

1 DR. LEE: So far we have had a very good
2 discussion and now we will introduce the section on
3 other updates, risk-based CMC review. Is Dr. Chiu
4 available?

5 **Other Updates**

6 **Risk-Based CMC Review**

7 DR. CHIU: I will need technical support.
8 Good morning.

9 [Slide]

10 Dr. Vilayat Sayeed and I will give you an
11 update to the CMC risk-based review. This is a
12 project initiated in the year of 2000.

13 [Slide]

14 As you recall, the project is actually
15 looking at performing CMC reviews based on risk of
16 the product, based on product quality risk. At the
17 time we proposed this we were looking at the
18 products and tried to find out the attributes and
19 also the acceptance criteria to define a product as
20 low risk. Then, if we compiled a list of drugs
21 which should be considered low risk, then we will
22 have reduced CMC oversight with respect to
23 information submitted to the agency. Perhaps we
24 will eliminate most of the supplements to the NDA
25 and the ANDA. What would be left would be mainly

1 the changes described in the law. We will reduce
2 the CMC information needed to be submitted to an
3 original ANDA and to the annual report of an
4 approved NDA and ANDA.

5 [Slide]

6 Over the years, since the year 2000, we
7 have had a number of internal discussions. We
8 brought the topic to the CMC, to the components
9 coordinating committee meetings. We had internal
10 scientific rounds. We had many meetings among the
11 reviewers. We also brought this topic to this
12 committee twice, once in November, 2000 and in July
13 2001. There was an AAPS workshop. Through those
14 meetings we received many useful, constructive
15 comments.

16 [Slide]

17 This project is a three-tier process, as
18 you know. The first tier includes two steps and we
19 are in the first tier. The first one, step A, is
20 to establish attributes and acceptance criteria
21 which we can use to define a low risk drug. We
22 are going to issue a draft guidance, hopefully
23 early next year, to define the attributes and
24 acceptance criteria. We will then have public
25 comments. After that, we will finalize the

1 guidance and based on the attributes and criteria
2 we will propose a drug list which will be
3 considered low risk with respect to quality. We
4 will publish that list as a draft. Then we will
5 have comments from the public on whether that list
6 is realistic, whether other products should be on
7 the list, whether some products should not be on
8 the list.

9 After receiving the comments, then we will
10 finalize the drug list after internal medical
11 consultation. That is tier two, which is the
12 medical safety evaluation. Once we finalize the
13 list, then applications for those drugs considered
14 low risk will have less FDA oversight. However,
15 whether a company will be eligible for that
16 privilege will be based also on their GMP
17 compliance history. So, that is tier three.

18 [Slide]

19 We talked among ourselves about the
20 general principle for the final list drugs. In
21 this diagram, on the Y axis is the probability of
22 detecting product defects or criteria attributes.
23 When you have a high probability of detection, then
24 the risk is low. When you have a lot probability
25 of detection the risk is high. On the X axis is

1 the complexity of the drug substance, drug product
2 characterization. So, simple molecules would be
3 considered low risk and macromolecules, complex
4 molecules or complex dosage forms would be
5 considered high risk. It also depends on the
6 complexity of the mechanism of product performance.
7 If it is simple immediate release, it would be low
8 dosage, low risk. If it is targeted release, then
9 it could be high risk. It also depends on
10 manufacturing technology. So, a simple synthesis
11 would be considered low risk. However, maybe
12 formation of recombinant cells, formation of
13 liposomal products would be considered high risk.

14 We are actually looking right now at this
15 high probability of detecting and low complexity as
16 low risk products. I believe, you know, in the
17 future when we gain experience with this project
18 and also ways for implementation of on-line or
19 in-line testing we will be able to expand this
20 area. The medium and low risk area could be
21 shrunk. So, this is what we are working on.

22 [Slide]

23 We formed two working groups to look at
24 the drug substance characteristics with respect to
25 attributes and acceptance criteria, and we have

1 another subgroup working on drug product. Now, you
2 know, we are more or less in the stage of
3 finalizing the draft guidance and soon it will be
4 out for internal comment. Dr. Sayeed will describe
5 to you our current thinking. So, without further
6 ado, Vilayat.

