

1 DR. TOKARS: Dr. Van Wyck.

2 DR. VAN WYCK: OR-10, please -- slide
3 on. The bioavailability of oral iron is
4 complete -- DO-23, I'm looking for. I'm sorry.

5 So we actually could calculate from
6 Jim Cook's formula total body iron, which
7 includes both hemoglobin and ferritin from
8 his population studies of estimates of body
9 iron status in North American populations,
10 that the utilization of administered iron was
11 about overall 88 percent. This is
12 essentially 100 percent of FCM used by day 42
13 in patients, because you were utilizing it
14 for either hemoglobin or for stores.

15 So this seems to be nearly
16 100 percent utilization in a short period of
17 time in patients who are in negative iron
18 balance. So on the other hand, the
19 utilization of oral iron was about 12 percent
20 of the administered dose of 7,300 milligrams.

21 DR. HENNESSY: Thank you. So with
22 that, we'll open up the floor to questions

1 having to do with the risk management plan and
2 post-marketing safety surveillance.

3 Dr. Davis.

4 DR. DAVIS: Yes.

5 DR. HENNESSY: You've been chomping at
6 the bit for risk management.

7 DR. DAVIS: Yes, I have. So my
8 question is, have the patient and provider
9 education materials been developed and
10 evaluated?

11 DR. TOKARS: Dr. Andrews, can you
12 answer questions on our risk management program?

13 DR. ANDREWS: Thanks. First, I'll say
14 that there are some materials that have already
15 been developed. For example, there's a brochure
16 I mentioned on hypophosphatemia. But the
17 content of most of the educational material
18 would really await the decision about the
19 recommended indications, and so it's a bit
20 premature.

21 But the plan would be to make sure
22 that those materials are developed with

1 significant input from the stakeholders, and
2 undergo some rigorous testing before their
3 cognitive interviews, making sure that the
4 intended individuals could read and
5 understand that the salient points are clear,
6 the messages are clear and understood before
7 finalizing the materials.

8 DR. DAVIS: The comment is, it's hard
9 for me to evaluate from my expertise what the
10 risk management plan -- what the information to
11 the patient and the provider is. My concern is
12 that risk is not going to be stated explicitly.
13 And I gather that because for me as a listener,
14 it wasn't stated explicitly this morning. And I
15 think that the risk information needs to be
16 crystal-clear. The FDA guidelines on medication
17 guides -- that's a little different -- state
18 that it needs to be non-technical,
19 understandable language, not promotional in tone
20 or content.

21 And sometimes in pharmaceutical
22 companies, the information for providers and

1 patients is written by a marketing group, and
2 so it has a promotional tone. It's easy to
3 pick up the benefit; it's much more difficult
4 to pick up the essential risk and safety
5 information.

6 DR. ANDREWS: I share your concern as
7 well. In this case, the information that I've
8 seen thus far has been extremely well-balanced,
9 and clearly articulates the findings of the
10 studies. There is the anticipation of a
11 medication guide which would be developed to
12 clearly communicate the specific risk as well as
13 the level of uncertainty or knowledge about
14 them, and what to do about them.

15 But it's also thought that the
16 medication guide by itself may not be
17 sufficient. So not only is there a plan for
18 more information available to patients by
19 written medium, also some website
20 information -- and more importantly, or
21 equally as important -- the training of their
22 practitioners so that they also understand.

1 So a very consistent campaign through which
2 the patient should be getting the same
3 message, and a very clear message,
4 consistently and in a reinforced manner.

5 DR. HENNESSY: Dr. Kramer.

6 DR. KRAMER: A couple of questions.
7 If I understood -- this is on the risk
8 management program. And so if I understood the
9 presentation correctly, there will be an attempt
10 to target hematologist infusion centers to the
11 patients that really are in need of something
12 beyond oral therapy, which if I understand
13 correctly is different than the indication you
14 are seeking. Is that correct?

15 So you'd have an indication in
16 which it would be -- it could be first-line
17 therapy, but in your marketing, you'd be
18 targeting people who would use it as just the
19 high-risk patients that don't tolerate oral
20 irons. Is that right?

21 DR. TOKARS: No, we are
22 intending -- our application right now is for

1 the indications of patients with postpartum
2 anemia and anemia from heavy uterine bleeding.
3 In our initial rollout, we're going to focus on
4 patients -- slide on please -- that need a more
5 rapid and predictable recovering hemoglobin.
6 These are the messages we're going to teach.

7 DR. KRAMER: Let's understand what
8 that means. Does that mean that you'd be
9 targeting your marketing towards that
10 indication, but that anybody, any physician --

11 DR. ANDREWS: No.

12 DR. KRAMER: Who wanted to could
13 prescribe this? For instance, it could be
14 prescribed for CKD patients; right? It's on the
15 market off-label. It's available. You're not
16 restricting distribution in a way --

17 DR. TOKARS: No, we're not --

18 DR. KRAMER: That it couldn't be used
19 off-label. I just want to make sure we're clear
20 that you are looking at one population, but the
21 exposure could be much broader than that. And
22 you wouldn't be looking at that broader exposure

1 because you're targeting samples of the people
2 you're intending to get it.

3 DR. ANDREWS: So what we're planning
4 to do is to target all the information. You're
5 right. It could be used, theoretically, in
6 other populations. You might want to hear from
7 some of the people experienced in treating
8 chronic kidney disease patients -- I think it's
9 very unlikely to be used in that population.

10 The risk management --

11 DR. HENNESSY: Dr. Andrews, I'm sorry
12 for interrupting. Can you tell me why you think
13 it is unlikely to be used in a chronic kidney
14 disease population?

15 DR. VAN WYCK: In our world, our
16 patients on dialysis come three times a week.
17 They get small doses of IV iron. We think
18 that's the best way to manage iron stores and to
19 maximize the hemoglobin and minimize the
20 EPO -- that larger doses given more infrequently
21 actually are associated with higher epid (?)
22 utilization. So we neither have the need for a

1 new drug, nor do we have any discomfort with the
2 drugs that we're using that are indicated for
3 this particular patient target population.

4 Peritoneal dialysis patients can be
5 given 200 mg of iron sucrose in a infusion in
6 an injection over five minutes once a month,
7 and most patients do just fine with that.
8 It's indicated, we have the safety
9 information, and we have the EPO information
10 about those patients. I don't see the need.

11 DR. HENNESSY: Thank you, sir. So
12 let's go back to --

13 DR. PAGANINI: Can I -- can I --

14 DR. HENNESSY: You want to follow-up
15 on that point real quick?

16 DR. PAGANINI: Rebut that a little
17 bit? David, your hemodialysis that comes in
18 three times a week, I'll give you that. Your
19 chronic home dialysis or your peritoneal
20 dialysis, the whole reason why Venofer went to
21 400 mg was to avoid having to have them come
22 back in two weeks, but they haven't come back in

1 a month or greater. I can see that as an area.

2 And in your whole CKD population
3 that don't want to come in for multiple
4 injections, even at small amounts, most
5 clinics now are looking at trying to increase
6 doses so that the patient -- for patient
7 convenience, which is one of the reasons why
8 you're doing this for your target population,
9 so that they don't have to come in.

10 So I see a great off-label use of
11 this drug in a market that has shown a fairly
12 high instability in compared trials. That's
13 what worries me, David. But I don't worry
14 about the kids, young people, who are maybe a
15 little bit of infections -- I worry about the
16 label stuff, because I think that you've
17 shown effectiveness, and the mortality rate
18 there are probably due to other causes;
19 that's fine.

20 My concern is the off-label use of
21 that. And so I would be in favor of
22 restrictive use, not just putting it on the

1 market and just serving that population that
2 you've seen. So I'm sorry, I have to differ
3 with you.

4 DR. HENNESSY: Let's have a response
5 to that point. We're eventually going to get
6 our way back to Dr. Andrews' answering
7 Dr. Kramer, but we'll make a slight detour.

8 Does the point about off-label use
9 want to be addressed by the sponsor at this
10 point?

11 DR. MANGIONE: I think the heart of
12 your issue is the concern about the non-dialysis
13 population data, as I understand it. And if I
14 could see the slide summarizing the cardiac
15 serious adverse events in the non-dialysis
16 patients. What we were talking about here, and
17 this was an issue that was presented by
18 Dr. Cooper originally, is that these numbers are
19 very small. This is from the core presentation
20 that Dr. Cooper presented.

21 And if you look at those numbers,
22 we're talking about -- it was 4 or 5 versus

1 2, as I believe, or 6 or 7 versus 2. And if
2 you look -- slide on, please. I believe that
3 this is the heart. This is the heart of the
4 concern. It's the cardiac series adverse
5 events that occurred in oral iron control
6 trials excluding the postpartum HUB, where
7 the cardiac events -- serious adverse events
8 were balanced. It was 2 versus 1. There's
9 no questions there.

10 And if you'll look at this list and
11 study it well, if you look the second from
12 the bottom, it was the palpitations in a
13 patient who had a pacemaker, her heart rate
14 was 70 -- never required any treatment or
15 intervention. It was serious because the
16 patient was hospitalized, not because it
17 truly was anything of a medical concern.

18 The tachycardia, again, the
19 inflammatory bowel disease, she was admitted
20 with a heart rate of 100. Her baseline was
21 120. It rose to 126 because her hemoglobin
22 was 6. Again, not primary cardiac

1 pathophysiology. If you look at the second
2 line, the cardiac arrest was discussed by
3 Dr. Cooper, the congestive heart failure was
4 balanced between the two arm. And we know
5 heart failure experts actually believe that
6 there's a methodological or theoretical
7 benefit in these small trials granted that's
8 been shown to have some benefit.

9 The two coronary artery disease
10 cases, these are people with pre-existing
11 disease -- again highly comorbid. The one
12 terminology was actually worsening the
13 coronary artery disease -- catheterization
14 showed it. And there's never been any risk
15 about accelerating atherosclerosis in a
16 matter of weeks related to iron, et cetera.

17 DR. PAGANINI: So that tells me
18 that -- you're saying your randomization failed.

19 DR. MANGIONE: No, no.

20 DR. PAGANINI: That's what you just
21 said. You said your randomization failed
22 because all these things happened to these

1 people that were in this other group. If
2 randomization was correct, you would have had
3 the same risk in the other group.

4 DR. MANGIONE: The events were rare.
5 And I'm not sure if we can come to a conclusion
6 related to that. And is there a drug that
7 causes toxicity by so many different mechanisms
8 to cause congestive heart failure, to
9 cause -- and if you listed from all the specific
10 things all the big bad wolves that have been
11 mentioned today, I'm personally in my years in
12 pharmacology -- almost up to 30, I'm not aware
13 of any drug that can cause a peripartum
14 cardiomyopathy, cause myocardial infarction,
15 cause a motor vehicle accident, colonic
16 perforation. There's nothing mechanistically,
17 there's nothing logically. We have no science
18 here.

19 In terms of the cardiac fear here,
20 we looked at the incidence of confirmed
21 serious ischemic events. They were balanced
22 in the two arms.

1 DR. HENNESSY: I'd like to hear from
2 Dr. Pazdur from --

3 DR. HARRINGTON: Just a comment. I
4 mean, the -- toxic effect is just almost
5 unbelievable.

6 DR. MANGIONE: I'm sorry -- I'm sorry
7 if -- my misstating, and I do get emotional.
8 But it was -- trying to find that there was a
9 pathophysiology here, or common pathophysiologic
10 link is not anything that has been evident in
11 any of our assessments.

12 DR. KLEIN: The hemoglobin-based
13 oxygen carrier --

14 DR. MANGIONE: May I just -- if I may
15 correct myself.

16 DR. KLEIN: Hemoglobin-based oxygen
17 carriers, perhaps by vasoconstriction, causes
18 problems in virtually every organ system.

19 DR. HENNESSY: Dr. Pazdur, you had
20 something to say.

21 DR. PAZDUR: I wanted to get into this
22 risk management issue. One of the whole

1 purposes of a risk management program is to
2 mitigate risk. The reason why we're here is to
3 discuss the imbalance of deaths here.

4 Let's get back to the central
5 reason of why we're here.

6 I fail to see however possible an
7 educational program with what we know now can
8 mitigate or change that risk. What are you
9 going to tell these patients? What are you
10 going to tell the physicians here? I think
11 there's a central element here that needs to
12 be resolved, and that's what are we going to
13 do about these risks? It seems from the
14 company's perspective that they don't want to
15 talk about them. They are due to something
16 else; they're due to automobile accidents,
17 they're due to this, they're due to that,
18 they're due to this.

