussion, rigorous discussion of bioequivalence. If we  
14 feel that the oral bioequivalence studies that we do, that  
15 they are accepted by everyone, and the way we evaluate them  
16 are accepted by everyone, then, we are far away from the  
17 science.

18           In fact, for the very same oral formulation that  
19 the previous speaker spoke, that there are recommendations  
20 that our methodologies should be more rigorous, our  
21 scientific and statistical criteria will be more rigorous,  
22 and I think it is our job, and again as one of the  
23 organizers of this workshop, our job is to see to it that we  
24 will advance ourself and advance our thinking with science.

25           So, whenever there is a better methodology, we

1 ought to use that. DPK should not be just compared with the  
2 oral bioavailability, it should also be compared with the  
3 clinical trials, which one is more sensitive to  
4 differentiate between two formulations, and I believe Dr.  
5 Williams made a very strong comment that we have to choose a  
6 method which better differentiates between two formulations,  
7 a method which will offer to detect as much as 20 percent  
8 difference between two formulations, and I will submit to  
9 you that no clinical trials will be able to do so.

10 Now, having said that, how do we in terms of  
11 dermal products, Dr. Shah mentioned to you today that we  
12 have one methodology, a pharmacodynamic methodology - how do  
13 we compare two products, two corticosteroids.

14 The technique is very similar except the surrogate  
15 marker in this particular case, instead of measurement of  
16 the drug in the stratum corneum, is in fact is in skin  
17 blanching technique or sometimes we refer to it as  
18 vasoconstriction.

19 The extent of blanching or discoloration of the  
20 skin is measured either visually or by chromometer. In  
21 order to assure objectivity, the FDA insists on measurement  
22 only by the chromometer, a chromometer reading. This is one  
23 technique and we were told by the brand company again this  
24 technique will never work, but in fact it does work. The  
25 pharmacodynamics methodology works beautifully.

1           The second technique which is used is the in-vitro  
2 release actually as a support, not as a measure of  
3 bioequivalence determination. We believe that for similar  
4 products, especially if they are quantitatively and  
5 qualitatively if they are similar, they will have the same  
6 in-vitro release methodology, the same in-vitro release  
7 rates.

8           The DPK method also reflects the penetration of  
9 the drug into the skin, into the stratum corneum, and I  
10 believe the measure of the drug in the stratum corneum will  
11 adequately reflect what has been released from the  
12 formulation and will definitively determine the  
13 bioequivalence between two products.

14           If you will read the consensus report, you will  
15 find out that the group has definitely indicated that the  
16 DPK method is more variable. It will indicate, it will show  
17 you that this variability can also be handled statistically.

18           The analytical methodology can be validated. It  
19 is true that we can see also more variability in this  
20 analytical method than analytical method of the plasma. I  
21 agree with the previous speaker that it is much easier to  
22 quantitate drug in plasma, that you can reanalyze the sample  
23 if you are not happy with the data, however, there is no  
24 reason that we cannot do the same thing in the skin, and  
25 there is no reason why we cannot apply our statistical

1 knowledge in order to deal with variability of the skin  
2 penetration. The pharmacokinetic aspect of it and the  
3 science of pharmacokinetics is very well know and the data  
4 analysis can be readily done.

5 Dr. Shah indicated to you that before one can  
6 really do dermatopharmacokinetics, there is a pilot study in  
7 order to define the protocol, the final protocol. I submit  
8 to you that other studies can be done like mass balance  
9 studies to assure that, in fact, what we are going to  
10 measure in the pivotal study is going to make sense, and  
11 then the pivotal study itself.

12 I am not going to worry about the intrasubject  
13 variability of 3-fold. We see it with other products day in  
14 and day out. The most beautifully observed product,  
15 warfarin, we just saw that the intrasubject variability can  
16 be in fact several fold, there is no question about it, but  
17 it is handled again, it is taken care of statistically. The  
18 statistics allow for that variability, and if two products  
19 are not bioequivalent, the statistics can take care of it.

20 Finally, please do not discount the value of in-  
21 vitro release. We find out with our corticosteroid products  
22 that the in-vitro release method does work and can provide  
23 further support in evaluation of products.

24 I would like to thank you very much for this  
25 opportunity.

1 DR. McGUIRE: Thank you, Dr. Yacobi.

2 We have two brief presentations. The first is by  
3 Dr. Shah, who will deal with considerations of  
4 bioequivalence with lower concentrations.

5 **Comments**

6 DR. SHAH: So far we discussed on the  
7 dermatopharmacokinetic aspects. I would like slightly now  
8 to focus on the second aspect that I would like the  
9 committee to consider and give us an advice and an input,  
10 and that being for the lower strengths.

11 Now, keeping in mind that the lower strengths for  
12 the topical drug products is very rare, it is not that every  
13 time for every product that you do see the lower strength,  
14 but we do see occasionally, and I can count only two or  
15 three products right now which have the lower strengths, but  
16 we talk of providing this option, so that we can proceed  
17 with what we need to do for the lower strength.

18 Again, that is the second question: Can in-vitro  
19 drug release be used for granting the bio-waiver for the  
20 lower strength of a generic product after the higher  
21 strength is approved as bioequivalent, and the only change  
22 is the amount of the active ingredient for the lower  
23 strength?

24 [Slide.]

25 This is somewhat similar to what we do for the

1 oral drug products. For oral drug products, immediate  
2 release dosage forms, the bioequivalency study is done at  
3 the highest dosage strength, and the lower strength products  
4 are approved based on the composition similarity and the  
5 dissolution profiles. Please note that it says that this  
6 composition is similar and the dissolution profile is  
7 similar compared to the higher strength.

8           So, similarly, the proposal is for locally active  
9 dermatological drug products, we do the biostudies and then  
10 can be approval of the lower doses based on the composition  
11 similarity and in-vitro drug release be granted or not.

12           We make the following assumptions--I am sorry for  
13 repeating it, but I think it is important for us to realize  
14 as to what we are trying to achieve--the formulations, the  
15 two strengths defer only in the concentration of the active  
16 ingredient. There is no difference in the manufacturing  
17 process and the type of the equipment used between the two  
18 strengths.

19           If you may recall, Professor Flynn showed some  
20 data earlier that when you manufacture the product  
21 differently, they are having exactly the same active  
22 ingredient, same thing, but the manufacturing process is  
23 different, you get the different release rate.

24           So, that is why I indicate here the manufacturing  
25 process is also exactly the same and there is no difference.

1 Then, we have additional requirements that the reference  
2 listed drug, the innovator product is also marketed at both  
3 the strengths, higher strength and the lower strength, and  
4 the generic product is determined to be bioequivalent no  
5 matter what we come to the final conclusions.

6 It may be a clinical study, it may be a blanking  
7 assay, or it may be a dermatopharmacokinetic study, but once  
8 the product is approved to be bioequivalent, then, we can  
9 approve the lower strength based on these principles.

10 So, keeping these things in mind, this addition is  
11 as far as the reference product is concerned, all the  
12 strengths are approved based on the clinical safety and  
13 efficacy.

14 With respect to the test product or the generic  
15 product, it is determined to be bioequivalent between the  
16 higher strength and the lower strength. Now we make the in-  
17 vitro release measurements, the reference product, higher  
18 strength, lower strength, and we determine the ratio.

19 Similarly, we do the same thing for the test  
20 product. We determine the ratio of the higher strength, the  
21 lower strength.

22 You heard from some of these speakers in the  
23 morning that release rate is an important part. It tells  
24 you how the formulation is behaving. It is the property of  
25 the formulation. It is the property of the product.

1           Now, knowing the concentrations of the two  
2 products, we can easily predict as to what will be the ratio  
3 of the two strengths. If we know that the drug is going to  
4 be in suspension, then, the ratio of the two strengths will  
5 be square root of  $Q_1/Q_2$ ,  $Q_1$  and  $Q_2$  being the two different  
6 concentrations.

7           If the drug is prepared in the solution form,  
8 then, the ratio is proportional to  $Q_1$  over  $Q_2$  rather than  
9 square root of that.

10           [Slide.]

11           I just have a few data to share with you here  
12 showing there to be three concentrations of tretinoin A  
13 which are on the market, 0.1, 0.05, and 0.025. This is the  
14 release rate data obtained, and it gives you a nice linear  
15 relationship, and if you just do the theoretical  
16 calculations,  $Q_1$  over  $Q_2$ , it gives you the ratios, and these  
17 are the practical ratios from the data.

18           In most of the cases, like 0.1 or 0.05, it is 2.24  
19 rather than 2, which is the theoretical, which is again  
20 within 25 percent of the variations that you can see, and  
21 the same thing is true with all the other concentrations.  
22 So, this is an example showing when the two drugs are in  
23 solution.

24           This is an example of when the two drug  
25 concentrations are not in solution, but they are in

1 suspension. This is the same data from the same sort of Dr.  
2 Gordon Flynn, his laboratory, where several different  
3 concentrations were studied, and you can find the nice  
4 linearity, with the theoretical ratios between the Q1 and  
5 Q2, you can see what is the theoretical ratio and the  
6 experimental ratio obtained from the data.

7           So, again, it is possible for us, knowing the  
8 concentrations, to predict as to what will be the ratio of  
9 the two release rates from the same manufacturer, because  
10 they are using the same technique and the same formulation.

11           At times this release rate is directly also  
12 proportional to the type of the formulation and the quality  
13 of the product, and I would like to show that on the next  
14 slide.

15           [Slide.]

16           Here, for the two different products, shows that  
17 when you have the concentration ratios here, 1 over 0.5, two  
18 different concentrations for hydrocortisone, and the ratio  
19 is 1.41, and the 20 percent plus or minus turns out to be  
20 between 1.13 and 1.69, and then by using two different  
21 manufacturers, at least here, manufacturer A and  
22 manufacturer B gives you almost the same ratios, but  
23 sometimes the formulation is significantly different, still,  
24 you may be able to predict the ratios and you can see that  
25 this is the manufacturer A, manufacturer B, completely using

1 the different formulation, but still comes out to be around  
2 the same.

3           So, again, it is important for us to make the  
4 comparison within the same manufacturer for the next  
5 strengths. Again, I would like to emphasize that here the  
6 importance of the in-vitro release rate.

7           I know some mentions were made that maybe we are  
8 doing all these DPK studies in normal healthy skins, but  
9 they are being applied to the diseased skins where maybe the  
10 horny layer is either disrupted, is not intact, so what can  
11 be done?

12           Well, if you compare the in-vitro release rate,  
13 that means it is releasing the drug directly from the  
14 formulation, which is saying that it is something if you  
15 don't have the barrier, the skin barrier or the stratum  
16 corneum barrier, the drug will be completely out.

17           So, maybe with the information from the DPK and  
18 in-vitro release, all the things, all the properties put  
19 together may provide us more valuable information for  
20 looking at the bioequivalency of these topical  
21 dermatological drug products, in other words, trying to  
22 complete and say that these things added together, the DPK,  
23 the in-vitro release characteristics, which is again also  
24 reflected on the particle size, because Dr. Flynn showed you  
25 very clearly that if the particle size of the active

1 ingredient is different when it is in the form of the  
2 suspension, it is reflected in the in-vitro release  
3 profiles.

4           So, these two tests together, the DPK plus the in-  
5 vitro release, may be a good tool for looking at the  
6 bioequivalency of the topical dermatological drug products.

7           I think that is my last slide. Thank you very  
8 much.

9           DR. MCGUIRE: Thank you, Dr. Shah.

10          Dr. Jonathan Wilkin.

11          DR. WILKIN: I would like to respond with a couple  
12 of comments about the lower strengths by ratio of release  
13 rates, and I would remind the committee that of all the  
14 concerns that I have listed here, they really ultimately,  
15 fundamentally come down except for the healthy skin issue to  
16 is there a vehicle difference between the brand name product  
17 and the generic product that might not be detected in the  
18 systems.

19                   [Slide.]

20          My understanding from reading Dr. Flynn's work and  
21 the folks in his laboratory is that when we are thinking  
22 about release rate, we are thinking about drug coming out of  
23 the semisolid matrix and being available at the surface of  
24 the stratum corneum.

25                   [Slide.]

1           That is distinct from flux which is the transit of  
2 the active across the stratum corneum and into the biophase,  
3 into one of the targets.

4           [Slide.]

5           I couldn't comprehend Dr. Flynn's equation, so I  
6 have to go with sort of a country boy dermatologist equation  
7 here, where flux is proportional to concentration of  
8 dissolved drug in the vehicle times partition coefficient  
9 times diffusion coefficient, and we can ignore pretty much  
10 the distance, because that is not going to change regardless  
11 of what product you are going to put on the skin.

12           So, flux is proportional to concentration, to  
13 partition coefficient, and diffusion coefficient.

14           [Slide.]

15           That is true for lower concentrations.

16 Interestingly, in Dr. Shah's proposal, he is not suggesting  
17 that the release rate will directly tell us what the flux  
18 is, and the flux, of course, is what is proportional to the  
19 pharmacodynamic effect, efficacy, and presumably safety, but  
20 he is telling us that you can get to it by looking at the  
21 release rate ratio, ultimately will tell us about the ratio  
22 of the amount of drug at the surface of the stratum corneum,  
23 and that that ratio would determine the flux ratio.

24           [Slide.]

25           So, this is allowing then that the absolute

1 release rates between bioequivalent, generic, and reference  
2 listed drug, the brand name product may be different. I  
3 mean that is what using ratios will allow.

4 [Slide.]

5 We know again that flux is proportional to the  
6 effect that is desired.

7 [Slide.]

8 And that the flux, if we know that we have a  
9 bioequivalent product, that the flux should be the same for  
10 generic and the reference listed drug, and that is also  
11 consistent with dermatopharmacokinetics as presented by Dr.  
12 Shah.

13 [Slide.]

14 So, if the absolute release rates are different,  
15 but flux must be the same, then, neither flux nor the  
16 pharmacodynamic effect are predicted by the absolute release  
17 rate.

18 [Slide.]

19 Flux involves the concentration, and that would be  
20 achieved by the release from the matrix of the semisolid at  
21 the surface of the stratum corneum, and also incorporates  
22 the notion of partition coefficient and diffusion  
23 coefficient, numbering effects which can be modified by the  
24 vehicle.

25 Importantly, diffusion coefficient and partition

1 coefficient possibly can be the controlling factors for flux  
2 at different concentrations, that while flux seems to be  
3 linear to these at low concentrations, that doesn't seem to  
4 be the case at higher concentrations.

5           There is a horizontal asymptote and the  
6 concentration flux relationship.

7           [Slide.]

8           So, absolute release rate does not account for the  
9 partition coefficient, there is no membrane in that system,  
10 at least not a stratum corneum-like membrane, nor does it  
11 account for the diffusion coefficient in the stratum  
12 corneum.

13           [Slide.]

14           As I have just mentioned, the relationship between  
15 concentration--that is labeled concentration on the  
16 container--and flux may be curvilinear.

17           [Slide.]

18           These are data from Fleischer & Maibach. There  
19 really aren't many data that look into this nonlinearity.  
20 You can see that there is linearity in the nitroglycerine  
21 concentration and the total amount absorbed at the lower  
22 concentrations, but at higher concentrations you can see  
23 that it begins to level off. You don't get nearly as much  
24 for the amount acquired.

25           [Slide.]

1           So, what I hear suggested is that we have a higher  
2 concentration of a product that is found to be  
3 bioequivalent, possibly by a clinical test or perhaps by the  
4 pharmacodynamic tests for corticosteroids, the multipoint  
5 McKenzie guideline, and from that, if one looks at the  
6 release rate ratio, we are to predict that at the lower  
7 concentration that flux would be the same, that the effect  
8 would be the same.

9           As it turns out, unless you really know the  
10 properties of the vehicle, you don't know that the  
11 curvilinear relationship between the reference listed drug,  
12 the brand name drug, and the generic are truly congruent  
13 curves.

14           [Slide.]

15           So, the ratios of release rates imply a linearity  
16 of flux that cannot be assumed.

17           There were a few minutes listed for me at the very  
18 end, and what I would like to do is just say a couple of  
19 words since Dr. Latriano, Dr. Yacobi, and Dr. Shah mentioned  
20 the APS workshop.

21           [Slide.]

22           I can give a different view from that particular  
23 meeting. There were 250 scientists there, but it was  
24 interesting that a lot of them came I think with a mission,  
25 and I would say that we could collectively look at all of

1 ourselves who came to the meeting and say that this was the  
2 guild of alternative method enthusiasts and researchers or  
3 gamers.

4           In this group, there are people who you could  
5 imagine might have a conflict of interest. I mean this  
6 would be financial gain if the method were adopted. It  
7 could also be financial loss if the method were adopted, and  
8 they had, you know, generic competition.

9           There is the possibility of intellectual bias,  
10 folks who might be sold on the methods beforehand, but I am  
11 happy to quote that like today, everyone has a balanced  
12 view. We are all optimistic about the possibilities, but we  
13 are awaiting results of the validation before advocating  
14 use.

15           [Slide.]

16           As it turns out, the gamers are the folks that  
17 really drive the system. I mean that is ultimately where we  
18 get new innovations. It comes from that group. So, the  
19 gamers interact with the regulatory folks and industry will  
20 certainly be looking at what we do from different points of  
21 view, as well.

22           [Slide.]

23           In the end, there should be a group--and I would  
24 suggest that the Dermatologic and Ophthalmic Drugs Advisory  
25 Committee could be such a group--that would review the data

1 when they finally come in that will validate these  
2 methodologies, because I would say that the bias that this  
3 group might have is only that they want good quality generic  
4 drugs for their patients.

5 [Slide.]

6 We have already agreed that the proposed method  
7 would replace a more difficult and perhaps less precise  
8 method that is currently being used. The question is  
9 whether we are getting imprecise information to the right  
10 question today, and we would be trading that for precise  
11 information to the wrong question tomorrow.

12 So, we do need to have more information about the  
13 validation of this methodology.

14 [Slide.]

15 I would suggest that, as Dr. Yacobi mentioned, we  
16 need to know how these tests actually work in practice, and  
17 we need to hear how the tests can be formally validated.  
18 There are a lot of important thought experiments and good  
19 logic that has gone into the construction of the  
20 dermatopharmacokinetics and getting to the lower strengths  
21 of these generics.

22 It is based on a lot of work in laboratories that  
23 really were not real world, where they weren't comparing a  
24 generic product versus a brand name product. They were  
25 looking at controlled vehicles within the laboratory, so I

1 am not sure that all those studies directly address these  
2 issues, but much important work has been done.

3           It has been brought together, I think used in a  
4 very compelling way by Dr. Shah and his group.

5           [Slide.]

6           But there still is the concern, and that is that  
7 we have the bricks and mortar being put together very  
8 artfully by all the different scientists out there from  
9 which he obtained this information, but in the end, it  
10 depends on the global view, how it is all assembled together  
11 whether it really functions or not, and my apologies to  
12 Mauritz Escher for Waterfalls, which points out that some  
13 things that look acceptable in local regions when you look  
14 at them, when you stand back and put them all together, they  
15 may not quite work the way one anticipates.

16           [Slide.]

17           So, I would close with Mencken's observation that  
18 science at bottom is really anti-intellectual, it always  
19 distrusts pure reason and demands the production of  
20 objective fact.

21           Thank you.

22           DR. MCGUIRE: Escher and Mencken in 10 seconds,  
23 that is unbelievable, Jon. You left out, Jon, Stuart Mill.

24           Well, we have a job on our hands for the remainder  
25 of the morning. One of the problems is that, to my

1 knowledge, none of the Advisory Committee had received any  
2 of the data that were presented this morning by Dr.  
3 Schaefer, Dr. Shah, and others except for the APS-FDA  
4 Workshop report, which I gather everyone received.

5 Jon, let me ask for a piece of advice. Can we  
6 continue the discussion over into the afternoon session, and  
7 postpone the closed session for a half-hour if we need a  
8 half-hour this afternoon?

9 DR. WILKIN: Sure.

10 DR. McGUIRE: It is 20 of 12:00. I would like to  
11 go ahead and start the discussion, open it to any of the  
12 members of the committee who would like to question any of  
13 the presenters from this morning.

14 Dr. Rosenberg.

15 **Committee Discussion**

16 DR. ROSENBERG: I just have some comments I wrote.

17 DR. McGUIRE: Bill, excuse me.

18 DR. ROSENBERG: Is this just questions?

19 DR. McGUIRE: No, no, I am going to give you time,  
20 but take a look at page 2, the Agency has presented us with  
21 questions, and we will try to deal with those in the course  
22 of the morning.

23 Excuse me, Bill. It is yours now.

24 DR. ROSENBERG: Nonetheless, I just wanted to make  
25 a few comments.

1           First of all, I appreciate the public policy is in  
2 favor of generics and that the Agency has responded so  
3 promptly to try and increase the efficiency and the  
4 correctness of how those things happen, and to hear the  
5 workshop and all the data, the thought that has gone into  
6 it, and then the process that would bring this before a  
7 group of largely clinical people is also appreciated very  
8 much, and I am cognizant of that.

9           Amongst the notes I made were, of course, animal  
10 versus human. Animals depend on their coat, their furry  
11 coat for what the human depends on stratum corneum, so it is  
12 very hard to transpose that kind of material.

13           As was brought out, in the clinical setting, we  
14 are using, for instance, corticosteroids largely in eczema  
15 and in psoriasis. In eczema, the stratum corneum has had  
16 all these holes punched in it by excoriation and scratching  
17 and rubbing. It is like a steel tank with bullet holes in  
18 it, it is hard to make sense out of it. In psoriasis, there  
19 is no stratum corneum. There is a collection of  
20 parakeratotic cells that lack the whole architecture and the  
21 product of the granular cells, which is the lipid, mortar,  
22 and so forth.

23           So, the findings are essentially meaningless, and  
24 both of those diseases, as they heal, stop the penetration,  
25 so that it is excellent. Another point, that diseases vary

1 this, and wouldn't somebody want something that would just  
2 fall into the follicle and not land on the skin as a  
3 treatment for acne, for instance, it would be wonderful to  
4 have an all-follicular drug. Of course, the whole problem,  
5 if you could bear to hear about nails again, comes up, let  
6 alone substantivity, where what is desired is they stay on  
7 the surface and just be there.

8           Just finally, there is a professor, a  
9 distinguished professor of pharmacology at the University of  
10 Tennessee. I am sure many of you know him--I won't mention  
11 him by name--who I remember talked about when he was a  
12 college student, had a summer job in Jersey City, he grew up  
13 in Newark, where the company then used to be around called  
14 the A&P Company had a laboratory where they developed with  
15 exquisite science Jane Parker products which could compete  
16 with brand names.

17           The summer he worked there, the whole effort of  
18 this organization was devoted to making A&P brand spaghetti  
19 that its own mother couldn't tell from the brand leader,  
20 which I won't name, but it had the name of a chef attached  
21 to it.

22           After a few weeks into this effort, the group  
23 there told the boss, you know, we can make a spaghetti that  
24 is a whole lot better than chef whatever spaghetti, and the  
25 people who ran A&P then said, of course, you can, but we

1 don't want to make a better spaghetti, we want to make one  
2 that is exactly the same as the other one because that is  
3 the way our system runs.

4           Are we doing that with some of this stuff? I mean  
5 the innovator came out with a product 15, 17 years ago, and  
6 it seems to me a whole lot easier to make a better one than  
7 it was then by tinkering with the delivery system when we  
8 are dealing with dermatologicals, are we locking ourselves  
9 into old technology by doing that?

10           Finally, even if it were better, what good is it  
11 on the prescription side, because what gets delivered is  
12 what the medical care organization warehouse bought on low  
13 bid and wants to distribute, which is another reason for the  
14 purity of the over-the-counter market as compared to the  
15 prescription side, where the true winners rise to the top,  
16 and to the degree that that policy can be implemented, we  
17 will continue to benefit.

18           DR. MCGUIRE: Thanks, Bill. I don't think  
19 identifying bioequivalence techniques is going to inhibit  
20 the innovators at all. I think they will continue doing  
21 what they want to do.

22           Does someone else have questions or comments?  
23 Yes, Dr. Drake.

24           DR. DRAKE: Well, I, too, want to acknowledge the  
25 efforts of the gamers and innovators. I think the goal is

1 admirable and appropriate. I think that it is certainly  
2 something that you should continue to strive for. However,  
3 I must say I think we are not there yet. I found lots of  
4 holes. I am not saying that in a critical manner, I am  
5 saying it as I am asked to give my opinion.

6           For example, we heard some very compelling data  
7 about adhesive backing being left on the skin, which was  
8 really remarkable to me, because I felt that was of a  
9 concern, not only that the adhesive backing is left, it  
10 affects the weight on the stripping, but it may actually  
11 affect the penetrability of the compound.

12           So, I heard a lot of interesting things today, and  
13 I will comment more on them later, but I do have a couple of  
14 specific questions that I thought maybe somebody, one of the  
15 gamers who is involved in this might be able to answer for me.

16           I didn't hear much about age--I mean Dr. Schaefer,  
17 by the way, Hans, whom I respect a great deal, for example,  
18 talked about, you assumed the vehicles were all the same,  
19 but, in fact, vehicles won't be all the same in the system,  
20 and maybe I misunderstood you. Didn't you make that  
21 statement, that the vehicles are all the same?

22           DR. SCHAEFER: No.

23           DR. DRAKE: Please help me clarify that.

24           DR. SCHAEFER: I said provided that the character  
25 of the vehicle is the same, and the compound is the same,

1 then, you can use this method in order to find out whether  
2 despite this sameness, there are still differences. That is  
3 what I said.

4 DR. DRAKE: Okay, good. Thank you. I appreciate  
5 that clarification.

6 Secondly, what about the age of the patient? Most  
7 people are using the forearm, but if you think about the age  
8 of the patient or the amount of photo damage that forearm  
9 may have, logistics influences this a great deal. For  
10 example, in photo-damaged skin, the stratum corneum is  
11 perturbed, the epidermis is thin, and the organization of  
12 the epidermal cells are perturbed.

13 There may be less gaglike material,  
14 glycosaminoglycans in there, and does that affect anything.  
15 I guess I had a little bit of concern--and normal aging even  
16 without it being photo-damaged, the skin is quite different  
17 in an elderly than it is in a middle-aged and in a child,  
18 and I didn't hear anybody mention, did you look at age  
19 differentials or exposure to photo-damaged skin  
20 differentials as you were exploring these techniques?

21 DR. SCHAEFER: Joe.

22 DR. MCGUIRE: Hans, yes.

23 DR. SCHAEFER: May I answer directly? There are  
24 several comments to make. First, a general comment, I am  
25 perhaps allowed to make a general comment, too. There are a

1 hundred reasons for a method not to work, and only one  
2 reason for making it work.

3           Of course, I first want to say that we  
4 investigated more than 50 compounds in different conditions,  
5 different vehicles in humans, not only in animals, in  
6 respect to this method, and there is still a study underway  
7 in Europe together with a competitor on the validation of  
8 the methods to find out where the limits are, because you  
9 are certainly right, whenever a compound or formulation is  
10 designed to stick to the upper layers of the horny layer,  
11 the result won't be the same.

12           But take this aside and look to all the other  
13 results, then, yes, there is variability and we have to live  
14 with it. No, this is no direct relationship between  
15 transepidermal water loss and permeability. There is a  
16 direct relationship between the change of transepidermal  
17 water loss and percutaneous absorption.

18           No, there is no linearity in percutaneous  
19 absorption, nowhere, and we have to take this into account.  
20 Unless people have followed this method with a reference  
21 substance and reference values as they have been published  
22 in the literature, they cannot judge the method. You have  
23 to do that; if not, you cannot.

24           Now, as to diseased skin, first of all, as much as  
25 I know, pharmacokinetics, systemic pharmacokinetics are done

1 in normal volunteers, and not in patients, and in diseased  
2 organisms, you have a different distribution. Take the  
3 inflamed joint. Then, the distribution of a drug from the  
4 serum into the joint is different from that in a normal  
5 joint, and the same happens in the skin.

6 Now, I have the privilege to be amongst the few  
7 who have investigated actively the penetration of drugs, of  
8 dermatological drugs into diseased skin, into scarred skin,  
9 into psoriatic skin, and, of course, is there a problem, but  
10 there is a normal, natural problem in that disease is never  
11 constant.

12 So, drawing from disease a conclusion on the  
13 behavior of a drug when you want to compare two drugs, that,  
14 I must say is absolutely physically impossible. Nobody in  
15 this world can ever do that, because it is just too heavy,  
16 too expensive, and you cannot simply replace stripping by  
17 punch biopsies.

18 Again, I tried that. It simply doesn't work  
19 because quantities you find in the punch biopsies are just  
20 too small in order to draw quantitative conclusions from  
21 that.

22 So, coming from there, I do not advocate the  
23 stripping method to be the final answer to  
24 dermatopharmacokinetics, certainly not, but what I do  
25 recommend is those who are interested, do the first step

1 before stating why it could possibly not work to try and  
2 find out, to take hydrocortisone and benzoic acid and  
3 testosterone, and caffeine, which are four wonderful  
4 reference substances.

5           Put them into preparations and test the method,  
6 and then come back and say okay, that is what I found. I  
7 finally recommend as to what we heard about the problems  
8 with variability. There is a clear-cut abnormality. We  
9 never saw a depression in stripping at the eighth strip.  
10 This most likely is due to the fact that the tape has been  
11 seasoned over one day, and its tack is normal, the same.  
12 This explains the discrepancy between what has been shown  
13 here and what is referred to in the literature.

14           DR. MCGUIRE: Lynn, a brief question, and then I  
15 would like to go around the table.

16           DR. DRAKE: Well, I didn't get my question  
17 answered.

18           DR. FLYNN: I would like to try.

19           DR. DRAKE: Dr. Flynn, I have known you, you  
20 became a consultant in my unit, and I have great respect,  
21 but I still would love to have my question answered  
22 directly.

23           DR. FLYNN: I don't think this microphone is  
24 working. It is not, is it?

25           DR. MCGUIRE: Try Joel's.

1 DR. FLYNN: The question was framed with a  
2 reference to age, but I think also disease differences, and  
3 so on. The stripping technique is done under circumstances  
4 where the same individual is used for both formulations, if  
5 you were talking about a generic product versus an  
6 innovator's product.

7 Paired sites are used, and lifetime damage from  
8 the sun and all is presumed to be comparable at these sites,  
9 and therefore, because of internal control that is involved  
10 in that choice that is available within the test, you  
11 normalize out a lot of the kinds of variability that you are  
12 particularly worried about.

13 Clearly, senile skin is different in its  
14 properties, and I would expect it to strip somewhat  
15 differently than juvenile skin, but if you are running  
16 comparisons, and you are making them directly within the  
17 senior group or within the junior group, within the middle-  
18 aged group, those comparisons will still be valid within the  
19 individual.

20 DR. DRAKE: But has the work been done? Has it  
21 been done that way, did you control it that way when you  
22 were doing the stripping? Did you make sure that people  
23 were graded the same on photo damage, that they were within  
24 the five-year or 10-year age difference?

25 I mean the data that was presented was kind of

1 just generic, and I guess my question is, have you actually  
2 done the studies to determine the differences between the  
3 different age groups? Maybe my question wasn't specific  
4 enough.

5 DR. FLYNN: Others are going to have to answer  
6 that because I have not done those tapes myself, so that  
7 answers that question for you.

8 DR. DRAKE: Thank you, sir.

9 DR. FLYNN: But the point I am making is still  
10 important. I would like to call on Hans himself again to  
11 deal with that other issue or on Lynn Pershing, who is here,  
12 to deal with that issue, because she can answer that  
13 question.

14 DR. PERSHING: I have actually looked at age  
15 differentials and gender differentials with this technique.

16 DR. MCGUIRE: Excuse me. Would you introduce  
17 yourself?

18 DR. PERSHING: Lynn Pershing, University of Utah,  
19 Department of Dermatology.

20 We did not see an age differential in the DPK  
21 profiles, okay, but what I will tell you is that for  
22 enrollment in a study for DPK study, we have a number of  
23 criteria that they must meet to be enrolled, and one is that  
24 they can't have significant differences along the test site  
25 in either hair density, moles, scars, any defects in the

1 skin, photo aging, sunburn, freckles, or anything else  
2 because there is variability in those areas.

3 Now, I have done some basic research on grafted  
4 human skin moles where UV exposure does influence drug  
5 uptake, but what is very important here is to remember this  
6 is a bioequivalence assessment, and in the same individual  
7 you are going to test both drugs under the same conditions  
8 at the same time points of data collection.

9 Therefore, if you are going to enroll someone who  
10 has some photo damage in their skin, for instance, it has to  
11 be consistent across the entire area that is going to be  
12 evaluated. If that is true, there will be no difference  
13 between the two products.

14 I would also like to say that the skin is a highly  
15 variable organ. You have to accept that. Any parameter you  
16 measure will have an intrasubject variability of  
17 approximately 25 to 35 percent in the general population.  
18 Some people have more variability, some people have less.

19 There is more variability up and down the forearm  
20 than there is side to side. I have not had problems with  
21 the adhesives I have used, which include both Transpore and  
22 Cuderm, because I must be very lucky in having very constant  
23 environmental conditions living in Utah. We have relatively  
24 low humidity, and I have noted with some of my peers that in  
25 areas of high humidity, environmental high humidity, and it

1 is not controlled, they will have more variability in how  
2 the adhesive performs, but if you do the same person with  
3 both products on the same day, you should still get very  
4 reliable data.

5 DR. DRAKE: Before you leave the microphone, you  
6 said in your opening comment that you saw no age difference.  
7 Are you telling me that--because this is contrary to what I  
8 have observed, and so please feel free to correct me--there  
9 is a difference in my opinion between tape stripping or any  
10 kind of stripping in an elderly versus a young person, and I  
11 thought you said that you found no age difference, and I  
12 can't hardly buy into that.

13 Could you clarify it for me?

14 DR. PERSHING: If you do both test and reference  
15 product, the profile in an elderly subject will be pretty  
16 much reproducible, okay, hopefully, if the formulations meet  
17 Q1. They may be different in two amounts of stratum corneum  
18 removed, if you weigh that between--maybe--a 6-year-old  
19 versus a 19-year-old, let's say.

20 But in the profiles of test versus reference, if  
21 there is no difference in an elderly person, there will be  
22 no difference in a younger person. The total amount of drug  
23 has, in my opinion, very little to do with the age, but more  
24 importantly, the individual person.

25 If I mark how much skin I remove from a male, it

1 is always less than what I can get from a female, but that  
2 male is very consistent on a day-to-day time basis. In  
3 fact, I have found some people over two years, doing them  
4 once every one or two months, they are very consistent  
5 within themselves, but there can be 3-fold difference  
6 between people.

7 The key in bioequivalence testing for topical  
8 drugs is using the same person with both products, under the  
9 same conditions, on the same day.

10 DR. MCGUIRE: I would like to go on to a--Louise,  
11 I am going to ask you a question in a minute--I would like  
12 to go on to a slightly different issue. It has to do with  
13 the technique.

14 When I originally read the Workshop report, I  
15 misread it and I thought the same site was being stripped at  
16 different times, which would, of course, introduce a  
17 unacceptable variable into the procedure, so it must be made  
18 clear that Dr. Shah is measuring the integrated value, the  
19 cumulative value of 8 to 10 strippings at a single site, and  
20 those are done at a single time. The other time points are  
21 similarly stripped 8 to 10 times and measured.

