1 in dissolution, and these people will confidently assert
2 that if you measure tablet hardness and there's no change
3 in tablet hardness, the good Lord said, there can be no
4 change in dissolution. I've got news for them. That ain't
5 true. Sometimes you get a change in hardness and there
6 will be no change in dissolution. Other times you'll get a
7 change in dissolution and there's no change in hardness.
8 And then something else that has been referred
9 to, many pharmaceutical scientists implicitly or explicitly
10 assume that since the rate of change of a simple chemical
11 reaction is governed by the Arrhenius equation, there must
12 be some comparable equation for any physical stress. For
13 example, many people, in looking at the rate of aggregation
14 of proteins or the rate of coalescence of emulsions or the
15 rate of sedimentation, try applying very high g forces in
16 the implicit assumption that you can use an Arrhenius type
17 approach to predict stability from high g forces to normal
18 g forces.
19 I know of no experimental data, pragmatic,
20 which shows that it works. I know of no theoretical data
21 which would require that it should work. Perhaps these
22 companies who carry out this type of work really have got
23 an eye to the future, and when they market material to be
24 sold on Saturn or Jupiter, they will have already stress-
25 tested their products. But it is very dangerous to make

1 the assumption that the Arrhenius type relationship is
2 obeyed by physical types of equation similar to that which
3 can be used in chemical testing.
4 What we need is additional attention to
5 developing validated methods of physical testing so that
6 different units, different companies, different research
7 labs can come up with data that is comparable.
8 We need additional attention to the stability
9 of products in the channel of distribution. Now, many of
10 you know that USP and FDA quite properly have been giving
11 attention to this important matter. What is particularly
12 important for physical stability is that very often a
13 product will show no physical change when stored at
14 controlled room temperature, in other words, isothermal.
15 Now, I am aware, of course, that the USP
16 definition of controlled room temperature allows for
17 occasional excursions to 30 degrees. That's a lovely
18 expression, ladies and gentlemen. It makes me think that
19 the stability manager takes the little samples out for a
20 walk once in a month so they can benefit from the sunshine.
21 (Laughter.)
22 DR. RHODES: But seriously, I think there are
23 many physical instability problems which you don't see with
24 retained samples. You don't see it when you've had the
25 samples kept at controlled storage room temperature. It's

1 only when the products get out into the channel of
2 distribution and you get substantial vibrational or
3 temperature stress that these problems do develop.
4 I want to emphasize the point that has been
5 made earlier. As long as our approach is purely empirical
6 and we don't understand mechanisms, we will, to some extent
7 at least, be groping in the dark. We do need to identify
8 root causes. We need to recognize that many of these
9 problems show significant batch-to-batch variability. We
10 need to look at such factors as temperature stress. Also
11 water activity is probably extremely important.
12 We need to be more knowledgeable on drug-
13 excipient interactions. Now, certainly some of the
14 techniques we've used in pre-formulation are very helpful.
15 Some of them may have been excessive. For example, mixing
16 a drug on a one-to-one ratio with an excipient when you
17 know that in the tablet you're only going to have 1 percent
18 of each of those two components, that may be overkill.
19 But the point I'd like to make to you this
20 morning is this is an area that does require more
21 attention. It requires more standardization, and what I
22 would like to see is a triangle of forces. Many of you
23 will recall from physics 101 the triangle of forces, and
24 the triangle of forces I see here is academia, regulatory
25 agencies, and industry working together so that we can move

1 forward.

2 Thank you.

3 DR. LEE: Thank you very much.

4 Are there any questions?

5 (No response.)

6 DR. LEE: Thank you. A very clear

7 presentation.

8 Dr. Chen?

9 DR. CHEN: Good morning. I would like to spend

10 the next 10 to 15 minutes to give you an overview of our

11 current practice which mainly is the ICH Q1A or Q1A(R) as

12 it relates to physical stability of drug products.

13 ICH Q1A was originally published in the U.S. in

14 1994, and it was recently revised, expanded, and

15 republished just three weeks ago on November the 7th. It's

16 a guidance that provides recommendations on how to design

17 and conduct stability testing of new drug substances and

18 products, and it tells you how to assemble the core

19 stability data package, so to speak, to support the

20 approval of an original application for new drug products.

21 The kind of physical stability that has already

22 been mentioned by Dr. Rhodes are the appearance, particle

23 size, polymorphic forms as appropriate, dissolution as

24 applicable to the dosage form, and suspendability of

25 products that are to be constituted, and viscosity, for

1 example, homogeneity for semi-solids, and so on. What I
2 would like to do is give you an outline of how Q1A(R)
3 addressed these issues.
4 Q1A(R) starts by -- sort of the first and
5 foremost issue is the stress testing of drug substance.
6 It's by doing this one-time testing of typically one batch
7 of drug substance by subjecting it to very extreme
8 conditions that are above and beyond the so-called
9 accelerated conditions, which I'll touch on later. These
10 conditions are at elevated temperature, elevated humidity,
11 light, oxidation, extreme pH, i.e., acid and base,
12 hydrolysis.
13 The purpose of this kind of stress testing on
14 the drug substance is to get a handle on how the drug
15 substance would behave in these extreme conditions and also
16 a handle on what may be expected, in the worst scenario, of
17 how the drug product may behave. It also helps the
18 development of stability indicating methods.
19 Where the ICH Q1A(R) isn't very helpful is the
20 stress testing on drug product. It's sort of vague on what
21 the scope of the stress testing on a drug product should
22 be. It only refers to photostability, which is in turn
23 referred to another document under ICH auspices. That's
24 Q1B dealing with photostability. Other than that, there's
25 no detail.

