

1 It can also be used to mathematically express the
2 degree of suppression that we get with this equation and
3 this model, then, allows us to predict how much cortisol
4 suppression we would observe for various treatments.

5 [Slide.]

6 This is a study that we have done some time ago on
7 triamcinolone acetonid after intravenous, oral and
8 inhalative administration. We measured the kinetics and,
9 based on the blood levels, then, model the effect on
10 cortisol and just see, for all three treatments, that it
11 works very nicely. The dashed line is the baseline pre-dose
12 line and the other line is the suppressed curve measured and
13 modeled.

14 [Slide.]

15 So this allows, us, then, then to make pretty good
16 predictions, basically to translate the pharmacokinetics of
17 the inhaled steroids, the serum concentrations, into the
18 expected degree of cortisol suppression. Again, the best
19 cumulative parameter to summarize this data is the AUC
20 between baseline and treated group and express it in
21 percent.

22 [Slide.]

23 We have developed a spreadsheet, an Excel
24 spreadsheet, that puts all this information together and one
25 location and one can, then, enter the drug, the dose, the

1 time of dose, which is important, and the device. Based on
2 population average parameters, the program then will
3 calculate an expected cortisol curve over 24 hours,
4 calculate the percent cumulative suppression.

5 [Slide.]

6 We have, then, compared these predictions with a
7 number of studies. All of these dots here represent major
8 clinical studies that were not done by us. These are
9 studies taken from the literature. We have shown a nice
10 correlation between the predicted cumulative cortisol
11 suppression based on the model that I have just shown you
12 and the measured and reported data in the literature.

13 So, really, all we are doing is we are translating
14 the kinetic information into the dynamic information and it
15 is quite consistent. That makes sense because
16 corticosteroids all work the same way. They have the same
17 exact mechanism of action.

18 [Slide.]

19 Briefly, on other systemic-dynamic parameters,
20 lymphocytes, the number of lymphocytes go down. This is
21 from the same study that I had shown you earlier, 200 and
22 500 micrograms of fluticasone, single dose and multiple
23 dose. You see, in red, placebo and, in black, the treatment
24 group. Again, there is a significant decrease but of small
25 magnitude.

1 [Slide.]

2 Only for the higher doses was it significant. The
3 same was true for flunisolide, here.

4 [Slide.]

5 Similar results can be observed on the
6 granulocytes, where we have the opposite effect. The number
7 of granulocytes goes up, dose-dependent. This is
8 flunisolide data here, 400 and 1000, single dose and
9 multiple dose. In only this case, in the multiple dose
10 situation, was it significantly different.

11 So, again, really, these parameters allow you to
12 compare different compounds but they do not really improve
13 the information that we get on systemic exposure if we
14 compare two different formulations of the same compound.

15 [Slide.]

16 So, if we summarize this, if the issue is
17 bioequivalence, we want to compare two formulations, we
18 should simply take the plasma concentrations and no other
19 data is really needed. Whereas, if we want to compare
20 different steroids, that is a different question. And then
21 24-hour serum cortisol at steady state seems to be the
22 parameter of choice.

23 [Slide.]

24 Now, let's move on the real hard question, and
25 that is local exposure. How can we express local exposure.

1 How can we measure how much drug gets to the site of action
2 in the lung. There are two different approaches. One is
3 direct and one is indirect. Unfortunately, the direct
4 measurements are limited to animal experiments.

5 Lung microdialysis is a very promising new
6 technique where one can put a probe into the lung and
7 measure directly the unbound concentrations. We are doing
8 this right now in animal studies and getting very nice data
9 but this is, unfortunately, not applicable to human studies.

10 Pulmonary-receptor occupancy; same issue. One can
11 measure the steroid occupancy with binding assays. Again,
12 unfortunately, this is only possible ex vivo and in animal
13 studies.

14 The third direct way is gamma scintigraphy where
15 one can follow the label. However, that has the downside
16 that one would no longer study the original formulation but
17 only after manipulation and introducing the label.

18 So we are really limited with indirect
19 measurements but I hope that I can show that they may be of
20 value. One way to go is to look at the pulmonary absorption
21 profile after application of charcoal and deconvolution. So
22 let's look at that a little more in detail.

23 [Slide.]

24 We have to keep in mind some basic pulmonary
25 delivery concepts. First of all, before the drug is active

1 in the lung, and the steroid needs to be dissolved and get
2 into the cell, the receptors on the cytosol. Also, only
3 unbound fraction of the drug is active, so binding is an
4 important factor.

5 Then, all of the drug that reaches the cytosolic
6 steroid receptor then will be absorbed systemically. So, of
7 all the components that are available so far, they will not
8 magically disappear but, then, the next step is systemic
9 absorption so one can really not have one without the other.

10 Thirdly, one should be very careful in looking at
11 the literature not using total tissue concentrations, not
12 using biopsy numbers, because they are hybrid numbers and
13 reflect the sum of the drug in the tissue and are very
14 difficult to interpret quantitatively.

15 [Slide.]

16 Furthermore, it is important to keep in mind that
17 the delivery efficiency is a very important factor. This is
18 a simulation to show that if you increase the percent of the
19 drug that is delivered into the lung that, then, the
20 targeting will be improved.

21 If you compare two compounds with an oral
22 bioavailability of 10 percent, drug A, and an oral
23 bioavailability of 0, drug B, then, if 10 percent gets into
24 the lung by our device, that means, then, the systemic
25 variability for compound A will be 19 percent, 10 percent

1 coming from the lung and 9 percent is 10 percent of the
2 remaining 90 percent, so that adds to 19 percent, whereas
3 for compound B, it is only the 10 percent that goes to the
4 lung which is a ratio of 1.9.

5 If you improve, for the same compounds, the
6 delivery to 30 percent and do the same calculations, you end
7 up with 37 percent systemically and 30 percent, and that is
8 a ratio of 1.2. So the oral bioavailability becomes less of
9 an issue the more you deliver to the lung. That makes
10 sense.

11 [Slide.]

12 So how can we differentiate, when we inhale, how
13 much of the drug goes in through the lung versus the GI
14 tract. There are three approaches. One is to simply use a
15 drug that doesn't have any GI absorption. That is, of
16 course, the easiest way. Or, if it is to block the GI
17 absorption with charcoal, the third approach in the
18 literature is utilize early time points where the pulmonary
19 absorption is dominant and oral absorption is not yet very
20 large.

21 [Slide.]

22 Fluticasone propionate will be an example for the
23 first case where we have oral bioavailability of less than a
24 percent, or around 1 percent, so one can assume that the
25 vast majority of the drug that shows up systemically comes

1 from the lung.

2 [Slide.]

3 Charcoal has been used to separate the route of
4 entry. This is a study on budesonide where two devices were
5 compared, Turbuhaler MD-MDI, with and without charcoal, and,
6 by calculation, then of the different profiles, one can show
7 that the contribution from the lung and the GI is different.

8 [Slide.]

9 This is the Turbuhaler here and we see that the
10 fraction that is coming through the lung is much, much
11 larger than from the MDI by comparison of the absorption
12 with and without charcoal. If one does it right, if the
13 charcoal application is optimized, one can almost
14 completely, or completely, block, the absorption.

15 [Slide.]

16 This is an example from not a steroid but
17 terbutaline. Oral bioavailability with and without charcoal
18 where it was possible to block the oral route almost
19 completely.

20 [Slide.]

21 So, what one can do now is to really find out how
22 the drug enters the body and also describe the time course
23 of absorption and, thereby, the time course of pulmonary
24 residence, is to use old-fashioned pharmacokinetics. What
25 is needed for that is a good characterization of the

1 disposition which one only can get by an intravenous study.

2 So, if an intravenous study is done and the
3 kinetic parameters are determined, like in this example of
4 fluticasone propionate, and then a clearance of distribution
5 is calculated after IV administration, then an inhalation
6 experiment is made and, again, the kinetic parameters are
7 calculated.

8 This is here an example from several studies from
9 our group and others on the resulting profiles. And then
10 you can use pharmacokinetic concepts such as deconvolution.

11 [Slide.]

12 This is one example, the so-called Loo-Riegelman
13 method, allows then to calculate an absorption profile which
14 is the rate of entry. If you block with charcoal, or have a
15 drop that is not already absorbed, it is equal, then, to the
16 pulmonary residence time--

17 [Slide.]

18 --you end up with a profile such as this
19 absorption profile. It is percent absorbed versus time that
20 allows you, then, to characterize and compare, in this case,
21 different compounds but also different formulations of the
22 same compound and would mirror, then, what is going on in
23 the lung.

24 [Slide.]

25 One noncompartmental way to express the same data

1 is to use a mean-residence-time approach where, again, you
2 need the intravenous data, calculate the mean-residence time
3 after intravenous administration and after inhalation. If
4 the inhalation is only through the lung, then the difference
5 between the two will be equal to the mean absorption time or
6 also equal to the mean pulmonary residence time. You would
7 have a quantitative way of comparing.

8 [Slide.]

9 The fourth way, and the one that we have heard in
10 the previous presentation, is to use pharmacodynamics as a
11 measure of local exposure. I think the data that we have
12 seen so far are very discouraging because, for the small
13 differences that we want to detect, particularly in
14 bioequivalence studies, the variability is very high and,
15 therefore, the ability to discriminate between products is
16 limited.

17 Another way to go would be to use surrogate
18 endpoints. There is a lot of work that is being done right
19 now to identify surrogate endpoints for steroid activity and
20 it is the big hope that, one of these days, we will find one
21 that is really reproducible and can, early on, tell us what
22 we can expect after chronic use of the drug.

23 But, so far, unfortunately, there is none
24 available that is really of that quality.

25 [Slide.]

1 So, I believe, right now, pharmacokinetics is our
2 best bet and I believe that it is much more than just a
3 measure of systemic exposure, that if you use kinetics
4 correctly, that it is able to give us information about the
5 local exposure as well so that one approach to tackle
6 bioequivalence problems with inhaled corticosteroids is,
7 first of all, of course, to have in vitro studies--and that
8 was the discussion we had this morning--to come up with good
9 criteria about in vitro equivalence.

10 After in vitro equivalence is shown, then follow
11 up with in vivo studies where equivalent systemic exposure
12 needs to be shown, and that can be done by just measuring
13 plasma concentration, and equivalent pulmonary-absorption
14 profiles that can be shown by showing equivalent absorption
15 profiles using deconvolution methods.

16 Obviously, the details would need to be worked out
17 and, very difficult, the goalposts need to be defined which
18 will be quite a challenge.

19 [Slide.]

20 Would like to close by thanking all the people who
21 have contributed to this data and thank you for your
22 attention.

23 DR. LEE: Thank you, Harmut. I just wonder
24 whether or not the subcommittee members have any questions.

25 I wonder whether or not you have looked at the

1 questions for discussion. Maybe, in a way, you have
2 answered this question, which is, are there situations where
3 the in vitro data plus systemic PK and PD data can be relied
4 upon to assure local drug delivery for either nasal or
5 inhaled drugs?

6 DR. DERENDORF: Yes; I believe that that may be
7 possible, that if you use the data well, that we can make
8 the conclusion that there will be sufficient--unfortunately,
9 we don't have any better ways right now to approach this.
10 If we would have a surrogate marker, a pharmacodynamic
11 surrogate marker that would be easily quantifiable for the
12 local activity, certainly that would be even better. But it
13 is not out there.

14 So I think what we have right now, this seems to
15 me the best approach.

16 DR. LEE: Were all the data you presented human
17 data?

18 DR. DERENDORF: Yes.

19 DR. LEE: Thank you.

20 DR. BEHL: One quick comment. Even if you have
21 some data that goes to the correlation of PK and PD, it is
22 very hard for me to believe that PK can be used as a means
23 to judge local effect.

24 DR. DERENDORF: What we are trying to do here is--
25 we have two different issues here. If it comes to

1 bioequivalence, the traditional, or the approach that it
2 used with bioequivalence for systemic drugs is if we show
3 equal or equivalent exposure within a certain range with
4 certain confidence, then we imply that the effects will be
5 equivalent.

6 This is exactly the same approach that I would
7 propose here. There is no need, in my opinion, for clinical
8 studies. The systemic equivalency can be done just by
9 traditional comparison of plasma concentrations. The more
10 difficult part is the indirectly characterization of the
11 local exposure that could be done by absorption profiles.

12 So, just as with any other bioequivalence, really,
13 there is no need to measure any kind of pharmacodynamics if
14 you follow the same logic that the same exposure profile
15 will result in the same effect.

16 DR. AHRENS: You made the statement that systemic
17 exposure, if you are using the same compound that you are
18 inhaling, that you only need pharmacokinetics, which makes
19 great sense to me, perhaps, except for beclomethasone
20 because of the fact that there is more than one active
21 species and the absorption profile, the plasma profile, for
22 BDP may not be same as between products and BMP.

23 How would you handle that? Can you do that with
24 kinetics alone?

25 DR. DERENDORF: Yes; I fully agree with you. I

at

212

1 think the concept still holds. It is more complicated to do
2 because you have several players which you need to interpret
3 and measure all of them and then add up the numbers.

4 Again, this is not new. There are other drugs for
5 systemic use where you have active metabolites and the same
6 issues exist there in bioequivalence situations. But, yes;
7 of course, you would need to measure the active metabolites
8 and interpret them correctly.

9 DR. LEE: I think that we ought to let him go. We
10 will come back to this towards the end. Your taxi is
11 waiting for you out there.

12 Let me talk about a few logistic changes because
13 of the shift in the program. We will now take a break and I
14 would like to come back at 3:25, about ten minute. When we
15 come back from the break at 3:25, Dr. Richard Ahrens will be
16 presenting his view on clinical studies for local delivery
17 of orally inhaled corticosteroids. And then the
18 surveillance will go into discussion. Then we will come
19 back on line with the rest of the schedule.

20 Thank you.

21 [Break.]

22 DR. LEE: Before I turn the podium over to Dr.
23 Ahrens, I would like to alert the clinician members of the
24 committee to begin thinking about addressing the three
25 questions in the upcoming sessions.

1 Dr. Ahrens will be talking about clinical studies
2 for local delivery of orally inhaled corticosteroids.

3 **In Vivo BA and BE:**

4 **Clinical Studies for Local Delivery**

5 **of Orally Inhaled Corticosteroids**

6 DR. AHRENS: Thank you.

7 [Slide.]

8 This is the point where I am, of course, supposed
9 to say I am happy to be here. It is particularly true this
10 time because the topic I am talking about here is an area
11 that I have been interested in for more than a decade in
12 terms of the general issue of the assessment of
13 bioequivalence of inhaled drugs used to treat asthma.

14 [Slide.]

15 The task of these clinical studies that I have
16 been asked to address is, first of all, to address the
17 issue, predominantly, of generic equivalence to determine
18 whether the innovator and generic inhaled corticosteroid
19 deliver bioequivalence quantities of drug to the site of
20 action in the lungs. In other words, even if there is a
21 difference in quantity delivered to the site of action, that
22 that quantity is not large enough to make an important
23 clinical difference.

24 The same approach to addressing this certainly
25 could also be applied to reformulations that are not

1 intended to be pharmaceutically equivalent, although, there,
2 it would be determining rather than proving bioequivalence,
3 determining the ratio of doses that are required to deliver
4 equivalent quantities of drug to the site of action.

5 For example, if an FHA inhaler delivered two or
6 three times as much drug to the site of action as an
7 innovator CFC preparation, that may well be okay and
8 approvable but, still particularly important, at least in my
9 opinion, that the clinician knows what that ratio is so that
10 he or she can adjust the dosing strategy appropriately.

11 [Slide.]

12 So the concept of how to address this issue of
13 bioequivalence. As we have heard earlier, there is a lot of
14 variability in clinical studies, particularly with inhaled
15 steroids, addressing the issue of bioequivalence.

16 The typical approach that I think is now
17 reasonably well established in precedence, at least with
18 beta agonists, is to look at formulations along the dose
19 axis rather than the response axis; that is, rather than
20 looking at a comparison of responses, are they equal or not
21 to a given dose level, coming up with a ratio of doses that
22 are likely to produce equal responses.

23 This is, in essence, using a pharmacodynamic
24 response, in this case a clinical outcome, to bioassay the
25 quantity of drug delivered to site of action. So, in a

1 sense, I have difficulty separating, in this context, the
2 issue of clinical study from a pharmacodynamic study because
3 they are getting after, in a sense, the same thing; are we
4 delivering, within the realm of not making a bit clinical
5 difference, an equivalent quantity of drug to the site of
6 action.

7 [Slide.]

8 This issue of using the dose axis rather than the
9 response axis is something that has a history relating to
10 albuterol, generic albuterol inhalers. Albuterol, of
11 course, went off patent in 1989. The initial studies that
12 were done to try to address bioequivalence of inhaled
13 albuterol, in fact, did look along the response axis
14 figuring that if you showed equivalent response to two
15 different inhalers at the same dose that they must be
16 bioequivalent, looking, in this case, at bronchodilatation.

17 At the prompting of some people, including myself,
18 a control was put in these studies where the innovator
19 product had more than one dose level. Then, in 1992, when
20 everybody got back together to look at the results of those
21 studies, in horror--Wally, I hope you agree with this
22 history; this is at least my interpretation of the history--
23 to everyone's horror, they discovered that the studies
24 couldn't discriminate between different dose levels of the
25 same product. And, if they couldn't do that, then how could

1 they be expected to differentiate different doses delivered
2 by different products.

3 That led to a search, more advisory committee
4 meetings and a search over the next several years for
5 acceptable and valid methodologies to accomplish this and,
6 ultimately, to the approval of the first generic inhaled
7 albuterol, at least in terms of the in vivo study, a
8 bioassay study, demonstrating bioequivalence.

9 [Slide.]

10 So the concept here, in essence, is to perform
11 more than one dose level to at least on preparation,
12 preferably both. In this case, this is a so-called two-by-
13 two bioassay because there are two doses of each
14 preparation. And then, instead of looking at a comparison
15 of responses, to look, essentially, at the distance between
16 the dose-response curves.

17 This is the ratio of doses that will produce an
18 equal level of effect. If it takes twice as much to produce
19 the same effect, that test preparation would, therefore, be
20 half as potent.

21 This is an old concept dating back, probably, to
22 the forties. With well-established validity criteria, you
23 have to have a significant dose-response curve, dose-
24 response relationship, to act as a standard curve. If you
25 don't, you don't have a valid bioassay. You need to have

1 responses that are in the same region--that is what this
2 means--and the response curves, of course, need to be
3 parallel.

4 With two inhalers delivering the same product, at
5 least, hopefully, you would expect that to be the case.

6 [Slide.]

7 We applied this approach, in my laboratory, to
8 Baker Norton's product. This is the product, the first
9 generic albuterol that was approved, using these data as the
10 in vivo demonstration of bioequivalence.

11 We looked at a response to histamine bronchial
12 provocation, PC20 FEV 1 versus dose, down here. As you can
13 see, the curves largely coincide. And then we applied
14 bioassay statistical methodology to come up with a
15 confidence interval. As you can see here, that was 0.69
16 1.40. This met the concurrently established bioequivalence
17 criteria of being between 0.67 and 1.5, essentially between
18 two-thirds and one-and-a-half times as potent since the
19 entire confidence interval was within that range.

20 [Slide.]

21 That was the analysis that we did using so-called
22 Finney bioassay. The FDA, I think for very good reasons,
23 chose a somewhat different statistical approach which they
24 called a dose-scale approach. We used two doses of each
25 preparation. They, instead, chose to use the reference as a

1 standard curve and then compare one dose of the test
2 preparation at a time.

3 The curve-fitting methodology was a little bit
4 different. The method for establishing the confidence
5 interval, we used Fieller's theorem as part of Finney
6 bioassay which relies on normal theory whereas they chose to
7 use the somewhat more robust methodology of bootstrap which
8 doesn't require normality.

9 It was comforting to find that the results by
10 these two methodologies were virtually the same.

11 [Slide.]

12 So that is the concept, at least as it was
13 developed in addressing inhaled albuterol. Now the problem
14 at hand is that this kind of bioassay approach has rarely
15 been applied to inhaled corticosteroids because it is not
16 very easy to do.

17 Furthermore, when it has been applied, it has
18 really met with very limited success. On the next slide, I
19 will give you an example of that.

20 [Slide.]

21 This is, in my humble opinion, the best bioassay
22 study, if you will, comparing inhaled corticosteroids. It
23 was a study done by 3M in the approval process of their HFT
24 BDP product comparing it to CFC BDP. This was an exceeding
25 rigorous clinical trial, clinical study, which involved

1 hundreds of subjects each of which came to the clinic at
2 least five days a week to perform lung functions in many
3 ways that are beyond that. It was an extremely rigorous,
4 carefully done study, not a typical study.

5 They did succeed in estimating a potency, a dose
6 ratio, that each microgram of HFA is equivalent to
7 2.6 micrograms of the CFC product. However, if you look at
8 the confidence interval, it stretched from 1.1 to over 11.0,
9 essentially, not a very clinically meaningful confidence
10 interval if it is over a ten-fold range.

11 The fact that it didn't encompass one indicates
12 that, at a statistically significant level, these two
13 preparations are not equivalent. It does not, even with the
14 best study that has been done to date, give you a clear
15 answer as to exactly what that potency ratio is, what the
16 bioequivalent dose is.

17 [Slide.]

18 This issue has been addressed by a number of
19 people, but, in this recent review by Peter Barnes and Bill
20 Busse and Soren Pedersen, first of all, they noted that this
21 was true that, in spite of dozens of studies that are in the
22 literature, it is very difficult to draw firm conclusions
23 comparing comparative efficacy.

24 It is hard to say that anything is different from
25 anything else in the way studies have been done and relate

1 that to things like study designs, control over important
2 confounding variables and, last but not least, the lack of a
3 strong dose response relationship for inhaled
4 corticosteroids.

5 [Slide.]

6 That leads to the common wisdom that the problem
7 with inhaled corticosteroids is that the dose-response curve
8 is just so darned flat that you really can't detect any
9 differences.

10 If this is really true, that the dose-response
11 curve is that flat then, first of all, the dose delivered
12 really doesn't seem to matter much, clinically. If you
13 can't tell a difference in dose, that may mean that the dose
14 doesn't really matter.

15 If that is true, then you don't need to, and, in
16 fact, can't really do a valid bioassay using the concept
17 that I just described simply because you don't have a valid
18 significant dose-response curve. Therefore, you don't have
19 a valid bioassay.

20 [Slide.]

21 You could, therefore, simply rely on clinical
22 trials going back to the concept of comparing responses. By
23 the way, this "no" doesn't belong there. My apologies.
24 Cross that out. You could use a clinical trial showing that
25 two formulations yield similar responses.

1 That is in fact what was done. This is a recent
2 publication which was presenting data that was at least part
3 of the basis on which a Baker Norton HFA product was
4 approved in the U.K. You can see, they studied morning peak
5 flows here in a group of mild, not so well-controlled,
6 asthmatics and more severe asthmatics. These are actually
7 two different studies, hence the different doses of BDP.

8 You can see that there are no significant
9 differences in response. Unfortunately, failure to show a
10 significant difference in response is not at all the same as
11 proving the two things are the same. This has lead to a
12 good deal of consternation, I am told, by Dr. Ganderton and
13 others in the U.K. as well as what I understand is a record
14 number of letters to the editor to respiratory medicine
15 particularly when this study and the fact that the Baker
16 Norton product was approved on a one-to-one, a one
17 inhalation equals one inhalation basis, with the next study.

18 [Slide.]

19 This will be familiar to you. This is the 3M
20 study I showed you earlier which shows a difference, a
21 significant difference, in potency. I have it on good
22 authority, although I could not vouch for it myself, based
23 on what was in those letters to the editor and other
24 discussions that have taken place, that these two inhalers
25 are very close to being pharmaceutically equivalent.

1 If that is true, that is what has led to the
2 consternation in that how could one be approved on a one-to-
3 one basis and this one be approved in the U.K. on a two-to-
4 one basis, two inhalations of CFC is equivalent to one
5 inhalation of the HFA.

6 [Slide.]

7 That leads me to the following question. That is
8 all based, by the way, on the fact that the dose-response
9 curve must be just so darned flat. That is what the letters
10 to the editor really addressed, that you really can't do
11 what the Baker Norton study did but there isn't,
12 necessarily, a good way to get around this problem.

13 I might just stop here at this point and say what
14 everybody says, it is just really hard to deal with inhaled
15 steroids so clinical studies may be not that useful.

16 I would like to now ask the question is it really
17 true that inhaled steroid dose-response curves are just that
18 flat.

19 [Slide.]

20 What has got me originally thinking about this is
21 what I will label here as the asthma clinician's paradox.
22 That is, in clinical studies, multiple clinical studies,
23 with hundreds of patients, it has been very difficult to
24 show anything but a very flat--dose-response curves that are
25 flat to nonexistent.

1 On the other hand, clinicians think they see
2 inhaled dose-response relationships in the clinic every day
3 in individual patients. Both of these cannot be true. One
4 says there is no dose-response relationship. The other
5 says, at least in some patients, there is an important,
6 clinically important, dose-response relationship that we all
7 see.

8 [Slide.]

9 So the question is, which is allusion and which is
10 reality. I would like to make a modest proposal here, for
11 the remainder of my talk, as to what the answer to this may
12 be. I will start out with this quote: "Good judgement comes
13 from experience. Experience comes from bad judgement." I
14 think we have all experienced that from time to time.

15 "Furthermore, experience teaches you to recognize
16 a mistake when you have made it again."

17 [Slide.]

18 What I would like to propose to you here is the
19 that the typical inhaled corticosteroid study design which
20 has been used over and over again with various modifications
21 but the same basic theme, in dozens of studies, is a mistake
22 that we keep repeating over and over again.

23 The typical study, as most all of you will recall,
24 is a parallel group study lasting varying lengths of time
25 but at least for a month or two. The general approach is

1 that you take baseline data in poorly controlled asthmatics
2 and then do something that none of us really do very often
3 as clinicians, is just place those poorly controlled
4 asthmatics on a inhaled steroid and wait for them to get
5 better of subsequent weeks, and then measure their response.

6 This is marked by very high variability in
7 response, the very shallow dose-response curves that we have
8 talked about and a tremendous reluctance to do crossover
9 studies because of the prolonged treatment time potential
10 carryover.

11 [Slide.]

12 Let's take a little further look at just what it
13 would take to do a good bioassay study using this kind of
14 methodology. I am not going to go into detail at all here
15 although, perhaps, Dr. Hauck and others would like me to as
16 to what methodology we use to do sample size, statistical
17 power and sample-size calculations.

18 For here, it is not a straightforward matter but
19 something that there have been some recent publications on
20 and my biostatistician, Dr. Singh Ho Hahn and I, have done
21 some work with. But, I will suffice it here to say that it
22 is not related simply to the variability of the response.
23 It is also related to the steepness of the dose-response
24 curve and, in fact, those two things do not function
25 independently. They function as a ratio.

1 The smaller that ratio, the more powerful and
2 discriminative the study.

3 [Slide.]

4 So we did some sample-size calculations with
5 assumptions that we were going to try to demonstrate using
6 two one-sided hypothesis testing, that a generic between 0.5
7 and 2.0 times as potent as the innovator, typical alpha and
8 power level using a two-by-two bioassay study design, two
9 doses of each preparation.

10 [Slide.]

11 Here is the S over B ratio that I talked about
12 earlier. Sample size calculated--this is using the data
13 from that 3M Busse study--looking like it would take in the
14 neighborhood of a thousand patients to really fulfill that
15 goal. This was an exceeding rigorous and difficult study to
16 do. I don't know for sure where typical studies are, but
17 they are probably--most other studies are up here someplace.

18 That is not a very practical number of patients to
19 do, particularly if you are a generic company trying to get
20 a product approved.

21 [Slide.]

22 Because of this problem, we launched into a pilot-
23 well, actually, we did a number of pilot studies searching
24 for the holy grail of a better outcome measure that would
25 give us greater reproducibility. This was part of that

1 series. It was a study that we did in collaboration with 3M
2 using their HFA preparation.

3 We did it as a crossover study and we justified
4 that in terms of dealing with carryover by the following, by
5 giving a prednisone burst at the beginning of the study to
6 essentially maximize carryover in patients, give everybody,
7 as near as we could, maximal steroid effect by maximally
8 improving their asthma.

9 That, in fact, models what clinicians do all the
10 time. If we see a patient who is in trouble with their
11 asthma, we generally give them a course of oral steroids and
12 then start them on their inhaled steroid to maintain that
13 control.

14 We then looked at the stability of asthma over the
15 subsequent three weeks, looked at virtually every outcome
16 measure, again, in search of that holy grail, that we could
17 think of expressed in every way we could think of for a
18 total of 58 different outcome variables searching for the
19 lowest S over B ratio.

20 [Slide.]

21 What we found was that, in this model, some
22 outcomes were terrible. There are some that are even up
23 here further, but look at the computed sample size here over
24 S over B ratio. We are up in the thousands.

25 I had this great idea that if patients got up at

1 4 a.m. routinely, set their alarm and did their peak flow
2 meters, that that would model morning dipping and that would
3 give us a good response. Not only did it not work, it got a
4 lot of patients angry with me. That wasn't a very good
5 idea.

6 Here, you can see maybe your other favorite
7 outcome, and there are others on this list, that didn't work
8 very well. I would now like to zoom in, down on this corner
9 down here.

10 [Slide.]

11 Computed sample size; now, we are dropping down to
12 100 or under. To my surprise, the best outcome measure was,
13 essentially, morning home spirometry. We had a portable
14 electric spirometer that gave us FEV 1, FEF 25, 75, as well
15 as peak flow. I am not sure that those differences are so
16 really important as the fact that it was upon-awakening
17 morning spirometry that turned out to give us the best
18 power.

19 But the remarkable thing is that it appears, in
20 contrast to that Busse study I showed you earlier, you could
21 achieve this sort of thing with 100 subjects or under.

22 [Slide.]

23 Now, I think, the most important issue with this.
24 Here are those same points that I just showed you down here
25 with the best outcome measures. Here are the same outcome

1 measures using the same pilot data but now doing sample-size
2 calculations for a parallel study, as if we had done this as
3 a parallel study rather than a crossover study.

4 It become apparent to me that these data suggest,
5 at least, that the problem with the traditional study that
6 we have done--there is the Busse study right in the middle
7 of it--of the outcome measures that turned out pretty good
8 in a crossover study.

9 The real study is not the outcome measures. The
10 problem is the study design. It is a parallel versus a
11 crossover study design.

12 [Slide.]

13 We are not the only ones to have stumbled upon
14 this although I think the implication has not been quite so
15 clear. This is a study done by Soren Pedersen a few years
16 ago looking at exercise-induced asthma in children, again, a
17 small number of children, yet got a highly significant dose-
18 response relationship.

19 By the way, in that study I just showed you with
20 those best outcome measures, the dose-response relationship
21 is with only twelve subjects. It was less than 0.0001.

22 There is nothing new under the sun. It is not
23 exactly a great revelation to Dr. Hauck that crossover
24 studies are more powerful than parallel studies. That is
25 old as the sun. So that is not exactly a revelation and yet

1 I think what is a revelation is that, in no place does it
2 seem to be more true than in dealing with inhaled-steroid
3 dose-response relationships and comparison of preparations.

4 I think this may be the answer to this asthma
5 clinician's paradox that I showed you earlier. It may well
6 be that there are very real dose-response relationships in
7 individual patients, that we are not deluding ourselves when
8 we think we see that. What these data suggest is that that
9 very real response, in at least some patients, gets lost in
10 a great deal of interpatient variability between asthmatics
11 which we, as clinicians, also, all know is there.

12 [Slide.]

