

1 DR. LAINE: In the people who were
2 negative initially become positive subsequently at
3 6 months?

4 DR. CRAFT: Not in our studies, but
5 clarithromycin is bactericidal. I would not say
6 that that's true of all therapies out there.

7 DR. FISHER: I guess that's, again, a
8 conceptual thing that in any therapy, you'd have
9 to look at whether it might be or might not be and
10 whether it's the same as other things if shown
11 that you do keep the same at 6 months.

12 And again, maybe for study design, it
13 might be appropriate in individual studies as
14 opposed to across the board.

15 Dr. Megraud?

16 DR. MEGRAUD: I didn't mention this
17 morning, but in European guidelines, we recommend
18 to do urea breath test up to three months just to
19 be sure.

20 DR. CRAFT: That certainly helps.

21 DR. FISHER: Okay. I'd like to go back
22 to Dr. Temple's question, which was: why do we

1 need to show ulcer healing?

2 Is that important? -- if that's what I
3 read correctly, Bob.

4 Is that what you were saying -- what you
5 were asking? No?

6 Dr. Temple --

7 DR. FREDD: But if they want to make a
8 claim --

9 DR. FISHER: Dr. Fredd's going now.

10 DR. FREDD: If they want to make a
11 claim --

12 DR. FISHER: Okay.

13 DR. FREDD: -- clearly that's so. But
14 if the indication --

15 DR. FISHER: Okay.

16 DR. FREDD: -- you're seeking is
17 prevention of recurrence of peptic ulcer -- DU,
18 GU, whatever -- why isn't eradication, 4 weeks
19 post-treatment, properly done, sufficient for that
20 claim --

21 DR. FISHER: Okay.

22 DR. FREDD: -- in two out of two

1 studies?

2 DR. FISHER: Does anybody want to
3 comment on that or --

4 Dr. Fanning, would you like us to
5 address the issues directly more than that or --

6 Would you like us to address the issues
7 directly?

8 DR. FANNING: Yes.

9 DR. FISHER: Okay. Let me just ask for
10 anybody -- does anybody want to comment more on
11 Dr. Temple's questions?

12 Does anybody feel that if you're just
13 doing for ulcer recurrence -- eradication for
14 ulcer recurrence, that you have to prove ulcer
15 healing first?

16 Dr. Elushoff?

17 DR. ELUSHOFF: I think most of the
18 studies that we have been shown that have looked
19 only in those who healed, but if you're going to
20 say that it prevents recurrence, then logically
21 you have to have shown that it was healed.

22 You could certainly say that you're just

1 lowering prevalence, in which case you wouldn't
2 have to show that it had been healed.

3 DR. FREDD: That is that you would state
4 that it reduces the risk of?

5 DR. ELUSHOFF: I think the other problem
6 is that the studies we have seen show that it
7 reduces the risk of, but in fact, that reduction
8 is all over the map so we don't know what it
9 reduces the risk to.

10 We have no good information about what
11 the reduction is, so what kind of levels then are
12 you going to use?

13 DR. TEMPLE: But looking at --

14 MS. DUNN: I mean, what's the success
15 then?

16 DR. TEMPLE: Looking at the acute --
17 knowing that ranitidine gives you an 80 percent
18 acute ulcer healing rate doesn't help you know
19 what the recurrent -- how does it help you to know
20 that Emiprisol heals 80 percent of ulcers at 4
21 weeks which you know -- which you know from --

22 How does that information contribute to

1 this? That's the question I'm asking.

2 You're saying maybe you should get
3 actual recurrence rates all the time. Well,
4 that's a different question.

5 MS. DUNN: Oh, but if you're going to
6 use the eradication as a surrogate for recurrence,
7 then it seems to me you ought to know what it
8 reduces the recurrence to.

9 DR. FREDD: Well, that's a very
10 important question.

11 When we were dealing with H2 receptor
12 antagonists for prevention of recurrence, there,
13 too, was a great difference, in terms of
14 particular point estimates of what it reduced the
15 risk to.

16 But as long as such drugs were safe and
17 effective, they could be approved as therapies
18 that could claim that.

19 Shall we handle this type of therapy for
20 reducing the risk of recurrence or preventing
21 recurrence differently than we have the H2's
22 because there, too, reducing the risk was

1 variable?

2 I guess my question is that if you have
3 adequate eradication by whatever level you define
4 it as -- even though that will reduce the risk in
5 all patients -- but from study to study, that will
6 be different -- does that matter to you, in terms
7 of the approval process?

8 DR. FISHER: Dr. Temple?

9 DR. TEMPLE: A number of people put it
10 this way: Healing is healing, eradication is
11 eradication, and you shouldn't confuse the two.

12 Any drug of either -- I mean, drugs of
13 both an acid-reducing class or an antibiotic
14 anti-infective class could affect either of those,
15 and you could study both of those questions.

16 But they're two separate matters, and
17 the main question I was asking is: why should
18 ulcer healing issues get into the question of
19 eradication issues?

20 Now, a completely separate question that
21 was just raised is whether it really is time to
22 call eradication a surrogate for improvement in

1 ulcer recurrence, but that's sort of the main
2 question the committee is being asked. So I
3 wasn't trying to raise that again.

4 But I was asking the rather narrow
5 question which is, if you were to conclude that
6 eradication is relevant to ulcer recurrence, why,
7 in these acute studies, would you have to -- not
8 whether you could, but why would you have to also
9 show that drugs you already know heal ulcers do
10 heal ulcers again?

11 DR. FISHER: Let me just -- I'm going to
12 get to Dr. Comer. But I just want to -- if we're
13 going to address some of these issues.

14 Dr. Fanning, there were three separate
15 sort of sets of issues. There's the one that came
16 up before this session --

17 DR. JUDSON: Well, you know, let me --
18 if I could try to articulate the problem here.

19 There are three different versions,
20 slightly different versions of these questions
21 that we're to discuss. The content I think
22 overall is probably the same.

1 The simplest versions consist of just
2 three questions interspersed in your agenda, going
3 one, two, three.

4 Then, as part of that at the end,
5 they're formatted slightly differently and two --
6 one has two parts, two has two parts, three has
7 one part with two letters.

8 Then the third version we have had
9 passed out and is the same as the overheads now
10 has three reformatted as three, part one, part --

11 Right. So A and B now become 1A,
12 subparts -- yeah. One, two.

13 DR. FISHER: So there are two versions
14 of it. Which version would you like us to --

15 DR. JUDSON: I think we squeezed more
16 questions out of the subsequent versions.

17 How do you want us to -- I think we want
18 to deal with just one of these and then tell
19 everybody which one we're going to arbitrarily
20 suggest.

21 DR. FANNING: I think actually the
22 simplest version is the one in the agenda and we

1 tried to reduce all of the issues into that one.

2 DR. FISHER: Okay. So back to the one
3 that I introduced this session with: is there
4 enough clinical benefit derived from eradication
5 of H. pylori to consider eradication alone as a
6 valid end point for the prevention of ulcer
7 recurrence?

8 If not, what other end point should be
9 considered? That's sort of issue number one.

10 Let me just read the other two points
11 that were under the version two, which was: should
12 HP eradication be the primary efficacy end point
13 in assessing the prevention of ulcer recurrence in
14 DU and GU, and what is the role of clinical trial
15 end points in H. pylori-associated GU clinical, DU
16 clinical trials?

17 I guess, Dr. Temple, the one thing that
18 I would -- before I get to Dr. Comer -- you could
19 almost say healing is healing, but what raises
20 this is: instead of eradication equals
21 eradication, does eradication equal no recurrence
22 or decreased recurrence in that same --

1 DR. TEMPLE: No. That's sort of the
2 main question, and I know you're going to get to
3 that.

4 If you were to say yes to that, then my
5 question would be: what's healing got to do with
6 it at all?

7 No. I understand that's the main
8 question.

9 DR. FISHER: Dr. Butt.

10 DR. BUTT: I think we need to know the
11 conditions of these experiments are the same as
12 the conditions in the past.

13 I remember when cimetidine was presented
14 to this committee too, it was only significantly
15 different from placebo at two weeks. And there
16 were reasons for that which were avoided in later
17 trials of other drugs.

18 But I think if we're proposing to
19 prevent recurrence, we certainly need to know that
20 the ulcer has healed initially, and we need to
21 know even though the drug that we're testing has
22 been proven to heal ulcers, we don't know that

1 it's been proven to heal an ulcer in this
2 situation, in this experiment.

3 DR. FISHER: Because I guess you could
4 say then is recurrence non-healing if you don't
5 know that it's healed initially.

6 DR. BUTT: Well, I guess I'd put the
7 question further.

8 Suppose you had someone who had the good
9 fortune not to have an ulcer at the present
10 moment, but he had one 6 months ago, and as H.
11 pylori.

12 So we know that that person's history is
13 going to recur, would you say that person
14 shouldn't be treated?

15 Is eradication not good for that person
16 just because you don't have an ulcer in your
17 hands?

18 DR. TEMPLE: No. I don't think -- I'm
19 not saying he shouldn't be treated. I'm just
20 saying he shouldn't be studied.

21 DR. FISHER: I would take it -- no. I
22 would take -- I'm looking at your question

1 differently in a way. I think that this is what
2 we have been talking about, and this is -- I'd
3 like to hear the rest of the people out in the
4 audience. I'll just put mine out first -- I think
5 that patient should probably be treated if they
6 had it 6 months ago.

7 The question is: if I come in with an
8 acute ulcer now and you're going to heal me, does
9 it make a difference to you or to anybody else in
10 the group that I'm healed before you consider me,
11 you know, a part of a trial or in the trial to
12 look at recurrence.

13 Or what if I sort of look like I
14 recurred three weeks after the healing -- you
15 know, three weeks after you think so, is there
16 recurrence or not?

17 I think what Dr. Sonnenberg said,
18 though, that made me convinced that perhaps you
19 don't need to go with healing initially is that
20 the therapies are much shorter and that healing is
21 something different, and you can still look at the
22 recurrence rate separately and not just include

1 people who are healing.

2 DR. TEMPLE: And also the various ulcer
3 healing regimens are considerably different in
4 potency and in how effective they are. Does that
5 make a difference?

6 Having established an antibiotic
7 regimen, do you now limit it only to the
8 particular acid reducer that it was studied with
9 or not?

10 Now, there may be a case for doing that
11 where effectiveness may be affected, but what's
12 the rationale all around?

13 DR. FISHER: Dr. Butt?

14 DR. BUTT: I think the rationale is to
15 control the conditions of the experiment so that
16 the subjects of the experiment are in as uniform
17 clinical condition as we can make them.