1 So, I'm just going to jump over to the so-
2 called formal stability testing on drug products. There
3 are three basic elements that constitute the formal
4 stability study. Number one, the batches, the selection of
5 batches, the number, the type of batches. Number two, the
6 tests or test attributes or specifications, and number
7 three, the storage condition, and lastly the amount of data
8 that is considered acceptable to support the application.
9 In terms of batch selection, the Q1A(R) says
10 that a minimum of three batches, two of which should be of
11 pilot scale, and the third one can be smaller. These
12 batches should have the same formulation and packaged in
13 the same container/closure as proposed for marketing.
14 These batches should be made using a manufacturing process
15 that simulates the process to be used for commercial
16 batches. Lastly, the batches should meet the same
17 specifications as proposed for marketing. In other words,
18 under the Q1A(R) recommendation, the batches to be put on
19 stability to support the marketing approval do not have to
20 be production size batches, but they do have to represent
21 the to-be-marketed production batches.
22 The second feature of the formal stability
23 testing deals with the tests or attributes. Q1A(R) says
24 that stability of the product should be monitored for those
25 attributes that are susceptible to changes during storage

1 and are likely to influence the product's quality, safety,
2 and/or performance. These attributes encompass chemical,
3 physical, microbiological and biological attributes, as
4 well as functionality tests, for those products that
5 involve a delivery system.
6 But Q1A(R) does not address what exactly those
7 attributes are. Q3A/B does provide more guidance on how
8 you select or exclude impurities or degradants. Q6A
9 further expands on test attributes, including how to
10 establish acceptance criteria for degradants, impurities,
11 and physical attributes such as polymorphic form, particle
12 size, dissolution.
13 The third aspect of the formal stability
14 testing is the storage conditions and the amount of data.
15 For products that are intended for "room temperature"
16 storage, which is the most common situation, for products
17 that are now packaged in semi-permeable or impermeable
18 containers are as follows. For long-term, the temperature
19 should be controlled at 25 degrees C plus/minus 2, with
20 humidity control at 60 percent. There will be an
21 accelerated condition that is expected, and that is 40
22 degrees C and 75 percent RH.
23 If the product fails at that condition after 6
24 months, it's expected that the intermediate condition
25 testing is also carried out. This is to cover the upper

1 bound, as Dr. Rhodes indicated, that the USP controlled
2 room temperature allows excursion to 30 degrees. So,
3 should the product fail at 40 degrees after 6 months, then
4 demonstration of stability for 12 months at 30 degrees C is
5 expected.
6 In terms of the amount of data at the NDA
7 submission, for long-term testing, we expect 12 months from
8 an ongoing study. For accelerated, it's 6 months from a
9 6-month study. Intermediate would be 6 months from a
10 12-month study.
11 I hope I'm not plagiarizing the definition of
12 excursion. I don't know if my colleague, Carol Easter,
13 from Merck, working with me on the ICH expert working group
14 is here, but she has once defined excursion as a pleasant
15 trip.
16 (Laughter.)
17 DR. CHEN: So, we can complement Dr. Rhodes'
18 description of how one conducts excursion outside of the
19 normal controlled storage condition as a pleasant trip.
20 I would like to skip this one. This is
21 basically the other two conditions for the product that may
22 be intended for storage. These are low temperature,
23 including refrigerated and frozen products.
24 What I would like to draw your attention to is
25 two aspects of the so-called significant change, which I

1 mentioned two slides ago. There are five aspects under
2 this definition of significant change, which is sort of a
3 new concept introduced into this ICH document. It's mainly
4 a trigger for intermediate testing, for those products
5 intended for room temperature storage, but also has
6 ramification on extrapolation and so on.
7 Those criteria that have relevance to our
8 discussion today are the fourth and fifth bullets on the
9 slide, one of which is the failure to meet, generally
10 speaking, appearance, physical attributes, and
11 functionality test. By itself, though, we've often
12 considered that to be part of the physical attributes, is
13 dissolution, and the criteria for that to be judged as a
14 failure is failure to meet acceptance criteria for 12
15 units.
16 What is the consequence of significant change
17 according to Q1A? If significant change occurs at an
18 accelerated condition, then there's a need to conduct
19 intermediate testing, as I explained earlier. And
20 extrapolation of shelf-life beyond the real-time data range
21 may not be appropriate.
22 If significant change also occurs at
23 intermediate, then the applicant needs to consider one of
24 the following options. Perhaps there's a need to
25 reformulate. Perhaps there's a need to qualify higher

1 impurity level or degradant level, maybe a more protective
2 container/closure system. What I have neglected to include
3 on the slide is the consideration perhaps that the product
4 is not suitable for room temperature storage. Perhaps
5 refrigerated.
6 Q1A(R) further discusses how you evaluate your
7 stability data once they are collected. Among those is the
8 allowance for extrapolation of shelf-life beyond the real-
9 time data range, but that's predicated on no significant
10 change at accelerated and also that there's a condition
11 that you have either the relevant supportive data from
12 developmental batches that don't quite fit the primary
13 stability batch definition and/or statistical analysis.
14 But, again, as Dr. Rhodes pointed out earlier, most of the
15 physical properties, physical attributes, don't really lend
16 themselves to the assumption that it will follow the
17 Arrhenius equation, i.e., linear regression, which is the
18 type of analysis that industry and FDA typically resort to.
19 This kind of shelf-life, if approved, i.e., if
20 it's extended beyond the real-time data range, and/or if
21 the shelf-life is based on less than production size, then
22 the shelf-life approval is something we call tentative.
23 And Q1A(R) also recognizes that. It recommends that post-
24 approval, this kind of tentative shelf-life should be
25 confirmed with data from three full production sized

1 batches.

2 In the U.S., we also expect firms to put on at

3 least one batch annually on stability as further

4 confirmation monitoring.

5 Lastly, I'd just like to sum it up. If we

6 follow the Q1A(R) guidance, can we reasonably predict

7 shelf-life for all future batches? Well, we can look at

8 this question from two aspects.

9 One is that we are relying on accelerated

10 testing or less than full shelf-life long-term data to

11 grant shelf-life, and is that predictive in all cases or

12 for all attributes?

13 Secondly, we rely on oftentimes pilot batches

14 made not at the intended commercial site. Are those data

15 predictive of future production batch behavior? Well, I

16 think a lot of that would depend on a combination of

17 factors and probably not all factors apply in all cases.