13 So, in summary, the task has been to develop a
14 capable method of demonstrating in vivo bioequivalence for
15 inhaled steroids. The concept I have presented is to use a
16 clinical bioassay dose-axis comparison. The common wisdom
17 is that the dose-response curve is just too darned flat to
18 really do this. I am presenting an iconoclastic potential
19 alternative that the real problem may just be that you can't
20 do this if you are going to persist in doing parallel
21 studies.

22 [Slide.]

23 The solution may be to not say we can't do
24 crossover studies because of carryover. For heaven's sake,
25 most parallel studies have to deal with carryover because

1 many of the subjects came into those studies already on
2 inhaled corticosteroids. There is carryover there to begin
3 with. So it is not a matter of getting rid of carryover so
4 you don't have to worry about it. It is a matter of how to
5 control it.

6 We presented at least one method by starting each
7 treatment period now with a wash-out but with a wash-in,
8 with a burst of oral steroids to minimize the potential for
9 carryover to be able to do these crossover studies.

10 This should allow accurate assessment of
11 bioequivalence if it really works with tens to hundreds
12 rather than thousands of patients. However, the proof of
13 the pudding is in the eating. This is just a pilot study.

14 There hasn't been a study that actually has
15 accomplished this yet. You will have to wait for that, this
16 is the commercial message, it is no great surprise that I
17 continue to look for additional opportunities, collaborative
18 opportunities, to address this issue.

19 Thanks for your attention.

20 DR. LEE: Thank you very much, Dr. Ahrens. I
21 invite you to take the hot seat and maybe entertain some
22 questions.

23 **Subcommittee Discussion**

24 DR. LEE: We now go into the discussion period.
25 There are two major groups of questions to be addressed

1 following the two presentations, one on nasal aerosols and
2 sprays and the other one on orally inhaled corticosteroids.

3 In order to keep the momentum, let me propose that
4 we take on the second group of questions first which is,
5 "Clinical studies for local delivery of orally inhaled
6 corticosteroids, ICS." These are two questions that the
7 agency would like to get input on.

8 The first one is, "A number of approaches have
9 been proposed to assess bioequivalence of ICS." You have
10 heard some of those. The question is, "Are any of these
11 study designs proven to offer better discrimination in terms
12 of dose-response sensitivity?"

13 Here, we will look to the clinician colleagues on
14 the committee to guide us.

15 DR. LI: I will make a comment. I appreciate the
16 discussion that we have had so far. I think that one of the
17 issues with the dose-response for inhaled corticosteroids
18 has to do with the usual doses at which we conduct our
19 studies and the usual doses that we use in clinical
20 practice. Those doses tend to be on the high end where we
21 get a maximal or a near maximal benefit. That may be
22 clinically appropriate.

23 But I think that the differences between
24 preparations or formulations may be more apparent at the
25 lower end of the scale. So one of the suggestions that I

1 have heard that makes some sense is when conducting a dose-
2 response study to use lower than usual doses to see if
3 differences can be apparent at the lower doses rather than
4 at usual doses.

5 DR. SZEFLER: This is an area Richard and I and a
6 number of people have discussed for a number of years. The
7 markers that seem to be attractive are exercise-induced
8 asthma, exhaled nitric oxide and then I would toss in a
9 third one which would be bronchodilator reversibility.

10 We are in a process now with the Asthma Clinical
11 Research Network of testing these in kind of a different
12 model. It is a little bit different than what Richard
13 proposed and we are trying to match up efficacy measures
14 with levels of cortisol suppression because, I think as you
15 pointed out earlier, you could do one measure and compare it
16 to another.

17 We kind of took the position of trying to assess
18 each of the individual steroids for levels of cortisol
19 suppression and then take those doses for given levels of
20 cortisol suppression and look at efficacy. We are now kind
21 of ending the third phase of that trial and we will have
22 some answers on that. But at least looking at the
23 literature, the things that seem to be appealing are the
24 study that Richard mentioned in terms of exercise-induced
25 asthma.

1 Exhaled nitric oxide, there are a few studies on
2 that, but people don't look at that as kind of a--it is not
3 acceptable yet as a surrogate marker of inflammation. It is
4 a nice bioassay, maybe.

5 The third one that I am kind of intrigued with
6 looking at that seems to be surfacing as a potential marker
7 of response is beta-agonist reversibility. So there are
8 three that I think I would look at. The other ones, like
9 FEV 1 and peak flow, the changes appear to be small.

10 John Toogood, early on, had identified that very
11 low doses can achieve your maximal effect but you need
12 higher doses to get more at the exercise-induced areas.

13 If you look at other levels of reactivity like
14 methacholine and histamine, you just can't differentiate
15 changes. That is probably because they are very slowly
16 reversible.

17 DR. AHRENS: The fact that, in what I just said
18 here, I emphasized the basic study design, parallel versus
19 crossover studies, doesn't diminish the importance of
20 selecting the right patients and choosing the right outcome.
21 In terms of the issue that was just brought up about
22 patients being often at the top of the dose-response curve
23 in typically clinically used doses.

24 For many patients, that is clearly true, even at
25 the very lowest dose. There are certain patients that it

1 takes almost--the biggest step in the dose-response curve
2 goes from nothing to something. Once you get to that,
3 anyplace else you go in the dose-response curve doesn't have
4 much effect.

5 For those patients, probably the dose-response
6 curve is very flat and the dose probably doesn't make a big
7 difference. A broad difference in dose delivered probably
8 wouldn't hurt those patients. But there are other patients
9 where the dose-response curve really is steeper. For sake
10 of time, I didn't go into the details for this pilot study,
11 for example, what patients we selected. But they clearly
12 were steroid-dependent patients in the sense that they were
13 not well-controlled unless they were on substantial doses of
14 inhaled steroids.

15 There are clues in other studies that have been
16 done that those patients are not a tiny minority, though,
17 that there is a substantial percentage of those patients
18 around. It is those patients we need to protect by having
19 properly done bioequivalence studies and, therefore, it is
20 those patients who really ought to be the subjects for those
21 studies.

22 So it isn't a matter of--what you said, James, I
23 think is correct that, for some patients, even at typical
24 clinical doses, they are at the top of the dose-response
25 relationship. But I don't think it is true for all subjects

1 and we ought to be able to develop entrance criteria to
2 studies to identify those patients during run-in periods.

3 DR. SZEFLER: There is some appeal, in terms of
4 your model from the ethics standpoint and the availability.
5 We try to recruit those patients and they are a challenge to
6 find because now of the extensive use of inhaled steroids
7 and also because of some of the problems we run into with
8 institutional review boards in terms of delaying treatment
9 and observation period.

10 So the attractiveness of your model is that you
11 can treat that right away and you can even take patients who
12 are in inhaled steroids because you are escalating the
13 treatment and then you are withdrawing and watching
14 carefully. So there are some ethical and, also, some
15 availability in terms of numbers of patients to look at that
16 offer some attractiveness in terms of your model.

17 DR. AHRENS: Stanley, you brought up the issue of
18 what outcome measures to choose. I think that is also an
19 important issue, that there are some outcome measures that
20 are clearly much less discriminative than others.

21 For what it is worth, it was only a small pilot
22 study, but bronchodilator reversibility was one of the
23 things that we looked at in the study and it didn't come out
24 very well. I was amazed that one of the simplest things,
25 just doing morning peak flows, is what turned out to be as

1 discriminative as anything. We didn't do exercise in the
2 study. It is certainly more cumbersome to do, but, based on
3 Pedersen's data, that also is right if you use his data to
4 do the same sample-sized calculations. It is right in there
5 with the morning spirometry, the peak flows that we looked
6 at.

7 It is not a lot better, but it is not worse
8 either. I think it is an alternative kind of model.

9 DR. SZEFLER: In our studies, we were really
10 trying to answer the question, are steroids different. I
11 think the question we have facing us today is, given a
12 steroid with a different delivery device, is it equivalent.
13 So it is kind of the opposite end of the spectrum.

14 So then you get into setting the goal posts with
15 the model in terms of what is acceptable, tight goal posts
16 or wide goal posts and everybody can kick a field goal.

17 DR. AHRENS: I guess I would respond to that by
18 saying the handling of those two situations is slightly
19 clinically different but not that much. In one, you want to
20 make sure, based on two one-sided hypothesis testing, that
21 the confidence intervals are inside the goal posts. For the
22 other, you don't have goals posts. You just want to know
23 what the truth is. If something is three times a potent,
24 you want to know that but there, again, you need to have the
25 same kind of confidence limits.

1 If you wanted to know between half and twice as
2 potent in terms of proving bioequivalence, if something is
3 three times as potent, you really want to know, okay, my
4 estimate is three times. Is it 1.5 to 6.0 or where? You
5 want to narrow the confidence interval on that estimate,
6 wherever it is, to the point where it is clinically useful
7 and not tenfold or more wide that isn't clinically useful.

8 DR. LEE: Let me interject here and ask the
9 question, is there any discriminatory study design known
10 today?

11 DR. AHRENS: Based on what I have presented here,
12 It should be obvious my opinion is, in terms of things that
13 have been done and proven and used in this kind of--
14 validated by having actually been used and been successful,
15 no. What I have been holding out here is that I think there
16 may be some promise looking at things a bit differently than
17 in the past.

18 But that still may be entirely doable. But it has
19 not been done yet, to the best of my knowledge, in a way
20 that would be truly usable for bioequivalence.

21 DR. LEE: So would question B2 be a logical follow
22 up to that, looking for surrogate markers that might be
23 sufficiently sensitive?

24 DR. AHRENS: As I think I was just saying, my
25 opinion to that is that that is an important thing to do

1 but, in itself, insufficient. We did a grand total of, I
2 believe it was six pilot studies searching for that holy
3 grail of what is the best outcome measure to make this
4 problem go away. It was in the sixth study, the sixth pilot
5 study, that we finally came around to the idea that the
6 problem really may not be the marker. It is the basics of
7 the study design.

8 That is important, but I think you are going to
9 have to come up with a way to do a crossover study or you
10 are never going to be able to use this in a bioequivalence
11 kind of approach, in a bioassay kind of approach, like was
12 done with albuterol, and apply that to inhaled steroids.

13 You can decide that you don't really want to do
14 that, that it is more trouble than it is worth. But if you
15 want to do it, then I think that is what it is going to
16 take.

17 DR. LEE: Other points or opinions? Could it be
18 because we don't understand the disease stage well enough?

19 DR. AHRENS: Stanley, do you want to respond to
20 that?

21 DR. SZEFLER: I think we understand its
22 manifestation. We don't understand totally its etiology.
23 But I think the variability is a problem. We would like to
24 think it is not product related and so we trust that the
25 products that we are working with would limit that

1 variability. But I think it is the disease variability that
2 makes it statistically hard to sort out.

3 DR. AHRENS: An asthmatic is not an asthmatic is
4 not an asthmatic even if you bring them into the study like
5 is often done within the same FEV1. Their FEV1 is between
6 50 and 70 percent of predicted, or whatever the criteria
7 are. You still, even though you do that, get some very
8 different people in terms of their characteristics of their
9 asthma and what apparently is the case in terms of their
10 responsiveness of inhaled steroids in that kind of study.

11 DR. LEE: Thank you.

12 Lester?

13 DR. HARRISON: We certainly support the crossover
14 study design as well. It is very appealing to us and, based
15 on our knowledge with BDP, it seems the way to go. We would
16 be very encouraged if you would--somebody would--actually do
17 the real definitive study and prove the point.

18 We were involved in the pilot study but that needs
19 to be taken the next step. It did seem like it has the
20 potential to actually discriminate.

21 DR. LEE: Very good. Wally, do you have the
22 information you need?

23 DR. ADAMS: Yes. I think that is helpful.

24 DR. LEE: Okay; great. Let's move on and talk
25 about question A1 and A2 which are similar to the ICS

1 situation. You may recall Dr. Roman's presentation about
2 the three models and the same question was posed to see
3 whether or not is it feasible to demonstrate a dose response
4 for locally acting drugs using any one of these designs.

5 Let me see what the committee has to say.

6 DR. BEHL: From what I have seen so far, and it is
7 for question B1, B2 questions also on the steroids, the
8 dynamics of locally acting compounds in the nose and in the
9 lung are such that I don't see how one could replace the
10 need of, if not a full-scale clinical trial, then at least a
11 bridging clinical trial to show that, after showing all the
12 pharmaceutical equivalence of the product and other
13 equivalence that can be easily shown, that the results of
14 therapeutically equivalent.

15 I don't see what we know today, in terms of valid
16 approaches which can be used in lieu of, if not a full-
17 scale, then a bridging clinical trial.

18 DR. LEE: Any opinion? Dr. Roman, you would like
19 to respond?

20 DR. ROMAN: Yes. I agree, actually, that the
21 crossover is a much better design in terms of controlling
22 some of the variability. However, I cannot, at the moment,
23 imagine any crossover design for nasal-allergy studies which
24 are very much depending on season and shortness of it, if
25 you wish.

1 Of course, the fact that the endpoint measurement
2 is not so reliable as the pulmonary-function test, the
3 rhinomometries. I don't know if it is in infancy or agony.
4 I am not quite sure which phase of this we are observing,
5 but it is not a very reliable method so far.

6 So I would be very hard-pressed to come with a
7 design which will be as elegant and interesting as Dr.
8 Ahrens. Another thing if, if I may ask and think here, will
9 this--you see, the problem is that most of the reference
10 drugs do not show much of the dose response in their full
11 development programs.

12 So the companies will have to do the reference-
13 drug study tests as well as the dose responses in addition
14 to the tested drugs.

15 DR. DALBY: In the hierarchy of acceptable
16 testing, you have the clinical test and, if that is found to
17 be nondiscriminating, you drop down to the in vitro tests.
18 It seems to me, although, again, it is not, perhaps, a
19 population thought that the intermediate ground is the
20 scintigraphic study of deposition which at least
21 incorporates the anatomy of the nose, and it is not such a
22 big stretch, in my opinion, to go from if the drug is
23 depositing equivalently in two formulations, that it will
24 act equivalent and it is not necessary to fall straight down
25 to the in vitro tests.

1 I fully accept the difficulty of validating the
2 labeling technique, but, by the same token, if we are going
3 to develop criteria that can find two products to be
4 bioequivalent, as Andy said, that is no different than
5 finding an innovator product to be the same as the labeled
6 innovative product.

7 So, putting those things together and accepting
8 that a nasal solution is probably the easiest type of dosage
9 form to reliably radiolabel with a deposition marker, it
10 would seem to me at least appropriate to consider
11 scintigraphy as a measure of equivalence.

12 DR. BEHL: It might be a case of trying to prove
13 the impossible. If the original innovator product in two
14 different dose strengths was approved, of course, there is
15 no burden on their part to show the equivalence or a good
16 inherent dose response, for example, that has just been on
17 the market.

18 If they go back and do them again, and prove the
19 dose response and prove that a 2-mg dose is better than a 1-
20 mg dose on the market, they might fail in doing that now.
21 It depends on what the suggestion is how we are going to
22 show the bioequivalence of the same dose but different
23 formulations, or same formulations and maybe a different
24 company.

25 Maybe we are asking to do something that is not

1 doable.

2 DR. MacGREGOR: I guess I have a couple of
3 comments on what you said and that is to get a nasal product
4 on the market, you had to run it against placebo. We all
5 know that the placebo response is 35 percent, is a typical
6 number. The response of the active drug is typically 45 or
7 50 percent.

8 So that is why you needed 400, 600, patients. So
9 there is a problem right there, if you had a three-way
10 study, parallel-group study, where you had placebo, the
11 innovator and the test, I guess what you are worried about
12 is that you ended up with going in the opposite direction
13 from the placebo or that you are just the same as the
14 placebo.

15 But it took a lot to get there so that is where I
16 see there is a problem studying. As far as your comment
17 about solutions, it is my understanding, in reading the
18 guidance, that solution formulations, there is no request
19 for bioequivalence of solutions. There is a request for
20 suspensions for multiphase products but not for a solution.

21 I have looked as hard as possible to see why you
22 would need a study for bioequivalence of a solution being an
23 innovator with a solution on the market, I am asked to look
24 at that and say, come up with a reason why someone has to do
25 bioequivalence, and I can't. Clinically, I just don't see--

1 once you show you have the same solution and the same
2 droplet size and plume pattern met, I don't see why there is
3 a need for a clinical trial.

4 I agree with the guidance from that point of view.
5 As far as a suspension, then you have other things going
6 about. The problem is, in the clinical trial, it took 600
7 patients to show that difference from 35 to, say, 45 or 50.
8 That is where I look for more innovation in the design. I
9 think we are too often going back to what it took to get the
10 innovator on the market.

11 That is why I am interesting in seeing
12 alternatives where we do crossovers or something along that
13 line, one nostril for this one, one nostril for that, and go
14 in and look for inflammation. What is there that we can do?

15 DR. DALBY: I am just concerned that, in the drop-
16 down from a clinical study to the in vitro testing, that it
17 is possible to design tests that are so discriminating but
18 completely irrelevant that you can falsely keep an
19 appropriate product from the market.

20 DR. MacGREGOR: I just think that scintigraphy in
21 a multiphase product, having done that in the past, is one
22 of the most difficult things, even going back and making--in
23 the case of the drug that we had, we made a hot bromine into
24 the molecule so that we could study it. I remember that,
25 because it was a multiphase system, it was just so difficult

1 to get it to be identical to what was on the manufacturing
2 line, because you are only making ten or fifteen of these
3 devices, it is technologically--if we walked in here, there
4 would be so many questions about the data that we would lose
5 sight of any clinical benefit that we had seen from it.

6 DR. HAUCK: I just wanted to take the discussion
7 back to a little bit of basics again. A key, really a
8 requirement, of anything to show bioequivalence is that it
9 be able to show differences. If you have a test that comes
10 back and says 7 all the time, then everything is equivalent
11 and it is real easy to show equivalence.

12 So I kind of had problems when we were hearing Dr.
13 Roman earlier, the note I wrote down is, "Why are we doing
14 these?" They didn't seem like they are going to
15 discriminate against anything so, showing equivalence out of
16 at least the parallel-design clinical studies that she was
17 discussing, don't seem terribly relevant.

18 I would much rather be, and now back to Dr.
19 Dalby's comments--I would much rather be in the overly
20 discriminating case because that is a goalpost question.
21 You just don't have to set a tight goalpost if it is
22 discriminating things that--if something is very tightly
23 discriminating, you just set a wider goalpost. But you have
24 to have the discrimination or you just can't do equivalence
25 at all.

1 Where that puts your labeling, that I can't help
2 you with.

3 DR. LEE: It seems to me, based on what I have
4 heard, it is not feasible to demonstrate dose response for a
5 locally acting drug; is that correct?

6 DR. HAUCK: That's what I hear.

7 DR. LEE: At the present time. And, if not, what
8 other approaches may we rely upon. I don't think we have
9 the answer.

10 DR. HAUCK: Wait a minute. That sounded like too
11 general a statement. I mean, it is an issue of the type of
12 study and the type of drug. We just saw a dose-response
13 study.

14 DR. LEE: That is for nasally acting drugs.

15 DR. HAUCK: He said locally acting.

16 DR. LEE: I'm sorry; for locally acting nasal
17 drugs.

18 DR. HAUCK: Is that a true statement for all
19 types, antihistamines as well, steroids? I just don't know,
20 but I raise that question.

21 DR. AHRENS: I am tempted to say it is true, but I
22 don't really know for sure.

23 DR. BEHL: From the dynamics of how they act and
24 the mechanics of what has to happen for them to show the
25 effect, I would say that that statement, even though not

1 shown for all compounds, is probably very close to be true.

2 DR. LEE: I think back to the old question again;
3 we need more data.

4 DR. HAUCK: I think it is hard for us to say that
5 such a thing can't exist. It is sort of the absence of data
6 is not the data for its absence, or something. Other than
7 saying we have not been shown it today.

8 DR. LEE: I guess a more prudent way to say it is
9 that we need to explore this further.

10 DR. DALBY: One thing I think would be worth
11 considering is, since, if I understand Harmut's presentation
12 correctly, for every known steroid that is now on the
13 market, it is possible to detect it in plasma. I wasn't
14 sure what his method was. If you have an equivalent plasma
15 time-profile, must that have resulted from an equivalent
16 deposition and an equivalent local concentration?

17 Could we not extrapolate that to equivalency
18 because pharmacokinetic profiling is the number-one
19 acceptable criteria that the age says it prefers.

20 DR. LEE: I think, along the same lines, Richard,
21 is basically discomfort about the scintigraphy studies is
22 that we are not certain what has been deposited is available
23 and, therefore, maybe some sort of sophisticated techniques
24 like receptor imaging is the way to go.

25 DR. AHRENS: It would seem to me, though, in

1 reference to that, that we are in a bit different ball game
2 here than with inhaled drugs intended to go to the lung.
3 Inhaled drugs intended to go to the lung, there can be some
4 real questions about aerosol particle behavior and where
5 they wind up in the lungs.

6 While there may be some of the same issues about
7 distribution in the nose, it has got to be a lot less
8 problematic in terms of knowing the total percentage of what
9 you spray in nose that winds up staying there. Maybe that
10 is the kind of thing--that could easily be done with
11 scintigraphy or, perhaps, other methodologies, so there is a
12 while issue about delivering something that is a long
13 distance away with chances for particles to misbehave versus
14 spraying it essentially directly on a topical surface.

15 So it seems to me that, if that is true, then it
16 may be that you could just go plasma pharmacokinetics for a
17 drug that is actively absorbed from the nose. If the time
18 profile is the same, and perhaps you could maybe combine it
19 with a charcoal block so you knew if it is orally absorbable
20 drug.

21 Therefore, what went in, must have gone in through
22 the nose. Wouldn't that reflect the dissolution-time
23 profile which is really the issue, isn't it? Isn't that the
24 reason that solutions, you wouldn't need to do all this,
25 but, suspensions, yes? It is because of the issue of the

1 dissolution profile of the particles.

2 DR. DALBY: I think, for most nasal products, that
3 criterion is met. You generally see, from an aqueous nasal
4 spray, a very small percentage getting through into the
5 lung, and there is support for that. So I think that it is
6 possible that it as least worth investigating.

7 DR. LEE: Dr. Szefler, the last word?

8 DR. SZEFLER: I was just going to say you could
9 combine this two-dose analysis in kind of a different way.
10 I think each drug has to be defined by a lowest effective
11 dose and a maximal safe dose, but you kind of work with
12 ranges with these drugs. I don't know the nasal literature
13 as well as I know the inhaled steroid literature, but it
14 would seem to me that you would have to define that your
15 lowest dose would be equivalent in terms of efficacy with
16 your lowest dose of the reference product, and that your
17 highest dose should not be any more toxic in terms of
18 systemic measures, whether you use blood levels or cortisol
19 suppression than your highest labeled dose of your reference
20 product.

21 So if you took those two and kind of set your
22 standards in terms of looking at comparative efficacy at the
23 low range, comparative systemic effect at the high range,
24 then you would kind of be able to pinpoint where the product
25 fits in in terms of equivalency, I think.

1 DR. DALBY: I just think it is important not to
2 mix up a safety study with an equivalency study although we
3 sometimes derive safety inferences from an equivalence
4 study.

5 DR. LEE: There is one more question to be
6 addressed, and that question might even be equally
7 challenging which is, what we have talked about so far is
8 based on the so-called seasonal allergic rhinitis. "How
9 much can bioequivalence, established based on that endpoint,
10 assure bioequivalence for other indications such as
11 recurrence of nasal polyps or other non-SAR conditions?"
12 This is question A2.

13 Wally, is that your territory?

14 DR. ADAMS: Yes. The concern here is that, in our
15 draft nasal BA/BE guidance, we have recommended that the
16 studies to document bioequivalence use the seasonal allergic
17 rhinitis model for all of the drugs, whether it be
18 antihistamine or cortical steroids or anticholinergic.

19 The question that we are asking here is is there
20 any reason to suspect that bioequivalence based upon the SAR
21 model does not establish bioequivalence for perennial
22 allergic rhinitis or for nasal polyps for the one drug,
23 beclomethasone, for which nasal polyps is an indication.

24 DR. LEE: Is that clear to the committee members?
25 Richard, do you want to take this on?

1 DR. AHRENS: I think we are all hesitating to
2 answer because any answer we give is likely to be right out
3 of the air. We have been saying all day we need more data,
4 but, in this area, I know of no correlations between those
5 two. If you went Richard's route with a drug that was well-
6 absorbed and you showed similar time plasma profiles that
7 must have to do with a similar dissolution pattern in the
8 nose, and, therefore, absorption across that mucosa, you
9 could be reasonably comfortable in that setting that, if
10 they behave the same, they would dissolve the same, and they
11 probably would act the same. It is the same compound.

12 DR. LEE: You can argue that the dose requirements
13 will be different.

14 DR. AHRENS: But the dose requirement will be
15 different for both preparations. So the issue is
16 bioequivalence between the two.

17 DR. LEE: Right.

18 DR. AHRENS: I think that is all you can do is
19 kind of reason it out of how it might be. But I know of no
20 way to really nail it down.

21 DR. DALBY: If you don't like it for the simple
22 case, you definitely wouldn't like it for this more
23 complicated case.

24 DR. ADAMS: Dick, are you suggesting, then, a
25 slightly different question, that if you have in vitro data

1 and PK data for nasal drug products that that would assure
2 bioequivalence?

3 DR. AHRENS: Assuming that that PK data was
4 discriminatory, we all know that there are some nasally
5 deposited products which are absorbed very little into the
6 systemic circulation that, obviously, isn't going to work
7 very well for those. For other products, where there is
8 substantial absorption from the nose and that is measurable
9 and is discriminative, I, personally--I haven't spent a lot
10 of time thinking about it, but, at least where I am sitting
11 here now, to me, that sounds reasonable. It is a very
12 different ball game, I think, from drugs that are inhaled
13 into the lung.

14 DR. ADAMS: And this would be a case where, with
15 charcoal block, you could prevent the drug coming in from
16 the GI tract or for a drug with low oral bioavailability.

17 DR. SZEFLER: A quick comment. I think you could
18 reverse the question by asking does that disease pathology
19 change the toxicity of the drug or the dynamics of the
20 delivery. I am not aware of any studies that would suggest
21 that the absorption is different in terms of allergic
22 rhinitis versus nonallergic rhinitis or polyps.

23 With polyps, it could be more but I don't know of
24 any data that suggests that it is changed in any way. So I
25 think you have to look at the question the reverse way, too,

1 in terms of--

2 DR. BEHL: My question to Wally is, given that the
3 PK can show that, then it is something very difficult to
4 show for even nasal products. The in vitro pharmaceutical
5 equivalence, for example, in my opinion is not sufficient to
6 show the therapeutic equivalence of locally acting compounds
7 intranasally. Having talked to a lot of others over the
8 years, I don't see how we can escape the need to do at least
9 a small bridging clinical trial to show the therapeutic
10 equivalence along with a need to show other equivalence that
11 can be shown very easily.

12 DR. DALBY: I guess I would turn the question
13 around and ask what phenomenon do you think could get in the
14 way of a finding that if you saw the same plasm
15 concentration time profile, you would not have had the same
16 profile of drug deposition and absorption in the nose.

17 DR. BEHL: One is the way a compound would travel,
18 through ciliary movement in the nasal tissue, the surface
19 area to cover from the spray, for example. The spray
20 patterns become very important. By changing them, you could
21 maybe still get the same PK information or the same PK data,
22 but not the same coverage of the same surface in the nose.

23 The rate of ciliary currents in the back of the
24 throat may be different from formasin(?) formation, may not
25 show much of a difference in the absorption depending on how

1 it is deposited in the nose; a number of factors. If we
2 have particles in the formulation, it makes it more
3 difficult.

4 [Slide.]

5 I think I need to move on. Obviously, Wally has
6 posed some very interesting questions which require some
7 educated guesses. I think that is the best that we can
8 offer.

9 We now move into the final session of today
10 dealing with PK and PD for systemic exposure of locally
11 acting drugs. Dr. Uppoor from the agency is going to
12 provide us with the FDA practices.

13 **PK and PD Studies for Systemic Exposure**
14 **of Locally Acting Drugs**
15 **Current FDA PK Practices**

16 DR. UPPOOR: Good afternoon, everyone.

17 [Slide.]

18 We have heard from Dr. Derendorf as to some of the
19 systemic PK studies that are done and some of the reasons--
20 what we can rely on and what we cannot. Let me go through
21 my presentation and I will talk about the current FDA
22 practices primarily for new oral inhalation and nasal
23 aerosol products.

24 During the course, I will actually point out the
25 level of systemic exposure.

1 [Slide.]

2 During my presentation today, I will be dealing
3 with the general pharmacokinetics and bioequivalence studies
4 that are needed for new molecular entities at the same time
5 they are developed as new inhalation or nasal-spray
6 products; as we have heard this morning from Dr. Adams, the
7 different steps or different approaches we can use to
8 generally assess bioavailability and bioequivalence; and
9 then go through the methods and some of the issues. Some of
10 these have been discussed in the previous discussion as
11 well.

12 Finally, I will go through something that we also
13 want to get your input on, is the role of systemic
14 pharmacokinetic and pharmacodynamic studies not only for a
15 generic product--that comes in--but even when product
16 changes are made for an innovative product. We want to hear
17 that from you.

18 [Slide.]

19 For a new molecular entity, from a
20 pharmacokinetics and biopharmaceutics perspective, we want
21 to know the fate of the drug. Obviously, we want to know
22 the mass-balance studies. We want to know the single dose,
23 the multiple dose pharmacokinetics. We would like to know
24 the absolute bioavailability and relative bioavailability of
25 the drug.

1 Dose proportionality is one of the key issues. As
2 we have been deliberating all day, bioequivalence studies
3 made between the product that was tested in the clinical
4 trials versus what is to be marketed.

5 [Slide.]

6 From a clinical pharmacological perspective, of
7 course we would like to know what the pharmacokinetics are
8 in the target population, especially if there are
9 differences in delivery in healthy volunteers versus the
10 target population.

11 Additional studies that are necessary to
12 understand and label the drug; the age, gender and race
13 effects; of course, special populations, what would happen
14 in the renal- and hepatic-impairment patients. One of the
15 things which is, of course, very important is to know what
16 kinds of drug interactions might be expected, so from a
17 pharmacokinetics perspective, we would like to see
18 appropriate drug-interaction studies conducted.

19 In addition, we would also like to see
20 pharmacokinetic and pharmacodynamic correlations established
21 wherever possible. For inhalation and nasal products
22 intended for local action, the pharmacodynamics that I am
23 going to focus on and talk about are from a systemic safety
24 perspective.

25 [Slide.]

1 So, as we have discussed, we know bioavailability
2 is an important factor, but from a product-quality
3 perspective as well as from a clinical pharmacology
4 perspective to understand the in vivo characteristics of the
5 drugs. However, with all the discussion, we still do not
6 believe that in vitro testing alone is sufficient for all
7 kinds of drug products. There may be some cases where in
8 vitro testing is sufficient.

9 [Slide.]

10 Knowing the sensitivity and accuracy of the
11 pharmacokinetic data, the CFR outlines clearly the different
12 approaches that can be used for bioavailability and
13 bioequivalence. Pharmacokinetic studies are, obviously,
14 preferred. However, there are issues with the products
15 intended for local delivery.

16 [Slide.]

17 I won't really go into detail today because Dr.
18 Derendorf talked about why we cannot rely solely on
19 pharmacokinetics, systemic plasma concentrations, for
20 bioequivalence and bioavailability purposes.

21 [Slide.]

22 Because systemic-exposure data helps characterize
23 the systemic safety for these locally acting drug products,
24 and to address the local delivery and efficacy issues.