22 Now, what I can't justify is that observation with  
23 one of the slides that Dr. Latriano showed, which is that  
24 when you looked at 24 hours, and you looked at strippings 11  
25 through 15, you did not find an increased amount of

1 material.

2 My concept of this is that the material should be  
3 moving through stratum corneum in some fairly reproducible  
4 fashion, and those concentrations, you should be able to--  
5 since you looked at different numbers of strippings, I am  
6 wondering why your findings don't fit with Dr. Shah's model.

7 I probably didn't get that into English.

8 DR. LATRIANO: I am not quite sure what the  
9 question was. You are puzzled why the amounts at 24 hours  
10 were lower than the amounts at 4 hours, the cumulative  
11 amounts?

12 DR. MCGUIRE: No. You grouped your strippings  
13 into 11 through 15. That would presumably be your deepest  
14 stripping, and I am wondering why--

15 DR. LATRIANO: That was the limits of the  
16 analytical assay. You are also limited if you keep going  
17 down, you might still have drug there, but you can't  
18 quantitate it.

19 DR. MCGUIRE: But even at 24 hours, you didn't  
20 find much material there.

21 DR. LATRIANO: No. If you notice, that was  
22 retinol, like retinoic acid is poorly absorbed, we know only  
23 from in vivo absorption studies, we know only 2 percent of  
24 that application is, in fact, absorbed, so the low amounts  
25 that actually get through the skin are not surprising.

1           What I didn't show is what went through the skin.  
2 I showed that data sort of out of context. That was the  
3 results of an in-vitro system. All the other data I  
4 presented were in-vivo data, which really there was no  
5 application involved. It was simply studies designed to  
6 explore how to sample, and all the variability that people  
7 have mentioned here, yes, we know that there is variability  
8 no matter what drug you take in the human population.

9           The variability that I spoke about was variability  
10 in the sampling technique. When we take a ml of blood to  
11 establish oral bioequivalence, we know we have a ml of  
12 blood.

13           DR. MCGUIRE: You have made that point.

14           Dr. Shah is about to show an overhead.

15           DR. SHAH: This is the same overhead, but may I  
16 ask for one clarification, Mr. Chairman? Did Dr. Latriano  
17 show the data, all the data in normal subjects or healthy  
18 human beings, all the different skin strippings, and all  
19 which were shown like 4 strips, 8 strips, 10 strips, were  
20 they in the live human subjects, or was it in in-vitro  
21 studies?

22           I got confused when I heard the last two  
23 statements from her that they were not really the studies,  
24 but in-vitro studies. Now I am confused on that. We will  
25 get a clarification on that.

1 DR. LATRIANO: May I clarify? The only data I  
2 presented that was in vitro was to show the concentration  
3 gradient in the skin. All the other data I showed was  
4 obtained in vivo from the same six subjects.

5 DR. DRAKE: Healthy subjects?

6 DR. LATRIANO: These were healthy subjects.

7 DR. MCGUIRE: Dr. Shah, go ahead with your  
8 overhead.

9 DR. SHAH: Here, I have the data which I showed  
10 earlier, that when we do the bioequivalence studies, I do  
11 want to reemphasize the fact, with the DPK, we are doing the  
12 study in the same subject comparing the two products at the  
13 same time, so we are making the side-by-side comparisons.

14 The data here shows that. If you go down each  
15 strip, at the lower end, it shows that when you have each  
16 strip calculated, the amount of the drug in each strip, it  
17 goes down log linearly. These are the data in human  
18 subjects, live human subjects, and used the same, more or  
19 less the data that you see.

20 After it is read, all the data are cumulative,  
21 again showing the fact that after 10 or 12 strips, you can  
22 still see the drug below in the stratum corneum, but then it  
23 acts on into more variability because the amount of the drug  
24 is much smaller, much lower, and you do not get any more  
25 valuable information for the determination of bioequivalency

1 than what you get only from 10 to 15 strips.

2 DR. MCGUIRE: Dr. Shah, while you have that  
3 overhead on, if you looked at the lower figure, at the lower  
4 two curves, if you looked at that at 24 hours instead of 6  
5 hours, what would it look like?

6 DR. SHAH: It would look nearly the same because  
7 we have those data--and Hans may expand on that further--  
8 with respect to the amount of the drug in the stratum  
9 corneum at the end of 24 hours.

10 DR. MCGUIRE: These are the only data you are  
11 showing in which you look at individual strips.

12 DR. SHAH: Yes. This is the only data with the  
13 individual strip, and because of this, we feel that there is  
14 no need to do the individual strip analysis.

15 DR. MCGUIRE: But wouldn't you expect to find the  
16 concentration gradient moving lower into the stratum  
17 corneum?

18 DR. SHAH: Well, that is what is happening. As  
19 you go down the strips, one strip after the other, lower,  
20 lower, lower, lower, you see the concentration is going  
21 down, and we stopped it.

22 DR. MCGUIRE: Right. That's the disappearance  
23 phase from the upper stratum corneum, but wouldn't you  
24 expect to see an increase in concentration at a later time  
25 point deeper in the stratum corneum?

1 DR. SCHAEFER: Never occurs.

2 DR. MCGUIRE: Because it is taken up so aptly by  
3 the papillary dermis?

4 DR. SCHAEFER: Exactly. The gradient is always  
5 towards the epidermal and dermal tissue, always. We have  
6 never, ever encountered an equilibrium between the different  
7 layers in the horny layer, and never, ever encountered an  
8 equilibrium between the lower part of the horny layer and  
9 the epidermis. It is always a continuous flux.

10 DR. MCGUIRE: So, your assumption is that it is  
11 quickly partitioned into the viable epidermis and on out  
12 into the papillary dermis.

13 DR. SCHAEFER: Absolutely.

14 DR. FLYNN: I am not sure Dr. Schaefer is  
15 answering your specific question. May I interject that  
16 point?

17 DR. MCGUIRE: Dr. Flynn.

18 DR. FLYNN: I think your question was if you put a  
19 drug on at one time point, and then you do a stripping some  
20 time after that, and you vary that time, will you see more  
21 drug or less drug as time passes in the collective  
22 stripping.

23 I think clearly, if you wait a microsecond and  
24 remove the formulation, your stripping, you are not going to  
25 have much drug on the stratum corneum, and if you wait some

1 substantially longer period of time, you are going to find  
2 some there, and if you wait an infinite period of time, you  
3 are going to find none there, so there is going to be a  
4 cumulation time profile that shows an increased amount and  
5 then a decreased amount, because you have competing  
6 processes of input and output.

7           However, you are never, ever going to see an  
8 increased concentration as you go down from strip to strip,  
9 and I think that is the question you were answering. So,  
10 there might be an optimum time to do the stripping in terms  
11 of getting the greatest amount of total accumulation in the  
12 tissue for a given formulation.

13           DR. McGUIRE: Then, the strategy of doing the  
14 cumulative measurement is the better strategy.

15           Dr. Rosenberg.

16           DR. ROSENBERG: Just comment on one issue that was  
17 just raised, healthy individuals or living individuals. It  
18 has been a long time since I worked in barrier, but my  
19 recollection is that the classic paper by Birchen Windsor--I  
20 think it is 1944--who showed that the water protective  
21 ability of the human skin is the same in cadavers as in  
22 living persons, established a firm footing for the stratum  
23 corneum, but not a living portion of the epidermis as the  
24 key factor here in penetration.

25           Unless somebody would tell me that those findings

1 of Birchen Windsor are no longer valid, I think we ought to  
2 make that clear.

3 DR. MCGUIRE: Would someone respond to Dr.  
4 Rosenberg's question? Dr. Schaefer.

5 DR. SCHAEFER: We have a much more differentiated  
6 answer. You take the whole horny layer away, and there is  
7 still a barrier. It is still not yet a water-like surface.  
8 The epidermis protects, too, not so much as the horny layer  
9 barrier, but it protects, too.

10 We have a much more differentiated view in that we  
11 know what the contributions of the different layers are. It  
12 is almost constant, almost, not completely constant. There  
13 are a lot of informations in respect to what you are asking,  
14 but it would take us a whole symposium to go into the  
15 details of the barrier function and its reservoir function.  
16 I have to emphasize this again and again and again.

17 We are looking after the reservoir function of the  
18 horny layer when we are talking in terms of bioequivalence,  
19 not into the absolute barrier. We are not saying that the  
20 stripping technique is always predictive in predicting what  
21 a new drug and a new formulation does.

22 We are always talking about comparison of the same  
23 compound, the same physical state, with a similar vehicle,  
24 and then, yes, there is a time kinetic, the maximum, to my  
25 experience, but that depends on the substance. In most

1 cases it is about 6 hours, where you have a maximum of  
2 distribution of the compound in the horny layer and already  
3 different concentration in the different layers, and we have  
4 followed that very carefully, step by step, concentration in  
5 the horny layers in every single strip, concentration in the  
6 epidermis, and subsequent concentrations in the dermis, and  
7 we have done that in vivo and in vitro, but it comes always  
8 back to the same point, there is never, ever an equilibrium,  
9 and there is always the reservoir.

10 Now, to answer to your question, Joe, because I  
11 didn't completely answer it, you apply a compound to the  
12 skin. You apply 3 mg/cm<sup>2</sup>. You leave it on for 20 hours.  
13 Then, you will never reach the status where it is emptied.  
14 You apply the same compound. You remove it 30 minutes after  
15 application, and then look after the kinetics, and the  
16 kinetics are different.

17 Now, you can do both. I always recommend in order  
18 to have clear-cut figures to apply something and then to  
19 remove the surplus in order to diminish the variability, to  
20 remove the surplus at a given point in time, and then to  
21 follow the kinetics. Again, the answer is, of course, is  
22 the kinetic better than the single point.

23 DR. MCGUIRE: Thanks, Hans.

24 Dr. Lamborn, you had a question.

25 DR. LAMBORN: A comment and then a question. With

1 regard to the issue of the association in oral  
2 bioavailability, the fact that we use normal individuals, it  
3 seems to me that that is a very different environment  
4 because there you assume that the process by which it is  
5 dissolved and gets into the blood, it may very well be  
6 normal even though the patient will be different, that's the  
7 endpoint. So, I think that to consider here that you have  
8 got normal skin versus diseased skin is perhaps a little bit  
9 of a different problem.

10 My question, I thought that one of the key points  
11 here was contrasting this as a proposal to what is currently  
12 being done and is this as good or better, and I wondered if  
13 somebody could clarify what the guideline currently is, if  
14 you currently have to use an efficacy study, how stringent  
15 is the efficacy study to demonstrate equivalence, because it  
16 is my sense that often that is not all that stringent, and,  
17 of course, will also not address the questions of  
18 equivalence in detail among older versus younger, so I would  
19 just like to have a perspective from which we are trying to  
20 compare this method versus the current efficacy measure.

21 DR. MCGUIRE: Let's deal with that, Dr. Shah, and  
22 then we have another question from the committee, and then I  
23 want to deal with at least some of the specific items, so if  
24 you can be right to the point.

25 DR. SHAH: Right to the point, at present we

1 require the clinical efficacy studies for the bioequivalency  
2 determinations of dermatological products other than  
3 glucocorticoids.

4 DR. LAMBORN: But the specific question is  
5 equivalence, efficacy within what kind of stringency. I  
6 mean because you can say some sense of the strictness of  
7 that equivalency requirement.

8 DR. WILKIN: Actually, typically, there are three-  
9 armed studies. There is the generic vehicle versus the  
10 generic active, and the active generic means to be  
11 statistically superior to the generic vehicle, and then the  
12 third arm is the brand name, which of course is only  
13 available as the active, and the comparison there is non-  
14 inferiority.

15 I think our statisticians are here if you want to  
16 hear actually how they calculate the non-inferiority part.

17 DR. LAMBORN: That's okay.

18 DR. McGUIRE: Thank you.

19 Dr. Brazeau.

20 DR. BRAZEAU: I just have one general issue, and I  
21 think it is related to, you know, it is more an assay or an  
22 analytical method. I think somewhere in the guidance there  
23 needs to be an assessment of how well the skin is being  
24 taken up into the tape.

25 I think if you can control for that, like, you

1 know, we take a blood sample, I think that this is a useful  
2 technique to look at these type of drugs, because I think  
3 where we are getting tied up is in the analytical  
4 methodology, and a properly designed study where you have  
5 assessed that you are getting consistent skin uptake and you  
6 can demonstrate that somewhere in the leg of the study will  
7 be useful.

8 My second concern, however, is what is going to  
9 happen with the inflammatory response, and I would like to  
10 know how this might impact at 24 hours if something is going  
11 to happen. If you have inflammatory response at one site,  
12 what is going to happen at adjoining sites? Can anyone  
13 address those issues?

14 DR. SCHAEFER: That is being investigated. If you  
15 try to strip after inflammation, normal correlation, you  
16 cannot do that, because there are so many factors  
17 interfering then, so it is never, ever being done except  
18 that there is a team in Berlin who looked after inflammation  
19 and took histology and showed clearly that there is edema,  
20 that there is inflammation, of course. There are no more  
21 wrinkles, and everything is unrelated.

22 So, to answer another question, stripping  
23 technique in diseased skin with eczema, eczematous skin, no  
24 way that you can do that. The skin, the horny layer will  
25 come off in very few strips, and there is no clear-cut

1 correlation between what you are seeing in one site relative  
2 to another site.

3 We tried it, but it's in vain, it's impossible.  
4 You can only do that in normal skin.

5 DR. MCGUIRE: But that doesn't really apply to the  
6 proposed technique. I mean that is not what Dr. Shah is  
7 proposing. Further, these repetitive strippings are done  
8 virtually at the same time. He doesn't do three strippings  
9 now and three strippings tomorrow. He will do all 10  
10 stripping after he has removed the surface excess.

11 DR. BRAZEAU: But I am talking about if you have--  
12 what I understand is that you will have x number of sites on  
13 the skins, and you will take one at four hours and one at  
14 six hours and one at eight, and you will do four strippings  
15 there, something to that extent.

16 My concern is, is that if I get an inflammatory  
17 process here at this site, how do I know that it is not  
18 affecting what I am seeing at a site that is adjacent to it.

19 DR. SHAH: I don't think we have seen that type of  
20 reaction.

21 DR. FLYNN: I have a thought on that. The stratum  
22 corneum is laid down over a period of days, and if you  
23 invoke an inflammatory response, it actually takes several  
24 days before the stratum corneum that existed before you  
25 invoked a response to be turned over and the new stratum

1 corneum formed, so you actually have a period of time to  
2 work with the same stratum corneum, and so up to a point you  
3 are not troubled with this particular variable.

4 DR. MCGUIRE: Well, I want to put this to rest if  
5 I can, but first say that tape stripping induces a number of  
6 pro-inflammatory cytokines within hours, not days, weeks,  
7 and so you have an increase in IL-1, you have an increase in  
8 TNF-alpha, and those are a response to the injury, and do  
9 they have a distal effect or is the effect only right at the  
10 site of the stripping, I certainly do not know, but I think  
11 the issue that you bring up needs to be considered.

12 What I would like to do is to focus more on the  
13 techniques now using the specifics as a guide.

14 Question 1 is: Can dermatopharmacokinetic  
15 methodology be used for bioequivalence determination of  
16 dermatological drug products such as--and we are going to  
17 have to take these one at a time, and actually let's start  
18 with antifungals because I think that is perhaps the  
19 cleanest, and with the antifungal, you really are not  
20 interested, unless someone can educate me, you really are  
21 not interested in getting systemic absorption at this point,  
22 you are interested in permeating stratum corneum, which is  
23 the site of the Malassezia or Trichophyton or whatever we  
24 are shooting at.

25 Is this going to be a successful technique for

1 determining bioequivalence of antifungals? Would anyone on  
2 the panel like to address that?

3 DR. DRAKE: I want to ask a question.

4 DR. MCGUIRE: Is it sort of on this?

5 DR. DRAKE: Well, I am a member of the panel,  
6 aren't I? May I ask a question, please?

7 DR. MCGUIRE: Yes.

8 DR. DRAKE: Thank you, sir.

9 The question I want to ask is as we move through  
10 this, and I think this is directed to the folks at the FDA,  
11 as we move through this, this afternoon, are you proposing  
12 this as an addition to, or are you proposing that we are  
13 eliminating, is this going to replace the human studies,  
14 because if it is going to replace the human studies, I am  
15 going to have a totally different response than if it's in  
16 addition to while we go through the validation process, but,  
17 you know, I don't see how you can ask us to answer questions  
18 right now, Mr. Chairman, without any more information than  
19 we have on the validation process, because I don't have any  
20 clue about the validity of these things, because we haven't  
21 had enough validity studies presented today for me to draw  
22 an assumption or conclusion of even answer these questions,  
23 and I think that is fundamental of the process.

24 DR. MCGUIRE: That is fair. Roger, is that one  
25 that you would like to address?

1 DR. WILLIAMS: There would be a spectrum of tests  
2 to replace the comparative clinical studies as a means of  
3 documenting bioequivalence both for a pioneer in the  
4 presence of certain kinds of post-approval change, as well  
5 as the generic.

6 That spectrum of tests might include physical-  
7 chemical tests, includes particle size, in-vitro release,  
8 and DPK.

9 Am I saying that right, Vinod? Do you want to  
10 check me?

11 DR. DRAKE: I still don't have a clear  
12 understanding.

13 DR. FLYNN: A question for clarification of your  
14 answer, Roger. We heard that there would be studies of  
15 comparison with formulations clinically from Jonathan, and  
16 there would be a study of the formulation against the  
17 vehicle.

18 Is this test meant to only replace the first of  
19 those two studies, or is the formulation versus vehicle test  
20 also replaced?

21 DR. WILLIAMS: Jonathan and Vinod can correct me,  
22 but my understanding is that the study Jonathan described,  
23 with three arms, was a clinical study, and the objective of  
24 what we are proposing is to replace that study entirely.

25 DR. DRAKE: Okay. Then, I have a comment to make,

1 Mr. Chairman, and my comment is I don't know how this panel  
2 today can make that, can even begin to presume that these  
3 studies could possibly replace the clinical studies without  
4 more information on validation.

5 I think this is very risky because my bottom line  
6 for being here is my patient, and our consumer advocate is  
7 not on the panel today, and I think the bottom line is the  
8 patient, and it is not even reasonable to assume that we can  
9 answer questions about what is good for our patients.

10 We are talking about throwing out the standard  
11 reviews for years and years of clinical research, I mean of  
12 looking at patients and the effect of drugs on patients, and  
13 there isn't a person in this room that doesn't understand  
14 there is a difference in vehicles, there is a difference in  
15 particle size.

16 There are so many variables, that to throw that  
17 out with as little validation as we have, I think it is a  
18 mistake and I don't see how we can answer these questions  
19 because we haven't seen the validation data by which to base  
20 our opinions.

21 DR. McGUIRE: Everybody wants to speak, but I get  
22 to speak first.

23 I am hoping that without--it is not the purpose of  
24 the Advisory Committee to tell the Agency to throw out  
25 analytic techniques, clinical techniques, and substitute

1 them with another technique.

2 I think what the Agency is asking us is whether in  
3 these specific examples, if the technique that has been  
4 proposed has any validity, and I think that these compounds  
5 or the groupings that are here are quite different.

6 For instance, CIRD Galderma has extensive  
7 experience with retinoids vis-a-vis particle size, and there  
8 is a critical particle size that puts the retinoid right  
9 into the follicle within minutes.

10 Glucocorticoids, where do you want the  
11 glucocorticoids to work? You don't want them to do anything  
12 to the stratum corneum, you want them to get through that  
13 barrier as quickly as possible and get down to where the  
14 action is.

15 Antifungals, similarly, have a different site of  
16 action, so I think we can go through these and make comments  
17 that may be of value to the Agency. I hope they can be.

18 That is my longest speech of the day. Jonathan,  
19 you are next.

20 DR. WILKIN: Just as a point of clarification,  
21 what needs to be demonstrated for a generic product is this  
22 bioequivalence, and that is really what the question is  
23 asking is can one use this technique to demonstrate  
24 bioequivalence, which will then lead to the notion of  
25 therapeutic interchangeability.

1 DR. McGUIRE: Dr. Brazeau.

2 DR. BRAZEAU: I guess I would sort of disagree  
3 with Lynn in that I think these again are techniques that--  
4 remember we are using these type of kinetic techniques as a  
5 surrogate marker for efficacy, as we heard earlier, and I  
6 think this type of technique provides a better handle to  
7 understand what kind of drug is getting to the various  
8 layers.

9 Now, I would like to perhaps address the first  
10 question and raise two questions. There are two questions  
11 that I would want to know if you could use the DPK method  
12 for bioequivalence.

13 The first thing I would want to know, like in  
14 pharmacokinetics, is what is going to be the relationship of  
15 the active concentration. When we think about systemic  
16 kinetics, we always think about free drug, so in this case,  
17 are these drugs going to be bound to other components in the  
18 tissue.

19 So, that to me is an area that has to be raised,  
20 what do antibacterials or antifungals bind to, and what is  
21 going to be, you know, in my limited knowledge, to MIC, what  
22 is going to be the concentration at that site.

23 The second issue I think that needs to be raised  
24 is to whether these can be used for these various classes of  
25 drugs is what is the nature of the concentration-response

1 relationship, is it a steep concentration response  
2 relationship or is this a flat, and if you are going to be  
3 able to differentiate between those two.

4 I would argue if you have a relatively flat  
5 concentration-response relationship, this method may not be  
6 able to discriminate between two formulations. If it is a  
7 steeper, it may be more likely.

8 So, I guess I am trying to answer your question by  
9 raising two additional questions, one related to the active  
10 concentration of drug at the site, and the second related to  
11 the concentration-response relationship for that particular  
12 class of drugs.

13 DR. MCGUIRE: Dr. Williams, did you have a  
14 comment?

15 DR. WILLIAMS: Well, first of all, I would like to  
16 say it has been a very useful discussion so far, and I  
17 really appreciate the discussion. The other thing I would  
18 like to say is unfortunately, I can't be here with the  
19 committee this afternoon, but I look forward to the reports  
20 from Jonathan and Vinod.

21 Thirdly, I would like to say I was actually going  
22 to agree with Lynn. I think the issue of validation is a  
23 critical question, and I thought Dr. Latriano's comments  
24 were very useful there.

25 I think we have to assure that either we are

1 sampling to no more drug in the sample, in the strip, or we  
2 are sampling to a constant amount, but I would argue that  
3 the Agency is very good at looking at assay validation,  
4 which I think this is, and we would try to assure the  
5 committee members that it was an adequately validated assay,  
6 and it may be the primary focus could be on the surrogacy  
7 question, does it adequately tell us enough about our safety  
8 and efficacy concerns to be used as a surrogate.

9 DR. McGUIRE: Other comments from the committee?

10 DR. BRAZEAU: I guess I want to go back to what  
11 Roger said. I think the key to writing this guidance is  
12 going to be again the assessment or the validation of the  
13 method, and being able to understand what is the uniformity  
14 of skin uptake on the tape, and being able to show or  
15 somewhere in the design of the experiment to assess for this  
16 parameter.

17 DR. McGUIRE: So, Gayle, you are telling me that  
18 you have not seen enough data?

19 DR. BRAZEAU: No, I think from what I have seen  
20 and from previous times, that if you have a method by which  
21 you can normalize for either the amount of skin taken up or  
22 something else, I think this will be a useful technique to  
23 ask if things are different, but it goes back to the  
24 question is what is going to be the class of drugs you are  
25 going to be evaluating.

1 I mean analytical methods can be fine-tuned and  
2 made sensitive enough that you can differentiate. When  
3 pharmacokinetics first came out years ago, what we were  
4 using, UV spectrophotometry, and that is not as analytical  
5 sensitive technique as what we have now. Now we are to LS,  
6 MS, NS, and we have got more techniques, and that comes  
7 through validation of the method and setting up a study that  
8 will have the appropriate controls to show that your system  
9 is consistent and isn't changing.

10 DR. ROSENBERG: Could I ask a question?

11 DR. McGUIRE: Yes, Bill.

12 DR. ROSENBERG: We saw pictures of the two  
13 hydrocortisones with this technique, one being superior to  
14 the other. Have there been any clinical studies done which  
15 show that the clinical study would not be able to discern  
16 those two, or that in fact, that this was a parallel for  
17 what came up in the clinic, or is that contemplated?

18 DR. McGUIRE: Dr. Shah.

19 DR. SHAH: As far as I know, both the products  
20 were clinically bioequivalent, because they both were using  
21 the clinical efficacy data. What Dr. Schaefer and we were  
22 making here is this is a most sensitive method before it  
23 goes to the clinicals, so therefore, if you find no  
24 differences using the dermatopharmacokinetic principles,  
25 that is going to give you more reasonable assurance that

1 both the products would behave clinically the same. If you  
2 see the difference, then, that would raise a question and  
3 you may have to go back and take a look at the clinical  
4 data.

5 DR. MCGUIRE: Yes, please.

6 DR. LAMHORN: I guess this gets to the question I  
7 was trying to ask earlier about the current methodology for  
8 demonstrating bioequivalence. My concern is that if you are  
9 talking about demonstrating equals active where you just do  
10 not reject equivalence, you could have substantial  
11 differences and still pass the clinical bioequivalence, so  
12 that there is definitely room to improve that situation by  
13 using this more controlled assay if it is sufficiently  
14 validated, and you may very well be in a position where we  
15 can improve the assurance to the patient that we are giving  
16 them something equivalent.

17 DR. MCGUIRE: Dr. Williams.

18 DR. WILLIAMS: Mr. Chairman, the question that I  
19 think is emerging is a very interesting one that maybe  
20 Jonathan can address, which is when you see different  
21 strengths of the innovator, do you see a dose-response  
22 relationship such that you could distinguish between those  
23 strengths.

24 DR. LAMBORN: And how different does the strength  
25 have to be before you can pick it up with the size study

1 that you are usually using for a bioequivalent comparison.

2 DR. WILLIAMS: Right, because we usually care  
3 about plus or minus 20 percent in a dose, but, Jonathan, I  
4 think your strengths maybe go like 0.1, 0.25, 0.5, 1.0, or  
5 something like that. I don't know quite what the range you  
6 see is.

7 DR. WILKIN: Unfortunately, we really do not have  
8 good efficacy data that we can analyze that way for  
9 different concentrations.

10 DR. MCGUIRE: I am going to try this one more  
11 time. The Agency has asked us if DPK methodology can be  
12 used for these classes of therapeutics, and I was  
13 unsuccessful the first time around, but let me try it again.

14 DR. DRAKE: I will try.

15 DR. MCGUIRE: Lynn, thank you.

16 DR. DRAKE: I will try. You want an opinion from  
17 one committee member, and I will tell you that in my  
18 opinion--

19 DR. MCGUIRE: Actually, I want an opinion from one  
20 committee member on one class of drugs.

21 DR. DRAKE: On antibacterials.

22 DR. MCGUIRE: Okay.

23 DR. DRAKE: I mean I will give it to you on all of  
24 them. I have the same answer for all of them.

25 DR. MCGUIRE: Okay.

1 DR. DRAKE: And my same answer for all is that  
2 this is a very intriguing notion. I think it should be  
3 explored further because it is intriguing and it has great  
4 potential. I think we are not there yet, and I would say  
5 that we have not reached--I agree that one of the statements  
6 that Dr. Wilkin made in his presentation, that no  
7 equilibrium has been established, I think that is the  
8 fundamental issue here, and so I would say that can it be  
9 used exclusively in lieu of clinical studies, I would say  
10 no, and that is for all the categories.

11 DR. McGUIRE: Okay. I really appreciate that, Dr.  
12 Drake.

13 DR. DRAKE: Thank you. I am answering your  
14 question.

15 DR. McGUIRE: Yes, you did. We have a position,  
16 and I would like to hear from others.

17 Dr. Flynn.

18 DR. FLYNN: I would like to speak to the dilemma,  
19 the great dilemma, and that is that the originator company  
20 had to show that its product was different than a placebo,  
21 and that is much easier to do and much less clinically  
22 costly than to show for the generic formulator that the  
23 products, the original formulator and the generic formulator  
24 are not different.

25 It takes a higher power study in order to show no

1 difference between two products that are supposedly not  
2 different than it does between two that one is a placebo,  
3 and the dilemma is that in their infinite wisdom, our  
4 Congress has said that they want competition in this  
5 business, and they have said that they want a products after  
6 the patents have expired to be open for competition, and  
7 this is easily done in the oral area because we can fall  
8 back to blood levels and blood level profiles, and show  
9 sameness in ways that for most of us scientific people are  
10 satisfying.

11 Our dilemma is we don't have anything anywhere  
12 close to that in the instance of a skin topical dosage one,  
13 so we are looking for a surrogate that makes scientific  
14 sense, that answers the concern of delivery.

15 It is a physical-chemical process, and I think  
16 what I tried to say earlier was that from a fundamental  
17 point of view, we would expect to get sameness in this test  
18 if, in fact, the products are the same, and we would expect  
19 to see a difference if they are not, but we don't have the  
20 kind of convincing clinical validation comparisons that make  
21 any one of us I think sitting around this table completely  
22 comfortable with the whole idea, but we also are not going  
23 to be able to require the generic administrator to run these  
24 comparative clinical tests at their enormous cost, so that  
25 is the dilemma.

1 DR. McGUIRE: I think that is a very clear  
2 statement and I would like to add to that, that, Dr. Shah, I  
3 guess my central concern about the stripping technique is  
4 that it puts the stratum corneum in a very key role, and the  
5 stratum corneum is either going to be a target for the  
6 pharmaceutical or it is going to be a barrier for that drug  
7 to get to where it really needs to work.

8 The targets that we have are viable keratinocytes,  
9 Langerhans' cells, melanocytes, mast cells, endothelial  
10 cells. There are a number of targets that we are now  
11 talking about, and so the barrier is either going to be the  
12 site of action of, for instance, the antifungal, or it is  
13 simply going to be a nuisance that has got to be penetrated  
14 before you can deliver the drug to the appropriate site, and  
15 I don't know how you nuance the system if you only  
16 information you have is multiple strippings with all the  
17 variability that we have heard about in the strippings.

18 Jon, did you want to make a comment?

19 DR. WILKIN: This actually relates to Dr. Flynn's  
20 comment and a comment that Dr. Lamborn made earlier, and I  
21 probably should have jumped in at that time because it came  
22 back up.

23 It is the analogy to the case for oral drugs that  
24 dissolve in gastric juice and then are absorbed, and one  
25 looks at the plasma levels, and then the plasma levels are

1 in equilibrium with the organ that is going to have the  
2 effect that we are all interested in, and it is analogous,  
3 but the strength of the analogy depends on the number of  
4 points with which there is relative similarity.

5 In this particular case, if you think of  
6 dissolving in the gastric juice, the gastric juice really  
7 becomes the vehicle, it really does, and that is fairly  
8 constant thanks to human body homeostasis from one  
9 individual to the next, and I am not sure that we know that  
10 the vehicle from the innovator and the vehicle from the  
11 generic firm are as similar as gastric juice from one person  
12 to the next.

13 The second point is we are looking at the stratum  
14 corneum and we are having thoughts about the kind of  
15 thoughts we have from plasma, that really, it would be more  
16 analogous to the lining of the stomach, and so I would ask  
17 the committee to think through that part of the metaphor.

18 DR. MCGUIRE: Dr. Lim.

19 DR. LIM: It is just a comment. Personally, I am  
20 also struggling with the issue. I fully agree with Dr.  
21 Flynn that indeed I think it is unrealistic to ask generic  
22 companies to run large clinical trials.

23 It would be nice to have an in-vitro testing of  
24 very simple tape stripping methods to be able to establish  
25 equivalency, however, I think the data that has been

1 presented has been quite difficult to just accept it at face  
2 value saying that it would be equivalent because of the  
3 variability that we all have discussed this morning, not  
4 only the concentration of the vehicle, the target organs or  
5 the target cell that this particular medicine is supposed to  
6 be working on, and that is a very significant reservation on  
7 my part.

8 DR. MCGUIRE: I think Dr. Flynn was next.

9 DR. FLYNN: I have been trying to stay out of this  
10 one, but I think something has to be said that brings us  
11 back to the stripping data.

12 I admire Dr. Latriano's enthusiasm for science and  
13 her integrity, but I have real questions about the data that  
14 we saw. I have questions on two counts.

15 The first count is the fact that it is clear from  
16 all the people that I know in this business of stripping  
17 that the kind of variability that she has reported to us has  
18 not been the general experience of other people, and that  
19 has not been said clearly, and that has not been articulated  
20 well enough here, and that includes myself. Although I  
21 haven't done this procedure itself, we have done a lot of  
22 tape stripping in our laboratory.

23 I would like to share with you another experience  
24 we had. We were getting negative weights on our tapes, as  
25 well, in an environmental condition that was relatively

1 constant over a period of 24 hours, so there wasn't even  
2 that much time for major changes in the environment.

3           We were in an air-conditioned room with the  
4 controlled temperature and humidity, and we did a simple  
5 experiment. We took the tape and we re-weighed it--not  
6 stripping on this tape now, just the plain tape--took a  
7 piece of tape and weighed it and weighed it and weighed it  
8 and weighed it, and we got substantially variable weights.  
9 We got weight differences which were greater than the amount  
10 of stratum corneum we were picking up, on a piece of tape  
11 that had never touched the skin.

12           We took a piece of foil of the same weight and  
13 weighed it and weighed it and weighed it over a period of 24  
14 hours, and we never got a weight that differed to a tenth of  
15 a microgram. Our conclusion was some of these materials  
16 that are used in these tapes, particularly backings that are  
17 made of cellulose, are extraordinarily hygroscopic, they  
18 almost act like hydrometers or something, and, in fact, you  
19 are picking up and losing moisture from these tapes in  
20 amounts that, in fact, overwhelm the amount of tissue  
21 pickup.

22           You must pick a tape, you must test it, you must  
23 validate the use of the tape you are going to use for these  
24 studies in order to get reasonable studies. We found other  
25 tapes, one other, I can't remember what the material was, in

1 fact, which didn't have this property, and we could get the  
2 same weight over a long period of time from that tape on a  
3 simple piece of tape, and it was those tapes that we showed  
4 we could, in fact, quantitate the amount of weight, the  
5 weight of tissue we picked up from an individual stripping.

6 I point to you a problem I have with the specific  
7 data we saw where we are given at one point a conclusion  
8 that there was an adhesive failure, which means that the  
9 weights were less than anticipated, and at the same time,  
10 the transepidermal water loss was increasing, which would be  
11 counter to that, in other words, you are picking up stratum  
12 corneum.

13 Now, there could be a tradeoff between two  
14 phenomena, but I don't think that is happening. I think  
15 there is a problem with those data, and you should know that  
16 when you are looking at this study.

17 DR. LATRIANO: I would like to address that before  
18 we go on.

19 DR. MCGUIRE: Louise, let me just one word  
20 procedural. We are not going to continue this discussion  
21 this afternoon, so we need to have some consensus, however  
22 loose it is, before we break for lunch, and then we will go  
23 into the closed session this afternoon.