18 But to top it all, I think it's the complexity

19 of the formulation and/or dosage form because that would

20 affect the reproducibility and perhaps the robustness of

21 the manufacturing process, which is what I list as the

22 second factor. The robustness of the manufacturing process

23 would have an impact on how successful you will be in

24 technology transfer and/or scale-up.

25 I think both Ajaz and Dr. Rhodes touched on the

1 sampling plan. How sound the sampling plan is may affect
2 the outcome of the stability testing results. You may
3 question how representative it is when you see the result.
4 Reproducibility of analytical procedure.
5 Certainly that will play a role in how reliable the data
6 are and how you project from pilot batches to future
7 batches.
8 And acceptance criteria need to be meaningful.
9 If it's too tight or too loose, well, certainly if it's too
10 tight, you run the risk of failing lots right from the
11 beginning, but if it's too loose, it doesn't really serve
12 the quality control purposes. So, from the regulatory
13 perspective, we need to consider that.
14 Lastly, the experience that the firm has with
15 the product based solely on the stability batches. This
16 obviously includes the number of batches that have been
17 made for the primary stability testing purposes as well as
18 developmental batches. Obviously, the more experience you
19 have, the more you can speak to the other factors. You
20 have more knowledge about the product as a whole and
21 various aspects of going into this product.
22 So, with that, I hope it will be helpful in our
23 discussion later and how they relate to the concerns that
24 Ajaz raised earlier. Thank you.
25 DR. LEE: Thank you very much.

1 Are there any questions for Dr. Chen before she
2 leaves the podium?
3 (No response.)
4 DR. LEE: Thank you.
5 Ajaz, would you like to --
6 DR. HUSSAIN: I had some questions on my last
7 slide, if we could put those back up again.
8 Vince, while that is happening, from Dr.
9 Rhodes' presentation, I think one aspect which I think adds
10 to the concerns that I have is physical attributes, how we
11 measure these attributes and what actually are we
12 measuring. There's a gap there.
13 Dr. Rhodes mentioned hardness. How do we
14 measure? We just put a tablet in the thing and it's the
15 crushing strength. It doesn't have the fundamental
16 attributes from a material properties perspective that we
17 really would need to understand what's happening from a
18 mechanistic basis. Tensile strength would be a better
19 approach. We don't measure tensile strength. It's the
20 hardness values.
21 But that points to the very fundamental aspect
22 of the method used to characterize that attribute.
23 Transdermal adhesives. How do we characterize? We don't
24 have good methods even to say that the system would
25 maintain its adhesiveness in different populations or in

1 different times and so forth.

2 I just wanted to point that out that I found

3 very interesting in Professor Rhodes' presentation.

4 The questions I wanted to pose to you in a very

5 broad way, as I said, we didn't get data and so forth to

6 present to you at this time, and there is difficulty in

7 getting that information to you. We have failure rates and

8 this and that, but we don't have any explanations.

9 So, one aspect that I would like you to

10 consider is should this topic be developed for a more

11 detailed discussion by ACPS. Is there a need for that? I

12 heard from Dr. Rhodes. I think he felt there was one. But

13 in order to do that, we really need to have some database,

14 some understanding of some mechanistic basis. I don't have

15 that data right now that I can bring to you for a very

16 rational discussion.

17 So, should FDA labs develop a research project

18 to elucidate certain mechanisms so at least we have some

19 examples?

20 The goal of that program would be essentially

21 to provide information on how to prevent stability

22 problems. My focus is prevention. We're doing extensive

23 work there. But there are still pockets of problems that

24 we see which need to be prevented. So, how do I push the

25 focus on the prevention mind set?

1 Especially, my concern comes from the
2 parenteral dosage form for one reason. I think I don't
3 want to be in a situation where I have to look at a
4 decision that there's a failure. Do we recall that
5 product? And if we recall it, do we take that product out
6 of the patient, which is already implanted? Things of that
7 nature. There's a potential for those questions to be
8 posed in the near future.
9 The aspect which I think I would like to add to
10 the parenteral dosage forms is we actually don't have good
11 dissolution test methods. If we look at the test methods
12 we use for dissolution for parenteral controlled-release
13 products, even liposomes, for example, we have in many
14 cases adopted what we have learned from oral tablets and
15 capsules. Those methods are getting translated into that
16 area. So, we lack fundamental methods that we would need
17 in that area.
18 But right now the initial next step is we have
19 a research unit in our Office of Testing and Research.
20 They have actually started collecting all the tools that we
21 need to establish physical characterization and so forth.
22 We participate in the Shelf-Life Extension Program to
23 maintain the national stockpile. We have a recall
24 database. I think a lot of those elements that we need to
25 identify problems and learn from those are happening. So,

1 I think we have an opportunity to actually start a research
2 project, and would that be the right thing to do at this
3 time would be my question to you.
4 Complex dosage forms. I had invited Diane
5 Burgess to spend her sabbatical, and she went through and
6 spent three months with us identifying some of the
7 problems. There are certain high risk issues in parenteral
8 controlled-release dosage forms that she identified for us.
9 So, this is sort of brewing. This will come
10 up, and how should I bring this back to you if you want
11 this back for discussion?
12 DR. LEE: Thank you very much.
13 Any response from the committee? I think Ajaz
14 wants us to work harder.
15 DR. BOEHLERT: Certainly for complex dosage
16 forms, sustained, controlled-release parenterals, there is
17 no guidance now in my understanding. And the companies
18 that are developing those products are pretty much
19 developing their own in-house methods based on some in
20 vivo/in vitro correlation. It would be helpful to have
21 some guidance in that area, because nothing exists now, to
22 ensure some consistency going forward. Right now everybody
23 is doing their own thing and I think a lot of these
24 products are fairly new. There aren't a lot of old-time
25 products.