7 DR. SAYEED: Good morning, everybody.

8 [Slide]

9 Yuan-yuan has basically explained the
10 objectives and other aspects of this initiative so
11 I am going to go right into what we have done for
12 to how to achieve this objective.

13 [Slide]

14 What I am going to do, I am going to
15 present the drug substance and drug product
16 decision trees which we have developed for
17 identifying low risk candidates. These trees were
18 developed by the general principle which was
19 discussed as to the probability of detection and
20 the complexity, and I am not going to go into the
21 details of this chart. The focus of the working
22 group was to find or identify drug substances and
23 drug products which would fit into this box, here,
24 where the failure for the probability of detection
25 is high and the complexity is low.

1 Having this principle in mind, the first
2 question which was raised for the drug substance
3 was what drug substance would actually fit into
4 these criteria. The general consensus in the
5 working group was that a synthetic drug substance
6 and simple inorganic salts would actually meet
7 these criteria.

8 [Slide]

9 So, the first question on the slide on the
10 drug substance decision tree is, is the drug
11 substance of synthetic origin or a simple inorganic
12 salt? If the answer for this is no, then this drug
13 substance is not suitable for low risk
14 consideration. If it is, then you move on to the
15 next level.

16 At this level there are certain
17 exclusions. The question was raised can all
18 synthetic drug substances fit into this concept?
19 The answer by the working group was no, not every
20 drug substance would meet this.

21 [Slide]

22 On this slide certain exclusions are
23 included. Here are the exclusions. If a drug
24 substance happens to be a radiopharmaceutical, a
25 peptide or an oligonucleotide, then if the answer

1 for this is yes, this drug substance cannot be
2 considered for low risk; and if it isn't, then you
3 move on to the next level.

4 For the next level we have addressed
5 issues relating to the drug substance
6 characterization, its specifications and its
7 stability issues. The question here, at this level
8 is, is the drug substance well characterized, and
9 are the specifications used to control the drug
10 substance contemporary, and is the drug substance
11 stable at ambient conditions? If the answer for
12 this is no, it is not, then the consensus in the
13 working group was that the drug substance is not
14 suitable for low risk consideration. If the answer
15 is yes, then the drug substance is a suitable
16 candidate for the low risk assessment.

17 [Slide]

18 Here you see a little box. What we have
19 done here, we have identified that if there are any
20 physical characterization issues with regard to the
21 drug substance. These issues will not be
22 considered at this level, whereas these issues will
23 be moved on and considered at the drug product
24 level. So, if there are any physical property
25 issues with the drug substance, those issues need

1 to be identified in the drug substance and will be
2 considered in the assessment of the drug product.

3 [Slide]

4 With the baseline established, the first
5 question asked for the drug product is, is the drug
6 substance assigned as a low risk? If the answer is
7 no, if it is not there, then the drug product is
8 not a suitable candidate for low risk
9 consideration. If the answer is yes, then you move
10 on to the next level.

11 [Slide]

12 At this level what we have done is we have
13 identified certain dosage forms which the working
14 group thinks will fit into that general principle
15 where the probability of detecting a failure is
16 high and the complexity of the product is low.

17 [Slide]

18 These drug products were identified as IR
19 oral solids or topical liquids or sterile solutions
20 of simple solids. So, this is what we think are
21 drug products or dosage forms which would fit into
22 this general principle concept. If the answer for
23 this is no, then the drug product is not a suitable
24 candidate for low risk consideration. If the
25 answer is yes, then you move on.

1 The same question was raised in the
2 working group whether all IR solids and liquids
3 will fit into these criteria. Obviously, the
4 answer was no. So, we have included some
5 qualifiers on the next slide.

6 [Slide]

7 The qualifiers are for the solids. We are
8 saying is the strength per unit at least one
9 milligram or one percent by weight? If it is
10 anything less than that, we think it is not a
11 suitable candidate. For the liquids we are not
12 using the strength; we are using the solubility
13 ratio, the intrinsic solubility ratio. We are
14 saying if it is not less than 1:30, then it may not
15 be a suitable candidate. If the answer for this is
16 no, then the drug product is not a suitable
17 candidate for low risk consideration. If the
18 answer is yes, then you move on and look into other
19 aspects of the drug product.