18 And if you mix patients who have healed
19 6 months earlier with patients who have healed in
20 the course of the experiment, you can't predict
21 what the outcome is going to be.

22 DR. FISHER: Dr. Comer?

1 DR. COMER: I agree with Dr. Butt. I
2 also think that we've sort of forgotten that the
3 main thing that someone else has mentioned: what
4 the patients care about is how they feel.

5 And if you cure their HP and they still
6 feel sick, they're still going come back to you.

7 And then I think that healing the ulcer
8 is important and it's also important in terms of
9 what you can expect from the treatment.

10 If you look on page 19 and some of these
11 other pages where they -- on 21, where they
12 accounted for unhealed patients and drop outs --
13 you see that the effectiveness and the preventive
14 recurrence was drastically different.

15 It still was different from -- you know,
16 they still found the statistical difference. But
17 the magnitude of the difference was much smaller.

18 So, I mean, you have to take healing
19 into account, as well as looking at eradication on
20 an intent to treat basis.

21 DR. TEMPLE: There are multiple things
22 being taught. No one is suggesting you shouldn't

1 try to treat someone's symptomatic ulcer.

2 The question is: what does a sponsor who
3 wants to get a claim for eradication have to do?
4 I'm not advocating being cruel and horrible.

5 DR. FISHER: Thank you.

6 DR. TEMPLE: The analysis you referred
7 to is a worst-case analysis. It's not just
8 putting -- it's not just putting dropped out
9 people back. It's putting them back in a way that
10 says they all did adversely.

11 That's not a true -- those are not real
12 results. They are worst-case results. And
13 naturally, they look terrible.

14 DR. FISHER: Dr. Fredd?

15 DR. FREDD: Can I just address this?
16 You know, people want a claim, let's say, for a
17 regimen to treat HP to prevent DU occurrence. If
18 they injured people into such a trial, all of whom
19 had DU healed, and they gave you an eradication
20 rate, there is no -- you would not ask for an
21 endoscopy at that point -- 4 weeks post-therapy --
22 because you don't have to establish their healing

1 status.

2 They heal and then, you know, you get
3 the eradication rate, and you can say it prevents
4 recurrence or reduces the risk, depending upon
5 what verbiage you want to use.

6 Yes, Jim?

7 DR. BUTT: The Axon Study was a very
8 interesting study. They continued to endoscope
9 patients after they had healed and they found that
10 there was a recurrence rate of ulcer disease --

11 DR. FREDD: Yes.

12 DR. BUTT: -- under therapy.

13 DR. FREDD: And that recurrence rate was
14 5 to ten percent, which was in the range, as David
15 Green said, of observer error, in terms of calling
16 whether you have an acute ulcer or not.

17 DR. BUTT: I can't believe you don't
18 want to endoscope these patients if they come to
19 the study healed and after you have treated them.
20 I can't believe that.

21 DR. FREDD: I'm not asking what I'd want
22 to do if I ever did an endoscopy.

1 The question I'm asking is: in clinical
2 trial design, how do you define an end point?

3 Unfortunately, there are many trials
4 that are going to be presented to you. Some may,
5 in realistic ways, provide these things, provide
6 the data. And one can work it out and see if it
7 makes any difference whether you define an
8 eradication rate with only healed patients versus
9 those of all treated patients.

10 But that, apparently, remains for the
11 future.

12 DR. FISHER: Dr. Reller?

13 DR. RELER: In my own mind, I'm trying
14 to think of a way that simplifies the concepts.

15 To me, there are 4 elements: The healing
16 and the ulcer. Then there is prevention of
17 recurrence, agents that decrease gastric acidity,
18 and then antimicrobials that affect H. pylori
19 alone or in combination.

20 And although they are interrelated, what
21 the claim is would seem, to me, is: what should be
22 required as a reasonable database for making that

1 claim?

2 For example, prevention recurrence --
3 one issue -- it could be that the very things that
4 prevent recurrence in fact, might, with an
5 adequate database, show some influence on healing
6 as well, but they don't necessarily have to.

7 Now, with that background, I wanted to
8 ask the question: has anyone looked at the
9 influence on the sequence of these things?

10 For example, we talk about, in all of
11 these trials, whether it's a single or a multiple
12 microbial, coupled with acid reduction as a
13 package treatment.

14 But can one influence the efficacy of
15 whatever anti-infective regimen one has by doing
16 that after a period of decreased acid secretion or
17 healing or whatever?

18 In other words, it could go either way.
19 I mean, can you augment success in either the
20 healing or the prevention of recurrence by whether
21 one is giving concomitant both conceptual arms of
22 therapy or doing them sequentially?

1 Are there any data along those lines?
2 Because it also comes into design of clinical
3 trials to come to specific end points having to do
4 with claims of safety and efficacy.

5 DR. FISHER: There is some data to that,
6 Dr. Temple.

7 DR. TEMPLE: You actually just saw some
8 in which healing rates with a given antibiotic
9 appeared to be enhanced when it was given with an
10 acid reducer.

11 You can think of reasons why that might
12 be true.

13 But that's sort of is sequence. That
14 means that if you gave -- if you gave that
15 antibiotic at the same time that you gave an acid
16 reducer, it would work better at eradication than
17 if you gave it later without the eradication.

18 Now, maybe that's not exactly what you
19 had in mind by sequence, but it is a time other
20 therapy interaction that would certainly be of
21 great interest.

22 Maybe that's not what you meant.

1 DR. FISHER: Dr. Elushoff?

2 DR. ELUSHOFF: That's pH dependent.

3 You're talking about a pH dependent.

4 DR. FREDD: There is another sequenced
5 bit of information which actually I think was
6 mistakenly stated or at least has not been proven
7 to be the case in the NIH consensus conference.

8 It was believed there that pretreatment
9 with Emiprisol, the proton pump inhibitor
10 anti-secretory agent decreased the effectiveness
11 of an antimicrobial regimen to eradicate HP.

12 More recent information, perhaps Astra
13 would like to comment on this, suggests that that
14 is not the case, but that subsequent therapy of an
15 antimicrobial after Emiprisol is not lessened, in
16 terms of eradication and in terms of more recent
17 information.

18 So the sequence in terms of healing with
19 a proton pump inhibitor or ranitidine or
20 cimetidine or whatever does not influence if you
21 wanted to use an antimicrobial agent following
22 that.

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1 DR. FISHER: I'm going to --

2 DR. NEIL: Can I just comment on that?

3 DR. FISHER: I was going to ask you, Dr..
4 Neil.

5 DR. NEIL: Yes. I don't have the data
6 to show you, but there are a number of studies
7 that have now shown that pretreatment with
8 Emiprisol does not affect the result.

9 But there is a lot of -- data, a lot of,
10 controlled trials Emiprisol plus antibiotics --
11 that show that the anti-secretory agent alone
12 doesn't work. The antibiotic alone doesn't work,
13 at least not very well, but you have to give the
14 combination simultaneously to get it to work.

15 So there aren't studies where one tries
16 to give them in various orders to see whether you
17 need to do that. But we have fairly good data
18 which shows us that the single agents don't work
19 well enough, which is why they have been combined,
20 as well as to boost the healing and to reduce
21 symptoms.

22 DR. LAINE: But we don't think it

1 matters if you give an anti-secretory for two
2 weeks and then give the H. pylori therapy, versus
3 giving it right away --

4 DR. NEIL: No.

5 DR. LAINE: -- to the patients in the
6 hospital. And I think that was what he was
7 asking.

8 DR. NEIL: Right.

9 DR. FREDD: You know, David Graham's
10 study -- after treating people with one the H2s to
11 heal them up, and then doing this randomization
12 between ranitidine and placebo, ranitidine triple
13 therapy -- found an enormous difference in
14 prevention of recurrence, as well as a difference
15 in eradication rates.

16 So the sequence doesn't seem to matter.
17 You can take an acute ulcer, heal it up, see if it
18 makes you feel better, and then randomize and see
19 what your eradication rates.

20 And it is true that there is some
21 percentage of patients within that 4 to 6 weeks,
22 who if you reendoscoped them, may have an acute

1 ulcer, but it's a small number of people.

2 DR. FISHER: Okay.

3 DR. FREDD: Plus, ulcers come and go.

4 DR. FISHER: All right. Let me just --

5 I want to go to Dr. Sonnenberg quickly, then to
6 Dr. Burks, Dr. Marshall.

7 And then I want to propose a statement
8 to the first part of the issue -- the one that's
9 up there -- and get a feeling from the group about
10 it.

11 Okay. Dr. Sonnenberg.

12 DR. SONNENBERG: The reason why we were
13 concerned about the acute ulcer and the ulcer
14 healing was related to simple facts about the
15 occurrence of the disease.

16 25 percent of the adult population in
17 the United States complain about some symptoms of
18 dyspepsia. If you don't look for an acute ulcer,
19 just look for H. pylori and symptoms of dyspepsia,
20 you're not -- you don't know what you're dealing
21 with. So that's why all trials looked initially
22 for acute ulcer disease.

1 The other reason is the patient may have
2 had peptic ulcer disease in the past -- let's say
3 15 or 20 years ago -- but does not have the
4 disease any longer.

5 Even though some people have questioned
6 the data by John Frye, there is still clinical
7 evidence that the disease, after a prolonged time
8 period, burns out.

9 So you may not need to treat patients
10 who had peptic ulcer disease 20 years ago but
11 don't have the disease any longer.

12 It is understandable, then, from a
13 practical point of view, that all studies that
14 tested the efficacy of antibiotic therapy on
15 peptic ulcer disease started the trial with acute
16 ulcers and tested the efficacy of the drug on
17 ulcer healing.

18 Although with respect to recurrence
19 rate, this may be a secondary issue.

20 DR. FISHER: Dr. Burks.

21 DR. BURKS: One of the problems we're
22 having here is -- in my mind, at least -- a

1 confusion of science and semantics.

2 Rosemarie, we need to define very
3 carefully what questions were being asked. I see
4 dramatic differences in the various versions of
5 the questions being posed to us. And the term
6 that worries me the most is the term "surrogate,"
7 because I think that may be the wrong term that's
8 leading us astray.

9 It seems to me if the trial is intended
10 to determine the efficacy of the regimen in
11 eradicating HP, then it should be designed in that
12 way. And that should be the end point.

13 If the trial is to measure ulcer healing
14 and recurrence, then I think that ulcer healing
15 and recurrence has to be measured.

16 Now, "recurrence" means -- for
17 recurrence to occur, there must have been a prior
18 healing. Now, it would be acceptable, to me, that
19 if a study is designed to measure recurrence, then
20 one could take healed patients under certain
21 defined conditions to make sure that they're --
22 you're starting from the same point and study

1 recurrence.