1 When it comes to conventional products, I think
2 you talked about 22 recalls this year. Is that right?
3 DR. HUSSAIN: 22, right.
4 DR. BOEHLERT: That's not very many.
5 DR. HUSSAIN: No, it's not. It's a small
6 number.
7 DR. BOEHLERT: So, I'm wondering what the
8 problem is. I agree absolutely with Dr. Rhodes. There are
9 a lot of issues with physical stability, particularly
10 dissolution. The companies don't understand the mechanisms
11 very well, but guess what? Very often they're able to
12 produce a product that is safe and efficacious and does not
13 fail.
14 So, I think you need to outline, for me at
15 least, just what is the problem. 22 recalls out of all the
16 products that are on the market are not very many.
17 DR. HUSSAIN: No. As I stated, in many ways
18 the conventional tablets and capsules and conventional
19 dosage forms -- I think we have been able to solve the
20 problem. It's not a major issue. But there are lingering
21 problems in that area. For example, I mentioned
22 carbamazepine. Failure of dissolution is linked to
23 biofailure and seizures and so forth. That problem has
24 never gone away. We saw it for the first time in 20 years.
25 It's still coming back again and again. So, it continues.

1 And some of them are older products. There's
2 not much opportunity to change that, but there needs to be
3 some improvement.
4 The problem is this. I think the mind set that
5 is occurring is what we have learned from tablets and
6 capsules in oral gets translated into other dosage forms,
7 parenteral dosage forms. That's where the mind set is.
8 The problem with oral stability problems are small. The
9 total number of quality recalls we had last year was 243.
10 Compared to all the products out there, that's a very small
11 number. So, we're doing a good job from that perspective.
12 So, I agree with that.
13 But the basic process by which we are achieving
14 that is through testing, testing, testing. You saw Dr.
15 Chen's presentation. We have extensive testing. But as we
16 move towards the more complex, with liposomes and
17 parenterals and so forth, we cannot translate the same
18 system that we have learned from tablets and capsules to
19 these. That's the problem I'm trying to illustrate. We
20 have to start somewhere in terms of understanding the
21 mechanisms.
22 For liposomes, we had a discussion with you
23 some time ago. We still use dissolution testing for
24 liposomes. What does that mean? What will that tell us?
25 One aspect with Dr. Rhodes' presentation was

1 this. There is a possibility that unless we have good
2 methods, physical methods for measurement what we see as
3 not a problem right now may not always be correct. There
4 may be problems existing because our physical method may
5 not be even catching that.
6 DR. LEE: I would like to go off line and to
7 see whether or not Dr. DeLuca is still there. Pat, are you
8 with us?
9 DR. DeLUCA: Yes, I'm still here.
10 DR. LEE: Pat, you've been very patient. I
11 would to make sure you have a chance to participate before
12 something happens to you.
13 DR. DeLUCA: I think I've enjoyed the
14 presentations, I think certainly an area that we have been
15 devoting a lot of time to is the controlled-release
16 parenterals and directing a lot of attention to in vitro
17 release methods. As we get into looking at these long
18 term, prolonged formulations, depot formulations where
19 we're looking at even longer than 30 days, going out to 6
20 months and probably even longer, then we need to have
21 accelerated methods for quality control purposes for in
22 vitro release and in vivo performance to be able to, after
23 a batch is produced, test that and then within a short
24 period of time -- let's say, within a week -- to be able to
25 say, well, this is a reliable form for a 6-month dosage

1 form. So, I think there's a need there to come up with the
2 methods to allow this to take place.
3 We're working and looking at accelerated
4 methods and Arrhenius treatments and other mathematical
5 treatments to allow one to be able to predict this. So,
6 it's not from a stability standpoint for these forms, but
7 mainly for the release characteristics, release
8 performance, and then of course, the in vivo performance.
9 So, I think this is an area that certainly needs a lot of
10 attention.
11 DR. LEE: Thank you. Can you see us?
12 DR. DeLUCA: Yes.
13 DR. LEE: You can.
14 DR. DeLUCA: Yes. I can see you well.
15 DR. LEE: But we cannot see you.
16 DR. DeLUCA: No, you can't see me.
17 DR. LEE: Anyway, I think that Dr. Rhodes'
18 presentation was designed for you with that in mind.
19 Steve?
20 DR. BYRN: I'd like to go on with what Pat was
21 saying. Even with simple dosage forms based on what Chris
22 was saying with the potential failure of Arrhenius'
23 equation and so on, it's very difficult to make predictions
24 or do accelerated studies. So, a better understanding of
25 that would be of significant assistance. I think we know

1 more about, although there's always controversy even in
2 chemical degradation, physical changes, and the
3 predictability of accelerated methods is a major issue I
4 think that would be worth understanding more.
5 And then the second thing, just to continue
6 with Dr. Rhodes, in the experiences I've had consulting,
7 problems are much more widespread than would be reflected
8 by the number of recalls. I assume that people solve them
9 prior to getting on the market, is my understanding. But
10 it's not a well understood area, I don't believe.
11 DR. LEE: Let me interject here. Did I
12 understand you correctly that the definition of shelf-life
13 is mostly with respect to the chemical species?
14 DR. HUSSAIN: No. I think the shelf-life, as
15 we defined, with all attributes, entire specifications that
16 we would have. But I think what Professor Rhodes was
17 mentioning is I think the mind set tends to be, in some
18 areas, it's the potency only. But, no, our shelf-life
19 would be based on the entire --
20 DR. LEE: So, let met talk about something that
21 is very close to me. The ophthalmic area with their
22 suspensions and what if the particle size changes and
23 there's no sign of chemical instability. What do you do
24 with that?
25 DR. HUSSAIN: If there is a specification for

1 particle size, that would be part of the stability program.
2 Chi-wan can correct me if I'm wrong, but I think we would
3 go through the entire aspects of attributes which are
4 critical for that and be part of that shelf-life program.
5 If I may, there were several points made. One
6 was Professor DeLuca was mentioning about need for an
7 accelerated dissolution test. I wanted to just share with
8 you some information on that. That is a very significant
9 challenge for us right now. Some of the parenteral dosage
10 forms are designed for release over 6 months, a year, and
11 so forth, and the release is extremely slow. So, how do
12 you even establish a quality control tool? For a month you
13 are doing a dissolution test or 6 months before you can
14 release the product. There is a need to accelerate that
15 test.
16 And my concern was the methods being used to
17 accelerate. One example I'll give you is use a .1 normal
18 HCL as a dissolution media. It's actually happened.
19 That's one way of accelerating. The conditions for
20 accelerating the release is nowhere linked to mechanism.
21 So, what we have done is we have actually positioned a
22 research contract with Diane Burgess on that very issue,
23 more mechanistic basis for accelerating dissolution test
24 for quality control, which eventually will be linked to in
25 vivo performance. So, we are exploring that as a research

1 project right now.