19 The problem here is attribution of
20 deaths is very difficult to do, as I
21 mentioned before. Yes, these might be the
22 causes of deaths that might be recorded, but

1 are there proximal events that preceded
2 these? And that's the major issue. So the
3 major issue of why we're here is this
4 imbalance of deaths. How is a risk
5 management program going to address that
6 issue?

7 That's what needs to be addressed.

8 DR. HENNESSY: I'll give the sponsor a
9 chance to respond to that. Then we'll hear from
10 Dr. Lockwood, and then we'll circle back to
11 Dr. Kramer.

12 DR. ANDREWS: Just restate a couple of
13 things. The data are consistent with an
14 increased risk; they're also consistent with no
15 increased risk because the numbers are small.
16 And you've said that in your briefing document,
17 and we've said that multiple times today. So we
18 really just don't know. And there isn't
19 anything specific that one can do to identify
20 particular people who are at high risk from this
21 theoretical risk to actively manage.

22 So what is commonly done in that

1 situation is to try to get as much
2 information as possible as early as possible
3 with the use of the product, and also make
4 sure that the product is used by individuals
5 for whom the benefits should most outweigh
6 the risk.

7 And I think this is getting back to
8 Dr. Kramer's question about the restricted
9 indication and how we'd know if it's being
10 used within this population that we think
11 would -- patients would benefit most or not.
12 And the answer to that is that we will be
13 carefully monitoring the actual use in terms
14 of the providers who are administering it,
15 and the patients who are -- and if there's a
16 discrepancy, then there'll be actions that
17 are taken and discussed at that time.

18 DR. HENNESSY: Dr. Lockwood, was there
19 a quick supporting question?

20 DR. LOCKWOOD: I think that -- I
21 certainly appreciate and am sensitive to the
22 notion that you're trying to minimize risk by

1 avoiding the drug being used in a population at
2 high risk, such as patients with chronic kidney
3 disease. So maybe you could explain to me on
4 page 124 why as part of your current prospective
5 control trials to investigate the safety of a
6 1000 mg single dose, you're using patients that
7 are both dialysis-dependent,
8 non-dialysis-dependent, who have chronic kidney
9 disease?

10 DR. TOKARS: Those patient populations
11 were chosen basically after a conversation with
12 FDA, who suggested that we pick populations that
13 may be more infirm, to show a difference in
14 the -- or equality between the two populations.
15 And so we chose the population that we were
16 going to market, which is the heavy uterine
17 bleeding patients and postpartum patients. And
18 then we chose the more infirm population to see
19 if we saw a balance in a prospective study that
20 was randomized appropriately.

21 DR. LOCKWOOD: So you're doing it at
22 the recommendation of the FDA.

1 DR. TOKARS: It wasn't a direct
2 recommendation. It was a suggestion at one of
3 our meetings.

4 DR. HENNESSY: Dr. Kramer, you must
5 have asked a good question, because it took us a
6 while to come back and to follow-up.

7 DR. KRAMER: I'd like to address
8 another question about the risk management
9 program, which is this issue about how you're
10 going to describe risk. Given what we just
11 heard about the concern about mortality, I'm
12 very interested in what exactly is going to be
13 said. I mean, I think a lot of the public
14 comments clearly express the need. But if you
15 said to patients I know you really need this, I
16 know you're feeling really tired, but there's a
17 chance you might die -- and they're 22 years
18 old -- that's pretty tough to hear. So what are
19 we really telling people? What is our risk
20 communication that we're proposing?

21 DR. TOKARS: Right now, the plan is
22 still in flux. We really haven't finalized the

1 plan. In fact, we've never spoke to FDA about
2 this plan. The materials that you're speaking
3 to haven't been yet developed.

4 DR. KRAMER: Okay.

5 DR. HENNESSY: Dr. Klein.

6 DR. KLEIN: Part of this is
7 pharmaco-surveillance that's part of the plan as
8 well. And I guess one of my concerns is that
9 the FDA thinks that there may be a signal about
10 cardiac toxicity. The company doesn't think
11 there's a signal. We haven't discussed that
12 yet, and we don't really have a position yet.

13 But if you're looking prospectively
14 for Phase 4 post-marketing surveillance,
15 you're looking at a group with a relatively
16 small risk, as these two groups are. A
17 death -- 1 in 3000 or 1 in 5000 would
18 probably be a tragedy if it was attributable
19 to the drug in a very low-risk population.
20 Nothing you've said will allow you to pick up
21 that risk. And you do a study of 2,500
22 people, no physician will see two of these,

1 and yet that would be a disastrous outcome.
2 So how are you going to really do
3 pharmaco-surveillance to address that issue?

4 DR. TOKARS: Dr. Andrews.

5 DR. ANDREWS: For events that are
6 extremely rare but serious, we'll probably not
7 detect them in a formal study of 3,000 or 6,000
8 patients. Those are likely, if drug-related, to
9 be identified hopefully by the providers who
10 have been extremely well-trained, and will
11 report them as quickly as possible should they
12 happen.

13 In the study that we were
14 envisioning as a prospect of cohort study, we
15 selected a sample size of 3,000 patients,
16 which should -- if there are no events of a
17 particular type, should provide some
18 reassurance that if the events of interest
19 occur at a rate of one out of a thousand,
20 that they would have been detected. So we
21 can basically rule that out.

22 Beyond that, we have the ability to

1 detect a relative risk of three or four
2 events that occur one out of thousand.

3 DR. HENNESSY: We have Harrington and
4 Burlington, Levin and Black.

5 DR. KLEIN: If I could just follow-up
6 for one second, I'm just very concerned that no
7 physician would see two of these events in their
8 practice lifetime, and yet for this population,
9 it would be a substantial risk if there were one
10 death in 3,000 related to the drug. I just want
11 to make that --

12 DR. HENNESSY: Dr. Harrington.

13 DR. HARRINGTON: Dr. Andrews, if you
14 could stay there, I'm curious that earlier
15 today, we heard about a patient population that
16 may be somewhere between 500,000 and 800,000
17 women a year potentially eligible for this
18 treatment. Why are then we talking about such
19 small sample sizes, given Dr. Klein's comment?

20 And my corollary to that is -- are
21 there independent academic groups who are
22 actually involved with the planning of these

1 studies? And is there some assurance that
2 the data would be out in the public realm, in
3 the publication, the peer-reviewed
4 literature, because I too am concerned that
5 with something this infrequent, and a lot of
6 explaining going on, what's the imperative of
7 getting information out to the public?

8 DR. ANDREWS: It's an ethical
9 obligation as an epidemiologist doing drug
10 safety studies to report finding as quickly as
11 possible. I'm an independent researcher. And
12 any contract, if I were doing a study, would
13 certainly allow the rights to publish and go
14 public with any safety information.

15 That's just a given.

16 DR. HARRINGTON: So I'm delighted to
17 hear that. Are you saying that you have an
18 agreement with the company that -- if you're the
19 person to do this, you have independent access
20 to all the data, with an unrestrictive right to
21 publish all the data. Is that your
22 understanding?

1 DR. ANDREWS: That's normally how drug
2 safety epidemiology studies are done.

3 DR. HARRINGTON: Everything I've been
4 reading in the literature the past couple of
5 weeks would suggest in fact, that's not the
6 case. But I'm delighted that that's the case
7 here. Have the data that we've been hearing
8 about today so far been published?

9 DR. TOKARS: We've written manuscripts
10 on our -- one was accepted. We have an accepted
11 postpartum manuscript. We've submitted the HUB
12 data multiple times. It's been accepted for
13 publishing -- Toni, would you like to come and
14 speak to this? Thank you.

15 DR. HENNESSY: Dr. Burlington will be
16 next.

17 DR. MANGIONE: Yes. The first
18 postpartum study we conducted has been published
19 in the Green Journal. And we've published the
20 second postpartum study and the heavy uterine
21 bleeding study in abstract form at major OB-GYN
22 meetings. And the manuscripts are in

1 preparation.

2 DR. HENNESSY: Dr. Burlington.

3 DR. BURLINGTON: With all due respect
4 to Dr. Pazdur's warning about not attributing
5 causes of death, as an infectious disease
6 internist, it seems at least there's an
7 imbalance in serious adverse events of
8 .9 percent versus .5 percent, and probably three
9 of the events, maybe a fourth one, was
10 contributed to by infection. One patient died
11 of TB, one of urosepsis, one of pneumonia, and
12 then the patient with the ruptured diverticulum.

13 So that leads me to ask, is there
14 anything that's practical that can or will be
15 included in the risk management plan to
16 reduce the potential for infectious disease
17 death or non-fatal infections?

18 DR. TOKARS: Like I said, the risk
19 management proposal program has not been
20 finalized. Certainly, we'd love to hear the
21 concerns and the advice of this panel in its
22 development.

1 DR. HENNESSY: Mr. Levin.

2 MR. LEVIN: First, I want to second
3 Dr. Pazdur's question about what does risk
4 management mean in this context. I didn't get
5 it, either. I don't know who you're educating
6 with what. I mean, what information are you
7 giving people? And so I would just say that's
8 really an important point, that that risk
9 management can be effective, but there are some
10 precursors that are necessary. You need to
11 understand what is the risk you're managing.
12 And I don't think we know here.

13 We have a signal of a problem, but
14 we don't really know what the problem is. So
15 I don't know how you educate or manage that
16 risk. That said, if we had a different
17 system of approval in this country that had
18 some sort of conditional step -- that's
19 something I've always been in favor
20 of -- particularly in circumstances like
21 this.

22 So how would you get to some

1 proximate of that? And that brings me back
2 to my distribution question. We've heard
3 what the pull is going to be for this drug,
4 in the public session. People want this
5 drug. They want the convenience of this
6 drug. So there's going to be a big pull to
7 use it off-label.

8 So it seems to me it's not enough
9 to talk about education, because we don't
10 understand what we're educating about. And
11 the only way you could really do
12 this -- manage it a little bit, at least, is
13 to really restrict distribution, and in a
14 sense, almost have -- I mean, I would call
15 it, for want of a better term, a treatment
16 IND situation, where you were learning more
17 in a larger population of patients before you
18 went out there and really fully marketed the
19 drug.

20 We don't have a conditional -- we
21 don't have room for conditional approval, but
22 we can limit distribution in a way that

1 doesn't allow the concerns about off-label to
2 sort of take off.

3 DR. HENNESSY: Was there a question
4 wrapped in there, Art?

5 MR. LEVIN: No. The question is, why
6 haven't you considered limited distribution as a
7 means of narrowing that exposure to off-label
8 use and inappropriate use?

9 DR. ANDREWS: Slide on, please. The
10 program that's being planned is something very
11 similar to what you're suggesting, which is a
12 very focus targeted rollout that starts out with
13 a very -- Luitpold is a small company. They
14 don't have huge resources for massive marketing.
15 So it's a gradual process, targeted to the
16 people who already are experienced with the
17 administration of IV iron, and in settings where
18 they can administer this safely, with only later
19 expansion to OB-GYNs as referral sources.

20 So to the extent that you can have
21 something like you're saying -- this is very
22 close to it, in my estimation. There was

1 another question about the size of the
2 population from Dr. Harrington, I believe,
3 and I didn't get a chance to answer that.
4 And I wanted to say that the numbers that you
5 saw earlier about possibly half a million
6 people with iron deficiency who might be
7 candidates who failed oral iron or whatever
8 that's an extrapolation based on a lot of
9 different assumptions, and probably the
10 maximum.

11 We see when new products come out,
12 the utilization is never anywhere close to
13 that. And if you restrict the population to
14 the three subgroups of women that we're
15 proposing, there's no epidemiology that I'm
16 aware of that quantifies the size of that
17 population.

18 So all I could say is I'm sure it's
19 much smaller than that estimate you saw
20 earlier, but don't know how big that is.

21 DR. HENNESSY: Dr. Black.

22 DR. BLACK: I'm also troubled by this,

1 but not necessarily by the same thing other
2 people are. Let's give you that it is going to
3 be used on-label, not off-label. I think,
4 off-label, we've already expressed our things.
5 The place where it seems to be most indicated to
6 me would be postpartum. There's a lot of people
7 who do deliveries, and patients don't stay very
8 long after those deliveries.

9 Now, those are the people I think
10 who would need to be educated, because I
11 think it's not going to take too much
12 imagination to understand that they're going
13 to be doing this, and they're going to be
14 doing it pretty aggressively. There's going
15 to be a demand for it, if not from other
16 physicians, but I think also from patients
17 once they hear about it.

18 Now, what I'm worried about is,
19 well, we'll go about this, and in a year,
20 we'll have a few events here and there which
21 also will have a pattern, and we won't have a
22 comparison group to look at who didn't get it

1 but would have been eligible for it.