2 But we have three different issues that
3 are all mixed up together: the eradication issue,
4 the healing issue and the recurrence issue. And I
5 think they're separate issues and we need to
6 address them separately.

7 DR. FISHER: Dr. Fanning?

8 DR. FANNING: Yes. I wanted to make a
9 comment about that.

10 The intent of asking this question is
11 around H. pylori eradication being used as either
12 a primary efficacy end point or the term
13 "surrogate," which has different connotations,
14 obviously, for people.

15 But if we use the term, "primary
16 efficacy end point," the intent of the question is
17 to say, should the decision about approving a
18 product or a group of products or combinations for
19 the prevention of ulcer recurrence be made in
20 studies where the primary efficacy end point is H.
21 pylori eradication and where endoscopy may in fact
22 not be done at all.

1 DR. BURKS: Then I think this would
2 depend on the claims that are to be made.

3 If the claim is that this treatment
4 eradicates H. pylori and that eradication of H.
5 pylori has been shown to reduce occurrence, I have
6 no problem.

7 DR. FISHER: Dr. Marshall.

8 DR. MARSHALL: I got up just to support
9 Dr. Fredd. And I think we've come full circle and
10 we're back to where we was ten minutes ago.

11 But the aim of the whole -- you have to
12 take it another step further.

13 We're going to do a microbiologic study
14 to show that treatment eradicates H. pylori. Then
15 we're going to use that and say that can be used
16 as an indicator that the treatment reduces
17 recurrence.

18 If you take it one step further, you
19 don't even have to use ulcer patients in that
20 study. You can use normal volunteers or anybody
21 who comes through the door with H. pylori.

22 And then the second thing is that you

1 can do the whole study in one month or 5 weeks.
2 And hopefully, in the new year, we're not going to
3 be spending ten million dollars every time we want
4 to get a new treatment which prevents ulcer
5 recurrence.

6 We're going to be spending, you know,
7 \$100,000 to get that data with the new therapy,
8 and things will start moving forward instead of
9 being all constipated as they are at the moment.

10 DR. FISHER: Dr. Fanning and then Dr.
11 Judson. And then --

12 DR. FANNING: Well, I think in a basic
13 infectious disease framework where you think about
14 things like colonization and disease caused by
15 microorganisms, you may have very different
16 situations with a patient who is completely
17 asymptomatic and harbors H. pylori.

18 And the person who has an acute ulcer
19 may actually have a much higher microbial load
20 which will influence the effect or efficacy of
21 therapy.

22 So that may not be -- we don't know

1 that. But certainly, it may not be a comparable
2 population to extrapolate from.

3 DR. FISHER: Dr. Temple, if it's quick.
4 I want to get to Dr. Judson.

5 DR. TEMPLE: That's no different from
6 the answer Dr. Freston gave earlier.

7 Basically, he said, "Well, you might be
8 able to do what Dr. Marshall says, but we'd like
9 to be a little sure because, you know, we're
10 relatively new in this process, so at least have
11 them be people who have had ulcers lately or were
12 cured sometime recently."

13 But that is the fundamental question. I
14 mean, the study or meta analysis Dr. Girardi and
15 Hopkins did tried to make the case, I think, that
16 eradication does predict the recurrence outcome.
17 And therefore, that's the very question.

18 DR. FISHER: Dr. Judson.

19 DR. JUDSON: I was trying to think how
20 one can get control over what is partially chaos.

21 And looking back on my visitation of
22 this subject, what occurred to me is that -- and

1 essentially I agree with Dr. Craft and I agree
2 with Dr. Megraud, who, I think, was saying many of
3 the same things.

4 I did look over the European guidelines
5 and I think that, because there is still real
6 doubt or incomplete knowledge about the
7 relationship between acid suppression and
8 bacterial eradication, it isn't possible yet to go
9 to some quick, easy approach to this if we ever
10 want to understand the pathophysiologic
11 interactions and relationships.

12 Also, because none of the tests that we
13 have -- the diagnostic tests -- have the
14 performance characteristics that would allow you
15 to rely upon it as a single test, we're also
16 really stuck with having to do multiple tests as
17 we continue to try to understand better and
18 quantify the performance characteristics --
19 sensitivity, specificity, all these things for the
20 different tests we have.

21 So it doesn't seem to me how we can
22 proceed in any one of these tests without

1 including, no matter how expensive, all these
2 different characteristics.

3 Looking at ulcers, doing the
4 microbiology tests and doing multiple tests, and
5 probably doing follow-up over a period of time, it
6 made sense to me that no single of those three
7 follow-up visits is probably going to be adequate
8 to give the FDA the information that they need.

9 Now, having said that, in trying to make
10 a little progress on getting through the issues
11 that have been posed here, we've made a second
12 decision and feel that the way the issues are
13 phrased in -- the ones that are interspersed in
14 the agendas, that there are more paragraphs and
15 it's hard to get a question out of it.

16 And if we're going to follow the
17 procedures we've done before -- which is that we
18 come up with, hopefully, a clean question, and
19 then poll the experts to get a sense of whether
20 there's consensus or not -- we're going to have to
21 go to what you have up there.

22 And even this is going to be tough

1 going. I think we can probably answer the first
2 question. We will then have to probably rephrase
3 the second one or break it down into should for
4 each of those subcomponents.

5 We can't have, "What is the clinical
6 role for three different end points" and then ask
7 people whether they agree or disagree, because
8 that's really all we can do if we're to follow
9 through with that format.

10 DR. FISHER: Dr. Parker just looked like
11 he was anxious to say something. And then Dr.
12 Smoot, quickly, before we go on to this. And then
13 I think perhaps --

14 DR. PARKER: Well, back to something
15 about definition of terms. I'm looking at for the
16 definition of "eradication" in the following way.

17 Someone comes in and has an ulcer and is
18 microbial negative. We treat them and cure the
19 ulcer.

20 Have we eradicated the organism? When
21 we start counting the numbers in these rates, how
22 do we count that person?

1 DR. FISHER: They're not -- they
2 shouldn't be included if they're HP negative.
3 They're not included. They're out of --

4 You can't eradicate them if they've got
5 -- well, you could eradicate the patient, I
6 guess --

7 DR. PARKER: I agree, but --

8 DR. FISHER: -- but you don't --

9 DR. PARKER: -- it occurs to me how some
10 of these --

11 DR. FISHER: -- you can't eradicate --

12 DR. PARKER: -- when they were counting
13 the rates in going from there to recurrence. Some
14 of those people that didn't have the organism at
15 first, are they then counting in those who did not
16 have --

17 DR. TEMPLE: That was only H.
18 pylori-positive ulcer patients.

19 DR. FISHER: Right. There was once I
20 think when Art was presenting his data, he gave an
21 overall incidence of H. pylori in the patients who
22 were all endoscoped, but it was only those

1 patients who were positive then who were included
2 in the trials after that.

3 So if you're found to be negative on the
4 initial therapy, you shouldn't be looked at
5 period. End of discussion.

6 DR. TEMPLE: Of course, that may have
7 been false negative HP cultures, but --

8 DR. FISHER: Well, I think, Dr. Smoot,
9 real quick. And then Dr. Temple real quick.

10 DR. SMOOT: I also think it's difficult
11 to determine the efficacy in the word "surrogate,"
12 as Dr. Burks mentioned. But if there's something
13 else in the language that says that if this is
14 effective in eradication, and therefore decreases
15 ulcer recurrence. And if that's something that
16 would be acceptable, then that's something that
17 would also make the studies more easily performed,
18 and then that language is what the industry is
19 looking for.

20 DR. FISHER: Dr. Temple?

21 DR. TEMPLE: I'll only do this if you
22 want. There was a reason in the early trials to

1 randomize people who either -- who both did and
2 did not have H. pylori. And that was a logical
3 academic thing to do.

4 It's probably not relevant anymore. But
5 the initial reason was that people could have said
6 that the ability to eradicate H. pylori and the
7 likelihood of occurrence were in some how -- in
8 some way related even though it wasn't the H.
9 pylori that was doing it.

10 So the initial sort of intent to treat
11 approach was crucial to our minds in establishing
12 that eradication really, per se, really did relate
13 to non-recurrence.

14 Now, once you believe that, of course,
15 you don't want to do eradication rates in people
16 who don't have the disease. So it wasn't a crazy
17 thing initially, but it may not be necessary.

18 DR. FISHER: I'm just going to add one
19 comment.

20 As we talk about eradication, I think
21 that it's very important that Dr. Judson made, is
22 when we were talking about eradication, I think

1 some people also getting hung up about, you know,
2 "Gee, do you want to make sure there isn't an
3 ulcer there?"

4 But it just hit me when you said it --
5 that the methods that we have available that we
6 feel are reliable now to judge eradication --
7 we're talking about two or three methods.

8 Until we know that the breath test is
9 there, they have to be endoscoped anyway to get
10 the tissue and look at the histology or look at
11 the CLOtest for eradication, and just sort of
12 ending up satisfying people who might say, "Are
13 you not looking for recurrence of the ulcer by
14 endoscopy as you're looking for eradication?"

15 And until we know that this breath test
16 is something that you could do totally, we're sort
17 of stuck in having to look for the ulcer
18 recurrence anyway, because you're looking at
19 having to go and get tissue as the gold standard.

20 DR. JUDSON: As I understand it, because
21 the sensitivity of the breath test is so suspect
22 or tends to be low, it's probably going to

1 misclassify a fair number up front, and could
2 never be used really to determine eradication
3 versus suppression.

4 Is that correct?

5 DR. FISHER: Well, Dr. Megraud is
6 telling us it may be different, but until we sort
7 of see that, I think we're still in Never-Never
8 land here --

9 DR. LAINE: But, in the beginning, it
10 was -- everybody agrees at the beginning, it's
11 very good. The only question is: would the data
12 by the Abbott presentation, that it may be bad
13 after treatment, although --

14 DR. MEGRAUD: Yes. I think it's the
15 first time I saw about the research with breath
16 test presumpter, because usually it's in a good
17 agreement with the other techniques.

18 So, rather than say that breath test is
19 no good, I would say that maybe it would be better
20 to look to this particular test made in the U.S.
21 to --

22 DR. FREDD: You also had data presented

1 to you on serology, which, if you follow out long
2 enough, can compliment a breath test, should a
3 breath test be approved.

4 We will certainly in the future have
5 data on breath test to present to the committees.

6 DR. MEGRAUD: That is, if it's possible.
7 The breath test has very good points that are
8 dependent of the observer of the technique.