2 That's what I was hoping to sort of mention to

3 you is when I get back, we'll have some data that we can

4 present to you in that regard.

5 But just to continue that thought, we have

6 conditions of tests for parenteral dosage forms with .1

7 normal HCL as a dissolution media. What will that tell me

8 in terms of shelf-life? What will that tell me in terms of

9 changes? I'm not sure. So, that's the underlying concern

10 that's throughout my presentation here, is yes, we have

11 tests which are measuring, but what are we measuring is the

12 underlying concern that I'm expressing.

13 DR. LEE: Yes. It seems to me that you are

14 just stressing the system in a different way. I think

15 we've been tied to using temperature as a way. There might

16 be others.

17 DR. DeLUCA: Yes. Just to add, I think we have

18 to be careful, when we're stressing, we're stressing it and

19 producing a chemical change that could affect the

20 stability. Or is one affecting a physical change and

21 trying to accelerate, whatever we're trying to accelerate,

22 if it's the stability testing or if it's release from a

23 prolonged-release form. I think that's another key issue.

24 You certainly can accelerate the release chemically, but

25 I'm not so sure that's a plausible way of going.

1 DR. LEE: So, Ajaz, I sense that you perceive
2 there's a gap and you'd like us to address that.
3 DR. HUSSAIN: Well, I perceive that as a gap.
4 I think the system is working fine, and I think we have a
5 good system. But if there are such gaps as I perceive, if
6 we don't fill those gaps, there is a potential for problems
7 that we'll face, and we will be in a reactive mode. And we
8 can prevent this from happening, especially for parenteral
9 controlled-release for long term and so forth. In my
10 opinion the risks are higher for failure and we want to
11 avoid those failures.
12 Chi-wan had something to say.
13 DR. CHEN: I would just like to add to Ajaz's
14 answer to your question, Dr. Lee. Yes, we do place as
15 important an emphasis on physical attributes when studying
16 shelf-life as chemical attributes, but it presents a great
17 deal of challenge to FDA, as well as the industry, because
18 of all the problems we outlined earlier. For example, the
19 non-predictability of accelerated data and less than full
20 shelf-life which is a recurring occurrence.
21 As the industry compressed their drug
22 development time line, there is no chance to really work
23 out all the bugs from their manufacturing process or have
24 enough long-term data for us to set a reasonable shelf-life
25 and acceptance criteria. So, everything that is approved

1 is predictive for future production batches. So that's a
2 real challenge.
3 DR. LEE: The committee has been pretty quiet
4 so far. Art, do have any comment to make?
5 DR. KIBBE: I have something completely off the
6 subject.
7 DR. LEE: Leon?
8 DR. SHARGEL: Given the fact that the number of
9 recalls on solid oral dosage forms are very small, it is
10 apparent the stability program, at least for those
11 products, seems to be working in general, although in
12 discussion --
13 DR. RODRIGUEZ-HORNEDO: I have a comment.
14 DR. LEE: Nair, would you please wait a second?
15 DR. SHARGEL: Given the fact that we have a
16 small amount of recalls, although they are there, and many
17 companies who have experience -- and one of the last points
18 on Dr. Chen's slide was on predictability of physical
19 stability expressed as a term, experience, number of
20 primary and supporting batches. So, there are companies
21 that have experience with the product. We've talked about
22 risk management and other items in which we may not need to
23 do stability on every batch, and yet there is apparent some
24 issues that even a company that has experience with a
25 product. So, I am interested that we find the mechanism

1 for the instability of why we're having failures.

2 On the other hand, knowing the resources of FDA

3 is not as large as we would like, would it be better to

4 identify those products that you would feel most important

5 to measure mechanisms for failure of stability, rather than

6 having a very broad question that you have here? Is there

7 some area that we really should be addressing as opposed to

8 being so wide an area?

9 DR. LEE: Ajaz, would you like to respond to

10 this before I go off line?

11 DR. HUSSAIN: One aspect which I will share

12 from my previous presentation this morning was on the time

13 to release a batch. Dr. Raju's MIT data set shows that

14 exceptions lead to significant extension of release time.

15 You know what happens most of the time? They throw it

16 away. So, one way of keeping the recalls to a minimum is

17 you don't even release a lot of those batches. So, that's

18 sort of built into that. Anyway, I just wanted to make

19 that point.

20 DR. LEE: I understand that we have Nair on the

21 line. Dr. Rodriguez? Dr. Berg? Nobody is there. This is

22 carried by what phone company?

23 (Laughter.)

24 DR. RODRIGUEZ-HORNEDO: Yes, Vince?

25 DR. LEE: Yes, Nair. Would you please

1 introduce yourself?

2 DR. RODRIGUEZ-HORNEDO: Yes. This is Nair

3 Rodriguez from the University of Michigan, and I have been

4 with you since the beginning of the meeting.

5 DR. LEE: You were pretty quiet. Can you see

6 us?

7 DR. RODRIGUEZ-HORNEDO: Yes. I can see you.

8 Realize that there is about 5-second delay from when I talk

9 to when you when you can hear me. So, if you ask if there

10 are any comments and you wait 2 seconds, you don't give us

11 a chance.