24 Louise, I beg your pardon. Go ahead.

25 DR. LATRIANO: That very property of the

1 hydroscopic nature of the adhesive and the backing was why  
2 we let those tapes equilibrate overnight, so that we had a  
3 constant weight, and the weight of the tape was not going to  
4 interfere with the weight of the sample, and that's why we  
5 chose right up from the front to use that constant  
6 environmental room.

7           In terms of the differences that we saw that you  
8 didn't, I am not aware of anyone who has conducted these  
9 studies with the degree of control that we applied to this  
10 or whether other people have truly looked at the  
11 differences. When I have looked at cumulative amounts of  
12 stripping, that line is not a straight line. You get  
13 variability. So, I don't think that data is inconsistent  
14 with what I have seen in the literature or in your  
15 statements today about the effect of moisture on the tapes.

16           As far as the cohesive failure, there were 24  
17 strips. You could have left some adhesive on and still be  
18 pulling up skin. So, I don't regard any of those findings  
19 as contradictory to what has been out there or what the  
20 general experience is.

21           DR. MCGUIRE: I would like Dr. Williams, but  
22 first, I would like to hear from some of the other members  
23 of the Advisory Committee who have not weighed in on this.  
24 Now, it is conceivable and it is in fact likely that we will  
25 not have a consensus, but at least the Agency should hear

1 from members of the committee who have not expressed their  
2 ideas on this.

3 Dr. Williams.

4 DR. WILLIAMS: Well, let me see if I can start off  
5 by saying this. I think we struggle with these questions  
6 all the time. I hope the committee appreciates that.

7 There is the issue of primary validation of the  
8 assay, and I would again say that I think the Agency can  
9 assure that, to the extent that we can, I would say DPK can  
10 be used.

11 I think again if you move beyond that step, you  
12 get to the issue of the metric from DPK, which is the area  
13 under the stratum corneum, concentration/time curve, if you  
14 will, and I keep coming back to the inferential goal there  
15 that somehow that will give a signal of comparable safety  
16 and efficacy, and that is the surrogacy question.

17 There is also the question of sensitivity versus  
18 variability, and I can tell you that I will always choose a  
19 more sensitive assay because I can handle the variability in  
20 the comparison. We frequently see people who want to choose  
21 insensitive tests, and that was the whole debate about the  
22 pharmacodynamic tests for albuterol metered dose inhalers.

23 It also came up in the debate about steady-state  
24 versus single-dose PK studies, so I would say the Agency's  
25 position is we will always choose sensitivity over

1 variability.

2           The final question--I have to come back to Dr.  
3 Drake's position--I don't think it is enough just to say we  
4 will need more information, and pending that information, we  
5 can't accept the new approach.

6           The reality is you probably already have accepted  
7 lesser degrees of information in your assumption that a lot  
8 of the post-approval changes for the innovator relate to the  
9 primary pivotal clinical trial data on which aging and  
10 efficacy were based.

11           Let me finish. The reality is we know those  
12 products have gone through innumerable changes over the  
13 years, probably with a lesser degree of scrutiny than we are  
14 talking about now for the generic.

15           I would argue that the Agency has to make a  
16 decision here, and my final point is how do you validate a  
17 surrogate when your clinical endpoint is so noisy that it is  
18 not possible to validate it. I mean I always have that  
19 question, and I would be interested in what the committee  
20 has to say.

21           DR. MCGUIRE: Dr. Drake. We are going to hear  
22 from Dr. Drake and then, Dr. Miller, get your position  
23 straightened out because you are going to be next.

24           DR. DRAKE: You sort of were speaking for me about  
25 what I might think, and you were wrong.

1 DR. WILLIAMS: No, I didn't think I was speaking  
2 for you, Dr. Drake.

3 DR. DRAKE: Oh, good. Maybe I haven't made myself  
4 clear. I think you are asking us if we think this is--I am  
5 going to make my answer very straightforward, so there can  
6 be no misunderstanding--I said earlier I think it is  
7 innovative, creative, and interesting, but I am unwilling as  
8 one member, just one member of this committee, to accept  
9 this test as a replacement for what we actually do in  
10 patients and see in patients, because my bottom line is what  
11 is good for our patients, and this test as far as I am  
12 concerned is still way far away from me being able to accept  
13 it as the best way to evaluate or accept judgment on  
14 equivalent drug because I just think we are not there yet,  
15 so let me make it very clear.

16 My answer is I do not think--if you want a  
17 definite answer--I do not think it is time to use this test  
18 in replacement at this point. I agree that the goal of  
19 trying to find a test to do so because I understand the need  
20 from generic companies to have a less expensive way of doing  
21 it, but I think at this point in time, with the information  
22 we have been presented, we are not there, and so I would  
23 speak strongly against it.

24 DR. MCGUIRE: Okay. We know exactly where you  
25 are.

1 DR. DRAKE: That's right.

2 DR. McGUIRE: Dr. Miller.

3 DR. MILLER: Okay. I will try to tell you exactly  
4 where I am. I think DPK could become a surrogate. I think  
5 that these are very different products and it might become  
6 the surrogate for antifungals, but not for retinoids and not  
7 for corticosteroids.

8 But I think in this infancy stage and with all the  
9 variables that we have and that have been discussed, that  
10 there certainly has to be clinical correlation with what we  
11 are seeing with the DPK, and can we consistently say the DPK  
12 showed this, and this is what the clinical correlation was,  
13 and then maybe we can go forward with it.

14 I would be interested--and this is a question for  
15 corticosteroids, you know, we have we have vasoconstriction  
16 tests--has there been any correlation done between DPK and  
17 the vasoconstriction and therefore the efficacy of topical  
18 steroids?

19 DR. McGUIRE: Dr. Shah, do you want to respond to  
20 that?

21 DR. SHAH: Yes, we have done the correlations, and  
22 we have seen it with respect to the DPK and the  
23 vasoconstriction assays. They are all hand in hand. I can  
24 show you the slide if people have the time. With the  
25 pharmacokinetic DPK of the two glucocorticoids and the

1 pharmacodynamic, the vasoconstriction assay of the two  
2 glucocorticoids, plus Dr. Pershing has done extensive work  
3 on six different potency categories of the glucocorticoids  
4 with the pharmacodynamic aspects and the  
5 dermatopharmacokinetic aspect, so we have that kind of  
6 information what you are requesting.

7 DR. MILLER: And there is correlation, you say?

8 DR. SHAH: Yes. The only problem, what we come  
9 back again, is the type of the validation that the people  
10 are requesting with respect to the clinical studies and the  
11 DPK. The problem is since we have not approved any of the  
12 generic products of all these other categories, it is really  
13 difficult to get the two products and make comparisons, and  
14 that is the reason why we are trying to look at a newer  
15 technique, not only a single point, but several different  
16 ways of looking at it and making the comparisons.

17 DR. McGUIRE: Fred, thanks very much.

18 Dr. Lamborn.

19 DR. LAMBORN: This would not be a vote from this  
20 committee, because, of course, I am not a member of this  
21 committee.

22 DR. McGUIRE: No, I am not asking you for a vote.  
23 I am asking you for an opinion.

24 DR. LAMBORN: My sense is that I am very concerned  
25 about the current clinical efficacy studies and their

1 insensitivity to bioinequivalence. At the same time, I feel  
2 that the argument for being ready to move forward right  
3 today, all the pieces have not been put together in a way  
4 that address the specific surrogacy.

5           Again, I don't know the dermatology well enough to  
6 say which of these classes, that this is what is happening  
7 in this AUC would be a sufficient surrogate, so I would like  
8 to see some additional information, but I would certainly  
9 hope that we could move to something like this in the near  
10 future.

11           DR. MCGUIRE: Thanks very much.

12           Dr. Schaefer.

13           DR. SCHAEFER: I would simply add some  
14 information. I have had four times in my life the occasion  
15 to do a concentration clinical efficacy study. That was in  
16 hydrocortisone, that was in amphenin, that was in  
17 [agmethoxlyn], [methosetrolin], and that was in adapalene.

18           In all cases could we not distinguish a  
19 concentration and half of this concentration. In all those  
20 four cases, we came to a difference in terms of clinical  
21 response only if we multiplied the concentration by 3 or  
22 divided by 3. Intermediate values could not be assessed in  
23 a reasonable number of patients.

24           DR. MCGUIRE: You have restated the problem.

25 Thank you.

1 Dr. Tschen.

2 DR. TSCHEN: I take the position of Dr. Miller. I  
3 think that this new technique should be used in addition to  
4 the clinical stories, and in using that, Dr. Wilkin's  
5 example, it will be the same as measuring the level just in  
6 the gastric juice, and not really in the serum, and  
7 essentially, that is what we are doing with the DPK is  
8 measuring in the stratum corneum, but not where the  
9 medication is really effective, whether it is low basis, or  
10 what have you.

11 So, although I think it is very valuable and  
12 clearly useful, I think broadly the only technique that can  
13 be used is lowering the power in the statistical method for  
14 the clinical stories or doing some manipulation in the  
15 statistics to decrease the number of patients requiring the  
16 force that you need to use, the number of patients, but I  
17 don't think just the DPK alone will satisfy me at this time.

18 DR. MCGUIRE: Thank you, Dr. Tschen.

19 Dr. Rosenberg.

20 DR. ROSENBERG: I think the Agency should respond  
21 to the mandate of the Congress and institute this policy now  
22 which would facilitate the change to generic, which is what  
23 is desired.

24 I think it is not right to ask generic people to  
25 do the kind of clinical studies that all of us would like to

1 see a few of done to give some added validation. I think  
2 the Agency should on its own commission a few studies in  
3 which products which are way different could be tested  
4 clinically, and those that are the same, maybe one or two  
5 could be tested to make sure that they were also valid.

6 I think everybody would feel better if that were  
7 done, but I don't see any reason why we have to wait for  
8 that.

9 DR. McGUIRE: Dr. Lim.

10 DR. LIM: The discussion this morning reminds me  
11 of the discussion ongoing currently in some of the  
12 photobiology community about fabrics, the sun protective  
13 properties of different fabrics, whether we need some in-  
14 vivo testing that is in patients versus just using  
15 transmission and in-vitro testing.

16 My position is that I think this is a very, very  
17 promising method to use, and it probably is useful for  
18 certain type of medications with certain actions. I think  
19 Dr. Miller mentioned about antifungal where the target is  
20 primarily in the epidermis, but I think there is still  
21 significant problems to address this as a sole criterion to  
22 assess bioavailability.

23 DR. McGUIRE: Thanks very much. You are implying  
24 that you are more comfortable with the transmission  
25 characteristics of the fabric than you are with stratum

1 corneum.

2 DR. LIM: No, no. My point on the fabric  
3 actually, my position on that is that it should be tested in  
4 vivo. I think it is very difficult to draw any conclusion  
5 based on in-vitro transmission.

6 DR. MCGUIRE: Lynn, did you want to add anything?

7 DR. DRAKE: No, sir.

8 DR. MCGUIRE: Dr. Kilpatrick.

9 DR. KILPATRICK: As you and others know, I am not  
10 qualified to speak to A through E from the clinical point of  
11 view. I can simply give you my feelings as a statistician  
12 hearing this discussion.

13 First of all, I have to say that I don't think the  
14 committee were well prepared to answer these questions in  
15 the material that we received ahead of time. Either that or  
16 I didn't get all of the material, which has happened before.

17 There has been some confusion in terms of the  
18 information presented to us today. I have heard conflicting  
19 reports as to whether DPK would be used in a serial fashion  
20 or whether it would be used as a replacement for clinical  
21 testing.

22 My feeling is that it should not and should  
23 probably never be used only on its own. It may need to be  
24 used with other methods, not necessarily clinical, the whole  
25 clinical armamentarium.

1 I would like to turn to some of the discussion  
2 about the variability and reiterate what has been said by  
3 the committee members, that here we have an opportunity in  
4 terms of stripping of testing one substance against a  
5 reference substance, in a sense using a controlled trial  
6 because of the person being his own control, and that  
7 certainly, as has been pointed out by other members of the  
8 committee, will reduce some of the intrinsic variability  
9 from person to person and from one person to another person  
10 at different times.

11 So, I am reasonably confident that the way that  
12 the analysis will be statistically robust against some of  
13 the assumptions. I would like to, in fact, go further and  
14 pose a question, which I don't know is feasible. I am  
15 suggesting, like other members of the committee, that we  
16 should look for more information on the conformability or  
17 coherence between clinical results and DPK results, and  
18 wonder whether it would be possible to do, in one or more  
19 trials, to do the same thing, comparison to DPK and clinical  
20 results in the same patients.

21 I don't know if that is feasible or not, but I  
22 would like to see matched results from DPK and plasma.

23 So, I am with Dr. Rosenberg in some sense, but I  
24 feel that we need more information before we can let DPK fly  
25 on its own.

1 DR. MCGUIRE: Thank you very much.

2 Dr. Brazeau.

3 DR. BRAZEAU: When I first heard about this in  
4 December at the last Advisory Board meeting, I was less than  
5 enthusiastic, but as I have had a chance to think about some  
6 of the data we saw and get a chance to re-read this or read  
7 this document provided to us earlier, I really think this is  
8 a useful technique for trying to assess differences between  
9 the name brand and generic product.

10 I think we need to have sensitive analytical, you  
11 know, methodologies have to be standardized, and I think if  
12 you plan a well-controlled study that includes the various  
13 concerns we have raised here, I think this will be a useful  
14 technique for discriminating between the brand name and  
15 generics.

16 Now, my concern is I can't necessarily address  
17 Items A through E also because I am not a clinician, but I  
18 will bring back the two questions that I raised earlier. I  
19 think it will be dependent on how different or the  
20 difference you are going to see is a going to be a function  
21 of the concentration-response relationship and the free  
22 concentration, how useful this technique will be.

23 Now, I would like to address Question 2, which I  
24 don't think anyone has really addressed here, about the in-  
25 vitro release. When I think about from a pharmacy point of

1 view what we teach our pharmacy students is that you have  
2 drug in a formulation, and it is a balance between how well  
3 the drug likes to stay in that formulation and how well the  
4 drug is going to want to partition into the skin.

5 I think what Dr. Flynn has presented to us has  
6 shown that you can, through release rates, you can see  
7 dramatic differences in how fast the drug is going to be  
8 released, and I think that using in-vitro testing should be  
9 useful for giving a bio-waiver for a lower strength drug,  
10 because if you make the assumption that you get it out of  
11 the vehicle at equivalent rate, and you do these ratios,  
12 then, I think you can see that you should be able to get the  
13 same ratio as it is going into skin.

14 So, I would like to say that I think the in-vitro  
15 drug release can be useful to look at a bio-waiver and that  
16 I think the DPK method is a method that should be looked at.  
17 The caution would be that in the development of the  
18 guidance, it needs to be stressed that you have got to have  
19 sufficient rigor and design in the analytical technique, you  
20 have got to be able to assess you are getting the same  
21 amount of skin and that the tapes are being taken care of  
22 and they are being handled properly, and I think it will be  
23 a useful technique, and I would recommend that we go forward  
24 and try to pursue its use in assessing generics versus name  
25 brand.

1 DR. MCGUIRE: Thank you, Gayle.

2 Dr. Flynn.

3 DR. FLYNN: I think my leanings here have been  
4 made obvious, and I believe the case made here this morning,  
5 however, has not been strong enough.

6 DR. MCGUIRE: Okay. Dr. Simmons-O'Brien.

7 DR. SIMMONS-O'BRIEN: I agree with Dr. Miller. I  
8 was thinking the same thing, that I think that DPK is  
9 probably a very viable and valuable method for certain drugs  
10 that we have listed here where the target sites are known,  
11 such as the antifungals, maybe the antibacterials.

12 My concern would lie using this technique in lieu  
13 of clinical studies with glucocorticoids, where these are  
14 medications that are necessary and used a lot, and used very  
15 frequently by physicians who are not dermatologists, and my  
16 concern would be that it would not be a clear understanding  
17 that the generic would actually have the same safety and  
18 efficacy as the primary, say, for the individual who can no  
19 longer afford the Class IV primary is given the generic  
20 approved based on DPK, and that generic might end up acting  
21 like a Class II. That makes a big difference.

22 DR. MCGUIRE: Dr. Mindel.

23 DR. MINDEL: In answer to the question about DPK  
24 used for bioequivalence, I would answer no to A, B, C, and  
25 E. As far as glucocorticoids, I think Dr. Miller's question

1 was very good. There is a surrogate endpoint, the  
2 blanching, and Dr. Shah seemed to answer that you could use  
3 the data, the data had shown that there was a correlation.

4 If the FDA felt that this correlation had been  
5 shown in a masked, randomized manner with multiple drug  
6 doses of different efficacies, then, I would say yes, then,  
7 it could be used, but that information, as Dr. Kilpatrick  
8 said, was not given us before, so I would leave that in the  
9 hands of the FDA to vote for me yes, if that really exists.

10 Finally, there is a conceptual problem--backing  
11 off, and this is my one aside for the whole morning--is that  
12 the problem really is that there is a difference between  
13 active drugs and excipients, which are inactive, and for  
14 topical products--and we face this in ophthalmology--that  
15 differentiation is impossible to make. There are really  
16 active preparations, not active and inactive components.

17 It would have been better if the law had been  
18 passed that would say that for topical medications, the  
19 manufacturer had to list every ingredient in every  
20 concentration in its entirety, and that it could be  
21 reproduced by both drug company under the same--every batch  
22 had to be the same, and the generic manufacturer could then  
23 go and make the same preparation using exactly the same  
24 criteria. It would make a label probably two pages long,  
25 but that I think would have been the ideal, and maybe

1 legislation can be encouraged in that direction.

2 DR. MCGUIRE: I am not going to summarize the  
3 morning. I would like to make--these are not chairmanly  
4 comments, they are my personal comments--I would encourage  
5 all of you to read the paper from CIRD Galderma that was in  
6 the June 1997 JAAD, which really goes to the heart of what  
7 you were saying, Joel, which is that the change in particle  
8 size in adapalene has a profound effect on the target and  
9 the penetration and the speed of penetration of the drug, so  
10 if there is to be bioequivalence, the preparation has to  
11 slavishly follow the proprietary.

12 The other point I will not make again, I have made  
13 it twice today, and that is that for certain classes of  
14 cutaneous drugs or dermatologic drugs, the stratum corneum  
15 is simply a nuisance; for other classes of drugs, you really  
16 want to concentrate material in stratum corneum, and the  
17 stratum corneum can't be thought of in the same way for all  
18 these different classes of drugs.

19 I feel a little apologetic to the Agency that we  
20 haven't been able to the questions head-on, but I think you  
21 have gotten maybe more than you wanted in terms of our  
22 concerns about the technique and our reluctance to abandon  
23 other techniques that are quite noisy and quite labor-  
24 intensive, quite expensive, but I don't think we are ready  
25 to relinquish those yet.

1           It is 10 after 1:00. We will reconvene at 1:45  
2 for a closed session.

3           [Whereupon, at 1:10 p.m., the luncheon recess was  
4 taken, to reconvene, in closed session, at 1:45 p.m.]

5                                 - - -

*CERTIFICATE*

I, Richard Colwell the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.



*Richard Colwell*

Richard Colwell

<p><b>\$</b></p> <hr/> <p><b>\$64,000</b> 49:18</p> <hr/> <p><b>0</b></p> <hr/> <p>0.025 81:13 0.05 81:13, 18 0.1 33:3; 46:2, 6; 81:13, 18; 128:4 0.15 46:2 0.2 46:3 0.25 56:25; 128:4 0.3 46:6 0.5 82:17; 128:4</p> <hr/> <p><b>1</b></p> <hr/> <p>1 22:5; 39:13; 40:5; 54:5; 65:13; 67:2, 3; 68:2; 82:17; 118:14 1.0 46:6; 128:4 1.13 82:20 1.41 82:19 1.69 82:20 1/h 51:4 10 4:15; 6:8; 22:9, 24; 49:4; 63:25; 91:22; 105:19, 21; 107:19; 108:21; 109:1; 117:9 10-year 101:24 100 10:10; 39:17, 20; 71:12 10:35 59:13 11 105:24; 106:13 12 29:3; 56:25; 108:21 12:00 92:10 12A-30 5:11 14 29:3 15 22:4; 95:5; 105:25; 106:13; 109:1 16 65:25; 66:3, 12 17 95:5 18 5:6 19-year-old 104:19 1944-who 111:20 1977 9:4 1992 28:23 1996 19:25 1997 28:24; 151:6</p> <hr/> <p><b>2</b></p> <hr/> <p>2 22:5; 39:13; 67:3; 68:2; 81:19; 92:20; 106:23; 147:23 2.24 81:18 20 75:7; 82:19; 92:10; 113:12; 128:3 208(b) 5:6</p>	<p>22 63:19 24 22:9; 64:19; 65:12; 66:12; 68:1; 70:22; 105:24; 106:9, 19; 109:4, 9; 116:10; 134:1, 13; 136:16 25 81:20; 103:17 250 88:23 250-plus 20:1</p> <hr/> <p><b>3</b></p> <hr/> <p>3 39:13; 54:5; 113:12; 142:21, 22 3-dimensional 56:13 3-fold 65:14; 68:24; 77:13; 105:5 3.0 46:6 30 113:14 35 66:7; 103:17</p> <hr/> <p><b>4</b></p> <hr/> <p>4 22:5, 9; 106:10; 107:19 4,800 58:3 40 66:8 400 33:6 49th 4:6</p> <hr/> <p><b>5</b></p> <hr/> <p>5 43:21 50 66:8; 98:4</p> <hr/> <p><b>6</b></p> <hr/> <p>6 22:9; 65:13; 109:4; 113:1 6,400 58:3 6-year-old 104:18 60 71:18</p> <hr/> <p><b>7</b></p> <hr/> <p>7 69:7 75 10:11; 51:23</p> <hr/> <p><b>8</b></p> <hr/> <p>8 22:9; 105:19, 21; 107:19 86 62:1</p> <hr/> <p><b>A</b></p> <hr/> <p>A&amp;P 94:14, 18, 25 a-Louise 105:10 A2/60 51:7 abandon 151:22 abbreviated 14:23, 24</p>	<p>ability 64:12; 71:25; 111:21 able 24:9; 35:2, 4; 63:20; 69:11; 74:5; 75:9; 82:24; 96:15; 106:4; 124:3, 6; 125:13, 14; 126:15; 130:23; 132:24; 139:12; 148:12, 20; 151:20 abnormality 100:8 absence 40:23; 41:7; 42:24 absent 40:21 absolute 51:13; 52:24; 53:5; 55:20; 56:24; 70:21; 85:25; 86:14, 16; 87:8; 112:19 absolutely 99:14; 110:13 absorbed 31:23; 69:23; 87:21; 106:22, 24; 131:24 absorption 11:1, 6; 13:17; 21:12; 51:18; 71:21; 72:4, 10; 98:17, 19; 106:23; 118:21 accelerate 39:25 accept 103:15; 133:1; 138:5; 139:8, 12, 13 acceptable 91:13 accepted 63:3; 74:15, 16; 138:6 access 8:22 accomplish 50:9 accordance 5:6 account 87:8, 11; 98:19 accounting 40:9 accumulation 111:11 accuracy 26:9 accurate 71:24 acetyl 56:8 acetylsalicylic 40:3 achieve--the 79:14 achieved 86:20 acid 40:3, 4, 4; 56:8, 9; 100:2; 106:22 acknowledge 27:16; 29:6; 95:24 acne 94:3 acquired 87:24 across 69:19; 85:2; 103:11 act 134:18 acting 16:8, 20; 17:20, 22; 149:20 action 31:24; 122:14, 16; 131:12 actions 144:18 active 6:22; 9:1, 2; 15:19, 19; 19:4; 27:1; 31:23; 49:6; 72:5; 78:22; 79:8, 15, 21; 83:25; 85:2; 115:10, 10, 13; 123:15; 124:9; 127:9; 150:13, 16, 16 actively 16:7; 30:5; 72:24; 99:7 activity 23:11, 15; 34:17; 53:19, 20; 54:18</p>	<p>acts 108:23 actual 48:23; 57:10 actually 31:20; 47:14; 49:5; 56:13; 65:4; 66:5; 67:7; 76:2; 90:16; 96:10; 102:1, 14; 106:25; 115:8, 16; 117:23; 118:1, 17; 124:21; 128:19; 131:19; 139:9; 145:3; 149:17 acyclovirs 25:25 adapalene 33:3; 142:17; 151:8 add 50:3; 57:17; 131:2; 142:13; 145:6 added 83:22; 144:1 addition 58:16; 80:10; 119:12, 16; 143:3 additional 80:1; 124:9; 142:8 address 5:19; 13:5; 37:2, 21; 91:1; 114:17; 116:13; 119:2, 25; 123:9; 127:20; 135:17; 142:4; 144:21; 147:16, 23 addressed 28:6; 147:24 addresses 4:22 addressing 36:21 adequately 76:11; 125:5, 7 adhere 6:9 adhesive 22:18; 63:10; 64:13; 65:7; 96:7, 9; 104:2; 135:8; 136:1, 17 adhesives 103:21 adjacent 68:9, 13; 117:18 adjoining 116:12 adjustments 54:17 administered 17:19 administration 21:10, 12, 15 administrator 130:23 admirable 96:1 admire 133:12 adopted 89:6, 7 advance 74:24, 24 adversaries 48:14 advice 78:9; 92:5 adviser 12:14 advisers 12:13 Advisory 4:7, 18; 28:22, 23; 62:4; 89:24; 92:1; 121:24; 136:23; 147:4 advocate 99:22; 121:6 advocating 89:13 affect 64:12; 96:11; 97:14 affecting 117:18 affects 11:12; 96:10 afford 149:19 afternoon 92:6, 8; 119:11; 124:19; 135:21, 23 afterward 72:16 again 22:4; 23:24; 24:23; 25:9, 13; 27:10; 35:10, 23;</p>	<p>39:20; 40:2; 41:19; 42:7, 23; 43:2, 6, 8; 44:5; 45:12; 46:21; 59:15; 74:22; 75:23; 77:17; 78:18; 81:19; 82:7; 83:3, 5, 23; 86:5; 94:5; 99:18; 102:10; 108:21; 112:16, 16, 16; 113:21; 123:3; 125:12; 128:13; 137:8, 11; 141:9; 142:5; 151:12 against 120:16; 139:23; 146:4, 12 age 97:6, 7, 18; 101:2, 24; 102:3, 14, 20; 104:6, 11, 23 age--l 96:16 aged 101:18 Agency 7:11; 8:1, 12; 9:3; 12:1; 92:20; 93:2; 121:24; 122:2, 17; 125:3; 128:11; 136:25; 137:8; 138:15; 143:20; 144:2; 151:19 Agency's 137:24 agenda 4:25; 5:13 agents 25:20 aging 97:15; 103:1; 138:9 agmethoxlyn 142:17 ago 51:23; 95:5; 126:3 agree 73:15; 76:21; 124:22; 129:5; 132:20; 139:18; 149:7 agreed 90:6 ahead 92:11; 108:7; 135:24; 145:15 air-conditioned 134:3 Albuquerque 34:8 albuterol 137:22 alcohol 56:8, 9 alkali 47:18 all-follicular 94:4 allay 47:20 allow 14:20; 15:25; 16:11; 77:18; 86:3 allowed 64:10; 65:23; 97:25 allowing 85:25 allows 7:13; 16:13; 20:24; 21:20, 24; 51:9; 58:16 alluded 16:3; 62:11; 70:5 allusion 33:25 almost 21:19; 25:19; 48:24; 69:1; 70:24; 82:22; 112:12, 12; 13:18 alone 94:6; 143:17 along 28:9, 10; 102:24 alpha 48:3, 7 already 5:13; 12:18; 14:21; 15:1, 23; 16:3; 39:20, 25; 62:11; 70:5; 90:6; 113:2; 138:6 alternative 31:1; 74:6, 6; 89:2 alternatives 49:9, 11 Although 133:20; 143:11</p>
--	---	--	--	--

aluminum 45:17  
always 20:14; 24:8;  
3; 41:23; 64:9; 91:18;  
100:1; 110:4, 5, 9; 112:20,  
22; 113:7, 9, 17; 123:16;  
137:18, 25; 138:18  
among 114:18  
Amongst 93:9; 99:6  
amount 19:4; 20:21;  
22:22; 23:2; 50:17, 20;  
57:11, 17; 62:25; 64:18,  
24; 65:2, 11, 14; 66:18;  
67:9, 14; 68:17; 69:12, 16;  
70:12, 19; 71:6, 19; 78:22;  
85:22; 87:21, 24; 97:8;  
104:22; 105:25; 108:16,  
23; 109:8; 111:4, 5, 11;  
125:2, 21; 134:9, 20;  
135:4; 148:21  
amounts 54:4; 64:9;  
68:1, 22; 70:10, 15;  
104:17; 106:9, 10, 11, 24;  
134:20; 136:11  
amphelin 142:16  
amplify 17:14  
analogous 132:2, 16  
analogy 35:23; 52:9;  
69:5; 131:23; 132:3  
analyses 70:6  
analysis 12:16; 22:25;  
2; 39:16; 47:8; 69:9,  
10; 70:25; 71:10; 77:4;  
109:14; 146:12  
analytic 121:25  
analytical 26:8; 64:9;  
71:23; 76:18, 20, 20;  
106:16; 115:22; 116:3;  
126:1, 4; 147:10; 148:19  
analyze 69:8, 16; 70:11;  
128:8  
angle 64:4  
angstrom 49:4  
animal 39:15; 43:16; 93:9  
animals 39:13; 43:11;  
93:10; 98:5  
announcement 4:22  
answer-I 139:17  
answered 36:4; 100:17,  
21  
answering 52:21; 53:10,  
11; 110:15; 111:9; 129:13  
anti-intellectual 91:18  
antiacne 25:23  
antibacterial 18:20  
antibacterials 123:20;  
128:21; 149:11  
antibiotics 26:1  
anticipated 135:9  
anticipates 91:15  
antifungal 18:19; 25:19;  
118:19; 131:12; 144:19  
antifungals 25:21;  
118:18; 119:1; 122:15;  
123:20; 140:6; 149:11  
antiviral 18:19; 25:25

anybody 97:18  
anyone 59:11; 64:6;  
116:12; 119:1; 136:8;  
147:24  
anyway 42:9; 71:4  
anywhere 130:11  
apologetic 151:19  
apologies 91:11  
apologize 6:15; 15:12  
apparent 64:20  
appearance 4:24  
appears 13:7; 47:12;  
62:7  
appendages 33:16;  
62:13  
applicability 36:17  
applicable 19:14, 18  
applicants 7:12; 8:1  
application 14:23; 15:3,  
16; 20:22; 21:20, 24; 30:7;  
33:5; 44:9; 54:11; 62:23;  
63:22; 64:1; 106:24;  
107:5; 113:15  
applications 54:14  
applied 22:12; 24:15;  
40:24; 43:23; 53:14, 22;  
54:4; 83:9; 136:9  
apply 11:19; 22:5, 18, 24;  
50:4; 51:16; 63:14, 23;  
76:25; 113:11, 12, 14, 18;  
117:5  
appreciate 64:7; 93:1;  
97:4; 124:17; 129:11  
appreciated 93:7  
appreciates 137:6  
approach 9:22, 23;  
12:15; 14:4; 18:1, 3, 6, 11;  
19:13, 14, 16, 17, 23, 24;  
20:15; 21:13; 36:3, 3;  
50:20; 138:5  
approaches 17:2, 3, 20;  
18:9, 22  
appropriate 63:12;  
70:14; 96:1; 126:8; 131:14  
approval 6:21, 24; 9:7, 8;  
11:16; 58:20; 79:10  
approve 80:9  
approved 6:25; 19:3;  
78:21; 79:4; 80:8, 12;  
141:11; 149:20  
approximately 103:17  
APS 88:20  
APS-FDA 92:3  
aptly 110:2  
architecture 93:20  
area 13:21; 17:11; 22:13;  
23:2; 29:7, 9; 34:3; 47:20;  
48:24; 67:13, 15; 71:3, 3;  
103:11; 123:19; 130:7;  
137:12  
areas 103:2, 25  
areas--and 67:10  
argue 6:22; 10:7, 9;  
11:25; 12:17, 22; 13:1;  
16:21; 124:4; 125:2;

138:15  
argument 142:2  
arises 9:11; 11:20; 16:24  
arithmetic 46:2  
arm 26:18; 68:2, 9, 12, 15;  
69:2; 115:12  
armamentarium 145:25  
armed 115:9  
arms 120:23  
around 4:17; 20:1; 53:5;  
59:20, 23; 83:1; 94:13;  
100:15; 128:13; 130:21  
artfully 91:8  
articulated 133:19  
as--and 118:16  
ascribe 34:8  
aside 98:12; 150:11  
aspect 8:7; 77:2; 78:8;  
141:5  
aspects 28:17; 78:7;  
141:4  
assay 57:7; 62:21; 80:7;  
106:16; 115:21; 125:3, 5;  
127:13; 137:8, 19; 141:1  
assays 47:1; 140:23  
assembled 91:10  
assess 33:1; 125:15;  
144:22; 147:8; 148:20  
assessed 116:5; 142:22  
assesses 20:11  
assessing 21:1; 148:24  
assessment 37:8; 49:7;  
103:6; 115:23; 125:12  
assimilate 49:25  
association 114:1  
assume 114:4; 121:8  
assumed 88:16; 96:18  
assumption 110:10;  
119:22; 138:7; 148:10  
assumptions 12:11, 25;  
13:3; 146:13  
assumptions-I 79:12  
assurance 57:20;  
126:25; 127:15  
assure 7:11; 73:3; 75:21;  
77:9; 124:25; 125:4; 137:9  
asymptote 87:5  
atopic 34:23  
attached 94:20  
attainable 55:5  
attempts 54:10  
attended 20:1  
attention 12:7; 32:20;  
46:21; 47:2  
attributed 65:5  
attributes 12:7  
AUC 142:7  
audience 12:9  
audio 59:16  
Auraham 72:17  
available 31:24; 84:23;  
101:10; 115:13  
average 48:4

awaiting 89:13  
aware 5:15; 136:8  
away 74:16; 112:6;  
139:12  
axioms 30:24  
axis 10:14; 51:8; 64:18