25 At this point, we definitely request that clinical

1 data be submitted to look at the efficacy.

2 [Slide.]

3 So, recapping, for a locally acting, orally
4 inhaled drug product is what I am focussing on now, but even
5 for an inhaled product, the general, conventional clinical
6 pharmacology and biopharmaceutic studies are needed. If it
7 is not a totally new drug, from the new product, we request
8 single dose, multiple dose, dose proportionality and
9 relative bioavailability as well, where as appropriate, and
10 PK/PD studies.

11 Generally, pharmacokinetic studies are done in
12 healthy volunteers. However, we have been sensitized with
13 several of the new dosage forms that are being developed.
14 These studies may be needed in the appropriate target
15 patient population if the drug delivery is expected to be
16 different.

17 [Slide.]

18 The two aspects that we have been touching upon a
19 couple of times today are--the first one is the inhalation
20 pharmacokinetics with the charcoal block. We really do not
21 require that this study be done. However, I think that it
22 does have merits that can be useful in the drug-development
23 perspective.

24 It is helpful in comparing relative dose delivery
25 to the lung from different formulations. The concern that I

1 have is that it really does not address the delivery to the
2 relevant biospace. It also doesn't really point out what is
3 the oropharyngeal deposition.

4 [Slide.]

5 Similarly, with the gamma scintigraphy studies, we
6 have been seeing a lot of activity in this area. It is very
7 useful. However, again, as concerns were expressed today,
8 we have concerns about possible lab-to-lab variation.
9 Obviously, the labeled drugs may have different aerodynamic
10 characteristics or even a modification to the original
11 product.

12 There is significant activity in terms of
13 standardization of these tests, but still, at this point, we
14 are not comfortable to use it from a regulatory perspective.

15 [Slide.]

16 So for new oral inhalation, and probably it could
17 even apply to the nasal products, in addition to the
18 pharmacokinetic studies, we do require clinical studies for
19 efficacy and safety. Some of the pharmacokinetic data can
20 be acquired through population pharmacokinetic and
21 pharmacodynamic studies. One other thing that I would like
22 to point out is when a specific topical claim is sought for
23 that drug and drug product, the special topical versus
24 systemic-effect studies may be necessary.

25 [Slide.]

1 Knowing this three-pronged approach of using the
2 in vitro data, and the in vivo data from efficacy as well as
3 pharmacokinetics or systemic pharmacodynamic data, I want to
4 actually discuss a little bit on where we might be able to
5 use the systemic pharmacokinetic and pharmacodynamic data,
6 especially for new drug products. When minor changes are
7 made to a well-characterized product, in vitro data as well
8 as systemic PK/PD may sufficient in those cases.

9 However, when major changes are made to the
10 product, either to the formulation or to the device,
11 additional clinical data is necessary in those cases and, at
12 this point, it has been a case-by-case scenario and it is a
13 consultation with the division. We would really like your
14 help to clarify some of these and where the comfort factor
15 lies.

16 We also know the pharmacokinetic studies are
17 recommended. But other pharmacokinetics data needs to be
18 collected when a product is being changed or, for example,
19 from a CFC to a non-CFC-based inhalation or nasal-dosage
20 form. We do our guidance points-to-consider document that
21 requests pharmacokinetic studies.

22 So I think, in summary, we have been talking about
23 use of pharmacokinetic studies all along. It is a sensitive
24 approach. There are some restrictions on how we can use
25 this for a locally acting drug product. However, the

1 sensitive assays that are being developed, we do have an
2 ability to measure or detect plasma concentrations after
3 oral inhalation in nasal products although we do have some
4 cases where we are still struggling with the measurement of
5 these plasma concentrations, or detecting and quantifying
6 these concentrations.

7 So I would actually say that we do require that
8 pharmacokinetic-based bioavailability studies be conducted,
9 both to understand from a clinical pharmacology perspective
10 as well as the product-quality perspective. However, for
11 orally inhaled and nasal drug products intended for local
12 action, it is multiple aspects that have to be address.
13 Bioavailability and bioequivalence cannot be solely
14 addressed based on pharmacokinetics.

15 But, because of the accuracy and, wherever
16 possible, we say pharmacokinetic studies are the first
17 choice to characterize the systemic exposure. However, that
18 alone is not sufficient. You need additional
19 pharmacodynamic data from a safety perspective as well as
20 clinical efficacy data where appropriate.

21 Thank you.

22 DR. LEE: Thank you very much.

23 Dr. Harrison, you have the last words, but you
24 only have twenty minutes.

25

Industry View

1 DR. HARRISON: Good afternoon. I want to thank
2 you for allowing me to be the last presenter.

3 [Slide.]

4 My topic is PK and PD studies for systemic
5 exposure of locally acting drugs. I am giving an industry
6 viewpoint.

7 [Slide.]

8 The value of PK for OINDP is that it measures
9 systemic absorption or systemic exposure. Both terms are
10 used in the guidance. I look at them as interchangeable.
11 Really, what they are doing is measuring systemic safety.
12 PK is an established bioequivalence metric. It can be
13 standardized. It can be validated. It is discriminating.
14 So certainly it has an awful lot of pluses for it.

15 [Slide.]

16 There are some concerns, however, with PK that
17 were raised. One is the low doses that are given nasally
18 and by inhalation, what limitations that imposes. The assay
19 lower limit of quantitation; there is quite a bit of
20 variability that is encountered in PK studies for the nose.
21 There could be draining of excess dose so that you really
22 don't get a good dose response. And, for oral inhalation,
23 the dosing technique is quite critical.

24 [Slide.]

25 What I want to do is address those concerns up

1 front. The first one is low doses. That really is not so
2 important anymore. The bottom line is can you quantitate.
3 With the new advances in analytical techniques, you can
4 usually do it. Low dose is not a big issue, I think,
5 especially when you have a therapeutic dose range, as has
6 been proposed in the new guidance--the nasal guidance, that
7 is--you can go, say, one puff, two puffs or even up to four
8 puffs. Whatever is recommended in the dosing
9 recommendations, it is fair game to use in the PK study.
10 That also will help in analytical sensitivity.

11 So that gives you a lot more dose options than
12 doing a PK study. To me, that is a good idea. The nasal
13 route, you may be limited by drainage on how much you can
14 give but, again, there is sensitivity there even for that.

15 [Slide.]

16 Looking at the assay lower limit of quantitation,
17 with LC mass spec/mass spec, now, you have got tremendous
18 capabilities to go into the peak of gram per ml range. In
19 many cases, you can get down to about 10 to 20.

20 What I have listed there are commercial assays
21 that are actually available. Say, if you were a generic
22 firm, you could find those assays available right now. For
23 BDP that is important because it has got a 17
24 monopropionate metabolite that is really the primary
25 material in plasma and it is the most active and there are

1 assays for that as well as BDP.

2 So you can do a good kinetic analysis of BDP as
3 well. Again, because the equipment is so pervasive, you
4 could get an analytical lab to help you out with whatever
5 assay you wanted, I believe. So that is not a big issue
6 anymore, either.

7 [Slide.]

8 Variability is a concern. There is large
9 intersubject variability. There is large intrasubject
10 variability. There is also variability with the dosing
11 technique. That needs to be addressed.

12 [Slide.]

13 This is just a slide showing, in one of the
14 treatments given nasal formoterol, perhaps an example of a
15 beta agonist, the variability you are seeing here with about
16 an N of 27 is roughly on the order of about 40 or so
17 percent. That is fairly typical. It is also, say, typical
18 of a topical product or a variable oral product and it is
19 something that would could live with.

20 DR. HAUCK: Here, with a N of 12, the variability
21 is a little bit higher. This is nasal triamcinolone. This
22 variation, by the way, was somewhat similar to what was
23 presented earlier by Dr. Derendorf or nasal fluticasone.

24 [Slide.]

25 Here, budesonide. Again, very similar. These are

1 standard errors but, again, it is coming out to be 40 to
2 50 percent variability that you are encountering in plasma
3 levels.

4 [Slide.]

5 This is oral fluticasone. Again, you can see the
6 range that you get in the plasma levels in these twelve
7 individuals. So they vary broadly, but the curve pretty
8 much is established by the mean. It is something I think
9 that we can live with. We can reduce variability. There
10 are various possibilities.

11 Replicate study designs is an interesting
12 possibility that I have not seen anybody, at least approach
13 in the literature. It is something that could be
14 investigated.

15 [Slide.]

16 What people have looked at, what we have looked
17 at, is increasing the subject number. With the nasal route,
18 you may need to reduce the dose.

19 What we have looked at for oral inhalation is
20 training the individuals to use proper technique. A
21 criticism there; it is not the real world and there are
22 actually even little computer machines that could teach a
23 person exactly how to inhale the product properly.
24 Certainly, we have used that in the past and with good
25 results as well.

1 [Slide.]

2 So what are the limitations of, then, doing
3 pharmacokinetics? There really is no correlation with
4 efficacy right now. That has been seen. I will show you
5 some examples of that for the corticosteroids. And it does
6 represent only a fraction of the dose, usually less than
7 30 percent.

8 As we talked about for nasal, it could be just a
9 few percent. Again, if you compare the nasal PK, you may be
10 working hard to get equivalence of an extremely small part
11 of the real dose and what is being positive in the nose,
12 where your efficacy is, may be completely different than
13 what you are focussing on.

14 Again, there are even concerns with the fine-
15 particle fraction. That is debatable. What are the right
16 ranges? So there is still some confusion there. That is,
17 again, a limitation of how you interpret it.

18 Really, when you look at it, PK is the summary
19 parameter. It represents absorption through many different
20 routes; the mouth, the GI tract and, on first pass, going to
21 the liver, the lungs. Actually, the appearances really have
22 different rates into the blood. We have seen some
23 sensitivities there. In terms of depending on how much goes
24 in the mouth versus the lungs, you actually can get some
25 confusion in your datasets.

1 [Slide.]

2 Here is an example of what I want to get at now is
3 that there is no good relationship between efficacy and
4 blood levels. This is a study with fluticasone given
5 nasally. C1 represents the concentration at one hour and
6 the symptom score represents your efficacy.

7 What you see here is that, for the oral products
8 and the placebo, you saw no difference in the symptom score
9 but the nasal administration, you did whereas, in the blood
10 levels, you had detectable levels only orally but not
11 nasally. So, again, they were separated. Blood levels were
12 seen orally. Efficacy was only seen nasally.

13 [Slide.]

14 The same thing was done through the oral-
15 inhalation route, again with fluticasone. Again, what you
16 are seeing is a very similar type of design where now you
17 are looking at your efficacy parameters, AM FEV1 and symptom
18 score and you are seeing activity with the inhaled route but
19 not the oral route.

20 Then, if you look at the Cmax and AUC as your
21 pharmacokinetic parameters, what you are seeing there are
22 your highest levels orally. They are easily twice that of
23 what is seen by your higher inhaled dose and yet you are not
24 seeing any activity associated with that.

25 So, once again, what you have is really a

1 dissociation between pharmacokinetics and efficacy. So that
2 is a limitation as well.

3 [Slide.]

4 The conclusions are that PK is useful to establish
5 systemic absorption. It really is not a surrogate for local
6 efficacy but it is doable. Right now, the assays are out
7 there. You can measure the levels, even nasally, and you
8 can reduce the variability to make it worthwhile and doable.

9 The next question to ask is can you actually do
10 systemic bioequivalence.

11 [Slide.]

12 We have got some examples there. We have done a
13 lot of work with BDP. What I want to talk about first, when
14 we are comparing two formulations. Formulations; we will
15 call them MDI-A, MDI-B. The study designs that we used were
16 single dose but multiple inhalations. They were asthmatics
17 with a crossover design and good inhalation technique.

18 So that will be common to the studies.

19 [Slide.]

20 In terms of the devices, if you look at the draft
21 nasal bioequivalence guidance, what you could say is Q1 and
22 Q2 were the same and identical, those two devices. The
23 particle-size distribution, the spray pattern, would meet
24 the criteria were essentially similar. The route size was
25 the same and the actuator, again, dimensions were

1 essentially the same.

2 So there wasn't a lot of difference between the
3 two.

4 [Slide.]

5 When we did the first study, it was in 18
6 asthmatics. The objective was comparability. What we found
7 was that we came close to matching confidence intervals but
8 we did not make it. You can see Cmax was on the low side of
9 the accepted 0.1 to 1.25. AUC was on the high side.

10 Coefficients of variability, about 50 percent for
11 Cmax, again, similar to what was seen in the earlier slides
12 I showed you with others. AUC also was variable.

13 [Slide.]

14 Another study was done, again with the exact same
15 MDIs, MDI-A, MDI-B. Here, the objective was systemic
16 bioequivalence. So, what we did is we increased in N number
17 to 45 and we actually looked at two doses, a low dose and a
18 high dose in this study.

19 [Slide.]

20 You can see here coefficients of variation were
21 reduced for the most part with a higher N number and now,
22 essentially, all the parameters did actually meet strict
23 bioequivalence criteria.

24 So we concluded from this that we could actually
25 show systemic equivalence but we also did local delivery

1 studies for efficacy. We did not stop there.

2 [Slide.]

3 Another example we have got is now looking at MDI-
4 C versus MDI-D. In this case, we actually had just
5 different strength products. So, it is the same dose. The
6 only thing different here to give the same dose is different
7 numbers of puffs because you had a different valve size.

8 So one MDI may require twice as much as the other
9 to get the same dose delivered. The study designs that we
10 looked at to analyze C versus D again were single-dose
11 asthmatics, crossover, and a good inhalation technique.
12 Similar to what we found in the previous examples, you have
13 everything matched identical in this case except for the
14 valve size.

15 So, again it was very similar, such as the same
16 formulation but different valve sizes and we did a study
17 with that. We are looking at systemic comparability here in
18 asthmatics and we came very close to getting
19 bioequivalence with an N of 18. It was just outside, 7.6
20 for Cmax. If you want to use a more liberal criteria of
21 7.5, it actually would make it.

22 CV wasn't that great in this case.

23 [Slide.]

24 If you look at the next study, when we went to 30,
25 we actually met the criteria. We could include equivalence

1 as the conclusion, therefore. We, again, had equivalence,
2 in this case with a reduced N number but we did run a local
3 delivery study to demonstrate efficacy as well. We did not
4 stop there.

5 [Slide.]

6 Looking at other PK options, we have talked about
7 charcoal block. It certainly allows differentiation of the
8 pulmonary or non-pulmonary absorbed drug. It has got a lot
9 of appeal there. The nice thing is it utilizes the same
10 drug assays and metrics so there is little added time or
11 cost. You really don't have to alter the reference or the
12 test formulations as you would have to do for, like, gamma
13 scintigraphy. So it has got a certain appeal to it.

14 [Slide.]

15 However, the limitations that I see with the
16 charcoal block is that there is no evidence that pulmonary
17 absorbed drug correlates, again, with efficacy. It is true,
18 it gets into lungs, but that is where the real correlation
19 stops. And it does not discriminate potentially important
20 product differences such as oropharyngeal deposition or
21 regional lung deposition.

22 I look at it as a very useful laboratory tool to
23 get at the pulmonary drug absorbed but I don't see it,
24 really as adding very much more to PK. It could be looked
25 at as a potential surrogate for local delivery, again if we

1 can establish that link between what is put in the lungs and
2 absorbed versus efficacy.

3 [Slide.]

4 Another option is urinary excretion. Supposedly,
5 when PK is not doable, that is a possibility. There are
6 examples of that in the literature. It has been reported
7 for the various products up there. There are references for
8 each one of them.

9 [Slide.]

10 Here is one, for instance, in nasal ipratropium.
11 It is highly variable. You can see the CV was 84 percent
12 and the dose excreted also was 89 percent. So, although
13 you can do it, it really doesn't seem to have a lot of added
14 value. So I look at it--it has got high variability. It
15 has got low sensitivity. And, therefore, it is unlikely to
16 be a reliable surrogate of what we are trying to do here.

17 [Slide.]

18 PD has been suggested as a surrogate when PK is
19 not doable. Now, the PD that I am considering is only
20 systemic PD. So you are looking at cortisol, markers of
21 bone growth, of demineralization, things like that. I am
22 not talking about FEV1s at all here. And, again, that
23 requires an appropriate study design.

24 You usually need a dose-response curve to show
25 that your PD measures are sensitive. It requires repeat

1 administration.

2 [Slide.]

3 Frankly, it is highly variable. It has got low
4 sensitivity. It requires, again, multiple dose levels. I
5 don't see that as being very valuable. If you can't do
6 pharmacokinetics, the likelihood of doing PD is very low.
7 If you are looking at, say, what is out there published with
8 nasal products, if you cannot do pharmacokinetics, I don't
9 know how you are going to deal with, say, urinary cortisol
10 or 24-hour cortisols. It just doesn't have the same
11 sensitivity.

12 You get the best results when you can do PK as
13 well so, therefore, I don't see that as a great surrogate
14 either.

15 [Slide.]

16 PK/PD. That is a very nice thing. There has been
17 a lot of work done there. It, again, allows correlation of
18 PK with PD. PK is linear. PD has got a dose-response
19 curve. It certainly offers increased understanding of what
20 is happening for systemic exposure and safety.

21 So it has got, again, a lot of appeal in helping
22 the understanding.

23 [Slide.]

24 It is sophisticated work, though. It requires
25 several dose levels, additional analyses and I don't think

1 it really increases the ability to discriminate which is the
2 bottom line for doing bioequivalence. So I look at as a
3 very useful laboratory tool but I don't see it as needed for
4 bioequivalence either.

5 [Slide.]

6 So, in summary, systemic PK assessment really is
7 what is needed to assure systemic safety and it really is
8 doable for most drugs. The state of the art is you can do
9 it, even nasally.

10 The other possibilities, PD, urine levels, are not
11 likely surrogates. Charcoal block and PK/PD, again, are
12 nice development tools but I don't really see them making
13 the leap, either.

14 [Slide.]

15 So my input into the last question, are there
16 situations where in vitro data plus PK, and, again, even PD,
17 can be relied upon to show assure local efficacy, they can
18 be relied on is the key thing. It really does imply
19 predictability and the list of drugs. It has not been
20 established, really, for any of them.

21 Certainly, there are a lot of questions there.
22 Until we can get better information, I think we need to have
23 caution and err on the side of caution and not really look
24 for situations where you can just do PK without having some
25 type of local delivery component.

1 DR. LEE: Thank you, Lester.

2 **Subcommittee Discussion**

3 DR. LEE: Wally, would you like to provide some
4 background for your question?

5 DR. ADAMS: Yes. I would like to ask Lester a
6 question concerning his last slide. Lester, you were
7 talking about in vitro data plus PK plus systemic absorption
8 PD in that case.

9 DR. HARRISON: Yes; that is correct.

10 DR. ADAMS: Our question was a general one related
11 to whether in vitro data plus PK data would be able to
12 assure bioequivalence. Lester, you are saying no; that is
13 your answer to this question?

14 DR. HARRISON: That's correct.

15 DR. ADAMS: Yet there are cases where you are
16 indicating if PK data are not doable, then you feel that the
17 PD is not going to contribute.

18 DR. HARRISON: That is my position. Based on what
19 I have experienced in the literature, I have never been
20 convinced that, if you can't do one, you can do the other.
21 It is a nice objective but, in reality, I have not seen it
22 done.

23 DR. ADAMS: You could have situations where
24 neither a test product nor a reference product may inhibit
25 the adrenal axis.

1 DR. HARRISON: Exactly; that is more likely to
2 happen. That is why going up in doses may be an absolute
3 necessity in cases like that. But, even for fluticasone,
4 you can do nasal fluticasone now and the assays are so good
5 that I think that it is getting to the point where we can
6 measure almost anything.

7 DR. LEE: Are there members of the committee who
8 can shed some light on this question?

9 DR. LI: I think, from the standpoint of orally
10 inhaled drugs, that are sufficient variables in regional
11 lung deposition, particle-size distribution, that the sort
12 of in vitro assessment along with pharmacokinetic data
13 without any clinical types of evaluation is probably not
14 going to be enough.

15 I would say that the orally inhaled products
16 should have an in vivo assessment.

17 If we kind of look back to some of the cascade
18 data that we saw and our attempts to use the chi square to
19 get a numerical handle on comparability, chances are that
20 any in vitro assessment for a new product is not going to be
21 exactly the same as the reference product. There are going
22 to be some differences, and the differences may be at
23 various stages of cascade or may be differences in particle
24 size and different ranges.

25 So it is going to be really impossible to predict

1 precisely the biological activity of that orally inhaled
2 product. So I, basically, would agree, at least certainly
3 in the area of orally inhaled products, that in vitro
4 assessment is important but not sufficient. Pharmacokinetic
5 data is also important but not sufficient. Some in vivo
6 assessment would be necessary.

7 DR. ADAMS: Just for clarity, Dr. Li, you are
8 talking about efficacy.

9 DR. LI: That's correct; for orally inhaled
10 products.

11 DR. BEHL: Which could be a bridging study also as
12 opposed to a full-scale study.

13 DR. LEE: Is Steve Forrester here? He left?
14 Okay.

15 DR. ADAMS: Just to follow up further on this
16 question, Dr. Uppoor, did you wish to ask the subcommittee
17 any question with regard to that last question?

18 DR. UPPOOR: I actually just want to find out,
19 even if you have an innovative product, for example, and
20 that has been shown to be clinically safe and efficacious
21 and you have done all these trials that have been approved,
22 and some minor, some type of change is made to that product
23 and it is the same product, you have a handle on what goes
24 on with that product, you have some understanding or,
25 hopefully, a reasonable understanding of the product, and

1 some minor changes are made, even in those cases, what I am
2 hearing is it doesn't matter what the change is, but if it
3 is an orally inhaled drug product, we would like some kind
4 of efficacy data in addition to in vitro and PK.

5 DR. LI: If you are addressing that question to
6 me, that would be a question that would, in my view, be
7 extremely focused. I did not, in fact, say that, in that
8 particular set of circumstances, one would necessarily need
9 to go through clinical studies and even to specify what kind
10 of in vitro studies would be necessary.

11 I think, in a very narrow sense, depending on what
12 those changes were, say, in the development of the product,
13 if they were such change where one might not expect any
14 significant, really, change in delivery, then probably I
15 would say how things are handled now, case-by-case, would be
16 the way to go.

17 If there are major changes in the formulation and
18 the production and changes in propellant, for example, that
19 would be an example. A change in propellant is probably
20 enough of a change that you would really need to do more
21 extensive testing.

22 DR. GORE: Just a comment from the perspective of
23 those of us in product quality that have a lot of experience
24 with cascade impactors, rather minor changes in the
25 formulation of the composition of the material can, in fact,

1 change what you are, in reality, measuring in the individual
2 stages of the cascade impactor.

3 So, because of formulation and what is deposited
4 on the cascade-impactor stage is a combination of excipients
5 as well as active ingredient. That is something that would
6 require a lot of validation if you were trying to make a
7 crossover between two different formulations.

8 DR. LEE: Are there any comments? I think we are
9 kind of supersaturated.

10 DR. LAGANIERE: I would just add that the
11 experience of Dr. Harrison concerning nasal drug
12 administration, he seems to be alluding to the fact that you
13 can increase the dose if you are not able to see it at the
14 small doses that are usually administered in therapeutics.

15 But, in the context of safety or exposure, I would
16 like to have maybe the opinion of physicians regarding the
17 relevance of using a so much higher dose that would be
18 usually higher than the recommended daily dose.

19 DR. HARRISON: Let me just clarify that before you
20 ask an opinion. I meant within the therapeutic dose range.
21 You increase the dose. As long as it is in the therapeutic
22 dose range, say up to four puffs per nostril, you can do
23 that much.

24 DR. LAGANIERE: Okay. So that would be a limit in
25 establishing whether a pre-case exposure study is feasible

1 or not.

2 DR. HARRISON: Yes. I went fast through my
3 slides, but what I did show is pharmacokinetically, you can
4 get a nice dose response with pharmacokinetics in the nose.
5 It has easily been shown by inhalation, but nasal as well.

6 DR. LEE: Wally, the short answer to your question
7 is that, apparently, nobody around this table has any
8 situations that would respond to your question.

9 DR. ADAMS: I hear that. Thank you, Vincent.

10 DR. LEE: Guirag and Wally, are there any other
11 questions for the committee before we adjourn the meeting?
12 Anybody else?

13 DR. GORE: May I ask more of a procedural question
14 because there was actually a comment made earlier about the
15 need for another meeting. I would like to say I think there
16 is a need for another meeting. There is a huge amount of
17 information, particularly in the CMC area, that was brought
18 forward in the afternoon that we did not have an opportunity
19 to discuss and also some proposals for ways to bring more
20 data into the discussion.

21 That is just my proposal. I think we need another
22 meeting.

23 DR. LEE: If there are no further comments, I
24 would like to thank everybody for participating openly. I
25 am surprised that I am still alive. I thank you for your

at

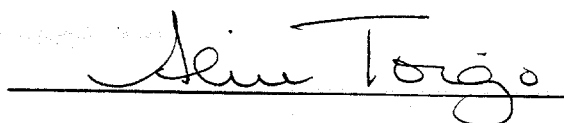
1 input and have a safe journey home. Thank you.

2 [Whereupon, at 5:08 p.m., the meeting was
3 adjourned.]

4

C E R T I F I C A T E

I, ALICE TOIGO, 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.

A handwritten signature in cursive script that reads "Alice Toigo". The signature is written in black ink and is positioned above a solid horizontal line.

ALICE TOIGO

Lawyer's Notes

0
0 55:14; 59:18, 20;
192:17; 193:19; 204:23
0.0001 228:21
0.05 29:13; 85:23
0.1 269:9
0.2 193:21
0.25 108:13
0.5 107:10; 108:16; 225:6
0.590 59:9
0.67 217:17
0.69 217:15
0.7 94:9, 11
0.8 91:19; 96:22
0.9 91:19

1
1 22:10; 24:24, 25; 41:19;
55:22; 59:20; 62:18;
76:11; 85:10; 91:19; 94:1;
96:21; 97:4; 99:10; 110:4;
116:18; 199:22; 205:24;
217:12; 227:14; 233:9;
242:19
1-micron 94:8, 11; 98:8;
102:11
1.1 219:8
1.2 91:8; 92:24; 97:20;
205:8
1.25 269:9
1.3 94:12, 18; 96:23
1.40 217:16
1.5 93:6; 217:17; 237:4
1.9 205:4
10 20:22; 21:11; 33:4, 20;
34:4, 6, 12; 44:11; 48:14;
62:18; 63:16; 75:14; 98:5;
124:22; 140:23; 197:1;
204:22, 23, 25; 205:1, 3;
263:19
100 29:24; 50:16; 55:14;
56:20, 21; 59:12, 13;
62:14; 63:3, 6; 180:8;
181:18; 186:18, 19;
193:14; 198:22; 227:12,
21
1000 62:13; 202:8
101 147:5
11.0 219:8
11.8 107:5
110 33:22
115 30:20; 41:7, 12
12 91:11, 12; 264:20
120 20:23; 22:5; 26:11;
29:19; 31:13; 46:5; 107:11
124a 177:2
12:35 139:6
12A-30 7:6
13.1 107:11
130 189:20

134a 175:19; 176:1, 4, 6,
16, 19; 177:11, 17
15 21:1, 6, 13; 22:2, 7, 15;
39:3
150 97:6
168 180:10
17 263:23
18 6:20; 20:22; 269:5;
270:18, 19
18-fold 199:1
18.83 58:16
19 204:25; 205:2
1989 32:24; 215:11
1992 215:19
1998 179:6
1999 19:22, 24, 25;
153:10; 177:21; 184:2
-1:30 38:13; 138:24;
139:7; 140:2

2
2 19:24; 24:24, 25; 32:15;
41:19; 69:9; 76:14; 86:11;
92:20, 24; 93:3, 3, 14, 14;
94:1, 3; 97:15, 15; 110:4;
116:18; 199:23
2-mg 242:19
2.0 225:7
2.5 109:6
2.6 219:7
2.7 92:25
2.8 97:20
2.9 97:20
2/2 97:22
20 21:2, 3, 11, 24; 22:12;
24:18; 34:4; 62:18, 19;
109:23; 193:20; 263:19
200 42:25; 149:13; 201:21
2000 181:12
208 6:20
21 192:22
22 34:17; 192:23
227 175:19; 176:1, 4, 6;
177:15, 18
23 33:15
24 199:10; 201:3
24-hour 197:25; 198:3;
202:21; 273:10
25 20:24; 21:4, 12, 25;
22:6, 13; 24:19; 39:5;
227:14
250 108:10, 13
27 22:9; 264:16
28 33:16; 97:21
28.3 109:19
288 175:24
295 175:24
2f2 59:15

3
3 41:15; 86:11; 90:19, 19,
19; 94:20; 116:19; 128:9;
181:14, 23; 199:23
3-M 9:10
3-micron 94:21; 97:8
3.0 93:6
3/30 63:5
30 21:2; 34:17; 43:2, 9;
44:11; 60:5, 9, 9; 61:4, 4,
9, 11, 16; 107:4; 188:3;
205:6, 7; 266:7; 270:24
31 192:24
33 60:14; 192:24
35 112:25; 113:25;
190:21; 243:5; 244:7
37 43:10; 205:7
38 114:1
381 176:15
3:25 212:14, 15
3:30 38:13
3M 218:23; 221:19;
225:13; 226:1
3N 60:16

4
4 94:1, 17, 18; 95:20; 97:3,
5; 111:7; 128:9; 192:17;
227:1
4-micron 98:4, 7
4.7 109:21
40 43:1, 2; 44:10; 264:16;
265:1
400 69:8; 202:8; 243:8
405 176:15
45 160:3; 243:6; 244:7;
269:17

5
5 31:11, 12; 33:3, 19; 34:5,
7; 61:18; 72:14; 75:13;
83:22; 118:2, 8; 121:13;
128:9; 180:17
5.9 180:16
50 55:15; 59:14; 92:23;
93:5, 16, 18; 122:10;
124:23; 186:18; 239:6;
243:7; 244:7; 265:2;
269:10
500 108:10, 17; 201:22
51 33:17
55 114:2
56--he 114:2
58 226:18
5:08 281:2

6
6 75:13; 94:2, 19; 95:21;
121:13; 180:13
6.0 237:4
6.2 193:20
6.5-micron 97:7
6.605 59:8
6.66 63:21
6.something 39:9
60 34:8, 11; 80:3; 107:8;
114:2, 2, 3
600 243:8; 244:6
65/135 30:10, 10

7
7 57:9; 94:19; 245:10
7-micron 94:21
7.25 58:9
7.288 59:3
7.5 270:21
7.6 270:19
7.66 62:6, 10
7.8 39:10
70 239:6
75 227:14
75/125 26:12

8
8 78:2; 94:2
8-micron 98:5, 6; 102:11
8.3 193:19
80 22:5; 26:11; 29:19;
33:10; 43:8; 46:5; 113:1;
193:14
8100 140:21
84 272:11
85 30:19; 41:7, 12; 154:3;
171:7; 174:6, 18
85/115 30:9
89 272:12
8:00 198:4

9
9 91:8; 181:14, 23; 205:1
9-and-a-half 180:13
90 30:15, 19; 31:12; 35:7,
10; 193:13; 205:2
90th 63:20
91 34:15
95 33:13; 35:5, 10; 61:18;
85:22
99 153:7