12 Anyway, my comment goes along the lines of the

13 physical stability in which I think the main focus of the

14 guidelines has been on the physical stability during

15 manufacturing and storage. And I am very glad to see that

16 there is a recommendation or at least a concern regarding

17 the possible changes, physical changes occurring during

18 dissolution. I think right now we have basically relied on

19 the endpoints which are measuring dissolution rates of

20 batches and not realizing that there are some active

21 ingredients that may be more vulnerable to physical

22 transformations during dissolution, such as the example

23 that Ajaz gave us this morning on the carbamazepine.

24 So, I think it's very important to consider

25 maybe eventually classifying some of the active ingredients

1 that we're dealing with and the dissolution media that we
2 develop in the methods for dissolution to identify which
3 products are more vulnerable to transformation during the
4 dissolution process.
5 DR. LEE: Thank you.
6 Anybody else? Yes, Marv.
7 DR. MEYER: Ajaz, what's being done currently
8 with those products that are implantable for many days or
9 months that are already marketed in terms of stability
10 testing, physical characterization, et cetera?
11 DR. HUSSAIN: Shelf-life is established the
12 same way as we would do for any controlled-release dosage
13 form and so forth. In many -- or at least four or five of
14 those products right now, we have would be considered as an
15 in vitro/in vivo correlation. So, in terms of knowing,
16 through the entire duration of intended use, the system was
17 stable, and that information, not only the safety and
18 efficacy, but pharmacokinetic information has been
19 translated into a correlation with an in vitro process.
20 So, probably 50 percent of the products have that. The
21 rest do not. There's a handful. About six or seven
22 products out there. There are not many.
23 DR. MEYER: Do people who use animal models,
24 implant these CR dosage forms into animals?
25 DR. HUSSAIN: The workshop we had on this very

1 topic about six-seven months ago made that as a
2 recommendation. Right now we do not really use animal data
3 in that way. I think there's an opportunity that we might
4 want to look at animal data.
5 DR. LEE: Ajaz posed two questions to us and I
6 would like to address them. The first one is, should this
7 topic be developed for a more detailed discussion by ACPS?
8 And the answer is? Yes.
9 And then the follow-up question is, what?
10 Would you like -- I'm talking to the committee -- to spend
11 some time talking about that? Or should we bounce the ball
12 back to Ajaz and say what are some of the problems that you
13 anticipate, you perceive?
14 DR. HUSSAIN: The focus right now -- we have
15 started a pilot project on a controlled-release parenterals
16 with Dr. Diane Burgess. And we are planning to have some
17 of that work in our labs too.
18 There has been, that I'm aware of, one recall
19 situation in that area where actually things had already
20 been implanted and we had to deal with that question. The
21 number of products are small. We are looking at less than
22 10 products. It's a small area and potentially high risk
23 areas and a potential area where you will see a growth in
24 number of products because of protein peptide molecules
25 being developed more and more. So, it is a small pilot

1 project that we have right now ongoing.

2 So, my thoughts were to use that as a focal

3 point and sort of build around that from a mechanistic

4 perspective in general, not dosage form specific, what sort

5 of changes that might occur that might lead to changes in

6 dissolution. But my use of dissolution is -- again as an

7 example, Dr. Rhodes pointed out there are many physical

8 attributes that may not even have the right test methods.

9 So, what I would propose to you is looking at

10 the list, looking at the information on all physical

11 attributes that might be critical, we could do a survey of

12 current methodologies, whether they're validated, not

13 validated, in terms of what are we truly measuring. Maybe

14 we can create that database for you and sort of bring that

15 back with the analysis saying that these physical

16 attributes, although we measured those, there may be some

17 gaps present in that. That then becomes a focus for

18 saying, all right, which areas of focused research should

19 we have?

20 The current approach for research that we have

21 was driven by the databases that we have recalled and so

22 forth. 80-90 percent of the products are solid. So,

23 although the recall numbers are small, we still play with

24 those dosage forms more so than the parenteral dosage

25 forms.

1 So, an examination of current physical methods,
2 potential gaps that may exist in those methods and
3 potential risk that may exist, even though recall numbers
4 may not be indicative of that, and then potentially a
5 program that would emerge from that, maybe a small update
6 on that next time and then develop a more detailed program.
7 DR. LEE: Dr. Rhodes, would you like to add
8 some comment?
9 DR. RHODES: I think this area is so important
10 that wherever you start is going to be useful.
11 However, having said that, I think that it
12 probably would be a very good idea to concentrate very
13 largely on factors affecting release of drug from drug
14 delivery systems. Even that is a huge area. The factors
15 that can cause a change. Well, firstly, it could just be
16 the drug substance changing its polymorphic form. It could
17 be as simple as that. That's not all that simple. It
18 could be an interaction between the drug and an excipient,
19 or it could simply be a case hardening on the surface of
20 the tablet or physical degradation of a liposome with no
21 obvious effect upon the drug. So, even looking at release
22 specifications is a big task.
23 May I make a plea? And that is, if you do
24 decide to go ahead in this way, you don't forget some of
25 the simple tests. When I go in as a consultant, looking at

1 stability protocols, I see lots of lovely charts with the
2 list of tests they carry out, and the first one is
3 appearance. And I always have a big laugh because there's
4 always a check mark on appearance, or 99.9 percent of the
5 time. How is appearance done, I ask. Oh, we look at it.
6 Do you have an SOP on appearance? Oh, no. So, one day
7 they're doing it with this type of light, another day
8 someplace else. One day you're using someone who has got
9 good eyesight; the next day you may be using a colorblind
10 person. So, there's some physical tests, very basic ones,
11 where a little bit of guidance is needed.
12 And one last point. Mention has been made that
13 the number of recalls in some of these areas is relatively
14 small. That is absolutely correct. What you don't know
15 about is the number of case when the product hasn't got out
16 onto the market and the company has detected a problem and
17 they've called in someone, in some cases me, and the
18 product never got on the market. But it has been a
19 problem. And if we had known more about the mechanism, we
20 would have been able to deal with it.
21 The number of cases I've been involved with,
22 with very conventional tablets, using that vile material
23 shellac as a controlled-release coating, and the number of
24 intermittent batch failures I've seen with that is awful.
25 So, I do commend this idea. I would suggest