20 [Slide]

21 On this slide what we have done is we have
22 looked into the interaction of the drug with the
23 excipient. What we are saying is if there are any
24 known interactions reported, if there are reported
25 interactions between the drug and the excipients,

1 then this product may not be a suitable candidate
2 for this CMC low risk assessment. If the answer
3 for this is yes, then the drug product is not a
4 suitable candidate for the risk assessment. If the
5 answer is no, then you can move on to the next
6 level.

7 [Slide]

8 At this level what we have done is we have
9 looked into the physical property of the drug
10 substance, which we have left open on the drug
11 substance tree and this is where we are capturing
12 that part. We are saying if there is a reported
13 impact, like if the physical properties of the drug
14 substance are known to have some impact on the
15 product performance, then this drug product may not
16 be a suitable candidate for this low risk. Are the
17 differences in the physical state of the drug
18 substance reported to have an impact on the
19 performance of the product? If the answer for this
20 is yes, then you are saying the drug product is not
21 a suitable candidate for low risk consideration.
22 If the answer is no, then you move on to the next
23 level.

24 In the following few levels, what we have
25 done is we have captured the aspect of the product

1 specifications, product stability, product
2 degradation and packaging and storage, and all of
3 those things are covered in the next few levels.

4 Here we are saying if the drug product
5 meets the contemporary standards, you know, if the
6 answer for this is no, then the drug product is not
7 a suitable candidate for low risk consideration.
8 If it is yes, that you do have product
9 specifications which conform to the contemporary
10 standards, then you move on to the next level.

11 [Slide]

12 At this level we are capturing the
13 stability and the degradation of the product. We
14 are saying do you know if the degradation of this
15 product is predictable and if the degradants are
16 controlled? So, the question is, is the drug
17 product degradation profile predictable and are the
18 degradants controlled? If the answer for this is
19 no, then the drug product is not a suitable
20 candidate for low risk consideration. If the
21 answer is yes, then you go on to the next level.

22 At this level we are capturing the product
23 storage and packaging. What we are telling here is
24 that for now we will only consider products which
25 are stored at controlled room temperature and which

1 do not require any special packaging. If the
2 answer for this is no, then the drug product is not
3 a suitable candidate for low risk consideration.
4 If the answer is that, yes, it doesn't have those,
5 then you move on.

6 [Slide]

7 At this level we are capturing a little
8 bit of product history. We think we need to know
9 at least a couple of years of real-time stability
10 of the product on a minimum of three commercial
11 batches for the product to be placed in this
12 program. So, if the answer for this is no, then
13 the drug product is not a suitable candidate for
14 low risk consideration. If the answer is yes, then
15 you do have a product which qualifies as a
16 candidate for low risk assessment.

17 [Slide]

18 In conclusion, I would like to acknowledge
19 the individuals who have spent a lot of time and
20 effort in developing these trees. Thank you.

21 DR. LEE: Thank you. Gloria?

22 DR. ANDERSON: Would you comment on your
23 definition of complexity? Based on what you said
24 about single synthetic components, something to
25 that effect, I am trying to get a picture of how

1 big a molecule would be, if that is how you define
2 complexity as opposed to some smaller molecule with
3 a really horrible function group on it.

4 DR. SAYEED: We are not going to
5 functional groups. Did you want to comment on
6 that?

7 DR. CHIU: Yes, we are not going to base
8 on molecular weight of the molecule. What we are
9 going to base on is how easy it is to characterize
10 the molecule. If one can use appropriate standard
11 methodologies such as IR, UV and MR, and element
12 analysis, then it is considered well characterized.
13 When we talk about macro protein molecules, even
14 with those tools you cannot characterize them.
15 When we talk about single molecules, because
16 sometimes you have combination products; you have
17 two or three drugs at the same time and you may
18 have multiple active ingredients, we will not
19 consider that, you know, simple.