A
a--it 233:2
a.m 198:4; 227:1
A1 239:25
A2 239:25; 250:12
AAPS 151:11; 152:6
AAPS/FDA/USP 19:22
aberrant 23:14
ability 192:4; 208:15;
261:2; 274:1
able 16:8; 32:22; 39:19;
49:15; 53:2; 59:24; 60:2,
25; 61:12; 63:8; 65:10, 13;
69:16; 89:23; 110:2;
129:4; 171:5; 209:4;
230:9; 235:1; 238:10;
245:9; 249:24; 260:4;
275:11; 279:13
above 118:9; 150:3
absence 68:8; 156:6;
247:5, 6
absent 189:7
absolute 54:22, 23;
58:25; 59:2; 64:11; 96:25;
120:5; 255:24; 276:2
absolutely 29:10; 70:4;
100:13; 105:15; 138:18
absorbable 248:19
absorbed 83:13; 204:6;
207:15, 19; 248:17; 251:6;
252:5; 271:8, 17, 23; 272:2
absorption 86:10, 13;
195:17; 196:20; 203:20;
204:9; 205:15, 17, 19, 19;
206:11, 14, 23; 207:13, 19;
208:5; 209:14; 211:11, 21;
251:8; 252:8, 21; 253:16,
25; 262:9; 266:19; 268:5;
275:7
academic 116:21; 133:7;
194:15, 21
accent 104:5
accept 29:15; 31:22;
44:22; 96:23; 242:1
acceptable 19:8; 20:22;
21:10, 22; 22:11; 31:19;
36:13; 39:25; 44:25;
46:15; 71:7; 72:7; 80:4;
216:5; 233:3; 236:15;
241:15; 247:19
acceptance 20:16;
22:19; 36:11; 46:5;
169:23; 177:4
acceptance-criteria
176:16
accepted 169:11, 15;
269:9
accepting 242:7
access 198:8
accessible 18:21
accessory 125:6
accommodate 106:3;
111:5; 120:9
accomplish 216:5

accomplished 230:15
accordance 6:20
scoring 82:20; 94:6;
5:4; 140:13, 20; 142:2;
144:15
account 32:3; 117:3;
199:3
accumulated 75:9
accuracy 257:10; 261:15
accurate 104:24; 230:10
acetonid 197:7; 200:7
achievable 38:2; 75:6,
10; 76:5; 77:19
achieve 30:1; 137:13;
153:2; 195:19; 196:9;
227:21; 233:11
achieved 168:21
achievements 160:23
acknowledge 78:17;
174:5
acknowledging 170:10;
173:23; 178:23
acquired 18:20; 259:20
across 68:2; 100:22, 22,
23; 107:19; 110:6; 111:8;
117:23; 123:5; 188:14;
251:8
act 216:24; 241:24;
246:23; 251:11
ACTH 198:6
acting 14:20; 16:2; 82:18;
4, 10; 156:17; 157:16;
194:14, 20; 195:3; 240:4,
8; 246:5, 14, 15, 16; 253:6;
254:11, 14; 257:23; 258:3;
260:25; 262:5
action 14:16; 81:4; 82:4,
7; 83:6; 90:12; 140:11;
144:23; 184:11; 186:9;
187:18; 201:17; 203:1;
213:20, 21; 214:4, 6, 25;
215:6; 256:22; 261:12
active 151:10; 166:15;
181:22; 191:23; 195:13;
196:4; 203:25; 204:3;
211:20; 212:5, 7; 243:6;
263:25; 279:5
active-substance 169:2
actively 248:17
activities 17:13; 19:19;
134:20; 154:11
activity 116:20; 180:1;
195:20, 20; 208:19;
210:12; 259:6, 12; 267:18,
24; 277:1
actual 23:24; 32:11; 74:5,
9; 105:21; 110:23; 116:5;
120:19; 149:20; 160:3;
172:12
actually 11:15; 25:13;
6:10; 27:8; 32:6; 33:9;
15, 20, 23; 35:20; 40:4,
13; 45:2; 50:7; 57:8; 62:19;
69:2; 75:19; 78:2; 90:4;
93:22; 95:22; 96:13, 17;
97:9, 16; 99:3; 100:5;
102:2, 19; 118:5; 120:3;

121:11, 12; 122:24;
123:16; 129:12; 130:7;
131:25; 133:25; 136:1;
143:9; 155:7; 164:5;
167:6; 185:10; 187:9;
221:6; 225:23; 230:14;
237:14; 239:20; 240:20;
254:24; 260:4; 261:7;
263:21; 265:22; 266:21,
24; 268:9; 269:17, 22, 24;
270:4, 21, 25; 277:18;
280:14
actuation 23:8; 42:25
actuators 141:4
actuator 23:6; 268:25
actuators 23:7
Adams 6:10; 9:2, 2;
80:23; 81:1; 89:6; 104:6;
127:12; 130:17; 131:7, 10;
132:12; 133:15; 134:15;
135:6; 136:6, 9, 21; 137:6;
239:23; 250:14; 251:24;
252:14; 255:6; 275:5, 10,
15, 23; 277:7, 15; 280:9
add 33:16; 38:8; 54:22,
25; 55:2, 9; 68:7; 105:19;
136:3; 145:12; 174:18;
212:3; 279:10
added 39:11; 59:2;
144:24; 176:14; 177:16;
271:10; 272:13
adding 58:8; 59:10;
147:9; 149:2; 271:24
addition 82:14; 83:1;
84:20; 87:3, 22; 88:4;
137:2; 152:19, 22, 25;
154:3; 158:8; 171:20;
172:7, 18; 241:13; 256:19;
259:17; 278:4
additional 6:24; 52:14;
56:5; 70:18; 82:12;
128:18; 132:18; 137:7, 21;
176:24; 230:17; 256:11;
260:11; 261:18; 273:25
address 7:13; 10:20;
11:2; 14:9; 15:4, 12; 17:19;
27:23; 47:22; 73:8; 77:7,
20; 103:20; 145:18; 158:8;
160:1; 171:10; 172:7;
194:25; 195:2, 16; 213:16,
16; 214:12; 215:12;
230:18; 257:24; 259:1;
261:12; 262:25
addressed 10:25; 12:24;
16:7; 20:5; 150:6; 152:25;
158:7; 163:12; 219:18;
222:10; 230:25; 250:6;
261:14; 264:11
addresses 6:16; 137:12
addressing 65:19;
151:24; 158:13; 212:24;
213:24; 214:15; 218:13;
278:5
adds 56:19, 21; 76:6;
205:2
adequate 21:10; 113:8;
114:17
adherence 71:8

adjacent 119:17
adjourn 280:11
adjourned 281:3
adjournment 16:13
adjust 214:10
administer 195:9
administered 279:14
Administration 9:3;
46:11; 108:9; 197:14;
199:8; 200:8; 207:5;
208:3; 267:9; 273:1;
279:12
admit 100:12; 106:5
adopt 26:23
adopted 88:18
adrenal 275:25
advanced 117:15
advances 196:17; 263:3
advantage 101:18;
160:24
advantageous 165:9
advantages 36:11; 75:2,
18
advice 15:22
advised 48:11
advisors 81:9
Advisory 9:19, 25; 11:18,
23, 25; 67:1; 183:4; 216:3
advocate 31:9
aerodynamic 259:9
aerodynamically 120:2
aerosol 88:6; 90:12;
91:18; 92:19, 23; 93:3, 13;
94:11, 22; 95:2, 3, 5, 6, 17;
96:17, 17, 19; 97:5, 15, 18;
98:5, 7, 7, 8, 17, 19, 20;
102:11; 106:16; 151:12,
23; 152:10, 11; 155:15;
248:4; 254:23
Aerosols 10:2; 14:13;
82:4; 87:12; 92:9, 9; 94:1,
16; 97:11; 116:18; 156:18;
175:12; 182:17, 20; 231:1
AFBS 9:22
affect 45:5; 135:12
affected 6:23; 180:23
affecting 42:15; 45:6;
99:13
affects 91:13; 112:23
affinities 198:20
afternoon 6:11; 16:12;
38:12; 48:24; 151:15;
155:4; 161:7; 164:6;
167:21; 170:22; 178:5;
182:21; 194:22, 25;
254:16; 262:1; 280:18
AFTERNOONPROC-
EEDINGS 140:1
afterwards 102:8
again 15:7, 18; 16:9;
17:17; 21:13, 17; 22:8;
23:3, 10; 28:5; 29:23;
30:17; 31:8; 32:15; 35:9;
39:9; 79:5, 22; 93:5, 14;
95:12, 18; 97:14; 98:4;

110:6; 111:15, 16; 112:15,
24; 121:8; 123:25; 148:8,
12; 149:2; 150:11; 160:17;
166:18; 167:2; 177:21;
181:2; 184:2, 13, 25;
185:5, 18; 186:23; 187:17;
188:2, 9; 190:23; 191:13;
198:13; 200:18; 201:24;
202:11; 203:11; 207:6;
208:1; 212:4; 223:16, 20,
22; 226:16; 228:16;
236:24; 241:18; 242:18;
245:7; 247:2; 259:7;
263:14; 264:3, 25; 265:1,
5; 266:9, 14, 17; 267:11,
15, 15, 25; 268:25; 269:11,
14; 270:10, 15; 271:1, 17,
25; 272:22; 273:4, 17, 21;
274:11, 16
against 62:1; 111:21;
114:11; 143:12; 243:4;
245:15
age 247:19; 256:12
agency 6:25; 7:5; 11:11;
13:9; 17:13; 18:5, 9; 19:8,
14; 25:13; 31:3, 10; 33:3,
6, 10; 35:10; 36:10, 12;
42:21; 43:20; 44:24; 45:1,
10; 48:6; 79:11; 104:8;
118:23, 25; 125:24; 145:4;
160:10; 161:1; 163:18, 20;
167:10, 14; 170:3, 7, 13;
171:16, 19, 22; 173:3, 15,
19, 24; 231:7; 254:11
agency's 19:9; 25:24
agenda 7:8; 16:7; 65:17;
182:14
agent 157:16
ages 180:13; 181:14, 23
aggregate 148:19
aggregated 52:12
aggregating 106:14
ago 25:13; 47:6; 100:20;
107:18; 200:6; 228:16
agonist 110:7; 264:15
agonists 214:18
agony 241:3
agree 45:20; 68:4, 6;
70:10, 17; 71:3; 72:8; 79:2,
4, 5; 80:13; 99:9; 101:22;
102:1; 124:9; 152:19;
155:24; 177:20; 211:25;
215:21; 240:20; 244:4;
277:2
agreed 155:22
agreement 28:17; 68:24;
152:17
ahead 6:13; 136:7;
199:19
AHRENS 47:5, 5, 18;
68:6; 77:6; 102:18;
108:20; 136:21; 211:16;
212:15, 23; 213:1, 6;
230:20; 233:17; 235:17;
236:17; 237:11, 24;
238:19; 239:3; 241:8;
246:21; 247:25; 251:1, 14,
18; 252:3

aid 6:25
air 251:3
airport 48:19
airways 17:12; 90:12;
91:7, 18, 20; 99:17;
100:15; 105:16, 17; 118:3;
128:13
alarm 227:1
albuterol 87:13, 17, 21;
88:6, 11; 215:10, 10, 10,
13; 216:7; 217:9; 218:13;
238:12
alert 212:23
aligned 162:11
alive 280:25
allergen 187:1
allergens 184:16; 187:3
allergic 14:18; 15:1;
180:12; 183:20; 250:8, 16,
22; 252:21
allergist 9:23; 178:8
Allergy 9:5, 19, 25; 179:6;
183:1, 7, 10, 18
allow 94:10; 95:16; 96:18;
111:12; 113:5, 7; 159:23;
163:10; 184:10; 190:4;
202:11; 230:10
allowable 45:1
allowing 100:18; 173:25;
178:6; 262:2
allows 39:4; 130:1;
184:13; 197:22; 200:3, 15;
207:13, 20; 271:7; 273:17
alluded 165:20; 172:20
alluding 279:12
allusion 223:9
almost 92:18; 188:24;
192:24; 206:13, 18; 276:6
almost-the 234:1
alone 157:15, 19; 211:24;
257:6; 261:18
along 89:19; 132:21;
146:11, 16; 149:17;
179:10; 214:18; 215:13;
244:12; 247:20; 253:10;
260:23; 276:12
alpha 28:25; 31:11;
33:20; 34:5, 7; 85:23;
225:7
Alpharma 8:15
alter 271:11
alterative 17:9
alternate 160:10; 162:18
alternative 19:11; 25:8;
28:16; 34:20; 88:24; 89:1,
7; 96:1; 101:18; 229:19;
236:8
alternatively 26:4
alternatives 244:12
although 35:25; 83:13;
87:25; 88:9; 106:6;
120:15; 214:1; 221:22;
224:15; 228:14; 241:18;
250:2; 261:3; 272:12
alveolar 91:15; 102:17

always 18:7; 36:21; 42:20; 71:7; 84:4; 107:13; 120:15; 129:6, 7
amazed 235:24
ambiguous 161:25
amenable 159:5
American 115:24
Americans 115:9
among 50:9; 71:6; 142:20; 148:13; 178:4, 11, 13, 16
amount 10:12; 59:12; 81:8; 99:4; 100:10; 109:20; 147:24; 148:1; 158:25; 171:6; 173:9; 280:16
amounts 119:16; 154:21; 176:23
analogous 35:14
analyses 273:25
analysis 13:4; 26:17; 28:8; 88:13, 14, 18, 24, 25; 89:8; 92:1; 98:25; 118:16; 119:3; 120:12; 121:8; 131:1, 8; 166:1; 217:21; 249:9; 264:2
Analytical 8:23, 25; 10:2; 24:5; 159:14; 165:7, 15; 196:17; 263:3, 10; 264:4
analyze 165:1; 199:19; 270:10
analyzed 95:15
anatomical 117:10
anatomy 241:21
ANDA 141:18
ANDERSON 8:11, 11; 37:8; 67:4; 91:5; 95:1, 2; 99:20, 23; 100:23; 109:19
Andy 85:4; 88:23; 119:8; 128:2; 242:4
Andy's 127:23; 128:17
angle 92:13; 112:13; 117:12
angry 227:4
animal 203:4, 8, 12
Anja 175:11
announce 179:9; 194:11
announcement 6:16
answered 210:2
anticholinergic 128:12; 250:18
anticipates 171:17
antihistamine 250:18
antihistamines 190:2; 246:19
anymore 121:17; 263:2; 264:6
anyplace 234:3
apart 118:12
apologies 220:23
apologize 43:24; 48:23; 91:7; 177:9
apparent 228:4; 231:24; 232:3

Apparently 136:19; 239:9; 280:7
appeal 235:3; 271:9, 13; 273:21
appealing 232:23; 239:14
appear 48:12; 83:17; 233:9
appearance 6:18
appearances 266:21
appears 36:18; 77:2; 90:15; 101:8; 164:17; 227:19
applicability 156:15
applicable 45:13; 59:14; 96:24; 105:2; 155:17; 203:9
application 13:8; 46:20; 129:3; 155:16; 159:8; 190:21; 203:21; 206:13
applications 18:12, 17
applied 24:25; 72:22; 79:21; 124:17; 193:11; 194:6; 213:25; 217:7, 13; 218:15, 17
applies 23:18; 25:20; 28:2; 45:13; 73:19; 90:1; 124:6
apply 38:25; 42:9; 49:9, 16; 56:11, 12; 72:19, 24, 25; 75:4; 97:4; 100:17; 101:20; 102:2, 7; 103:2; 117:12, 23; 120:11; 151:6; 156:16, 19; 159:17; 166:15; 238:12; 259:17
appreciate 231:15
approach 12:20; 13:10, 13; 28:16; 31:18; 32:14; 33:2; 36:3, 19; 37:19; 39:17, 20, 21; 42:5; 43:5; 45:10, 21; 47:7, 10, 11; 49:8, 11; 50:13, 14; 52:11; 70:8; 75:11; 76:2, 19, 20; 78:23; 79:10; 80:2, 8, 13; 85:1, 6; 90:15, 24; 100:5, 17; 101:18; 102:24; 103:8, 11; 120:7; 122:16, 18; 124:3; 126:23; 127:5, 25; 128:2, 4, 7, 17, 24; 129:17, 24; 130:1, 15, 15; 132:16; 153:2; 161:11, 13; 163:2; 164:24; 186:10; 188:23; 198:6; 199:21; 205:17; 208:1; 209:5; 210:9, 15; 211:1, 6; 213:24; 214:16; 217:7, 23, 24; 218:14; 223:25; 238:11, 11; 260:1, 24; 265:12
approaches 14:21; 15:8, 18; 19:8, 12; 25:8; 43:25; 44:4, 5; 76:15, 17, 22, 24; 79:23, 24; 82:20; 85:4; 132:13; 160:12; 162:18; 198:10; 203:2; 205:14; 231:8; 240:16; 246:8; 255:7; 257:12
approaching 166:24
appropriate 13:13;

17:11; 24:8; 37:12; 75:7; 82:23, 24; 83:7; 84:14; 88:16; 101:23; 120:17; 122:18; 138:5; 168:21; 170:12; 231:22; 242:10; 244:19; 256:18; 258:9, 14; 261:20; 272:23
appropriately 100:4; 103:14; 214:10
appropriateness 131:5, 7
approvable 214:8
approval 18:12; 156:3, 7; 216:6; 218:23
approved 38:6, 7; 43:13; 44:2; 87:17; 88:10; 136:12; 147:2; 217:9; 221:4, 16; 222:2, 3; 225:20; 242:14; 277:21
approximately 48:3; 154:3
aqueous 249:3
aqueous-based 19:3
Aradigm 155:7
archives 109:13
are--the 258:19
area 10:13, 25; 12:3; 16:1; 38:23; 105:12; 126:16; 146:22; 151:10; 164:13; 165:6, 14; 166:9, 11, 23; 168:19; 213:10; 232:5; 251:4; 253:19; 259:6; 277:3; 280:17
areas 7:2; 67:22; 98:14; 106:9; 122:6; 126:3; 158:4; 161:13; 162:15; 163:3; 164:23; 165:2, 4; 199:14; 233:12
arena 42:2
argue 103:15; 105:10; 251:12
argued 104:6
arguing 91:22; 104:10
arguments 108:6
arm 189:20; 191:19
around 8:5; 37:6, 11; 65:21; 69:8; 77:1; 78:14; 91:8, 19; 94:11, 12, 18, 19, 20; 95:20; 97:6; 123:3; 128:21; 136:19; 138:21; 143:25; 187:2; 188:7, 17; 193:19; 198:3; 205:24; 222:12; 234:18; 238:5; 253:13; 280:7
array 40:9
art 116:2; 156:25; 274:8
artificial 187:7
aspect 107:14; 117:20
aspects 106:7; 113:11; 136:17; 258:18; 261:12
assay 262:18; 263:16; 264:5
assays 196:25; 203:11; 261:1; 263:20, 22; 264:1; 268:6; 271:10; 276:4
assembling 71:19

assess 15:8; 157:19; 196:7, 22; 231:9; 232:17; 255:8
assessed 181:20
assessing 107:24; 113:14; 171:13
assessment 70:20, 21; 71:18; 105:5; 114:21; 117:18; 160:5, 17; 172:12, 14; 196:19; 198:14; 213:12; 230:10; 274:6; 276:12, 16, 20; 277:4, 6
assessments 117:1, 4
assigned 47:12
assist 171:21; 173:19
associated 68:12; 156:14; 172:3; 267:24
associates 184:21
association 152:10
assume 16:14; 35:21; 47:10; 75:11; 122:13; 205:24
assumes 47:7
assuming 143:14; 252:3
assumption 35:22; 47:13, 16; 61:14; 71:7; 148:3, 6
assumptions 22:20; 40:18; 156:15; 225:5
assurance 132:18
assure 15:2; 16:4; 132:15; 157:17; 168:13; 210:4; 250:10; 252:1; 274:7, 17; 275:12
assures 170:3
asthma 213:13; 222:21; 226:8, 11, 14; 228:16; 229:4; 232:8, 10, 25; 239:9
asthmatic 239:3, 3, 4
asthmatics 110:17; 221:6, 6; 224:1, 4; 229:10; 268:16; 269:6; 270:11, 18
AstraZeneca 108:12; 111:18; 158:18
asymptotic 61:15
Atlanta 8:13
attached 50:17
attempt 34:2; 172:7
attempting 105:12; 116:22
attempts 276:18
attended 67:21
attention 17:9; 44:1; 112:7; 117:16; 161:2; 174:10; 190:15; 194:9; 209:22; 230:19
attracted 117:15
attractive 232:7
attractiveness 235:10, 16
attributes 32:7, 9; 33:18; 34:19; 36:4; 47:17; 158:22
AUC 200:19; 267:20; 269:9, 12
audience 10:10; 37:5;

65:13; 104:4
audit 167:5
August 11:21, 24; 177:21
author 181:12
authority 221:22
Auty 107:18
availability 112:2, 2; 235:4, 15
available 17:22; 18:13; 38:1, 4, 20; 49:15; 70:13; 111:17; 157:2; 167:12; 171:13; 181:10; 182:8; 187:8; 188:7; 197:4; 204:7; 208:24; 247:22; 263:21, 22
Aventis 170:24
average 30:12; 43:1, 2; 52:7; 54:6, 22; 55:21, 22; 57:24; 58:2, 6, 12; 61:10; 109:22; 113:24; 114:1; 147:24; 201:2
averaged 57:24
avoid 42:24; 43:5, 11; 71:4
aware 7:9; 17:23; 37:5; 179:25; 195:12; 252:20
awareness 169:8
away 92:20; 123:14; 140:4; 145:10; 235:11; 238:4; 248:13
awful 262:14
axis 93:2, 23; 96:8; 98:4; 179:24, 25; 180:6, 23; 181:1, 15; 182:1; 198:12, 14; 214:19, 19; 215:8, 9, 13; 275:25

B

B 149:19; 204:23; 205:3; 225:11; 226:19, 24
B1 240:7
B2 237:21; 240:7
BA 48:20; 80:24; 82:9, 10, 21; 83:1, 8; 84:4, 19; 182:18; 213:3
BA/BE 80:25; 81:4, 13, 15, 21; 82:3, 5, 10; 83:18; 85:1; 86:7, 16; 136:11; 152:19; 155:2, 3, 9, 14; 156:1, 16, 23; 158:6, 9; 171:10, 19; 172:3, 4; 173:8, 20; 182:15; 250:15
BAASKE 8:14, 14; 67:23
back 30:3, 21; 34:3; 38:14, 16; 40:24; 45:11; 47:17; 48:17; 65:15, 17; 69:7; 72:14, 16; 100:2; 101:21; 102:25; 104:12; 109:13; 111:16; 112:1; 118:20; 121:25; 124:3, 16; 129:24; 182:14; 212:10, 14, 15, 19; 215:20; 216:21; 220:22; 242:18; 244:9, 22; 245:7, 10, 18; 247:2; 253:23; 276:17

background 17:2; 37:3; 80:25; 81:4, 13, 16; 89:11; 164:15; 171:9; 174:7; 5:4
bad 223:13
Baker 217:8; 221:3, 15; 222:11
balance 160:19
ball 248:1; 252:12
bane 36:21
bar 57:14
Barnes 219:19
based 14:18; 15:1; 18:14; 19:2; 47:12; 62:9; 75:23; 80:5; 83:1; 85:10, 18; 86:8, 9, 10; 87:14, 17; 88:10; 99:21; 100:9; 106:2, 5; 111:22; 123:16; 128:3, 6; 129:16; 131:9; 153:16; 157:2; 159:12, 21; 160:7; 164:7; 175:12; 177:4; 182:5; 200:9; 201:1, 11; 221:22; 222:8; 236:2, 20; 237:11; 239:14; 246:3; 250:8, 9, 20; 261:14; 275:18
baseline 87:22; 187:13; 190:22; 192:2, 3, 5, 19, 21, 22; 199:22, 23; 200:11, 20; 224:1
bases 156:23
basic 114:19; 120:19; 7:10; 183:22; 203:24; 23:21; 233:18
basically 70:17; 100:24; 106:8, 22; 108:5; 109:3, 12; 111:1, 5; 115:16, 25; 137:6; 147:3; 177:10; 200:16; 247:21; 277:2
basics 238:6; 245:7
basis 24:12; 43:9; 68:23; 118:16; 129:13; 136:10, 18; 143:5; 181:5; 221:3, 17; 222:3, 4
batch 20:12, 21; 21:9, 22; 22:11; 26:18, 21; 27:4; 29:1, 5, 10, 20, 22; 30:6, 11, 12, 19; 31:13; 33:9, 11, 13; 34:11, 15; 35:7; 36:14; 44:1, 2, 2, 6, 16, 18, 25; 74:3, 15, 20; 78:9
batch--that 20:7
batch-to 20:11
batch-to-batch 168:13
batches 44:10; 45:7; 69:5, 10; 78:5, 12; 85:17; 89:16; 109:18; 159:13
Bath 110:14; 148:25, 25
BDP 180:17, 19, 25; 197:9; 198:23; 211:22; 218:24, 24; 221:7; 239:15; 63:23; 264:1, 2; 268:13
ear 6:4, 10; 120:15
bearing 157:18
because--well 105:11
beclo-methasone 179:23; 180:5, 10; 181:8;

198:24; 211:19; 250:23
become 75:9, 16; 76:5; 79:8; 94:16; 121:19; 136:15; 228:4; 253:20
becomes 51:24; 52:2; 55:5; 58:8; 121:18; 129:19; 165:23; 171:13; 205:8
before--if 142:16
began 153:9
begin 212:24; 230:2
beginning 20:11; 21:17, 19; 22:1, 14; 30:24; 41:6, 15; 42:19; 56:14; 65:14, 16; 73:6, 25; 74:6; 104:12; 116:2; 118:11; 226:5
behalf 155:9; 175:10
behave 40:21; 251:10
behavior 106:2; 248:4
behind 89:25; 162:1
BEHL 9:20, 20; 72:8, 24; 73:4, 15, 24; 74:19; 78:4; 79:5; 121:20; 126:21; 127:9; 210:20; 240:6; 242:12; 246:23; 253:2, 17; 277:11
believes 155:16; 157:19; 159:4; 176:8
belong 220:23
belongs 185:25
below 30:14, 18
benefit 143:14; 231:21; 245:5
benefitted 196:16
best 13:19; 16:15; 46:13; 47:3; 76:2; 116:24; 132:14; 141:14; 150:5; 153:2; 154:20; 189:6, 14; 190:11, 25; 200:18; 209:2; 210:15; 218:21; 219:14; 227:12, 17, 25; 228:20; 237:19; 238:3; 254:7; 273:12
bet 209:2
beta 29:8; 110:7; 129:9; 214:18; 264:15
beta-agonist 233:7
better 15:14; 36:4; 40:20; 46:1; 58:20; 59:11, 17, 18; 61:25; 65:14; 72:9, 10; 77:16; 78:7; 80:3; 87:25; 103:2; 106:25; 124:17; 160:11; 184:8, 22; 210:9, 12; 224:5; 225:24; 231:11; 236:7; 240:21; 242:19; 274:22
between-canister 26:6
Beyond 74:13; 125:16; 219:3
bias 162:4
BID 180:10
bidose 73:8, 12, 15
big 59:19; 94:22; 95:3, 9, 19; 104:18, 18; 186:19; 193:8; 208:20; 234:6; 241:22; 263:4; 264:5

biggest 234:1
Bill 8:22; 219:19
binding 196:3; 203:11; 204:3
bio 82:14
bioactivity 178:19
bioassay 214:24; 216:8, 13, 25; 217:14, 22; 218:6, 14, 21; 220:16, 19; 224:13; 225:8; 229:16; 233:4; 238:11
bioavailability 11:4; 12:5, 6; 13:1, 3; 14:7; 15:20; 80:22, 24; 82:12; 130:9; 182:5; 195:2, 24; 204:22, 23; 205:8, 23; 206:17; 252:16; 255:8, 24, 24; 257:1, 12, 20; 258:9; 261:8, 13
bioavailability/bioequivalence 7:3
Bioequivalence 9:11; 11:5; 12:5, 7; 13:2, 3; 14:8, 25; 15:2, 8, 20; 35:15; 61:24; 71:18; 80:22, 24; 82:16; 83:17; 84:7; 85:11, 13, 20; 86:1; 87:7, 16; 88:14; 89:16; 121:1, 8; 127:2; 129:20; 130:9, 19, 19; 131:6; 132:15; 133:14; 136:14, 25; 140:13, 20; 141:21; 142:7; 144:9, 16; 145:10; 156:5, 9; 157:6, 11, 16, 20; 178:18; 183:15; 184:17; 186:13; 187:21, 25; 188:22; 189:15, 24; 193:12; 194:4; 195:2; 196:9; 202:17; 208:14; 209:6; 211:1, 2, 12; 212:6; 213:13, 19; 214:2, 13, 15; 215:12; 216:8; 217:10, 16; 229:14; 230:11; 231:9; 234:19; 237:2, 20; 238:10; 242:22; 243:19, 22, 25; 245:8; 250:9, 10, 16, 20, 21; 251:16; 252:2; 255:3, 8; 256:2; 257:13, 20; 261:13; 262:12; 268:10, 21; 269:16, 23; 270:19; 274:2, 4; 275:12
bioequivalent 132:20; 215:16; 219:16; 242:4
biologic 71:9
biological 17:11; 277:1
biopharmaceutical 258:6
biopharmaceutics 255:20
biopsy 204:12
biospace 259:2
Biostatistics 9:7
biostatistician 224:20
bit 25:11; 28:18; 39:15; 46:10; 47:6, 7; 64:13; 98:23; 103:2, 2; 105:18; 111:16; 113:19; 119:9; 131:23; 185:9; 193:10; 198:23; 215:4; 218:3; 232:12; 237:16; 245:7;

248:1; 260:4; 262:19; 264:21
black 30:7; 201:23
blind 190:9
blinded 160:3; 190:12
blinding 190:6, 10
block 57:23; 205:16; 206:14, 18; 207:14; 248:19; 252:15; 258:20; 271:7, 16; 274:11
blood 146:5; 196:22; 198:10; 200:9; 249:18; 266:22; 267:4, 9, 11
blue 92:11
BMP 211:22
Bo 100:18; 111:17, 17; 158:13, 17
board 183:4
boards 235:8
body 206:22
Boehringer 110:19; 167:23
Boehringer-Ingelheim 8:9, 23
boiling 149:10, 12
bold 112:8
bone 272:21
books 28:24; 29:8
bootstrap 218:7
Borgstrom 109:12
boring 186:2
both 10:23; 11:4; 18:6; 27:9; 28:5; 31:16; 37:14; 41:8; 44:4, 5; 66:10; 80:5; 82:2; 83:11; 87:17; 100:21; 102:17; 110:16; 117:2; 123:4, 6; 124:14, 17; 126:25; 127:10; 138:11; 150:21; 152:16; 155:18; 156:19; 177:5; 179:7, 13; 180:1; 193:24; 196:7, 7, 10; 199:9; 216:12; 223:3; 251:15; 261:9; 262:9
bothers 131:23
bottom 13:23; 89:17; 93:23; 94:20; 95:6, 6; 99:14; 101:6; 103:7; 122:22; 199:8; 263:2; 274:2
bottom-line 39:23
bound 73:17; 85:23
boundaries 85:20
bounded 98:11
brand 143:12; 145:9
break 48:11, 15; 196:6; 212:13, 15, 21
breathe 117:25
Bricanyl 108:14
bridging 240:11, 17; 253:9; 277:11
brief 17:2; 133:18; 151:21
briefly 64:21; 165:4; 172:1; 201:19
bring 40:4; 91:21;