---

**B**

---

B 82:22, 25; 149:24  
BA/BE 18:9  
back 8:9; 31:4; 67:8, 16;  
72:2; 91:14; 100:6; 113:8;  
125:10, 23; 127:3; 130:8;  
131:22; 133:11; 137:14;  
138:2; 141:9; 147:18  
background 20:18;  
56:20  
backing 65:7; 96:7, 9;  
136:1  
backings 134:16  
baklava 32:13  
balance 39:15, 21; 40:10;  
64:10; 77:8; 148:2  
balanced 89:11  
Baltimore 60:11  
band-aid 64:6  
bar 67:25  
barrier 55:2; 63:2, 4;  
66:16; 83:15, 15, 16;  
111:18; 112:7, 9, 15, 19;  
122:13; 131:6, 11  
base 121:19  
Based 4:25; 10:5; 57:2;  
63:10; 71:2; 79:4, 10; 80:9,  
12; 90:22; 138:10; 145:5;  
149:20  
baseline 65:22, 22  
basic 103:3  
basically 70:6; 71:11  
basis 19:25; 105:2; 143:9  
batch 150:21  
batting 48:4  
bear 37:7; 94:5  
bears 59:4  
beautifully 51:11; 75:25;  
77:14  
became 100:20  
Beclevian 47:16  
become 64:20; 140:4, 5  
becomes 9:18; 11:5;  
12:16; 31:24; 46:10;  
57:16; 70:13; 132:7  
beforehand 89:10  
beg 135:24  
begin 121:2  
begins 87:23  
behalf 8:15  
behave 127:1  
behaves 45:9  
behaving 80:24  
behavior 99:13  
behind 59:10; 67:12

beings 107:18  
believe 14:5; 17:7; 30:3;  
32:9; 48:11; 55:25; 58:15,  
22; 72:2; 73:14; 74:5, 8;  
75:4; 76:3, 10; 149:4  
below 38:24; 108:22  
benefit 95:17  
benzoic 40:3, 4; 100:2  
Berlin 116:18  
best 139:13  
beta 48:3  
betamethasone 24:23  
better 35:4; 74:25; 75:6;  
94:24; 95:1, 6, 10; 111:14;  
113:22; 114:12; 123:6;  
144:6; 150:17  
between--maybe--a  
104:18  
beyond 137:11  
bias 89:9; 90:2  
bid 95:13  
big 149:21  
Bill 60:25; 92:17, 23;  
95:18; 126:11  
bind 123:20  
bio-waiver 78:19; 148:9,  
15  
bio-waivers 19:1  
bioavailability 9:5;  
10:23, 24; 11:4; 12:4, 19;  
13:10, 24, 24; 16:1, 23;  
17:12; 18:13; 20:20;  
24:12; 31:18, 22; 75:2;  
114:2; 144:22  
bioavailability/bioeq-  
uivalence 12:6; 52:25  
Bioequivalence 4:4;  
11:5, 9, 22; 12:19; 13:11,  
25; 15:23; 16:1, 23; 17:12;  
18:13, 18; 20:7; 21:2;  
27:13, 20; 32:2; 34:11;  
35:23; 37:3, 9; 61:25; 69:6;  
71:13; 72:3, 7; 74:13, 14;  
76:3, 13; 78:4; 95:19;  
103:6; 105:7; 107:11;  
108:10; 112:18; 118:15;  
119:1; 120:3; 122:22, 24;  
123:12; 127:8, 11; 149:24;  
151:10  
bioequivalence--and  
12:5  
bioequivalency 19:8;  
20:15, 20; 24:12; 26:6;  
27:5, 7; 28:12; 48:24, 25;  
53:8; 55:22; 79:2; 83:20;  
84:6; 108:25; 115:1  
bioequivalent 19:3;  
21:5, 6; 31:12, 17; 77:19;  
78:21; 80:4, 8, 15; 86:1, 9;  
88:3; 126:20; 128:1  
bioinequivalence 142:1  
bioinequivalency 19:21  
biological 63:1  
Biopharmaceutics 7:7;  
8:6, 16; 16:17; 17:9, 12  
biophase 32:21; 85:2

biopsies 99:17, 19  
**biopsy** 67:21  
**biostatistician** 61:8  
**Biostatistics** 60:16  
**biostudies** 79:9  
**Birchen** 111:19, 112:1  
**bit** 14:18; 39:25; 59:9;  
 63:13; 66:6; 97:15; 114:8  
**blanching** 75:17, 19;  
 150:2  
**blanking** 80:6  
**blood** 16:24; 21:11;  
 35:20; 49:3; 69:7, 12, 14,  
 17; 107:10, 12; 114:5;  
 116:1; 130:8, 8  
**blotted** 70:3  
**Board** 147:4  
**body** 39:17, 22; 46:17;  
 132:8  
**Book** 16:13; 46:1, 14  
**boss** 94:23  
**both** 6:1, 8; 9:1; 10:2, 20;  
 11:12, 17, 19; 28:18;  
 46:15; 63:5; 64:3, 25; 80:2;  
 93:24; 101:4; 103:7, 21;  
 104:3, 14; 105:8; 113:17;  
 120:3; 126:19, 20; 127:1;  
 150:21  
**bother** 15:6  
**bottom** 16:19; 35:19;  
 50:11; 55:19; 91:18;  
 121:5, 7; 139:10  
**bought** 95:12  
**bound** 123:17  
**boundary** 50:8  
**boxes** 6:18; 7:2  
**boy** 85:6  
**Brand** 63:11, 11; 73:13;  
 74:8; 75:23; 84:16; 86:2;  
 88:12; 90:24; 94:16, 18,  
 19; 115:12; 147:9, 14;  
 148:25  
**branded** 73:24  
**brands** 22:19; 45:5  
**BRAZEAU** 60:14, 14;  
 115:19, 20; 117:11; 123:1,  
 2; 125:10, 19; 147:2, 3  
**break** 59:8, 8, 11; 135:22  
**bricks** 91:7  
**brief** 22:11; 25:17; 35:10;  
 78:2; 100:14  
**briefing** 30:7  
**bring** 49:20; 93:6;  
 118:11; 147:18  
**brings** 133:10  
**broadly** 143:12  
**brought** 32:19; 91:3;  
 93:13  
**build** 7:16; 49:16  
**Building** 5:11  
**built** 53:5  
**bulk** 6:24  
**bullet** 93:17  
**business** 50:23; 130:5;

133:16  
**buy** 104:12  
**bypass** 28:2

---

**C**

---

**C** 149:24  
**C0** 51:3  
**cadavers** 111:21  
**caffeine** 40:4; 100:3  
**calculate** 51:9; 115:16  
**calculated** 108:16  
**calculations** 81:16  
**California** 29:5; 61:7  
**Call** 4:2; 14:8; 26:5; 51:8;  
 102:10  
**called** 18:1, 12; 28:22, 23;  
 94:13  
**calls** 68:8  
**came** 20:5; 65:15; 88:24;  
 89:1; 95:5; 126:3, 17;  
 131:21; 137:23; 142:20  
**can** 7:19; 9:16; 12:7, 14;  
 13:8, 13; 14:23; 15:6, 13,  
 18, 24; 16:3, 10; 17:15, 24;  
 18:17, 23, 25; 19:7; 20:20;  
 23:9, 11; 24:23; 27:11;  
 28:8; 29:1; 30:11, 12, 14;  
 31:2, 20; 32:1; 33:15, 22;  
 34:3, 4, 11; 37:7, 24, 24;  
 39:24; 41:6; 42:9; 43:6, 21,  
 22; 44:3, 5, 12, 16, 19, 20;  
 45:3; 46:3, 6, 22; 47:6, 14,  
 24; 49:4; 52:9, 16; 54:9;  
 64:6, 12, 24; 67:2, 12, 15;  
 68:3; 69:13; 70:10; 71:17;  
 72:16; 76:17, 18, 19, 22;  
 77:4, 5, 8, 15, 19, 22;  
 78:14, 16, 18; 79:10; 80:8;  
 81:2, 20; 82:3, 5, 24;  
 83:10; 85:9, 20; 86:23;  
 87:1, 20, 22; 88:22; 90:17;  
 92:5; 94:23, 25; 95:16;  
 97:1; 99:15; 102:12;  
 105:1, 5; 108:21; 113:17;  
 114:24; 115:6, 25; 116:6,  
 12, 24; 117:4; 118:5, 14,  
 20; 119:17; 120:21; 121:2,  
 2, 8, 18; 122:16, 17, 23;  
 123:24; 125:21; 126:1, 2;  
 127:15, 20, 25; 128:8, 11;  
 129:8; 130:7; 131:14;  
 137:4, 8, 9, 9, 18, 19;  
 139:5; 140:11, 13, 23;  
 143:12; 145:11; 146:24;  
 148:6, 6, 12, 15; 149:18;  
 151:1  
**care** 13:19; 26:7; 64:8;  
 77:17, 19; 95:12; 128:2;  
 148:21  
**carefully** 113:4  
**Carry** 15:8, 9  
**case** 11:4, 11; 51:20;  
 58:1; 69:6, 8; 73:4; 74:4;  
 75:15; 87:4; 123:16;  
 131:23; 132:5; 149:4  
**cases** 46:15; 81:18;

113:1; 142:18, 20  
**categories** 129:10;  
 141:3, 12  
**category** 16:7  
**caution** 148:17  
**CDER/OPS** 5:23  
**cell** 32:15; 133:5  
**cells** 93:20, 21; 97:12;  
 131:9, 9, 10  
**cellulose** 134:17  
**Center** 5:25, 25; 6:13, 16,  
 20; 7:8, 16, 19, 23; 12:23;  
 59:24; 60:7, 21; 61:10  
**centimeter** 23:2  
**central** 17:21; 131:3  
**certain** 9:14; 22:12;  
 27:17; 40:25; 58:18;  
 120:4; 144:18, 18; 149:9;  
 151:13  
**certainly** 12:23; 14:11;  
 31:8; 48:19; 89:20; 96:1;  
 98:9; 99:24; 118:10;  
 140:10; 142:8; 146:7  
**Chair** 6:8; 8:16  
**Chairman** 107:16;  
 119:18; 121:1; 127:18  
**chairmanly** 151:3  
**challenge** 11:25; 16:24  
**challenging** 6:23; 10:7;  
 16:21  
**chance** 147:5, 6  
**change** 11:14, 16, 21;  
 19:3; 54:21; 56:21; 57:17;  
 66:4; 78:21; 85:10; 98:16;  
 120:4; 143:22; 151:7  
**changed** 47:6; 59:3  
**changes** 37:20, 22;  
 46:20; 52:5; 58:4, 4, 18;  
 134:2; 138:8, 12  
**changing** 54:19; 126:9  
**character** 96:24  
**characteristics** 10:9, 17;  
 83:23; 144:25  
**cheaper** 30:17, 25  
**check** 120:10  
**chef** 94:20, 24  
**chemical** 120:7  
**Chemistry** 7:5; 10:20  
**chemists** 29:20  
**child** 97:17  
**choice** 101:10  
**choose** 74:9, 10; 75:5;  
 137:18, 20, 25  
**chose** 136:5  
**chromometer** 75:20, 22,  
 22  
**circumstances** 10:2;  
 27:17, 19; 47:12; 50:6;  
 56:22; 101:3  
**CIRD** 122:6; 151:5  
**cite** 14:25  
**City** 94:12  
**clarification** 97:5;  
 107:16, 25; 120:13;

122:20  
**clarify** 96:23; 104:13;  
 108:1; 114:13  
**class** 19:14; 124:12;  
 125:24; 128:20; 149:19,  
 21  
**classes** 18:22; 123:24;  
 128:12; 142:6; 151:13, 15,  
 18  
**classic** 70:24; 111:19  
**classical** 23:23  
**clean** 22:12, 15  
**cleanest** 118:19  
**clear** 41:19; 57:2; 105:18;  
 112:2; 120:11; 131:1;  
 133:15; 139:4, 15; 149:16  
**clear-cut** 41:19, 22;  
 42:24; 43:2; 45:17; 100:8;  
 113:18; 116:25  
**clearly** 39:6; 40:16;  
 41:12; 42:5, 8, 10; 43:6;  
 44:11, 20; 45:21, 22, 23,  
 24; 46:3; 58:5, 13; 66:13;  
 83:25; 101:13; 110:23;  
 116:19; 133:19; 143:12  
**clinic** 54:5; 126:17  
**Clinical** 4:5; 7:7; 10:4;  
 16:5; 17:4; 19:9, 10; 23:11,  
 16; 30:19; 46:5; 47:1, 11,  
 15; 53:13; 54:3, 13, 24;  
 55:13; 75:3, 9; 80:6, 12;  
 88:3; 93:7, 13; 115:1;  
 120:2, 23; 121:3, 11, 25;  
 126:14, 15, 21; 127:3, 11;  
 129:9; 130:20, 24; 132:22;  
 138:9, 17; 140:10, 12;  
 141:10, 25; 142:15, 20;  
 143:4, 14, 25; 145:10, 20,  
 24, 25; 146:17, 19; 149:13  
**clinically** 46:10; 59:1;  
 120:15; 126:20; 127:1;  
 129:21; 144:4  
**clinicals** 126:23  
**clinician** 26:12, 12;  
 147:17  
**close** 40:5; 59:5; 91:17;  
 130:12  
**closed** 92:7; 135:23  
**clue** 119:20  
**Cmax** 71:18  
**coarser** 58:11  
**coat** 93:10, 11  
**coated** 45:8, 16, 17  
**coating** 45:6, 8  
**Code** 5:6  
**coefficient** 51:2, 2, 10;  
 52:8; 85:8, 9, 13, 13;  
 86:22, 23, 25; 87:1, 9, 11  
**coefficients** 51:14, 14  
**cognizant** 93:8  
**coherence** 146:17  
**cohesive** 65:5; 136:16  
**collapse** 50:21  
**collect** 69:7; 70:10  
**collection** 93:19; 103:8

**collective** 110:21  
**collectively** 47:24; 88:25  
**College** 60:13, 15, 17;  
 61:1; 94:12  
**colored--this** 7:21  
**combined** 30:13  
**comfortable** 130:22;  
 144:24  
**coming** 6:12; 84:22;  
 99:22; 137:14  
**comment** 5:21; 73:1;  
 75:5; 96:13; 97:24, 25;  
 104:6; 111:16; 113:25;  
 120:25; 121:1; 124:14;  
 131:18, 20, 20; 132:19  
**comments** 29:9; 78:5;  
 84:12; 92:16, 25; 95:22;  
 97:24; 122:16; 124:23;  
 125:9; 151:4  
**comments--I** 151:4  
**commission** 144:2  
**Committee** 4:7, 18; 5:1,  
 3; 6:11; 8:2, 6, 16, 17, 18;  
 13:7; 14:10; 15:6, 13;  
 16:17; 17:10; 18:7, 16;  
 28:22, 23; 59:8, 19; 60:19;  
 62:4; 73:7, 16; 78:9; 84:13;  
 89:25; 92:1, 12, 15;  
 114:22; 121:24; 124:19;  
 125:5, 9; 128:17, 20;  
 132:17; 136:23, 137:1, 6;  
 138:19; 139:8; 141:20, 21;  
 145:14; 146:3, 8, 15  
**committee--and** 73:5  
**committees** 6:2; 7:18,  
 24; 8:11; 13:2; 16:19;  
 17:21  
**commonly** 63:18  
**community** 144:12  
**companies** 30:18;  
 132:22; 139:20  
**company** 73:18, 22, 24;  
 75:23; 94:13, 14; 129:19;  
 150:21  
**comparability** 10:1; 17:5  
**comparable** 13:20; 21:3,  
 7; 31:17; 101:8; 137:15  
**comparative** 11:5; 17:4;  
 19:10; 120:2; 130:24  
**compare** 21:10; 41:6;  
 75:13; 83:12; 99:13;  
 114:20  
**compared** 39:13; 42:17;  
 43:16; 67:21; 75:1, 2; 79:7;  
 95:14  
**comparing** 11:6; 13:23;  
 90:23; 108:12  
**comparison** 23:5; 68:16;  
 83:4; 112:22; 115:13;  
 120:15; 128:1; 137:20;  
 146:19  
**comparisons** 16:5, 6;  
 101:16, 18; 108:13;  
 130:20; 141:13, 16  
**compartment** 46:15, 16  
**compartments** 41:9

**compelling** 91:4; 96:6  
**compete** 94:15  
**competing** 111:5  
**competition** 9:11; 89:8; 130:4, 6  
**competitor** 98:7  
**complete** 31:5; 39:16; 83:22  
**completely** 23:20; 44:25; 82:25; 83:16; 112:12; 113:11; 130:21  
**complex** 35:22; 50:5, 10, 16; 51:15; 56:17; 62:12  
**complicated** 11:23; 15:18; 17:1  
**components** 54:15; 123:17; 150:16  
**composition** 79:4, 6, 10  
**compositional** 54:17  
**compound** 37:4; 38:2, 4; 41:8; 46:22; 96:11, 25; 98:9; 112:23; 113:2, 11, 14  
**compounds** 39:11, 11; 40:3; 41:15; 45:13; 98:4; 122:4  
**comprehend** 85:5  
**conceivable** 55:5; 136:24  
**concentrate** 151:16  
**centration** 13:22, 22; 11; 22:2; 23:13; 24:17; 25:11; 33:12; 38:3; 50:11; 51:3; 52:7; 56:21; 57:3, 5; 69:11, 21; 70:16; 79:15; 82:17; 85:7, 12; 86:19; 87:6, 15, 21; 88:2, 7; 108:2; 109:16, 20, 24; 111:8; 113:3, 4, 5; 123:15, 22; 124:1, 10; 133:4; 142:15, 19, 19, 21; 147:22; 150:20  
**concentration--that** 87:15  
**concentration-response** 123:25; 124:5, 11; 147:21  
**concentration/time** 21:7; 26:23; 137:13  
**concentrations** 21:4; 22:6; 23:20; 24:11, 15, 16; 39:12; 41:24; 42:16, 19; 46:4; 62:9; 69:14; 70:13; 78:4; 81:1, 6, 12, 21, 25; 82:3, 8, 18; 85:15; 87:2, 3, 4, 22, 22; 106:4; 113:6; 128:9  
**concept** 8:18, 22; 9:24; 10:6, 7, 15, 19; 14:22; 106:2  
**concepts** 11:18  
**conceptual** 150:10  
**conceptually** 62:8  
**concern** 32:11; 91:6; 96:9; 116:8; 117:16; 127:8; 130:14; 131:3; 147:16; 149:12, 16

**concern--and** 97:15  
**concerned** 47:23; 48:6; 59:2; 80:11; 139:12; 141:24  
**concerns** 32:4, 10; 35:1; 47:17, 20; 84:14; 125:8; 147:13; 151:22  
**concludes** 18:5  
**conclusion** 27:7; 29:19; 33:16, 19; 48:5; 99:12; 119:22; 134:15; 135:7; 145:4  
**conclusions** 30:23; 68:21; 80:5; 99:20  
**concurrence** 59:7  
**concurrently** 21:25  
**condition** 133:25  
**conditions** 31:18; 37:5; 38:9, 12, 21; 39:10; 40:7; 50:8, 8; 54:22; 63:8; 98:4; 103:7, 23; 105:9  
**conducted** 63:16; 66:22; 136:8  
**confidence** 14:8; 47:24; 49:16; 69:13  
**confident** 146:11  
**confirm** 66:11  
**Conflict** 4:12, 20, 22; 89:5  
**conflicting** 145:18  
**conformability** 146:16  
**confused** 107:22, 24  
**confusion** 52:22; 145:17  
**Congress** 130:4; 143:21  
**congruent** 88:12  
**connection** 34:11  
**consensus** 62:2; 72:25; 73:16; 76:14; 135:21; 136:25  
**consider** 78:9; 114:7  
**consideration** 27:20, 23  
**considerations** 78:3  
**considered** 17:20; 51:21; 118:11  
**consistent** 64:11; 65:2; 71:13, 14; 86:11; 103:11; 105:2, 4; 116:5; 126:9  
**consistently** 140:11  
**constant** 63:23, 24; 71:3; 99:11; 103:22; 112:12, 12; 125:2; 132:8; 134:1; 136:3, 5  
**constraints** 25:17; 35:6  
**construction** 90:19  
**consultant** 29:5; 100:20  
**consultants** 5:7  
**consumer** 10:18; 74:6, 9; 121:6  
**contact** 30:13, 13; 69:23  
**container--and** 87:16  
**contains** 53:15, 24  
**contemplated** 126:17  
**content** 64:12  
**context** 13:15; 107:2

**continue** 15:11; 92:6; 95:17, 20; 96:2; 135:20  
**continuing** 14:13  
**continuous** 110:9  
**continuously** 54:19  
**contract** 25:1  
**contradictory** 136:19  
**contrary** 104:7  
**contrasting** 114:11  
**contribution** 33:17  
**contributions** 29:7; 112:11  
**control** 49:14; 54:6; 57:6; 58:17, 22; 101:9, 21; 115:25; 136:9; 146:6  
**controlled** 63:17, 22; 90:25; 104:1; 127:13; 134:4; 146:5  
**controlling** 87:1  
**controls** 10:20; 126:8  
**convenience** 64:21  
**Convention** 66:7  
**converted** 56:9  
**convincing** 130:20  
**coordinating** 7:18, 24; 8:2, 6, 10, 16; 16:17; 17:9  
**coping** 15:5  
**copy** 5:9; 20:3  
**corneum** 20:12; 21:14; 22:23; 23:13, 21; 24:16; 25:3, 4; 32:13, 15; 34:4, 10, 12; 35:6, 12, 14, 16, 19; 37:12, 16; 43:9; 53:17; 54:25; 62:22; 63:4; 64:19; 65:11, 21; 66:2, 6, 9, 12; 68:1, 22; 69:4; 70:1, 8, 9, 22; 75:16; 76:9, 10; 83:16; 84:24; 85:2, 22; 86:21; 87:12; 93:11, 15, 19; 97:10; 104:17; 106:3; 108:22; 109:9, 17, 23, 25; 110:25; 111:23; 117:22, 24; 118:1, 2, 22; 122:12; 131:4, 5; 132:14; 134:10; 135:12; 137:13; 143:8; 145:1; 151:14, 16, 17  
**corneum--is** 22:4  
**corneum--time** 21:5  
**corneum-like** 87:10  
**correctness** 93:4  
**correlation** 39:21; 66:17, 19; 116:15; 117:1; 140:10, 12, 16; 141:7; 150:3, 4  
**correlations** 140:21  
**corticosteroid** 77:21  
**corticosteroids** 75:13; 88:4; 93:14; 140:7, 15  
**cost** 130:24  
**costly** 129:22  
**couldn't** 85:5; 94:19  
**count** 78:14; 133:15  
**counter** 135:11  
**country** 28:18; 85:6  
**counts** 133:14  
**couple** 32:4; 47:9; 56:3;

84:11; 88:18; 96:13  
**course** 6:23; 8:4; 11:19; 13:19; 14:1; 31:3; 54:17; 57:20; 65:19; 85:18; 92:21; 93:9; 94:4, 25; 98:3; 99:9; 105:16; 113:21; 114:17; 115:12; 116:20; 141:20  
**covering** 54:25  
**cream** 56:7, 14  
**create** 41:4; 52:22  
**creative** 139:7  
**crevices** 69:24  
**criteria** 74:21; 102:23; 150:24  
**criterion** 144:21  
**critical** 10:19; 12:17; 13:10; 36:14; 42:3; 96:4; 122:8; 124:23  
**cross-cutting** 7:17  
**crystals** 56:16  
**Cuderm** 63:19; 67:1; 103:22  
**Cuderm's** 22:20  
**cumulation** 111:4  
**cumulative** 65:11, 15; 67:25; 105:19; 106:10; 108:20; 111:14; 136:11  
**current** 5:19; 30:25; 31:2, 8; 114:20; 127:7; 141:25  
**currently** 90:8; 114:11, 13, 14; 144:11  
**curve** 13:22; 34:4, 15; 51:22; 55:9; 137:13  
**curves** 21:5, 7; 34:1; 40:15; 88:13; 109:4  
**curvilinear** 87:16; 88:11  
**cut** 63:20  
**cutaneous** 151:14  
**cytokines** 118:6

**D**

**D** 51:2  
**D-Squame** 63:19; 64:23; 65:3, 15; 66:14  
**damage** 97:8; 101:7, 23; 103:10  
**data** 10:5; 25:3, 7, 10, 12, 18, 20, 23, 24; 28:9; 31:4; 39:19; 40:2; 47:25; 48:22; 56:3; 61:24; 64:22, 23; 65:10; 67:24; 68:20; 71:1, 2, 16, 23, 25; 76:23; 77:3; 79:20; 81:11, 14, 17; 82:1, 6; 87:18, 19; 89:25; 92:2; 93:5; 96:6; 101:25; 103:8; 104:4; 107:2, 3, 4, 17, 17; 108:1, 3, 9, 14, 17, 19, 20; 109:10, 12; 121:19; 125:18; 126:21; 127:4; 128:8; 132:25; 133:11, 13; 135:7, 15; 136:13; 138:9; 147:6; 150:3, 3  
**data--and** 109:7  
**data--when** 56:21  
**day** 44:24; 77:13, 14; 100:11; 104:3; 105:9; 122:18  
**day-to-day** 105:2  
**days** 39:16; 74:12; 117:22, 24; 118:6  
**deal** 8:17; 12:23; 56:9; 70:6, 14; 77:1; 78:3; 92:21; 96:17; 97:9; 102:11, 12; 114:21, 23  
**dealing** 22:14; 38:2; 51:15, 21; 56:23; 95:8  
**deals** 12:23; 17:17  
**dealt** 73:8  
**debate** 6:12; 137:21, 23  
**December** 28:24; 147:4  
**decision** 15:21; 138:16  
**declare** 16:11  
**decrease** 143:15  
**decreased** 111:5  
**deep** 41:8  
**deeper** 42:19; 66:6; 70:8; 109:25  
**deepest** 106:13  
**defects** 102:25  
**defer** 36:8; 79:15  
**define** 77:7  
**definite** 139:17  
**definitely** 76:15; 127:12  
**definitively** 76:12  
**degree** 95:16; 136:9; 138:13  
**degrees** 138:7  
**delay** 15:12  
**deliberately** 54:21; 55:4  
**deliver** 131:14  
**delivered** 33:15; 46:16; 95:11  
**delivery** 51:17; 52:20; 54:17; 55:15, 17; 95:7; 130:14  
**demands** 91:19  
**demonstrate** 71:14; 114:15; 116:6; 122:23  
**demonstrated** 35:24; 39:6; 122:21  
**demonstrating** 127:8, 9  
**density** 102:25  
**Dental** 29:10, 13; 60:3  
**Department** 60:14, 23; 61:2; 102:19  
**Departments** 60:6, 10, 20  
**departure** 54:23  
**depend** 93:10  
**dependency** 52:1, 5; 55:10, 17; 57:10  
**dependent** 26:24; 62:15; 147:19  
**depending** 42:17; 48:4; 54:8; 66:13; 67:14; 70:19  
**depends** 51:1; 91:10;

93:11; 112:25; 132:3  
**depicted** 21:9; 40:17  
**depicts** 42:10  
**deposition** 52:10  
**depression** 100:9  
**depth** 33:6; 42:18, 18;  
 50:12  
**depths** 32:16  
**Deputy** 5:25  
**dermal** 37:8; 74:4; 75:11;  
 110:5  
**dermatitis** 34:23  
**Dermatologic** 4:6; 6:4;  
 15:21; 17:23; 29:10, 13;  
 30:18; 60:2; 89:24; 151:14  
**Dermatological** 4:4;  
 18:19; 19:8, 19; 20:8;  
 27:13, 21; 79:9; 83:21;  
 84:6; 99:8; 115:2; 118:16  
**dermatologicals** 49:1;  
 95:8  
**Dermatologist** 61:9;  
 85:6  
**dermatologists** 149:15  
**Dermatology** 60:10, 20,  
 23, 25; 61:3, 12; 102:19;  
 142:5  
**dermatopharmacok-**  
**inetic** 14:3; 18:17, 22;  
 19:17, 24; 20:10, 14; 21:1;  
 23:8, 15; 24:19; 25:14;  
 27:12; 28:9, 16, 20; 78:7;  
 80:7; 118:14; 126:24;  
 141:5  
**dermatopharmacok-**  
**inetics** 17:3; 18:2, 9, 12;  
 28:5; 31:7; 32:1, 23; 35:11;  
 37:15; 61:25; 72:23; 77:6;  
 86:11; 90:20; 99:24  
**dermatophytes** 35:20  
**dermis** 35:21; 110:3, 12;  
 113:6  
**describe** 18:6; 20:9;  
 22:11; 34:4  
**described** 32:2; 120:22  
**describes** 50:11  
**describing** 18:15; 26:4  
**description** 32:7  
**design** 12:16; 125:15;  
 148:19  
**designed** 7:25; 98:10;  
 107:5; 116:4  
**desired** 86:6; 94:6;  
 143:23  
**desk** 44:25  
**despite** 97:2  
**detail** 42:9; 114:18  
**detailed** 24:2  
**details** 40:18; 41:18;  
 112:15  
**detect** 24:10; 44:3; 75:7  
**detected** 45:21, 22, 23;  
 46:9; 84:17  
**detection** 38:25  
**determination** 18:18;

27:13, 21; 28:11; 76:3;  
 108:25; 118:15  
**determinations** 20:16;  
 115:2  
**determine** 19:7; 66:21;  
 70:12; 76:12; 80:18, 20;  
 85:23; 102:2  
**determined** 5:2; 9:9;  
 20:21; 27:2, 6; 37:17; 80:4,  
 15  
**determining** 119:1  
**Detroit** 60:24  
**developed** 94:14  
**developing** 73:20  
**development** 13:8;  
 61:16; 148:17  
**devoid** 41:5  
**devolve** 14:16  
**devoted** 94:18  
**diameter** 43:21  
**differed** 134:14  
**difference** 23:9; 35:8;  
 37:24, 25; 40:23; 41:2;  
 43:3, 12; 44:8, 11; 45:7,  
 18, 20; 54:12; 58:1, 25;  
 64:5; 65:21; 67:3, 4, 5;  
 68:4, 5; 75:8; 79:16, 25;  
 84:16; 101:24; 103:12;  
 104:6, 9, 11, 21, 22; 105:5;  
 121:14, 14; 127:2; 130:1,  
 19; 142:20; 147:20;  
 149:21; 150:12  
**difference--sorry** 44:7  
**differences** 19:12;  
 24:10, 11; 37:9; 40:16;  
 41:20, 22; 42:4, 10, 24;  
 43:7, 14; 44:3; 45:22, 23,  
 23; 46:2, 6; 55:17; 57:21;  
 68:17; 97:2; 101:2; 102:2,  
 24; 126:24; 127:11; 134:9;  
 136:7, 11; 147:8; 148:7  
**different** 12:21; 19:7;  
 22:7; 23:7, 14, 15, 18, 19,  
 20; 24:15; 27:22; 30:12;  
 35:21; 36:19; 37:10;  
 39:11, 11, 12, 12; 40:3;  
 43:16; 44:20; 45:1, 5, 6, 7,  
 8, 9, 15, 15, 21; 48:8; 53:4;  
 55:20; 56:1, 16; 57:18;  
 59:2; 67:18; 69:19; 70:10;  
 79:23, 23; 81:5; 82:2, 16,  
 18, 20, 23; 83:1; 84:1;  
 86:2, 14; 87:2; 88:22;  
 89:20; 91:8; 97:16; 98:4, 5;  
 99:2, 4; 101:13; 102:3;  
 104:17; 105:12, 16; 106:5;  
 107:18; 110:6; 112:11;  
 113:3, 3, 16; 114:3, 6, 9;  
 119:15; 122:5, 15; 125:23;  
 127:20, 24; 128:9; 129:20,  
 24; 130:2; 140:5; 141:3,  
 15; 144:3, 13; 146:10;  
 147:19; 150:6; 151:18  
**differential** 102:20  
**differentials** 97:19, 20;  
 102:15, 15  
**differentiate** 75:4; 124:3;  
 126:2

**differentiated** 58:13;  
 112:5, 10  
**differentiates** 75:6  
**differentiation** 57:2;  
 150:15  
**differently** 79:21; 101:15  
**difficult** 15:21; 17:18;  
 19:9; 21:18; 49:6; 70:14;  
 71:21, 24; 90:7; 133:1;  
 141:13; 145:4  
**diffusion** 41:25; 50:7, 23;  
 51:1, 9, 10, 13, 22; 53:15,  
 20, 21, 23; 55:7; 85:9, 13;  
 86:22, 25; 87:11  
**diffusion-speak** 54:12  
**diffusional** 55:6  
**dilemma** 129:18, 19;  
 130:3, 11, 25  
**diminish** 113:19  
**diminished** 38:21  
**dioxide** 45:2, 6, 8  
**dipropionate** 24:23  
**direct** 32:9; 57:7; 98:14,  
 16  
**directed** 119:10  
**direction** 24:1; 151:1  
**directly** 26:24; 43:20;  
 82:11; 83:13; 85:17; 91:1;  
 97:23; 100:22; 101:16  
**Director** 5:25  
**disagree** 123:2  
**disappear** 34:3; 37:25  
**disappearance** 109:22  
**disasters** 15:5  
**discard** 22:21  
**discarded** 70:4  
**discern** 126:15  
**discernible** 45:24  
**discerning** 36:19  
**disciplines** 7:22; 8:12  
**discoloration** 75:19  
**discount** 77:20  
**discrepancy** 100:12  
**discrete** 32:14  
**discriminate** 35:4; 124:6  
**discriminating** 47:14;  
 58:23; 147:14  
**discrimination** 47:15  
**discriminatory** 38:16  
**discs** 63:19  
**discuss** 29:14; 40:20;  
 42:9  
**discussed** 5:3; 28:20,  
 21; 78:6; 133:3; 140:9  
**discussing** 28:16  
**discussion** 14:1; 37:14;  
 42:9; 52:18; 59:12; 72:16;  
 74:13, 13; 92:6, 11, 15;  
 124:16, 17; 135:20;  
 144:10, 11; 145:12; 146:1  
**discussions** 5:12; 28:18  
**disease** 36:1; 99:10, 12;  
 101:2

**diseased** 35:3, 3, 8; 83:9;  
 98:24; 99:1, 8; 114:8;  
 116:23  
**diseases** 93:24, 25  
**disregarding** 40:9  
**disrupted** 83:10  
**dissimilarity** 53:11  
**dissolution** 79:5, 6  
**dissolve** 131:24  
**dissolved** 38:4; 44:21;  
 85:8; 114:5  
**dissolving** 132:6  
**distal** 118:9  
**distance** 85:10  
**distinct** 85:1  
**distinguish** 44:20; 46:6;  
 69:22; 127:22; 142:18  
**distinguished** 46:3; 94:9  
**distorted** 71:17  
**distorting** 71:20  
**distribute** 95:13  
**distribution** 28:10; 38:5;  
 45:9; 99:2, 3; 113:2  
**distrusts** 91:19  
**divided** 142:22  
**Division** 29:10, 13, 15;  
 32:5  
**document** 15:25; 16:8;  
 18:3; 147:7  
**documentation** 16:22  
**documented** 31:6  
**documenting** 17:4;  
 120:3  
**done** 6:7; 21:14; 23:25;  
 25:1, 25; 26:19; 27:5; 30:9;  
 58:20; 61:20; 63:8; 77:4, 8;  
 79:2; 83:11; 91:2; 98:25;  
 101:3, 20, 21; 102:2, 6;  
 103:3; 105:20; 113:7;  
 114:12; 116:17; 117:7;  
 126:14; 130:7; 133:21, 21;  
 140:16, 21; 141:2; 144:1, 7  
**dosage** 46:2; 79:2, 3;  
 130:12  
**dose** 128:3; 137:22  
**dose-response** 26:20;  
 127:21  
**doses** 79:10; 150:6  
**double** 69:17  
**down** 34:6; 50:9, 10;  
 53:20; 62:16; 68:12;  
 70:24; 84:15; 103:19;  
 106:17; 108:14, 17;  
 109:19, 21; 111:8; 117:22;  
 122:13  
**DPK** 18:15; 20:7; 23:16;  
 25:3, 18; 31:20; 33:22;  
 35:10, 24; 36:2, 12; 71:16;  
 75:1; 76:8, 16; 83:8, 17,  
 22; 84:4; 102:20, 22;  
 108:11; 120:8; 123:11;  
 128:11; 137:9, 12; 140:4,  
 11, 11, 16, 22, 25; 141:11;  
 143:7, 17; 145:19; 146:17,  
 19, 22, 24; 148:16; 149:8,