20 DR. ANDERSON: I understand that but is it
21 possible you could have a compound, a molecule that
22 is easy to characterize, that can be well
23 characterized and have a really bad functional
24 group on there that could put it in another
25 category? That is really what I am talking about.

1 DR. CHIU: That would be caught by the
2 other criteria in terms of stability, if you have
3 degradation products whether you would detect that.
4 So, the specifications and the stability will catch
5 your concern.

6 DR. ANDERSON: So this is the first step
7 here.

8 DR. CHIU: Right.

9 DR. ANDERSON: Okay, thank you.

10 DR. CHIU: Yes, the first step.

11 DR. LEE: So, I guess everything is
12 relative.

13 DR. CHIU: Because there are three
14 elements you have to fit all three elements
15 together to be considered low risk.

16 DR. LEE: I see.

17 DR. CHIU: So, it is not either/or.

18 DR. SHEK: A couple of quick questions.
19 I will start from the end. The last one says are
20 there at least two years real-time stability data.
21 My question is does that apply to NDAs as well as
22 ANDAs, this decision tree?

23 DR. SAYEED: Yes, this decision tree
24 applies to all applications basically.

25 DR. SHEK: So, by definition, two years

1 data wouldn't apply for NDAs?

2 DR. CHIU: No, the idea of three years
3 data does not mean the specific product from a
4 single company. It means whether you ever have two
5 years data for that drug, regardless who makes
6 that.

7 DR. SHEK: Right, but if it is a new
8 chemical entity and an NDA is being filed, by
9 definition it wouldn't fit into this category.
10 Right? So, a new chemical entity will never be
11 able to through this decision tree.

12 DR. CHIU: Well, not necessarily because
13 some NDAs do have more than two years stability
14 data in the file.

15 DR. SHEK: On commercial batches?

16 DR. CHIU: Yes, because not necessarily
17 are all NDAs first time around in this country.
18 You know, occasionally we get NDAs with batches
19 from Europe but those will be rare. So, I think
20 you are right, most of the time a molecular entity
21 may not fit as a low risk, but occasionally will.
22 Most ANDAs will be qualified so that is why we
23 proposed this truncated ANDA.

24 DR. SHEK: If we go up the tree will we
25 come out with a definition of what are contemporary

1 standards?

2 DR. CHIU: Yes. Yes, in the draft
3 guidance we will explain what is contemporary
4 standards. We propose mainly following ICH or FDA
5 guidance.

6 DR. SHEK: And if we go to the top of the
7 tree, I think this is just the CMC aspect, and
8 maybe it was there and I just missed it, but will
9 there be any evaluation even before that of whether
10 there is a therapeutic index?

11 DR. CHIU: Yes. That would be the second
12 tier, the medical consultation. Yes, there we
13 would look at the safety and the medical risk.

14 DR. SHEK: And that will happen first?

15 DR. CHIU: That will happen after we
16 propose the list of drugs. Then the medical people
17 can look at those drugs and decide.

18 DR. SHEK: Thank you.

19 DR. LEE: Art?

20 DR. KIBBE: Just a couple of questions.
21 The question I have is about drug excipient
22 compatibility issues. If there are known excipient
23 compatibility issues but the product in question
24 doesn't contain that excipient, and most good
25 manufacturers would try to avoid excipients where

1 there is a problem, then it would still be no?

2 Even though there was a known issue with a
3 different excipient, the product would not pass?

4 DR. CHIU: No, no, that is not the case.
5 We are talking about the excipients used in the
6 product.

7 DR. KIBBE: Right, not just that there is
8 an issue.

9 DR. CHIU: No.

10 DR. KIBBE: I noticed that if they have a
11 milligram or less than one percent they are not
12 considered low risk, which means that all
13 homeopathic remedies are high risk and we should
14 start to evaluate those!

15 [Laughter]

16 I just throw that out. The question I
17 also have is would you accept a petition from a
18 manufacturer for exception based on data they have
19 that would answer the issue on any one of these
20 decisions?