2 Is there any idea that you have to
3 help us sort that out later on? I mean, had
4 that one postpartum cardiomyopathy not been
5 due to this and had been in the placebo
6 group, everything would have been different.

7 DR. ANDREWS: There is certainly the
8 large patient cohort study that we're proposing
9 still may not get at the numbers of events that
10 occur less than 1 out of 1000, and there
11 certainly hasn't been the background
12 epidemiologic work done to quantify these things
13 in the baseline population. I would expect that
14 would be part of the active development of the
15 epidemiology program.

16 DR. BLACK: Have you thought about
17 looking at subgroups that are a particular
18 high-risk, and educating the people who take
19 care of those -- those women, so that you get
20 some comparisons there?

21 DR. ANDREWS: Presumably, that will
22 occur in the hospital setting. And I mean,

1 these are good suggestions to add to the
2 development of this program, which as we keep
3 saying, is still very much under development.
4 So these thoughts are very helpful.

5 DR. HENNESSY: Dr. Peterson.

6 DR. PETERSON: I think this is
7 distilling down to an argument of proven
8 efficacy, raises hemoglobin, versus potential
9 toxicity, and how do you communicate that to the
10 professional and lay communities in a way that's
11 transparent and takes into account that a
12 potential concern for the drug is for people
13 with underlying heart disease and potential for
14 infection who may encounter increased risk of
15 death.

16 DR. HARRINGTON: How do you plan to
17 address communicating these issues, not only for
18 pregnant ladies, who with the denominator of
19 5 million you're going to get some of these
20 folks -- but the wider penumbra of use which
21 this drug will undoubtedly encounter?

22 DR. HENNESSY: After we hear the

1 answer to this, we'll move into the risk-benefit
2 balance segment of the questioning.

3 DR. GOODNOUGH: Just a few comments on
4 the perceived risk-benefit, and what we'd tell
5 patients either in educational materials or per
6 the informed consent process. We have a
7 high-risk OB program of about 6,000 deliveries a
8 year, and we transfuse about a half a dozen
9 women a week. And it's always in these clinical
10 settings for this indication where you have a
11 symptomatic women, or you have a woman who's
12 iron loss through bleeding exceeds any hope of
13 an oral iron medication being to correct that
14 problem.

15 And so when you decide to treat
16 iron deficiency anemia, there's only three
17 ways to do that -- either oral iron, and
18 we've shown that that's inferior in this
19 setting, or it's intravenous iron, or it's a
20 blood transfusion.

21 We had a near miss on June 12th on
22 labor and delivery, where we sent a unit of

1 blood up, and the mother looked up and said
2 that's not my blood type. It was a wrong
3 specimen sent to the blood bank. We had no
4 previous record on her. And that mother had
5 to save herself from us. So when you talk
6 about risk-benefit and you talk about remote
7 risks of this product, you're comparing that
8 to the known risks of a blood transfusion,
9 which are also similarly low.

10 We had a second wrong specimen from
11 labor and delivery two days ago. We caught
12 that, fortunately. So mismatch transfusions
13 because of wrong patient specimens is just
14 one example of a blood risk that I think is
15 part of the informed consent process when you
16 decide you have to treat a woman.

17 And I don't think that iron
18 deficiency anemia in these settings, you have
19 the luxury of not treating. And this risk of
20 infection I think is overblown. Because
21 again, to treat anything you do, whether it's
22 a blood transfusion, IV iron, or oral iron,

1 you're giving iron. I've never met a patient
2 whose infectious disease risk was lowered
3 with iron deficiency anemia. We actually
4 tried that in the Middle Ages, centuries of
5 bloodletting, and to my knowledge, that was
6 not proven to be effective.

7 So my premise from a clinical point
8 of view is you have to treat the iron
9 deficiency anemia. Anything you do to treat
10 it is going to contain iron. And you compare
11 the risk-benefit of the IV iron to the
12 possibility of a blood transfusion as well as
13 more iron therapy which would be suboptimal
14 in these targeted settings.

15 DR. LOCKWOOD: I'd like to say just
16 one thing. And Cassandra I'm sure will also say
17 something. But we have about 5,000 deliveries a
18 year at Yale. And we don't have that number of
19 transfusions a quarter, not to mention a week.
20 I'm not even sure, honestly, that we have that
21 major transfusions a year, never mind a week.
22 So either practices toward transfusion are

1 radically different in New Haven, Connecticut,
2 or I'd like to see your data -- what --

3 DR. HENNESSY: Let's move to
4 risk-benefit balance, and questions on that.

5 The members of the panel have -- so
6 I'll ask one. So from the available data, it
7 looks like our best guess of the effect of
8 the new drug versus alternatives is that it
9 increases the risk of death by about a factor
10 of three, although that's got wide confidence
11 intervals.

12 I'm wondering whether, given that
13 this is given to a largely healthy
14 population, one might argue that it's better
15 to follow-up that signal and have conclusive
16 evidence of safety rather than arguing the
17 way the cases of death that occurred. And
18 then if the studies do end up showing an
19 increased risk of death from this product,
20 whether many, many people would have
21 unnecessarily been exposed to the product.

22 DR. BRITTENHAM: Was there a question

1 in that?

2 DR. HENNESSY: The question is what's
3 the rationale for continuing -- for marketing
4 the product rather than doing additional studies
5 at this point to quantify this potentially
6 important safety signal that a three-fold
7 increase in the risk of death?

8 DR. TOKARS: Dr. Andrews, would you
9 like to speak to that?

10 DR. ANDREWS: What you would really
11 like to do is exclude a doubling of risk of
12 death. The death rate is very high -- if I
13 could have -- slide on, please. If we look at
14 the baseline mortality rate in this population,
15 we estimate that it would require about 320,000
16 individuals in a study in order to exclude a
17 relative risk of two.

18 DR. HENNESSY: Dr. Henderson.

19 DR. HENDERSON: I respectfully -- I
20 actually am offended by the fact that you're not
21 able to get a large-enough sample to prove that
22 it's safe. And therefore, I should counsel my

1 patients that it's probably a good thing to do.
2 I'm not so much concerned about being able to
3 prove that it is safe; I would just like to be
4 able to have a plausible explanation for what
5 we've seen. So if we could explain it and maybe
6 identify a high-risk group of patients that it
7 shouldn't be given to, I'd be comfortable then,
8 because then it could not be safe.

9 But I could tell patients that if
10 you don't have this risk, it's probably okay,
11 and maybe you do this. But if you do have
12 it, there is a risk. And if you in adequate
13 informed consent want to take that risk,
14 that's fine. But I don't have enough
15 information to actually give them a
16 legitimate risk-benefit ratio.

17 So the fact that we don't -- it's
18 not convenient to have a large-enough sample
19 size to power a study to actually look at the
20 risk makes me as an obstetrician, one who has
21 been sued, as I think every obstetrician has
22 ever been in this country -- very, very

1 uncomfortable with trying to distribute this
2 product.

3 DR. HENNESSY: Response.

4 DR. TOKARS: Dr. Mangione.

5 DR. MANGIONE: Well, if we talk about
6 deaths, there was a total of eleven in a
7 development program, and eight of those eleven
8 deaths occurred in chronic kidney disease
9 patients, either hemodialysis-dependent or
10 non-dialysis-dependent chronic kidney disease.

11 That seems to be the one conclusion
12 that we agree, and our experts agree, that is
13 a predictor, whether or not it's directly
14 related to the underlying disease or this is
15 the higher-risk population that these varied
16 events were seen. But what's striking is
17 that we're talking about a population that
18 has anywhere up to a 20 percent annual
19 mortality rate of the chronic kidney disease
20 group.

21 DR. HENNESSY: Dr. Kramer.

22 DR. KRAMER: I have two questions.

1 One is to try to understand the risk-benefit
2 ratio, I'd like to know what the indication is
3 in Europe?

4 DR. TOKARS: I can read that for you.
5 Indication -- the product is known as Ferinject
6 in Europe. And the indication is -- Ferinject
7 is indicated for the treatment of iron
8 deficiency when oral preparations are
9 ineffective or cannot be used. Iron deficiency
10 anemia.

11 DR. KRAMER: So it doesn't limit the
12 population.

13 DR. TOKARS: No.

14 DR. KRAMER: So the next question I
15 have is, I'm trying to understand the basis for
16 the sponsor withdrawing the CKD indication. It
17 could be what we just heard earlier, that people
18 thought that it wasn't the best preparation.
19 But part of that question is -- we heard it's
20 not feasible to conduct a controlled trial just
21 in the postpartum heavy uterine bleeding
22 population. But you have much higher risk, and

1 if you did a controlled trial on the CKD
2 population, you could at least say if you were
3 just very unlucky in your previous
4 randomization, or whether this is borne out with
5 a higher mortality rate with FCM.

6 DR. TOKARS: We withdrew the
7 hemodialysis indications. The CKD indication
8 was submitted after -- the CKD -- excuse me.
9 The CKD application has not been submitted for
10 approval. It's been submitted as a supplement
11 to our response to the non-approval letter.

12 DR. KRAMER: For safety. But I'm
13 asking why couldn't you -- since this is a very
14 tough thing to say -- I share Dr. Henderson's
15 concern that we can't determine what it is, so
16 let's just let it out there and hope. I don't
17 think we're very comfortable with that. So
18 could you tell me why you haven't proposed doing
19 a controlled trial in a broader population prior
20 to approval?

21 DR. TOKARS: We're doing -- prior to
22 approval. We are doing the ongoing CKD study

1 now. That's the safety study. That's a
2 randomized trial, randomizing between Ferinject
3 and standard of care. That trial hopes to
4 enroll 500 patients.

5 DR. KRAMER: How many patients?

6 DR. TOKARS: Five hundred, right now.

7 DR. KRAMER: When would that be done?

8 DR. TOKARS: It would take years. You
9 remember, this patient population is
10 well-treated with iron. So finding patients
11 that can meet our criteria to get enrolled is
12 very difficult. The CKD population is
13 well-treated with iron right now.

14 DR. HENNESSY: Other questions having
15 to do with the risk-benefit balance of the drug?

16 Go ahead.

17 DR. RIEVES: Dr. Hennessy, just to be
18 sure we're all on the same page, that European
19 indication is different now. The sense of
20 restriction can vary. It's not approved -- and
21 correct me on this -- it's not approved as an
22 alternative to oral iron. It's in patients who

1 are intolerant, or -- I forget the exact
2 words -- but I wanted to be sure we all
3 understand that.

4 DR. HENNESSY: At this point, I'd like
5 to call a 15-minute break. We'll come back at
6 20 after, and at that point, the committee will
7 address the questions that FDA would like us to
8 help them with.

9 So we'll return at 20 minutes after
10 3:00.

11 (Recess)

12 DR. HENNESSY: Let's get started.
13 This is the voting portion. And so some of
14 these questions are listed as for discussion
15 only, some of those are listed for voting. The
16 first question is listed as for discussion, but
17 I've since been advised that the FDA would like
18 us to take a vote on that. So we're going to
19 take a vote on the first question, even though
20 it's not listed as such.

21 Let me spend a minute or two on the
22 voting procedures. The new voting procedures

1 were implemented to avoid groupthink. And
2 here's what the new voting procedures are. I
3 will read the question into the record. I
4 will sequentially call on all permanent and
5 temporary members to address or provide
6 comments to the specific question, and can
7 express issues of concern as well as
8 positives.

9 After each member has provided
10 comment, I will call for a vote; the Chair,
11 me -- will ask all members voting yes to
12 raise their hands. While the members' hands
13 are raised, I'll ask each member voting yes
14 to state for the record their name and that
15 he or she is voting yes. Next, I will ask
16 for all members voting no to raise their
17 hands, and similarly, I will ask those voting
18 no to state their name and their no vote into
19 the record, and then I'll do the same thing
20 for the abstentions.

21 Upon the close of the vote, the
22 designated federal official will read the

1 final count of yes, no and abstentions into
2 the record. Are there any questions about
3 the procedures?

4 Okay. Yes, there's a question
5 about the procedure.

6 DR. KLEIN: Is the wording of each
7 question written in stone?

8 DR. HENNESSY: Yes. Because if we
9 start crafting questions, we will not leave at
10 the appointed hour. So if you don't like a
11 question and you think it's uninterpretable, you
12 can abstain; that's probably the best advice.

13 So the first question says,
14 "Injectafer is proposed for use in the
15 treatment of iron deficiency anemia among
16 postpartum patients with heavy uterine
17 bleeding, and patients with heavy uterine
18 bleeding, including patients who might
19 otherwise receive treatment with oral iron.
20 Oral iron was the controlled treatment within
21 most randomized clinical studies, although
22 some studies compared Injectafer to Venofer

1 or a placebo. Of concern were numerical
2 imbalances in adverse events, including
3 mortality, as follows -- mortality: for all
4 randomized trials, for all randomized
5 multicenter studies, Injectafer 5 out of
6 1206, for a cumulative incidence of
7 .4 percent, versus in the controls, 1 out of
8 994, which is .1 percent."