9 It's very easy to perform, and therefore
10 I think it would be important in the future.

11 DR. JUDSON: Well, I certainly defer to
12 your expertise.

13 I think we've got to go on and try to
14 pose a couple of these questions to make a little
15 bit of headway hopefully for FDA. And the first
16 one is the easiest because I think there is only
17 one dissenter as I listen to the different
18 presentations.

19 So perhaps we can go ahead and just go
20 around and poll people. This would be a yes or no
21 answer. Can you do that, Rosemarie?

22 DR. FISHER: Do you allow us to give

1 qualifications? Our committee has gotten used to
2 giving some qualifications along the way, as
3 opposed to a yes or no.

4 DR. JUDSON: If we qualify this --

5 DR. FISHER: No. I mean, just a
6 statement like, "I would" -- I'll start out with
7 it, okay?

8 I'll be the brave one to go forth and
9 say that I think eradication could be the primus.
10 As Dr. Burks said, you can equilibrate eradication
11 with the decreased incidence of recurrence. And
12 thus, if you get eradication, you can predict the
13 decreased incidence of recurrence.

14 What I want to qualify by that is that I
15 think we have to, for the sake of clinical trials,
16 somehow start out, as Dr. Butt and somebody else
17 have said, with the same group of patients that
18 you're going into the trial with at the beginning
19 to say what you're doing as far as eradicating and
20 preventing recurrence in that patient.

21 You have to start with the uniform
22 population or you may want to stratify them to

1 somebody who had an ulcer 6 months ago, somebody
2 who has an active ulcer now, somebody who had one
3 healed a month ago.

4 But then eradication being equal or
5 standing for -- I don't want to use the S word,
6 standing for recurrence, decreased recurrence is
7 out of the question.

8 Go ahead.

9 DR. JUDSON: Okay. I guess we'll --

10 DR. RELLER: Was that a yes?

11 DR. FISHER: That's a yes with a
12 follow-up occasion for ratification at the
13 beginning of the study.

14 DR. RELLER: Why don't you just do yes
15 or no?

16 DR. FISHER: I can't do that.

17 DR. JUDSON: Let's just go with yes, no
18 or abstain, or we'll never make it through this.

19 DR. FISHER: Well, I think that this was
20 the only truly clear consistent data that I saw
21 all day, where the power of the association
22 appears to be pretty good under most conditions.

1 Dr. Reller?

2 DR. RELLER: Yes.

3 DR. FISHER: Dr. Henry?

4 DR. HENRY: I abstain.

5 DR. FISHER: Dr. Kirschner?

6 DR. KIRSCHNER: Yes.

7 DR. FISHER: Dr. Francis?

8 DR. FRANCIS: Yes.

9 DR. FISHER: Let me know if I'm going
10 too fast.

11 Dr. Bertino?

12 DR. BERTINO: I abstain.

13 DR. FISHER: Well, this may not be as
14 simple as you thought, Dr. Judson?

15 DR. JUDSON: Well, it's only going to
16 get worse.

17 DR. FISHER: Dr. Owyang?

18 DR. OWYANG: Yes.

19 DR. FISHER: Dr. Bright?

20 DR. BANKS-BRIGHT: Yes.

21 DR. FISHER: Dr. Burks?

22 DR. BURKS: "Yes" with what the question

1 means. "No" with what it says.

2 DR. FISHER: Does that mean you're
3 saying yes to what I said before?

4 DR. BURKS: I think I'm in agreement
5 with you that I would say, yes, this is a very
6 useful end point.

7 I did not agree that it directly
8 assesses prevention of recurrence. There's an
9 association.

10 DR. FISHER: Dr. Thorpe?

11 DR. THORPE: Yes.

12 DR. FISHER: I think everybody else is
13 non-voting down on that end, correct? We come
14 around to here. And where do I stop with the
15 voters?

16 DR. JUDSON: Excuse me for interrupting,
17 but sometimes we have invited our consultants who
18 may have more expertise and experience than the
19 rest of us to go ahead and give a non-binding
20 opinion.

21 DR. FISHER: Dr. Craig.

22 DR. JUDSON: I always like to see if

1 they still feel the same way they did when they
2 gave their lectures.

3 DR. FISHER: Dr. Craig?

4 DR. CRAIG: I would say yes.

5 DR. FISHER: Do we want to ask Dr.
6 Fanning?

7 DR. JUDSON: Sure.

8 DR. FISHER: Dr. -- is this legal?

9 DR. FANNING: I'll abstain.

10 DR. FISHER: Dr. Hopkins?

11 DR. HOPKINS: Abstain.

12 DR. FISHER: Everybody else then are --

13 DR. JUDSON: Abstaining.

14 DR. FISHER: Right.

15 DR. JUDSON: Dr. Megraud?

16 DR. FISHER: Dr. Megraud?

17 DR. MEGRAUD: Definitely yes.

18 DR. FISHER: Okay. Dr. Temple, Dr.
19 Fredd, you're going to abstain?

20 DR. TEMPLE: We don't vote. You'll
21 figure out what we think.

22 DR. FISHER: All right. Okay. All

1 right. All right. Dr. --

2 DR. FREDD: No. We give for your
3 expertise.

4 DR. FISHER: Dr. Laine?

5 DR. LAINE: Yes.

6 DR. FISHER: Dr. Sonnenberg?

7 DR. SONNENBERG: Yes.

8 DR. FISHER: Dr. Smoot?

9 DR. SMOOT: Yes.

10 DR. FISHER: Ms. Kay?

11 MS. DUNN: I would say that I agree with
12 Dr. Burks. There is an association. It does not
13 predict recurrence. It predicts a decrease in
14 recurrence, and there should be some sort of
15 risk-benefit ratio attached, because some of the
16 decrease was very small.

17 DR. FISHER: I think we may get into
18 that when they refer the question down the line as
19 to what is acceptable incidences of recurrence.

20 Dr. Parker?

21 DR. PARKER: Yes.

22 DR. FISHER: Dr. Elushoff?

1 DR. ELUSHOFF: In recently healed
2 patients, eradication predicts a significant drop
3 in 6-month ulcer recurrence.

4 DR. FISHER: Dr. Comer?

5 DR. COMER: Yes. But I'd like to later
6 on discuss how we're going to assess eradication.

7 DR. FISHER: Dr. Melish?

8 DR. MELISH: Yes.

9 DR. FISHER: That was a yes, in case it
10 didn't get into the mike.

11 Dr. Butt?

12 DR. BUTT: I agree with Rosemarie. I
13 always agree with Rosemarie.

14 DR. FISHER: Oh, thank you. Dr. Azimi?

15 DR. AZIMI: Yes.

16 DR. FISHER: Okay. Question number two.

17 DR. JUDSON: Can I take a crack or ask
18 one of the --

19 DR. FISHER: Go ahead.

20 DR. JUDSON: I'll just take a crack at
21 posing that as a single question or picking it
22 apart and putting it into questions that can be

1 answered yes, no.

2 And I guess one way of doing that is
3 endoscopic visualization of the ulcer and test of
4 cure essential to these trials. I mean, that's
5 partly what we're getting at -- whether we have to
6 see the ulcer and prove that it has disappeared --

7 DR. COMER: Is endoscopy necessary?

8 DR. JUDSON: -- or whether we can get by
9 with --

10 DR. COMER: Is endoscopy necessary?

11 DR. FISHER: Well, that -- I mean,
12 you're talking -- the way it's phrased here, I
13 think you're looking at two different things
14 again.

15 You're looking in the acute ulcer
16 healing --

17 DR. JUDSON: Can I make a comment?
18 Isn't endoscopic proof of ulcer presence and ulcer
19 resolution essential to these studies?

20 DR. FISHER: Dr. Hopkins, do you want to
21 tell us what you mean.

22 DR. HOPKINS: One way to approach this

1 is to consider that the answers just may be
2 eradication alone, ulcer healing alone, ulcer
3 recurrence alone. And then three different
4 versions of overall success.

5 A would-be clinical definition is that
6 you have to assess healing at some point to find
7 when later. You have to assess healing at some
8 point and ulcer recurrence. That would be a
9 clinical definition of overall success.

10 And a combined microbiologic and
11 clinical definition -- using the word
12 "surrogate" -- of overall success would be a
13 combination of eradication in healing using
14 eradication as a surrogate.

15 And then the most strict conservative
16 definition, which you have already agreed not to
17 do, would be a combination of eradication, healing
18 and no recurrence.

19 And so there might be 6 possible
20 answers. Pick one.

21 DR. FREDD: What is the claim, Bob, that
22 relates to overall success that is different than

1 eradication somehow linked to reduction of risk,
2 prevention of duodenal ulcer recurrence?

3 Let's say there has been major agreement
4 related to eradication being somehow linked to
5 some claim yet not written on prevention of DU
6 occurrence, what more is going to be gotten by
7 some other endoscopic overall success end point?

8 What's the claim there?

9 DR. HOPKINS: Well, for overall success,
10 you're going to get -- you're going to show the --
11 I mean, if you're just going to look at recurrence
12 alone, you're going to be right in the label in
13 patients who have healed because you have to have
14 a heal before you can even talk about recurrence.

15 Most study --

16 DR. FREDD: No, we haven't --

17 DR. HOPKINS: -- designs include anti-
18 secretory agent or something that heals and also
19 an antimicrobial combination. And so you're going
20 to get both healing and reduced ulcer recurrence.

21 DR. FREDD: I don't think they have as
22 yet come to the conclusion that the eradication

1 primary end point is going to be applied only to
2 patients who have healed. That's something we
3 have yet to discuss.

4 DR. HOPKINS: That's true.

5 DR. FREDD: The question is overall
6 success, what more do you think it's going to give
7 a sponsor in terms of a claim?

8 This antimicrobial, anti-secretory
9 combination therapy is approved for overall
10 success in duodenal ulcer disease?

11 DR. HOPKINS: No. It's approved for
12 healing and reduction of recurrence.

13 DR. FREDD: Okay. So we're dealing with
14 an acute --

15 DR. HOPKINS: Two things.

16 DR. FREDD: -- acute healing claim. Now
17 we have -- they have not said that eradication
18 itself is in any way related to acute healing and
19 that acute healing -- if you would take acute
20 healing out of this and consider whether endoscopy
21 needs to be done, the document -- the benefits for
22 acute healing I think we might get some general

1 agreement on that.

2 DR. RELLER: It seems to me that we
3 could clarify this question by approaching it in
4 the following way:

5 That if one wants to make a claim about
6 any of these elements, one has to show objective
7 proof of meeting that claim. And we have some of
8 the boundaries for that that have been discussed
9 before, and I don't think we need to get into
10 those details.