21 DR. CHIU: We will issue a draft guidance
22 to explain all those criteria, and we will get
23 input from manufacturers and from the public and
24 then we will finalize that. I also said we will
25 propose a drug list and then we will seek comments

1 from outside. At that time the pharmaceutical
2 companies can propose drugs which are not on our
3 proposed list. In the future, when this is
4 finalized, we will continue to accept petitions
5 from companies if they have, for example, improved
6 their specifications; they now have contemporary
7 specifications so they should be included in the
8 list. We will continue to revise our list of
9 drugs.

10 DR. KIBBE: Thank you.

11 DR. LEE: Judy?

12 DR. BOEHLERT: I have a few questions. In
13 the drug substance decision tree you say that the
14 drug has to be stable under ambient conditions. I
15 am wondering if you are going to define what you
16 mean by that because stable is in the eye of the
17 beholder, and what do you mean by ambient? ICH
18 conditions?

19 DR. CHIU: Yes, ICH conditions. We really
20 mean ICH conditions. If you store under ICH
21 conditions and it shows that it is stable.

22 DR. BOEHLERT: Stable means meets
23 requirements?

24 DR. CHIU: It means it meets the
25 specifications.

1 DR. BOEHLERT: Right now it doesn't really
2 say that. The other issue that you talk about are
3 physical properties. The way it sounds now is that
4 if you need to set a specification for a physical
5 property, such as particle size or maybe even
6 polymorph, then it would automatically not qualify
7 for this treatment and I am wondering why--

8 DR. CHIU: No, no. I don't think that is
9 the case.

10 DR. BOEHLERT: That is what I heard.

11 DR. SAYEED: What we are trying to say is
12 you identify those characteristics in the drug
13 substance but those characteristics will not be
14 used in saying whether this drug substance is high
15 risk or low risk. What we are going to do is what
16 kind of impact those characteristics they will have
17 on the drug product performance.

18 DR. BOEHLERT: Well, say they do have an
19 impact on drug product performance but you have
20 contemporary specifications; they are controlled;
21 you know what they are and they are controlled in
22 every batch, why would that change things?

23 DR. CHIU: I see.

24 DR. SAYEED: That is a good thing because
25 again we go back to the level of controls we have.

1 I mean, at least for now we want to deal with
2 things that are just straightforward and simple.
3 We don't want to get into how much control we can
4 have on each company and each product. So, for now
5 we want to keep it simple and maybe as time goes on
6 and we learn more about it we can move into that
7 area of you have the control so you can go ahead
8 and use it.

9 DR. BOEHLERT: If you don't want to use
10 the term contemporary specifications because I have
11 applied some of these newer controls such as--

12 DR. SAYEED: I mean, most of these things
13 may have the controls but we are saying even if
14 these controls happen to have any effect on the
15 performance, then we will not use it. That doesn't
16 mean that you are not going to control it; you
17 control it but you can't use that drug substance.

18 DR. CHIU: The proposal right now is that
19 we would like to be rather more conservative at the
20 beginning so we will take comments. If people
21 strongly believe this is well controlled and they
22 should be on the low risk drug list we will
23 consider that. But at this time, you know, we just
24 want to be rather more conservative.

25 DR. LEE: We will take two more questions,

1 so Marv and then John.

2 DR. MEYER: The one milligram as a cut-off
3 point, how was that selected and what will you do
4 with multiple strengths, say half a milligram and a
5 one milligram tablet? Where will it fall?

6 DR. CHIU: The reason we picked one
7 milligram is because we thought that for blend
8 uniformity there may be issues so we thought it may
9 not be considered a risk. I see your point about
10 multiple doses and we haven't discussed that.
11 Maybe we will go back to think about when there are
12 multiple doses.

13 DR. MEYER: Any idea how many drug
14 products will fall into the low risk category?

15 DR. CHIU: Actually, it is very difficult
16 to come up with physical attributes or chemical
17 attributes so we asked our reviewers, based on
18 their review experience, which drugs they consider
19 to be really, really low risk, and we actually
20 obtained something like 60 drugs. Then we went
21 back to look at more than 300 applications and
22 based on that data mining we came up with those
23 criteria. So, I believe we will, you know, have
24 many more than just 60 drugs.