9 The asterisk indicates that the
10 control group was oral iron, Venofer or
11 placebo. In the second line, it says,
12 "Randomized multicenter oral iron-controlled
13 trials; 4 out of 1057, .4 percent control; 0
14 out of 834, 0 percent."

15 "Correlates to the mortality data
16 include a slightly higher rate of serious
17 cardiac events among patients receiving
18 Injectafer than oral iron; .9 percent versus
19 .4 percent in oral iron-controlled studies,
20 and the relatively common occurrence of
21 Grade 3 hypophosphatemia -- 8 to 70 percent,
22 versus 0 in oral iron-controlled postpartum

1 and heavy uterine bleeding studies."

2 We finally come to the question.

3 "Do the clinical data indicate that
4 Injectafer is associated with a mortality
5 disadvantage compared to oral iron?"

6 So I think what we should do -- and
7 you could tell me if this is right or
8 wrong -- we go around the table, you can
9 discuss, you can give your spin on that
10 question if you want to -- if not, you don't
11 have to, and then we'll have the vote.

12 Does that sound like what we're
13 supposed to do?

14 DR. WATKINS: Mostly just ask for if
15 there's any confusion on the meaning of the
16 question or things along that line, your input
17 on that, and then we'll begin to do the vote
18 around the table.

19 DR. HENNESSY: Dr. Burlington, you
20 don't vote; is that correct?

21 Mr. Levin?

22 MR. LEVIN: I know we've been told we

1 can't fiddle with language, but the
2 clarification is, how does the FDA define
3 "associate" for me? Big, big question.

4 DR. HENNESSY: What does "is" mean?
5 There's a definition --

6 DR. PAZDUR: There's no regulatory
7 definition of "associate." It's the one that
8 you'd find in the Webster's Dictionary, and I
9 don't have copy of the Webster's Dictionary.

10 MR. LEVIN: That was my comment.

11 DR. HENNESSY: Any comments or
12 questions, Ms. DeLuca?

13 MS. CORKERY-DeLUCA: I'll pass right
14 now.

15 DR. HENNESSY: Okay.

16 DR. MACIK: I don't have any questions
17 right now.

18 DR. HENNESSY: Dr. Kramer.

19 DR. KRAMER: Maybe this is a request
20 for clarification, but the way I read this
21 question, the key thing is the term "mortality
22 disadvantage." I think most people from the

1 discussion this morning are sure that there's
2 not enough patients to have a statistically
3 significant definite increase in mortality with
4 this drug. But am I correct that the term
5 "mortality disadvantage" could just be that it's
6 trending in the wrong direction, or there's some
7 basis for concern?

8 DR. HENNESSY: Clarification question?

9 DR. BLACK: I have one clarification.
10 You begin question one talking about what's
11 indicated for -- which is for postpartum
12 patients and those with heavy uterine bleeding;
13 does the question refer to those patients or to
14 all patients?

15 DR. HENNESSY: Does the FDA want to
16 clarify that?

17 DR. RIEVES: Since we're seeking
18 marketing approval for the postpartum and HUB;
19 it applies directly to that. But the
20 pattern -- the data are largely very similar in
21 both.

22 DR. HENNESSY: Are we allowed to

1 consider the fact that the drug may have
2 off-label use in answering this question?

3 DR. RIEVES: Yes. The question is
4 about the data here; it's not specifically about
5 the indication.

6 DR. HENNESSY: Any other comments or
7 questions or clarification? So the question is,
8 do the clinical data indicate that Injectafer is
9 associated with a mortality disadvantage
10 compared to oral iron? I would ask all people
11 voting yes to raise your hand.

12 DR. WATKINS: And then we'll start at
13 the far end of the table and --

14 DR. HENNESSY: With Mr. Levin.

15 MR. LEVIN: Arthur Levin, yes.

16 DR. WATKINS: Please keep your hand
17 raised.

18 DR. MACIK: Gail Macik, yes.

19 DR. BRITTENHAM: Gary Brittenham, yes.

20 DR. PETERSON: Peterson, yes.

21 DR. HENNESSY: We'll come back for the
22 abstainers and nos.

1 DR. KRAMER: Kramer, yes.

2 DR. LESAR: Timothy Lesar, yes.

3 DR. HENDERSON: Yes.

4 DR. HENNESSY: Could you say that
5 through the microphone, please?

6 DR. HENDERSON: Cassandra Henderson,
7 yes.

8 DR. HENNESSY: Sean Hennessy, yes.

9 DR. BLACK: Henry Black, yes.

10 DR. DAVIS: Terry Davis, yes.

11 DR. BLACK: I'm sorry, excuse me.

12 DR. PAGANINI: Emil Paganini, yes.

13 DR. HARRINGTON: Robert Harrington,
14 yes.

15 DR. HENNESSY: All those voting no,
16 please raise your hand.

17 Dr. Harrington, you were yes?

18 DR. HARRINGTON: I was yes.

19 DR. HENNESSY: All those voting no,
20 please raise your hand. State your name and
21 your vote, please.

22 MS. CORKERY-DeLUCA: JoEllen Deluca,

1 no.

2 DR. LINCOFF: Lincoff, no.

3 DR. HENNESSY: All those abstaining,
4 please raise your hand.

5 DR. KLEIN: Harvey Klein, abstained.

6 DR. LOCKWOOD: Charles Lockwood.

7 DR. HENNESSY: Dr. Greenland, are you
8 on the phone?

9 DR. WATKINS: Twelve voted yes, two
10 voted no, and two abstained, for a total of
11 sixteen.

12 DR. HENNESSY: Question number two
13 also calls for a vote, and --

14 DR. LINCOFF: Is there no discussion?
15 I mean, you've been defining questions.

16 DR. HENNESSY: So the point was when
17 we were going around talking about
18 clarifications, if you wanted to have a
19 discussion point, that was --

20 DR. LINCOFF: I thought that was just
21 on clarifications and --

22 DR. WATKINS: Mic on, please.

1 DR. LINCOFF: I thought that was just
2 on clarification if you didn't understand the
3 question. I mean, at no point in this whole
4 session have we had a chance to talk -- I mean
5 aside from asking a specific question, to sort
6 of discuss our impressions of these. If that's
7 not the format we're doing, then that's --

8 DR. HENNESSY: Go ahead.

9 DR. LINCOFF: As one of the few
10 dissenting votes, I thought it might be
11 worthwhile to sort of discuss it a bit.

12 DR. HENNESSY: It wasn't my intention
13 to cut off discussion.

14 DR. LINCOFF: I understand.

15 DR. HENNESSY: The first thing in my
16 mind was trying to facilitate that by going
17 around the table --

18 DR. LINCOFF: I think at some point,
19 we have to talk. There's been a lot of talk
20 today about too much explaining and explaining
21 away the numbers and things like that. But what
22 we have here is a trend that's not significant;

1 that's a "signal," that's the term in use
2 throughout. And it is a signal, but a signal
3 means you're entitled to look at it in more
4 detail, or you should look at it -- obligated to
5 look at it in more detail.

6 It's not a significant finding;
7 it's not the primary endpoint. It is a
8 signal that's concerning that merits an
9 requires further looking. And then when you
10 look, it becomes very hard to be plausible.
11 And I realize there's a lot of concern here
12 about the hypophosphatemia; there's been
13 questions about free iron and oxidative
14 stress, and yet there isn't any evidence that
15 anybody had these very low levels of
16 phosphate.

17 There's no evidence outside in
18 other test settings that there's increased
19 oxidative stress, and that may be a unifying
20 principle that would explain deaths occurring
21 in multiple organ systems with multiple
22 different etiologies -- if it happened -- but

1 we don't really have an evidence that that's
2 happening. And these really are widely
3 variant modes of death.

4 I don't know of any substance that
5 causes cardiomyopathy in seven days. And
6 this patient had -- the one patient in the
7 group that we're studying -- there may be
8 Cytoxan I think in very high doses can
9 cause -- if you look, we have infections in
10 patients with pre-existing infections; we
11 have one thrombosis and acute infarction, you
12 have cardiomyopathy.

13 So I think that we're being
14 overwhelmed here by a signal, and sort of
15 degrading the value of looking at that signal
16 in detail in adjudication. We accept
17 adjudication in other settings for primary
18 endpoints for adjudication committees, et
19 cetera, and I think when you get your own
20 impressions looking at the data, when you
21 have experts who have looked at the data, and
22 you can't make any science fit into that,

1 that it's at least worth being somewhat
2 skeptical.

3 And so those are my concerns.

4 DR. BLACK: Even though I voted yes
5 because of the constraints of the question and
6 what you meant by associate, and I think you had
7 to, considering what you have -- it doesn't mean
8 that we really addressed the problem
9 appropriately. The way I see it, this is a
10 problem that's currently poorly treated, that
11 the current options are not necessarily
12 acceptable, and where I'm somewhat little
13 concerned about this, I think we have to be
14 really careful when it comes to withholding this
15 from people where it might help based on what I
16 think is very soft data, which may be right.
17 But it's very soft data relative to the benefit.

18 DR. HENNESSY: Dr. Henderson?

19 DR. HENDERSON: I just think that for
20 healthy people, we have to be very skeptical
21 about giving something that may cause death. I
22 think that we're talking about a very healthy

1 population of women 18 to 45 years of age who
2 for the most part will live with whatever this
3 problem is, and then you're asking them to
4 undertake something that may increase the risk
5 of mortality, without enough data to say this is
6 bad. I don't know how to give them a
7 risk-benefit, and that's what makes me so
8 concerned.

9 DR. HENNESSY: Dr. Lockwood?

10 DR. LOCKWOOD: For all the reasons
11 that Michael outlined, it was very difficult for
12 me to vote yes, because these events were
13 disparate; there wasn't a common theme. But on
14 the other hand, I actually disagree a little bit
15 with what you just said. In fact, the
16 application of this drug in the postpartum
17 setting is most likely to occur in folks that
18 aren't healthy; people that had prolonged
19 labors, chorioamnionitis; therefore uterine
20 atony that had severe preeclampsia and platelet
21 dysfunction, and therefore extensive postpartum
22 bleeding, that perhaps had placenta accreta.

1 And so in fact I'm worried that the
2 postpartum patients this is most likely to be
3 used in are going to be more reflective of
4 the chronic renal disease multi-system
5 failure patients where the signal appeared to
6 be the most disturbing. I guess the reason I
7 couldn't vote yes is that the statistics here
8 are so absolutely weak, and the lack of a
9 common theme weren't persuasive enough to
10 vote yes.

11 DR. HENNESSY: Dr. Harrington?

12 DR. HARRINGTON: I think that Mike's
13 bringing up the key points. But for me, the
14 classifications that Dr. Kramer and Dr. Levin
15 raised as to what was meant by associated, and
16 what was meant by disadvantages as opposed to
17 saying something as clearly, do the data
18 indicate, or do the data indicate that the drug
19 is statistically significantly associated with a
20 mortality disadvantage.

21 That's very different, and I think
22 that we tried to parse through that. You

1 know, the third option here that I would have
2 liked to have taken was "maybe," and that was
3 not an option. But I want to clarify
4 something that Mike said, is that -- because
5 I fully agree with the FDA comments about the
6 proximate causes of deaths -- having sat on
7 multiple clinical and committees over the
8 years, death is one of the most difficult
9 things to adjudicate in terms of its
10 causality.

11 I don't think these events were
12 actually adjudicated. I think that the
13 company had a mortality finding after all
14 their data were in, and then they convened a
15 group of experts to review the data and
16 provide some insight into the data. That to
17 me is different than in a blinded prospective
18 way examining all the causes of death,
19 unaware of treatment assignment, and unaware
20 of the results of the trials and then
21 assigning causality. I think those are very
22 different -- if I'm wrong, that it was

1 prospectively defined, adjudicated, et
2 cetera, that would be helpful to have that
3 corrected.

4 DR. HENNESSY: Dr. Pazdur?

5 DR. PAZDUR: The only point that I
6 want to make is, I think the question might
7 actually get into some of the concerns that
8 these people have regarding risk-benefit
9 relationships here. And here again, we
10 understand the concerns of the people.
11 Obviously, we realize that there's not a
12 statistically significant finding here that's
13 obvious. We've said that. However, we have to
14 make some decisions here.

15 I also want to point out that the
16 votes -- we're more interested in people's
17 reasoning and in their discussion points than
18 pure votes here; okay? And here again,
19 that's why we do want you to give opinions
20 when we're going around the table, and that's
21 part of it. But I think some of the
22 clarification might come out in other,

1 especially the second question.