124:10; 190:15; 239:4; 280:19
British 103:23
broad 79:20; 113:1; 153:25; 234:7
broader 169:23
broadly 112:3; 114:10; 128:14; 265:7
bromine 244:23
bronchial 217:11
bronchodilator 232:9; 235:22
bronchodilation 87:15; 215:16
bronchoprovocation 15:10; 87:15
brought 104:8; 233:21; 235:17; 280:17
Brown 8:12
buckle 146:3; 147:14; 150:21; 151:6
budesonide 197:7; 199:6; 206:4; 264:25
build 93:10
Building 7:6; 110:6; 117:24; 166:25; 170:4
built 48:1
bulk 169:17
Bullets 86:11
bunch 59:23
burden 46:23; 242:15
burst 226:5; 230:8
business 42:7, 14
Busse 219:20; 225:13; 227:20; 228:6
buy 143:1, 5
by-product 75:18

C

C 270:4, 10
C1 267:5
calculate 35:3, 11; 53:3; 57:1; 58:5, 16, 24; 59:24; 60:3, 21; 61:7, 9; 63:7, 8; 201:3, 4; 207:13; 208:2
calculated 35:6; 99:6, 20; 100:20; 207:5, 7
calculated--this 225:12
calculation 57:21; 59:1; 206:6
calculations 205:6; 224:17; 225:4; 228:2; 236:4
calibration 120:10
California 8:4; 155:8
Call 7:24; 28:7; 51:11; 54:23; 100:8; 115:8; 123:15; 268:15
Callaway 8:12
called 17:15; 34:25; 47:25; 69:24; 100:7; 110:21; 178:19; 217:24

calls 162:17
came 49:9; 53:1; 219:1; 230:1; 238:5; 269:7; 270:18
can 14:25; 15:1, 23; 16:4; 33:1, 14; 34:16; 35:3; 38:11; 39:3; 42:20; 43:19, 20; 46:2, 9, 13, 15; 47:3, 17; 48:8; 49:1, 25; 52:11; 54:14, 20; 56:5; 58:13, 17, 18; 59:6, 18; 61:7; 64:2, 20; 65:5, 7, 9, 12, 14; 66:11; 74:10; 75:1; 76:16; 79:8; 80:14, 18; 89:12; 92:24; 93:9; 94:5; 95:11; 96:18, 22; 100:17; 102:2, 7, 15; 105:23; 106:6, 19; 107:4, 19, 20; 108:5, 12, 14; 109:4, 5, 21; 110:3, 24; 111:8, 24; 112:17, 24; 113:3; 114:20; 120:21; 121:4; 122:4; 126:2, 5, 9; 127:6; 135:11; 144:4; 146:14; 147:2, 9, 23; 150:4, 5; 153:1, 19; 160:8, 25; 163:21; 164:18, 19; 165:20; 166:3; 171:22; 174:21; 178:25; 181:4; 182:4, 5; 183:23; 187:2; 188:10; 190:3, 11, 18; 195:13, 15, 23; 196:7, 15, 18, 25; 197:2, 3, 10, 13; 198:16, 22; 199:19, 21; 200:1, 25; 202:5, 25; 203:1, 6, 10, 15, 19; 204:9; 205:12, 24; 206:6, 13, 21; 207:1, 10; 208:21, 22; 209:12, 14; 210:3, 7, 22; 211:8, 23; 214:10; 217:12, 15; 221:4, 8; 227:6; 232:3; 233:11; 235:11, 11; 236:16; 238:13; 240:13, 16; 242:3; 244:14, 18; 248:3; 250:9; 251:12, 18; 253:3, 8, 11; 254:7, 20; 255:7; 257:12; 258:22; 259:19; 260:24; 262:12, 13; 263:2, 3, 7, 13, 19; 264:2; 265:5, 9, 9; 266:24; 268:7, 8, 9; 269:8, 20; 272:1, 11, 13; 273:12; 274:8, 17, 17, 22, 24; 275:20; 276:4, 5, 8; 278:25; 279:13, 22; 280:3
Canada 187:10
canister 27:1; 50:25; 51:19, 21; 52:16, 17, 18, 20, 21, 24; 53:1, 8, 9; 57:3, 14; 59:25; 61:7
canister-to-canister 47:11
canisters 26:21, 25; 27:22; 31:15; 52:19; 53:2, 11, 12; 57:3; 59:23; 60:5, 15; 62:14; 63:2, 3; 64:23; 69:8, 10; 79:13
capabilities 24:4; 263:18
capability 68:1; 160:4
capable 117:16; 229:14

capsule 146:7; 148:5
capsules 148:3
capture 106:3; 112:14
care 144:4
careful 204:10
carefully 105:24; 178:22; 181:20; 219:4; 235:14
Carole 161:4, 9; 172:20
Carolina 151:19
carried 105:7; 109:15
carries 185:22
carry 109:25
carrying 118:15
carryover 224:10; 226:4, 6; 229:24, 25; 230:2, 3, 9
cart 132:8
cascade 13:5; 50:10; 54:9; 84:25; 88:25; 89:8; 91:5; 95:1, 14; 119:4, 23; 276:17, 23; 278:24; 279:2
cascade-impactor 50:6, 8; 127:14; 128:8; 279:4
cascading 51:23
case 22:10; 41:17; 43:16; 51:20; 64:6; 73:18; 75:22; 87:9; 90:18; 91:14; 92:20; 93:7; 98:5; 104:10; 105:5, 9, 10; 110:7; 115:3; 129:24; 139:3; 144:6; 145:16; 148:5, 9, 22; 149:3, 18; 177:17; 202:9; 205:23; 207:20; 214:24; 215:16; 216:12; 217:5; 239:9; 242:12; 244:23; 245:20; 251:22, 23; 252:14; 270:4, 13, 22; 271:2; 275:8
case-by-case 24:12; 260:12; 278:15
cases 42:6; 73:11; 143:3, 7; 146:8; 149:13, 20; 162:19; 163:6; 174:23, 24; 196:18; 199:9; 257:7; 260:8, 11; 261:4; 263:19; 275:15; 276:3; 278:1
casts 116:23
cat 187:4
catch 16:14; 48:19
categorical 88:15
categories 23:23; 125:8, 10, 11; 161:23
categorization 125:13
categorize 125:25
category 23:24; 24:1, 11, 13, 15, 20; 25:1; 43:14; 52:1; 126:13
cause 179:1; 195:14
causing 46:23
caution 274:23, 23
CDER 9:16
cds 53:24; 54:4
ceases 42:14
cedar 185:8
cell 204:2
cells 198:10

celsius 149:13
Center 9:18; 178:9; 187:8
centimeter 180:20
centimeters 180:16, 17
central 73:23, 24; 74:18, 19; 78:10; 128:13
central-limit 47:25
certain 7:2; 22:20; 23:2; 27:15; 68:13; 85:9; 121:23; 125:16; 126:10; 147:23; 156:15; 161:19, 20; 179:3; 181:5; 211:3, 4; 233:25; 247:22; 271:13
certainly 10:20; 16:7; 31:25; 35:22; 36:7, 18; 45:23; 65:8; 67:5; 68:14; 96:25; 100:5; 105:4; 117:21; 128:22; 135:12; 210:12; 213:24; 236:2; 239:13; 262:14; 265:24; 271:7; 273:19; 274:21; 277:2
cetera 90:19; 185:2
CFC 43:17; 214:7; 218:24; 219:7; 222:4; 260:19
CFC-containing 17:6; 176:11
CFR 144:15; 257:11
CFT 82:20
cGMP 168:22; 169:8, 11, 15, 22, 25; 170:9, 14; 173:4
chain 169:9, 12, 16
Chair 8:2, 12, 19; 11:16
Chairman 8:3; 9:13; 79:19; 104:3
chairs 6:8
challenge 83:4; 198:6; 209:18; 235:5
challenges 17:24; 18:15
challenging 250:7
CHAMBERLIN 6:3; 81:9; 138:23; 139:4; 140:3; 145:20
chance 29:9; 45:2; 76:9; 77:25; 148:18
chances 248:13; 276:19
change 6:9, 11; 44:12; 91:6, 21, 21, 24; 92:10, 12; 93:4, 10; 95:8; 96:12, 18, 18, 23; 97:2, 3, 5, 18; 98:6, 11, 15; 103:3; 120:19; 130:12, 17; 148:9, 9; 150:20; 162:3; 167:5; 190:22; 192:20; 194:11; 252:19; 277:22; 278:2, 13, 14, 19, 20; 279:1
changed 252:24; 260:18
changes 38:4; 92:17; 94:4; 95:25; 97:16; 98:13; 130:12, 13, 16; 212:12; 233:9, 15; 255:16; 260:6, 9; 278:1, 12, 17, 18, 24
changing 133:8; 191:6; 253:20

channel 98:13
characteristic 111:2
characteristics 51:17; 120:18; 133:19; 134:2, 10, 14, 17; 142:4; 239:8; 257:4; 259:10
characterization 71:11; 114:19; 125:12; 162:24; 165:7, 15; 206:25; 211:10
characterizations 116:3
characterize 71:17; 125:25; 207:20; 257:22; 261:17
characterizing 84:14; 109:20; 120:16
Charan 9:20; 122:14; 127:12
charcoal 203:21; 205:17; 206:3, 5, 12, 13, 17; 207:14; 248:19; 252:15; 258:20; 271:7, 16; 274:11
charcoal-block 109:3; 111:23
chart 90:14; 96:16
chemically 166:16
chemistry 7:2; 8:12; 9:4; 10:2; 12:4, 14; 16:23; 67:16; 147:5, 10; 175:21
chi 13:13; 55:17; 56:9; 58:7, 9, 14; 61:7, 24; 64:14; 90:21; 92:4; 95:25; 96:6; 97:9, 25; 99:2; 100:2; 101:21; 102:12; 103:7; 121:10; 123:11; 127:25; 131:1, 7; 276:18
chi-square 13:12; 56:4; 58:17, 19; 85:1, 2; 122:18; 130:5, 25
Chiesi 110:21
Children 178:3; 179:1, 4; 180:9; 181:14, 18, 22; 228:16, 17
choice 202:22; 261:17
choices 47:15
cholinergic 129:8
chose 31:18; 47:2; 96:20; 235:18
choosing 33:4; 102:13; 127:24; 128:5; 233:20
chose 217:23, 25; 218:6
chosen 60:16; 90:18
CHPA 9:1
chronic 208:22
ciliary 253:18, 23
circadian 199:21
circulation 83:13; 195:13; 252:6
circumstances 136:2; 278:8
cited 17:18
claim 20:24; 21:1, 3, 4, 6, 12, 14, 25; 31:4, 13; 32:13; 259:22
clarification 162:16; 165:10

clarify 47:6; 162:6; 260:14; 279:19
clarity 277:7
Clark 85:5; 88:23; 89:2; 103:9; 121:9; 122:24; 123:4; 124:1, 22
class 129:14; 179:7
classes 75:23; 129:15
classical 115:8; 192:16
classification 39:17
cleaned 23:6
clear 28:1; 41:10; 42:22; 46:25; 71:20; 75:9, 16; 76:5; 107:24; 110:25; 121:21; 124:5; 145:16; 151:2; 165:8, 11; 190:4; 219:14; 228:15; 250:24
clearance 196:1; 207:4
cleared 195:25
clearer 177:10
clearly 44:12; 64:13; 77:10, 12; 135:9; 182:2; 198:4; 233:24; 234:11; 235:20; 257:11
Clinic 9:24; 89:24; 219:1; 223:2
clinical 14:12; 15:6, 9, 16; 46:20; 79:15; 82:22, 25; 86:8, 10, 14, 19; 88:13; 116:5, 9; 123:15, 16; 124:2; 129:1, 5, 6, 18, 24; 133:5; 136:2; 138:14; 156:23; 157:10; 178:9, 10, 14; 182:17, 19; 183:19; 188:5; 201:8; 211:7; 212:16; 213:1, 4, 15, 23; 214:14, 24; 215:2, 4; 218:25, 25; 220:21, 24; 222:15, 22, 22; 229:16; 231:5, 19; 232:10; 234:24; 240:10, 11, 17; 241:16; 244:3, 6, 16; 245:5, 16; 253:9; 256:3, 6; 257:3, 25; 258:5; 259:18; 260:11; 261:9, 20; 276:13; 278:9
clinical-trial 29:11; 45:12
clinical-trials 28:7
clinically 138:16; 219:9; 220:12; 223:6; 231:22; 233:23; 236:19; 237:6, 7; 243:25; 277:20
clinician 71:5, 12; 212:23; 214:9; 231:13
clinician's 222:21; 229:5
clinicians 79:12; 223:1; 224:3; 226:9; 229:11
close 114:14; 119:13, 15; 149:13; 183:1; 193:4, 4, 18; 209:20; 221:25; 247:1; 269:7; 270:18
closed 19:21, 25
closely 65:9; 166:20
closer 193:5
closes 80:20
closest 188:6
closing 130:24; 157:25

closure 17:10
cloud 105:20, 21; 106:15;
107:22; 109:21; 118:8, 14
ues 234:15
Cmax 267:20; 269:8, 11;
270:20
CMC 12:13, 23; 16:20;
17:16, 18; 19:9, 10; 84:21;
140:14; 141:22, 24; 142:2,
6, 9; 143:19; 144:8;
152:23; 153:19; 158:19;
159:4; 161:6, 12; 163:21;
168:5, 9, 11; 171:10, 19;
173:10, 20; 175:5, 7;
280:17
co-leader 173:3
Coefficients 269:10, 20
cognizant 128:19
cohort 184:13
coincide 217:13
collaborate 168:4
collaboration 78:2;
151:13, 14, 21; 152:4;
153:6, 8, 24; 154:2, 19, 24;
168:2; 170:1, 21; 171:2,
14; 172:13; 173:7, 13, 16;
174:1, 8, 9; 226:1
collaborative 153:9;
230:17
colleague 65:25; 76:20;
86:25; 195:4
colleagues 72:9; 76:15;
107:18; 111:18; 231:13
collect 28:8; 116:7;
138:2; 160:2, 16; 163:4;
168:24
collected 27:14; 172:13;
260:18
collecting 160:25; 163:7,
9; 164:24; 171:12; 185:2
collection 78:3; 154:6;
155:11; 192:6, 14
collective 159:21
College 8:13
column 33:6, 8; 99:5
combination 60:10, 14,
16, 17, 17, 22; 102:5;
168:21; 279:4
combinations 30:13;
61:2; 62:10; 63:4; 84:1;
129:11
combine 123:5; 248:18;
249:9
combined 127:5
comfort 260:14
comfortable 40:19;
49:21; 251:9; 259:14
comforting 218:9
coming 45:11; 51:12;
53:3; 145:5; 188:5;
175:1; 206:10; 214:21;
252:15; 265:1
comment 7:15; 12:9;
19:21; 24:6; 25:1; 26:1;
27:2; 31:23; 39:15; 41:22,
23, 24; 43:12; 69:16;

70:18; 74:1; 80:7; 127:23;
130:5, 24, 25; 131:4;
133:18; 162:15; 210:20;
231:15; 243:16; 252:17;
278:22; 280:14
commented 124:20
commenting 170:15
comments 19:23; 23:22,
24; 24:13, 20; 42:16; 68:6;
78:17; 122:12; 128:23;
131:12; 136:21; 138:20;
140:10; 156:18; 162:16;
174:3; 175:11, 18, 19;
177:8, 20; 243:3; 279:8;
280:23
comments-1 245:19
commerce 74:16
commercial 230:16;
263:20
commercially 165:17
commitment 151:25;
153:22; 171:5; 174:7
commitments 154:12
committed 154:19, 23;
158:1; 164:13; 167:9;
171:12, 14; 172:2, 4, 10,
16, 22
committee 6:21; 7:18,
21; 9:25; 11:18, 24, 25;
30:8; 48:8; 49:1, 24; 67:1,
23; 79:22; 81:19, 19; 89:4;
103:19; 117:7; 122:13;
124:9; 131:11; 153:13, 14;
154:4; 173:6; 174:19;
177:23; 178:6; 182:1, 6;
212:24; 216:3; 231:14;
240:5; 250:24; 276:7;
280:11
committee's 6:23
committees 79:11
common 197:21; 220:6;
229:16; 268:18
commonly 198:21
communicate 126:18;
134:7
community 115:25;
179:2
companies 6:22; 45:14;
77:21; 133:8; 153:24, 25;
154:6, 23; 160:2; 164:25;
171:10; 241:12
Company 9:21; 36:14;
46:24; 73:17; 110:21;
146:2; 190:8; 192:10;
225:19; 242:24
comparability 13:17;
104:1, 2; 136:22; 269:6;
270:17; 276:19
comparable 62:25;
83:25; 124:23, 24; 157:17
comparative 13:24;
49:5; 51:8; 84:7; 88:10;
114:18; 120:4; 122:18;
136:18, 24; 189:11;
219:23; 249:22, 23
comparative-profile
13:12

compare 89:12; 103:10;
107:14; 108:13, 18;
118:12; 130:15; 143:12;
166:1, 15; 181:4; 197:22;
202:12, 14, 17, 19; 204:21;
207:20; 218:1; 232:15;
266:9
compared 17:24; 38:20;
44:2; 51:10; 62:3; 97:21;
107:22; 108:8; 115:9;
180:19; 192:18; 193:18,
25; 201:6; 206:5
comparing 13:6; 90:4;
116:8; 137:11; 199:5;
208:7; 218:22, 24; 219:23;
220:22; 258:24; 268:14
comparison 13:11;
38:19; 49:5; 50:12, 13, 14;
56:22; 61:23; 85:6; 108:6;
111:3, 12; 113:19; 114:7,
8; 119:4, 10; 121:2;
122:17, 17; 126:23, 24;
127:5, 7, 7, 14; 128:8;
130:5; 160:21; 177:12;
198:21; 206:11; 211:9;
214:20; 216:14; 229:3, 16
comparisons 84:23, 24;
85:7
compartments 114:23
complete 39:14; 41:18
completed 14:10;
100:25; 154:22; 163:16;
171:6; 172:6; 174:1
completely 8:21; 108:1;
116:14; 118:5; 183:12;
187:7; 206:14, 14, 19;
244:18; 266:12
completing 172:11, 17,
23
complex 17:23; 113:16;
187:12
complexity 76:6
compliance 159:24;
169:1, 8, 22; 184:19, 23;
188:24; 189:3
complicated 69:11;
125:5; 212:1; 251:23
complication 120:13
comply 80:10
Component 9:11;
104:18, 19; 142:9; 145:7;
154:2; 158:24; 162:24;
165:11; 168:3; 169:2, 4, 9,
16, 25; 170:8, 10; 173:4;
191:23; 274:25
components 18:1, 3;
24:5; 48:1; 58:7, 8; 130:12;
142:5; 143:3, 4, 6; 144:20;
145:9; 148:22; 150:18;
166:25; 167:1, 3; 168:6,
10, 11, 14, 19; 170:15;
204:7
composed 166:19
composite 55:5
composition 278:25
compound 202:14;
204:25; 205:3; 207:22;

211:17; 251:11; 253:17
compounds 196:16;
198:21; 202:12; 204:21;
205:5; 207:21; 240:8;
247:1; 253:6
comprised 152:6
comprises 176:2
compromised 113:10
computed 226:23;
227:11
computer 265:22
concentrate 74:23;
79:12, 14
concentrating 36:13;
116:18
concentration 46:11;
83:22; 105:20; 184:16;
187:1; 196:3; 209:13;
247:16; 253:15; 267:5
concentrations 188:17;
196:16, 18; 197:1, 3, 8, 11,
14, 16; 199:10; 200:17;
202:18; 203:7; 204:11;
211:9; 257:19; 261:2, 5, 6
concept 31:10; 39:1;
49:12; 70:11; 212:1;
214:12; 216:10, 21;
218:12; 220:16, 22;
229:15
concepts 203:25; 207:10
conceptual 69:23
concern 83:11, 14;
119:20; 132:2; 144:19;
153:19, 22; 250:14;
258:25; 264:8
concerned 130:25;
152:7; 244:15
concerning 17:3; 23:23;
37:15; 42:19; 85:5;
127:13, 23; 131:16; 171:1;
172:25; 275:6; 279:11
concerns 86:8; 88:5;
119:2, 7; 161:18; 167:17;
171:10; 259:7, 8; 262:16,
25; 266:14
conclude 173:22
concluded 269:24
concludes 175:4
concluding 170:19, 21;
171:1
conclusion 122:8;
180:18, 24; 210:8; 271:1
conclusions 72:10;
122:4; 157:3, 18; 158:3, 5;
219:22; 268:4
concur 159:15
concurrently 217:16
conditions 22:19, 21, 25;
23:9, 17; 150:11; 191:7;
250:11
conduct 185:15; 186:24;
188:7; 231:18
conducted 13:24; 88:7;
136:24; 168:25; 190:17;
192:10; 256:18; 261:8
conducting 185:6; 232:1

cone 96:3; 97:25
confer 19:16
confidence 35:1, 5; 53:4;
61:13, 18, 20; 62:2; 63:8;
84:6; 85:22; 193:13, 19;
211:4; 217:15, 19; 218:4;
219:8, 9; 236:21, 25;
237:5; 269:7
configuration 112:9;
115:17
configurations 115:2, 3
confirm 135:7
confirmation 127:3
Conflict 6:2, 14, 16
confounding 220:2
confuse 35:2
confused 94:24; 125:8;
126:21
confusion 266:16, 25
congratulate 122:24
conjunction 19:13;
126:24; 144:10
connected 119:23
consensus 77:1; 78:15;
175:1
consensus-building
153:8
consequence 67:18
consequences 69:1
Consequently 83:6;
88:16; 113:22; 120:11, 14
consider 23:19; 42:4;
51:7; 70:9; 76:17, 24;
79:23, 24; 131:10; 159:16;
182:6; 242:10
consideration 44:16;
50:22; 69:3, 4, 20; 154:25
considerations 65:4;
128:18
considered 13:5; 14:3;
20:21; 21:10, 22; 24:8;
119:4; 122:9, 14; 131:18;
133:22; 136:17; 170:12
considering 22:10; 84:6;
174:3; 247:11; 272:19
considers 64:24; 133:21
consistency 20:4
consistent 60:9; 68:16;
201:15
consistently 68:20
consists 20:18; 21:18;
153:13
consortia 176:2
consortium 101:2;
151:12, 23; 152:10
constant 142:24; 148:25
constant-scale 143:20
consternation 221:12;
222:2
constituting 99:17
constructive 174:7
constructively 104:7
construed 25:23
consultant 81:10

consultation 260:13
consumer 28:23; 29:6; 31:11; 33:3; 42:7, 15; 44:3; 45:1, 5; 143:13
contact 150:14, 17
contained 177:2
container 17:9; 20:8, 10; 21:23; 26:19; 73:5, 5, 19; 84:15; 85:8; 148:8, 10, 11, 12; 149:25; 150:7
container-closure 18:2; 144:20; 145:3
containers 20:19; 26:20
containing-uniformity 25:3
contains 73:5
content 10:22; 12:15, 18; 16:20, 23; 18:14; 20:5, 9; 26:18; 30:13, 20; 34:9; 35:8; 37:15, 19; 47:8; 65:20; 66:1, 13; 67:18; 69:2; 70:20, 22, 25; 77:10; 78:14; 85:8, 13; 147:16, 21; 152:20; 158:16
content-uniformity 12:13, 21; 25:15; 26:2, 7; 37:16, 21; 65:22; 66:17; 67:13; 72:12; 77:22
context 29:11, 16; 31:6; 40:7; 45:12; 46:10, 12; 47:16; 215:1; 279:15
continuation 130:7
continue 11:11; 12:19; 37:18; 45:21; 78:22; 79:3; 103:23; 125:1; 153:4; 163:21; 169:10; 173:15; 230:17
Continued 65:18
Continuing 15:16
continuous 60:21
contract 25:21; 154:1
contracting 182:23
contrast 118:12; 227:20
contrasting 106:22; 148:21
contribute 99:11; 157:12, 13; 275:17
contributed 209:21
contributing 117:18
contribution 114:20; 117:1; 206:7
contributions 104:23; 105:6; 110:7
control 36:15; 62:1; 68:17; 110:16; 111:2; 119:23; 142:9, 9; 143:19; 162:11; 164:10; 166:24; 167:5, 17, 20; 168:1, 18; 169:17, 22; 184:8, 19; 188:24; 191:18, 22; 192:1, 13; 215:18; 220:1; 226:13; 230:5
controlled 23:10; 187:1; 224:1, 3
controlling 80:11; 240:21

controls 7:2; 12:4, 14; 16:23; 18:3; 144:7; 162:25; 168:22; 175:22; 186:25
convene 48:13
conventional 17:25; 88:20; 258:5
conversely 12:17
convert 30:3
converting 198:25
convinced 173:13; 198:13; 275:20
cooked 193:6
cooling 148:24
cooperation 116:12, 22
copies 145:21
copy 7:4; 177:10
core 168:10
Corey 81:10
corner 227:8
Corporation 146:2; 155:8
correctly 39:1; 198:15; 209:4; 212:8; 247:12
correlate 129:4
correlated 56:23; 112:3
correlates 271:17
correlation 111:25; 112:15; 165:20, 23; 166:4, 4, 7; 201:10; 210:21; 266:3; 271:18; 273:17
correlations 111:16; 251:4; 256:20
correspond 34:5; 119:14
corresponds 29:18; 30:18; 39:20
cortical 198:7; 250:18
corticosteroid 195:22; 213:18; 223:19
corticosteroids 15:7, 17, 21; 75:25; 178:11, 24, 25; 179:4, 7, 13, 14, 15, 18; 180:2; 181:5, 6; 182:3, 4, 7; 195:8; 197:5, 22; 198:9; 201:16; 209:6; 212:17; 213:2, 5; 218:15, 22; 220:4, 7; 230:2; 231:2, 6, 17; 266:5
cortisol 197:20, 20; 198:1, 3, 4, 16; 199:10, 13, 20, 22; 200:3, 10, 18; 201:3, 10; 202:21; 232:14, 18, 20; 249:18; 272:20; 273:9
cortisols 273:10
cost 78:11; 188:3; 189:20; 271:11
cost-effect 158:24
cost-of-product 45:6
Council 169:19
counsel 15:22
count 56:20
country 185:7; 187:9; 188:7
couple 22:18; 33:21;

43:16; 66:10; 165:3; 243:2; 258:19
course 18:7; 23:18; 24:6; 42:9; 76:22; 82:16; 93:8; 95:7; 96:17; 97:17; 98:20; 99:10; 104:8, 13, 24, 25; 105:3, 7, 9; 106:6; 108:3; 114:14; 116:11; 117:16; 120:13; 130:11; 149:15; 155:10; 165:3; 167:11; 180:8, 20; 184:7, 9, 19, 23; 186:5; 187:6; 189:1, 13; 191:1; 194:15; 195:14; 205:16; 206:22, 23; 209:7; 212:7; 213:8; 215:11; 217:2; 226:11; 241:1; 242:14; 254:24; 256:7, 13, 15
courser 92:20; 94:16
cover 17:20; 82:9, 10, 12; 198:11; 253:19
coverage 30:5, 17; 253:22
coverage--that 30:15
covered 78:21; 190:9
covers 19:2, 3
CPMP 27:10; 32:8, 16
CPN--actually 28:6
CPNP 26:16
create 19:16; 60:3
created 156:24
creating 41:14; 163:20
creation 171:21
criteria 20:16; 22:19; 24:17; 25:15; 26:15; 27:9; 28:2; 38:7; 39:11; 41:10; 42:9; 45:3; 52:12, 13; 53:5; 68:21; 70:2; 92:25; 93:21; 97:4; 133:4; 138:8, 13; 143:20; 177:4; 193:22; 194:3; 209:9; 216:22; 217:17; 235:1; 239:6; 242:3; 247:19; 268:24; 269:23; 270:20, 25
criterion 24:22, 23; 26:15; 27:15, 24; 29:6, 19; 34:10; 35:20; 36:11; 39:25; 64:21, 23, 24; 65:1; 70:4, 8; 85:11, 13, 18; 94:6, 10; 98:15; 124:6; 160:19; 166:13; 249:3
criterion--that 34:3
critical 126:3, 9; 148:17; 161:21; 163:21; 165:11; 168:18; 173:10; 262:23
criticism 265:21
cromolyn 107:2, 16
Cross 220:24
crossover 87:21; 88:7; 187:20, 21; 224:8; 226:3; 228:3, 8, 11, 23; 229:24; 230:9; 233:19; 238:9; 239:13; 240:21, 23; 268:17; 270:11; 279:7
crossovers 244:12
crucial 27:18
crude 118:6

crystal 147:9; 149:2, 4, 5
crystallization 148:21; 149:2, 6
cumbersome 236:2
Cummings 151:10, 15, 18
cumulative 54:1; 121:11, 12; 200:19; 201:4, 10
cumulatively 121:14
cumulatively 54:4
currency 197:21
current 7:13; 16:21, 24; 18:23; 19:10; 34:3, 9; 36:18; 51:2, 5; 61:3; 77:15; 80:25; 81:4; 87:20; 88:9; 154:11; 155:14; 156:17; 157:3, 9; 159:23; 168:25; 254:15, 21
currently 17:21; 20:16; 40:8, 18; 46:17; 68:9; 72:22; 77:9; 156:3; 157:2; 163:9; 177:16, 18; 182:8
currents 253:23
curve 30:8, 15, 18; 88:1; 91:1; 108:22; 200:12; 201:3; 216:23, 24; 218:1; 220:7, 11, 18; 222:9; 224:24; 229:17; 233:22; 234:1, 3, 6, 9; 265:7; 272:24; 273:19
curve-fitting 218:3
curves 42:24; 199:14; 216:16; 217:2, 13; 222:17, 24; 224:7
cutoff 49:19, 21; 55:15; 62:11, 23; 121:23
CV 62:15, 18; 270:22; 272:11
cycle 130:11, 16, 18
cycling 148:16
Cyclohaler 112:6
Cynthia 170:20, 24; 174:11
cytosol 204:2
cytosolic 204:5

D

d 54:17; 270:10
daily 143:5; 279:18
DALBY 8:19, 19; 43:24; 44:14, 20; 45:9, 17; 68:14; 79:25; 119:7; 131:22; 133:6, 16; 137:9; 241:15; 244:15; 247:10; 249:2; 250:1; 251:21; 253:12
Dalby's 245:19
dandruff 187:4
danger 119:11
dangerous 137:21
darned 220:8; 222:9; 229:17
dashed 200:11
data 12:20; 13:6; 16:3, 3; 27:14, 15, 15; 28:8, 8, 9;

35:3; 36:5; 40:5, 7, 22; 41:20; 46:17; 47:21, 22; 48:7; 49:10; 50:23; 56:12; 66:3, 5, 7, 9, 12, 16, 25; 67:3; 68:4, 9, 11, 15, 20, 25; 69:15, 19; 71:20; 75:8; 76:8; 77:2, 3, 5, 6, 18; 78:3, 3, 16, 16; 80:5; 84:4, 7, 25; 86:16; 87:22; 88:13, 14, 25; 92:7; 100:17, 19, 22; 101:5; 108:18; 109:13; 111:17; 112:24; 113:20, 21; 116:3, 4, 7; 120:12; 124:17; 127:14, 15; 128:8; 129:7; 140:10; 144:19; 153:1; 154:7, 14; 158:4, 5; 160:15; 161:21; 162:22; 163:5, 7, 10, 10; 164:25; 165:1; 166:7; 168:24; 171:13; 176:4; 182:5; 184:25; 192:10; 193:5, 15; 197:9, 15; 199:5, 8, 22; 200:19; 201:12; 202:8, 19; 203:8; 207:25; 208:2, 11; 209:21; 210:3, 3, 7, 16, 17, 21; 217:9; 221:2; 224:1; 225:12; 228:1, 4; 229:8; 236:3, 3; 245:4; 247:3, 5, 6; 251:3, 25; 252:1, 3, 24; 253:21; 257:11, 22; 258:1; 259:19; 260:2, 2, 3, 5, 7, 11, 17; 261:19, 20; 274:16; 275:7, 11, 11, 16; 276:12, 18; 277:5; 278:4; 280:20
data--covers 35:6
data-driven 154:20; 155:12; 159:11; 163:18
database 76:16; 160:3, 5, 10, 16, 25; 172:12
dated 167:9
dataset 70:12, 13; 101:3; 102:20
datasets 45:25; 79:3; 266:25
date 12:2; 160:1, 16; 163:11; 174:1; 219:14
dating 216:21
Dave 132:22; 164:1, 4, 5
David 81:10; 103:24; 121:15; 137:1
day 10:17; 27:25; 32:17; 142:14; 187:9, 10; 190:19; 199:22, 23, 23; 223:2; 251:3; 256:2
days 184:6, 9; 186:15; 199:9; 208:20; 219:2
days-in-the 14:16
days-in-the-park 86:22
DCU 23:25; 24:12; 73:8; 159:24; 160:4, 10; 172:12
deadline 66:25
deal 13:4; 14:12; 17:8; 52:2; 61:21; 71:6, 8; 102:14; 136:15; 179:17; 184:17; 221:12; 222:14; 229:10, 25; 273:9
dealing 46:18; 67:23; 71:23; 98:19, 20; 136:14;