11 And overall success to me is that if I
12 were the patient and I had a duodenal ulcer and
13 was not taking corticosteroids or one of the other
14 things and had H. pylori, I'd want to have my H.
15 pylori eradicated.

16 I'd want to have my ulcer healed and I'd
17 want it to be looked at later and show that it
18 didn't come back. I mean, I'd want all of those
19 things. That would be overall success.

20 But I think where we get into difficulty
21 is when we take one element and extrapolate so
22 that it is somehow going to be predictive of some

1 of these other things, but it's not without
2 looking at the independent database.

3 So if one wants a claim for H. pylori
4 eradication, you've got an objective evidence that
5 you've eradicated.

6 If you want to show that the ulcer
7 doesn't recur, that you have some follow-up period
8 that it doesn't recur. And I think that would be
9 helpful.

10 But if you want any of these things or
11 all of them, if you want all of them, you have to
12 demonstrate all of them. If you want one of them,
13 you have to demonstrate that in terms of --

14 DR. FISHER: I agree. Dr. Fanning?

15 DR. FANNING: I think that that actually
16 is the key here -- having had the first issue
17 discussed and an agreement that H. pylori
18 eradication is an important primary end point --
19 the question then becomes: are endoscopic
20 evaluations of the disease process necessary?

21 And I think Dr. Reller has actually
22 clarified that quite well.

1 DR. FISHER: Dr. Temple?

2 DR. TEMPLE: Is what you said was: if
3 you wanted to say that the antibiotic regimen
4 contributed to ulcer healing, then of course,
5 you'd have to show improved ulcer healing, but
6 that if you did not want to say that, then the
7 endoscopy might not be a very important part of
8 that study.

9 Is that -- I think that's --

10 DR. RELER: One has to objectively
11 demonstrate that you've satisfied efficacy safety
12 criteria for the claim that you're making. And if
13 that claim is ulcer healing, you have to have some
14 evidence of that and some marker is not going to
15 -- well, make it.

16 DR. TEMPLE: For the most part, the
17 people in the audience have been primarily
18 interested in showing that particular antibiotic
19 regimens and effective regimens can reduce H.
20 pylori presence in a month, and concluding from
21 that that these are regimens that will prevent
22 recurrence.

1 I understand people's reservations about
2 how exactly that's expressed, but that's mostly
3 what they're interested in.

4 And I guess the question is: if that's
5 mostly what they're interested in, are they
6 responsible for showing anything else?

7 DR. RELER: Well, it seems to me that
8 if you want to say that your regimen eradicates by
9 good sensitive techniques, one cannot show the
10 presence of H. pylori at one month to 6 months by
11 doing this -- and that's all you want to say --
12 then, fine.

13 I think Kay Dunn and others pointed out
14 very clearly that to extrapolate that you're not
15 going to get an ulcer again, that's stretching it.

16 DR. FISHER: But that's what --

17 DR. TEMPLE: Well, actually --

18 DR. FISHER: -- all this data is that
19 we've shown.

20 DR. TEMPLE: This is very important
21 because I think we understood you to be saying in
22 the answer -- let me make a premise. I think we

1 would all agree with this.

2 Eradicating an organism whose
3 eradication serves no purpose is not something we
4 would be prepared to approve ordinarily.

5 The only reason that we would
6 contemplate approving eradication of H. pylori is
7 because we believed that as the sole end point as
8 a basis for claims -- because we believed and
9 thought you believed that that meant it
10 corresponded to a clear clinical benefit seen
11 later -- that is, diminished recurrence.

12 If you don't believe that, then why
13 would anybody do this treatment?

14 DR. FISHER: I think it's a matter of
15 being very precise in sticking with the scientific
16 database.

17 For example, if I had a duodenal ulcer
18 and I had H. pylori, I would like to have that
19 eradicated. I think that people who have duodenal
20 ulcers, the data presented to eradicate this
21 organism is a good thing for the individual, you
22 might say, and the public's health to -- but why

1 exactly?

2 Because the odds favor that one will not
3 have recurrence, and if you don't get rid of it,
4 there's a high likelihood -- you know, when one --

5 DR. TEMPLE: Do you doubt a causal
6 relationship there?

7 DR. FISHER: Well, one has to be very
8 careful here because it would be so easy then to
9 get into, well, we have a test that's pretty good.
10 for showing the likelihood of having this
11 organism, that if you don't have it, you have a
12 lesser likelihood.

13 And then you look at those serologic
14 data of how many people have this organism and I
15 can see us getting into a witch hunt to look for
16 this organism and eradicate it on a test that is
17 associated --

18 I mean, the possibilities --

19 DR. TEMPLE: Well, let's say we're not
20 that silly and the companies aren't that
21 mean-spirited to do that, and they define it as
22 people who have documented ulcer disease -- recent

1 or documented ulcer disease -- and it's limited to
2 that.

3 Do you then doubt that the eradication
4 of H. Pylori has something to do with the
5 non-recurrence?

6 DR. FISHER: Well, those specific
7 delineations that you've just mentioned is exactly
8 what I started out with. Let's be very precise
9 about what we're saying and not go beyond what the
10 database allows.

11 And it doesn't mean, in practical terms,
12 that we necessarily are on different sides of the
13 issue.

14 DR. TEMPLE: Okay.

15 DR. FISHER: But I think it's very
16 specific that you do not put into a claim
17 something that goes beyond what you can be certain
18 about.

19 DR. TEMPLE: I have to press you on this
20 because it's really important to the whole
21 enterprise.

22 The first question was asked because we

1 thought a yes answer meant that you thought that
2 for people with documented ulcer disease who were
3 the subjects of this meta analysis, eradication of
4 H. pylori predicted a decreased risk of getting an
5 ulcer, you know, in much the same way that
6 lowering blood pressure leads to a decreased risk
7 of getting stroke. It's not one-to-one. No
8 guarantee, but it reduces the risk.

9 DR. FISHER: Right.

10 DR. TEMPLE: Do you -- and the labeling
11 would say something like that presumably if people
12 showed that this particular antibiotic regimen
13 could eradicate, according to proper standards and
14 proper measures, H. pylori.

15 So it would -- on the basis of the
16 showing of decreased H. pylori, the labeling could
17 refer to a decreased likelihood of ulcer
18 recurrence.

19 I think we were thinking of going that
20 far, depending on what the committee thought.

21 DR. FISHER: But not prevention -- not
22 total prevention.

1 DR. TEMPLE: Nobody gives guarantees,
2 just reduction in rate. And we could give some
3 data.

4 DR. FISHER: I think that's what some of
5 us was saying -- reduction in risk.

6 DR. RELLER: Because I think it would be
7 helpful to come to, you know, closure on this
8 point.

9 I think your analogy with blood pressure
10 and strokes is actually a good one. And I think
11 it's a very big difference by saying this drug
12 lowers blood pressure.

13 Now, we know that lowering blood
14 pressure is associated among other issues in terms
15 of prevention of strokes. But I think to get too
16 cozy a relationship between saying that a drug
17 that lowers blood pressure prevents strokes --
18 there's a fine line there that one does not want
19 to cross. And I'm just urging that we keep that
20 in mind.

21 DR. JUDSON: Yes, but I think there are
22 number of other infectious disease correlations

1 that are very similar to the one that some of us
2 are having with H. pylori most of the time, but
3 there are quite a few exceptions to that that need
4 to be addressed.

5 In a sense, what I get here is something
6 like that. Yes, H. pylori is associated with the
7 disease, but it seems to be quite a spectrum of
8 the other things that can go along with this.

9 And I don't see that as clearly defined,
10 unless you had clinical trials that do address the
11 ulcer healing to some degree or another in
12 occurrence and what not.

13 DR. TEMPLE: There are clinical trials
14 that do that. They weren't presented because
15 we're missing some data on how H. pylori was
16 eradicated.

17 But they are very powerful trials that
18 prove, to my eye, that eradication matters. These
19 were trials in which every patient with an ulcer
20 was randomized at therapy or non-therapy and then
21 recurrence was watched.

22 So other factors, you know -- for

1 example, the ability to heal might predict a
2 better ulcer outcome. That was eliminated by
3 that. These were intent to treat trials and they
4 took care of everybody.

5 What they seem to show, our
6 interpretation was that if you get rid of the H.
7 Pylori, you decrease the rate of recurrence.

8 Now, I'm having trouble understanding
9 what your reservations are and what you want us to
10 do about it.

11 DR. FISHER: Maybe I can clarify
12 something in a way, because I like the analogy
13 again as you said about the lowering blood
14 pressure and reducing the risk. And I think that
15 was what we're sort of saying here.

16 But I think what some of us -- you know,
17 I think some of us are thinking or maybe the
18 thinking isn't -- maybe I'm wrong, that you're
19 going to say, Okay. You've eradicated it. You've
20 tested it at 4 weeks. It's eradication. That's
21 it. You don't follow-up anymore.

22 Do you feel comfortable with that? And

1 I think that was what we were hearing here
2 before -- you need to continue to see eradication
3 at a longer time out than 4 weeks after therapy to
4 say it -- or no, are we not saying that?

5 DR. FREDD: This question here is not
6 the indication as it would be written or your
7 input would be given.

8 You know, it would -- you know, there
9 are many things that would be done before any drug
10 would be approved in terms of assuring how
11 eradication would be done, when it's done, what
12 the language of an indication would be.

13 I think this question is trying to help
14 to the people analyzing the trials, in-house, as
15 to whether they can analyze primarily eradication
16 and present that to you, if the claim is something
17 related to prevention of ulcer as being proof that
18 the drug regimen works in that type of way.

19 Later, you would get to methods of
20 eradication. Later, you would get to labeling and
21 you would see all of that.

22 But this isn't meant to box you into a

1 point of view that this is going to be the way the
2 indication is written.

3 DR. FISHER: Dr. Judson.

4 DR. JUDSON: I'm going to propose that
5 we simply not attempt to answer these questions.

6 I think the benefit of today's
7 discussions are to air all these issues and to
8 bring as all sides to bear on them.

9 We're not necessarily in the position to
10 decide definitively for you. I would hope that as
11 it relates to these questions, the FDA now feels
12 that if they didn't before, that they have more
13 complete information, discussion.

14 I think if we had an application on the
15 table, that makes it easier, too.

16 We're not really I think very
17 experienced with dealing with theoretical
18 applications. So let's -- I would propose now
19 that we go ahead for our break and we'll move on
20 to the -- try to catch up right after this.

21 DR. FISHER: We're going to start out
22 with issue number two: should a minimal level of

1 efficacy be established for clinical end points
2 and in what scenario would lower levels be
3 acceptable?