2 DR. HENNESSY: Dr. Paganini.

3 DR. PAGANINI: My real concern here is
4 not necessarily with this particular question,
5 but with the group of drugs per se, IV iron
6 overall. If you look at IV iron overall
7 compared to orals, you may start to see some
8 flutter. And I don't know if that's really been
9 well-defined. So I think this company has
10 brought to the table some very good data that
11 needs to be reviewed in a subgroup of patients
12 that are not CKD patients. I think it's valid;
13 it does supposed what it's to do, and I don't
14 think it's a big risk.

15 In the patient that's going to
16 probably be associated with off-label use,
17 there's a lot of indications there and a lot
18 of problems there, and perhaps a broader
19 question would be to look at that
20 subpopulation -- the CKD or the home PD
21 patient -- and see whether or not there's an
22 increased risk of mortality with IV iron

1 preparations per se, not necessarily just
2 with this particular drug.

3 DR. HENNESSY: Dr. Klein?

4 DR. KLEIN: Yes, my vote was a
5 "maybe," and I think it was probably the first
6 time I've ever voted as a maybe on an FDA-type
7 committee. And I think that I'd like to explain
8 that, because this committee's votes are not
9 binding on you; they're just advisory. And I
10 had a lot of difficulty with the wording. It
11 suggested to me causality, and we know that
12 there's no statistically significant difference
13 here. I've looked at all of these cases; I'm
14 concerned that they're not related. But I think
15 there's a signal, as you all have said, and if
16 you'd use the word "signal," if you'd used the
17 word "trend," I could have voted yes.

18 Given the wording of the question,
19 my concerns did not allow me to vote no, so I
20 voted "maybe."

21 DR. HENNESSY: Dr. Macik? Were there
22 any other comments or questions?

1 Let's go to question 2, which is
2 again a voting question, and I'll read that
3 into the record.

4 "Injectafer is proposed for use in
5 the treatment of iron deficiency anemia in
6 postpartum women or women who are anemic
7 secondary to heavy uterine bleeding.
8 Injectafer has been shown to replenish iron
9 and improve hemoglobin concentrations in
10 these patients."

11 "Some women with anemia secondary
12 to PP condition or HUB can be successfully
13 treated with oral iron. Clinical studies
14 were not designed to assess the safety and
15 efficacy of Injectafer specifically among
16 women who had an unsatisfactory response to
17 oral iron or were intolerant of oral iron.
18 In addition, FDA has identified safety
19 concerns of increased mortality and
20 hypophosphatemia as noted in question 1."

21 The question itself: "Do the
22 available efficacy and safety data support a

1 favorable benefit-risk assessment for
2 Injectafer in the treatment of iron
3 deficiency anemia in PP women or women with
4 HUB without qualifiers or restrictions in
5 this proposed usage?"

6 Let me open it up for clarification
7 questions or for discussion without
8 specifically going around, because that
9 didn't seem to work last time.

10 Dr. Black?

11 DR. BLACK: In part B, you're asking
12 just for HUB? You're just asking for just HUB
13 in part B. Does that mean -- is that what that
14 says?

15 DR. HENNESSY: No, it says --

16 DR. BLACK: Oh, PP or --

17 DR. HENNESSY: PP or HUB.

18 DR. BLACK: If you think it might be
19 indicated in one but not the other, do you have
20 any way you can vote?

21 DR. HENNESSY: I think you can
22 abstain.

1 DR. RIEVES: The point of question A
2 pertains to the proposed indication from the
3 company, which is in postpartum or women with
4 heavy uterine bleeding. That's the broad
5 first-line treatment. Part B is a bit more
6 restricted. It would apply to that population
7 of PP and HUB patients who are intolerant or
8 have an unsatisfactory response.

9 So there's a slight restriction in
10 part B. But part A is the broader, in PP and
11 HUB.

12 DR. HENNESSY: A is what we're voting
13 on now.

14 DR. HARRINGTON: Can I get another
15 clarification from you, Dr. Rieves? You only
16 know note restriction in question B, which is
17 intolerant. But throughout the day, we've had
18 discussion about -- I've written down at least
19 three or four different restrictions or
20 qualifiers. Would that be the time we address
21 those doing the discussion of that part B?

22 DR. RIEVES: Part B ties -- the first

1 question on the table is the company's proposed
2 indication, yes or no. And then you're exactly
3 right; the subsequent question is one that is
4 intended to stimulate discussion, and we have a
5 specific question on that. But as Dr. Pazdur
6 knows, we're particularly interested in the
7 discussion; the possibilities on part B.

8 DR. HENNESSY: Ms. Deluca?

9 MS. CORKERY-DeLUCA: I think in
10 looking at some women with anemia, sort of like
11 the Marine Corps looking for a few good
12 men -- in order to answer that question, you
13 have to be looking for just a few good women,
14 because I don't think that it really -- the
15 slide shows a preponderance of success. I just
16 can't quite see, because the next question can
17 move into the RiskMap map, but I just can't
18 quite see that the paragraph at the top matches
19 either A or B in what they're asking for.

20 DR. HENNESSY: Is there any discussion
21 further on 2a? Dr. Peterson?

22 DR. PETERSON: I think my query would

1 be regarding qualifiers and restrictions. I
2 interpret restrictions as restricting the
3 population that would be targeted. Qualifiers,
4 does that imply labeling, or how do you
5 distinguish between the two? That would be
6 my -- because an unqualified label would be
7 highly unusual.

8 DR. RIEVES: That's exactly right;
9 we're becoming a bit semantic there. But the
10 point here is to vote upon the proposed
11 indication statement. It's important to note
12 that marketing derives most notably from the
13 labeling. Companies can say FDA, we promise
14 that we'll not promote this product in such and
15 such a manner.

16 But the actual regulatory status
17 there; the ability that we have to control
18 that marketing, is derived from the labeling,
19 and particularly from the indications. So
20 we're talking here about the indication
21 statement particularly. And that's what
22 we're somewhat struggling and looking for an

1 independent opinion about.

2 DR. HENNESSY: Dr. Henderson?

3 DR. HENDERSON: The question, can we
4 interpret it or add probable favorable
5 risk-benefit, or do we just have to say
6 favorable risk-benefit?

7 DR. RIEVES: We need a conclusion if
8 at all possible. Yes or no.

9 DR. HENNESSY: Dr. Klein?

10 DR. KLEIN: Since this is the time for
11 discussion, I'm going to discuss. I think that
12 I'm convinced that this is effective, that it's
13 as effective as oral iron, or more effective
14 than oral iron. So if the question is if you
15 can't take oral iron or you don't respond to
16 oral iron, what do you do? You don't leave
17 people severely anemic or likely to get less
18 anemic. Probably what you do is use one of the
19 licenses for other applications -- intravenous
20 preparations which you give off-label.

21 One of them is clearly more
22 dangerous in my mind than this one. The

1 other one is probably just as dangerous, or
2 at least may be. Or you give blood
3 transfusions, which are inappropriate unless
4 in an emergency.

5 So I think that we have to think in
6 terms of risk-benefit of what else would be
7 done in these situations.

8 DR. HENNESSY: Dr. Lincoff.

9 DR. LINCOFF: I think this is the
10 place -- correct me if I'm wrong -- where if we
11 have concerns about relative risk-benefit in
12 different populations, or a degree of doubt
13 outweighing a degree of benefit, then this is
14 where we express it, because what they're asking
15 for is an unrestricted indication of the
16 population. So if we feel that the compromise
17 is that there's a restricted indication and if
18 you want more, you do the trials to do it, I
19 suspect that this is about the place where we
20 begin to indicate that.

21 DR. HENNESSY: Dr. Macik?

22 DR. MACIK: Just to reiterate a couple

1 of comments that were made; when you look at
2 this, oral iron doesn't work well, either
3 because they don't take it or it just doesn't
4 work well, doesn't work as fast. So you have to
5 feel that to go on to the IV doesn't really make
6 a lot of sense, because everybody will probably
7 feel that.

8 But how do you get them back to
9 give them then this product? So when you're
10 looking at risk-benefit, I think there seems
11 to be some difference of opinion just between
12 our own obstetricians whether iron deficiency
13 is a big enough problem that requires
14 treatment, then you have the question, we're
15 going to treat it. It is a big enough
16 problem, we do need to treat it; do we give
17 everybody oral iron first?

18 The data says oral iron -- both the
19 data that's here and in the clinical trial
20 suggest anywhere from 60 to 80 percent in the
21 oral iron group that actually had compliance
22 with the drug; it's going to be far less than

1 that in the real world. You know, if you
2 make it a requirement they do that, first, is
3 that really going to work? I think it's very
4 difficult with we have here to make a clear
5 choice between going to step B -- that is to
6 say, okay, we're going to just restrict it to
7 people who have failed oral iron. So it
8 really gets back to -- you have to make a
9 choice on step A. Is the risk-benefit in
10 favor of going with a product that has a
11 trend towards significant risk?

12 DR. HENNESSY: Dr. Paganini.

13 DR. PAGANINI: I think the issue of
14 hypophosphatemia was well-defined by Dr. Dennis,
15 and I don't see that as a major risk factor at
16 all in any of these people. And I would agree
17 that forcibly having somebody to go through oral
18 iron to prove that they're resistant or not
19 favorably inclined to respond to that before you
20 give this drug in this period of time for this
21 subgroup of patients is foolish.

22 DR. HENNESSY: Dr. Harrington.

1 DR. HARRINGTON: While it may be true
2 that people have great difficulty adhering to
3 the oral iron regimen, at least the data in the
4 randomized trial says that oral iron does work.
5 Clearly, the IV stuff works better. But oral
6 iron does work.

7 I mean, there are other issues
8 about clinical trials, clinical practice et
9 cetera, but here we have increased greater
10 than 2 grams during six weeks, 96 percent
11 versus 94, and then hemoglobin greater than
12 12 any time during this six weeks; 91 versus
13 67. Now, that's the biggest difference to
14 me. Clearly these are people in a clinical
15 trial; I'll accept all of that. But I don't
16 think it's fair to say that oral iron doesn't
17 work.

18 DR. HENNESSY: Dr. Kramer.

19 DR. KRAMER: Just listening to the
20 discussion, I just want to make sure that we all
21 understand at least in part A, if we said yes to
22 that question, that we'd basically be saying

1 that for any patient who has iron deficiency
2 after delivery, that this is a reasonable
3 option, and it can be marketed for that. So I
4 think we need to understand we're really saying
5 first-line treatment.

6 DR. HENNESSY: Dr. Macik.

7 DR. MACIK: Actually, one of the
8 things that came back -- I meant to say earlier,
9 how do you define iron deficiency? And I think
10 that's where the bigger issue comes in, and
11 we've been discussing that. The criteria used
12 for iron deficiency in some of these trials
13 seemed a little generous; what their iron
14 saturation and what their ferritin levels were
15 to define iron deficiency.

16 So I think if you're going to put
17 any restriction on, it would be having to
18 document a little bit better what are you
19 treating. Are you treating somebody who has
20 true iron deficiency and -- the parameters
21 were a little difficult to assess.

22 DR. HENNESSY: Are we ready to vote on

1 this thing?

2 DR. BRITTENHAM: Yes, I'd just like to
3 reiterate that the underlying condition being
4 treated has a vanishingly small risk of
5 death -- the iron-deficiency anemia itself in
6 this population. For me, the data are
7 inadequate to exclude the possibility that
8 Injectafer causes death. And so without clear
9 evidence that we can proceed without subjecting
10 women who would not otherwise die to the risk of
11 dying by taking this preparation, I feel we have
12 to vote no.

13 DR. HENNESSY: Let's call the
14 question. I'll read just the question part.
15 "Do the available efficacy and safety data
16 support a favorable benefit-risk assessment for
17 Injectafer in the treatment of iron deficiency
18 anemia in PP women or women with HUB, without
19 qualifiers or restrictions in this proposed
20 usage?"

21 Those voting yes, please raise your
22 hand.

1 Dr. Paganini?
2 DR. PAGANINI: Emil Paganini, yes.
3 MS. CORKERY-DeLUCA: JoEllen Deluca,
4 yes.
5 DR. HENNESSY: Those voting no, please
6 raise your hand. We'll start on this side.
7 Dr. Harrington.
8 DR. HARRINGTON: Robert Harrington,
9 yes -- I mean no.
10 DR. LINCOFF: Michael Lincoff, no.
11 DR. BLACK: Henry Black, no.
12 DR. DAVIS: Terry Davis, no.
13 DR. HENNESSY: Sean Hennessy, no.
14 DR. LOCKWOOD: Charlie Lockwood, no.
15 DR. HENDERSON: Cassandra Henderson,
16 no. And also, I still disagree with the idea --
17 DR. HENNESSY: Sorry, during this
18 point -- this is just voting, there's no
19 discussion.
20 DR. HENDERSON: All right -- no.
21 DR. LESAR: Tim Lesar, no.
22 DR. KRAMER: Judith Kramer, no.