1 that perhaps, even though you don't forget simple things
2 like appearance, perhaps factors causing a change in
3 release rates would be the most fruitful area and the one
4 which is probably most clinically important.
5 DR. LEE: So, along the same lines, let make
6 one follow-up thought. Perhaps what you are going after,
7 Ajaz, is some kind of a modified checklist for the
8 reviewers as to what to look for from this point onward.
9 Judy?
10 DR. BOEHLERT: Yes. I was just going to
11 comment. You might also ask those folks that review
12 stability submissions to take a look at the actual data
13 because while you don't have a lot of recalls, what you do
14 see are a lot of OOS results on stability that are tested
15 until they just barely pass. So, you have a lot of
16 marginal values and get a clearer picture of just how big
17 the problem is.
18 DR. LEE: Let me speak with Pat and Nair. Feel
19 free to interject at any time. Just give me a signal. I
20 don't know what that would be.
21 DR. DeLUCA: Pardon?
22 DR. LEE: If you would like to make comments,
23 don't be shy.
24 DR. DeLUCA: Yes. Well, I think I'd like to
25 emphasize and just carry a little further what Chris was

1 talking about. I think that one must pay more attention to
2 the surface properties and the surface phenomenon here and
3 how the surface is changing with time even during
4 dissolution testing or during storage. So, I think that's
5 an area that maybe has been overlooked and needs to be
6 considered. I think it comes in even this morning's
7 discussion about the sensor technology. We've got methods
8 to determine composition, but surface properties I think
9 play a significant role here in stability and performance,
10 the dissolution performance. So, I think that's another
11 area that we have to concentrate on, methods that can
12 really distinguish differences in the surface properties of
13 a dosage form, of a batch.
14 DR. LEE: Thank you.
15 So, the answer to the first question is that we
16 commend you for raising the conscientiousness about this
17 particular issue, but we look to you for further guidance
18 as to how to proceed.
19 DR. HUSSAIN: If I may summarize, essentially
20 what I've heard is I think it's an important issue. I
21 think there needs to be more information developed for more
22 discussion. But the focus I think, in my mind, is trying
23 to learn so that we can prevent these problems from
24 occurring and focus on understanding the mechanisms.
25 To give you an example, although the recall

1 numbers are small, even in that small database, I've been
2 looking for patterns of failure. Can I identify something
3 that's going wrong repeatedly? More companies are doing
4 that so that we can prevent this. This is a high risk
5 practice.
6 One thing that sort of pops up is when you have
7 a combination, regardless of the drug, whatever the drug
8 might be, if you have dicalcium phosphate dihydrate and
9 Explore Tab as the two ingredients -- Explore Tab is a
10 disintegrating agent -- there tends to be a higher
11 percentage of dissolution failures if that product is
12 packaged in a blister pack. What you're looking at is
13 movement of water within the system, hydrating the Explore
14 Tab. The tablet is intact, hardness is fine, everything is
15 fine, but the tablet doesn't disintegrate. You have lost
16 the functionality of that disintegrating agent. It doesn't
17 happen in a bottle. That sort of mechanistic understanding
18 leads you to say we can avoid this.
19 DR. LEE: Yes.
20 DR. MEYER: It seems to me it will be hard for
21 an FDA lab to investigate mechanisms because it's to some
22 extent certainly active-ingredient-specific, source-of-raw-
23 material-specific, other excipients that are present, and
24 the dosage form, et cetera. So, they could do a lot of
25 artificial things but not really gain the insight into

1 company X's problem.

2 In my view, they're not really responsible for

3 solving company X's stability problems. If they repeatedly

4 put those ingredients together in a blister pack, well,

5 tough. You guys will know that they're going to fail. But

6 it's not your responsibility to solve that problem for

7 them.

8 I think what is important, from a research

9 aspect perhaps, is how to evaluate things like the

10 controlled-release parenterals, the liposomes. What kind

11 of physical and chemical tests are appropriate that will

12 really discern what's going on with that dosage form and

13 not so much try to fish around and find a laundry list of

14 mechanisms that may not apply in the real world.

15 DR. LEE: Very good point.

16 Other comments?

17 DR. HUSSAIN: In my mind, when I come back to

18 you next time, either an update and so forth, probably an

19 update, my proposal is since we have started work in

20 collaboration with the University of Connecticut with Diane

21 Burgess, why don't I update you on that. The focus there

22 is a meaningful mechanistic base to accelerated release

23 test for long-acting parenteral dosage forms. And then

24 start the discussion from that aspect.

25 DR. LEE: To set the stage for this afternoon's

1 discussion, I wonder whether this would be something
2 appropriate for PQRI.
3 DR. HUSSAIN: Yes. With PQRI, what we have
4 been trying to do is define the research project very
5 carefully. Here is the thought process leading to a
6 definition right now.
7 DR. LEE: So, I think that we more or less have
8 migrated into the second question, and I think that Marv
9 may have answered it on behalf of the committee.
10 (Laughter.)
11 DR. LEE: Would the rest of the committee
12 agree?
13 Well, I think that we should focus attention on
14 how to evaluate. I think by addressing that particular
15 issue, that raises the conscientiousness of the companies
16 as to what you might expect. I think that would be the
17 major benefit to the American public.
18 Yes, Efraim.
19 DR. SHEK: If I might just say, talking about
20 mechanism and the complexity, we raised already how
21 complicated it's going to be. But the issue with
22 mechanism, at least from my experience, especially when you
23 develop a sophisticated drug delivery system, you look at
24 the mechanism. You have a theory there why it works.
25 The path is how do you translate it now to a QC