20, 23  
**DR** 4:3; 5:24; 6:19; 14:5;  
 15:8, 9; 18:6, 10, 10; 19:6;  
 21:22; 29:9, 12; 30:15, 19;  
 31:3; 32:5, 24; 33:11;  
 34:19; 35:12; 36:10, 11,  
 13, 22; 38:14; 47:3, 3, 6;  
 55:23; 57:13; 59:7, 15, 24;  
 60:1, 2, 4, 6, 9, 12, 14, 16,  
 20, 23, 25; 61:2, 4, 6, 9, 11,  
 15, 17, 19; 62:11; 72:12,  
 12, 19; 73:9, 9, 11, 11, 11,  
 11, 12, 13, 18; 74:11; 75:4,  
 11; 77:5; 78:1, 1, 3, 6;  
 82:1; 83:24; 84:9, 9, 10,  
 11, 20; 85:5, 16; 86:11;  
 88:19, 19, 19; 90:15; 91:4,  
 22; 92:2, 3, 9, 10, 14, 16,  
 17, 18, 19, 24; 95:18, 23,  
 24; 96:16, 22, 23, 24; 97:4,  
 21, 22, 23; 100:14, 16, 18,  
 19, 19, 23, 25; 101:1, 20;  
 102:5, 8, 9, 14, 16, 18;  
 104:5, 14; 105:10, 18, 23;  
 106:6, 8, 12, 15, 19, 21;  
 107:13, 14, 15, 16; 108:1,  
 5, 6, 7, 7, 9; 109:2, 2, 6, 10,  
 12, 15, 18, 22; 110:1, 2, 4,  
 10, 13, 14, 14, 17, 17, 18;  
 111:13, 15, 16; 112:3, 3, 4,  
 5; 113:23, 24, 25; 114:21,  
 21, 25; 115:4, 8, 17, 18,  
 19, 20; 116:14; 117:5, 6,  
 11, 19, 21; 118:4; 119:3, 4,  
 5, 7, 8, 24; 120:1, 11, 13,  
 21, 25; 121:21; 122:20;  
 123:1, 1, 2; 124:13, 13, 15,  
 23; 125:9, 10, 17, 19;  
 126:10, 11, 12, 18, 18, 19,  
 21; 127:5, 6, 17, 17, 18,  
 24; 128:2, 7, 10, 14, 15,  
 16, 19, 21, 22, 23, 25;  
 129:1, 6, 11, 11, 13, 15,  
 17, 18; 131:1, 2, 19, 19,  
 20; 132:18, 18, 19, 20;  
 133:8, 8, 9, 12; 135:17, 19,  
 25; 136:21, 21; 137:3, 4;  
 138:2, 21, 21, 22, 22, 24;  
 139:1, 2, 3, 24; 140:1, 2, 2,  
 3, 19, 19, 21; 141:2, 7, 8,  
 17, 18, 19, 22, 24; 142:11,  
 12, 13, 24; 143:1, 2, 2, 4,  
 18, 18, 19, 20; 144:9, 9,  
 10, 19, 23; 145:2, 6, 7, 8, 8,  
 9; 146:23; 147:1, 2, 3;  
 148:5; 149:1, 2, 3, 6, 6, 7,  
 7, 22, 22, 23, 25; 150:2, 7;  
 151:2  
**drafting** 72:25; 73:8  
**DRAKE** 60:20, 20; 95:23,  
 24; 96:23; 97:4; 100:16,  
 19; 101:20; 102:8; 104:5;  
 108:5; 119:3, 5, 8; 120:11,  
 25; 128:14, 16, 21, 23;  
 129:1, 12, 13; 138:21, 22,  
 24; 139:2, 3; 140:1; 145:7  
**Drake's** 138:3  
**dramatic** 41:2; 66:4;  
 148:7  
**draw** 69:5; 99:20; 119:21;

145:4  
**drawing** 99:12  
    vn 50:2  
**drive** 52:13; 89:17  
**driven** 53:17, 24  
**droplets** 56:8  
**dropped** 73:15  
**Drug** 4:4; 5:25; 6:4, 16,  
21, 25; 7:5; 8:8, 8; 9:5, 17,  
18, 19; 10:24, 25; 12:20,  
20, 24; 13:8, 14, 15; 14:23,  
25; 15:15, 20; 16:8, 8, 9,  
20, 22; 17:19, 22, 23; 18:3,  
4, 19, 25; 19:8, 15, 19;  
20:8, 11, 13, 21, 22, 24,  
25; 21:3, 10, 11, 14, 14,  
15, 22; 22:1, 3, 5, 7, 8, 22;  
23:20; 24:17, 24, 25; 25:8,  
8; 27:13, 14, 21; 28:10, 12,  
22; 29:13; 31:23; 34:1, 4,  
15, 17; 52:20; 53:15, 24;  
56:17, 22; 57:3, 11; 58:10,  
13; 59:24; 60:3; 61:16;  
62:9, 15; 69:19; 70:2, 15;  
71:6, 19, 22; 72:5; 75:16;  
76:9, 10, 22; 78:12, 19;  
79:1, 1, 9, 11; 80:2; 81:3,  
7, 24; 83:13, 16, 21; 84:6,  
22; 85:8, 22; 86:2, 10;  
88:11, 12; 94:4; 99:3, 13;  
103:4; 104:22; 106:17;  
    8; 108:16, 22, 23;  
    8; 110:19, 21, 21, 25;  
    112:21; 118:16; 123:7, 16;  
    124:10; 125:1; 131:6, 14;  
    139:14; 148:2, 3, 4, 7, 9,  
    15; 150:5, 21; 151:9  
**drug's** 54:18  
**Drugs** 4:7; 7:5; 17:15, 18;  
29:11; 32:21; 33:12, 15;  
34:24; 46:5; 47:5; 49:5;  
81:22; 89:24; 90:4; 99:7, 8,  
13; 103:7; 105:8; 116:2;  
121:12; 123:17, 25;  
124:12; 125:24; 128:20;  
131:23; 149:9; 150:13;  
151:14, 14, 15, 18  
**due** 67:17; 100:10  
**duplicate** 69:9  
**during** 8:23; 9:6; 10:17;  
11:13; 39:15; 62:22

## E

**E** 145:10; 147:17; 149:25  
**each** 22:1; 23:22; 26:5;  
52:17; 108:14, 15, 16  
**earlier** 14:9; 19:6; 21:22;  
25:12; 46:25; 72:3; 79:20;  
108:10; 123:5; 127:7;  
    16; 131:20; 139:6;  
    7, 18  
**early** 33:4; 39:7  
**ease** 26:19  
**easier** 65:12; 67:24;  
76:21; 95:6; 129:21  
**easily** 81:2; 130:7

**Easter** 7:21  
**easy** 12:1  
**eczema** 93:14, 15;  
116:23  
**eczematous** 116:23  
**edema** 116:19  
**Eduardo** 61:2  
**educate** 118:20  
**effect** 51:9; 71:20; 85:19;  
86:6, 16; 88:7; 118:9, 9;  
121:12; 132:2; 136:15;  
151:8  
**effective** 143:9  
**effectively** 49:13  
**effects** 86:23  
**efficacies** 150:6  
**efficacious** 35:5  
**efficacy** 6:22; 8:24; 10:5;  
12:22; 13:20; 16:25;  
23:16; 31:15; 39:1; 72:1;  
80:13; 85:19; 114:14, 15,  
20; 115:1, 5; 123:5; 125:8;  
126:21; 128:8; 137:16;  
138:10; 140:17; 141:25;  
142:15; 149:18  
**efficiency** 93:3  
**effort** 68:11; 94:17, 22  
**efforts** 95:25  
**eight** 117:14  
**eighth** 100:9  
**eighties** 39:7  
**either** 9:11; 38:4; 75:20;  
83:10; 102:25; 124:25;  
125:21; 131:5, 11; 145:15  
**elderly** 97:17; 104:10, 15,  
21  
**elegance** 29:15, 16, 20,  
24; 30:4, 24; 31:1  
**elegant** 29:17  
**eliminating** 119:13  
**elimination** 20:13, 25;  
21:13, 15; 22:7; 24:25;  
25:8; 35:15; 71:22  
**else** 95:22; 103:1; 125:22  
**embodied** 9:22  
**emerged** 32:4  
**emerging** 127:19  
**emphasize** 11:9; 13:9;  
40:6; 43:12; 83:5; 112:16  
**emptied** 113:13  
**emulsified** 56:7  
**emulsion** 58:5  
**encountered** 38:13, 22;  
110:6, 7  
**encourage** 151:4  
**encouraged** 151:1  
**end** 36:5; 59:22; 88:18;  
89:23; 91:9; 108:15;  
109:9; 149:20  
**ended** 33:16  
**endothelial** 131:9  
**endpoint** 114:7; 138:17;  
150:1  
**ends** 9:15, 16; 47:7; 54:3

**English** 106:7  
**enhanced** 34:23  
**enhancers** 38:18, 19  
**enormous** 130:24  
**enough** 27:17; 47:21, 21;  
58:23; 102:4; 119:21;  
125:7, 18; 126:2; 133:20;  
138:3; 142:5; 149:5  
**enroll** 103:9  
**enrolled** 102:23  
**enrollment** 102:22  
**enter** 43:24, 25; 44:1, 12;  
45:2  
**entering** 41:13  
**enters** 37:19, 19; 38:10,  
11; 40:24  
**enthusiasm** 133:12  
**enthusiastic** 147:5  
**enthusiasts** 89:2  
**entire** 70:11, 21; 103:11  
**entirely** 14:17; 120:24  
**entirety** 150:20  
**entrance** 36:25  
**environment** 114:3;  
134:2  
**environmental** 64:11;  
103:23, 25; 133:25; 136:6  
**environmentally** 63:16  
**epidermal** 63:2; 97:12;  
110:5  
**epidermis** 37:20; 97:11;  
110:9, 11; 111:23; 112:8;  
113:6; 144:20  
**equals** 127:9  
**equation** 50:10, 15, 16,  
22, 22, 25; 51:7, 16, 23;  
52:1; 85:5, 6  
**equations** 49:24; 50:4, 6  
**equilibrate** 64:10; 65:23;  
136:2  
**equilibrium** 34:12, 16;  
35:24; 110:6, 8; 113:8;  
129:7; 132:1  
**equipment** 79:17  
**equivalence** 9:24; 15:17;  
16:11; 114:15, 18; 115:5;  
127:10  
**equivalency** 53:1; 55:24;  
115:7; 132:25  
**equivalent** 9:20; 10:3;  
31:7, 13; 49:2; 72:4;  
127:16; 133:2; 139:14;  
148:11  
**errors** 48:3  
**escape** 46:21  
**Escher** 91:12, 22  
**especially** 54:25; 67:20;  
76:4  
**essence** 31:19; 45:6  
**essentially** 93:23; 143:7  
**establish** 9:5; 26:20;  
107:11; 132:24  
**established** 7:18; 51:6;  
55:24; 111:22; 129:7

**estimate** 71:21  
**estimates** 32:2  
**estradiol** 41:16, 22  
**Europe** 28:19; 98:7  
**Eva** 60:9  
**evaluate** 74:2, 15; 139:13  
**evaluated** 20:14; 103:12  
**evaluating** 125:25  
**Evaluation** 5:25; 6:17;  
20:8; 59:25; 77:23  
**evaporation** 63:3  
**even** 4:24; 23:10, 11;  
37:18, 22; 44:19; 45:13;  
51:18; 65:14; 66:14, 16;  
67:19; 68:16; 95:10;  
97:15; 106:19; 114:6;  
119:22; 121:2, 8; 134:1  
**event** 5:12  
**eventually** 67:13  
**every** 58:20; 78:12, 13;  
105:4; 113:5; 150:19, 19  
**Everybody** 121:21;  
144:6  
**everyone** 20:3; 74:15,  
16; 89:11; 92:4  
**everything** 116:21  
**evidence** 22:14  
**evolved** 9:4, 23  
**exactly** 21:17; 26:13;  
36:1; 52:7; 55:12; 66:11;  
79:21, 25; 95:2; 110:4;  
139:24; 140:3; 150:23  
**exaggerating** 41:3  
**examined** 68:25  
**example** 13:21; 22:3, 8;  
23:12; 24:4, 7, 14, 19, 22;  
25:13; 26:21; 30:13;  
34:21; 81:22, 24; 96:6, 17;  
97:10; 143:5  
**examples** 38:17; 39:8;  
122:3  
**excellent** 93:25  
**except** 75:14; 84:15;  
92:3; 116:17  
**exception** 42:8  
**excess** 30:2; 70:2;  
117:10  
**excipients** 9:2; 150:13  
**excited** 74:2  
**exciting** 14:12  
**exclude** 5:15  
**excluded** 62:1; 73:2  
**exclusion** 5:16  
**exclusively** 129:9  
**exclusivity** 9:12, 15  
**excoriation** 93:16  
**excretion** 39:16  
**excuse** 92:17, 23; 102:16  
**Executive** 4:11; 60:18  
**exerts** 55:2  
**existed** 117:24  
**existing** 24:11  
**exists** 69:15; 150:9

**expand** 13:12; 109:7  
**expect** 10:12, 16; 25:9;  
37:24; 49:25; 52:9;  
101:14; 109:15, 24;  
130:17, 18  
**expected** 45:7; 53:11  
**expensive** 19:11; 31:9;  
99:16; 139:20; 151:24  
**experience** 64:2; 112:25;  
122:7; 133:18, 23; 136:20  
**experiment** 66:23;  
125:15; 134:5  
**experimental** 48:22;  
82:6  
**experiments** 65:19;  
90:18  
**expertise** 63:13  
**expired** 130:6  
**explain** 64:16  
**explained** 14:20  
**explains** 100:12  
**explore** 61:21; 107:6  
**explored** 34:20; 129:3  
**exploring** 97:20  
**exposure** 97:19; 103:4  
**express** 11:1; 23:1  
**expressed** 137:1  
**exquisite** 94:15  
**extensive** 63:10; 74:12;  
122:6; 141:2  
**extensively** 28:21  
**extensiveness** 30:10  
**extent** 11:1, 6; 13:16;  
31:22; 47:25; 72:4, 10;  
75:19; 117:15; 137:9  
**extract** 22:25  
**extraordinarily** 134:17  
**extrapolate** 35:2  
**extremely** 14:12; 45:13;  
49:6; 55:1

## F

**fabric** 144:25; 145:2  
**fabrics** 144:12, 13  
**face** 133:1; 150:14  
**faces** 59:21, 21  
**facilitate** 143:22  
**fact** 16:24; 27:16; 47:13;  
48:21; 50:20; 51:6; 55:14,  
25; 57:18; 59:2; 64:7;  
67:17; 74:18; 75:16, 24;  
77:9, 16; 91:20; 96:19;  
100:10; 105:3; 106:24;  
108:11, 21; 114:2; 126:16;  
130:18; 133:15; 134:18,  
20; 135:1, 4; 136:24;  
146:13  
**factor** 111:24  
**factors** 28:1; 62:16; 87:1;  
116:16  
**failure** 65:5; 135:8;  
136:16  
**fair** 48:5; 49:3; 119:24

fairly 49:9; 50:10; 56:17;  
106:3; 132:7  
fairness 5:19  
fall 94:2; 130:7  
falls 71:4  
familiar 50:23; 59:21  
family 53:7  
far 66:2; 74:16; 78:6;  
80:11; 124:16; 126:19;  
136:16; 139:11, 12;  
149:25  
fashion 106:4; 145:19  
fast 148:7  
fate 44:4, 12; 45:1  
favor 37:23; 38:19; 93:2  
FDA 5:14; 25:1; 58:20;  
60:1; 68:7; 75:21; 119:10;  
150:4, 9  
FDA's 5:10  
feasible 19:17, 24;  
146:14, 21  
federal 9:12  
feel 23:7; 62:5; 74:14;  
104:8; 109:13; 142:1;  
144:6; 146:24; 151:19  
feeling 145:22  
feelings 145:11  
felt 96:8; 150:4  
female 105:1  
few 13:9; 15:13; 20:10;  
28:6; 49:20; 57:13; 81:11;  
88:17; 92:25; 94:22; 99:6;  
116:25; 144:1, 2  
fewest 29:18, 21  
fibroblasts 43:25  
field 63:18  
figure 109:3  
figures 27:6; 113:18  
filled 38:15  
final 28:11, 13; 30:15;  
34:19; 77:7; 80:5; 99:23;  
138:2, 16  
Finally 15:22; 77:20;  
90:1; 94:8; 95:10; 100:7;  
150:10  
financial 5:1, 14, 20;  
89:6, 7  
find 20:18; 43:9; 45:7;  
57:6; 70:14; 73:7; 76:15;  
77:21; 82:3; 97:1; 98:8;  
99:19; 100:2; 105:25;  
106:20; 109:15; 111:1, 3;  
126:23; 139:19  
finding 74:2  
findings 93:23; 106:6;  
111:25; 136:18  
finds-and 31:3  
fine-tuned 126:1  
fineness 58:4  
finer 58:12  
finish 15:13; 138:11  
finishes 4:13  
firm 5:4, 20; 111:22;  
132:11

firms 5:13  
first 15:15; 22:21; 27:11;  
28:16; 30:6, 8; 32:11;  
36:17; 40:9; 48:14; 57:6;  
58:19; 69:25; 70:1, 4;  
72:22; 78:2; 93:1; 97:24;  
98:3, 24; 99:25; 118:5;  
120:18; 121:22; 123:9, 13;  
124:15; 126:3; 128:13;  
133:15; 136:22; 145:13;  
147:3  
fit 106:6  
five 33:4; 70:4; 73:10  
five-year 101:24  
flat 124:2, 4  
Fleischer 87:18  
Florida 60:15  
flux 85:1, 7, 12, 17, 18,  
23; 86:5, 8, 9, 15, 15, 19;  
87:1, 2, 6, 16; 88:7, 16;  
110:9  
fly 56:3; 146:24  
Flynn 47:4, 6; 60:12, 12;  
73:11; 79:19; 82:2; 83:24;  
100:18, 19, 23; 101:1;  
102:5, 9; 110:14, 17, 18;  
117:21; 120:13; 129:17,  
18; 132:21; 133:8, 9;  
148:5; 149:2, 3  
Flynn's 84:20; 85:5;  
131:19  
focus 8:11; 12:5; 14:18;  
16:19; 17:21; 18:16, 24;  
19:16; 32:22; 36:13; 78:8;  
118:12; 125:6  
focuses 6:20, 21; 7:8, 10;  
8:6  
focusing 12:19  
foil 134:12  
fold 77:16  
folks 84:21; 89:10, 16, 19;  
119:10  
follicle 33:4, 6; 37:1, 19;  
40:21; 41:14; 44:2; 94:2;  
122:9  
follicles 36:24; 38:10;  
41:5, 5, 6, 7, 25; 43:10, 15,  
16  
follicular 27:19, 23; 28:1,  
2, 5; 35:18; 36:12, 21, 25;  
37:7, 23; 38:13; 42:24, 25;  
45:24; 46:20; 47:18  
follow 44:12; 113:21;  
151:11  
follow-up 18:21  
followed 23:24; 98:20;  
113:4  
following 4:21; 25:10;  
26:7; 27:4, 14; 63:8; 66:23;  
79:12  
footing 111:22  
for-l 15:4  
force 63:23; 143:16  
forces 53:18, 25  
Ford 60:24  
forearm 22:6; 68:3; 97:7,

8; 103:19  
form 20:3; 81:7; 84:1  
formally 90:17  
format 4:8  
formed 118:1  
forms 21:12; 79:2  
formula 56:10, 18; 57:3, 6  
formulas 58:1; 59:1  
formulate 38:14  
formulation 24:18; 37:4;  
53:14, 16, 17, 22; 54:4, 19,  
20; 56:6; 57:21; 74:18;  
76:12; 80:24, 25; 82:10,  
12, 23; 83:1, 14; 98:9;  
110:24; 111:12; 112:21;  
120:16, 19; 148:2, 3  
formulations 19:12;  
21:3, 6; 23:10; 37:18;  
47:14; 49:15; 53:1; 54:15,  
16; 55:14; 57:12; 75:4, 6,  
8; 79:14; 101:4; 104:16;  
120:15; 124:6  
formulator 129:22, 23,  
23  
forth 93:22  
forward 124:19; 140:13;  
142:2; 148:23  
found 33:4, 6; 43:21;  
45:8; 88:2; 96:3; 100:6;  
104:11; 105:3; 134:24  
four 7:2; 19:7; 39:10, 16,  
24; 40:3; 64:21; 73:12;  
100:3; 117:13, 14; 142:14,  
20  
Fourier 51:24  
fractions 41:13  
frame 6:11  
framed 101:1  
France 29:3  
Francisco 61:7  
Franz 29:5  
freckles 103:1  
Fred 61:9; 141:17  
free 104:8; 123:16;  
147:21  
Freedom 5:10  
French-here 44:8  
frequently 11:15; 12:8;  
13:3; 137:20; 149:15  
45:24; 46:20; 47:18  
friends 48:13  
front 49:24; 50:1; 52:3, 5;  
136:5  
fulfill 30:4  
full 27:5; 71:19  
fully 73:16; 132:20  
function 20:12; 50:12;  
63:4; 112:15, 15, 17;  
147:20  
functionally 54:11  
functions 91:11  
fundamental 49:22;  
52:13; 55:21; 119:23;  
129:8; 130:16  
fundamentally 84:15

furrows 32:16  
furry 93:10  
further 18:7; 29:1; 44:5;  
50:16; 52:18; 59:4; 77:23;  
109:7; 117:7; 129:3;  
146:13  
furthers 31:1  
future 142:10

**G**

gaglike 97:13  
gain 89:6  
Galderma 122:6; 151:5  
gamers 89:3, 16, 19;  
95:25; 96:15  
gastric 131:24; 132:6, 6,  
11; 143:6  
gastrointestinal 51:17  
gather 92:4  
Gayle 60:14; 125:17;  
149:1  
Geisinger 61:9  
gender 102:15  
general 5:6; 9:22; 17:11,  
13; 19:9; 60:22; 97:24, 25;  
103:17; 115:20; 133:18;  
136:20  
generally 12:14; 17:15;  
19:18, 20; 38:6  
generate 26:22  
generating 7:24  
generation 8:23  
Generic 7:5; 9:19; 10:3;  
11:10, 13, 17, 20; 14:17,  
18; 15:12, 16; 19:2; 21:23;  
28:22; 30:18; 53:2; 73:18,  
20, 23; 78:20; 80:4, 14;  
84:17; 86:1, 10; 88:12;  
89:8; 90:3, 24; 101:5;  
102:1; 115:9, 10, 10, 11;  
120:5; 122:21; 129:22, 23;  
130:23; 132:11, 21;  
138:14; 139:20; 141:12;  
143:22, 24; 147:9; 149:17,  
19, 20; 150:22  
generics 31:11; 90:21;  
93:2; 147:15; 148:24  
gentlemen 48:13  
gently 22:16  
gets 16:2; 64:5; 70:7;  
95:11; 114:5; 127:6  
gift 44:24  
given 111:12; 113:20;  
135:7; 149:19; 150:8  
gives 23:22; 25:7; 34:1;  
81:14, 16; 82:22  
giving 127:15; 148:9  
glad 62:3  
glass 44:22  
glistening 66:9  
global 91:10  
glucocorticoid 24:4, 23  
glucocorticoids 18:20;

19:15; 25:15, 19; 115:3;  
122:10, 11; 140:25; 141:2,  
3; 149:13, 25  
glycosaminoglycans  
97:14  
go-l 73:25  
goal 6:6, 11; 30:8, 24;  
95:25; 137:14; 139:18  
goalposts 14:8  
goes 108:17; 125:23;  
126:23; 151:6  
Good 4:3, 21; 7:16, 17;  
10:10, 12; 26:15, 17;  
33:19; 48:4, 5; 59:15;  
61:19; 62:8; 66:17; 71:5,  
23; 74:7; 84:5; 90:3, 18;  
95:10; 97:4; 114:12;  
121:9; 125:3; 128:8;  
139:3, 11; 150:1  
Gordon 47:3; 60:12; 82:2  
graded 101:23  
gradient 51:5; 69:19;  
70:16; 108:3; 109:16;  
110:4  
gradual 34:6  
gradually 34:3  
grafted 103:3  
granted 5:7; 79:11  
granting 19:1; 78:19  
granular 93:21  
graph 34:5  
graphs 67:25  
great 41:15; 56:9; 64:8;  
68:5; 69:1; 96:17; 97:9;  
100:20; 129:3, 19  
greater 54:9; 134:9  
greatest 111:11  
grew 94:12  
group 16:20, 21; 17:18;  
30:20; 31:4; 32:6, 9; 76:15;  
89:4, 18; 90:3; 91:4; 93:7;  
94:22; 101:17, 17, 18  
group's 32:20  
group-and 89:23  
group-that 89:25  
grouped 106:12  
groupings 122:5  
groups 16:17, 19; 102:3  
guess 97:15; 102:1;  
123:2; 124:8; 125:10;  
127:6; 131:3  
guidance 17:13, 25;  
24:1; 26:3; 115:22;  
125:11; 148:18  
guidances 17:10  
guide 118:13  
guideline 88:5; 114:13  
guild 89:2

**H**

hair 102:25  
hairy 41:3; 42:7; 43:11  
half 22:4; 69:16; 142:19

half-hour 92:7, 8  
head 54:6; 70:19; 140:23,  
handle 26:15, 17; 123:6;  
137:19  
handled 76:17; 77:17;  
148:22  
handout 20:3  
handout--you 73:7  
hands 91:24; 150:9  
Hans 24:1; 28:6; 29:4;  
36:11; 48:9; 61:4; 96:17;  
97:22; 102:10; 109:7;  
113:23  
happen 40:22; 48:11;  
58:6; 72:1; 93:4; 116:9, 11,  
12  
happened 145:16  
happening 27:24;  
109:18; 135:14; 142:6  
happens 39:15; 41:8;  
63:13; 99:5  
happy 76:23; 89:11  
hard 66:10; 67:7, 11;  
69:22, 24; 72:9; 93:12, 18  
hardly 37:14; 104:12  
Harvard 60:22  
Hatch-Waxman 31:11  
haven't 72:20; 119:20;  
هنا 19; 133:21; 139:3;  
20  
head-on 151:20  
headed 6:19  
heal 93:24  
health 6:23; 60:21  
healthy 34:20; 35:2, 6, 8;  
36:2; 83:8; 84:15; 107:17;  
108:5, 6; 111:17  
hear 8:4; 14:2, 4; 15:7;  
18:1; 29:9; 88:1; 90:17;  
93:4; 94:5; 96:16; 97:18;  
115:16; 129:16; 136:22,  
25; 138:21  
heard 48:21; 61:22;  
80:22; 96:6, 12; 100:7;  
107:22; 120:14; 123:5;  
131:17; 145:18; 147:3  
hearing 59:9; 61:14, 15,  
18; 72:14; 145:12  
heart 151:6  
heavy 99:15  
held 61:25  
help 7:25; 96:23  
helps 8:13; 49:16  
Henry 60:23, 24  
here--we 56:23  
herself 49:14  
هنا 55:24; 103:25, 25  
ier 19:2; 25:11;  
41:24; 42:16; 78:20; 79:7;  
80:3, 16, 17, 20; 87:4, 22;  
88:1; 129:25  
highest 29:23; 69:20, 21;  
79:3  
highly 13:20; 14:7; 55:1;

62:6; 70:5; 103:14  
him--I 94:10  
himself 102:10  
histology 66:11; 116:19  
holes 93:16, 17; 96:4  
homeostasis 132:8  
homogeneous 69:14  
homogenizer 58:2  
honored 73:16  
hope 8:11; 11:24; 45:20;  
122:17; 137:6; 142:9  
hopefully 104:16  
hoping 121:23  
Hopkins 60:11  
horizontal 8:22; 10:14;  
87:5  
horny 39:3, 14; 42:6;  
44:1, 4, 10; 45:10; 46:18;  
83:10; 98:10; 110:7, 8;  
112:6, 8, 18; 113:2, 5;  
116:24  
Hospital 60:22, 24  
hour 22:5; 52:17  
hours 22:5, 9; 33:5; 42:8,  
21, 23; 105:24; 106:9, 10,  
19; 109:4, 5, 9; 113:1, 12;  
116:10; 117:13, 14; 118:6;  
134:1, 14  
Howard 29:6; 39:18  
HPLC 23:1  
human 32:15; 93:10, 11;  
103:4; 107:8, 18, 20;  
108:17, 18; 111:21;  
119:13, 14; 132:8  
humans 39:19; 40:2;  
43:13; 98:5  
humidity 63:17; 103:24,  
25, 25; 134:4  
hundred 98:1  
hurdle 15:4, 15, 16, 17,  
22  
hurdles 16:10  
hydrocortisone 24:5;  
34:22; 42:12; 57:1; 58:9,  
11; 82:18; 100:2; 142:16  
hydrocortisones  
126:13  
hydrometers 134:18  
hydroscopic 134:17;  
136:1  
hydroxide 57:17  
hyperpigmentation  
67:14  
hypothesis 20:19, 19

**I**

idea 71:5; 130:22  
ideal 150:25  
ideas 137:2  
identicality 10:1  
identified 33:14  
identifying 95:19

ignore 85:9  
II 149:21  
IL-1 118:7  
illustrated 62:16  
Imagine 40:21; 89:5  
immediate 79:1  
impact 5:4; 38:25; 116:10  
implementation 62:7  
implemented 95:16  
implications 5:5  
imply 88:15  
implying 144:23  
importance 41:15; 83:6  
important 10:6; 16:13;  
19:23; 24:22; 26:24;  
27:20; 32:21, 25; 33:20;  
36:3; 49:3; 64:2; 69:5;  
79:13; 80:23; 83:3; 90:18;  
91:2; 102:10; 103:5  
Importantly 86:25;  
104:24  
impossible 48:25; 67:8;  
99:14; 117:3; 150:15  
imprecise 90:9  
improve 127:12, 15  
improving 32:7  
in-vitro 18:25; 47:11;  
76:1, 6, 6; 77:22; 78:18;  
79:11; 83:6, 12, 18, 23;  
84:2; 107:3, 20, 24; 120:7;  
132:23; 144:15; 145:5;  
148:8, 14  
in-vivo 107:4  
inability 71:1  
inactive 150:13, 16  
incidently--done 58:10  
inclinations 54:8  
include 17:2; 103:21;  
120:6  
Included 7:4; 73:8  
includes 26:9; 120:7;  
133:20; 147:12  
including 40:10; 73:9  
inconsistent 136:13  
incorporated 43:22  
incorporates 86:21  
increase 93:3; 109:24;  
118:7, 7  
increased 34:22; 105:25;  
111:4, 8  
increasing 135:10  
IND 9:6  
indeed 132:21  
indefinitely 10:13  
indicate 6:12; 23:25;  
28:15; 62:20; 76:16; 79:24  
indicated 70:10; 76:15;  
77:5  
indicating 66:5, 15  
indication 23:17  
indicator 23:9  
individual 56:12; 101:4,  
19; 103:6; 104:24; 109:11,

13, 14; 132:9; 135:5;  
149:18  
individuals 111:17, 17;  
114:2  
induces 118:5  
industry 73:13, 13; 89:19  
infancy 140:8  
inferential 137:14  
inferiority 115:14  
infinite 111:2; 130:3  
infinitely 54:11  
infinitly 50:20  
inflamed 99:3  
inflammation 67:13;  
116:15, 18, 20  
inflammatory 116:9, 11;  
117:16, 23  
influence 28:1; 103:4  
influences 97:9  
Information 5:11; 8:1,  
13, 24; 18:7; 24:2; 25:7,  
21; 27:18; 28:2, 11; 30:1;  
48:18; 52:4; 62:4; 72:9;  
83:17, 19; 90:9, 11, 12;  
91:9; 108:25; 119:18;  
121:4; 131:16; 138:4, 4, 7;  
139:21; 141:6; 142:8, 14;  
145:18; 146:16, 24; 150:7  
informations 112:13  
informative 30:17, 25  
ingredient 9:2; 19:4;  
27:1; 31:23; 78:22; 79:16,  
22; 84:1; 150:19  
inhalation 17:18  
inhalers 137:22  
inherent 72:8  
inhibit 95:19  
initial 23:9; 46:21; 50:8  
initially 28:22  
injury 118:8  
innovations 89:18  
innovative 139:7  
innovator 9:10; 11:12;  
53:1; 68:8, 10; 80:2; 95:5;  
127:21; 132:10; 138:8  
innovator's 101:6  
innovators 95:20, 25  
innumerable 138:12  
input 29:1; 78:9; 111:6  
insensitive 19:11;  
137:21  
Insensitivity 142:1  
insists 75:21  
instance 93:14; 94:3;  
103:10; 122:6; 130:12;  
131:12  
instances 13:13  
instead 14:2; 32:14;  
75:15; 109:4  
institute 143:21  
intact 83:10  
integrated 105:18  
integrity 65:20; 133:13

intellectual 89:9  
intensive 151:24  
interact 89:19  
interactive 4:9  
intercept 51:7  
interchangeability  
16:14; 122:25  
interchangeable 15:2;  
31:14  
Interest 4:12, 20, 22;  
5:14, 19; 89:5  
interested 74:1; 99:25;  
118:20, 21, 22; 132:2;  
138:19  
interested--and 140:14  
interesting 6:3; 14:7, 14;  
57:3, 16, 25; 65:24; 88:24;  
96:12; 127:19; 139:7  
interestingly 64:25;  
85:16  
interests 5:1  
interfere 136:4  
interference 55:9  
interfering 116:17  
interfollicular 35:11;  
36:23  
interfollicularly 37:20  
interject 110:15  
Intermediate 142:22  
Internal 60:10; 101:9  
interpreted 66:1  
intersubject 26:17; 63:5;  
65:13; 66:22; 68:24  
interval 22:12  
intervals 14:8; 22:8  
into 7:13; 9:20; 14:21;  
18:15; 25:4; 27:23; 33:12;  
36:25; 37:19, 20; 39:5;  
40:11, 18, 24; 41:8, 13, 25;  
43:20, 22, 24, 25, 25; 44:1,  
12; 45:2, 5; 48:9; 49:4;  
51:2; 53:16; 55:10; 59:4;  
62:15, 15, 17; 63:20; 66:2,  
6; 67:13; 68:18; 69:24;  
70:8; 76:9, 9; 85:2, 3;  
87:19; 90:19; 92:6; 93:5;  
94:2, 22; 95:9; 98:19; 99:4,  
8, 8, 9; 100:5; 104:12;  
105:17; 106:7, 13; 108:23;  
109:16; 110:11, 12;  
112:14, 19; 114:5; 115:24;  
122:9; 135:23; 148:4, 13  
intrasubject 26:17; 63:6;  
68:25; 77:12, 15; 103:16  
intriguing 129:2, 3  
intrinsic 146:8  
introduce 4:14; 6:7;  
59:18, 20; 102:16; 105:16  
introduced 47:17  
introducing 4:17  
invasive 67:22  
investigated 39:21;  
43:13; 45:1; 98:4; 99:7;  
116:14  
investigations 46:5

investigator 26:13, 13  
invoke 117:23  
invoked 117:25  
involve 5:12  
involved 72:25; 73:20;  
96:15; 101:9; 107:5  
involvement 5:16, 20  
involves 86:19  
irritation 30:13  
is-I 139:4  
isotropic 50:2; 51:11, 18  
issue 4:22; 10:19; 11:11;  
13:7, 10; 14:17, 18; 16:2;  
20:6; 28:8, 13; 32:19;  
37:14; 53:4; 58:22; 69:4;  
84:15; 102:11, 12; 105:12;  
111:16; 114:1; 115:20;  
118:11; 123:23; 124:22;  
129:8; 132:20; 137:7, 12  
issues 5:2, 23; 61:21;  
91:2; 116:13  
it-not 134:5  
item 34:19  
items 114:23; 147:17  
itself 13:18; 26:25; 53:7;  
55:21; 62:24; 77:11;  
133:21  
IV 149:19  
IV.B 17:25