4 And we will start out with the talk on
5 minimal efficacy levels by Dr. Hopkins.

6 (Recess)

7 DR. HOPKINS: Yes. This is Bob Hopkins
8 from the Division of Anti-Infective Drug Products.

9 This is going to be a short talk. I
10 wasn't sure exactly what was going to pan out in
11 the first discussion on efficacy end point.

12 So, generally, when we think about
13 threshold levels, most people talk about minimal
14 efficacy of eradication -- you know, should we
15 accept a 90 percent eradication or an 80 percent
16 eradication, for that matter? Since nothing's
17 approved, maybe 40 percent is okay.

18 But really you could conceive of this
19 minimal level of efficacy in terms of any of the
20 end points that you may or may not have decided
21 upon.

22 And so, if you do accept a minimal level

1 of efficacy, when should you accept a lower level
2 of efficacy?

3 And the possible considerations include
4 the low level of secondary resistance -- that is,
5 a resistance which develops on therapy -- regimens
6 which may have good compliance and regimens that
7 have good side-effect profiles.

8 And although the FDA does not take into
9 consideration costs in approval of drug regimens,
10 certainly the physician will consider and HMOs
11 will consider this as a factor, in terms of
12 whether to accept a lower level of efficacy to use
13 regimens.

14 So that's all I really wanted to say. I
15 just wanted to open it up. And we have two
16 industry representatives from Glaxo Wellcome and
17 from Abbott and we look forward to these
18 presentations.

19 DR. FISHER: Dr. Hopkins, maybe you can
20 help me. I only have one person speaking on the
21 agenda after --

22 DR. HOPKINS: They must have changed the

1 agenda.

2 DR. CRAFT: Recently, I did a search of
3 the literature. And there were over 3,000
4 articles which were referenced to H. pylori.
5 Several hundred of these talked about different
6 therapies, but only two of these were done in
7 well-controlled clinical trials.

8 This is not dissimilar to what happened
9 in the '70s with cancer chemotherapy. At that
10 time, every cancer center had their recipe for
11 treating cancer patients.

12 It was very good in getting enthusiasm
13 for cancer chemotherapy, but it was very confusing
14 to those trying to decide what was the best cancer
15 chemotherapy.

16 Fortunately, the National Cancer
17 Institute stepped in and put in some standards for
18 how to do clinical trials.

19 I think we're at that point with H.
20 pylori right now.

21 What are some of the approaches we can
22 take in establishing an acceptable eradication

1 rate?

2 Well, one and the one that we most
3 commonly use is that we just pick an arbitrary
4 target number and say, "This is it." So I say
5 it's 100 percent.

6 For scientific purposes, let's establish
7 criteria for assessing rates, then determine from
8 the highest obtainable rate in true life, rather
9 than what we think.

10 What is the outcome of the current
11 target approach?

12 Frequently, the physician is very
13 confused. Just the other day, a physician called
14 us and he said, "Well, what is the treatment du
15 jour?"

16 Well, this kind of not knowing exactly
17 what therapy very quickly leads to disappointment
18 for physicians when they have expectations of 90
19 or 100 percent eradication and then they treat
20 their patients, they don't get those rates.

21 This makes them skeptical. They're not
22 really sure whether H. pylori is really associated

1 with ulcer disease and they become apathetic and
2 they go back to their original way of treating
3 ulcers and we lose patients to this type of
4 mentality.

5 So what are some of the deficiencies in
6 the target number approach?

7 The suggestion is that there is an
8 inherent value to the number that we choose that
9 presumes that the eradication rate is directly
10 correlated with efficacy forgetting that you have
11 to heal the patient, you have to make sure the
12 patient tolerates it, and follow up with what
13 happens to the patient long term.

14 It encourages selective analysis and
15 sets biases that will lead your eradication rates
16 to be much higher than what you can really get it
17 in real life.

18 It ignores the difficulties inherent in
19 proving the absence of infection. It fosters a
20 biased study design needed to come up with these
21 types of numbers. It impedes the comparisons of
22 treatment.

1 We would advocate a criteria for
2 determining eradication rates. Not unlike what I
3 said this morning, we think it should be done in
4 well-controlled trials to FDA standards that all
5 evaluable patients should be used for the
6 randomization throughout the entire study and that
7 you must demonstrate reproducible eradication
8 rates in two or more studies.

9 You must prove that your therapy is
10 bactericidal and we must do this using multiple
11 accurate diagnostic tests and multiple time
12 points.

13 The benefits of establishing these
14 criteria are that it emphasizes the clinical
15 outcome which is the most important thing to the
16 patient, it emphasizes the importance of
17 well-controlled trials and acknowledges the
18 difficulty of proving the absence of infection,
19 thus providing the accurate reproducible data that
20 facilitates the comparison from one trial to the
21 next.

22 So what is my conclusion? I still think

1 100 percent is the ideal rate because as a
2 patient, everything else is zero.

3 Scientific purposes, we must set
4 standards by which we can determine what is the
5 highest rate in a well-controlled trial that is
6 reproducible and accurate.

7 Thank you.

8 DR. FISHER: Questions for Dr. Craft
9 quickly.

10 DR. FREDD: One question.

11 DR. FISHER: Dr. Fredd.

12 DR. FREDD: When you were talking about
13 the highest rate demonstrated in well-controlled
14 trials, do you mean of a regimen compared to
15 another regimen or only a particular regimen
16 compared to a placebo or what?

17 DR. CRAFT: Well, the best way to
18 compare something is head to head in a trial.

19 DR. FREDD: Right.

20 DR. CRAFT: Everything else --

21 DR. FREDD: So if one had a gold
22 standard something, triple therapy --

1 DR. CRAFT: Triple therapy.

2 DR. FREDD: -- of 90 percent, are you
3 suggesting a head-to-head comparison with that?

4 DR. CRAFT: I think that's the best way
5 to know whether it's truly similar or better.

6 But the main thing is knowing that you
7 have a standard by which you can assess these
8 tests since having them all done the same way.

9 DR. FISHER: Any other questions,
10 comments?

11 Dr. Sonnenberg? I need you to talk
12 straight into the microphone.

13 DR. SONNENBERG: How are we going to
14 deal with the fact that one antibiotic is --
15 contributes to therapy that is 70 percent and
16 contributes to another therapy?

17 Let's say one is dual and the other one
18 is triple where it's 90 percent effective?

19 DR. CRAFT: Well, you don't know that
20 unless you actually do a head-to-head comparison.
21 You might be surprised.

22 DR. FISHER: Dr. Francis?

1 DR. FRANCIS: One question I had is as
2 well as comparing the regimens head-to-head, how
3 about in different populations, gender and --

4 For example, if you compared a Nigerian
5 group to a Japanese one, are those relevant issues
6 that need to be addressed also?

7 DR. CRAFT: I think that you need to
8 make sure that your populations are as similar as
9 possible. It can be very difficult to compare a
10 study from the U.S. and a study in Peru.

11 DR. FRANCIS: Well, you don't need to do
12 that. You can do that right here in the United
13 States. That's why I'm asking.

14 But I think the issue I was trying to
15 get at though is we're looking at -- as you said
16 earlier, a very homogenous population. But my
17 senses from the data presented, the different
18 populations which are included in our country, the
19 presumptions we're making about efficacy may not
20 hold true for a lot of different populations.

21 DR. CRAFT: Well, we really won't know
22 that until we do standardized tests that are done

1 in a similar fashion so that you know that they're
2 comparable.

3 DR. FISHER: The efficacy that you can
4 probably ask here is not so much different
5 populations but resistance in the organism in
6 different areas of the country without even race
7 differences or sex differences, gender
8 differences.

9 Dr. Laine, you looked like you had a
10 question.

11 DR. LAINE: No.

12 DR. FISHER: Dr. Sonnenberg, into the
13 microphone, please.

14 DR. SONNENBERG: I think that your
15 suggestion is somewhat impractical, though,
16 because you have, in most therapies, three or 4
17 drugs. And each drug can be given, let's say, in
18 two or three doses.

19 So you end up with a tremendous number
20 of possible treatments.

21 I mean, you end up with 400 possible
22 therapies. How are you going to compare all those

1 head-to-head?

2 DR. CRAFT: I didn't say that. I
3 said --

4 DR. SONNENBERG: That was how you
5 answered my first question.

6 DR. CRAFT: Then I must have
7 misunderstood your first question.

8 What I said was that you need to compare
9 therapy to therapy.

10 If you have dual therapy and you want to
11 see how it compares to triple therapy, you must
12 compare them head-to-head.

13 I'm not sure that we need all of the
14 factorial designs where you have each and every
15 agent get in the combination once you establish
16 some type of therapy.

17 I think you will be surprised though
18 when you start doing those factorials that some of
19 the things you thought from the beginning are not
20 true.

21 So there is some basis why you might
22 want to do some factorial type studies.

1 DR. FISHER: Any other questions? If
2 not, maybe -- Dr. Temple?

3 DR. TEMPLE: I'm not sure I understand
4 the advice that you're giving us.

5 We're going to have some trials that
6 will have an eradication rate of a certain
7 percent, say 70 percent. They may or may not be
8 comparative trials with any other anti-infective
9 regimen.

10 And since we haven't proved any, it
11 would be hard for us to say we know anything about
12 it any particular regimen.

13 DR. HOPKINS: What would you --

14 DR. FISHER: Bob, into the mike, please.

15 DR. HOPKINS: Sorry. What would you
16 have us do tomorrow?

17 DR. CRAFT: I think as long as you have
18 done the studies to a high enough standard, then
19 you can accept those results. Once you -- this
20 body has provided us with a comparison of some
21 approved agent, I think then you need to do your
22 trials against that agent.

1 DR. HOPKINS: But -- so until you --

2 DR. CRAFT: It's very hard from the
3 beginning.

4 DR. HOPKINS: So until there's an
5 approved agent, as long as it would be zero?

6 DR. CRAFT: Right.

7 DR. FISHER: I mean, one of the things
8 Dr. Hopkins raised in his -- and I think he put --
9 I'm not sure if he put it up or it was just in our
10 handout -- is that one of the current standards
11 we've looked at for risk reduction of recurrence
12 is what happens with H2 blockers and that is an
13 acceptable recurrence rate on maintenance therapy
14 that eradication should stand up to, at least, if
15 not better.

16 People on the committee, do you want to
17 comment?

18 Dr. Francis?

19 DR. FRANCIS: I think that's a good
20 suggestion. I also want to remind the committee,
21 there's also -- there is a clinical structure
22 that's already in place to do that kind of thing.

1 With the AIDS clinical trials unit, we
2 have sort of a gold standard, whether it be using
3 just the H2 blockers or some agent. You do the
4 comparison and then look for the best outcomes.