184:14; 191:1; 226:4;
229:2; 254:10; 255:2
deals 69:21; 173:7
alt 18:15
dear 106:20, 20
debatable 266:15
debate 121:4
debated 122:11
decade 18:18, 20; 38:6;
43:14; 213:11
decide 45:14; 127:20;
238:13
deciding 44:22; 131:3
decision 27:14; 28:12;
40:3; 67:5, 11; 68:5; 76:11;
193:23
deconvolute 119:24
deconvolution 203:21;
207:10; 209:15
decrease 201:24
decreases 92:21; 192:2
deemed 44:25
deep 173:24
defend 47:2
define 87:25; 132:3;
143:25; 156:15; 249:14
defined 62:16; 86:12, 13;
92:16; 165:6, 15; 209:17;
249:10
defines 72:15
defining 107:21; 118:7
definitely 79:3; 251:22;
257:25
definition 165:11; 166:7;
176:12
definitional 86:11
definitions 164:16; 189:7
definitive 239:17
degradation 148:11
degree 200:2, 18
degrees 149:13
delay 71:10; 140:22;
141:15
delaying 235:8
delete 24:22, 25
deliberate 118:24
deliberating 256:2
deliberation 194:7
deliberations 23:20;
171:18
delineate 18:23; 151:1
delineated 81:14
deliver 17:10; 147:23, 25;
148:13; 175:1; 205:9;
213:19; 214:3
deliverables 172:1, 3;
173:17
delivered 38:21; 73:7;
115:9; 135:11; 146:4;
150:2, 2, 4, 8; 184:20, 22;
190:7; 204:19; 213:21;
214:5, 25; 216:1; 220:11;
234:7; 270:9
delivering 147:25; 215:4;

217:4; 248:12
delivery 14:13; 15:6;
16:4; 18:2; 40:12; 83:12;
86:8; 116:18; 117:21;
125:5; 126:6; 134:5, 6, 23;
135:18; 137:8; 144:19;
145:23; 157:13; 162:2;
182:19; 195:11; 203:25;
204:17; 205:6; 210:4;
212:16; 213:2, 4; 231:5;
236:12; 252:20; 256:9;
257:15, 24; 258:15, 24;
259:1; 269:25; 271:3, 25;
274:25; 278:14
delta 193:21
deluding 229:7
demineralization 272:21
demonstrate 14:20;
33:10; 101:7; 171:5;
176:5; 225:5; 240:3;
246:4; 271:3
demonstrated 31:5
demonstrates 31:11
demonstrating 216:8;
229:14
demonstration 217:10
denominator 60:12; 86:4
Department 9:13
departures 19:15
depend 105:8; 189:4
dependence 105:1;
135:10, 18
dependent 88:15;
188:25; 189:2, 8; 191:9
depending 12:18; 69:9;
97:6; 122:5, 8; 130:20;
133:25; 134:9; 174:16;
240:24; 253:25; 266:23;
278:11
depends 90:25; 105:19;
198:13; 242:21
deposit 55:24
deposited 91:18, 20;
94:22; 97:12; 102:4;
105:16, 19; 119:17; 128:9,
12; 129:16; 247:22; 252:5;
254:1; 279:3
depositing 99:17; 241:23
deposition 89:25; 91:13,
16; 94:14; 96:24; 97:2, 6,
16, 21; 98:6, 16; 99:5;
100:8, 21; 101:4; 102:24;
104:19, 20; 105:11; 107:2;
109:5, 9, 10, 23; 110:9;
111:21, 25; 112:20;
117:19; 118:3, 3, 15;
119:25; 128:3; 157:5;
241:20; 242:9; 247:16;
253:16; 259:3; 271:20, 21;
276:11
deposition--that 109:4
depression 23:7
depth 107:22
depths 118:15
Deputy 9:15
Derendorf 6:12; 9:12, 12;

70:17; 79:4; 121:25;
138:6; 194:12, 22; 210:6,
18, 24; 211:25; 254:18;
257:18; 264:23
derivation 115:20
derive 116:2; 250:3
derived 116:4
derives 111:10
describe 50:4; 53:9;
54:17; 206:22
described 51:15; 115:5;
137:10; 157:8; 158:3;
168:17; 173:18; 220:17
describes 155:21
describing 111:20
description 177:11;
183:22
descriptions 66:3
design 13:19; 14:2;
32:24; 33:4; 36:15; 46:15;
87:21, 24; 114:15, 16;
116:24; 131:16; 142:3;
181:17; 187:22; 192:11;
223:19; 225:8; 228:10, 11;
233:18; 237:9; 238:7;
239:14; 240:21, 23; 241:7;
244:8, 17; 267:16; 268:17;
272:23
designated 11:17
designed 14:13; 115:18;
116:8, 14, 17
designing 32:18; 45:14;
116:12; 132:14, 24; 170:3;
171:22
designs 14:14, 18; 15:13;
33:3; 191:25; 220:1;
231:11; 240:4; 265:11;
268:15; 270:9
desirable 36:7; 40:22;
123:7, 18; 196:4
desired 154:16
detail 144:8; 176:17;
203:22; 224:14; 257:17
detailed 177:3, 11;
183:22
details 209:16; 234:10
detect 208:13; 220:8;
247:13; 261:2
detectable 176:22;
267:10
detecting 188:18; 198:4;
261:5
determinant 105:17
determination 20:20
determinations 20:25;
21:2, 8, 9, 20, 21; 22:4, 9;
116:5; 132:6
determine 14:4; 45:22;
49:19; 62:9; 70:8; 75:7;
133:1; 143:23; 166:14;
213:17
determined 24:12;
85:15, 17; 193:13; 207:3
determines 29:14
determining 90:11; 91:2;
131:18; 214:2, 3

develop 12:20; 45:21;
143:25; 144:1, 2; 163:2;
169:25; 175:1; 229:13;
235:1; 242:3
developed 11:3; 45:24;
141:7; 194:7; 199:20;
200:23; 218:13; 255:5;
258:13; 261:1
developing 14:4; 39:16;
73:15; 80:9; 81:20;
117:10; 156:23; 173:4;
182:25
Development 8:25;
11:11; 13:7; 18:16; 37:18;
42:5; 69:4; 78:22; 84:10,
24; 120:9; 141:13, 13;
143:20; 144:11; 146:3;
152:1; 158:24; 159:13, 19;
162:22; 241:11; 274:12;
278:12
developments 118:10;
142:8
deviation 30:5, 13, 14;
39:9
deviations 101:1
device 14:2; 24:5; 68:1,
18; 74:9; 84:1; 106:13;
110:19, 20; 111:12; 113:2,
4, 6, 14, 21, 22, 25; 114:5,
5, 9, 10, 16, 19; 115:4, 18;
117:24; 120:17; 125:6;
131:17, 25; 132:4, 4, 7, 17;
133:9, 9, 11; 134:11;
135:23; 201:1; 204:24;
236:12; 260:10
devices 67:24; 68:2;
69:17; 83:24; 106:14;
110:15, 22; 111:5, 9;
125:6; 126:6; 132:5;
133:20; 134:13; 135:14;
136:1; 137:25; 190:7;
206:4; 245:3; 268:20, 22
devote 37:12
dexamethasone 198:22;
199:2
diagram 119:22; 162:14
dialogue 46:22; 163:23;
173:14
diaries 189:5; 192:6
diary 192:15
dichotomy 34:21
Dick 251:24
differ 134:8
difference 14:1; 49:13;
52:13; 53:21; 54:2, 15, 21;
55:2, 3, 3, 5, 19, 24; 56:2;
57:13; 58:2, 5, 25; 59:2,
13; 62:1; 63:13, 17, 24;
64:8, 9, 12, 16; 79:18;
90:7; 91:5, 11, 12, 14;
94:14, 21, 23; 95:15, 18,
19, 21; 97:21; 102:11;
109:5; 119:14; 121:10;
146:17; 150:22; 153:1;
181:7; 194:1; 208:4;
213:21, 23; 215:5; 220:13;
221:10, 20, 21; 234:7, 7;
244:7; 253:25; 267:8;

269:2
differences 59:2, 11, 24;
64:25; 85:18, 19; 86:3, 3;
91:25; 92:5; 98:21;
103:13; 135:23; 147:13;
178:4, 11, 13, 16, 18;
182:3; 188:18; 192:4;
193:8, 25; 198:5; 208:13;
220:9; 221:9; 227:15;
231:23; 232:3; 245:9;
256:9; 271:20; 276:22, 22,
23
different 12:17; 18:17;
20:6; 26:24; 27:7, 8; 28:19;
39:2; 50:10, 18, 24; 54:20;
56:16; 57:5; 58:22; 60:12;
62:10; 66:20; 67:24; 68:2;
69:17; 70:2, 2, 4; 72:15;
75:23, 25; 78:5, 5; 85:5;
86:19; 92:13, 14; 94:1, 17;
95:13; 96:2; 100:22, 23;
102:2; 106:17; 111:4;
114:23; 116:14, 23;
117:11, 14; 119:19; 120:1,
9; 122:1, 4; 126:6; 127:2,
10, 18, 19; 129:10; 133:25,
25; 134:2, 3, 22; 140:22,
22; 141:3; 146:18; 159:18;
165:9; 188:17; 191:16;
197:15, 21, 23; 198:6, 20;
199:6, 7; 202:10, 12, 14,
20, 20; 203:2; 206:6, 7;
207:21, 21; 210:25;
215:15, 24; 216:1, 2;
217:23; 218:4; 219:24;
221:7, 7; 226:18; 232:11,
12; 236:10, 12, 19; 239:8;
242:4, 14, 22, 23; 248:1;
249:9; 251:13, 15, 25;
252:12, 21; 253:24; 255:7,
7; 257:11; 258:16, 25;
259:9; 266:12, 19, 22;
270:5, 6, 6, 7, 16; 276:24;
279:7
differentiate 122:1;
205:12; 216:1; 233:14
differentiation 108:19;
271:7
differently 99:1; 237:16
differs 161:13
difficult 49:13; 52:6; 68:8;
71:5; 76:10; 113:20;
114:7; 122:25; 137:18;
190:14; 191:14; 204:14;
209:17; 211:10; 219:22;
222:23; 225:15; 244:22,
25; 253:3; 254:3
difficulty 51:4; 52:9;
64:6; 190:6; 215:1; 242:1
dimensional 97:15
dimensions 116:19;
268:25
diminish 233:19
dip 149:24, 25; 150:9
dipping 227:2
dipropionate 180:10;
198:24
direct 203:3, 3, 14

direction 71:13, 19; 75:3; 243:12
directives 176:1
directly 45:13; 96:24; 147:18; 154:4; 196:15, 19; 197:11; 203:7; 248:14
Director 8:17, 22, 24; 9:15; 10:1; 175:9; 178:8; 182:23
disadvantage 44:21; 101:19; 102:18
Disadvantages 102:13
disagree 135:8
disappear 204:8
disappoint 183:5
discern 192:4
disclaimer 25:20
disclosed 118:17
discomfort 247:21
discounted 118:5, 5
discounting 118:8
discouraging 208:12
discovered 215:23
discrepancy 124:21
discriminate 208:15; 215:24; 239:20; 245:15; 271:19; 274:1
discriminating 157:10; 191:17; 244:17; 245:20, 22, 23; 262:13
discrimination 15:14; 190:5; 231:11; 245:24
discriminative 225:2; 235:20; 236:1; 252:9
discriminatory 237:9; 252:4
discuss 10:20; 11:2, 25; 25:4; 49:4; 69:3; 110:3; 131:11; 260:4; 280:19
discussed 232:6; 255:10; 257:1
discussing 7:18, 20; 71:5; 245:17
discussion 6:23; 11:8; 13:7; 14:10; 19:6, 14; 20:13; 37:4, 4, 11, 20, 23; 38:14; 48:18, 25; 60:6; 65:18; 67:7; 118:22; 124:16; 163:21; 166:9, 12; 182:15; 194:18; 209:8; 210:1; 212:18; 230:23, 24; 231:16; 245:6; 255:10; 257:5; 275:2; 280:20
discussions 7:7, 23; 10:16; 15:24; 166:23; 221:24
disease 191:6; 238:18; 239:1; 252:18
disposition 207:1
dissimilarity 89:14
dissociation 268:1
dissolution 55:11, 15; 249:1; 251:7
dissolution-time 248:22
dissolution-type 92:22

dissolve 251:10
dissolved 204:1
dissolves 149:4
distance 51:9, 10, 12; 52:16, 20, 21, 22; 53:8, 10, 10, 22; 54:1, 12, 23; 55:6, 8, 8, 10, 13, 18; 56:4, 10; 57:25; 58:14; 59:5; 90:3, 15, 16, 22; 91:11; 94:8; 101:21; 141:15; 216:15; 248:13
distance-type 103:1
distances 55:1; 90:21, 22, 25; 102:9; 140:22; 141:3
distill 149:17
distill 104:15
distillation 149:14, 15
distinct 60:17; 63:4; 76:20
distinction 64:14
distinctly 67:24
distinguish 157:21; 161:22; 190:14
Distinguished 8:9; 65:25
distribute 50:17
distributed 47:19; 53:17; 57:4; 128:14; 148:4; 193:15, 19
distribution 35:21; 47:8; 49:14, 16; 50:6, 8, 9, 12; 51:22, 25; 54:7, 9; 61:13, 15, 17, 21; 64:24, 25; 65:2; 83:5; 84:16, 16; 90:17, 17; 91:1, 11, 24; 92:5, 8, 9, 14, 18; 93:5, 11, 20; 94:8; 99:12, 23, 24; 100:3, 15; 101:9; 102:9, 14, 25; 103:4; 105:21; 115:20; 117:11; 119:12, 15; 121:11, 12; 128:6; 130:3; 135:11; 138:2; 157:5; 158:16, 22; 160:15; 207:4; 248:7; 268:23; 276:11
distribution--ie 92:13
distributions 49:16; 89:13; 90:5, 10, 18, 23; 93:17; 101:16, 20; 118:12
disturbing 24:6
diversification 188:9
diversity 185:17
divide 25:12; 54:24; 55:21; 146:15; 174:21
divided 55:9; 58:6
dividing 118:14
Division 9:9; 19:14; 260:13
divisions 82:13
doable 191:21; 237:18; 243:1; 268:6, 8; 272:5, 19; 274:8; 275:16
document 41:4; 87:16; 155:15; 159:9; 171:21; 175:1; 250:16; 260:20
documentation 17:16; 19:10; 83:8; 158:6; 175:22

documents 66:8; 152:18; 153:20; 156:9; 163:22; 170:11; 171:11
dominant 205:19
dominating 107:20
dominator 58:17
done 22:24; 35:15; 39:16; 46:2; 71:23; 74:7; 80:20; 81:9; 95:12; 99:19; 100:20; 109:3, 19; 115:13, 14; 123:20; 125:16, 21; 126:24, 25; 130:6; 138:8; 141:16; 142:2, 3; 182:9; 183:23; 185:18, 19, 22; 187:2; 192:12; 200:6; 201:8; 207:2; 208:18; 209:12; 211:8, 11; 215:12; 218:23; 219:4, 14, 25; 221:1; 224:20; 228:2, 15; 234:16, 19; 237:13, 19; 238:12; 239:5; 244:21; 248:10; 254:19; 258:11, 21; 267:14; 268:12; 269:14; 273:17; 275:22; 277:21
done--there 228:6
door 45:3, 7
dosage 40:12; 115:10; 156:20; 159:9; 161:19; 162:6, 7; 163:14; 171:23; 172:20; 242:8; 258:13
dose 14:20; 17:10; 20:4, 4, 23; 22:3, 12, 13, 16; 25:2, 14; 26:6, 17, 19; 38:22; 43:3, 7; 50:9, 9, 11, 15, 18; 51:21; 68:16; 73:7, 20, 21; 74:5, 8; 84:14; 85:8; 87:25; 90:11; 91:2, 6, 21; 94:14, 23; 95:20, 22; 96:12, 18, 23; 98:14; 99:13, 18; 107:5, 25; 108:1, 16, 19; 111:20; 112:2, 3, 19; 113:8; 114:6, 11; 115:21; 118:7; 135:11, 11; 146:6; 150:5, 8; 152:20; 158:16; 162:2; 163:13; 186:9, 11; 189:11, 25; 190:1, 18; 191:13, 22; 192:21, 24; 200:25; 201:1, 22, 23; 202:8, 9, 9; 214:18, 21; 215:8, 15, 19, 24; 216:11, 23; 217:12; 218:1; 219:5, 16; 220:3, 11, 13, 13; 228:17; 232:1; 233:25; 234:6, 7; 240:3; 241:10, 13; 242:14, 16, 19, 19, 20, 22; 246:4; 249:11, 11, 15, 16, 17, 19; 251:12, 14; 255:22, 23; 256:1; 258:8, 8, 8, 24; 262:21, 22; 263:4, 5, 11; 265:18; 266:6, 11; 267:23; 268:16; 269:17, 18; 270:5, 6, 9; 272:12; 273:4, 25; 279:13, 17, 18, 20, 21, 22; 280:4
dose-acceptance 24:17
dose-axis 229:16
dose-content 20:3, 6, 12, 18; 21:16, 23; 23:23;

27:23; 29:16; 157:4; 158:21
dose-dependent 202:7
dose-response 15:14; 108:21; 186:10; 191:19; 216:16, 23; 220:7, 10, 18; 222:8, 17; 223:2, 4, 6; 224:7, 23; 228:20; 229:3, 6, 17; 231:12, 17; 233:22; 234:1, 3, 5, 9, 24; 246:12; 272:24; 273:18
dose-scale 88:18; 217:24
dose-to-dose 20:8, 9
dose-uniformity 38:19
doses 27:1; 43:2, 9; 73:6; 97:1; 112:23; 184:12; 188:19; 190:5, 20; 191:16, 17; 192:13, 14; 193:24; 194:1; 197:16; 199:7; 202:2; 214:3, 21; 216:1, 13, 17; 217:24; 221:7; 225:9; 231:18, 19, 20; 232:2, 3, 4, 19; 233:11, 12, 23; 234:13, 24; 262:17; 263:1; 269:17; 276:2; 279:14
dosing 214:10; 262:23; 263:8; 264:10
dots 201:7
double-blind 180:7; 183:23; 190:12
doubled 108:15
doubling 21:7; 22:8
down 34:7, 12; 46:21; 70:1; 75:22; 91:19; 93:23; 96:8; 97:3, 7; 98:3; 101:6; 124:8; 126:5, 10; 196:6; 201:20; 217:12; 227:8, 9, 11, 24; 241:17, 24; 244:16; 245:13; 251:20; 263:19
downside 70:3; 76:7; 203:15
downweighting 123:12
dozens 219:21; 223:21
DPI 17:15; 23:18; 72:17, 22; 106:16, 23; 133:2, 3; 137:11
DPIs 17:7; 19:2; 82:6; 103:25; 104:2; 131:16; 132:23; 136:17; 137:18
Dr 6:10, 11, 12, 15; 7:25; 8:8, 11, 14, 16, 19, 22; 9:2, 4, 6, 9, 12, 15, 17, 20, 23; 10:1, 3, 5, 9; 11:6; 16:9, 17, 17, 20, 25; 25:4, 6, 7, 9; 37:2, 7, 8, 8, 24; 38:5, 8, 9, 10, 11, 15, 18, 24; 39:6, 8, 13, 13, 18; 40:4, 13; 41:9; 42:17, 18; 43:24; 44:5, 14, 15, 20, 24; 45:9, 11, 17, 18, 20; 46:3, 4, 4, 7, 9, 13; 47:5, 6, 9, 18, 20; 48:10, 16, 16, 21; 49:1; 60:8; 65:6, 7, 9, 12, 19; 66:1; 67:4, 23; 68:6, 11, 14, 24; 69:13, 23; 70:10, 17; 71:4; 72:8, 14, 18, 21, 24; 73:1,

4, 13, 15, 18, 22, 24; 74:17, 19, 23; 76:8, 20; 77:1, 6, 13, 24; 78:4, 13, 18, 25; 79:2, 4, 5, 10, 17, 19, 21, 25; 80:15, 17, 19, 23; 81:1, 14; 84:9, 25; 85:4; 86:25; 88:23; 89:2, 6; 90:5; 92:16; 96:1; 99:2; 102:18; 103:6, 9, 15, 17; 104:3; 117:6, 8, 9, 13; 118:1, 4, 18, 19, 20, 23; 119:7, 21; 120:8, 23, 25; 121:9, 20, 25; 122:12, 20, 24; 123:4, 23, 25; 124:1, 22; 125:2, 4; 126:20, 21; 127:8, 9, 11, 12; 128:23, 24; 129:13, 25; 130:17, 22, 24; 131:7, 9, 10, 13, 21, 22; 132:10, 12; 133:6, 15, 16, 17, 18; 134:15, 15, 19; 135:3, 6, 7; 136:4, 6, 7, 9, 19, 21, 21, 23; 137:6, 9, 10, 24; 138:3, 6, 16, 18, 19; 139:1, 5; 140:7, 12; 144:3; 145:15, 17, 18, 18, 24; 151:8, 10, 15; 155:1, 4, 4; 158:12, 13, 17; 160:12; 161:3, 7; 163:25; 164:1, 4; 167:16; 170:18, 22; 172:15; 174:11, 13, 15, 16, 21, 23, 25; 175:2, 3, 6, 8; 177:25; 178:2, 5; 182:11, 16, 21; 183:25; 187:9; 194:10, 11, 22; 209:23; 210:6, 16, 18, 19, 20, 24; 211:16, 25; 212:9, 15, 22, 22; 213:1, 6; 221:12; 224:15, 20; 228:23; 230:20, 20, 24; 231:15; 232:5; 233:17; 235:3, 17; 236:9, 17; 237:8, 11, 21, 24; 238:17, 19, 21; 239:3, 11, 13, 21, 23, 24; 240:1, 6, 18, 18, 20; 241:7, 15; 242:12; 243:2; 244:15, 20; 245:6, 12, 18; 246:3, 6, 7, 10, 14, 15, 16, 18, 21, 23; 247:2, 4, 8, 10, 20, 25; 249:2, 7, 7, 8; 250:1, 5, 14, 24; 251:1, 12, 14, 17, 18, 21, 24; 252:3, 14, 17; 253:2, 12, 17; 254:11, 16, 18; 255:6; 257:17; 261:22, 23; 262:1; 264:20, 23; 275:1, 3, 5, 9, 10, 14, 15, 18, 23; 276:1, 7, 9; 277:7, 7, 9, 11, 13, 15, 16, 18; 278:5, 22; 279:8, 10, 11, 19, 24; 280:2, 6, 9, 10, 13, 23
draft 6:25; 12:2; 14:14; 24:21; 25:15; 82:9; 84:13; 85:10; 86:18; 131:1; 137:3; 140:13; 141:5; 151:24; 152:13; 155:14; 156:17; 157:9; 159:24; 161:12; 164:8; 165:19; 168:5, 9; 170:16; 171:10; 175:20; 176:14; 177:1, 13, 17; 183:13; 250:15; 268:20

drafted 168:17; 169:18
drafting 17:14; 136:11
drainage 263:13
draining 262:21
dramatically 119:17
draw 27:3; 68:2; 158:4; 219:22
drawing 72:9; 114:5
drawn 199:24
drifted 122:15
driven 153:2; 161:21; 162:21
drop 41:15; 111:6, 8; 117:23; 137:13; 207:15; 241:17; 244:15
droplet 84:15; 244:2
dropping 107:6; 227:11
drug 7:1; 9:2, 5, 19, 21, 25; 10:23; 11:5, 12; 12:3, 8, 16; 16:4; 17:7, 8, 15, 21, 23, 25; 18:4, 11, 17; 19:11; 24:3; 37:17; 46:11; 66:20, 21; 68:23; 69:1; 73:9, 10, 12, 16, 19; 74:25; 75:25; 76:1; 81:4; 82:11, 11, 18; 83:4, 10, 21, 23; 84:16; 85:21; 87:9; 101:14; 105:16, 18, 19, 20; 107:10; 125:5; 128:9; 129:2; 135:18; 137:8; 147:24; 148:1, 3, 4, 13; 150:2, 3; 156:10, 19; 158:25; 159:5; 165:16, 21; 181:22; 184:20, 22; 185:11; 189:2; 192:14, 22; 195:9, 11, 15, 23; 196:18; 200:25; 203:1, 25; 204:3, 5, 13, 19, 22, 23; 205:13, 15, 25; 206:22; 208:22; 210:4; 213:19; 214:4, 6, 25; 215:5; 241:13, 22; 243:6; 244:23; 246:5, 12; 248:17, 20; 249:10; 250:22; 251:5; 252:1, 15, 16, 19; 253:16; 255:21, 25; 256:12, 16; 257:7, 23; 258:4, 7, 15; 259:23, 23; 260:6, 25; 261:11; 271:8, 10, 17, 23; 278:3; 279:11
drug--for 128:11
drug-by 68:22
drug-by-drug 129:13
drug-development 18:10; 258:22
drug-interaction 256:18
drug-only 133:2
drug-plus-lactose 133:3
drug-product 20:4
drug-uniformity 39:17
drugs 14:15, 21; 16:2; 18:13; 83:13, 25; 87:7, 17; 92:5; 129:11, 16; 136:12; 156:17; 182:25; 184:10, 11; 186:2, 9, 15; 187:20, 23; 188:25; 194:14, 20; 195:3; 210:5; 211:2; 212:4; 213:13; 240:4;

241:10, 14; 246:14, 17; 248:2, 3; 249:12; 250:17; 252:12; 254:11, 14; 257:5; 259:9; 262:5; 274:8, 19; 276:10
dry 132:13
dry-powder 13:16; 67:25; 84:5; 104:11; 107:7; 108:7, 18; 111:21; 136:12; 175:21
dry-power 107:24
ds 53:19, 20
DUC 173:10
Due 17:13; 188:15
Dugger 145:18, 24; 146:1
duration 23:18; 184:6, 10; 186:11, 24; 187:10; 188:10
during 15:23; 18:16; 130:18; 138:24; 158:9; 171:4; 172:8; 195:16; 235:2; 254:24; 255:2
dynamic 201:14
dynamics 240:8; 246:23; 252:19

E

E 58:4; 209:16
earlier 43:13; 77:14; 81:15; 92:17; 99:2; 107:17; 124:16; 181:2; 201:21; 214:13; 221:20; 225:12; 227:20; 229:5; 232:15; 245:13; 264:23; 269:11; 280:14
early 19:21, 23, 25; 20:1; 67:1; 141:4; 169:12; 194:12; 205:18; 208:21; 233:10
easier 53:14; 77:7; 93:22; 97:19; 126:18
easiest 196:14; 205:16; 242:8
easily 18:21; 147:9; 148:24; 210:11; 240:13; 248:10; 253:11; 267:22; 280:5
Easton 178:9
easy 52:4; 110:12; 149:7; 184:17; 186:24; 218:16; 245:11
eating 230:13
echo 69:13
edited 162:6
editor 221:14, 23; 222:10
educate 80:1
educated 254:7
effect 34:9; 46:12; 107:16; 113:14; 122:7, 8; 129:1; 137:15; 146:4; 150:16; 179:3, 16, 21, 22, 24; 180:4, 6, 15, 25; 181:1, 13; 182:1; 185:12; 186:11, 15; 187:24; 198:16; 200:9; 202:6; 210:23; 211:15;

216:18, 19; 226:7; 233:11; 234:4; 246:25; 249:23
effective 107:25; 134:6; 190:17, 19; 191:18, 23; 249:10
effects 121:21; 178:2, 3, 20; 180:9; 181:15, 25; 195:14, 21; 198:12; 211:4; 256:13
efficacious 74:10; 99:13, 18; 158:25; 277:20
efficacy 83:12; 86:20; 87:4; 88:4; 121:3, 22; 156:12; 157:13, 15; 183:8; 186:9; 187:18; 188:11; 189:4, 10; 190:3, 21, 24; 191:8, 24; 193:3, 18; 219:23; 232:13, 20; 249:15, 22; 257:24; 258:1; 259:19; 260:2; 261:20; 266:4, 12; 267:3, 6, 12, 17; 268:1, 6; 270:1; 271:3, 17; 272:2; 274:17; 277:8; 278:4
efficiency 109:7, 23; 113:3; 114:19; 204:17
efficient 110:4
effort 171:8
efforts 18:10
eight 72:15; 95:8; 187:11
eighth 72:16, 20
either 16:4; 32:1; 47:2; 70:5; 74:5; 86:14; 87:14; 90:21; 92:10, 20; 94:4; 96:7; 102:15; 108:10; 138:15; 210:4; 236:8; 260:10; 264:6; 273:14; 274:4, 13
elaborate 136:9
elaborated 115:5
elaboration 115:19
electric 227:14
elegant 241:7
element 104:24
elementary 67:9
elementary-school 67:8
elements 105:6; 117:17; 169:11; 170:14
eleven 138:24
eliminated 23:11
ellipse 93:19, 20; 94:5, 6; 96:7, 9
ellipses 96:5
else 11:16; 14:22; 46:3; 80:15; 125:3; 149:17; 219:25; 234:3; 280:12
elsewhere 135:10
embrace 115:25
emerged 150:4
emitted 22:13
emphasis 74:25; 128:9; 173:9, 10
emphasize 101:14; 134:19
emphasize--if 55:1

emphasized 233:18
empirical 123:14
employing 116:13
emulsions 146:19
encompass 219:11
encountered 262:20
encountering 265:2
encourage 125:1
encouraged 159:9; 239:16
encourages 19:13; 169:23
encouraging 10:12
end 20:11; 21:17, 19; 22:1, 14; 36:7; 39:14; 41:6, 15; 42:19; 44:12, 13; 47:10; 48:2, 2; 66:24; 69:21; 70:14; 73:6, 25; 74:6; 91:4; 94:19, 20; 97:5, 7, 8; 100:4; 103:4; 113:9; 119:15; 123:5; 132:20; 158:2; 160:5, 17; 166:25; 167:2; 170:5; 172:6, 11; 180:14; 181:21; 205:6; 207:18; 212:10; 231:20, 25; 236:13
endeavors 172:15
ended 243:12
ending 232:21
Endocrine 179:5
endorses 169:21
endpoint 183:11; 189:18; 190:22; 241:1; 250:9
endpoints 46:18; 87:13, 18; 88:11, 16; 183:8; 208:18, 19
ends 94:24; 95:13
engagement 48:23
enhance 55:3; 56:2
enlarged 55:5
enlighten 80:18
enormous 44:23; 68:18; 107:13, 20
enough 28:9, 10; 45:7; 80:16; 89:23; 158:5; 213:22; 238:18; 276:14; 278:20
enough--that 47:20
enrolled 188:16
enrollment 184:13; 188:15
enter 44:9; 195:15; 200:25
enters 206:22
entertain 230:21
entire 77:25; 174:13; 217:19
entirely 237:18
entities 255:4
entity 255:19
entrance 235:1
entry 133:10; 195:15; 206:4; 207:14
envelope 69:7

environment 183:19; 184:14; 186:22, 25
environmental 86:23; 186:25; 191:7
environmental-exposure 14:17
equal 207:15; 208:5, 6; 211:3; 214:20, 22; 216:18
equally 18:21; 109:7, 7; 250:6
equals 92:23; 93:18; 221:17
equation 85:25; 86:1, 2; 121:7; 199:24; 200:2
equipment 50:6, 7, 8; 264:3
equivalence 13:18; 14:5; 49:7, 19; 50:20; 56:17; 62:5; 64:18, 21; 83:19; 125:15, 15; 126:1; 127:21; 129:22; 131:19; 132:17, 18; 155:25; 193:17; 209:9, 10; 213:17; 240:12, 13; 242:11, 15; 245:11, 15, 24; 250:3; 253:5, 6, 10, 10; 266:10; 269:25; 270:25; 271:1
equivalency 211:8; 247:17; 249:25; 250:2
equivalent 13:20; 14:23; 126:25; 133:20, 22; 134:9, 12, 13, 23; 135:5; 138:9; 196:9; 209:11, 13, 14; 211:3, 5; 214:1, 4; 215:5, 14; 219:6, 13; 221:25; 222:4; 236:12; 240:14; 241:24; 245:10; 247:14, 15, 16; 249:15
equivalently 241:23
ergonomic 135:23
Eric 9:15; 10:5; 81:14
err 274:23
error 28:19, 20, 25; 29:8; 48:1; 185:22; 193:10
errors 265:1
es 54:5
escalating 235:12
escape 253:8
especially 69:16; 169:12; 256:8; 260:6; 263:5
essence 96:5; 214:23; 216:10
essential 155:24
essentially 17:20; 18:19; 49:11; 68:9; 70:8; 77:14; 111:19, 22; 119:10; 133:9, 10, 21; 181:17; 216:15; 217:17; 219:9; 226:6; 227:13; 248:14; 268:24; 269:1, 22
establish 13:18; 14:23; 15:20; 24:11; 43:6; 82:21; 86:19; 87:6; 156:5, 8; 157:16; 170:13; 191:14; 250:21; 268:4; 272:1
established 15:1; 83:1; 111:21; 112:3, 20; 165:20;