**J**

J 61:16, 16  
JAAD 151:6  
Jane 94:15  
Jersey 58:6; 94:12  
Jim 60:16  
job 74:22, 23; 91:24;  
94:12  
Joe 61:11; 97:21; 113:10  
Joel 60:6; 73:13; 151:7  
Joel's 100:25  
Johns 60:10  
joint 99:3, 4, 5  
Jon 91:23, 23; 92:5;  
131:18  
Jonathan 29:9, 12;  
36:14; 60:2; 84:10;  
120:15, 21, 22; 122:18;  
124:20; 127:20; 128:3  
judge 98:22  
judged 21:6  
judgment 139:13  
juice 131:24; 132:6, 6, 11;  
143:6  
jumped 131:21  
June 151:6  
junior 101:17  
justify 105:22  
juvenile 101:15

**K**

K 51:2  
Kaplan 73:19  
Kathleen 61:6  
keep 37:13; 46:21; 58:17;  
106:16; 137:14  
keeping 78:11; 80:10  
kept 71:3  
keratinocytes 43:25;  
131:8  
ketoconazole 25:22  
key 7:11; 13:2; 31:12;  
34:14; 37:14, 21; 39:1;  
105:7; 111:24; 114:10;  
125:11; 131:4  
KILPATRICK 60:16, 16;  
145:8, 9; 150:7  
kind 30:1; 34:5; 45:7;  
93:12; 101:25; 104:10;  
115:5; 123:7; 130:20;  
132:14; 133:17; 141:5;  
143:25  
kinds 36:4; 101:11; 120:4  
kinetic 43:3; 45:23;  
112:24; 113:22; 123:4  
kinetics 40:11; 41:19, 23;  
42:7, 12; 43:2; 44:4, 19;  
113:15, 16, 21; 123:16  
knowing 81:1; 82:7  
knowledge 63:10; 77:1;  
92:1; 123:21  
known 51:21; 62:14;  
100:19; 149:10

**L**

label 150:24  
labeled 87:15  
labeling 6:25  
labor 151:23  
laboratories 48:22;  
90:22  
laboratory 36:5; 49:7,  
12; 56:4; 82:2; 84:21;  
90:25; 94:14; 133:22  
lack 93:20  
ladies 48:13  
lag 51:9  
laid 117:22  
LAMBORN 61:6, 6;  
113:24, 25; 115:4, 17;  
127:24; 131:20; 141:18,  
19, 24  
LAMHORN 127:6  
land 94:2  
Langerhans 131:9  
large 64:24; 67:3; 132:22  
largely 93:7, 14  
last 7:19; 17:7; 28:8; 29:3,  
8; 84:7; 107:22; 147:4  
late 39:7  
later 8:4; 41:9; 96:13;

109:24  
Latriano 61:15, 17, 19;  
72:12; 88:19; 105:23;  
106:8, 15, 21; 107:16;  
108:1, 6; 135:17, 25  
Latriano's 124:23;  
133:12  
law 31:11; 150:17  
layer 39:3, 14; 42:6; 44:2,  
4, 10; 45:10; 46:18; 70:1;  
83:10; 98:10; 110:7, 8;  
112:6, 8, 18; 113:2; 116:24  
layers 32:12, 14, 15;  
42:19; 43:24; 54:22;  
62:12, 21; 65:1; 69:20, 25;  
98:10; 110:7; 112:11;  
113:3, 5; 123:8  
lead 6:24, 24; 7:23; 8:12;  
29:22; 32:2; 122:24  
leader 94:19  
leadership 24:1  
leads 50:15, 21; 71:1  
leanings 149:3  
least 19:6; 22:13, 24;  
26:4; 31:7; 66:19; 68:7, 14;  
71:12; 82:21; 87:10;  
114:23; 136:25  
leave 11:8; 104:5;  
113:12; 150:8  
leaves 61:11; 67:12  
left 6:17; 16:18; 17:13;  
40:25; 63:24; 65:7; 71:4;  
91:23; 96:7, 9; 136:17  
leg 116:6  
legal 8:20  
legislation 151:1  
less 31:8; 35:5, 7; 43:9,  
15; 74:8; 90:7; 97:13;  
103:18; 105:1; 108:19;  
110:21; 129:21; 135:9;  
139:20; 147:4  
lesser 53:4; 138:7, 13  
level 23:21; 24:24; 35:19;  
38:25; 52:23; 58:18;  
87:23; 130:8; 143:5  
levels 16:25; 25:3, 4;  
49:3, 5; 52:21; 130:8;  
131:25, 25  
liberally 54:7, 7  
lie 149:12  
lieu 129:9; 149:12  
life 10:16; 142:14  
lifetime 101:7  
lift 34:20  
light 67:10; 72:19  
lightly 22:13  
likely 48:11; 59:10;  
100:10; 124:7; 136:24  
likes 148:3  
LIM 60:23, 23; 132:18, 19;  
144:9, 10; 145:2  
limitations 62:7  
limited 50:20; 106:16;  
123:21  
limits 98:8; 106:15

line 23:23; 51:8; 55:19;  
71:11; 121:5, 7; 136:12,  
12; 139:10  
linear 24:9, 17; 66:19;  
69:15; 70:16; 81:14; 87:3  
linearity 82:4; 87:20;  
88:15; 98:18  
linearly 108:17  
lining 132:16  
link 39:3  
lipid 93:21  
lipophilic 41:15  
list 35:10; 150:19  
listed 9:19; 14:22, 25;  
15:15, 20; 21:21; 80:2;  
84:14; 86:2, 10; 88:11, 17;  
149:10  
literature 98:22; 100:13;  
136:14  
little 57:16; 59:9; 63:13,  
24; 65:12; 66:6; 67:10;  
97:15; 104:23; 114:8;  
121:17; 151:19  
live 98:13; 107:20; 108:18  
living 43:24; 103:23;  
111:17, 22, 23  
local 91:13  
locally 16:8, 20; 17:20,  
22; 79:8  
locking 95:8  
log 108:17  
logic 90:19  
logical 19:18; 42:1; 43:8  
logistics 97:9  
long 8:10; 10:14; 67:15;  
111:18; 135:2; 150:24  
longer 111:1; 112:1;  
149:19  
longest 122:18  
look 30:8; 34:2, 3, 7; 41:8;  
53:4; 63:3; 87:19; 88:25;  
91:13, 13; 92:20; 97:18;  
98:12; 109:5, 6, 11;  
113:15; 116:2; 124:19;  
127:3; 141:14; 146:16;  
148:15  
looked 43:20; 45:5; 48:9;  
69:1; 102:14; 105:24, 24;  
106:5; 109:3, 4; 116:18;  
136:10, 11; 148:16  
looking 35:1; 36:2; 42:18;  
55:16; 59:4; 64:17; 68:8;  
83:20; 84:5; 85:20; 89:20;  
90:25; 112:17; 121:12;  
125:3; 130:13; 132:13;  
135:16; 141:16  
looks 88:5; 131:25  
loose 135:22  
Loreal 61:5  
losing 134:19  
loss 63:3; 65:4, 8; 89:7;  
98:15, 17; 135:10  
lost 54:15; 67:14  
lot 56:11; 67:4; 68:4, 21;  
70:7; 88:24; 90:18, 22;

94:24; 95:6; 96:12;  
101:11; 112:13; 133:21;  
138:7; 149:14  
lots 96:3  
Louise 61:15; 135:19, 24  
love 100:21  
low 87:3; 95:12; 103:24;  
106:24; 143:9  
lower 19:1; 36:8; 41:25;  
55:25; 68:15; 69:2; 70:7;  
78:4, 10, 11, 13, 15, 17,  
20, 22; 79:3, 10; 80:3, 9,  
16, 18, 21; 84:12; 85:15;  
87:21; 88:6; 90:20;  
106:10; 108:15, 24; 109:3,  
3, 16, 19, 20, 20, 20;  
110:8; 148:9  
lowering 143:13  
lowest 55:5; 56:25  
LS 126:5  
lucky 63:11; 103:22  
Lumpkin 6:19  
lunch 135:22  
luxury 74:9  
Lynn 25:2; 29:4; 60:20;  
100:14; 102:11, 18; 123:3;  
124:22; 128:15; 145:6

**M**

Mac 6:19  
magnesium 45:16  
magnitude 11:21; 44:11  
magnitudes 52:6  
Maibach 29:6; 39:18;  
73:12; 87:18  
main 20:19; 48:10  
mainly 67:7; 69:22  
maintain 10:16  
major 54:11, 23; 55:17;  
134:2  
make-these 151:3  
makes 49:6; 56:14; 64:4;  
71:24; 130:13; 149:21  
making 18:11; 71:20;  
94:18; 98:2; 101:16;  
102:9; 108:13; 126:22;  
141:16  
Malassezia 118:23  
male 104:25; 105:2  
malfunction 15:10  
Management 6:19; 7:1;  
12:24; 61:4  
Manager 61:15  
mandate 143:21  
manifested 62:24  
manipulation 143:14  
manner 96:4; 150:5  
manufacture 79:20  
manufacturer 9:10;  
14:25; 58:17; 82:9, 21, 22,  
25, 25; 83:4; 150:19, 22  
manufacturers 9:16, 20;  
10:3; 11:12, 13, 15, 17, 18,

20; 82:21  
**manufacturing** 10:20;  
5, 21; 57:24; 79:16;  
4  
**many** 7:8, 20; 10:9, 9;  
12:2; 32:8; 35:18; 36:4;  
49:11; 51:23; 87:19;  
94:10; 116:16; 121:16  
**mark** 104:25  
**marker** 13:5; 75:15;  
123:5  
**market** 14:21; 43:22;  
81:13; 95:14  
**marketed** 80:2  
**marketplace** 7:13, 14;  
9:9, 21; 10:11, 13; 15:1;  
16:12, 14  
**Marty** 73:12  
**Maryland** 60:11  
**masked** 150:5  
**mass** 77:8; 131:9  
**Massachusetts** 60:22  
**master** 51:23  
**matched** 146:22  
**material** 10:4; 39:14, 23;  
40:23; 44:21; 45:14;  
46:16; 93:12; 97:13;  
106:1, 2, 20; 134:25;  
145:15, 16; 151:16  
**materials** 58:12, 12;  
15  
**mathematical** 29:18;  
50:18  
**mathematically** 50:19  
**mathematicians** 29:17  
**matrix** 84:23; 86:20  
**matter** 17:14; 53:10;  
80:5; 107:8  
**matters** 5:6  
**Mauritz** 91:12  
**maximum** 112:24; 113:1  
**may** 5:4, 9, 21; 21:1, 5;  
22:15; 23:18; 24:10, 11;  
27:17; 28:2; 48:2, 23;  
55:14; 62:13; 71:18, 18;  
79:19; 80:6, 6, 7; 82:24;  
83:19; 84:5; 86:2; 87:16;  
91:15; 96:10; 97:9, 13, 23;  
104:17; 107:15; 108:1;  
109:7; 110:15; 114:5;  
119:6; 122:17; 124:5, 7;  
125:6; 127:3, 14; 145:23  
**maybe** 22:4, 14; 23:5;  
27:23; 30:23; 83:7, 9, 17;  
96:14, 20; 102:3; 127:19;  
128:4; 139:3; 140:13;  
144:4; 149:11; 150:25;  
151:21  
**GUIDE** 4:3; 15:8; 47:3;  
15; 61:11, 12; 72:12;  
78:1; 84:9; 91:22; 92:10,  
17, 19; 95:18; 97:22;  
100:14, 25; 102:16;  
105:10; 106:12, 19;  
107:13; 108:7; 109:2, 10,  
15, 22; 110:2, 10, 17;

111:13; 112:3; 113:23;  
114:21; 115:18; 117:5;  
118:4; 119:4, 7, 24;  
121:21; 123:1; 124:13;  
125:9, 17; 126:11, 18;  
127:5, 17; 128:10, 15, 19,  
22, 25; 129:11, 15; 131:1;  
132:18; 133:8; 135:19;  
136:21; 138:21; 139:24;  
140:2, 19; 141:17, 22;  
142:11, 24; 143:18; 144:9,  
23; 145:6, 8; 147:1; 149:1,  
6, 22; 151:2  
**McKenzie** 88:5  
**me--there** 104:8  
**mean** 21:4; 22:5; 31:3;  
32:9; 52:24; 59:1; 71:9;  
86:3; 89:5, 17; 95:4; 96:16;  
101:25; 115:6; 117:6;  
121:11; 126:1; 128:23;  
138:18  
**meaning** 51:13; 54:14  
**meaningful** 32:12; 72:9  
**meaningless** 93:23  
**meanings** 8:21  
**means** 21:1; 40:8; 71:6;  
83:13; 115:10; 120:2;  
135:8  
**meant** 6:15; 120:18  
**measure** 13:14; 49:5;  
56:24; 63:1; 65:20; 76:2,  
10; 77:10; 103:16; 114:20  
**measured** 24:16; 39:4;  
65:19; 75:20; 105:21  
**measurement** 20:24;  
75:15, 21; 111:14  
**measurements** 16:4, 5;  
18:12; 28:3, 5; 40:17; 62:8;  
80:17  
**measures** 17:16  
**measuring** 70:17;  
105:18; 143:5, 8  
**Medical** 60:7, 17, 22;  
61:10; 95:12  
**medication** 143:9  
**medications** 144:18;  
149:14; 150:18  
**Medicine** 60:10; 61:1;  
133:5  
**medium** 54:13; 56:22  
**meet** 102:23; 104:16  
**meeting** 4:6, 23, 24, 25;  
5:8; 14:9; 28:22; 88:23;  
89:1; 147:4  
**melanocytes** 131:9  
**member** 119:5; 128:17,  
20; 139:8, 8; 141:20  
**members** 4:18; 5:7; 6:1;  
13:6; 59:19; 92:12; 125:5;  
136:22; 137:1; 146:3, 7, 15  
**membrane** 50:2, 12, 13,  
18; 51:1, 2, 4, 4, 6, 12, 18;  
52:8; 53:16, 23, 23, 24;  
54:22, 24; 55:1, 2, 5, 8;  
87:9, 10  
**membrane's** 55:9

**membrane--obviously**  
53:14  
**membranes** 50:5; 51:15  
**Mencken** 91:22  
**Mencken's** 91:17  
**mention** 94:10; 97:18  
**mentioned** 14:22; 36:14;  
37:14; 38:14; 40:15;  
65:18; 74:12; 75:11;  
87:14; 88:19; 90:15;  
107:7; 144:19  
**mentions** 83:7  
**messages** 48:10  
**met** 16:10  
**metaphor** 132:17  
**metered** 137:22  
**method** 19:20; 20:7, 9,  
11; 23:1; 24:9; 26:8; 30:25;  
36:18, 18; 37:8, 17; 47:18;  
49:8, 10; 63:3; 75:6, 7;  
76:8, 16, 20, 20; 77:22;  
89:2, 6, 7; 90:6, 8; 97:1;  
98:1, 6, 20, 22; 99:23;  
100:5; 114:20; 115:22;  
123:11; 124:5; 125:13, 20;  
126:7, 22; 143:13; 144:17;  
148:16, 16; 149:9  
**methodologies** 74:2, 20;  
90:2; 147:11  
**methodology** 18:17;  
27:12; 30:21; 31:2, 8; 32:7;  
35:17; 36:7; 61:22; 62:8;  
66:10; 74:25; 75:12, 12,  
25; 76:6, 18; 90:13; 116:4;  
118:15; 127:7; 128:11  
**methods** 31:1, 2; 57:25;  
89:10; 98:8; 126:1;  
132:24; 145:24  
**methosetrolin** 142:17  
**metric** 137:12  
**Mexico** 61:3  
**mg/cm2** 54:5, 5; 113:12  
**MIC** 123:21  
**micella** 56:12, 13, 15  
**micelles** 56:12  
**Michigan** 60:12, 24  
**miconazole** 25:22  
**microbeads** 44:4  
**microcomedones** 33:8  
**microgram** 134:15  
**micrometer** 43:21  
**micrometers** 33:6  
**microphone** 4:10;  
100:23; 104:5  
**microphones** 4:16  
**microsecond** 110:23  
**middle** 7:1; 50:24; 54:9;  
101:17  
**middle-aged** 97:17  
**might** 12:22; 27:24; 31:4;  
35:3, 7; 36:1; 47:13; 49:19;  
53:7, 8; 57:19; 70:18, 19;  
84:17; 89:5, 10; 90:3;  
96:15; 106:17; 111:10;  
116:10; 120:6; 138:25;

140:5; 149:20  
**Mike** 60:1  
**mild** 22:15  
**Mill** 91:23  
**MILLER** 61:9, 9; 138:22;  
140:2, 3; 141:7; 143:2;  
144:19; 149:7  
**Miller's** 149:25  
**milliliter** 69:12  
**milliliters** 69:7  
**mind** 26:3; 37:13; 46:21;  
72:14; 78:11; 80:10  
**MINDEL** 60:6, 6; 149:22,  
23  
**minor** 18:25; 37:22;  
40:16  
**minus** 82:19; 128:3  
**minute** 8:9; 13:12  
**minute--l** 105:11  
**minutes** 6:6; 15:14;  
20:10; 22:4; 28:7; 33:4;  
42:16; 57:14; 88:17;  
113:14; 122:9  
**misleading** 48:2  
**misread** 105:15  
**mission** 58:14; 88:24  
**mistake** 57:5; 121:18  
**misunderstanding--l**  
139:6  
**misunderstood** 96:20  
**mixed** 56:8  
**ml** 69:16, 17; 107:10, 11  
**mm** 63:19  
**modalities** 15:25  
**model** 41:2; 106:6  
**modeled** 36:1  
**modified** 86:23  
**modifying** 32:6  
**moiety** 6:23; 9:1; 15:19,  
20  
**moisture** 64:12; 134:19;  
136:15  
**molecules** 53:21  
**moles** 102:25; 103:4  
**moment** 64:20  
**months** 32:8; 105:4  
**more** 10:10; 17:1; 22:14,  
24; 24:2; 30:17, 25; 35:22;  
41:18; 42:6; 43:9; 46:12;  
47:13, 13; 52:4; 54:14;  
57:16; 58:15, 15; 67:21;  
70:22; 72:19; 74:20, 21;  
75:3; 76:16, 19; 83:19;  
90:7, 12; 96:13; 98:4;  
103:18, 19; 104:1, 23;  
108:18, 23, 24; 110:20;  
112:5, 10; 115:21; 116:20;  
118:12; 119:18; 121:4;  
124:7; 125:1; 126:6, 25;  
127:13; 128:10; 132:15;  
137:19; 138:4; 144:24;  
146:16, 18, 24; 151:21  
**morning** 4:3, 15, 21; 8:4;  
11:19; 13:2; 14:1, 10;  
31:20; 47:10; 59:15, 16;

61:19; 62:17; 71:2; 80:23;  
91:25; 92:2, 13, 22; 133:3;  
144:10; 149:4; 151:3  
**morning--is** 150:11  
**mortar** 91:7; 93:21  
**most** 13:13; 15:20; 19:19,  
23; 26:19; 48:6, 6; 50:21,  
22; 53:17; 57:25; 63:18;  
66:8, 24; 77:14; 81:18;  
97:6; 100:10; 112:25;  
126:22; 130:9  
**mother** 94:19  
**mountains** 34:8, 9  
**move** 119:9, 11; 137:11;  
142:2, 9  
**movement** 53:21  
**moving** 106:3; 109:16  
**Mt** 60:7  
**much** 18:8; 25:11; 33:20;  
34:7; 35:7; 46:11; 54:9;  
59:6; 64:5; 65:25; 68:14;  
72:12; 75:7; 76:21; 77:24;  
84:8; 85:9; 87:23; 91:2;  
93:8; 96:16; 98:24;  
104:16, 25; 106:20;  
108:24, 24; 110:25; 112:5,  
8, 10; 129:21, 21; 134:2;  
141:17; 142:11; 144:23;  
147:1  
**multi-source** 9:19;  
14:20; 15:19  
**multiple** 9:16; 21:25;  
22:6; 131:16; 150:5  
**multiplied** 142:21  
**multiplier** 88:4  
**must** 9:20; 14:25; 15:15;  
21:18; 41:2; 86:15; 96:3;  
99:14; 102:23; 103:22;  
105:17; 134:22, 22, 22  
**myself** 6:9; 12:9; 73:19;  
102:6; 133:20; 139:3

**N**

**n** 68:24  
**nails** 94:5  
**name** 5:24; 84:16; 86:2;  
88:12; 90:24; 94:20, 20;  
115:12; 147:9, 14; 148:24  
**name--who** 94:11  
**names** 94:16  
**nanogram/square** 23:2  
**nanoparticles** 45:2  
**nasally** 17:19  
**natural** 53:18, 25; 99:10  
**nature** 26:25; 27:1;  
123:25; 136:1  
**near** 142:9  
**nearly** 87:23; 109:6  
**necessarily** 59:1;  
145:24; 147:16  
**necessary** 149:14  
**need** 5:15; 11:22; 26:4;  
15; 27:23; 30:19; 33:17;  
35:13; 69:9; 72:3; 78:17;

90:12, 16, 17; 92:7;  
109:14; 135:21; 138:4;  
139:19; 143:16; 144:13;  
145:23; 146:24; 147:10  
**need—that** 31:5  
**needlestick** 67:21  
**needs** 115:23; 118:11;  
122:21; 123:23; 131:7;  
148:18  
**negative** 65:16; 66:14;  
133:24  
**neither** 86:15  
**net** 65:4, 7  
**networks** 56:13  
**Neurological** 61:6  
**new** 6:21; 7:5; 12:24;  
13:8; 14:13; 26:11; 58:6;  
59:21; 60:8; 61:3; 74:2;  
89:18; 112:21, 21; 117:25;  
138:5; 143:3  
**Newark** 94:13  
**newer** 141:14  
**next** 6:6; 12:25; 13:9;  
15:4, 22; 17:6; 36:11;  
39:24; 41:1, 16; 47:3; 58:3;  
59:18; 61:13; 82:13; 83:4;  
122:19; 132:9, 12; 133:8;  
138:23  
**nice** 24:16; 81:14; 82:3;  
132:23  
**nit** 53:20  
**nitroglycerine** 87:20  
**Nobody** 99:14  
**noisy** 138:17; 151:23  
**non** 115:13  
**non-inferiority** 115:16  
**non-invasive** 21:19;  
67:20  
**non-stationary** 51:22;  
52:2, 11  
**none** 57:4; 92:1; 111:3  
**Nonetheless** 92:24  
**nonlinearity** 87:19  
**nor** 86:15; 87:10  
**normal** 21:10; 37:16;  
41:13, 20, 23; 42:5, 7, 13,  
17; 43:7, 10, 13; 44:9, 13;  
70:4; 83:8; 97:15; 99:1, 4,  
10; 100:11; 107:17; 114:2,  
6, 8; 116:15; 117:4  
**normalize** 69:11; 70:12;  
71:1; 101:11; 125:21  
**normalized** 71:2  
**note** 79:5  
**noted** 5:16; 103:24  
**notes** 93:9  
**nothing** 30:1  
**notice** 106:21  
**notion** 29:15, 24, 25;  
30:4; 86:22; 122:24; 129:2  
**novel** 73:21  
**nowhere** 98:19  
**NS** 126:6  
**nuance** 131:15

**nuisance** 131:13; 151:15  
**number** 29:18, 21; 30:10;  
62:21; 66:12; 67:2; 68:20;  
71:5; 102:22; 117:12;  
118:5; 131:10; 132:3;  
142:23; 143:15, 16  
**numbering** 86:23  
**numbers** 51:12; 54:9;  
106:5  
**numerous** 62:12

**O**

**o'clock** 4:15; 6:8  
**objective** 91:20; 120:23  
**objectivity** 75:21  
**observation** 91:17;  
105:22  
**observed** 77:14; 104:8  
**obtained** 5:9; 64:22, 23;  
81:14; 82:6; 91:9; 108:4  
**obvious** 149:4  
**occasion** 142:14  
**occasionally** 78:14  
**occasions** 12:2  
**occluded** 54:21  
**occur** 38:11  
**occurring** 55:8  
**occurs** 38:4; 110:1  
**Odds** 47:7  
**off** 52:23; 65:6; 87:23;  
116:25; 137:4; 150:11  
**offer** 74:6; 75:7  
**Office** 5:11; 6:18; 7:3, 5,  
5, 6, 6; 12:24; 60:4  
**often** 30:9, 19; 32:24;  
54:14; 114:16  
**ointment** 22:15  
**Oklahoma** 60:21  
**old** 95:9  
**older** 114:18  
**once** 27:4; 66:4; 80:7;  
105:4  
**one** 4:10; 7:16; 8:5, 17;  
11:6; 12:1, 1; 16:6; 17:7,  
21; 19:14; 23:4; 24:7; 26:5,  
12, 13; 29:14, 18; 30:6, 15,  
15; 31:12; 33:3, 11; 34:1;  
35:1, 3, 7; 38:13; 41:5, 5;  
44:5; 45:16, 17; 48:10;  
52:12, 17; 54:10; 57:24,  
25; 58:1, 2, 61:14; 65:18;  
66:9; 68:7; 72:13, 24;  
74:22; 75:3, 12, 22; 77:5;  
85:3; 88:5; 91:15, 25; 95:1,  
2, 6; 96:14; 98:1; 100:11;  
102:23; 105:4, 23; 107:16;  
109:19; 110:19; 111:16;  
114:10; 115:20; 116:11;  
117:1, 13, 13, 14; 118:17;  
119:24; 122:23; 124:9;  
126:13; 127:19; 128:10,  
17, 19, 20; 129:5; 130:2,  
12, 21; 131:24; 132:8, 11;  
133:10; 134:25; 135:7, 19;

139:8, 8; 144:4; 146:4, 9,  
18; 150:11  
**one-inch** 63:21  
**ones** 7:21; 58:19  
**ongoing** 144:11  
**only** 4:10; 12:9; 19:3, 14;  
35:1; 38:12; 39:10; 41:12;  
44:16; 52:3; 58:1; 61:14;  
69:7; 70:19; 71:18; 75:22;  
78:14, 21; 79:15; 90:3;  
96:9; 98:1, 5; 106:22, 23;  
108:1; 109:1, 10, 12;  
115:12; 117:4; 118:9;  
120:18; 131:15; 133:4;  
141:8, 15; 142:21; 143:12;  
145:23  
**onset** 63:10  
**onto** 64:19; 68:17  
**open** 28:18; 54:14; 61:13,  
18; 72:14; 92:11; 130:6  
**opening** 104:6  
**operation** 26:19  
**Ophthalmic** 4:7; 89:24  
**Ophthalmology** 60:7  
**ophthalmology—that**  
150:14  
**opinion** 96:5; 104:9, 23;  
128:16, 18, 19; 141:23  
**opinions** 121:20  
**opportunity** 6:2; 62:3;  
63:12; 77:25; 146:3  
**optimistic** 89:12  
**optimize** 30:12  
**optimum** 111:10  
**option** 78:16  
**oral** 17:18; 21:6, 10, 11;  
34:1; 69:6; 74:14, 18; 75:2;  
79:1, 1; 107:11; 114:1;  
130:7; 131:23  
**orange** 8:5; 16:13  
**Order** 4:2; 9:20; 29:22;  
39:25; 52:6; 55:15; 64:11;  
66:21; 75:21; 77:1, 7; 97:1;  
99:20; 113:17, 19; 129:25;  
134:24  
**orders** 44:10  
**ordinary** 57:20; 58:19  
**organ** 62:12; 103:15;  
132:1  
**organic** 29:19  
**organisms** 99:2  
**organization** 94:18;  
95:12; 97:11  
**organizational** 6:18; 7:1  
**organizationally** 6:13  
**organizers** 72:24; 74:23  
**organs** 34:16; 133:4  
**original** 129:23  
**originally** 61:24; 105:14  
**originate** 32:15  
**originator** 129:19  
**others** 35:20; 92:3;  
102:5; 129:16; 145:9  
**ought** 73:1; 75:1; 112:1

**ourself** 74:24  
**ourselves** 89:1; 95:8  
**out** 19:6; 20:5, 18; 21:22;  
29:2; 32:13; 34:5, 20;  
48:17; 51:11; 53:15;  
65:15; 67:19; 71:4; 73:7,  
15; 76:15; 77:14, 21;  
82:19; 83:1, 16; 84:22;  
88:9; 89:16; 91:8, 12, 23;  
93:13, 18; 95:5; 97:1; 98:8;  
100:2; 101:11; 107:2;  
110:11; 121:10, 17, 24;  
126:3; 133:9; 136:19;  
138:23; 146:7; 148:10  
**outcomes** 52:10; 53:12  
**outer** 69:20  
**outline** 34:9  
**output** 111:6  
**over** 6:10; 7:2, 19; 8:5;  
10:9; 15:4; 18:6; 30:8;  
32:7; 35:10; 54:6, 17, 22;  
71:14; 81:8, 16; 82:17;  
92:6; 100:11; 105:3;  
117:22, 25; 134:1, 13;  
135:2; 137:25; 138:12  
**over-the-counter** 95:14  
**overall** 66:10  
**overhead** 15:24; 107:14,  
15; 108:8; 109:3  
**overhead—and** 17:6  
**overhead—focuses** 7:22  
**overnight** 64:10; 136:2  
**Overview** 5:23; 11:24;  
16:16  
**overwhelm** 134:20  
**own** 94:19; 144:2;  
145:23; 146:6, 25  
**oxide** 45:17

**P**

**package** 30:7  
**packaging** 9:3  
**page** 92:20  
**pages** 150:24  
**Paired** 101:7  
**panel** 17:13, 17, 22;  
119:2, 5; 121:1, 7  
**paper** 33:7; 73:6, 6;  
111:19; 151:5  
**papers** 33:12, 14  
**papillary** 110:3, 12  
**parakeratotic** 93:20  
**parallel** 126:16  
**parallels** 49:22  
**parameter** 64:3; 103:15;  
125:16  
**parameters** 13:21; 27:2;  
63:9; 65:18  
**pardon** 135:24  
**Paris** 61:5  
**Parker** 94:15  
**Parklawn** 5:11  
**part** 4:23; 7:8, 11; 52:21;

53:17; 70:13; 80:23;  
110:8; 115:16; 132:17;  
133:7  
**participant** 5:14  
**participants** 5:2, 15, 18  
**participating** 5:8  
**particle** 28:9; 38:5, 16,  
16; 45:14; 58:9, 12; 83:24,  
25; 120:7; 121:15; 122:7,  
8; 151:7  
**particles** 38:5; 43:21, 23;  
44:22  
**particular** 5:4; 6:13, 20;  
7:9; 8:2; 15:24; 16:16;  
20:6; 21:23; 50:15; 74:4;  
75:15; 88:22; 118:3;  
124:11; 132:5; 133:5  
**particularly** 6:21; 55:15;  
64:3; 101:12; 134:16  
**partition** 51:2, 14; 52:7;  
85:8, 13; 86:22, 25; 87:9;  
148:4  
**partitioned** 110:11  
**pass** 50:19; 127:11  
**passed** 150:18  
**passes** 110:21  
**passing** 42:14  
**passive** 30:3  
**past** 66:4  
**patent** 9:12, 15  
**patents** 130:6  
**path** 25:10; 35:18  
**pathway** 27:20; 28:1, 2;  
32:22, 25; 33:18, 21, 22;  
41:14; 42:24, 25  
**pathways** 27:24; 29:20;  
32:20; 36:12; 47:18  
**patient** 10:18; 97:6, 8;  
114:6; 121:6, 8; 127:15  
**patients** 90:4; 99:1;  
121:9, 12, 12; 139:10, 10,  
11; 142:23; 143:15, 16;  
144:14; 146:20  
**pay** 12:7  
**peak** 13:22; 43:3  
**Pediatrics** 61:12  
**peer** 31:2  
**peers** 103:24  
**pending** 138:4  
**penetrability** 96:11  
**penetrated** 22:22; 50:18;  
131:13  
**penetration** 33:18;  
34:22, 24; 35:7; 36:1, 21,  
23, 24, 25; 37:7, 23; 38:18,  
19, 20, 20; 39:5; 45:24;  
46:20; 51:1, 17; 62:14;  
76:8; 77:2; 93:24; 99:7;  
111:24; 151:9, 9  
**Pennsylvania** 61:10  
**people** 28:25; 49:12;  
50:23; 54:6; 59:17, 19;  
73:9, 12, 18; 74:1; 89:4;  
93:7; 94:25; 97:7; 98:20;  
101:22; 103:18, 18; 105:3,

6; 107:6; 130:9; 133:16,  
18; 136:10; 137:20;  
24; 141:9; 143:24  
23:2; 69:12  
**percent** 33:4; 39:17, 20;  
56:25; 71:12, 18; 75:7;  
81:20; 82:19; 103:17;  
106:23; 128:3  
**percutaneous** 33:18;  
34:21, 23; 35:7, 25; 98:17,  
18  
**perform** 54:10  
**performance** 10:8, 21,  
22; 11:10; 17:5; 54:18  
**performs** 104:2  
**perhaps** 35:3; 47:11;  
88:3; 90:7; 97:25; 114:8;  
118:18; 123:9  
**perifollicular** 33:13  
**period** 8:23; 9:6, 6, 8, 10;  
10:14; 11:13; 50:1; 51:5;  
55:10; 71:15; 111:1, 2;  
117:22; 118:1; 134:1, 13;  
135:2  
**permeability** 98:15  
**permeating** 118:22  
**permeation** 39:5; 52:2  
**Pershing** 25:2, 20; 29:4;  
73:11; 102:11, 14, 18, 18;  
104:14; 141:2  
**erson** 64:1; 73:24;  
2, 10, 21, 22, 24;  
105:8; 121:13; 132:11;  
146:6, 9, 9, 9  
**personal** 151:4  
**personally** 38:21; 48:11;  
132:19  
**persons** 111:22  
**perspective** 8:3; 114:19  
**Perspectives** 5:23;  
29:11  
**perturbation** 65:25  
**perturbed** 97:11, 12  
**Pharma** 73:19  
**Pharmaceutical** 7:3, 12,  
25; 15:17; 28:24; 60:4;  
131:6  
**Pharmaceuticals** 72:18;  
73:19, 20  
**Pharmaceutics** 60:15  
**pharmacodynamic**  
16:4; 19:13; 23:10; 75:12;  
85:19; 86:16; 88:4;  
137:22; 141:1, 4  
**pharmacodynamics**  
17:2; 40:16; 75:25  
**pharmacokinetic** 13:21;  
16:4; 17:15; 23:23; 24:18;  
17; 47:7; 69:11; 70:25;  
11, 25; 77:2; 140:25  
**pharmacokinetics**  
13:14, 18; 40:22; 61:16;  
77:3; 98:25, 25; 123:14;  
126:3  
**Pharmacology** 7:7; 60:7;  
94:9