5 You not be able to do the head-to-head
6 because we don't have an exact mechanism of
7 pathophysiology.

8 But the outcomes and the best outcomes
9 can be obtained by structures that already exist..

10 DR. SONNENBERG: Let me ask you: 50
11 percent cure rate with Amoxycillin, Emiprisol,
12 would that be acceptable to you?

13 It was tested in a well-designed
14 clinical trial.

15 DR. CRAFT: Well, it's not whether it's
16 acceptable to me. It's acceptable to you. You
17 have to make those decisions.

18 But I'm trying to tell you that what you
19 should make sure is that when you say 50 percent,
20 that it's really 50 percent; that you've done the
21 trials to a standard where you're assured that
22 it's not just a number that we've reached out of

1 the sky and grabbed like you see in clinical
2 trials in the literature where one week it's 90;
3 then the same therapy next week is 80.

4 DR. FISHER: Dr. Judson?

5 DR. JUDSON: Can -- since we're at
6 almost all points dealing with two different end
7 points, the ulcer healing and the bacterial
8 eradication, can we not use the word "cure," or --
9 and maybe go to -- we have bacterial eradication,
10 we have ulcer healing or maybe ulcer cure.

11 But sometimes the word is coming up
12 again "cure," and I'm not sure what we're applying
13 that to. Usually we're not going to be talking
14 about bacterial eradication --

15 DR. CRAFT: As a cure in itself --

16 DR. JUDSON: Yes.

17 DR. CRAFT: -- because we've only cured
18 -- it doesn't come back.

19 DR. JUDSON: Right.

20 DR. FISHER: Dr. Laine.

21 DR. LAINE: Yes. I just want to say I
22 don't think we actually have an answer from this

1 about what the lowest level of efficacy would be.

2 But in any event, I think Dr. Hopkins
3 raised an interesting question about resistance.
4 And the question is would you -- do the panel
5 members feel that you would alter your acceptable
6 level of efficacy if you were using drugs that
7 were either safer and/or had less resistance?

8 In other words, you might accept a
9 slightly lower efficacy rate if they had less side
10 effects and/or if it had -- if it wasn't going to
11 cause resistance or you weren't going to hurt
12 yourself down the line.

13 DR. FISHER: Well, the question I would
14 say back to then, yeah, would you -- if it had
15 less of an incidence of developing resistance, but
16 you got only a 20 percent eradication rate as
17 opposed to something that had a ten percent
18 incidence of resistance but had a 70 percent
19 eradication rate, you know, which one would you
20 want and should there be a minimal standard?

21 Steve, Dr. Fredd?

22 DR. FREDD: I was just getting back to

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1 the comparison on H2 blocker.

2 When we approve other H2 blockers for
3 prevention of recurrence, we do not require that
4 they be compared to one already on the market and
5 show an equivalent rate of recurrence reduction.
6 They are generally compared to placebo.

7 Now, that may not be the model that is
8 reasonable to apply to this because you have
9 questions of resistance and potential, at least in
10 terms of what you read in the literature and what
11 is your package in terms of 90 percent cure, of
12 getting that high.

13 So, I wonder if -- I wonder if you think
14 the H2 model and relative efficacy to something
15 else is necessary or whether you believe some
16 minimal standard should be there rather than
17 comparison to placebo?

18 The reason for that is yes, we will be
19 dealing with applications based on regimens that
20 were done a year or two ago. The field is rapidly
21 moving. And the question, I suppose, that we
22 have, as far as a public health agency, is if we

1 can approve drugs that are safe and effective
2 based on their data and publish that, and what
3 will that regimen that we are approving look like,
4 compared to what is in the public domain and
5 public knowledge of regimens that get better cure
6 rates?

7 So I think that's why I think this idea
8 of a minimum level of cure, if appropriately done
9 and numbers that are well-understood and
10 well-documented, but would 20, 30, 50 percent be
11 adequate when there is the potential of 80 or 90
12 percent?

13 Dr. Megraud?

14 DR. MEGRAUD: I just would like to
15 comment that if you should accept it, I think it's
16 a good thing in terms of public health to accept a
17 very high eradication rate because you can convert
18 the control of eradication if almost all of your
19 patients would be eradicated in the future. I
20 mean you can practice.

21 Also your vote is your current of
22 resistance. If there is not strains anymore, you

1 don't have any more resistance.

2 And I think we know that now we have
3 regimen which are able to achieve this higher
4 eradication rate.

5 In other kinds of infectious disease,
6 would you accept a low eradication rate for the
7 bacteria? I should doubt. You know that you can
8 do better.

9 DR. FISHER: I'll let -- would you
10 accept a 20 percent cure rate for syphilis when
11 you know you can get 70 percent?

12 DR. JUDSON: I was just thinking along
13 that same line that 30 or 40 or 50 percent, there
14 is no model in treatment of infectious diseases
15 for accepting anything that low. And when you
16 consider the potential disadvantages to
17 individuals in populations of treating them with
18 three antibiotics and to get a 20 or 30 percent
19 eradication rate, I think that's not something
20 that we would recommend the FDA approve in this or
21 any other area.

22 DR. FISHER: I guess that gets into the

1 risk benefit ratio of things.

2 Dr. Bertino?

3 DR. BERTINO: In line with some of the
4 eradication information we've heard today, we've
5 heard some varying percentages.

6 I guess the question that I have is, do
7 we know why patients that have H. pylori that get
8 treated with these triple antibiotic regimens and
9 Emiprisol, why some of them do not eradicate the
10 organism?

11 And so what I'm thinking of is, are
12 there other reasons that maybe aren't being
13 investigated right now?

14 For example, maybe one dose doesn't fit
15 everybody in these studies in terms of antibiotic
16 therapy and maybe we need to use varied doses,
17 things like that?

18 Is it because they have resistant
19 organisms? Is it because they're recolonized with
20 a different organism?

21 I was reading one of Dr. Reller's papers
22 on Graham negatives and reinfection versus new

1 infections recently.

2 So I would be interested if there is any
3 information on some of these questions as they
4 pertain to eradication.

5 DR. FISHER: Could we just get the
6 lights up before we go?

7 DR. JUDSON: What are the -- asking our
8 experts -- what are the highest eradication rates
9 that have been shown in large well-controlled
10 trials?

11 What is a reasonable target?

12 DR. BERTINO: Well, 90 percent probably.

13 DR. MEGRAUD: Yes, even I think 95
14 percent in the one -- when certain arms of the
15 micron study.

16 DR. LAINE: Well, that was a protocol
17 cure rate, so we just need to be careful whether
18 we're talking about all patients treated or
19 protocol cure rates.

20 DR. MEGRAUD: That's definitely more
21 than 90 percent when several multi-centered large
22 studies were performed in Europe.

1 DR. SONNENBERG: The most important risk
2 factor for success rate is compliance. Patient
3 compliance is the single most effective factor.

4 And that again relates to the simplicity
5 of the therapy. Triple or quadruple therapy that
6 involves Pepto-Bismol, ranitidine, Metronidazole,
7 and Tetracycline amounts to 17 tablets per day for
8 two weeks.

9 And if the compliance rate drops, then,
10 the eradication drops.

11 I think this may also play a role. The
12 fact is that you alluded to like resistance in
13 different types of organisms. But compliance is
14 the single most important risk factor.

15 DR. BERTINO: But did -- am I mistaken
16 that folks from Glaxo Wellcome presented -- I
17 think it was Glaxo Wellcome -- a 75 percent
18 eradication rate with -- I think it was
19 clarithromycin and RBC?

20 I suspect that's not 17 tablets a day
21 unless -- but I don't know anything about it.

22 DR. FISHER: Either or Duane, if you can

1 answer that.

2 DR. OLSON: Can I speak first? In
3 answer to your question --

4 DR. FISHER: Can you identify yourself?

5 DR. OLSON: Carol Olson from Abbott
6 Laboratories.

7 In answer to your question regarding
8 eradication rates, in the literature for
9 well-controlled trials with multiple test for
10 proof of eradication, there are only two published
11 trials: one is with Amoxycillin and Emiprisol.
12 And the highest eradication rate with
13 clarithromycin and Emiprisol is 83 percent.

14 The trials that Professor Megraud
15 reported recently are not well-controlled trials,
16 in the sense that the eradication in those trials
17 is only assessed by the breath test.

18 So, therefore, there is no literature
19 available in a well-controlled trial that is
20 higher than 83 percent eradication rate.

21 And therefore, that has to be considered
22 when you're looking at the data in the literature:

1 How was the eradication rate assessed.

2 DR. FREDD: Can I ask a question of this
3 speaker?

4 Could you tell me how David Graham
5 assessed eradication in his trials of ranitidine
6 and triple therapy?

7 DR. OLSON: David Graham used three
8 diagnostic tests. However, David Graham's studies
9 are not multi-center well-controlled trials. It's
10 a single center study.

11 DR. FREDD: Oh, all right. Now it's not
12 a well-controlled trial because it's a
13 single-center trial?

14 DR. OLSON: It's my understanding that
15 the FDA definition of a well-controlled trial is a
16 randomized double-blind --

17 DR. FREDD: That is not so.

18 DR. OLSON: -- multi-center trial.

19 DR. FREDD: That is not so. It does not
20 have to be multi-center.

21 DR. TEMPLE: Our entire definition can
22 be found in 314.126 and multi-center is not in it.

1 We'd like multi-center trials.

2 DR. FISHER: But it's not required? Can
3 we have Art answer the question? Dr. Megraud then
4 can follow-up on it.

5 DR. MEGRAUD: It's true that I mention
6 one of my studies which are not yet published.
7 But these studies are being performed and they do
8 exist and they will be published. But it's true
9 that they are not published yet.

10 DR. FREDD: But Dr. Graham's is
11 published. It was done at one center and that
12 eradication rate is 89 percent.

13 DR. LAINE: And along those lines,
14 related to compliance -- I apologize -- I think
15 compliance is the most important factor.

16 But again, if we're doing an all
17 patients treated analysis that takes into account
18 the compliance, that's more in the real world.

19 In other words, if all patients treated
20 have a 90 percent or 85 percent eradication rate,
21 that is with or without bad compliance or good
22 compliance. In other words, that takes that into

1 account.

2 So I think as long as you're doing all
3 patient-treated analysis, we're getting in more
4 real -- it's not real world. In a sense, it's not
5 absent the real world, but at least we're looking
6 at the effect of compliance because we're
7 including all patients.

8 DR. FISHER: Art?

9 DR. CIOCIOLA: Yes. I'd like to address
10 a question that was raised several minutes ago
11 basically regarding controlled clinical trials.