169:25; 214:17; 217:16;
250:9; 256:20; 262:12;
265:8; 274:20
establishing 24:8;
154:20; 156:4; 159:1, 8;
187:13; 218:4; 279:25
estimate 73:7; 157:5, 11,
13; 237:4, 5
estimating 219:5
et 90:19; 185:2
ethical 235:14
ethics 235:4
etiology 238:22
Europe 104:13, 17;
115:13, 23; 117:3; 159:2
European 26:16; 100:19;
104:14; 115:6
European-American
116:12
Europeans 115:8
evaluate 12:20; 27:14;
66:5; 163:10; 167:12;
169:1; 189:8
evaluated 45:25
evaluating 13:6; 37:19;
192:15
evaluation 25:14, 18;
66:11; 70:19; 74:15, 20;
104:11; 108:24; 109:15;
112:10; 127:16; 154:6;
155:12; 184:8, 25; 192:5;
276:13
evaluations 189:4
evaluator 190:11
Evans 161:5, 7, 9
even 6:18; 42:8; 56:10;
70:5; 71:22; 75:1; 79:11;
106:25; 133:14; 135:23;
141:19; 142:10, 13;
143:17; 148:5; 154:15, 22;
190:24; 193:17; 197:3;
210:12, 20; 213:20;
219:13; 226:22; 233:24;
234:23; 235:11; 239:4, 7;
244:22; 246:25; 250:6;
253:4; 255:15; 258:4;
259:10, 17; 263:7, 14;
265:22; 266:14; 268:7;
274:9, 16; 276:3; 277:19;
278:1, 9
evening 182:22
event 7:7; 148:21
eventual 46:19
everybody 10:4; 12:12;
13:25; 71:4; 101:22;
215:20; 222:14; 226:6;
236:16; 280:24
everybody-the 13:23
everyone 8:6; 65:21;
66:24; 180:14; 254:16
everyone's 215:23
evidence 47:18; 271:16
evident 28:5
evolving 156:23
EVP 9:20
ex 203:12

exact 201:17; 269:14
exactly 34:16; 36:25;
47:23; 109:14, 25; 115:16;
138:23; 147:21; 174:17;
178:13; 193:6; 211:6;
219:15; 228:23, 25;
265:23; 276:1, 21
exaggerating 123:10
examine 160:3, 18
example 38:25; 42:25;
43:2; 49:15; 57:1, 2, 9, 21;
58:24; 62:17; 69:2; 72:21;
73:2; 75:11; 91:4; 99:5;
102:3; 134:4; 161:25;
162:3, 10, 19; 165:10;
176:18; 205:22; 206:16;
207:3, 8, 12; 214:5;
218:19; 234:11; 242:16;
253:5, 19; 260:18; 264:14;
267:2; 270:3; 277:19;
278:18, 19
examples 15:9, 18;
33:21; 71:21; 72:4;
140:14; 147:12; 149:9;
196:24; 197:6; 266:5;
268:12; 270:12; 272:6
exceeding 218:24;
225:15
Excel 200:23
excellent 112:18
except 35:15; 58:12;
115:17; 211:19; 270:13
excess 93:6; 262:21
exchangeability 193:22;
194:3
exchangeable 193:3
excipient 169:2, 17
excipients 83:21; 168:7,
10, 14, 20; 169:19, 23;
175:18; 176:1, 6, 10; 279:4
exciting 181:3
exclude 7:10
excluding 73:11
exclusion 7:11
excreted 272:12
excretion 272:4
exercise 90:20; 236:1
exercise-induced
228:16; 232:7, 24; 233:12
exhaled 15:11; 232:8;
233:1
exist 46:17; 169:17;
212:6; 247:5
existing 49:16; 68:10;
75:15
exit 194:12
expand 46:9; 47:7
expect 113:2; 150:4;
208:22; 217:5; 278:13
expectation 130:14
expectations 170:14
expected 10:11; 38:23;
53:11; 151:4; 200:18;
201:3; 216:1; 256:16;
258:15

expecting 42:17; 127:8
expedite 18:12
expensive 113:16
experience 40:20;
159:21; 223:13, 13, 15;
278:23; 279:11
experienced 223:14;
275:19
experiences 18:15
experiment 207:6
experimental 103:10;
115:3
experimentation 113:17
experiments 203:4
expert 122:19
expertise 6:24
explain 7:16
explanation 24:2, 7;
89:11; 108:21
explicitly 36:15; 52:6
explore 247:9
exposed 184:15
exposure 16:2; 83:15;
86:9, 12; 87:5, 8; 88:5;
138:12, 15; 156:11;
157:12, 17; 194:14, 19;
196:8, 10, 14, 19; 197:19,
22; 202:13, 25, 25; 208:11;
209:3, 5, 11; 211:3, 11, 14,
17; 254:10, 13, 25; 261:17;
262:5, 9; 273:20; 279:15,
25
exposure-unit 86:23
express 37:10; 151:25;
173:24; 200:1, 20; 202:25;
207:25
expressed 30:12;
193:20; 226:17; 259:7
expresses 192:20
expressing 25:22
extend 105:18
extended 159:8
extending 117:21
extends 58:9
extensive 168:12; 170:4;
176:3; 235:6; 278:21
extensively 168:9
extent 80:9; 151:25;
189:1; 196:10
extra 44:3
extract 164:19
Extractable 164:6;
165:12
extractables 164:1, 11,
16; 165:7, 16, 21; 166:2;
167:13; 168:20; 172:22;
173:1
extraction 149:11
Extractions 164:3
extrapolate 247:17
extremely 166:11; 219:3;
266:10; 278:7

F

f2 55:12, 12, 14, 16;
58:25; 59:3, 4, 7, 8, 13, 15,
16, 17; 61:8; 64:5, 9;
84:25; 90:21; 92:4, 16, 21,
23; 93:5, 15, 18; 95:24;
97:4, 9, 24; 98:12, 15;
100:2; 101:21; 102:12;
121:10, 10; 122:1, 2, 2, 10;
128:1
f2-50 92:25; 93:21; 94:6,
10; 95:3, 7, 16; 96:21;
98:4, 16; 124:19
f2-50-you 98:12
face 120:22
faced 18:16
facilitate 18:11
facing 236:11
fact 31:3; 74:9; 75:6;
87:16; 107:17; 108:1, 19;
109:18; 110:1, 24; 113:24;
114:5; 116:17, 24; 117:25;
124:23; 127:17; 128:10;
132:19; 133:2; 148:6;
165:20; 178:17; 179:9;
211:20; 215:13; 219:11;
220:16; 221:1, 15; 222:8;
224:24; 226:9; 227:16;
233:17; 241:1; 278:7, 25;
279:12
factor 51:23; 55:12, 12;
69:3; 99:10; 100:8; 101:4;
122:2; 131:3; 148:10;
204:4, 17; 257:2; 260:14
factors 23:10, 19; 55:16;
99:9, 21; 101:22; 102:13,
21; 127:24; 128:1, 3, 6, 16;
133:1; 254:1
fail 96:7; 242:20
failure 55:16; 78:4; 221:9
fair 36:17; 263:9
fairly 264:17
fairness 7:13
fall 31:16; 34:22; 43:14;
47:17; 67:1; 80:4; 146:22;
185:7; 241:24
fallen 29:20, 22
falling 30:19
falls 31:13; 32:10; 33:11,
13; 34:11; 35:12; 40:14, 23
false 29:1; 32:1
false-negative 29:7
false-positive 28:22;
29:12, 14; 75:12
falsely 119:18; 244:18
familiar 55:11; 152:14;
183:17; 221:19
Fanning 184:1
far 66:1; 75:3; 78:12;
80:13; 90:15; 116:25;
117:15; 152:16; 186:13;
204:7; 208:12, 23; 231:16;
240:6; 241:5; 243:16;
244:5; 250:7

Farr 155:2, 4, 7
farthest 187:6
fashion 171:15; 181:13
fast 120:20; 134:4; 280:2
faster 107:6, 10; 120:14
fate 255:21
favor 143:10
favorite 227:6
FDA 7:8, 23; 9:5, 16; 10:6;
12:19; 16:22, 24; 19:17;
20:17; 25:21; 26:22; 27:3,
9; 28:3, 5; 32:8, 16; 34:3,
9, 9; 35:20; 37:18; 42:4;
45:20; 65:8; 78:22; 80:25;
81:4; 115:25; 131:2;
151:3, 24; 154:21; 160:24;
161:13; 176:3, 20, 25;
177:16; 178:22; 179:9, 12;
181:10; 183:4; 193:11;
217:22; 254:12, 15, 21
FDA's 27:24; 29:19;
81:21
far 129:14; 151:3
feasible 14:19; 240:3;
246:4; 279:25
feature 56:22
features 14:2; 17:24;
131:17; 195:22; 196:4
February 181:11
feedback 49:25
feeds 40:24
feel 49:21; 84:13; 124:17;
161:14, 20; 162:5; 165:7,
10; 166:10; 275:16
feeling 25:11; 46:2;
65:21; 66:19; 146:10
feels 182:21
FEF 227:14
FEV 217:12; 227:14;
233:9
FEV1 239:5, 5; 267:17
FEV1s 272:22
few 6:8, 9; 19:5; 28:19;
74:13; 100:19; 103:21;
119:7; 138:22; 151:20;
167:24; 178:12; 187:8;
194:16; 212:12; 228:15;
233:1; 266:9
FHA 214:5
field 28:21; 29:4; 236:16
Fieller's 218:5
fifteen 37:12; 174:21;
245:2
fifty 31:21
fifty-three 169:3
figure 62:23; 89:22;
109:22
figured 33:24
figures 111:11
figuring 215:14
file 45:15
filed 177:16
fill 97:14
final 40:2; 60:7; 131:15;

136:23; 166:23; 171:19;
178:1; 254:9
nalizing 144:13
nally 11:14; 16:1;
 101:17; 154:18; 162:8;
 167:9; 177:19; 188:5;
 238:5; 255:12
financial 7:9, 14
find 72:1; 125:13; 133:6;
 142:1; 149:3; 199:14;
 206:21; 208:20; 218:9;
 235:6; 242:3; 263:22;
 277:18
finding 242:5; 253:14
findings 155:16; 171:15
fine 29:10; 96:19; 98:19;
 111:19; 112:3; 114:6;
 266:14
fine-particle 112:19, 23;
 114:11; 115:20, 21; 118:7
finer 92:21
finish 36:23; 115:1
finished 11:1; 116:20;
 169:4
Finney 217:22; 218:5
firm 7:14; 13:19; 14:4;
 132:13, 19, 24; 135:2;
 219:22; 263:22
firms 7:8; 125:24
first 13:2, 4; 14:12, 19;
 16:11, 19; 17:2; 19:1, 20;
 26:6, 17, 19; 21:18; 22:20;
 24:22; 26:1, 14, 23; 27:2;
 7; 28:23; 31:2; 33:6, 9, 14;
 37:14, 20; 39:2, 9; 41:3, 5;
 42:18; 50:4; 52:17; 53:15;
 54:14, 14; 57:14, 22, 23;
 62:13; 63:12; 67:4; 72:8;
 74:4; 78:11, 22; 80:20;
 89:4; 96:16; 104:13;
 116:16; 117:13; 119:2, 3;
 121:9; 122:21; 123:4;
 125:11; 135:3; 138:11;
 144:1; 165:6; 168:24;
 170:8; 173:23; 175:24;
 182:16; 183:21; 199:12;
 203:25; 205:23; 209:7;
 213:16; 216:6; 217:8;
 219:20; 220:11; 231:4, 8;
 258:19; 261:16; 263:1;
 266:20; 268:13; 269:5
first-pass 195:16
Firstly 161:18; 166:1;
 172:3
fit 48:4; 75:15; 125:14
fits 69:24; 70:11; 199:25;
 249:25
five 94:1; 99:8; 100:22,
 23; 139:2; 143:6; 153:13,
 15; 174:20, 21; 179:20;
 199:9; 219:2
re-stage 110:1
fixing 71:14
flat 94:25; 95:13; 96:3;
 220:8, 11; 222:9, 18, 25;
 229:17; 234:6
flat-dose-response

222:24
flattens 95:3, 5
flawed 104:23; 116:6
Flemington 146:1
flexibility 101:19
flexible 48:10; 102:2
flights 16:14
flip 29:6
floor 77:10; 120:24
Florida 9:14; 195:5
flow 23:17; 106:23;
 107:20; 110:2, 15, 24;
 111:9; 112:22, 25; 113:2,
 6, 24; 114:12; 115:3;
 120:1, 10; 121:18; 132:23,
 23; 134:3, 17, 21; 135:15;
 136:1; 137:8, 12, 14, 23,
 23, 25; 138:4; 227:1, 15;
 233:9
flow-rate 135:10, 18
flows 221:5; 235:25;
 236:5
flunisolide 197:7; 202:3,
 8
Fluor 175:12, 15
Fluorides 175:9
fluticasone 196:25;
 197:6, 15; 199:1, 6;
 201:22; 205:22; 207:4;
 264:23; 265:5; 267:4, 15;
 276:3, 4
Flynn 170:20, 22, 24;
 174:13, 16, 23; 175:2
Focus 9:22; 27:21; 73:22;
 138:10; 151:11, 22; 152:5,
 5; 158:21; 164:23; 168:9;
 195:8; 256:23
focused 278:7
focussing 26:10; 27:24;
 258:4; 266:13
follow 23:1; 154:9;
 203:15; 209:10; 211:14;
 237:21; 277:15
follow-up 44:20; 136:25
followed 23:5
following 6:16; 35:4;
 155:22; 157:3; 169:21;
 222:7; 226:4; 231:1
follows 168:18; 189:25
Food 9:2
foot 66:9
force 23:7, 8; 71:22
forces 42:10; 79:11
foreground 171:8; 174:6
form 27:17; 31:1, 7; 86:2;
 124:9; 141:9; 144:14, 18;
 162:6, 7; 182:14; 191:8;
 242:9; 260:20
formal 11:18
formally 170:9
formasin 253:24
format 160:6
formation 253:24
formed 153:16; 166:18

formerly 9:24
formoterol 264:14
forms 35:19; 38:24;
 40:12; 115:10; 144:15;
 156:20; 159:9; 161:19;
 163:14; 171:23; 172:20;
 258:13
formula 55:13; 59:4;
 105:4; 114:15
formulation 14:3; 17:25;
 83:18; 84:1; 130:13, 17;
 131:17; 132:1, 17; 149:11,
 21; 203:16; 254:2; 260:10;
 270:16; 278:17, 25; 279:3
formulation-dependent
 166:3
formulations 17:9;
 86:15; 132:7; 151:1;
 202:14, 17; 207:21;
 214:18; 220:25; 231:24;
 241:23; 242:23, 23;
 243:18; 258:25; 268:14,
 14; 271:12; 279:7
Forrester 277:13
forth 19:7; 23:8; 30:4, 21;
 159:6; 185:14
forthcoming 66:10;
 165:24
forties 216:22
forty 31:21
forward 11:11; 40:5, 9,
 11, 17; 123:2; 174:4;
 280:18
found 13:20; 153:17;
 179:22; 226:21; 241:16;
 269:6; 270:12
Founder 182:23
four 33:17; 37:7; 111:11;
 125:7; 139:4, 5; 141:11;
 151:20; 161:18; 164:23;
 165:2, 4; 167:11; 172:17,
 24, 25; 173:10, 18; 176:24;
 179:20; 196:6; 263:7;
 279:22
fourth 166:23; 208:9
fraction 91:20; 100:10,
 14, 21; 102:24; 204:3;
 206:10; 266:6, 15
fractions 99:15; 100:7;
 118:14
framer 132:10
frames 172:2
Frankly 273:3
free 162:3
Freedom 7:5
freezing 148:20
frequent 190:21; 191:25
frequently 23:6; 185:12;
 186:8; 187:17; 189:10;
 190:16; 197:20
frighten 80:6
front 69:16; 76:8; 155:20;
 263:1
fulfill 225:14
full 6:7; 16:7; 152:17;
 240:16; 241:10

full-scale 240:10; 277:12
full-time 8:3
fully 23:12; 117:3;
 211:25; 242:1
function 90:21; 92:19;
 93:4; 106:23; 107:3;
 135:19; 137:8; 224:24, 25
functionally 83:24;
 133:11
functioning 48:12
functions 219:2
fundamental 72:11
furoate 181:8, 14, 19, 21,
 24
further 39:16; 65:3;
 130:6; 135:21; 136:9;
 143:18; 152:1; 154:13;
 156:22; 162:5, 9; 163:7,
 23; 199:19; 224:12;
 226:23; 247:9; 277:15;
 280:23
Furthermore 82:17;
 83:24; 157:8; 196:2;
 204:16; 218:17; 223:15
future 12:9; 40:11; 57:6,
 7; 67:2; 78:7; 154:11;
 171:23; 172:19; 174:4

G

gain 66:5
GAMBERTON 118:4
game 248:1; 252:12;
 263:9
gamma 104:21; 105:3;
 107:1, 9; 109:2; 137:17;
 203:14; 259:5; 271:12
Ganderton 103:24;
 104:3; 117:9, 13; 118:19;
 120:8; 132:22; 137:10;
 221:12
Ganderton's 119:21;
 137:1
gasket 150:14, 18
gave 47:12; 87:1; 227:14
GDS 93:6
geared 123:11
gender 256:12
general 7:21; 28:22;
 69:22; 83:7; 134:12;
 153:14, 17; 159:23;
 161:18; 164:24; 169:14;
 181:6; 189:23; 213:12;
 223:25; 246:11; 255:3;
 258:5; 275:10
general-matters 6:20
generally 83:14; 88:8;
 137:16; 155:16; 169:11,
 15; 226:11; 249:3; 255:8;
 258:11
generate 136:1
generated 100:19;
 108:1; 135:16; 137:14
generating 107:25
generation 40:11;
 114:11; 154:14
Generic 87:16, 17;
 103:12; 135:2, 5, 6;
 136:12; 182:25; 192:10;
 213:17, 18; 215:10; 216:6;
 217:9; 225:6, 19; 255:15;
 263:21
genesis 17:3; 132:12
gentlemen 81:1; 155:5
geographic 188:9
geography 185:20
geometries 117:14
geometry 84:17; 162:23
Georgia 8:13
Germany 175:13
gets 45:3; 90:12; 95:2, 5;
 96:13; 98:14; 100:15;
 125:16; 128:5; 195:25;
 203:1; 204:23; 229:9;
 271:18
GI 195:15; 205:13, 15, 16;
 206:7; 252:16; 266:20
given 7:20; 15:18; 16:13;
 32:23; 33:21; 35:23; 36:6;
 63:24; 72:17; 108:10;
 109:6; 122:22; 140:19;
 173:17; 174:8; 176:17;
 214:21; 232:19; 236:11;
 253:2; 262:17; 264:14;
 267:4
given-we 66:8
gives 51:20, 21; 100:11;
 263:11
giving 33:7; 36:21; 71:21;
 89:6, 6; 226:5; 262:5
Gloria 8:11; 37:8
GMP 168:25
goal 49:6; 72:5, 6; 75:10;
 76:4; 123:6, 7; 141:17;
 196:11; 225:15; 236:14,
 15, 16, 16, 21
goalpost 138:14; 245:20,
 21, 23
goalposts 122:8; 209:17
goals 38:2; 236:22
god-given 122:10
goes 97:11, 18; 195:13;
 202:7; 205:3, 13; 210:21;
 234:2; 266:23; 277:23
going-of 116:10
gold 6:9; 177:21; 179:25
Good 6:3; 8:16; 10:9;
 16:25; 25:9; 28:9, 10;
 32:20; 33:12; 42:20;
 48:21; 65:15; 81:1; 89:2,
 22; 102:24; 112:18;
 115:11; 123:1, 20, 20;
 137:20; 142:7, 8; 143:10,
 19; 144:3; 151:15; 155:4;
 158:17; 161:7; 167:21;
 170:22; 178:5; 182:21, 22;
 186:5; 187:3; 194:22;
 197:20; 200:15; 206:25;
 209:8; 217:22; 221:12, 21;
 222:12; 223:12; 224:13;
 227:3, 4; 228:7; 239:21;
 242:15; 254:16; 262:1, 22;

263:12; 264:2; 265:24;
267:3; 268:17; 270:11;
276:4
Gordon 167:23
GORE 8:22, 22; 38:11;
39:13; 40:4; 68:24; 69:14;
77:24; 278:22; 280:13
graded 57:6
grail 225:24; 226:16;
238:3
gram 263:18
grand 238:1
grandfathered 43:19
granted 6:21
granulocytes 202:6, 7
graph 30:11
Graphically 57:12
grateful 155:8; 158:18
gratitude 173:24
great 17:8; 184:23; 190:6;
211:19; 226:25; 228:23;
229:10; 230:16; 239:24;
270:22; 273:13
greater 33:22; 109:9;
118:2; 184:24; 188:14;
225:25
greatest 66:18
greatly 110:22
grew 180:16, 17
ground 241:19
Group 9:22; 34:24; 49:9;
76:1; 100:19; 101:3, 25;
151:11, 22; 152:5, 5;
166:18; 170:20; 179:5, 6;
180:16, 17, 19, 19; 181:14,
23, 24; 186:19; 190:18;
199:5, 11; 200:20; 201:24;
207:9; 221:5; 223:24;
231:4
groups 81:23; 115:12;
151:9; 152:4, 16; 153:9;
173:23; 175:5; 180:23;
188:2; 192:4; 230:25
growth 178:1, 3, 20;
179:1, 4, 8; 180:3, 9, 15,
18, 25; 181:15, 23; 182:8;
198:11, 11; 272:21
growth-suppression
179:21, 22
growth-suppressive
179:16
GSD 90:19; 92:11, 12, 24;
93:2, 3, 14, 15, 23; 94:3, 4,
9; 96:8; 97:15, 20
GSD/MMAD 98:3
guess 27:25; 44:20;
46:18; 69:23; 71:16; 76:3;
89:10, 15, 19; 90:2, 9;
91:22; 101:12; 102:18, 22;
122:22; 135:7, 20; 236:17;
243:2, 11; 247:8; 253:12
guesses 254:7
guests 81:7
guidance 7:1; 12:6;
14:14; 17:3; 18:22; 19:5,
15, 24; 24:1, 2, 16, 21;

26:16; 72:10; 73:11, 14,
17; 81:21; 83:18; 84:13;
85:1, 10; 86:18; 123:23;
124:25; 131:1, 2, 5;
136:11; 137:4; 140:14, 20;
141:5, 24; 142:2; 144:8, 9,
24; 145:2, 13; 146:10, 15;
150:25; 152:18; 155:15;
156:1, 9, 17, 23; 157:9, 21;
161:22, 25; 162:20;
163:12; 170:10; 171:11;
175:20; 177:13, 17;
183:14; 243:18; 244:4;
250:15; 260:20; 262:10;
263:6; 268:21
guidance--the 263:6
guidances 11:12; 12:2;
17:14; 18:6, 10, 14, 19, 25;
19:7, 20; 25:16; 81:20;
82:2, 3, 9, 15, 17; 151:24;
152:13; 153:3, 18; 154:21;
156:21; 159:25; 160:24;
161:12; 162:5, 8; 163:20;
164:8; 168:5, 9, 11, 16;
171:20
guide 231:14
guideline 19:7; 66:17;
159:7; 169:22, 25; 170:9,
14; 173:4
guidelines 45:10; 76:23;
79:14; 152:2; 158:23;
159:1; 165:8, 19, 24;
169:16, 16; 170:16
guidepost 78:18
Guirag 9:4; 16:21; 26:3,
7, 18; 40:23; 46:21; 80:15;
119:8; 280:10
Guirag's 29:4
Gurthor 195:5
Gur 86:25
gut 66:19; 196:21
guys 124:4

H

Hahn 224:20
half 138:7; 180:10, 11;
181:18, 19; 216:20; 237:1
halt 124:10
hand 116:1; 138:5;
218:14; 223:1
handle 131:13; 211:23;
276:19; 277:23
handled 20:13; 43:20;
278:15
handling 236:18
handout 30:8; 145:22;
180:5, 22
hands 135:21; 189:3
Hanover 175:13
Hansen 167:18, 21, 23
happen 135:14; 246:24;
256:13; 276:2
happened 101:8; 119:13
happening 273:20

happens 35:18; 63:22;
91:17; 97:17; 100:13;
130:11; 135:21; 150:13
happy 28:9; 120:21;
213:9
hard 68:2; 104:7; 113:15;
121:2; 126:12; 131:21;
135:14; 174:5; 191:17;
202:24; 210:22; 219:24;
222:14; 239:2; 243:21;
247:4; 266:10
hard-pressed 241:6
harder 77:18
harmonization 115:23;
162:9, 17; 163:7
harmonized 158:23;
159:1
harmony 115:12
Harmut 209:23
Harmut's 247:11
Harris 151:18
HARRISON 9:9, 9; 45:20;
70:10; 79:2; 120:25;
122:13; 130:24; 131:9, 21;
137:24; 138:18; 197:9;
239:13; 261:23; 262:1;
275:9, 14, 18; 276:1;
279:11, 19; 280:2
Harry 146:1
Hartmut 194:11, 16
has--but 56:10
hat 96:4
HAUCK 9:6, 6; 25:4, 7, 9;
38:9; 39:13, 18; 40:13;
44:5, 24; 45:11; 46:4, 7,
13; 47:6, 9, 20; 49:1; 60:8;
65:9; 69:23; 78:25; 79:21;
122:20; 123:25; 144:3;
160:13; 172:15; 224:15;
228:23; 245:6; 246:6, 10,
15, 18; 247:4; 264:20
Hauck's 129:13
Hayward 155:8
Head 9:7; 79:1
healthy 88:8; 199:22;
256:9; 258:12
hear 26:22; 38:12; 48:6;
65:14, 14; 131:20; 246:6;
255:16; 280:9
heard 24:23; 37:3; 47:6;
78:13; 90:5; 121:5;
128:23; 130:4; 131:9, 11;
138:3; 178:15; 181:3;
208:9; 214:13; 231:10;
232:1; 246:4; 254:18;
255:6
hearing 85:4; 120:6;
122:12; 140:6; 147:1;
245:12; 278:2
heaven's 229:24
height 181:19
held 19:22
Helmut 9:12
help 18:10; 30:3, 21; 41:2;
46:15; 49:1; 67:19; 70:8;
135:3; 136:24; 170:13;

172:15; 183:3; 195:2;
246:1; 260:14; 263:10;
264:4
helpful 40:4, 6, 15;
127:20; 136:22; 163:19;
239:23; 258:24
helping 123:1; 273:21
helps 257:22
hence 99:17; 221:7
hepatic-impairment
256:14
here--that 66:9
here--this 91:4
herself 8:6
hesitating 251:1
HFA 219:6; 221:3; 222:5;
226:2
HFA134a 176:14; 177:5
HFA227 175:16; 176:14;
177:6
HFAs 176:11
HFT 218:23
hierarchy 241:15
high 18:13; 22:23; 23:3;
34:1; 42:25; 62:20; 63:14,
15, 18, 19; 66:9; 99:15;
108:2; 132:23; 149:10;
171:5; 186:1, 14; 188:3,
13; 191:9; 192:24; 195:20;
196:1, 2; 208:14; 224:6;
231:20; 249:23; 269:9, 18;
272:14
high-quality 171:21
higher 33:24, 24; 99:15;
113:22; 114:6; 190:20;
202:2; 233:12; 264:21;
267:23; 269:21; 279:17,
18
highest 249:17, 19;
267:22
highlight 158:4
highlighted 172:5;
177:22
Highly 8:8; 65:25;
113:10; 123:17; 228:17;
272:11; 273:3
himself 8:6
histamine 217:11;
233:14
history 77:8, 23; 215:9,
22, 22
Ho 224:20
Hochhaus 195:5
hold 38:13
holding 173:24; 237:15
holds 212:1
holes 125:13; 126:5
holy 225:24; 226:16;
238:2
home 227:13; 281:1
homogenous 147:2, 8,
18; 148:7
honest 90:5
hope 16:8; 104:4; 117:2;
160:25; 163:21; 164:18,

20; 183:4; 203:19; 208:20;
215:21
hopefully 16:11; 118:16;
136:13; 217:5; 277:25
horror 215:23
horror--Wally 215:21
horse 132:8
hot 230:21; 244:23
hour 267:5
hours 187:11; 199:10;
201:3
HP 180:23
HPA 198:8, 12, 14
HPI 179:24, 25; 180:6;
181:1, 15; 182:1
huge 102:8; 280:16
human 156:11; 203:9;
210:16
humble 218:21
hundreds 171:8; 174:7;
219:1; 222:23; 230:11
hurt 234:8
HVA134a 175:16
hybrid 204:12
hypotheses 27:19
hypothesis 27:22; 30:25;
31:1, 3; 34:4; 159:22;
225:6; 236:20