25 DR. MEYER: I would caution you that the

1 reviewer system didn't work very well in picking up
2 drugs with a high risk for therapeutic problems in
3 the generic field. You had some very strange drugs
4 on that list.

5 DR. CHIU: That will be the next tier.
6 The second tier will look at the medical safety.
7 So, right now we are just looking at the physical
8 characteristics, chemical characteristics. But we
9 will take into account the medical safety.

10 DR. LEE: John?

11 DR. DOULL: I would like to go back to the
12 excipient issue. You said that the yes/no question
13 for excipients was whether they interacted with the
14 active ingredient, drug. How about the inherent
15 toxicity of the excipient? That is not part of the
16 consideration? In other words, you could put a
17 drug in a low risk category even though it had a
18 highly toxic excipient. Is that true?

19 DR. CHIU: Well, the toxic excipients will
20 be studied during your NDA stage and the safety
21 data to assure that the excipients used are not
22 toxic. When you have an ANDA the review process
23 will also catch toxic excipients. So, I think that
24 probably will not be an issue.

25 DR. DOULL: I was just concerned that if

1 that is the criteria, then it omits the toxicity,
2 inherent toxicity of these.

3 DR. CHIU: You know, there is no
4 difference from active ingredient, toxic or not.
5 The agency evaluation includes the toxicity
6 evaluation.

7 DR. LEE: Maybe I should ask a question to
8 close it. It may be a silly question. What is the
9 motivation behind this?

10 DR. CHIU: The motivation behind this, we
11 have a multiple motivation because we are looking
12 at everything. When we do an evaluation we look at
13 the risk. Even the CMC review is to identify what
14 are the risk factors; what are not risk factors so
15 you can determine what is the critical process
16 control and what are the release specifications.
17 This is just an additional part of the risk
18 assessment and risk management.

19 The second reason is because the agency
20 always has limited resources. We want to put our
21 resources in places where more extensive review and
22 evaluation is needed rather than giving every drug
23 the same intense evaluation. For those low risk
24 drugs, you know, we do not need such an oversight
25 as high risk drugs. So, those are the reasons.

1 DR. LEE: So, this is some kind of a
2 triage.

3 DR. CHIU: Yes.

4 DR. LEE: Thank you.

5 DR. MEYER: Can I ask a real quick
6 question?

7 DR. LEE: Me?

8 DR. MEYER: No, no, I want to ask someone
9 who knows!

10 [Laughter]

11 Would recall history play a role in this?
12 Would you look at that also?

13 DR. CHIU: I think in the GMP compliance
14 part of the history we will look at recalls; we
15 will look at deviations such as a warning and all
16 those factors involved in GMP.

17 DR. LEE: Toby, one last question?

18 DR. MASSA: On August 8 of '01, industry
19 provided a readout from the workshop that Dr. Chiu
20 and I co-chaired on this topic. I would suggest
21 for the committee could get insight on over 500
22 participants both from industry and FDA, that the
23 AAPS has a web site containing those comments and
24 many of the comments that Dr. Chiu mentioned are
25 contained in that document.

1 To the point that you raised, the key
2 thing that industry felt is the ability to control
3 and characterize; complexity, not as big an issue;
4 dosage form, not as big an issue as long as it is
5 characterizable and controllable. Those are the
6 things that industry really felt very strongly
7 about. There is an extensive amount of information
8 on the feed-out from that workshop for the
9 committee's consideration.

10 DR. LEE: Do you have to be a member to
11 access those sites?

12 DR. MASSA: No, I think that is available
13 to the public.

14 DR. CHIU: Yes, the report is on the web
15 site of AAPS.

16 DR. LEE: Thank you very much. Well, I
17 think that we are getting back on schedule and we
18 come to a very interesting topic, blend uniformity.
19 Ajaz Hussain will tell us about what is going on.

20 Blend Uniformity

21 DR. HUSSAIN: This is an update since we
22 had an extensive discussion on the PQRI proposal.

23 [Slide]

24 Let me sort of walk through the background
25 history here. The issue that we are talking about