12 The data that I showed a little earlier
13 was ranitidine bismuth citrate plus clarithromycin
14 and that was 500 milligrams per day TID. And in 4
15 separate studies, the ranges were between 82 and
16 94 percent eradication rate.

17 And I did want to add that this
18 particular regimen is the ingestion of 5 tablets
19 per day; that is RBC twice a day and
20 clarithromycin three times per day.

21 And we have data to show that 95 percent
22 of the patients were in compliance with this

1 regimen.

2 DR. FISHER: What you were remembering
3 with the 75 percent was the prevalence rate across
4 those 5 studies.

5 DR. CIOCIOLA: Yes. The --

6 DR. FISHER: That was the 75 percent.

7 DR. CIOCIOLA: The 75 percent was the
8 prevalence prestudy infection rates that we
9 observed across all 6 of those studies in the U.S.
10 And I apologize. In the United States.

11 DR. FISHER: Dr. Reller?

12 DR. RELLER: Focusing on what we'll have
13 to take a poll on issue two, it seems to me that
14 trying to have a particular specific number below
15 which one would not approve something is ill
16 advised because this is a rapidly evolving field.
17 There are many factors that go into it. And it's
18 a big market.

19 It's a question partly posed for
20 industry about the utility of the marketplace in
21 the evolution of these things, but if one
22 considers the natural history of therapies for

1 syphilis, for example -- I mean, arsphenamine or
2 mercury or whatever -- I mean, maybe it had a poor
3 cure rate.

4 But when penicillin came along --
5 because, maybe, if the FDA theoretically had
6 cleared one of these treatments that was better
7 than nothing but was still not very good -- I mean
8 it becomes an issue later on.

9 Why not have, instead of perfection
10 being the enemy of good, look at what the reality
11 is.

12 I mean, if you have some treatment
13 that's used now and you do anything -- let's say
14 Amoxicillin added to Emiprisol -- and you get not
15 only the same cure rates of ulcer that you had
16 with the reduction in gastric acid, but you have
17 an effect on H. pylori having to do with the risk
18 probability of recurrence -- and let's just pull a
19 number out that it's safe -- and it's 30 percent
20 efficacious in reducing.

21 In the literature, there are data that
22 this new regimen that is reasonably -- people

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1 reasonably comply with it, achieves 80 percent, I
2 mean what is the utility of having FDA clearance
3 for the 80 percent regimen that the firm would
4 come and get that?

5 Whoever has 30 percent and you have
6 something else just as easy to take that's 80
7 percent -- I mean, it sort of works its way out in
8 the end.

9 You may start out with versus placebo
10 and then versus a 30 percent regimen and then a 50
11 percent and then an 80 percent versus a 50. And
12 it sort of escalates up until the job is done.

13 And I think the fix at this point in the
14 evolution of the understanding with how many
15 regimens are out and all the possible
16 permutations, combinations and issues of
17 resistance and compliance is sort of -- I mean we
18 could debate forever whether it should be 57
19 percent, 67 percent, whatever.

20 And it seems to me it's not necessary to
21 do. Is it better than something that is used? I
22 mean and better than what has already been cleared

1 and it will sort of escalate over time as a
2 practical approach to this issue?

3 DR. FISHER: Let me just ask because
4 we're getting short on time after Dr. Reller's
5 comment as to whether -- I think maybe we should
6 call the question and get an opinion of the
7 committee?

8 I'll take just one short one from one
9 person in front, okay?

10 MR. JENNINGS: Dennis Jennings, TAP
11 Holdings. Speaking as a statistician, though,
12 just to make sure that it's clear how because of
13 the designs that have been done, very often
14 eradication has been twisted up with healing.

15 We just had statements moments ago about
16 being that all patients randomize totals.

17 I don't think the numbers we just heard
18 from elsewhere are all patients included. I think
19 it's eradication rates in patients who were
20 healed.

21 I think we just have to make sure we
22 always look at this carefully.

1 DR. FISHER: Okay. Let's call the --
2 get an opinion around the table from people on
3 question number one under issue number two.

4 Should a minimal level of efficacy be
5 established for clinical trials end points?

6 DR. JUDSON: Are we talking about
7 microbiological cure alone? That's --

8 DR. FISHER: Microbiological cure we're
9 asking here.

10 DR. JUDSON: Can we rephrase that,
11 bacterial eradication or -- Okay. We'll --

12 DR. FISHER: No. I'm looking -- I'm not
13 looking at you.

14 DR. JUDSON: Should there be a minimal
15 level of bacterial eradication established for
16 clinical trials and for a clinical trial end
17 point?

18 DR. FISHER: Can I just ask for a
19 clarification?

20 Are we planning on some of these
21 regimens that get approved, including that sort of
22 -- I mean that information will be included within

1 packages and so forth about this regimen who's
2 shown a X percent eradication rate or something
3 like that along the way, right?

4 So I think what Dr. Reller is saying --
5 I'm agreeing with Dr. Reller's comment that I
6 don't think we should necessarily set a minimal
7 end point at this point, but see what things are
8 like if they're going to be published in the data.

9 So my answer is no.

10 DR. JUDSON: No.

11 DR. FISHER: Dr. Reller?

12 DR. RELLER: No.

13 DR. FISHER: No. Dr. Henry?

14 DR. HENRY: No.

15 DR. FISHER: Dr. Kirschner?

16 DR. KIRSCHNER: Can I just make a
17 comment? I mean -- you know, I understand it's a
18 very complicated issue but we've approved drugs
19 where it is significant. And I'm kind of worried
20 about not having some minimal standard because we
21 get a lot of minimal standard things passed.

22 DR. FISHER: Well, I think that, again,

1 the question is: do you decide that now, or do you
2 decide on risk benefit ratio on individual
3 applications that come before you, as to what's
4 reasonable, as far as Dr. Temple and I have gotten
5 into these discussions about clinical efficacy or
6 clinical significant versus statistical
7 significant.

8 Do we really want to, at this session --
9 without seeing what the applications are and what,
10 the concerns are and compliance and so forth --
11 put a number to something that needs to be
12 approved?

13 That's my concern, as Dr. Reller's is, I
14 think about putting a number to something. And I
15 understand your concerns about that and agree with
16 them.

17 But I don't know that we want to box --
18 personally I don't know that we want to box
19 ourselves into something.

20 DR. JUDSON: I think we're saying we
21 don't have a credible basis right now for setting
22 any minimum, and moreover, that minimum is likely

1 to change with time as further studies are done.

2 If you say yes, then you've got to tell
3 us what the minimum is.

4 DR. KIRSCHNER: I was going to say yes
5 and figured there would be enough nos that we
6 wouldn't have to address that issue.

7 DR. FISHER: Well, why don't we say yes
8 for you and then we'll see what it comes around
9 to.

10 Dr. Francis?

11 DR. JUDSON: That's why we're voting
12 now.

13 DR. FRANCIS: I vote no. It notes that
14 the -- actually, if you turn Dr. Judson's and Dr.
15 Fisher's comments into a question, I agree with
16 that.

17 I'm not sure this is saying the same
18 thing as you are, but as I understand what you're
19 saying. No.

20 DR. JUDSON: We rephrased a little
21 there.

22 DR. FISHER: And I think the agency is

1 hearing what we've said on that as well.

2 Dr. Bertino?

3 DR. BERTINO: No.

4 DR. FISHER: Dr. Owyang?

5 DR. OWYANG: No.

6 DR. FISHER: Dr. Banks-Bright?

7 DR. BANKS-BRIGHT: No.

8 DR. FISHER: Dr. Burks?

9 DR. BURKS: No.

10 DR. FISHER: Dr. Thorpe?

11 DR. THORPE: No. But I want to ask will
12 there -- will we approve drugs for the indication
13 or eradicating H. pylori or when we do, will we
14 have a minimum bacterial eradication rate
15 established?

16 DR. JUDSON: We may not. We may end up
17 saying or the committee may end up advising the
18 FDA that 30 percent is the best we can do right
19 now. And that goes into the label, carries 30
20 percent of --

21 DR. FISHER: You know, we may find that
22 the eradication rate is 50 percent but the

1 complication rate is 40 percent, and thus the risk
2 benefit ratio is too high and it's not worth
3 approving at that point.

4 Dr. Craig?

5 DR. CRAIG: No.

6 DR. FISHER: Now we'll ask the
7 consultants. Dr. Megraud?

8 DR. MEGRAUD: I'm sorry, but my personal
9 opinion would be yes. Yes. I think that if a
10 benefit shows, it is valuable to have a minimum.

11 DR. JUDSON: And what is the minimum?

12 DR. MEGRAUD: For me, it would be around
13 90 percent because otherwise, if during your
14 clinical trials, if you don't reach 90 percent,
15 you know, as a real practice, it should be much
16 lower. And I think it's a minimum to acceptance.
17 It's my personal belief.

18 DR. JUDSON: Thank you.

19 DR. FISHER: Dr. Kirschner, now that
20 somebody has set a -- Dr. Kirschner, do you want
21 to give us a percentage now that somebody has
22 given us -- you've got another person saying yes,

1 giving a percentage?

2 DR. KIRSCHNER: Well, it would seem to
3 me that this could be something that we would
4 decide as we're evaluating the projects and we see
5 them coming in.

6 I mean, the way I see it now, if there
7 is no standard, somebody comes in at 20 percent
8 better than a placebo and we have no grounds with
9 which to deny the claim.

10 DR. FISHER: I think what you're saying
11 is the same sort of thing that we've been saying,
12 as opposed to just sort of rephrasing the question
13 and all.

14 All right. We're leaving it as yes and
15 we're going to decide.

16 Dr. Temple?

17 DR. TEMPLE: I just am curious. I
18 understand no one thinks they could set a rate now
19 because we haven't seen data.

20 But you're not quite saying that the
21 rate doesn't matter.

22 DR. FISHER: No.

1 DR. TEMPLE: A very low rate if you had
2 other data might matter. You just don't know --

3 DR. FISHER: Right.

4 DR. TEMPLE: -- what it's going to be
5 yet?

6 DR. FISHER: And the risk benefit ratio
7 is also going to be a difference.

8 I mean getting somebody again who has a
9 30 percent cure rate and a 15 percent incidence of
10 colitis or something like that or something none
11 of us are really going to feel -- at least I
12 wouldn't feel comfortable with.

13 Dr. Laine?

14 DR. LAINE: As strict
15 constitutionalists, we cannot set a minimum rate.
16 That's all.

17 DR. TEMPLE: Let me just throw out one
18 other thing.

19 In general, you know, we were told by
20 the legislators who wrote the effectiveness
21 requirement that relative effectiveness was not
22 supposed to be on our minds.