I

ICA 76:23
ice 148:25
ICH 76:23; 159:2, 6, 6, 11;
160:24; 162:11; 166:15
iconoclastic 229:18
ICS 231:6, 9; 239:25
idea 29:19; 30:11; 78:16;
89:25; 95:24; 128:25;
142:20; 226:25; 227:5;
238:5; 263:12
idealistic 66:14
identical 245:1; 268:22;
270:13
identically 32:14
identified 38:2; 161:13,
17; 162:14; 164:22;
165:19; 233:10
identify 71:2; 175:24;
198:15; 208:19; 235:2
identifying 134:21
II 32:18; 176:3
IIIF(1) 142:1
IIIG 142:1
imagine 54:9; 240:23
imaging 247:24
impact 23:9; 45:8
impactor 13:5; 50:10;
84:25; 88:25; 89:8, 12;
90:5; 95:1; 99:14; 115:19;
116:13, 17; 119:4, 23, 25;
121:16; 129:18; 279:2
impactor--a 91:5

impactor--the 95:14
impactors 106:9; 116:13; 178:24
impacts 120:3
imperfect 110:8
impinger 110:1
impinges 149:15
implemented 169:12
implication 69:15, 21; 91:6; 127:1; 228:14
implications 120:18
implies 119:22; 184:7
implore 115:24
imply 119:24; 211:4; 274:18
importance 55:25; 99:3; 115:11; 117:11; 118:2; 164:10; 233:19
important 18:12; 19:6; 26:14, 21; 65:19; 79:12; 80:1, 6; 99:12; 100:4; 103:3; 104:22; 116:19; 117:4, 14, 17; 120:8; 127:10; 131:24; 132:3, 7; 135:22; 137:23; 138:10; 152:23; 159:15; 166:9, 11; 197:25; 201:1; 204:4, 16, 17; 213:22; 214:8; 220:1; 223:5, 6; 227:16, 23; 235:19; 237:25; 238:8; 250:1; 253:20; 256:15; 277:2; 263:2, 23; 271:19; 274:5
importantly 23:12; 171:14; 181:25
impose 111:6, 8
imposes 262:18
imposing 102:21
impossible 177:9; 242:13; 276:25
impractical 80:12
imprecise 104:25
impression 71:16
improve 191:12; 202:12; 205:5
improved 112:17; 196:17; 204:20
improvement 169:10; 192:22, 23
improvements 197:3
improving 77:19, 22; 169:9; 226:8
impurities 162:11; 176:24; 177:1, 12
impurity 176:16, 16, 17
impurity-by-impurity 177:4
in--but 255:15
inactivation 195:16
inactive 83:19; 188:19; 198:24
inches 140:4
incidence 186:1
inclined 68:21
include 146:11; 167:4;

270:25
included 87:24; 155:25; 177:19
includes 122:3; 135:19; 154:13; 160:12
including 57:5; 122:5; 152:20; 154:1; 176:7; 215:17
incoming 142:4
incorporated 23:25
incorporates 241:21
incorporation 138:4
increase 42:20; 108:16; 204:18; 279:13, 21
increased 65:1; 108:16; 269:16; 273:19
increases 274:1
increasing 192:3; 265:17
incur 44:3
indebted 111:17
Indeed 157:21
independent 56:24
independently 93:9; 224:25
index 55:6
indicate 54:18; 81:22; 86:24; 135:4; 162:20
indicated 39:14; 82:14; 84:9; 85:9
indicates 19:11; 24:20; 55:23; 219:11
indicating 275:16
indication 66:22; 250:23
indications 15:2; 250:10
indirect 203:3, 18
indirectly 211:10
individual 12:18; 24:16; 43:3, 6, 8; 52:8; 53:2; 55:19; 56:22, 23; 58:1, 6; 113:14; 133:24; 162:7; 223:3; 229:7; 232:18; 279:1
individuals 81:24; 153:24; 154:3; 265:7, 20
induction 115:18
indulgence 104:12
industrial 116:22
industry 7:19; 14:22; 41:25; 42:10, 13, 14; 69:21; 152:1; 153:23; 154:1, 18; 158:23; 161:14; 166:19; 168:3; 170:3, 8; 171:22; 175:20; 176:10; 261:25; 262:5
industry-wide 169:24
inertia 106:5
inertial 106:2; 112:4; 120:9, 17
inexpensive 186:20
infancy 241:3
inference 27:3
inferences 250:3
inferior 198:4
infinity 59:19

inflammation 233:3; 244:14
influence 107:20; 138:4; 185:21
influences 191:3
inform 157:25
Information 7:6; 11:10; 17:3; 18:20; 19:9; 38:12; 67:19, 20, 22; 75:14, 20; 80:6, 16; 84:20; 86:2; 113:16; 155:12; 157:2; 159:16; 161:1; 164:13; 169:3; 171:17, 20; 179:2; 186:6; 187:14; 200:24; 201:14, 14; 202:13; 209:4; 239:22; 253:21; 274:22; 280:17
informative 182:13
informing 150:6
Ingleheim 167:23
ingredient 166:16; 279:5
ingredients 83:19
Inhalanda 115:8
inhalation 12:7; 17:8, 17, 21; 18:1; 19:10; 82:6; 87:12; 88:5; 117:10; 134:4, 5; 146:12, 23; 151:11, 22; 152:5, 7; 156:2, 10; 164:12; 175:16; 176:4; 195:10; 197:8; 207:5; 208:3, 4; 221:17, 17; 222:5; 254:22; 255:5; 256:21; 258:19; 259:16; 260:19; 261:3; 262:18, 22; 265:19; 267:15; 268:17; 270:11; 280:5
inhalation-device 168:6
inhalations 222:4; 268:16
inhalative 200:8
inhalator 110:19
inhale 131:25; 205:12; 265:23
inhaled 7:1; 10:23; 12:3, 16; 15:7, 17, 21; 16:5; 37:16; 38:19; 72:13; 75:24; 81:3; 82:6; 97:11; 136:11; 152:2; 155:18; 156:19; 159:5, 9; 179:13, 18; 180:1; 195:8, 22; 197:4; 198:9; 200:17; 209:6; 210:5; 212:17; 213:2, 5, 13, 18; 214:14; 215:12; 216:6; 218:13, 15, 22; 220:3, 7; 222:14, 17; 223:2, 19; 224:4; 226:12; 229:15; 230:2; 231:2, 5, 17; 234:14; 235:6, 12; 238:12; 239:10; 248:2, 3; 249:13; 252:12; 258:4, 5; 261:11; 267:18, 23; 276:10, 15; 277:1, 3, 9; 278:3
inhaled-steroid 229:2
inhaler 67:25, 25; 84:5, 5; 107:8; 108:8, 8, 18; 110:5; 115:10; 132:14; 175:21, 21; 214:5

inhalers 13:17; 17:15; 84:12; 107:25; 111:21; 132:16; 136:12; 162:14; 163:13; 215:10, 15; 217:4; 221:24
inhalers--I 104:11
inhaling 211:18
inherent 242:16
inhibit 275:24
inhibits 176:10
initial 22:10; 160:5, 17; 172:11, 14; 215:11
initiated 149:6; 160:2, 16
initiative 17:14; 169:24
inner 24:18
innovating 130:10
innovation 244:8
innovative 133:12; 242:6; 255:16; 277:19
innovator 89:17; 103:12; 213:18; 214:7; 215:18; 225:7; 242:5, 13; 243:11, 23; 244:10
input 136:5, 6; 231:7; 255:13; 274:15; 281:1
insensitivity 189:18
inside 93:20; 94:6; 96:9; 98:6; 236:21
inspiration 106:13; 107:3, 6, 11, 16, 19, 21, 25
inspirational 114:12; 117:22
inspirations 120:20
inspiratory 105:22; 110:15, 24; 111:8; 134:3
inspire 110:25
inspired 118:14
inspiring 113:23
instance 128:7, 11; 133:3; 134:18; 147:16; 148:16; 272:10
instances 42:8; 161:24
instead 34:17; 55:20; 59:1; 140:8; 167:1; 183:12; 216:14; 217:25
institutional 235:8
instructions 134:8, 20
instrument 95:12; 121:17, 19
insufficient 238:1
insure 20:3; 167:3
integrity 149:16
intelligent 67:11; 118:13
intended 14:15; 135:5; 137:2; 146:5; 176:4; 214:1; 248:2, 3; 256:22; 257:15; 261:11
intending 27:3, 23
intent 38:13; 73:13; 135:8; 162:1; 163:13
intention 132:21, 25; 137:6
inter 20:7
inter-batch 20:12; 41:10

inter-container 20:17
inter-unit 20:7
interact 71:1
interactions 256:16
interactive 173:14
interchangeable 133:22; 262:10
Interest 6:2, 14, 17; 7:9, 13; 8:1; 10:13; 16:10; 18:8; 79:17; 89:21; 151:25; 165:6, 14
interested 15:22; 18:5, 22; 33:25; 56:5, 7; 57:18; 120:6; 128:17, 22; 196:22; 213:11
interesting 101:2; 110:8; 116:21; 118:10; 128:4; 130:2; 179:22; 241:7; 244:11; 254:6; 265:11
interests 6:22
interim 28:8
interject 237:8
intermediate 241:19
International 8:18; 151:12, 23; 152:9; 162:10; 169:18
internationally 158:23
Internet 81:21
internist 9:24
interpatient 229:10
interpret 119:18; 204:14; 212:2, 8; 266:17
interpretation 189:5; 190:25; 215:22
interpretive 120:5
intersubject 264:9
interval 29:18, 18, 20, 22; 30:4, 16, 18; 32:10, 13; 33:11, 14, 15; 34:11, 15, 22; 35:5, 6, 11, 12, 12, 13; 40:25, 25; 41:1; 46:15, 22; 47:9, 14, 14; 53:4; 61:13, 20; 63:8; 193:13; 217:15, 19; 218:5; 219:8, 10; 237:5
intervals 34:25; 35:2, 2, 16, 18; 36:3, 24; 84:6; 193:19; 236:21; 269:7
intervals--first 35:1
into 23:25; 32:3; 36:5; 40:24; 43:14; 44:9, 16; 49:11; 50:22; 52:13; 53:3; 55:1, 5, 13; 57:4; 58:8; 60:1; 69:3, 9; 71:25; 75:16; 76:16; 83:13; 88:19; 96:13, 18; 99:12; 100:9, 15; 107:5, 10; 112:9; 115:18; 116:15; 117:3; 118:14; 121:13; 122:15; 125:10, 14, 15; 126:4, 13; 132:19; 133:5, 10; 135:25; 138:21; 142:14, 15; 145:12; 146:4, 22; 147:10, 13, 18; 150:8; 159:1; 160:8, 21; 162:7; 167:1, 7; 182:4; 195:13, 21; 196:6; 199:3; 200:17; 201:14; 203:6; 204:2, 19, 23;

212:18; 224:14; 225:22;
230:1, 24; 234:10; 235:7;
236:14; 239:4; 244:23;
249:4; 252:5, 13; 254:9;
257:17; 263:18; 266:22;
271:18; 274:15; 280:20
intra 21:22; 41:17
intra-batch 20:8
intra-container 21:16;
41:4
intra-unit 20:10
intranasal 179:7, 13, 23;
180:5, 9; 187:23; 188:25;
190:2, 16; 191:15; 192:11
intranasally 253:7
intrasubject 264:9
intravenous 200:7;
207:1, 2; 208:2, 3
intrigued 119:21; 233:5
introduce 8:1, 6
introduced 112:9
introducing 203:17
introduction 10:6, 8;
16:18; 104:4
introductions 6:15
intuitive 56:14; 193:2
intuitively 54:14; 68:16
inverted 92:18; 96:3;
150:17
investigate 160:10
investigated 265:14
investigating 249:6
investigation 17:22;
101:12
investigator 185:22
investigators--so
185:19
investing 71:25
invite 37:9; 103:18;
140:7; 230:21
invited 81:7
inviting 10:5; 89:5; 183:2
involve 7:7
involved 81:20, 23;
147:17; 152:4; 153:24;
178:10; 179:2; 182:24;
218:25; 239:18
involvement 7:10, 14
involves 184:6
involving 135:1; 153:8;
180:5
Iowa 47:5
IPAC 9:10; 151:12;
152:17; 153:3, 7; 171:12
IPAC/ITFG 154:19
IPACT 176:3; 177:21
IPEC 169:18, 22
ipratropium 272:10
irrelevant 196:20; 244:18
is--you 263:7
isolation 70:22
isopropanol 149:19
issuance 152:18

issue 10:22; 12:6; 28:4;
43:18; 44:11; 52:9; 72:11;
73:8; 74:12, 21, 22; 82:2;
17; 86:12; 112:22; 117:14;
123:3, 9; 128:5, 19, 21;
130:19, 20; 133:14;
136:13; 141:21; 142:6;
145:18; 167:13, 17;
173:11; 178:6; 179:17, 18;
195:16; 198:9; 202:16;
203:10; 205:9; 213:12, 17;
214:12, 15; 215:2, 8;
219:18; 227:23; 230:18;
233:21; 235:17, 19;
246:11; 248:12, 23, 25;
251:15; 263:4; 264:5
issued 12:8; 19:24
issues 6:24; 7:23; 11:9;
23; 12:2; 18:15; 20:5;
31:16, 17; 74:4; 80:25;
81:5, 13, 14; 125:5, 15;
126:7; 128:15; 135:1;
136:15; 152:19, 23;
153:19; 158:7; 163:21;
168:4; 173:8, 10, 20;
175:6, 7; 195:2; 210:25;
212:6; 231:17; 248:6;
255:9; 256:1; 257:14, 24
it--it 272:14
it--of 228:7
Italian 110:20
Item 32:15
ITFG 151:11; 152:17;
153:3, 9; 171:12
ITFG/IPAC 78:1; 151:14;
153:6; 161:6; 167:25;
170:21; 171:1, 17; 173:13;
174:1, 8
IV 142:1; 207:5
Iwanted 47:6
Izabela 182:22

J

jackets 84:21
Jai 86:25
James 9:23; 37:8; 234:22
Japan 159:2
Japanese 32:7
Jefferson 9:7; 25:22
Jewish 9:17
Jim 78:18; 81:10
job 8:3; 32:17; 89:6;
101:24
John 233:10
joint 179:5
jointly 195:4
journey 281:1
JP 27:10; 34:24
judge 103:13; 210:23
judged 92:25; 93:21;
94:7, 12
judgement 223:12, 13
judgment 106:7
July 160:5, 17; 172:11;

179:6
jump 57:6; 144:6
June 19:23, 24; 76:21;
81:22; 153:7; 158:2;
172:6; 184:1
justification 78:8; 79:7;
8; 141:5
justified 78:11; 159:17;
161:15; 226:3
justify 129:12, 21

K

Kaushik 164:4
keep 45:11; 50:1; 107:14;
125:8; 138:1; 150:7;
195:23; 198:19; 203:24;
204:16; 223:22; 231:3;
244:18
Keeping 165:25; 198:23
Ken 175:8
key 123:3; 158:22, 23;
161:19; 168:4; 170:13;
171:10; 172:18; 177:22;
245:7; 256:1; 274:18
kick 236:16
kilopascal 111:11
kilopascals 111:7
kind 10:15; 26:1; 28:16;
33:7; 35:14; 38:3; 46:11;
50:23; 64:2; 70:21; 71:10;
77:3, 9, 21; 78:18, 21;
80:10; 119:20; 120:7;
122:15; 123:3, 6, 14;
124:2, 3, 3, 14; 125:21, 23;
126:4, 5, 7, 8, 10, 11, 12,
17; 135:25; 166:4; 192:6;
194:7; 211:13; 218:14;
224:13; 232:11, 17, 20;
233:2, 5; 236:8, 13, 25;
237:13; 238:11, 11;
239:10; 245:12; 248:10;
249:9, 11, 21, 24; 251:19;
276:17; 278:3, 9; 279:9
kindly 109:15
kinds 72:15; 78:5; 147:3;
256:16; 257:7
kinetic 201:14; 207:3, 6;
264:2
kinetics 200:8; 209:3;
211:24
knew 248:19
knowing 248:8; 257:10;
260:1
knowledge 156:25;
237:19; 239:15
known 23:3; 148:6;
178:25; 183:24; 237:9;
247:12
knows 77:3; 214:9
KOS 10:2

L

lab 264:4
lab-to-lab 259:8
label 203:15, 17; 222:21;
256:12
labeled 20:24; 21:1, 3, 4,
6, 12, 14, 25; 27:13; 30:13;
20; 31:13; 32:13; 242:5;
249:19; 259:9
labeling 135:1; 150:6;
178:23; 179:7, 10; 242:2;
246:1
Laboratories 151:19;
161:10
laboratory 217:7;
271:22; 274:3
labs 100:22, 23
lack 43:24; 185:17;
188:24; 189:25; 190:3;
220:2
ladies 81:1; 155:5
LAGANIERE 8:16, 17;
46:4, 9; 279:10, 24
LANGANIERE 68:11
language 28:17, 18;
32:5, 15; 161:24; 165:10
large 44:1, 13; 47:2; 55:2,
5, 24; 56:1, 2; 58:21;
60:18, 20, 22, 22; 63:23;
64:14, 14; 154:21; 189:18;
205:20; 213:22; 264:8, 9
Largely 26:9; 162:21;
217:13
larger 36:20, 21, 25; 44:6,
8, 8; 55:5; 59:16, 18;
64:13; 95:20; 118:2;
142:18; 206:11
largest 62:1
Lars 109:12
laser-diffraction 140:21
last 18:18, 20; 25:1;
31:23; 34:2; 38:6; 43:14;
76:21; 81:22; 119:22;
127:23; 137:9; 142:17;
155:23; 171:4; 174:5;
192:9; 194:4; 220:2;
249:7; 261:23; 262:2;
274:15; 275:6; 277:17
lasting 223:24
Lastly 145:1; 173:2
late 16:12; 19:20
later 38:14; 53:14; 57:6;
79:1; 197:9
Latin 115:9
Laughter 8:10, 21; 79:1
launched 225:22
LC 263:17
LCEs 43:8
Leachable 164:6; 165:22
leachables 149:9, 11, 16,
18; 164:1, 3, 11, 17;
165:15, 17, 21; 166:3, 10;
167:13; 168:20; 172:22,

25
leaches 164:20
lead 36:20; 38:3; 155:21;
181:12; 221:11
lead-in 129:6
Leader 9:5
leading 115:17
leads 49:18; 108:3;
220:6; 222:7
leakage 148:11
leaning 76:13
leap 274:13
learn 78:6; 147:4
learned 192:2
least 30:19; 31:12; 33:10;
34:11; 35:7; 36:12; 44:15;
60:9; 67:20; 121:6;
128:18; 143:15; 185:7;
186:10; 214:8, 17; 215:22;
216:7, 11; 217:5; 218:12;
219:2; 220:2; 221:2;
223:5, 25; 228:5; 229:9;
230:6; 232:22; 240:10;
241:20; 242:10; 245:16;
249:6; 252:10; 253:8;
265:12; 277:2
leave 27:20; 31:20; 65:8;
101:17; 117:6
led 216:3; 222:1
Lee 6:15; 7:25; 8:2; 9:23;
10:3; 11:6; 16:9, 17; 25:6;
37:2; 38:8, 10, 15; 42:17;
45:18; 46:3; 48:10, 16;
65:6, 12, 19; 73:22; 74:17;
77:1; 78:13; 79:17; 80:15;
19; 88:23; 103:6, 17;
117:6; 118:18, 20, 23;
120:23; 122:12; 123:23;
125:2; 126:20; 127:8, 11;
128:23; 129:25; 130:22;
131:13; 132:10; 133:17;
136:4, 7, 19, 23; 138:3, 16,
19; 139:1, 5; 140:7;
145:15, 18; 151:8; 155:1,
4; 158:12; 161:3; 163:25;
167:16; 170:18; 174:11,
15, 21, 25; 175:3; 177:25;
182:11; 194:10; 209:23;
210:16, 19; 212:9, 22;
230:20, 24; 237:8, 21;
238:17; 239:11, 21, 24;
240:18; 246:3, 7, 14, 16;
247:2, 8, 20; 249:7; 250:5,
24; 251:12, 17; 261:22;
275:1, 3; 276:7; 277:13;
279:8; 280:6, 10, 23
left 277:13
legal 7:17
legible 106:25
lengths 223:24
Les 9:9; 197:8
less 29:13; 56:7; 73:6;
74:21; 109:21; 114:17, 17;
117:15; 118:8; 142:23;
184:7, 14; 185:19; 186:16;
190:19; 205:8, 23; 228:21;
235:20; 248:7; 266:6

Lester 122:13; 131:8;
239:12; 275:1, 5, 6, 12
letters 221:14, 23; 222:9
 el 35:4; 36:6; 39:24;
 43:20; 52:16, 20, 22; 53:8;
 68:18; 80:9; 125:23;
 126:18; 129:5; 146:5;
 169:8; 171:5; 214:21;
 215:19; 216:11, 18;
 219:12; 225:8; 254:25
levels 39:25; 166:14;
196:22; 197:5; 200:9;
215:24; 232:14, 18, 19;
233:13; 249:18; 265:3, 6;
267:4, 10, 10, 11, 22;
268:7; 273:4, 25; 274:10
LI 9:23; 37:8; 38:18; 39:6;
74:23; 78:18; 79:10;
117:8; 118:1; 133:18;
134:15, 19; 135:3, 7;
231:15; 276:9; 277:7, 9;
278:5
liberal 270:20
lies 260:15
lieu 240:16
life 50:24; 84:15; 85:9;
130:11, 16, 18; 140:23;
148:8, 10; 193:6
light 127:10; 132:11;
276:8
likelihood 13:20; 273:6
likely 132:4; 214:22;
 1:2; 274:11; 276:1
limit 32:12; 49:19; 61:19;
24; 62:2, 3, 4, 5, 9; 64:18;
75:22; 94:25; 142:24;
238:25; 262:19; 263:16;
279:24
limitation 33:22; 51:4;
266:17; 268:2
limitations 75:21; 99:8;
262:18; 266:2; 271:15
limited 76:7; 82:18;
187:7, 14; 189:25; 190:3,
23; 195:7; 203:4, 18;
208:16; 218:18; 263:13
limiting 71:3
limits 6:6; 24:18; 62:2;
142:22; 143:11; 176:16;
177:4; 236:25
line 13:23; 74:1; 92:11;
98:8; 103:7; 122:22;
180:21; 181:11; 199:24;
200:11, 12, 12; 212:19;
244:13; 245:2; 263:2;
274:2
linear 273:18
lines 123:6; 132:22;
146:16; 175:24; 176:15;
179:10; 247:20
Lingual 145:23; 146:3,
 ?; 149:9
link 272:1
liquid 110:1; 148:22, 23
list 145:5; 185:4; 227:7;
274:19
listed 81:24; 85:21;

164:23; 177:1, 12; 263:20
listened 67:6
lists 84:13
literature 28:7; 32:20;
46:17; 129:7; 179:12;
201:9, 12; 204:11; 205:18;
219:22; 232:23; 249:12,
13; 265:13; 272:6; 275:19
liters 107:4, 8, 11;
109:19; 112:25; 113:1;
114:1, 3
little 10:10; 25:11; 28:18;
39:6; 46:10; 48:1; 64:12;
89:10; 94:16; 99:2, 11;
103:2; 105:18; 111:15;
119:9; 126:21; 131:23;
136:9; 185:9; 203:22;
218:3; 224:12; 232:12;
245:7; 252:5; 260:4;
264:21; 265:22; 271:10
live 264:19; 265:9
lively 117:1
liver 266:21
local 14:13, 15; 15:6;
16:4; 81:4; 82:4, 7; 83:11;
86:8; 102:4; 105:17;
138:12, 15; 145:8; 156:11;
157:11, 13, 14; 182:17, 19;
195:11, 20; 196:8, 10;
202:25, 25; 208:11; 209:5;
210:4, 12, 23; 211:11;
212:16; 213:2, 4; 231:5;
247:16; 256:22; 257:15,
24; 261:11; 268:5; 269:25;
271:2, 25; 274:17, 25
locally 14:20; 16:2;
82:18; 83:4, 10; 156:17;
157:15; 194:14, 20; 195:3;
240:4, 8; 246:5, 15; 16;
253:6; 254:10, 14; 257:23;
258:3; 260:25; 262:5
location 200:25
log 90:18; 93:16
log-normal 92:8, 9; 99:22
logic 211:14
logical 237:21
logistic 212:12
long 23:5; 43:19; 44:24;
104:6; 131:16; 149:24;
185:13; 195:23; 248:12;
279:21
long-term 187:24;
188:11
long-winded 123:19
longer 120:5; 184:10, 12;
188:9; 203:16
Loo-Riegelman 207:12
look 12:17; 27:7, 11; 31:6;
32:9, 16; 40:7, 9, 11;
42:10; 46:1; 48:2; 49:24;
51:9; 52:17, 19, 19, 21;
53:1; 54:15; 60:4, 4, 10;
61:24; 63:20; 68:14, 25;
69:1, 14; 70:21; 75:15;
76:14; 78:4; 79:6, 23; 89:7;
90:25; 92:4, 16; 93:16, 22;
97:19; 101:5, 13, 15;

102:3; 103:1, 11; 106:11,
19; 108:23; 109:4, 13;
111:4; 112:22; 121:11;
123:7; 127:19; 128:7, 16;
132:5; 135:24; 136:17;
137:24; 140:18; 141:24;
142:13, 15, 16; 144:8;
145:12; 174:4; 178:15, 21;
203:20, 22; 214:18;
215:13, 20; 216:15; 219:7;
224:12; 226:23; 230:17;
231:13; 232:20; 233:2, 8,
13; 235:15; 243:23; 244:8,
14; 252:25; 258:1; 262:10;
266:18; 267:20; 268:20;
270:24; 271:22; 272:14;
274:2, 23; 276:17
looked 26:17; 28:7;
42:11; 48:7; 68:22;
100:21; 127:10; 178:22;
179:3; 180:9; 181:13;
209:25; 217:11; 226:14,
15; 235:23; 236:5; 243:21;
265:16, 16, 19; 269:17;
270:10; 271:24
looking 13:5; 26:14;
49:11; 53:22; 66:8; 70:19;
76:9, 16; 77:4; 91:15; 95:8;
107:2; 108:6, 7; 109:10;
111:19; 114:10; 117:22;
127:15; 128:10; 137:17,
22; 143:9; 148:18; 160:21;
165:17, 25; 167:1, 7;
178:10; 185:9; 193:1;
204:10; 214:20; 215:16;
216:14; 228:16; 232:22;
233:6; 237:16, 22; 249:22;
263:16; 267:17; 270:3, 17;
271:6; 272:20; 273:7
looks 35:20; 62:23; 149:5
loose 36:19
looses 43:1
lose 245:4
loses 43:2
lost 43:10; 229:9
lot 35:20; 39:23; 45:21;
49:20; 50:25, 25; 60:5;
62:14; 63:3; 66:2, 2; 68:7,
17; 69:25; 70:12; 73:19;
81:11; 89:19; 94:13;
116:2; 117:16; 118:16;
119:2; 124:7; 128:8;
142:6; 143:4, 6, 8, 12, 14;
145:6; 164:20; 167:2;
178:15; 181:3; 186:4;
190:10; 208:18; 214:13;
227:4; 236:7; 243:15;
248:7; 252:9; 253:7;
259:6; 262:14; 263:11;
268:13; 269:2; 271:8;
272:13; 273:17, 21;
274:21; 278:23; 279:6
lot-to-lot 141:20
lots 48:1; 51:1; 60:4;
62:14; 63:1, 1; 65:10;
140:24; 141:19, 20; 142:5,
10, 21; 143:1, 7, 15, 23, 24
low 62:18, 21; 63:14, 15,
18, 19; 87:8; 99:10; 101:5;

132:23; 187:25; 191:10;
195:24; 233:11; 249:23;
252:16; 262:17; 263:1, 4;
269:8, 17; 272:15; 273:3, 6
low-resistance 114:4
lower 43:8; 62:20; 108:2;
113:9, 23; 146:6; 180:18;
185:24; 188:18; 197:3, 14;
231:25; 232:2, 3; 262:19;
263:16
lower-upper 61:18
lowest 30:8; 192:21;
226:19; 233:25; 249:10,
15, 16
Lubbock 48:24; 194:13
lung 91:3, 13, 21; 95:19;
96:23; 97:6, 16, 22; 98:6,
13, 16; 99:17; 100:10;
102:4, 5, 16; 106:4;
107:10; 109:4, 9, 23;
110:9; 111:21; 112:19;
116:18; 118:3; 121:17, 18;
157:5; 195:10, 23; 196:21;
203:2, 5, 6; 204:1, 19, 24;
205:1, 4, 9, 13; 206:1, 7,
10; 207:23; 208:4; 219:2;
240:9; 248:2, 3; 249:5;
252:13; 258:25; 271:21;
276:11
lung-deposition 99:6,
21; 108:25; 109:8
lung-function 108:9, 23
lungs 17:11; 94:15, 22;
95:22; 96:13, 19; 97:12;
99:12; 107:5; 213:20;
248:5; 266:21, 24; 271:18;
272:1
lymphocytes 201:20, 20

M

MacGREGOR 8:8, 8;
66:1; 128:24; 243:2;
244:20
machines 265:22
MAD 59:8, 10; 61:8
Magellan 151:18; 161:9
magically 204:8
magnitude 201:25
main 30:7; 89:11; 140:17
mainly 10:20; 89:18;
121:21
maintain 226:12
maintained 142:5
major 91:21; 98:18;
101:19; 114:20; 175:18;
198:8; 201:7; 230:25;
260:9; 278:17
majority 205:25
makes 41:12; 42:6;
45:21; 47:13; 78:2; 80:8;
94:22; 95:19; 112:5;
148:3; 201:15; 205:9;
211:18; 232:1; 239:2;
254:2
making 36:2, 4; 40:2;

42:8; 71:20; 72:10; 117:3;
120:17; 145:7; 166:20;
172:24; 215:4; 245:2;
274:12
making-in 244:22
Manager 175:12
maneuver 105:22;
134:22
manifestation 238:22
manipulation 203:17
manner 18:21; 74:10
manufacture 169:3, 5
manufactured 177:2
manufacturer 7:2;
143:5, 13; 145:6; 168:13;
175:15; 176:19
manufacturers 68:2;
152:11; 154:1; 169:17;
173:4
manufactures 177:13
manufacturing 12:4, 14;
16:23; 24:4; 33:12; 48:5;
69:5; 159:14; 175:22;
245:1
many 10:11; 17:23; 42:8,
8; 53:12; 54:20; 55:9;
66:20; 69:9; 81:24; 146:7,
12, 13; 148:19; 149:13;
150:21; 152:23; 154:5;
172:8; 174:12; 219:2;
230:1; 233:24; 245:4;
263:19; 266:19
March 19:22
marked 224:6
marker 210:10, 11;
233:3, 6; 238:6; 242:9
markers 15:19; 232:7;
237:22; 272:20
market 40:6; 43:20; 73:2,
3, 10; 133:10; 143:2;
159:18; 242:17, 20; 243:4,
23; 244:10, 19; 247:13
marketed 40:8; 110:20;
135:5; 175:17; 256:4
Marketing 175:9
marketplace 40:10
marry 100:13
Mary 184:1
Maryland 8:20
mass 38:4; 160:19;
263:17
mass-balance 255:22
massive 171:6
match 34:16; 59:25;
70:23; 77:11; 89:23; 98:1;
101:15; 135:13, 17, 18;
232:13
matched 270:13
matches 101:13
matching 60:2; 269:7
material 99:4; 100:10;
101:6; 109:20; 263:25;
278:25
materials 76:9; 120:16;
169:4