1 DR. KLEIN: Harvey Klein, no.

2 DR. PETERSON: Peterson, no.

3 DR. BRITTENHAM: Brittenham, no.

4 MR. LEVIN: Arthur Levin, no.

5 DR. HENNESSY: Abstainers, please
6 raise your hand. Name and vote into the record,
7 please.

8 DR. MACIK: Gail Macik, abstained.

9 DR. WATKINS: There are 2 yes votes,
10 13 nos, and one abstention.

11 DR. HENNESSY: Sander, are you on now?

12 DR. GREENLAND: Yes. I said no.

13 DR. HENNESSY: We've just voted
14 question 2a.

15 DR. WATKINS: 2a.

16 DR. HENNESSY: 2a, thank you. We've
17 just voted on question 2a.

18 Do you have a vote on 2a?

19 DR. GREENLAND: Yes, it was a no.

20 DR. HENNESSY: So can you state your
21 name and your vote, please.

22 DR. GREENLAND: Sander Greenland, no.

1 DR. HENNESSY: Thank you.

2 DR. WATKINS: Then let me restate the
3 totals. It's 2 yes, 14 no, and 1 abstention,
4 for a total of 17 votes.

5 DR. HENNESSY: Question 2b is also a
6 vote. If you voted no in 2a. So I don't -- I
7 assume that all of us get to vote on this one
8 regardless of whether -- so only those no voters
9 for 2a get to vote on 2b? What's that?

10 So everyone gets the vote. So
11 imagine that you voted no on 2a.

12 "Do the available efficacy and
13 safety data support a favorable benefit-risk
14 assessment for Injectafer in the treatment of
15 iron-deficiency anemia in PP women or women
16 with HUB who have had an unsatisfactory
17 response to oral iron or were intolerant of
18 oral iron. Note, this population was not
19 studied, and the safety issues identified in
20 question 1 have not been examined in this
21 population in a randomized trial in which
22 Injectafer was compared to other parenteral

1 or parenteral iron compounds."

2 So let's open this up for some
3 minutes of discussion.

4 Dr. Kramer, did you have your hand
5 up?

6 DR. KRAMER: I don't know if this is
7 appropriate or not, but one of the things that
8 bothers me about answering a question like this
9 is that if you said that it was a favorable
10 response for profiling the subset that wasn't
11 studied, you would also be approving the drug
12 and it could be used much more broadly
13 off-label. So are we just addressing the
14 risk-benefit profile for the subpopulation, or
15 the risk-benefit profile to the population
16 exposed if it were approved?

17 DR. HENNESSY: To this population as
18 defined in the question.

19 DR. KRAMER: So to the discussion
20 about that population, we've already heard from
21 a nephrologist that it's really not easy to
22 define this population or to use this exclusion.

1 And it seems to me that the data from the CKD
2 population is clearly applicable, and so our
3 concern about mortality that we just expressed
4 in Part A should be the same. And so I don't
5 understand if you voted no to A, how you would
6 vote yes to B.

7 DR. HENNESSY: Dr. Lincoff.

8 DR. LINCOFF: I think what B does,
9 although I agree that it's problematic to take a
10 subset that really wasn't studied as a subset,
11 so I guess it's a twofold question. One is, you
12 have to ask yourself, do you think there's any
13 role at all for this drug. And then if you do,
14 to me, this is a way to say this shouldn't be
15 your first line of therapy for iron deficiency
16 anemia in this population; you should try oral
17 therapy, and if that doesn't work, this is now
18 available to you.

19 So although the methodologic
20 weaknesses that this specific population has
21 not been studied because the proper
22 comparative would have been the parenteral

1 compounds, not the oral, and you come into
2 all the difficulties there what you're
3 comparing to. We know it's effective, so I
4 don't think the issue is would it be
5 effective.

6 And we're just left with, do we
7 think it's substantially less safe in this
8 population than would be in all of the
9 population of patients who have iron
10 deficiency anemia associated with pregnancy
11 and with heavy uterine bleeding.

12 So I think this has a role; it has
13 a role if you want the drug to be available,
14 but you don't want it to be first-line for
15 this population.

16 DR. HENNESSY: Dr. Macik?

17 DR. MACIK: I keep going back and
18 forth between trying to be a scientist and
19 looking at the questions correctly and being the
20 practical clinician with what do you have to do.
21 And I'm frequently in the position of having to
22 treat patients with menorrhagia, with heavy

1 blood loss, my bleeding disorders patients who
2 have to go to IV iron. And right now, many of
3 the questions being addressed and
4 discussed -- and I've had a lot of eye-opening
5 at this meeting, I have no clue what I'm doing
6 with my current preparations. So based on that,
7 I would much rather use this product that I have
8 some information on than the couple of products
9 that I would otherwise be using in this group of
10 patients, and do use in this group of patients.

11 So I think it's another Catch-22,
12 when you're kind of the first product to
13 answer a question and there are other
14 products in use, but they never answered that
15 question, what is your role in trying to
16 define that answer? Would heparin or
17 coumadin be approved today by the FDA?
18 Probably not, yet those are standards of
19 care.

20 So in addressing this, I would say
21 that I right now use IV iron in these
22 patients because -- I have usually, because

1 they have failed oral iron, even though it is
2 sometimes difficult to get them back, or
3 because they live six hours away and I know I
4 can't get them back; I give them the IV iron.
5 And I think in addressing all of these
6 questions, I would much rather have a drug
7 with some information, and probably have
8 talked myself into trying oral iron first
9 because of the trend to bad outcome with
10 IV iron. But having this product available
11 to me when I can't use oral iron, I prefer to
12 have something with data than to use the
13 other iron preparations that I'm currently
14 using.

15 DR. HENNESSY: Ms. Deluca.

16 MS. CORKERY-DeLUCA: I think I'm just
17 mirroring in my layperson's way what Dr. Macik
18 said. It just felt, particularly with the
19 phrase, "Were having unsatisfactory response to
20 oral iron or were intolerant of oral iron" sort
21 of negated the fact that it seems to be a really
22 fine product and that had overwhelmingly

1 well-presented data. And it just seems like
2 apples and oranges were here, but the question
3 that was being asked was the lemon.

4 DR. HENNESSY: Dr. Henderson.

5 DR. LOCKWOOD: I'm pleased with the
6 academic sophistry and actually talking like a
7 real clinician; the reality is that to
8 presuppose this question actually represents a
9 true clinical problem. These patients would
10 come back to us in a week and we'd still -- you
11 know, we're feeling terrible, we draw another
12 CBC and their hematocrit wouldn't move much, and
13 then the alternative would be basically, she
14 can't tolerate the iron and she's not responding
15 to the iron, does she need a transfusion or is
16 there an alternative?

17 And I think that given that level
18 of raising of the risk-benefit ratio, it
19 would be a reasonable thing to offer. But I
20 think if it's -- you asked us to nuance a
21 really tough sort of question. It depends on
22 all kinds of clinical vagaries.

1 DR. HENNESSY: That's why you get the
2 big money.

3 Dr. Klein.

4 DR. PAZDUR: Could I just mention one
5 thing. I think we've realize this a difficult
6 question. But I think it goes back to the point
7 that Dr. Brittenham was trying to get at during
8 his comments, that you have this signal -- if
9 you want to use that word -- out there, and even
10 if you redefine the population, does that
11 outbalance the safety issue? And that's the
12 bottom line here that we're trying to get at,
13 because it kind of reverts back to
14 Dr. Brittenham's comments.

15 DR. HENNESSY: Dr. Paganini.

16 DR. PAGANINI: I think that's the
17 question, and I see this being a foolish vote,
18 because the issue is that many of these kids
19 come in at pregnancy delivering anemic. They
20 had all the opportunity to take their oral iron;
21 they didn't, and any time you're going to be
22 motivated to do something it's for your baby,

1 they -- now you're asking them postpartum to say
2 now, I want to you to try this oral iron to see
3 if it works or not.

4 This population as studied didn't
5 seem to have a negative risk-benefit -- this
6 population. I have major problems with CKDs.
7 And I've said that multiple times through
8 here, but this population, to come in, have
9 their baby or they are so heavily bleeding
10 that oral is ridiculous because they're
11 bleeding so heavily, then why are we
12 restricting this? Why do you have to try
13 something first and then come back to it when
14 you know you're going to come back to it
15 anyway?

16 DR. HENNESSY: Dr. Black.

17 DR. BLACK: I'm kind of concerned. I
18 think people who see patients have really
19 articulated this beautifully. It's not
20 reasonable really to expect an oral trial very
21 often to be helpful, and I guess the concern is
22 the question of whether this is going to be a

1 foot in the door so it will be used widely
2 off-label for things that we don't think the
3 safety's been proven.

4 So I think this is an effective
5 product that seems to me from what I can see
6 as effective, if not more so than what's
7 available. And I think the practicalities
8 may outweigh our concerns right now.

9 DR. HENNESSY: Dr. Klein.

10 DR. KLEIN: The problems I see with
11 the question are that I think most of us agree
12 that this is effective. And I think that that
13 then becomes a risk-benefit analysis. And in
14 looking at that analysis, the question is what
15 is done with these women who do not respond to
16 iron or simply cannot tolerate iron. On the one
17 hand, some of them simply go home and maybe it's
18 12 months there, their hemoglobin is back
19 up -- I think that's probably few. We heard
20 from Dr. Brittenham, and that's absolutely
21 correct that very few of these individuals die,
22 but what happens is something else is done to

1 them.

2 And that something else is probably
3 iron dextrose, which frankly I think we have
4 a lot of data on and that's not a good
5 alternative; or iron sucrose, which we have
6 far fewer data on, but that's probably not a
7 terrific possibility, or something that's
8 been studied as effective.

9 But there's a signal there for
10 which we could require post-marketing
11 surveillance. We can't for the other
12 alternatives. The third possibility is blood
13 transfusion, and I would propose to you
14 although it's very safe, we know that deaths
15 are involved. So we know that there's a
16 toxicity there and it's not indicated, but
17 clearly it's being used.

18 DR. HENNESSY: Dr. Henderson.

19 DR. HENDERSON: The randomized
20 clinical trial show that the iron does work in a
21 study -- in a randomized trial. But also as a
22 clinician, I have had patients who went home

1 severely anemic, and in discussing diet and iron
2 therapy, they have taken iron and they've gotten
3 better. Now, there are some who didn't do it
4 earlier primarily because they didn't feel
5 badly. But when they go home and they're a
6 little tired, they might take it. So I mean,
7 going home if they're not willing to take it,
8 then I think if they have another option such as
9 this, that makes sense rather than doing a blood
10 transfusion.

11 But to immediately -- because
12 someone has a hemoglobin of 9, to say this is
13 an option so you don't have to take these
14 prenatal vitamins, to use this. And that,
15 I'm uncomfortable with, given the signal.

16 DR. HENNESSY: Dr. Kramer?

17 DR. KRAMER: I think a lot hinges on
18 whether we believe that the signal which really
19 showed up in the CKD population is applicable to
20 this population. It's fine to say we didn't see
21 it in this population, but the fundamental thing
22 we're grappling with is that it might be an

1 indication, and we just didn't see it because of
2 such a low rate of death as a baseline. So to
3 look at mortality is very difficult. And to get
4 to what Dr. Lincoff said -- does this agent have
5 a role for this indication?

6 To me, this discussion hinges on if
7 this is the only data we have, that's it, we
8 have to make a decision, it excludes the
9 question that I asked earlier, which is:
10 would it be helpful to have additional
11 controlled data even if it were in a CKD
12 population, which we know it will be
13 used -- from what I have heard from the
14 experts, will be used in that population once
15 it's on the market off-label. And we might
16 be able to get some valuable controlled
17 information, but it wouldn't mean approval
18 now.

19 DR. HENNESSY: I think we're getting
20 close to a vote. We have some more questions to
21 get through, so try to restrict your comments to
22 things that haven't already been said in

1 substance already.

2 Dr. Harrington.

3 DR. HARRINGTON: The conundrum for me
4 here is the opening the door into the off-label
5 population, which really troubles me. And in
6 the above question, it says "without qualifiers
7 or restrictions," and here the only restriction
8 is the specific group who haven't tolerated oral
9 iron.