**Pharmacy** 60:13, 15;  
147:25; 148:1  
**phase** 21:12, 13; 24:25;  
71:22; 109:23  
**phases** 20:13  
**phenomena** 135:14  
**photo** 97:8; 101:23;  
103:1, 10  
**photo-damaged** 97:10,  
16, 19  
**photobiology** 144:12  
**physical** 112:23; 120:6  
**physical-chemical**  
130:15  
**physical/chemical** 37:4;  
38:3; 45:15  
**physically** 99:14  
**physician** 74:10  
**physicians** 149:15  
**pick** 55:4, 6; 57:19;  
127:25; 134:22  
**picked** 135:5  
**picking** 134:10, 19;  
135:11  
**pickup** 134:21  
**picture** 6:16; 71:4  
**pictures** 126:12  
**piece** 25:1; 92:5; 134:7,  
10, 12; 135:3  
**pieces** 142:3  
**pilo-sebaceous** 33:13  
**pilot** 26:5, 7; 27:2, 7; 77:6  
**pioneer** 9:10; 10:2;  
11:11, 12, 17, 20; 14:17;  
120:3  
**pivotal** 10:4; 26:6; 77:10,  
11; 138:9  
**PK** 137:24  
**place** 43:14  
**placebo** 129:20; 130:2  
**places** 28:19; 58:25  
**plain** 134:6  
**plan** 48:17; 147:12  
**Plaque** 4:5  
**plasma** 21:7; 33:25; 34:2,  
14, 15, 16; 35:23; 46:15,  
17; 69:12; 72:5; 76:20, 22;  
131:25, 25; 132:15;  
146:22  
**please** 37:13; 41:16;  
46:21; 48:15; 72:19;  
77:20; 79:5; 96:23; 104:8;  
119:6; 127:5  
**plot** 71:10, 11, 17  
**plotting** 65:15  
**plus** 26:16; 82:19; 84:4;  
128:3; 141:2  
**point** 8:9; 9:14, 15, 18;  
25:12; 28:8; 31:5; 32:12;  
37:2; 40:20; 48:22; 49:2, 3,  
3, 50:25; 52:16; 53:25;  
58:24; 67:19; 93:25;  
102:9; 107:13; 109:25;  
110:16, 19; 113:8, 20, 22;  
114:24, 25; 118:2, 21;

122:20; 130:17; 132:13;  
135:6, 7; 138:16; 139:18,  
21; 141:15; 145:2, 10;  
147:25; 151:12  
**point-to-point** 53:21  
**pointed** 19:6; 21:22;  
146:7  
**points** 27:6; 33:11; 36:14;  
47:9, 21; 89:20; 91:12;  
103:8; 105:20; 114:10;  
132:4  
**policy** 7:17, 17, 23, 25;  
93:1; 95:16; 143:21  
**polymorphism** 38:6  
**poorly** 106:22  
**population** 103:17;  
107:8  
**portion** 51:22; 69:8;  
111:23  
**pose** 12:8; 146:14  
**position** 50:13; 56:1;  
127:14; 129:15; 137:25;  
138:22; 143:2; 144:16;  
145:3  
**position-I** 138:3  
**positive** 73:6  
**possibilities** 89:12  
**possibility** 89:9  
**possible** 19:20; 55:5;  
82:7; 122:13; 138:18;  
146:18  
**possibly** 87:1; 88:3;  
100:1; 121:3  
**post-approval** 11:13;  
120:4; 138:8  
**postpone** 92:7  
**potassium** 56:10; 57:17  
**potency** 141:3  
**potent** 38:18, 19  
**potential** 129:4  
**power** 36:19; 129:25;  
143:13  
**practical** 62:6; 81:17  
**practice** 90:16  
**preapproval** 8:23  
**precise** 71:23; 90:7, 10  
**precision** 26:9; 36:18;  
63:20  
**preclude** 4:24  
**predict** 71:25; 81:2; 82:8,  
24; 88:6  
**predicted** 31:14; 86:16  
**predicting** 112:20  
**predictive** 112:20  
**preferentially** 33:9  
**premise** 37:3  
**premises** 31:12  
**preparation** 37:24;  
150:23; 151:10  
**preparations** 43:22;  
46:22; 100:5; 150:16  
**prepared** 14:11; 72:20,  
20; 81:7; 145:14  
**prepublication** 20:4

**prescription** 95:11, 15  
**presence** 40:23; 41:7;  
120:4  
**present** 31:4; 61:20;  
62:3, 6; 63:7; 114:25  
**presentation** 12:18;  
18:5, 11; 61:14; 72:13, 13,  
21; 129:6  
**presentational** 15:5  
**presentations** 6:8; 8:5;  
78:2  
**presented** 14:4; 32:11;  
36:10; 61:24; 65:10;  
67:25; 86:11; 92:2, 20;  
101:25; 107:4; 108:2;  
119:21; 133:1; 139:22;  
145:18; 148:5  
**presenters** 92:13  
**presenting** 6:11; 28:25  
**pressure** 22:20  
**presumably** 85:19;  
106:13  
**presume** 121:2  
**presumed** 101:8  
**pretty** 12:15; 85:9;  
104:15  
**previous** 5:20; 25:6;  
51:24; 55:19; 61:23; 73:2,  
14; 74:19; 76:21; 125:20  
**price** 74:8  
**primarily** 12:5; 26:18;  
144:20  
**primary** 125:6; 137:7;  
138:9; 149:18, 19  
**principal** 20:5; 55:2  
**principally** 26:4  
**principle** 21:24; 36:22;  
47:17  
**principles** 24:3, 3; 25:14,  
18; 26:8; 28:17, 20; 47:5;  
49:20; 50:4; 51:16; 53:12;  
80:9; 126:24  
**printed** 4:8  
**prior** 9:6; 10:18; 44:9  
**privilege** 99:6  
**pro-inflammatory** 118:6  
**probability** 48:5  
**probably** 34:7; 52:17;  
64:6; 66:8; 68:11; 69:21;  
70:22; 106:7; 131:21;  
138:6, 13; 144:17; 145:23;  
149:9; 150:24  
**problem** 36:21; 67:1;  
70:25; 94:4; 99:9, 10;  
114:9; 135:6, 15; 141:8,  
11; 142:24; 150:12  
**problem-backing**  
150:10  
**problems** 66:10; 91:25;  
100:7; 103:20; 144:21  
**procedural** 135:20  
**procedure** 22:11; 47:11,  
13; 48:23; 51:20; 64:16;  
105:17; 133:21  
**proceed** 29:1; 78:16

**PROCEEDINGS** 4:1  
**process** 6:21; 13:8; 52:2;  
53:12; 55:3, 7; 63:23; 64:1;  
79:17, 22, 25; 93:6; 114:4;  
117:17; 119:16, 19, 23;  
130:15  
**processes** 52:14; 53:25;  
111:6  
**processing** 57:20; 58:17  
**produce** 21:3  
**producing** 57:4  
**product** 5:4; 6:25; 7:10,  
10; 8:8, 19, 25; 9:6, 17, 18;  
10:8, 10, 21, 22, 25; 11:7;  
12:7, 20; 13:15; 15:1; 16:9,  
11; 18:4; 19:2, 8, 21;  
21:21, 21, 23, 23, 25;  
22:12; 23:6, 6, 7; 26:5, 25,  
25; 27:1; 28:12; 29:21, 22;  
31:23; 53:2; 57:4; 58:17,  
21; 59:4; 68:9; 70:17;  
77:14; 78:13, 20; 79:20;  
80:2, 4, 8, 11, 14, 15, 17,  
20, 25; 82:13; 84:16, 17;  
85:11; 86:2, 9; 88:2; 90:24,  
24; 93:21; 95:5; 101:5, 6;  
104:15; 122:21; 129:20;  
147:9  
**production** 57:19; 58:6;  
91:19  
**Products** 4:4; 5:5, 13, 20;  
6:4; 7:13; 10:11, 12, 16;  
13:23; 14:21; 15:21; 16:8,  
20, 22; 17:19, 22, 23;  
18:19; 19:15, 19; 20:8;  
21:2; 23:12, 18, 19; 24:13;  
27:14, 14, 21; 29:13;  
31:13, 17; 48:8; 60:3;  
72:10; 73:21, 21; 74:3, 4,  
6, 7; 75:11, 13; 76:4, 13;  
77:13, 18, 21, 23; 78:12,  
15; 79:1, 1, 3, 9; 81:2;  
82:16; 83:21; 84:6; 94:15;  
103:13; 104:3; 105:8;  
108:12; 115:2; 118:16;  
126:19; 127:1; 129:23;  
130:1, 5, 18; 138:12;  
140:5; 141:12, 13; 144:3  
**products-and** 150:14  
**Professor** 24:1; 25:2, 20;  
28:6; 29:3, 4, 5, 6; 79:19;  
94:8, 9  
**professors** 73:10  
**profile** 26:23; 34:10;  
71:20; 79:6; 104:15; 111:4  
**profiles** 20:14; 23:23;  
24:19; 79:5; 84:3; 102:21;  
104:20; 130:8  
**profound** 151:8  
**progesterone** 41:15, 18  
**program** 4:8, 14; 27:3  
**progress** 65:1  
**promising** 144:17  
**promptly** 93:3  
**proof** 29:18  
**properly** 116:4; 148:22  
**properties** 38:4; 45:15;

50:3; 52:10, 13; 83:18;  
88:10; 101:14; 144:13  
**property** 80:24, 25;  
135:1, 25  
**proportional** 81:8;  
82:12; 85:7, 12, 18; 86:5  
**proposal** 79:8; 85:16;  
114:11  
**proposals** 14:2  
**proposed** 49:8, 23; 90:6;  
117:6; 122:4  
**proposing** 117:7;  
119:11, 12; 120:24  
**proprietary** 151:11  
**protection** 9:11, 11, 14,  
16  
**protective** 111:20;  
144:12  
**protects** 112:8, 9  
**protocol** 68:7; 77:7, 7  
**prove** 45:4; 46:25  
**provide** 17:11; 18:7;  
21:1, 7; 28:2, 10; 77:22;  
83:19  
**provided** 96:24; 147:7  
**provides** 31:11; 123:6  
**providing** 24:2; 78:16  
**provisions** 9:12  
**pseudoclinical** 49:13  
**Psoriasis** 4:6; 93:15, 18  
**psoriatic** 34:24; 99:9  
**public** 6:23; 28:18; 59:9;  
61:13, 14, 18; 72:14; 93:1  
**published** 9:3; 20:2;  
25:21; 98:21  
**Puerto** 58:6  
**pulled** 65:6  
**pulling** 136:18  
**punch** 99:17, 19  
**punched** 93:16  
**pure** 91:19  
**purity** 95:14  
**purpose** 38:14; 45:5;  
121:23  
**pursue** 148:24  
**put** 25:6; 50:9; 52:3, 4;  
54:12, 22; 57:24; 83:18;  
85:11; 91:7, 14; 100:5;  
110:18; 118:4; 142:3  
**puts** 122:8; 131:4  
**putting** 57:5  
**puzzled** 106:9

**Q**

**Q1** 81:5, 8, 16; 82:4;  
104:17  
**Q1/Q2** 81:5  
**Q2** 81:5, 8, 16; 82:5  
**qualified** 145:10  
**qualitatively** 76:5  
**quality** 6:3; 7:10, 10; 8:7,  
19, 25; 9:1; 10:17, 21, 22;

12:7; 57:6, 20; 58:22; 74:7;  
82:12; 90:3  
**quantify** 33:20  
**quantitate** 33:17; 76:22;  
106:18; 135:4  
**quantitative** 39:3; 99:20  
**quantitatively** 76:4  
**quantities** 99:19  
**question—I** 138:2  
**quickly** 48:19; 54:15;  
55:11; 67:5; 110:11;  
122:13  
**quite** 41:25; 67:15; 74:1;  
91:15; 97:16; 106:8;  
122:5; 128:5; 133:1;  
151:23, 23, 24  
**quote** 89:11  
**quoted** 33:13

**R**

r 40:5  
**radioactive** 39:23  
**radioactivity** 39:20  
**raise** 66:15; 123:10;  
127:2  
**raised** 27:22; 111:17;  
123:19, 23; 147:13, 18  
**raising** 124:9  
**ran** 58:3; 94:25  
**randomized** 150:5  
**range** 54:9; 128:5  
**rare** 78:12  
**rat** 41:5  
**rate** 11:1, 6; 13:16; 31:22;  
58:4; 72:4, 9; 79:23; 80:23;  
81:14; 82:11; 83:6, 12;  
84:22; 85:17, 21; 86:17;  
87:8; 88:6; 148:11  
**rates** 36:9; 76:7; 82:9;  
84:13; 86:1, 14; 88:15;  
148:6  
**rather** 5:4; 30:23; 43:10;  
57:21; 58:19; 81:8, 19  
**rating** 16:13  
**ratio** 36:9; 37:18; 38:10;  
43:8; 80:18, 20; 81:2, 4, 8;  
82:5, 6, 8, 18; 84:12;  
85:21, 21, 23, 23; 88:6;  
148:13  
**rational** 56:1  
**ratios** 81:16, 17; 82:4, 17,  
22, 24; 86:3; 88:15; 148:11  
**rats** 41:4  
**raw** 71:5  
**re-read** 147:6  
**re-weighted** 134:5  
**reach** 113:13  
**reached** 68:20  
**reached—I** 129:5  
**reaching** 48:5  
**reaction** 117:20  
**read** 4:12; 6:16; 48:19;

73:6; 76:14; 105:14;  
108:20; 147:6; 151:5  
**readily** 77:4  
**reading** 75:22; 84:20  
**ready** 142:2; 151:24  
**real** 54:6; 90:23; 133:13  
**reality** 11:11; 72:5; 138:6,  
11  
**realize** 79:13  
**realized** 67:5  
**really** 6:15; 8:15; 13:19;  
19:11; 23:17; 30:1, 4;  
32:20; 33:19, 22; 34:10;  
35:2, 15; 47:23; 49:25;  
65:25; 66:2; 67:17; 69:25;  
70:1, 20; 71:5; 73:23; 77:6;  
84:14; 87:19; 88:9; 89:17;  
90:23; 91:11, 18; 96:8;  
107:4, 23; 117:5; 118:19,  
20; 122:22; 124:17; 128:7;  
129:11; 131:7; 132:6, 7,  
15; 141:12; 143:6, 9;  
147:7, 24; 150:9, 12, 15;  
151:6, 15  
**reanalyze** 76:22  
**reason** 16:23; 25:11;  
52:3, 4; 59:2; 64:20; 76:24,  
25; 91:19; 95:13; 98:2;  
141:14; 144:7  
**reasonable** 18:3; 58:18;  
67:9; 121:8; 126:25;  
134:24; 142:23  
**reasonably** 146:11  
**reasons** 72:2; 98:1  
**recall** 79:19  
**receive** 14:23; 15:3, 16  
**received** 92:1, 4; 145:15  
**receives** 16:12  
**Recess** 59:14  
**reciprocal** 51:4  
**recognize** 11:15  
**recognizing** 12:6  
**recollection** 111:19  
**recommend** 58:21;  
99:25; 100:7; 113:17;  
148:23  
**recommendations** 8:12;  
17:11; 73:3; 74:19  
**record** 4:23; 5:17  
**recovered** 68:18  
**recovery** 39:17; 69:4;  
70:21, 25; 71:12, 13, 14,  
17, 18  
**red** 41:4  
**reduce** 30:9; 68:11;  
146:8  
**reemphasize** 46:14;  
108:11  
**reestablished** 11:22  
**refer** 73:5; 75:17  
**reference** 14:25; 21:20,  
21, 21, 25; 23:6, 7; 72:10;  
80:1, 11, 17; 86:1, 10;  
88:11; 98:20, 21; 100:4;  
101:2; 104:14, 20; 146:5

**referent** 68:8  
**referred** 32:24; 35:13;  
100:13  
**refers** 8:19; 9:1; 17:13  
**refined** 9:4  
**refinement** 30:11  
**reflect** 76:11  
**reflected** 83:24; 84:2  
**reflects** 76:8  
**regard** 4:23; 114:1;  
136:18  
**Regarding** 4:5; 72:9  
**regardless** 85:10  
**regions** 33:13; 91:13  
**regular** 49:23; 58:11  
**regulations** 9:3, 13;  
15:25; 17:14  
**regulatory** 8:21; 29:24;  
30:4, 24; 31:1; 73:9; 89:19  
**reintegration** 51:25  
**reiterate** 146:2  
**reject** 127:10  
**relate** 8:18; 138:8  
**related** 10:15; 13:3;  
37:15, 16; 39:19, 20;  
43:20; 47:8; 62:21; 69:22;  
115:21; 124:9, 10  
**relates** 6:3; 8:7, 23;  
10:24; 12:25; 14:7; 15:18;  
131:19  
**relation** 71:6  
**relations** 42:4  
**relationship** 8:25; 24:17;  
26:21; 44:17; 50:18;  
52:12, 19; 69:15; 81:15;  
87:6, 14; 88:11; 98:14, 16;  
123:14; 124:1, 2, 5, 11;  
127:22; 147:21  
**relative** 6:13; 10:4, 22;  
11:3, 7; 13:24; 33:21; 42:6;  
49:8; 53:3; 67:21; 117:1;  
132:4  
**relatively** 48:19; 51:12;  
67:20; 103:23; 124:4;  
133:25  
**release** 8:8; 10:24; 12:20;  
13:14; 16:8, 25; 18:3; 19:1;  
28:10; 36:9; 47:8; 49:23;  
52:20; 53:1, 6, 22; 54:10,  
12, 20; 55:4, 7, 11, 16, 20,  
24; 56:2, 20; 57:2, 18;  
58:4, 13; 76:2, 6, 6; 77:21,  
22; 78:19; 79:2, 11, 23;  
80:17, 23; 81:14; 82:9, 11;  
83:6, 12, 18, 23; 84:2, 5,  
12, 22; 85:17, 21; 86:1, 14,  
16, 20; 87:8; 88:6, 15;  
120:7; 147:25; 148:6, 15  
**released** 76:11; 148:8  
**releasing** 83:13  
**relevant** 46:11; 62:6  
**reliable** 104:4  
**relinquish** 151:25  
**reluctance** 151:22  
**rely** 13:4, 13; 14:2; 16:24;

17:15  
**relying** 13:21  
**remain** 9:21; 10:12; 37:17  
**remainder** 4:14; 59:16;  
91:24  
**remains** 46:24  
**remarkable** 96:8  
**remember** 35:14; 94:11;  
103:5; 123:4; 134:25  
**remind** 84:13  
**reminds** 144:10  
**removal** 40:8; 62:22, 23;  
63:22; 64:1, 3  
**remove** 22:16, 21, 25;  
63:14; 64:4, 13; 104:25;  
110:24; 113:14, 19, 20  
**removed** 22:8; 44:10;  
62:22; 63:1; 64:5, 6, 19,  
25; 65:2, 11, 14; 66:9, 15,  
18; 68:1, 17, 22; 104:18;  
117:10  
**repaired** 15:11  
**repeat** 37:22  
**repeating** 79:13  
**repertoire** 58:16  
**repetitive** 117:7  
**replace** 31:2; 90:7; 99:16;  
119:13, 14; 120:2, 18, 24;  
121:3  
**replaced** 120:20  
**replacement** 30:16, 24;  
139:9, 18; 145:20  
**report** 20:2, 4, 6; 62:2;  
72:25, 25; 73:8, 16; 76:14;  
92:4; 105:14  
**reported** 5:1; 133:17  
**reports** 124:19; 145:19  
**represent** 68:2  
**representation** 67:24  
**representing** 73:23  
**represents** 22:22; 56:3;  
65:21; 73:25  
**reproduced** 150:21  
**reproducibility** 26:10  
**reproducible** 104:16;  
106:3  
**request** 5:10; 73:17, 17  
**requesting** 141:6, 10  
**require** 115:1; 130:23  
**required** 30:10  
**requirement** 115:7  
**requirements** 80:1  
**requiring** 143:15  
**resample** 67:8, 16  
**Research** 6:1, 17; 7:6;  
59:25; 61:4; 103:3; 121:11  
**research-based** 73:22  
**researchers** 89:2  
**resembles** 46:15  
**reservation** 133:6  
**reservoir** 37:13, 17;  
38:15; 39:4, 14; 40:24;  
46:4, 13, 14, 14, 18;

112:15,17; 113:9  
**reservoir--and** 37:13  
**stance** 55:6  
**assistant** 55:1, 1  
**resolve** 67:15  
**resolved** 51:24  
**resonates** 32:8  
**resources** 30:14  
**respect** 5:18; 28:4;  
37:23; 43:4; 44:21; 45:9;  
13; 46:13; 80:14; 96:17;  
98:6; 100:20; 109:8;  
112:13; 140:22; 141:10  
**respected** 73:17  
**respects** 36:15  
**respond** 84:11; 112:3;  
140:19; 143:20  
**responded** 93:2  
**response** 116:9, 11;  
117:23, 25; 118:8; 119:15;  
124:1; 142:21  
**responsibility** 7:4  
**rest** 12:15; 67:24; 118:4  
**restated** 142:24  
**restricts** 71:24  
**rests** 8:24  
**result** 98:11  
**resulting** 65:7  
**results** 23:1; 31:6; 49:17;  
0; 62:1, 5, 19; 64:15;  
; 66:24, 24; 89:13;  
98:13; 107:3; 146:17, 17,  
20, 22  
**retention** 39:16  
**rethinking** 32:6  
**Retin** 24:15  
**retinoic** 106:22  
**retinoid** 122:8  
**retinoids** 18:20; 24:20;  
122:7; 140:6  
**retinol** 106:22  
**reveal** 55:7  
**Review** 6:19; 31:3; 89:25  
**reviews** 121:11  
**Richmond** 60:17  
**Rico** 58:7  
**right** 7:3; 16:18; 17:9, 17;  
19:14; 29:25; 30:18; 33:9;  
52:23; 63:9; 78:15; 90:9;  
98:9; 109:22; 114:24, 25;  
118:9; 119:18; 120:9;  
122:8; 128:2; 136:5;  
140:1; 142:2; 143:24  
**righthand** 50:21  
**rigor** 148:19  
**rigorous** 74:13, 20, 21  
**Riley** 4:11, 13, 21; 60:18,  
95:15  
**risky** 121:5  
**robust** 146:12  
**Roger** 4:13; 5:24; 59:22,  
24; 119:24; 120:14;  
125:11

**role** 131:4  
**roller** 63:24  
**Room** 5:11; 63:17; 64:11;  
121:13; 127:12; 134:3;  
136:6  
**root** 55:17; 57:11; 81:5, 9  
**ROSENBERG** 60:25, 25;  
92:14, 16, 18, 24; 111:15,  
16; 126:10, 12; 143:19, 20;  
146:23  
**Rosenberg's** 112:4  
**rotostater** 58:2  
**routine** 58:21  
**rpm** 58:3, 3  
**rubbing** 93:17  
**run** 49:13; 130:23; 132:22  
**running** 49:12; 58:2;  
59:9; 101:15  
**runs** 95:3

**S**

**safety** 6:22; 8:24; 10:5;  
12:22; 13:20; 16:25;  
31:15; 72:1; 80:12; 85:19;  
125:7; 137:15; 149:17  
**sake** 64:21  
**sale** 10:18  
**salt** 40:4  
**same** 9:17; 10:3; 15:19;  
22:7, 24; 23:24; 27:10;  
28:24; 29:19, 25; 31:15,  
15; 34:5, 25; 37:4, 4, 18;  
38:2, 2, 3, 4, 5, 6; 39:19;  
41:7, 22; 42:21; 43:6, 8;  
44:16; 45:14; 46:22; 48:9;  
49:15, 15; 52:7; 54:1;  
65:10; 66:22, 23; 67:9;  
68:10; 74:18; 76:5, 6, 24;  
79:21, 22, 25; 80:19;  
81:21; 82:1, 1, 9, 10, 10,  
22; 83:2, 4; 86:9, 15; 88:7,  
8; 95:2; 96:18, 19, 21, 25,  
25; 98:11; 99:5; 100:11;  
101:4, 23; 103:6, 7, 8;  
104:2, 3; 105:8, 9, 9, 15;  
107:15; 108:4, 12, 13, 18;  
109:6; 111:21; 112:22, 23;  
113:8, 14; 117:8; 118:2;  
127:1; 128:24; 129:1;  
130:18; 134:12; 135:2, 9;  
142:1; 143:5; 144:4;  
146:19, 20; 148:13, 20;  
149:8, 17; 150:22, 23, 23;  
151:17  
**same--every** 150:21  
**sameness** 9:25; 10:19;  
11:10; 37:3; 53:11; 54:3;  
97:2; 130:9, 17  
**sample** 68:18; 70:21;  
76:22; 107:6; 116:1;  
125:1; 136:4  
**samples** 21:11, 18; 64:8  
**sampling** 26:22; 27:6;  
67:18; 70:2, 9; 71:15; 72:8;  
107:10; 125:1, 2

**San** 61:7  
**Sandia** 34:7  
**satisfactory** 36:6  
**satisfy** 143:17  
**satisfying** 130:10  
**save** 30:14; 69:8  
**saw** 35:12; 65:4; 67:3;  
71:2; 77:15; 100:9; 104:6;  
126:12; 133:14; 135:7;  
136:7; 147:6  
**saying** 49:10; 52:24;  
83:14; 96:4, 5; 112:19;  
120:9; 133:2; 137:5; 151:7  
**scar** 41:4, 12, 20, 23, 24;  
42:6, 6, 13, 17; 43:7, 8, 13  
**scarred** 99:8  
**scars** 102:25  
**scenario** 69:19  
**Schaefer** 24:2; 28:6;  
29:4; 36:11, 13; 48:10;  
61:4, 4; 73:11; 92:3; 96:16,  
22, 24; 97:21, 23; 110:1, 4,  
13, 14; 112:4, 5; 116:14;  
126:21; 142:12, 13  
**Schaefer's** 32:24; 33:12  
**schedule** 6:10  
**schedules** 27:4  
**schematic** 56:6  
**Schering** 73:14  
**School** 60:22  
**Science** 7:3; 11:25; 60:5;  
73:25; 74:5, 17, 24; 77:3;  
91:18; 94:15; 133:12  
**Sciences** 28:24; 60:21  
**scientific** 7:22; 29:1;  
74:21; 130:9, 13  
**scientists** 20:1; 27:22;  
29:7; 49:4; 53:7; 88:23;  
91:8  
**Scotch** 22:19  
**scratching** 93:16  
**screening** 58:11  
**scrutiny** 138:13  
**seasoned** 100:11  
**seated** 59:17  
**second** 15:16; 18:24;  
26:6; 27:25; 30:11; 32:19;  
38:18; 50:16; 52:16, 16,  
23; 72:17; 76:1; 78:8, 18;  
116:8; 123:23; 124:10;  
132:13  
**secondly** 36:18; 44:12;  
97:6  
**seconds** 63:25; 91:22  
**Secretary** 4:12; 60:19  
**section** 33:16  
**seeing** 67:6; 117:1, 18;  
140:11  
**seem** 87:3  
**seemed** 33:8; 150:2  
**seems** 32:11; 56:18;  
87:2; 95:6; 114:3  
**segment** 6:20  
**selected** 63:18

**selection** 26:22  
**selectively** 33:15  
**semi** 56:14  
**semi-infinite** 54:13  
**semisolid** 84:23; 86:20  
**senile** 101:13  
**senior** 101:17  
**sense** 8:11; 11:24; 52:24;  
53:5; 55:20; 57:8; 77:10;  
93:18; 114:16; 115:6;  
130:14; 141:24; 146:5, 23  
**sensitive** 26:12; 40:7;  
44:14; 45:13; 46:1, 12;  
49:11; 75:3; 126:2, 5, 22;  
137:19; 147:10  
**sensitivity** 26:9; 30:14;  
137:17, 25  
**September** 19:25; 62:1  
**Sequeira** 73:13  
**serial** 145:19  
**series** 6:17; 7:17; 17:10;  
28:17  
**serious** 47:17  
**serum** 49:3; 69:13; 99:4;  
143:6  
**serve** 53:7; 62:13  
**session** 59:17; 92:6, 7;  
135:23  
**set** 16:18; 50:7; 54:20;  
68:20; 70:11  
**sets** 64:21  
**setting** 36:5; 93:13; 126:7  
**seven** 73:8  
**seventies** 39:7  
**several** 6:6; 7:19; 15:25;  
34:24; 35:12; 48:22;  
58:24, 24; 77:16; 82:2;  
97:24; 117:23; 141:15  
**severely** 71:24  
**severity** 34:22  
**Shah** 14:5; 18:6, 10;  
30:15, 20; 31:3; 32:5;  
36:10; 40:14; 55:23;  
57:13; 60:4, 4; 75:11; 77:5;  
78:3, 6; 84:9; 86:12; 88:19;  
91:4; 92:3; 105:18;  
107:14, 15; 108:7, 9;  
109:2, 6, 12, 18; 114:21,  
25; 117:6, 19; 126:18, 19;  
131:2; 140:19, 21; 141:8;  
150:2  
**Shah's** 34:19; 35:12;  
85:16; 106:6  
**shape** 71:20  
**share** 52:10; 81:11;  
133:23  
**shared** 32:5  
**shelf** 10:16, 17  
**shift** 38:9, 24; 42:14;  
46:9, 23  
**shooting** 118:24  
**short** 50:1  
**show** 23:12; 31:17;  
37:10; 38:17; 39:10; 41:1;  
43:19; 44:11; 45:20;

57:13; 62:19; 72:4; 76:16;  
82:13; 107:1, 14, 17;  
108:2; 125:14; 126:8, 15;  
129:20, 22, 25; 130:8;  
140:24  
**showed** 23:4; 25:23;  
26:21; 40:14; 68:13, 22;  
70:15; 79:19; 83:24;  
105:23; 107:2; 108:3, 9;  
111:20; 116:19; 135:3;  
140:12  
**showing** 25:13; 34:2;  
56:21; 81:12, 22; 108:21;  
109:11  
**shown** 23:19; 33:3;  
70:23; 71:10; 100:12;  
107:19; 148:6; 150:3, 5  
**shows** 24:14, 16; 25:18;  
44:16; 57:12; 58:25;  
67:10; 82:16; 108:14, 15;  
111:4  
**shunt** 32:25; 33:1, 17;  
41:14  
**side** 24:25; 41:5, 6; 69:1,  
2; 95:11, 15; 103:20, 20  
**side-by-side** 68:16;  
108:13  
**signal** 19:20; 137:15  
**significant** 8:20; 38:25;  
64:5; 102:24; 133:6;  
144:21  
**significantly** 23:7, 14;  
74:8; 82:23  
**similar** 5:5; 21:13; 25:10,  
24; 31:18; 37:4; 38:3;  
46:22; 64:16; 75:14; 76:3,  
5; 78:25; 79:6, 7; 112:23;  
132:11  
**similarity** 79:4, 11; 132:4  
**Similarly** 24:22; 79:8;  
80:19; 105:21; 122:15  
**SIMMONS-O'BRIEN**  
60:9, 9; 149:6, 7  
**simple** 21:19; 49:9; 50:2,  
22; 51:11; 56:18; 132:24;  
134:4; 135:3  
**simpler** 30:17, 20, 25  
**simply** 99:16, 18; 107:5;  
131:13; 142:13; 145:11;  
151:15  
**simulations** 25:9  
**Sinai** 60:7  
**single** 22:1, 1; 64:1;  
105:19, 20; 113:5, 22;  
141:15  
**single-dose** 137:24  
**site** 20:21; 22:1, 24;  
31:24; 33:9; 34:13, 16;  
62:15; 63:24; 67:9, 18;  
68:2, 2; 70:20; 72:5;  
102:24; 105:15, 19;  
116:11; 117:1, 2, 17, 18;  
118:10, 23; 122:15;  
123:22; 124:10; 131:12,  
14  
**sites** 21:25; 22:6; 35:21;  
62:9, 13; 63:25; 68:4, 9,

13; 101:7, 8; 116:12;  
117:12; 149:10  
**sitting** 52:1; 59:19; 69:23;  
130:21  
**situation** 41:3, 7; 48:7, 8;  
49:13; 53:13; 54:4, 13, 24;  
55:13; 127:12  
**situations** 36:20; 44:20;  
45:18  
**six** 6:18, 18; 42:8, 23;  
68:14, 24; 108:4; 117:14;  
141:3  
**size** 28:9; 38:5, 16, 16;  
45:14; 56:16; 58:12;  
83:24, 25; 120:7; 121:15;  
122:7, 8; 127:25; 151:8  
**sizes** 58:9  
**skill** 49:12  
**skilled** 49:10  
**skin** 20:9, 21, 25, 25;  
21:4, 11, 18; 22:2, 17;  
25:4; 26:10, 16; 32:21;  
33:15; 34:21, 24, 25; 35:2,  
3, 3, 8, 13, 15, 15, 18, 22,  
22; 36:2; 39:5; 40:24, 25;  
41:4, 4, 9, 12, 13, 20, 23,  
24; 42:5, 6, 6, 7, 7, 13, 13,  
17, 17, 18; 43:8, 9, 11, 13,  
16, 23, 24; 44:1, 8, 9, 13;  
45:3; 46:18; 49:5; 50:5;  
51:15, 17; 53:14; 54:19,  
25; 62:11, 15, 25; 63:2;  
64:5, 13, 25; 65:1, 7, 14;  
66:9, 16, 18; 67:11, 14;  
68:17; 69:20, 23; 70:3, 16;  
71:7, 19; 75:16, 20; 76:9,  
24; 77:1; 83:15; 84:15;  
85:11; 94:2; 96:7; 97:10,  
16, 19; 98:24; 99:5, 8, 8, 9;  
101:13, 15; 103:1, 4, 10,  
14; 104:25; 106:25; 107:1,  
18; 108:3; 111:21; 113:12;  
114:8, 8; 115:23; 116:5,  
23, 23, 24; 117:4; 125:14,  
21; 130:12; 134:11;  
136:18; 148:4, 13, 21  
**skin—could** 37:16  
**skin—here** 21:4  
**skin—meaning** 22:3  
**skins** 83:8, 9; 117:13  
**skip** 39:24; 44:16  
**slavishly** 151:11  
**Slide** 6:5; 7:15; 8:14, 19,  
20; 11:8; 12:3; 14:15;  
16:15; 17:8; 18:14; 19:5,  
22; 20:17, 23; 21:8, 9, 16;  
22:10; 23:3; 24:6, 21; 25:5,  
6, 16; 26:2; 27:9, 11, 11,  
15; 28:14, 15; 29:8; 30:22;  
31:10, 16, 21, 25; 32:3, 18;  
33:2, 10, 24; 34:18; 35:9;  
36:16; 37:6, 11; 38:1, 8,  
23; 39:2, 9; 40:1, 13, 19;  
41:11, 17, 21; 42:2, 11, 15,  
20, 22; 43:1, 5, 18; 44:6,  
15, 18, 23; 45:11, 19, 25;  
46:8, 19; 48:14, 16; 49:21;  
50:9, 11, 14; 51:19, 24;