1 test where you're assured that this product consistently
2 will behave. At least from my experience, every dosage
3 form might have a different mechanism. With liposomes, it
4 depends on how you make them and how they're going to
5 behave. One liposome might behave different from another.
6 So, it's a combination of the drug substance and the
7 composition.
8 So, mechanism-wise, maybe this information is
9 being developed during the development of the product. The
10 question is now when you've got to register the product, to
11 have some requirements and expectations. And then you come
12 out with tests like saying, okay, you don't wait six months
13 to find out the dissolution. So, you try to compress it or
14 even solid dosage form which lasts for a day and you want
15 to find out over two or three hours whether it's being
16 released. So, this aspect would be of interest
17 deliberating a little bit. It's not so much the mechanism,
18 but adopting appropriate methods to test it.
19 DR. HUSSAIN: I just wanted to respond to that.
20 I hope I didn't leave the impression with the .1 normal HCL
21 media for the parenteral dosage form was not justified in
22 the NDA process. There was a justification before we
23 accept something like that. But I think when Diane Burgess
24 spent the time going through some of that, when she
25 provided the report to me, she said, you're missing the

1 mechanism. Yes, it is accelerating but it's not
2 mechanistic phase. That miscrosphere undergoes erosion in
3 that, and .1 normal HCL is not inducing the same mechanism.
4 So, what are you learning? So, those are the sort of
5 things I just wanted to point out.
6 DR. LEE: Yes. I think it's a very important
7 topic. In fact, I learned this many years ago and I think
8 for the first time I began to think about, when you said
9 stability, what are you talking about. I think that the
10 committee commends you for raising this issue, and I think
11 that the committee would like to hear more about that, some
12 examples. And we'd like the agency to focus on the
13 evaluation aspect.
14 I think this might be a fine example about how
15 the regulatory agency can move and elevate its standards.
16 Other comments to make? Yes, Bill.
17 DR. JUSKO: There's been mention several times
18 of the Arrhenius equation which is based on fundamental
19 thermodynamics, and as you develop these evaluation
20 methods, one should keep in mind that all sorts of
21 chemical/physical and physical/chemical things are based on
22 a lot of fundamental laws of nature. So, as you
23 characterize these mechanisms, you should couple them with
24 additional mathematical thinking as to how things relate to
25 basic processes that govern everything that happens in

1 life.

2 DR. DeLUCA: I support that.

3 DR. LEE: Thank you, Pat.

4 Anything else?

5 DR. DeLUCA: I didn't have a chance to make

6 some comments this morning because I wasn't on the phone,

7 but I just wanted to interject this point.

8 We talked about the technology for process

9 controls and that sensor technology, and we talked about

10 education in a sense pertaining to dissemination of

11 knowledge. But I really want to emphasize here that

12 academe needs to be more involved in the research and

13 development of these technologies. Ajaz had mentioned in

14 his talk of the downsizing of industrial pharmacy programs

15 in academe, and that's happening. So, I think there needs

16 to be more of an emphasis on looking to academe for

17 research and development in these areas and I think that

18 probably more connection with pharmaceutical engineering

19 programs in academe as well.

20 Somehow I think we need to stress that. Most

21 of our graduate students -- probably 80 percent of the

22 graduate students -- out of pharmacy schools go into

23 industry. I think there needs to be concern that there is

24 a downsizing of industrial pharmacy programs in the

25 colleges.

1 I think maybe the subcommittee they talked
2 about this morning should be an issue that needs to be
3 addressed too.
4 DR. LEE: Good. Thank you very much.
5 DR. MEYER: Vince, one comment to Pat. I
6 applaud that and I certainly support. We have some
7 industrial activity at the University of Tennessee, but you
8 have to realize that there are a number of chancellors and
9 provosts that say if you don't have NIH money, you don't
10 get promoted and tenured. It's very hard to get NIH money
11 for this kind of work. So, I think that's a battle that
12 will rage for some time.
13 DR. DeLUCA: And that exists at my institution
14 here too. I think what we have to do is we have to look at
15 pharmacy schools as maybe being a little different in that
16 regard. We have responsibility to produce practitioners as
17 well as graduate students that are going out for the
18 industry. So, I think that, one, when it comes to support
19 and funding, I really feel that the chancellors will be
20 receptive if they understand that the industry, the
21 regulatory agencies have some emphasis that they have to
22 look to pharmacy schools for that kind of research and
23 development. Maybe they'll be more amenable to accepting
24 industry funding as being on the same basis as the NIH
25 funding. So, I think it's a battle we have to continue to

1 fight together.

2 DR. BYRN: Vince, I have to just comment.

3 DR. LEE: Is it the same issue?

4 DR. BYRN: It's been my experience that it's
5 the overhead issue. I don't want to get way off the
6 subject, but now that the issue has been raised. What
7 we've done at Purdue and the reason our program is strong
8 -- and actually we're going to try to expand at least three
9 faculty in this area and probably at least 10 grad students
10 over the next few years. The reason we've been able to do
11 this is because we are paying overhead on our industrial
12 grants. Maybe people thought it wasn't a very good idea,
13 but I can see this because I've had NIH funding. So, when
14 we started building up this program, we said any industrial
15 money of large quantity has to pay overhead just like a NIH
16 grant. Since doing that, we haven't had any problem. In
17 academe, it's really the overhead dollars that people worry
18 about, not where they came from. So, if you can pay those,
19 you can build up your program. I don't want to reduce
20 everything to economics.

21 DR. LEE: I have more to say about that, but I
22 don't want to prolong the agony.

23 (Laughter.)

24 DR. LEE: Anything else aside from funding?

25 (No response.)

1 DR. LEE: Well, if not, we had a very
2 productive morning. We talked about the up and coming
3 Process Analytical Technology Subcommittee, and we also
4 touched upon what appears to be an old subject, but
5 actually a very important subject that needs a fresh look.
6 On that note, I will thank everybody for
7 participating. Pat and Nair, you can go ahead and do
8 whatever you're doing and please rejoin us at 1:30 with the
9 open hearing. Thank you.
10 DR. DeLUCA: Okay, thank you.
11 (Whereupon, at 12:22 p.m., the committee was
12 recessed, to reconvene at 1:30 p.m., this same day.)
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