10 I've heard from the patient
11 representatives from the Ob-Gyn community and
12 the hematologists that this is a drug that
13 they would like to have in their
14 armamentarium. But I can't get my brain
15 beyond the fact that once it's out there,
16 it's wide open. I think that Dr. Levin said
17 it nicely earlier, that we don't have in this
18 country an approval system which is very
19 conditional.

20 Lot of recommendations can be made,
21 et cetera, but once it's out there, it's out
22 there. And that, Sean, is what I'm having

1 trouble coming to grips with.

2 DR. HENNESSY: Dr. Brittenham.

3 DR. BRITTENHAM: Yes. And to follow
4 that comment, we do know that the approved
5 products have rates from the FDA MedWatch
6 database that say that the risk of adverse
7 events, whatever the limitations of the
8 database, are less than 10 per million. We have
9 10 per 2,000 here. We have adverse events,
10 whatever the case. And so it's not that there's
11 no choice of an intravenous iron preparation.

12 There are four available -- there
13 are now -- this is a fifth. And so it's not
14 that we're choosing, if we don't approve
15 this, to deprive individuals of intravenous
16 iron. They're subject to different
17 limitations, but there are intravenous iron
18 preparations that are available, and with the
19 available post-marketing surveillance, have
20 low risk, have risk of adverse events that
21 appear to be orders of magnitude lower than
22 what we're seeing.

1 DR. HENNESSY: Dr. Kramer?

2 DR. KRAMER: I'd like to respond to
3 that statement. I think it's very uncomfortable
4 with comparing rates from the MedWatch
5 post-marketing surveillance system, where we
6 know that we may have like 1 percent of cases
7 reported that actually occur, and comparing that
8 to a randomized clinical trial. And we don't
9 have any direct randomized comparison with the
10 IV iron preparation. So I think we have to be
11 very careful to make those comparisons.

12 DR. BRITTENHAM: I certainly agree
13 that the lack of comparison to the approved iron
14 medications is a problem.

15 DR. HENNESSY: Dr. Macik, and then
16 let's --

17 DR. MACIK: Very quickly just to say
18 that I don't report all my reactions to iron
19 dextran, which are many. And I hate giving that
20 drug, and that's kind of what I have to do now,
21 or iron sucrose -- much fewer, but I can give
22 such a small dose at a time. A patient who

1 lives two or three hours away has to come back
2 to get four and five, six infusions, whereas
3 this drug gives me an option for treating.

4 So there are some
5 differences -- that I'm forced to use drugs
6 now somewhat off-label and with
7 characteristics that aren't good. And at
8 least to have some data on this drug that
9 suggests that might help in that population.

10 DR. HENNESSY: Let's hear from
11 Dr. Burlington and see if Dr. Greenland has
12 anything to say, and then let's take a vote on
13 this one.

14 DR. BURLINGTON: Sure. I'm obviously
15 not going to vote on this question, but I'd like
16 to correct what I think may be a misimpression
17 in the discussion here. Eight weeks from today,
18 the provisions of the new law will go into
19 effect, and FDA will in fact have the authority
20 and a wide latitude to impose all sorts of
21 conditions on the approval.

22 And in effect, we'll be entering a

1 regime where we have conditional approval for
2 these products. And I think that's
3 specifically why they're looking for our
4 advice on what sort of conditions would be
5 appropriate.

6 DR. HENNESSY: Dr. Greenland, anything
7 to add?

8 DR. GREENLAND: First of all, on 2B,
9 and it's simply that the way this has worded to
10 me strictly says that given the absence of data,
11 the only choice that I can see for me as is a no
12 vote, because there isn't data that can answer
13 the question.

14 DR. HENNESSY: So the question we're
15 now going to vote on is, if you voted no in
16 2A -- and I think we can ignore that part of the
17 question -- do the available efficacy and safety
18 data support a favorable benefit-risk assessment
19 for Injectafer in the treatment of iron
20 deficiency anemia in postpartum women or women
21 with HUB who have had an unsatisfactory response
22 to oral iron or were intolerant to oral iron?

1 All those voting yes, please raise
2 your hand. Let's start with Dr. Macik.
3 DR. MACIK: Gail Macik, yes.
4 DR. PETERSON: Peterson, yes.
5 DR. KLEIN: Harvey Klein, yes.
6 DR. LESAR: Tim Lesar, yes.
7 DR. HENDERSON: Cassandra Henderson,
8 yes.
9 DR. LOCKWOOD: Lockwood, yes.
10 DR. HENNESSY: Hennessy, yes.
11 DR. BLACK: Black, yes.
12 DR. LINCOFF: Lincoff, yes.
13 DR. HARRINGTON: Harrington, yes.
14 DR. HENNESSY: Those voting no, please
15 raise your hand.
16 Okay. Mr. Levin.
17 MR. LEVIN: Levin, no.
18 DR. BRITTENHAM: Brittenham, no.
19 DR. KRAMER: Kramer, no.
20 DR. DAVIS: Davis, no.
21 DR. HENNESSY: Dr. Greenland, do you
22 have a vote?

1 DR. GREENLAND: Vote with no.

2 DR. HENNESSY: All those abstaining,
3 please raise your hand.

4 DR. PAGANINI: Point of clarification,
5 please. I voted yes on one.

6 DR. HENNESSY: So a yes on one would
7 be an obvious yes on this. Did you mis-vote,
8 did you -- do you wish to --

9 DR. PAGANINI: No, no, no. I voted
10 yes on one, and I didn't vote at all on this,
11 because I assumed that since I voted yes on
12 one --

13 DR. HENNESSY: So that means you
14 abstained on this one.

15 DR. PAGANINI: I'll abstain. That
16 would be fine.

17 DR. HENNESSY: Okay. So Ms. Deluca,
18 your vote is yes, no, or abstain?

19 MS. CORKERY-DELUCA: I hadn't
20 really -- I guess it would have to be abstain;
21 otherwise -- since I voted yes on the first.

22 DR. HENNESSY: I think that's some

1 good guidance for the question writers in the
2 future.

3 DR. GREENLAND: Can I say that part of
4 it is in the nature of the wording.

5 DR. HENNESSY: Yes.

6 So we're tallying the votes.

7 DR. WATKINS: There were 10 yes, 5
8 nos, and 2 abstentions, for a total of 17 votes.

9 DR. HENNESSY: We have two questions
10 left; neither of these requires a vote. So the
11 first is, if you recommend marketing approval,
12 please discuss designs for studies that FDA
13 should request the manufacturer conduct
14 post-marketing. Anybody want to open up with
15 this?

16 Dr. Harrington?

17 DR. HARRINGTON: I voted yes quite
18 reluctantly. And I voted yes quite reluctantly
19 because I think that the evidence base is less
20 than what I usually would like to see to get a
21 drug approved and put on to the market. What
22 I'd like to see is there to be very restrictive

1 prescribing around this drug that gets to the
2 heart of what we talked about earlier in terms
3 of limiting it to certain groups of physicians
4 with intensive education.

5 I'd like to see randomized clinical
6 trials that are almost an order of magnitude
7 larger than what are currently planned, if
8 this is truly a situation that affects many
9 hundreds of thousands of patients. And I
10 understand there may be some disagreement
11 over that.

12 And I'd like to see an
13 independently-run registry of these women in
14 the treatment where we can begin to -- in
15 large numbers of women, not 3,000 women, but
16 many, many tens of thousands of women that we
17 can get some hands-on whether or not in fact
18 there's an increased risk. So Sean, highly
19 restrictive, enforced restriction, and much
20 more expansive clinical trials and registries
21 than I heard described today.

22 DR. HENNESSY: Dr. Lincoff, did you

1 have anything to say?

2 DR. LINCOFF: I'm always concerned
3 about observational studies and what you do with
4 small point estimates, because that's what you
5 get -- you get events. There'll be 3,000
6 people, there's probably going to an event, and
7 the descriptions that were given were, well, if
8 we don't have any, if we have zero then we can
9 have an upper limit on our confidence interval
10 that would exclude a certain endpoint. But it's
11 unlikely that that'll happen.

12 And so I'm always concerned about
13 observational studies. In that regard, in
14 the inability to get a very good comparative
15 study -- a comparative group other than
16 through randomization. So I think it's
17 difficult as it is, particularly with the
18 size, other randomized trials with
19 populations similar in size to what the total
20 cumulative is now in a group that includes
21 any renal.

22 Because the problem with the renal

1 failure is that you don't have much in the
2 way of comparative data, or as much. Many of
3 those are the noncomparative. So I think
4 that if one focuses on a high-risk group in a
5 randomized fashion, then one can either rebut
6 this unlucky set of circumstances that gave
7 you the clustering of events, the signal, or
8 see that that in fact is real.

9 DR. HENNESSY: So I've been instructed
10 that we should go on the table and take comments
11 individually. If what you're going to say has
12 been said by someone else, feel free to not
13 repeat it and pass.

14 Dr. Paganini.

15 DR. PAGANINI: The non-CKD studies,
16 specifically to the population that I felt met
17 the criteria, would be restricted -- heavily
18 restricted to just those folks. I would suggest
19 that phosphate levels be done either pre or post
20 or 14 days, that you continue your post-approval
21 SAEs, and specifically in two general areas,
22 both in infection and in cardiac. And

1 specifically, in infection and all-cause (?)
2 infection and sepsis as a secondary underlying
3 cardiac arrhythmias.

4 I would do it as two phases, 0 to
5 30 days or 28 days, and then for six months
6 after that for any long-term effect. I would
7 further suggest that it not be used
8 off-label. In fact, on the label, it should
9 say this is not indicated for CKD, period,
10 and in that label, the company, if they want
11 the indication for CKD, should in fact take
12 that population and study that population
13 with -- in a true prospective randomized
14 controlled fashion to either get that as a
15 potential label indication or identify the
16 problems with that subpopulation.

17 DR. BLACK: I just want to add one
18 thing to what Gail was saying before. She
19 described very nicely a set of patients where
20 she would like to have this, where there was an
21 active comparative. That might be something
22 that could be studied. People who are

1 intolerant to oral iron that she would have to
2 give some other IV preparation to, and that
3 might be one of those things.

4 That seems to be what we said or we
5 approved for. We didn't talk about CKD or
6 anything else, but we did talk about an
7 iron-intolerant person that you would take
8 care of who is iron-deficient for some other
9 reason. And there you have a connective
10 comparative that probably wouldn't take very
11 long or need to be that large.

12 DR. DAVIS: The label thing concerned
13 me. If I was clear that if you said do not use
14 in this population, it wouldn't be used in the
15 population, I think I would have voted
16 differently. But I can't imagine how that would
17 work. But that's not --

18 DR. HENNESSY: Dr. Greenland, do you
19 have any suggestions regarding future studies
20 that FDA should require?

21 DR. GREENLAND: I agree with -- you
22 would -- continue monitoring data coming up, but

1 I don't have any other specifics that --

2 DR. HENNESSY: Dr. Lockwood.

3 DR. LOCKWOOD: I would agree with
4 virtually everything that Dr. Harrington said.
5 I would include -- I think this is a
6 particularly important group. Postpartum
7 patients who are complicated, who had
8 preeclampsia, chorioamnionitis, chronic
9 hypertension, whose hemoglobins were less than
10 9. This is a group that in many ways mirrors
11 the level of complexity of the chronic renal
12 disease patient.

13 And if anybody is going to be at
14 risk for toxicity, it's going to be this
15 group. And so to have a sufficiently large
16 group, and of at least a thousand, maybe
17 more, in that setting it would be
18 particularly important, because if we're
19 going to see a problem, I think it's in
20 actually in that group rather than the heavy
21 uterine bleeding group.

22 DR. HENDERSON: I have nothing to add.

1 DR. HENNESSY: Dr. Lesar?

2 DR. LESAR: Some tangential comments
3 regarding the use of iron sucrose in large
4 doses, which you see more and more publications
5 related to studies in which 500, 800 milligrams
6 of iron sucrose have been given, we're making
7 the assumption here that this may be as safe a
8 compound as that. I think it raises the old
9 issue about large IV iron -- that's the safety
10 signals have we've seen raise some issues
11 related to the practice of giving large iron IV
12 doses.

13 And I think also my concerns in
14 terms of the off-label use has to do with the
15 extension and extrapolation of this
16 information to the use of other iron products
17 such as iron sucrose, which there's no data
18 supporting its safety. And considering the
19 type of signals we see here, those are very
20 much unlikely to be picked up in the type of
21 publications that we've seen that are trying
22 to support the use of high dose iron sucrose.

1 So I see a tangential impact here that might
2 be a problem.

3 DR. KRAMER: Although I voted no, I'd
4 like to comment, which is that if we think it's
5 difficult now to make a decision and draw some
6 reasonable conclusions, I think it's going to be
7 very difficult if this is -- if this is on the
8 market, your ability to actually enroll in
9 controlled studies where we'll be able to
10 address this is going to go down substantially.