52:1, 15; 54:2; 55:18; 56:5,  
19; 57:9, 15, 23; 58:8;  
62:10, 16, 18; 63:15;  
64:14; 65:9, 17; 66:20;  
67:10, 23; 68:6, 19; 69:3;  
71:8; 78:24; 81:10; 82:14,  
15; 84:7, 19, 25; 85:4, 14,  
24; 86:4, 7, 13, 18; 87:7,  
13, 17, 25; 88:14, 21;  
89:15, 22; 90:5, 14; 91:5,  
16; 140:24  
**slides** 23:4; 35:12; 41:1;  
72:20; 105:23  
**slightly** 45:15; 78:7;  
105:12  
**slope** 34:5, 6; 40:5; 57:22  
**slopes** 57:10  
**small** 64:9; 99:20  
**smaller** 43:14, 14; 108:24  
**so-called** 49:18; 52:20  
**soap** 22:16; 56:11  
**society** 9:9; 10:25  
**sodium** 40:4  
**sold** 89:10  
**sole** 144:21  
**solid** 44:21; 56:15  
**solidified** 56:7, 14  
**solubility** 57:1  
**solubility—even** 56:24  
**solution** 56:17; 81:7, 23,  
25  
**solve** 51:7  
**somebody** 94:1; 96:14;  
111:25; 114:13  
**somehow** 32:12; 137:15  
**someone** 95:22; 103:9;  
112:3; 118:20  
**something** 22:18; 35:4,  
5; 43:19; 48:6; 55:14;  
57:18; 58:5, 20; 59:3;  
83:14; 94:1; 96:2; 113:18;  
116:10; 117:15; 125:22;  
127:16; 128:5; 133:10;  
134:18; 142:9  
**Sometimes** 9:25, 25;  
10:1; 11:3, 9; 15:18; 17:3;  
30:11, 14; 75:17; 82:23  
**somewhat** 78:25; 101:14  
**somewhere** 115:22;  
116:6; 125:15  
**sortBy** 79:12  
**sort** 29:25; 30:3; 70:24;  
82:1; 85:6; 107:2; 119:4;  
123:2; 138:24  
**sought** 63:9  
**Sound** 15:10; 21:18;  
59:10, 12; 72:15  
**source** 66:21  
**sources** 67:7  
**space** 36:23; 53:21  
**spaghetti** 94:18, 23, 24;  
95:1  
**speak** 6:2; 12:9, 13;  
121:21, 22; 129:18;  
139:23; 145:10

**speaker** 14:5; 36:11;  
47:3; 59:18; 61:13; 70:5;  
72:17; 73:2, 14; 74:19;  
76:21  
**speakers** 4:14; 6:9;  
61:23; 80:22  
**speaking** 8:15; 38:7;  
47:10; 61:13; 138:24;  
139:1  
**speaks** 13:16  
**special** 22:19; 44:24  
**specific** 20:10; 96:14;  
102:3; 110:15; 114:23;  
115:4; 122:3; 135:6; 142:4  
**specifically** 8:18; 36:20  
**specificity** 26:9  
**specifics** 118:13  
**spectrophotometry**  
126:4  
**spectrum** 120:1, 6  
**speech** 122:18  
**speed** 64:4; 151:9  
**spend** 14:10  
**spent** 14:9  
**spheres** 43:21  
**spoke** 72:3; 74:19; 107:9  
**sponsor** 14:24; 30:1  
**sponsors** 7:12, 25; 8:13;  
17:11; 30:8  
**spread** 54:7  
**square** 55:16; 57:11;  
81:5, 9  
**squares** 63:21  
**stability** 10:8  
**Stable** 4:5  
**stage** 140:8  
**stand** 91:14  
**standard** 23:1; 121:10  
**standardization** 40:8, 8  
**standardize** 63:9  
**standardized** 40:7;  
147:11  
**standpoint** 49:7; 58:14  
**Stanford** 61:12  
**start** 48:14; 59:13, 16, 22;  
92:11; 118:17; 137:4  
**started** 39:6  
**starting** 52:23  
**state** 50:7; 51:22; 52:2,  
11, 12; 58:5; 112:23  
**Statement** 4:12, 20;  
96:21; 131:2  
**statements** 5:9; 107:23;  
129:5; 136:15  
**States** 9:24; 14:19, 21, 24  
**stating** 100:1  
**statistical** 48:4; 49:16;  
74:21; 76:25; 143:13  
**statistically** 76:17;  
77:17; 115:11; 146:12  
**statistician** 145:11  
**statisticians** 115:15  
**statistics** 77:18, 19;

143:15  
**status** 113:13  
**statute** 9:12; 11:2; 13:16;  
15:24; 17:14  
**stay** 7:13; 10:3; 38:24;  
44:1; 94:6; 133:9; 148:3  
**steady** 50:7; 52:11  
**steady-state** 23:13, 21;  
24:24; 137:23  
**stearate** 45:16; 56:10  
**stearic** 56:8, 8, 9  
**steel** 93:17  
**steep** 124:1  
**steeper** 124:7  
**step** 44:5; 99:25; 113:4, 4;  
137:11  
**stepping** 57:13  
**steps** 29:19, 21; 50:16  
**steroids** 140:18  
**stick** 98:10  
**sticking** 22:16  
**still** 22:16; 32:10; 65:15;  
68:16; 70:7; 82:23; 83:1;  
91:6; 97:2; 98:6; 100:21;  
101:18; 102:9; 104:3;  
106:17; 108:22; 112:7, 7;  
120:11; 127:11; 136:17;  
139:12; 144:20  
**stomach** 132:16  
**stone** 57:13  
**stop** 93:24  
**stopped** 109:21  
**stories** 143:4, 14  
**story** 15:12  
**straight** 136:12  
**straightened** 138:23  
**straightforward** 49:9;  
139:5  
**strategy** 111:13, 14  
**stratum** 20:11; 21:5, 14;  
22:4, 23; 23:13, 21; 24:16;  
25:3, 4; 32:13, 15; 34:4,  
10, 12; 35:6, 11, 14, 16,  
19; 37:12, 16; 43:9; 53:16;  
54:25; 62:22; 63:4; 64:18;  
65:11, 20; 66:2, 6, 8, 12;  
68:1, 22; 69:4; 70:1, 8, 9,  
22; 75:16; 76:9, 10; 83:15;  
84:24; 85:2, 22; 86:21;  
87:10, 11; 93:11, 15, 19;  
97:10; 104:17; 106:3;  
108:22; 109:8, 16, 23, 25;  
110:25; 111:22; 117:21,  
24, 25; 118:2, 22; 122:12;  
131:4, 5; 132:13; 134:10;  
135:11; 137:13; 143:8;  
144:25; 151:14, 16, 17  
**strength** 19:2, 3; 55:25,  
25; 56:25; 78:13, 17, 20,  
21, 23; 79:3, 3, 7; 80:3, 3,  
9, 16, 16, 18, 18, 20, 21;  
127:24; 132:3; 148:9  
**strengths** 36:9; 53:3, 4;  
78:10, 11, 15; 79:15, 18;  
80:3, 12; 81:3, 4; 83:5;  
84:12; 90:20; 127:21, 23;

128:4  
**stressed** 148:18  
**strictness** 115:6  
**stringency** 115:5  
**stringent** 114:14, 16  
**strip** 23:22; 100:9;  
101:14; 108:15, 16, 16;  
109:13, 14, 19; 111:8, 8;  
113:5; 116:15; 125:1  
**stripped** 67:12; 105:15,  
21  
**stripping** 20:9; 22:21;  
26:11, 16; 32:14; 36:17,  
18, 20; 37:8, 15, 17; 39:4,  
14, 22; 41:9; 42:4, 10;  
43:6, 7; 46:1, 10, 11;  
61:22; 62:21; 67:20;  
69:18; 96:10; 99:16, 23;  
100:9; 101:3, 22, 104:9,  
10; 106:14; 110:19, 22, 24;  
111:10; 112:20; 116:22;  
117:10; 118:5, 10; 131:3;  
132:24; 133:11, 16, 22;  
134:6; 135:5; 136:12;  
146:4  
**strippings** 105:19, 24;  
106:5, 12; 107:18; 117:7,  
8, 9, 14; 131:16, 17  
**strips** 40:9; 65:12, 25;  
66:3; 68:1; 70:11, 18, 23;  
107:19, 19, 19; 108:21;  
109:1, 11, 19; 116:25;  
136:17  
**strive** 96:2  
**strong** 52:12; 75:5; 149:5  
**strongly** 139:23  
**structure** 43:15; 56:12,  
15  
**struggle** 14:13; 137:5  
**struggles** 12:2  
**struggling** 132:20  
**Stuart** 91:23  
**student** 94:12  
**students** 148:1  
**studied** 31:18; 82:3  
**studies** 25:9; 26:5, 19;  
61:20; 62:5, 19; 63:7;  
64:15; 71:3; 74:14; 77:8, 9;  
83:8; 91:1; 102:2; 106:23;  
107:5, 21, 23, 24; 108:10;  
115:1, 9; 119:13, 14, 21;  
120:2, 14, 19; 121:3, 3;  
126:14; 129:9; 134:24, 24;  
136:9; 137:24; 141:10, 25;  
143:25; 144:2; 149:13  
**study** 12:16; 26:5, 6, 7;  
27:3, 5, 7, 8; 30:19; 33:3;  
40:15; 47:12, 15; 68:13;  
77:6, 10, 11; 79:2; 80:6, 7;  
98:6; 102:22, 22; 108:12;  
114:14, 15; 116:4, 6;  
120:16, 22, 23, 24; 126:7,  
15; 127:25; 129:25;  
135:16; 142:15; 147:12  
**stuff** 22:16; 95:4  
**subject** 22:1; 34:25;  
49:14; 65:13, 13; 66:13;

67:2; 70:20; 104:15;  
108:12  
**fects** 64:25; 65:22;  
23; 67:4; 68:3, 5, 14,  
25; 107:17, 20; 108:4, 5, 6,  
18, 18  
**submit** 8:1, 13; 75:8; 77:7  
**submitted** 4:25  
**submitting** 5:10  
**subsequent** 14:4; 39:5;  
113:6  
**substance** 8:8; 10:25;  
12:20; 13:14; 16:9; 18:4;  
98:21; 112:25; 146:4, 5  
**substances** 37:10;  
45:21; 100:4  
**substantial** 54:16; 57:21;  
127:10  
**substantially** 111:1;  
134:8  
**substantivity** 94:6  
**substitute** 121:25  
**substituting** 47:11  
**substitution** 30:17  
**successful** 55:12;  
118:25  
**sufficient** 11:21; 28:11;  
142:7; 148:19  
**sufficiently** 127:13  
**gest** 30:12; 89:24;  
5  
**suggested** 33:7; 53:6;  
73:2; 88:1  
**suggesting** 57:7; 85:16;  
146:15  
**suitable** 55:21  
**summarize** 151:2  
**summer** 94:12, 17  
**sun** 101:8; 144:12  
**sunburn** 103:1  
**SUPAC** 58:15  
**SUPAC-SS** 52:21; 53:5  
**superficial** 35:21  
**superior** 115:11; 126:13  
**support** 63:11; 76:2;  
77:23  
**supposed** 133:5  
**supposedly** 130:1  
**sure** 12:12; 14:6; 24:8;  
34:9; 47:22; 48:13; 52:22;  
91:1; 92:9; 94:10; 101:22;  
106:8; 110:14; 132:9;  
144:5  
**surface** 23:2; 32:17;  
40:24; 44:9; 84:23; 85:22;  
86:21; 94:7; 112:7; 117:10  
**surface-and** 53:15  
**factant** 56:11  
**gery** 61:7  
**surplus** 40:9; 113:19, 20  
**surprising** 106:25  
**surrogacy** 13:4, 7; 16:2;  
47:10; 125:6; 137:16;  
142:4

**surrogate** 13:4, 19, 23;  
14:3; 16:25; 33:23; 48:1,  
23; 53:8; 72:6; 75:14;  
123:5; 125:8; 130:13;  
138:17; 140:4, 6; 142:7;  
150:1  
**suspension** 55:15; 81:4;  
82:1; 84:2  
**suspensions** 56:23  
**symposium** 112:14  
**synthetic** 29:21; 53:23  
**system** 11:24; 15:10;  
56:17; 57:1; 87:9; 89:17;  
95:3, 7; 96:19; 107:3;  
126:8; 131:15  
**systemic** 98:25; 118:21;  
123:15  
**systems** 84:18

## T

**t** 51:6  
**table** 4:17; 59:20, 22;  
100:15; 130:21  
**tack** 100:11  
**talk** 7:2, 9; 8:3, 7, 10;  
10:22, 22; 11:9; 12:4, 18;  
13:10; 16:18; 29:17, 20;  
66:25; 72:23; 78:16  
**talked** 11:23; 15:23;  
94:11; 96:18  
**talking** 8:3; 11:4, 19;  
30:8, 16; 31:19; 35:14, 15,  
16; 36:8; 41:3; 52:24, 25;  
53:3, 19; 101:5; 112:18,  
22; 117:11; 121:10; 127:9;  
131:11; 138:14  
**tank** 93:17  
**tape** 22:18, 19, 25; 32:14;  
61:21; 62:21, 23; 63:14,  
19, 20; 64:4, 22, 23; 65:2,  
3, 5, 6, 6, 12, 25; 66:3, 12,  
25; 67:12, 20; 68:1, 18;  
69:18; 70:11, 18, 22;  
100:10; 104:9; 115:24;  
118:5; 125:14; 132:24;  
133:22; 134:5, 6, 7, 10, 22,  
23; 135:2, 3; 136:3  
**tape-took** 134:6  
**tapes** 63:17; 64:10, 19,  
19, 21; 70:4; 102:6;  
133:24; 134:16, 19, 25;  
135:3; 136:2, 15; 148:21  
**target** 20:21; 34:12;  
46:16; 62:9, 13, 15; 72:5;  
131:5; 133:4, 5; 144:19;  
149:10; 151:8  
**targeting-this** 38:13  
**targets** 32:21; 35:18;  
85:3; 131:8, 10  
**Taro** 72:17; 73:19, 20  
**teach** 148:1  
**team** 39:19; 116:18  
**technically** 10:7  
**technicians** 12:16  
**technique** 21:19; 23:8, 8,

16; 26:11, 11, 16; 36:20;  
37:16; 39:4, 19, 22; 40:7;  
41:10; 42:5, 10; 43:7;  
44:13; 45:12, 21; 46:1, 10,  
11; 67:8; 69:6; 70:3; 72:8;  
75:14, 17, 23, 24; 76:1;  
82:10; 101:3; 102:15;  
105:13; 107:10; 112:20;  
116:2, 23; 117:6; 118:25;  
122:1, 3, 23; 123:6;  
125:22; 126:5, 13; 131:3;  
141:15; 143:3, 12; 147:8,  
14, 22; 148:19, 23; 149:12;  
151:22  
**techniques** 95:19; 97:20;  
118:13; 121:25, 25; 123:3,  
4; 126:6; 151:23  
**technology** 11:25;  
63:11; 95:9  
**telling** 41:14; 43:20;  
47:13; 48:1; 85:20; 104:7;  
125:17  
**tells** 64:2; 80:23  
**temperature** 63:17;  
134:4  
**templated** 63:25  
**Tennessee** 61:1; 94:10  
**tenth** 134:14  
**term** 37:13; 50:21  
**terms** 10:20, 21; 11:1;  
12:15; 13:16, 23; 17:5;  
23:14, 16; 29:16, 20;  
40:10, 22; 41:18, 22; 43:3;  
44:3, 19; 46:3; 48:5, 7;  
49:11; 51:13; 52:5, 12;  
72:1; 75:10; 111:10;  
112:18; 136:7; 142:20;  
145:17; 146:4; 151:21  
**test** 11:5; 21:20, 23, 24;  
23:5, 6; 30:12, 17, 25;  
31:1, 2, 2; 47:8; 48:8, 25;  
49:18, 23; 52:10, 11, 20;  
53:6, 7; 54:10, 20; 55:4, 7,  
16, 20, 21; 56:2; 58:13, 15,  
21, 22, 25; 68:10; 70:17;  
72:10; 80:14, 19; 88:3;  
100:5; 101:10; 102:24;  
103:7; 104:14, 20; 120:18,  
19; 130:17; 134:22; 139:9,  
11, 17, 19  
**test-and** 56:20  
**tested** 144:3, 5; 145:3  
**Testing** 7:6; 48:24; 53:22;  
55:24; 105:7; 132:23;  
144:14, 15; 145:21; 146:4;  
148:8  
**testosterone** 100:3  
**tests** 28:1; 30:9, 10, 12;  
58:16; 84:4; 88:4; 90:16,  
17; 120:1, 6, 7; 130:24;  
137:21, 22  
**tests-has** 140:16  
**TEWL** 63:2; 65:20, 21;  
66:1, 5, 15, 17, 18; 68:23  
**Thanks** 95:18; 113:23;  
132:8; 141:17; 142:11;  
144:23  
**that-because** 104:7

**that-we** 69:8  
**themselves** 5:15; 59:20;  
105:5  
**Theoretical** 47:7, 20;  
49:20; 71:11; 81:15, 19;  
82:4, 5  
**theorist** 51:23  
**theory** 49:24  
**therapeutic** 16:11; 39:1;  
122:25  
**therapeutically** 31:13  
**therapeutics** 62:14;  
128:12  
**therefore** 31:13; 56:11;  
62:2; 67:16; 70:9, 17;  
101:9; 103:9; 126:23;  
140:17  
**thermodynamic** 53:19;  
54:18  
**thick** 54:11, 22  
**thickness** 51:3, 4; 52:8  
**thin** 97:11  
**think-if** 139:16  
**thinking** 30:5; 74:24;  
84:21, 22; 149:8  
**third** 115:12  
**thirdly** 36:19; 124:21  
**Thirty** 42:16  
**this-but** 52:4  
**though** 11:10; 37:10;  
66:14, 16; 67:5, 20; 114:6  
**thought** 13:12; 19:23;  
90:18; 93:5; 96:14;  
104:11; 105:15; 114:10;  
117:21; 124:23; 151:17  
**thoughts** 59:5; 132:14,  
15  
**three** 12:8, 10; 17:10;  
20:5; 22:13; 24:14; 36:15;  
50:15; 58:9; 74:12; 78:15;  
81:12; 115:8; 117:8, 9;  
120:23  
**three-day** 14:9  
**throughout** 35:22;  
64:16; 65:19  
**throughput** 52:11  
**throw** 121:16, 24  
**throwing** 121:10  
**Thus** 46:20; 54:16  
**tied** 116:3  
**time/concentration**  
34:1, 15  
**times** 19:11; 22:13, 24;  
30:5; 56:25; 82:11; 85:8, 9;  
105:16, 21; 125:20;  
142:14; 146:10  
**timing** 41:18; 43:4  
**tinkering** 95:7  
**tissue** 22:13; 46:17, 17;  
72:8; 110:5; 111:12;  
123:18; 134:20; 135:5  
**tissues** 62:12; 70:11  
**titanium** 45:1, 6, 8  
**title** 47:7

**TNF-alpha** 118:8  
**to--there** 12:8  
**today** 6:2; 7:9; 30:16;  
40:21; 61:20; 62:4, 20;  
75:11; 89:11; 90:10;  
96:12; 119:21; 121:2, 7;  
136:15; 142:3; 145:18;  
151:13  
**today's** 5:8  
**together** 25:7; 39:18;  
83:19, 22; 84:4; 91:3, 7,  
10, 14; 98:7; 142:3  
**told** 75:23; 94:23  
**Tom** 29:5  
**tomorrow** 90:11; 117:9  
**took** 51:23; 58:6; 64:8;  
116:19; 134:5, 12  
**tool** 84:5  
**tools** 63:12  
**top** 7:21; 50:16; 52:23;  
69:23; 95:15  
**topic** 6:3, 7, 14; 7:9;  
12:16; 14:6, 9, 16  
**Topical** 4:4; 17:22; 19:2,  
19; 20:8, 22; 21:2, 15;  
28:12; 30:19; 33:5, 12;  
46:5; 47:5; 52:19; 53:13,  
22; 69:18; 72:7; 78:12;  
83:20; 84:6; 105:7;  
130:12; 140:17; 150:14,  
18  
**topics** 14:7  
**total** 39:15; 57:11; 70:12;  
71:6; 87:21; 104:22;  
111:11  
**totally** 119:15  
**touched** 134:11  
**towards** 110:5  
**Tracy** 4:11, 19; 60:18  
**tradeoff** 135:13  
**trading** 90:10  
**traditional** 4:17  
**trans** 63:2  
**transdermal** 51:16  
**transepidermal** 32:22;  
33:22; 36:24; 38:19;  
46:23; 98:15, 16; 135:10  
**transepidermally** 38:11  
**transfollicular** 32:24;  
33:21; 38:20; 46:23  
**transformation** 51:25  
**transient** 55:10  
**transit** 85:1  
**translate** 25:4  
**transmission** 144:15,  
24; 145:5  
**transparencies** 48:18  
**transparency** 50:17, 24;  
57:12  
**Transpore** 22:20; 63:20;  
64:22; 66:25; 103:21  
**transport** 49:23; 55:2  
**transpose** 93:12  
**treatment** 33:8; 94:3

trend 66:17  
**tretinoin** 24:7; 26:21; 81:12  
**tretinoin**s 25:24  
**trial** 10:4; 138:9; 146:5  
**Trials** 4:5; 17:4; 19:10; 75:3, 9; 132:22; 146:19  
**Trichophyton** 118:23  
**tried** 37:21; 99:18; 117:3; 130:16  
**tries** 7:11; 9:5  
**troubled** 118:3  
**true** 11:16; 48:12, 25; 51:13, 14; 71:21; 76:19; 81:21; 85:15; 95:15; 103:12  
**truly** 88:12; 136:10  
**try** 8:21; 23:22; 36:13; 92:21; 93:3; 100:1, 18, 25; 116:15; 125:4; 128:10, 13, 14, 16; 140:3; 148:24  
**trying** 79:14; 83:21; 114:19; 124:8; 127:7; 133:9; 139:19; 141:14; 147:8  
**TSCHEN** 61:2, 2; 143:1, 2, 18  
**tube** 54:6  
**turn** 17:1; 18:5; 146:1  
**turned** 117:25  
**turns** 67:13; 82:19; 88:9; 89:16  
**twice** 28:21; 151:13  
**twists** 32:16  
**two** 13:23; 18:16, 17; 19:12; 21:2, 3, 6; 22:19; 23:10, 12, 19; 24:10, 12; 25:6; 26:4; 28:24; 32:20; 33:5; 37:18; 38:12, 21; 40:9; 42:21; 52:21; 53:1; 57:24; 66:7; 73:13, 18; 75:4, 6, 8, 13, 13; 76:13; 77:18; 78:2, 14; 79:15, 17; 81:1, 3, 4, 5, 22, 24; 82:9, 16, 17, 20; 84:4; 99:13; 103:13; 104:17; 105:3, 4; 107:22; 108:12; 109:4; 120:19; 123:10, 10; 124:3, 6, 9; 126:12, 16; 130:1, 2; 133:14; 135:13; 140:25; 141:1, 13; 144:4; 147:18; 150:24  
**type** 23:23; 26:25; 52:9; 58:2; 79:17; 82:12; 116:2; 117:19; 123:4, 6; 141:9; 144:18  
**typically** 54:4; 115:8

**U**

**U.S** 5:6; 16:14  
**ultimately** 29:22; 84:14; 85:21; 89:17  
**unacceptable** 105:17  
**unbelievable** 91:23

**uncertainty** 40:11; 47:16  
**under** 6:18; 13:22; 17:25; 23:25; 25:1; 27:17, 19; 29:3, 4; 31:18; 34:3; 37:2; 38:9; 40:6; 47:12; 50:6; 56:22; 101:3; 103:7; 105:8; 137:13; 150:21  
**undergo** 54:16  
**underlying** 31:12; 50:4; 51:16; 52:13; 53:12  
**undermines** 35:25  
**underway** 98:6  
**undetected** 46:24  
**unfortunately** 124:18; 128:7  
**uniform** 22:20; 50:3  
**uniformity** 125:13  
**uninvolved** 34:25  
**unique** 5:3  
**unit** 7:4; 100:20  
**United** 9:24; 14:18, 21, 24  
**units** 6:18; 7:2; 16:18  
**University** 25:2; 60:12, 15, 21; 61:1, 3, 7; 73:10; 94:9; 102:18  
**unless** 34:11; 70:21; 74:5; 88:9; 98:20; 111:25; 118:20  
**unpublished** 25:24  
**unrealistic** 132:21  
**unrelated** 116:21  
**unsuccessful** 128:13  
**unusual** 65:3  
**unwilling** 139:7  
**up** 4:14; 15:13; 33:16; 34:2, 6; 38:15; 43:10; 50:7, 10, 22; 51:8, 12, 25; 54:20; 57:19; 58:3, 25; 64:19; 65:11; 68:11; 94:5, 12; 103:19; 110:2; 115:24; 116:3; 118:2, 11; 125:21; 126:7, 17; 127:25; 131:22; 134:10, 19; 135:5, 11; 136:5, 18; 137:23; 149:20  
**upon** 5:21; 32:7  
**upper** 68:2, 15; 69:2; 98:10; 109:23  
**uptake** 20:13, 25; 21:14; 22:3; 24:24; 25:8; 35:15; 39:22; 103:5; 116:5; 125:14  
**use** 9:25, 25; 10:1, 18; 18:21; 29:16, 17; 33:22; 47:25; 54:21; 66:25; 71:25; 72:5; 74:5; 75:1; 89:14; 97:1; 114:2, 14; 122:23; 123:11; 134:23, 23; 136:5; 139:17; 143:16; 144:17; 148:24; 150:2  
**used** 13:20; 15:5; 16:7; 18:18, 23; 19:1, 20; 22:19; 25:14, 18; 27:12; 48:23; 58:2; 59:3; 63:18, 25; 64:9, 19; 76:1; 78:19; 79:17; 90:8; 91:3; 94:13; 101:4, 7; 103:21; 108:18; 118:15;

123:24; 125:8; 128:12; 129:9; 134:16; 137:10; 143:3, 13; 145:19, 20, 23, 24; 149:14, 14, 24; 150:7  
**useful** 33:7; 34:14; 36:6; 51:12; 56:2; 57:8; 116:1, 7; 124:16, 24; 125:22; 143:12; 144:17; 147:8, 13, 22; 148:9, 15, 23  
**using** 20:15; 22:25; 27:2, 5; 54:10; 55:23; 63:8, 23; 82:10, 20, 25; 86:3; 93:14; 97:7; 105:8; 118:13; 123:4; 126:4, 20, 24; 127:13; 128:1; 143:4; 144:14; 146:5; 148:8; 149:12; 150:23  
**usually** 4:9; 12:23; 63:25; 69:7, 12, 20; 128:1, 2  
**Utah** 25:2; 29:4; 102:18; 103:23  
**utility** 35:25  
**UV** 103:4; 126:4

**V**

**vain** 117:3  
**valid** 101:18; 112:1; 144:5  
**validate** 90:1; 134:23; 138:16, 18  
**validated** 76:18; 90:17; 125:5; 127:14  
**validation** 26:8, 10, 16; 31:5; 61:21; 89:13; 90:13; 98:7; 119:16, 19; 121:4, 17, 19; 124:22; 125:3, 12; 126:7; 130:20; 137:7; 141:9; 144:1  
**validity** 37:7; 119:20, 21; 122:4  
**valuable** 58:16; 83:19; 108:25; 143:11; 149:9  
**value** 66:18; 69:10; 77:20; 105:18, 19; 122:17; 133:2  
**values** 29:14; 65:16, 21, 22; 66:1, 5, 7, 17; 68:23; 98:21; 142:22  
**vanishing** 56:7, 14  
**variability** 26:18; 62:20, 24, 25; 63:1, 5, 5, 6; 64:24; 65:13; 66:22; 68:11, 14, 21, 23, 24, 25; 69:5, 21; 70:7; 72:8; 76:17, 19; 77:1, 13, 15, 18; 98:13; 100:8; 101:11; 103:2, 16, 18, 19; 104:1; 107:6, 7, 9, 9; 108:23; 113:19; 131:17; 133:3, 17; 136:13; 137:18, 19; 138:1; 146:2, 8  
**variable** 70:6; 76:16; 103:15; 105:17; 118:3; 134:8  
**variables** 52:6, 6; 121:16; 140:9  
**variation** 40:12; 67:17

**variations** 81:20  
**varies** 65:14; 66:13  
**variety** 62:16  
**various** 14:13; 32:16; 62:13; 123:7, 24; 147:12  
**vary** 93:25; 110:20  
**vasoconstriction** 75:18; 140:15, 17, 23; 141:1  
**vastly** 70:10  
**vehicle** 38:3; 51:3; 55:8, 11; 84:16; 85:8; 86:24; 88:10; 96:25; 112:23; 115:9, 11; 120:17, 19; 132:7, 10, 10; 133:4; 148:11  
**vehicles** 39:12; 45:22; 90:25; 96:18, 19, 21; 98:5; 121:14  
**versus** 11:10; 14:17; 34:24; 35:8; 37:19; 42:13, 24; 43:7; 46:23; 68:8; 69:24; 90:24; 93:10; 101:5; 104:10, 19, 20; 114:8, 18, 20; 115:9; 120:19; 137:17, 24; 144:14; 148:24  
**vessels** 35:21  
**via** 7:17; 9:3, 12  
**viable** 20:7; 110:11; 131:8; 149:9  
**view** 88:22; 89:12, 21; 91:10; 112:10; 130:17; 145:11; 148:1  
**vigorously** 30:20  
**Vinod** 40:14; 60:4; 120:9, 21; 124:20  
**Virginia** 60:17, 17  
**virtually** 117:8  
**vis-a-vis** 122:7  
**visually** 75:20  
**vitro** 16:6; 17:3; 19:20; 28:10; 47:13; 77:21; 80:17; 84:5; 108:2; 113:7; 147:25  
**vivo** 16:5; 106:23; 108:4; 113:7; 144:14; 145:4  
**volar** 68:3  
**volatile** 54:15  
**volume** 69:16  
**volunteers** 99:1  
**vote** 141:19, 22; 150:9

**W**

**wait** 110:23, 25; 111:2; 144:7  
**waiver** 5:9  
**waivers** 5:6  
**walk** 8:21  
**walking** 4:17  
**wants** 95:13; 121:21  
**warehouse** 95:12  
**warfarin** 77:15  
**watch** 34:2

**water** 63:3; 98:15, 17; 111:20; 135:10  
**water-like** 112:7  
**Waterfalls** 91:12  
**way** 7:23; 16:6; 17:4; 21:10; 29:19; 30:12; 32:9; 34:5; 38:15; 46:25; 55:6; 56:6, 10; 59:3; 70:14; 74:15; 91:4, 15; 95:3; 96:17; 101:21, 21; 116:24; 128:8; 139:12, 13, 20; 142:3; 144:3; 146:11; 151:17  
**ways** 7:16; 14:14; 19:7; 55:21; 58:24; 130:9; 141:16  
**week** 14:9; 66:23; 67:3, 3, 6, 6, 17  
**week-to** 67:16  
**weeks** 94:22; 118:6  
**weigh** 104:18  
**weighed** 64:21; 134:7, 7, 8, 13, 13, 13; 136:23  
**weighing** 64:8, 9  
**weight** 62:25; 63:24; 65:4, 8; 96:10; 134:9, 12, 14; 135:2, 4, 5; 136:3, 3, 4  
**weights** 66:14; 68:23; 133:24; 134:8; 135:9  
**WEINTRAUB** 60:1, 1  
**Welcome** 4:2  
**well-of** 67:11  
**well-controlled** 147:12  
**well-established** 9:23  
**weren't** 90:23  
**whenever** 74:25; 98:9  
**whereas** 46:4  
**wherein** 40:23  
**white** 71:10  
**whole** 43:3; 69:7, 17; 93:20; 94:4, 17, 24; 95:6; 112:6, 14; 130:22; 137:21; 145:24; 150:11  
**whose** 5:20  
**wide** 62:20  
**widespread** 5:5  
**Wilkin** 29:9, 12, 12; 36:15, 22; 60:2, 2; 62:11; 73:9; 84:10, 11; 92:9; 115:8; 122:20; 128:7; 129:6; 131:19  
**Wilkin's** 143:4  
**Wilkin-when** 38:14  
**Williams** 4:13; 5:24, 24; 15:9; 18:10; 19:6; 21:22; 59:24, 24; 73:9; 74:11; 75:5; 120:1, 21; 124:13, 15; 127:17, 18; 128:2; 136:21; 137:3, 4; 139:1  
**willing** 12:12; 13:1  
**wind** 50:10, 22; 51:8, 12  
**Windsor** 112:1  
**winsor-l** 111:19  
**winner** 95:15  
**wired** 72:15

wisdom 130:3  
wish 5:21  
wished 73:15  
within 28:6; 29:14; 45:9;  
49:23; 81:20; 83:4; 90:25;  
101:10, 16, 17, 17, 18, 23;  
105:5; 115:5; 118:6; 122:9  
Without 15:3; 41:6;  
58:19; 59:11; 66:11;  
71:23; 97:16; 119:18;  
121:3  
without-it 121:23  
wonder 146:18  
wondered 114:12  
wonderful 94:3; 100:3  
wondering 106:6, 14  
word 9:25; 10:1; 29:16;  
135:19  
words 13:9; 15:1; 37:12;  
38:24; 44:13; 45:12; 46:9;  
62:25; 65:6; 68:9; 83:21;  
88:19; 135:11  
work 23:25; 25:1, 25;  
29:2; 32:24; 39:6; 49:19,  
19; 63:16; 75:24, 24;  
77:22; 84:20; 90:16, 22;  
91:2, 15; 98:1, 2; 99:18;  
100:1; 101:20; 118:2;  
122:11; 131:7; 141:2  
worked 94:17; 111:18  
working 4:10; 7:11;  
16, 18; 17:10, 24;  
23:17; 30:20; 59:11;  
100:24; 133:6  
works 7:16; 51:11; 75:25  
workshop 19:25; 20:6;  
61:24; 62:2; 73:1, 8; 74:11,  
23; 88:20; 92:4; 93:5;  
105:14  
workshops 28:18  
world 20:2; 90:23; 99:15  
worried 101:12  
worry 77:12  
worth 52:17  
wrinkles 116:21  
writing 125:11  
written 5:10; 48:17, 18;  
50:6; 53:13  
wrong 57:5; 90:11;  
138:25  
wrote 92:16

**X**

x 51:8; 117:12

**Y**

Yacobi 72:17, 19; 78:1;  
88:19; 90:15  
years 7:19; 10:9, 10, 11;  
29:3; 51:23; 95:5; 105:3;  
121:11, 11; 126:3; 138:13

yesterday 44:25  
yield 29:23  
yielding 22:1  
yields 32:15  
York 60:8  
you-and 52:3  
young 104:10  
younger 104:22; 114:18  
yours 92:23

**Z**

zero 55:14