11 Because if people can get a drug by
12 just having their doctor prescribe it and
13 their doctor's convinced it's the best thing,
14 then you substantially inhibit the ability to
15 successfully conduct these controlled
16 situations. Having said that, if we could, I
17 would certainly want to see randomized
18 controlled trials probably both in CKD and in
19 this serious significant anemia population
20 postpartum, comparing to the intravenous
21 preparations, because I think I heard that
22 that's what we really want to be doing.

1 It's awkward, though, and I'm not
2 sure you can do it. If you don't have an
3 indication for the other agent, I suspect
4 that's probably why the sponsor compared to
5 oral iron. You don't have an indication in
6 this postpartum population for the
7 intravenous preparations. Is that correct?
8 So I don't know how you mount a randomized
9 controlled trial with a comparative group
10 that's being studied off-label.

11 DR. HENNESSY: Dr. Klein?

12 DR. KLEIN: I too voted yes
13 reluctantly, and what I'd like to advise the
14 agency to do if they have the legal authority,
15 is to require a study of this agent and people
16 and women who are intolerant, poorly responsive,
17 or don't respond rapidly enough to oral iron
18 compared with the standard of care, compared
19 with whatever people are doing out there, which
20 is probably off-label iron and blood
21 transfusion.

22 I think that could be done, and

1 would give people a lot of better information
2 than any kind of registry or any other kind
3 of surveillance could do. If you can't do
4 that, then I would recommend some kind of
5 very comprehensive pharmaco-surveillance
6 system -- pharmaco-vigilance.

7 DR. HENNESSY: Dr. Peterson?

8 DR. PETERSON: I think the agency is
9 being asked to play Solomon here in a difficult
10 situation. I feel kind of like Mark Twain who
11 was asked how it felt to be 7 years old -- said
12 he have to consider the alternative.

13 Unfortunately, the alternatives here are not
14 good either. And I think a Phase 3 randomized
15 trial with the alternative, which is what Harvey
16 is trying to get at, is desirable if feasible.

17 And the question then comes, what's
18 the optimum alternative, and I'm not sure I
19 can speak to that right now. The other thing
20 I'd also emphasize is that yes, follow-up or
21 Phase 4-type surveillance in this indicated
22 population would be critical, and you'd want

1 to do the studies in the group that would
2 potentially benefit most; i.e., the
3 postpartum ladies, I think before you do the
4 CKD ones.

5 And then finally, I would vote for
6 the non-transferrin-bound iron study
7 following doses, which is a fairly easy study
8 to do, of the compound probably for 42 days
9 out to see if those levels are up or down,
10 which would at least alleviate one concern.

11 DR. HENNESSY: Dr. Brittenham.

12 DR. BRITTENHAM: I don't believe the
13 available data are adequate to support marketing
14 approval. And so I don't believe that there are
15 studies that can be done post-marketing.
16 Perhaps for the next section, we can discuss
17 studies that could be done prior to approval.

18 DR. HENNESSY: Dr. Macik.

19 DR. MACIK: Some of my comments have
20 already been made. One of the concerns I have
21 is in looking at limiting it to physicians, we
22 have a lot of experience with restricting

1 something to the hematologist or to the IV
2 person. And that becomes very cumbersome very
3 quickly. So in this population, I think it's
4 something we could look at. But we really also
5 have to look at the limitations of restricting
6 to a single specialty to give this.

7 The other concern that I have is,
8 when we talk about -- you can gain in this
9 system fairly easily because if you gave all
10 of your patients an enteric coded iron with
11 8 milliequivalents of iron in it, they would
12 fail very quickly and then you could go to
13 your IV. So we have to be very careful that
14 we kind of capture that data. And I think
15 that's probably one many women out there do
16 fail oral iron, is even if they do take it,
17 there's such a wealth on the market of
18 inadequate replacement iron tablets, they
19 don't have side effects because they have no
20 iron in them. And so we have to kind of
21 address that also.

22 And one of the things I would offer

1 to help with this off-label use. For
2 example, I frequently give IV iron at higher
3 doses than on-label to an Osler-Weber-Rendu
4 patient with frequent nosebleeds that if I
5 don't give iron, I have to transfuse. Can we
6 have an orphan use column in which you would
7 ask, you say okay, I've got a patient I need
8 to give IV iron, I prefer to use your
9 product.

10 And I will enroll them in a
11 registry to gather information, to get some
12 information from this patient, allow me to
13 treat a patient that's very difficult right
14 now for me to treat. And now I'm even having
15 doubts about how I'm maltreating him with
16 some of my other high dose options. I'd like
17 to have ability to get this forward and let
18 indications, other indications in a somewhat
19 controlled manner.

20 That's enough.

21 DR. HENNESSY: Thank you. Ms. Deluca.

22 MS. CORKERY-DELUCA: Yes, my thoughts

1 were having voted the yes, that a risk map would
2 be helpful, I think, for doctors and for
3 patients. A lot of us are more inquiring now.

4 Certainly, I don't want to -- I
5 think it was brought up earlier by one of the
6 people speaking -- to have an arm where it
7 could exist because somebody doesn't want to
8 take pills. I think that should be thrown
9 out the window.

10 But I'd like to see a trial where a
11 large organized amount of data is both
12 maintained as it currently is, and also
13 shared with the greater general public. I'd
14 like to see something that would be in
15 another modality besides this that would be
16 symposia. Let's get larger audiences to
17 think on the subject and release a clinic
18 journal, and that would be through the
19 medical community.

20 I was pleasantly surprised and
21 pleased that the amount of evidence-based
22 medicine that was presented. And I'd like to

1 ask that you include patient advocates in
2 anything that would be going out as a
3 marketing tool. It's one thing to say look
4 at third-grade level or look at sixth-grade
5 level reading. That really doesn't apply
6 when you're talking about medical materials.

7 I've taught from kindergarten
8 through high school, and even in college.
9 And you really have to speak to the topic.
10 And I think that that could really help a lot
11 with a marketing tool here, a beta toolkit,
12 beta tool guide, beta guide, whatever is
13 beyond for the MDs, for the infusion room
14 ladies, the nurses in there. They're alone
15 until a problem comes up and they have to ask
16 the doctor. And even patients. There could
17 be things in waiting rooms -- either charts
18 or little pamphlets that would explain to
19 people why this is a good thing to do.

20 DR. HENNESSY: Thank you. Mr. Levin.

21 MR. LEVIN: Since I don't recommend
22 marketing, I think the point is moot. But I

1 could say wait for 4.

2 DR. HENNESSY: You'll get a chance in
3 a second. Dr. Burlington. This isn't a vote.
4 So I think you can discuss if you like, or then
5 get ready because I'm going to start with you on
6 the next one.

7 DR. BURLINGTON: No comment at this
8 point.

9 DR. HENNESSY: So ladies and
10 gentlemen, we have one question between us and
11 the door. This has been a terrific meeting, and
12 I want to thank you all in advance because I
13 know sometimes once we get to the end of the
14 questions, people start heading for the door.

15 So with that, I'd like to start
16 with the last question, number 4, a
17 discussion question as well. "If you do not
18 recommend marketing approval, discuss the
19 important features of additional clinical
20 studies to characterize safety and establish
21 net clinic benefit for Injectafer." And I'll
22 start at that end of the table with

1 Dr. Burlington, if you'd like to offer a
2 comment.

3 DR. BURLINGTON: My first comment
4 would be given the data that we have already; it
5 would be who's accompanying to make sure that
6 they have a balanced allocation to the arms of
7 the studies. And also, I'd like to see the
8 relative risk profile vis-à-vis alternative
9 injectable therapies as opposed to looking at
10 alternative oral therapies.

11 DR. HENNESSY: Thank you. Mr. Levin.

12 MR. LEVIN: I've lost track of
13 what -- the study as it's ongoing now. And I
14 think it's going to be 500 patients. But they
15 indicated, when we asked when it was going to be
16 completed, that there were enrollment problems
17 and they didn't -- I mean, there's something
18 going on.

19 So the question is, can that be
20 built upon and sped up, and also made to
21 address some of these questions. There is a
22 beginning here, and the company is committed

1 to continuing that.

2 Is that an opportunity, one, to get
3 that whatever data is there and then to
4 really sort of redesign a trial based on that
5 and see if that could be sped up, and so they
6 would come back to this process with a lot
7 more data.

8 DR. HENNESSY: Thank you.

9 Ms. Deluca.

10 MS. CORKERY-DELUCA: I think the only
11 thing that I would really look at would be
12 comparators to what we're doing now and agree
13 that it's difficult, since what I mostly do now
14 is off-label.

15 DR. HENNESSY: Mr. Brittenham.

16 DR. BRITTENHAM: I think we need
17 prospective randomized trials, adequately
18 powered to provide us some assurance that
19 there's no increased risk of mortality. And
20 that we need physiologic studies of the effects
21 of Injectafer on iron metabolism, specifically
22 on -- with measurements on the

1 non-transferrin-bound iron compartment and
2 studies of the fate of Injectafer and
3 macrophages after. And not only in healthy
4 individuals, but also in the populations it will
5 be used in whom iron metabolism may be very
6 different.

7 DR. HENNESSY: Dr. Peterson.
8 Dr. Klein.

9 DR. KLEIN: I voted yes to marketing,
10 but should you not take my advice, I would still
11 recommend the controlled study with the standard
12 of care. And I absolutely agree that the iron
13 studies that Dr. Brittenham has recommended
14 should be done whether or not the drug is
15 marketed.

16 DR. KRAMER: I think it's very
17 important to -- obviously, I voted no above. So
18 I think it's very important that we study the
19 population in the way that we anticipate it's
20 going to be used. And I certainly took from the
21 discussion today that this will be used widely
22 in the CKD population.

1 I believe the company said -- I'm
2 not sure I got this right, that there were
3 two products that they had -- dextran and
4 iron sucrose, and that the predominant drug
5 being used was iron sucrose. So it seems
6 like you could mount a study in that
7 population, compare to the agents that are
8 actually being used. And that we could get a
9 better sense of the net clinical -- of the
10 risk. I mean, it's going to be very hard to
11 get the mortality, and that's why I think
12 you're more likely to get at it form starting
13 the CKD population.

14 DR. HENNESSY: Dr. Henderson.

15 MR. HENDERSON: I recommended
16 approval, of course. But I'd like to recommend
17 to the sponsors that they undertake and develop
18 information for practitioners about the use of
19 this agent in women who are not iron-deficient.
20 My thought is that once it becomes available,
21 that obstetricians are likely going to use it.
22 It would be very easy to use, obviously, in the

1 postpartum patient, which is why this is being
2 recommended.

3 But we as a group are not noted for
4 our anemia work-up. So I wonder -- just to
5 put out there that if there may be a risk for
6 women who are not iron-deficient who have
7 just had chronic hemoglobins of 9, and now
8 they've lost a little extra blood and they
9 get this medication, are there any risks that
10 people should be aware of?

11 DR. LOCKWOOD: We may not be noted for
12 our work-ups of anemia, but we are very noted
13 for our fear of litigation.

14 And I do suspect that that will
15 have a dampening effect on the application of
16 this in postpartum patients. I would say
17 that if you choose not to approve, in
18 addition to the fairly large study I
19 described in complicated postpartum patients
20 with iron as the control, oral iron as the
21 control, I do like the idea of a smaller
22 study comparing it to IV iron sucrose. I

1 think that'd be very useful.

2 DR. HENNESSY: Dr. Greenland.

3 DR. GREENLAND: I have nothing to add.

4 DR. HENNESSY: Okay.

5 DR. GREENLAND: But I submit -- I
6 would reinforce the need for the further study
7 as people described.

8 DR. HENNESSY: Thank you. Dr. Davis.

9 DR. DAVIS: I agree totally with
10 Dr. Kramer, randomized controlled trials,
11 Injectafer versus other injectables in a broader
12 audience, because my concern is once it's out
13 there, it's going to be used off-label. And so
14 with these other populations I think would be
15 important.

16 DR. BLACK: I don't have anything new
17 to say. But I enjoy those reluctantly wish it
18 approved.

19 DR. HENNESSY: I'm going to pass. So
20 at this point, I'll ask FDA if they have any
21 concluding comments. I'm seeing shaking of
22 heads no.

1 DR. PAZDUR: So I hereby -- we just
2 want to thank everybody for their information
3 and their advice that they gave to us.

4 DR. HENNESSY: Thank you.

5 This meeting is adjourned.

6 (Whereupon, at approximately 4:34
7 p.m. the PROCEEDINGS were
8 adjourned.)

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