

Committee Questions to Dr. Packer

JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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Highlights

- **UNADJUSTED P-VALUES OF <.05 MAY NOT TRULY BE “SIGNIFICANT”**: Dr. D’Agostino asked how the APPROVe study, that had a small number of events (45 vs. 25) but good identification of events, should be interpreted. Dr. Packer said that you have to be “a lot more careful” but that “doesn’t mean you can’t make judgments”; his main point was that clinical investigators rely on p-values and that these may be less valid than we think. A trial can have “prespecified, adjudicated endpoints” but with “small-number events” you have “very imprecise estimates”.
- **PRACTICAL PROBLEM OF DOING A TRIAL LARGE ENOUGH TO RULE OUT A CLINICALLY IMPORTANT EFFECT**: Dr. D’Agostino asked if “we could live with” a result in a non-inferiority trial that ruled out a “1.3 relative risk” since with such a risk “people may be dying”. Dr. Packer said “I wish I knew the answer to that” but that “one learns very little from doing a lousy trial”.
- **HANDLING DROPOUTS**: Dr. D’Agostino asked how to deal with dropouts in long-term trials, both patients that can be followed up for possible delayed effects, and those that “just stop coming”. Dr. Packer said that with an efficacy trial everything reasonable is done to maintain adherence, but that in a non-inferiority trial investigators and sponsors may be “less motivated” on adherence since they realize that an adherence problem “works in their favor”.
- **SHOULD SAFETY AND EFFICACY DATA BE INTERPRETED USING DIFFERENT STANDARDS?** Dr. Shapiro asked about Dr. Packer’s comment that safety and efficacy data should be evaluated in comparable fashion, as she felt that it is not just a question of whether a problem occurs but also its prevalence and severity. Dr. Packer said that it was a question of the “risk-to-benefit relationship” and that it might be reasonable not to pursue evaluation of a minor safety issue with a drug that prolongs life, whereas one would want to pursue the same issue with “a drug for a symptomatic or cosmetic condition”.

Prevalence and severity are just part of the risk-to-benefit equation.

- **WHAT IS A “WIDE” CONFIDENCE INTERVAL?** Dr. Cush asked about how one decides that a confidence interval is “wide”. Dr. Packer said that this is a function of the extent to which the upper or lower bound crosses the point of 1.0 relative risk, and that one looks at “wide” differently for confidence intervals below 1.0 (where the lowest possible value is zero) and above 1.0 (where there is no limit on the upper bound).
- **COMBINED IMPRECISION OF CONFIDENCE INTERVAL AND DIFFERENT POPULATION:** Dr. Cush asked how one takes into account the combined imprecision of a wide confidence interval, and the application of this confidence interval to a different population. Dr. Packer said that “we do that all the time” and that “There is a general sense that efficacy is not extrapolatable across diseases but safety that is not disease-specific is extrapolatable.... If we didn't do that, the problem that I put forward would be really impossible...”.
- **URGENCY OF SAFETY DECISIONS AFTER DRUG ON MARKET:** Dr. Shafer said that how to evaluate small number events depends on whether they occur before or after marketing approval. In the post-approval situation, “clinical and regulatory decision making” is “based on imprecise information” and “a daily decision is being made by patients and their physicians as to whether or not they need to take the drug”. Dr. Packer said that efficacy estimates are “almost always” more precise than

safety estimates. So one can have a situation with a precise estimate of a small efficacy effect and an imprecise estimate of a possible safety effect with “a big risk”. Although one might think of a “statistical model” to address this issue, he is “much more comfortable with people doing that” as “people have the ability to integrate all of this, especially a group of people” and we should not replace “the human, very important human, element here”.

- **HOW CAN WE HAVE CONFIDENCE OF ABSENCE OF EFFECT?** Dr. Farrar asked about “thinking about it the other way around” , where “you have ten studies that show no safety issue with a well-measured process, whether you can then say, well, maybe the 11th study is going to show it somehow”. Dr. Packer said that one should determine if it is valid to “combine the data across the studies” and, if so, come up with a more precise estimate with smaller confidence intervals.
- **SOME EXAMPLES OF TRIALS INAPPROPRIATE:** Dr. Domanski questioned some of the trials Dr. Packer presented as examples (e.g., ISIS 4). Dr. Packer conceded that not all of his examples might be appropriate and that others might know more than him about specific studies. However, “the number of examples here is just overwhelming”.
- **REPLICATION WITH COX-2 DRUGS:** Dr. Wood said that for the COX-2 drugs “we have replication” of the safety signals.
- **EARLY TRENDS MAY CORRECTLY PREDICT**

PROBLEM: Dr. Furberg said that there are “examples showing the other side, how trends in smaller studies were confirmed in definitive trials”. Dr. Packer agreed but said he was not saying that early trends are “worthless” but such a finding “is just not as reliable as we think it is”.

- **SHOULD STATISTICAL THRESHOLD FOR ACTION BE DIFFERENT FOR SAFETY AND EFFICACY?** Dr. Wood suggested that Dr. Packer was saying that the level on which we act for an efficacy endpoint (say, 2 studies with $p < .05$) should be less stringent than for a safety endpoint. Dr. Packer disagreed, saying that “when you have a p less than 0.05” on the primary efficacy endpoint in two trials, that is not the same as “having a p less than 0.05 on two imprecise estimates which are combined together”. Dr. Wood said that Dr. Packer was “overselling the point a bit. Let’s move on”.
- **STOPPING DECISIONS NOT BASED ON PRE-SPECIFIED STOPPING RULE:** Dr. Jenkins asked how one should interpret the stopping of the APPROVe trial when the actual stopping rule was supposed to be based on the combined data from APPROVe and two other trials. Dr. Packer said “I don’t come with any answers” but “I am very comfortable with the human process of doing so, as long as the human process incorporates an understanding of how difficult and imprecise this is, and the fact that, in the past, although it has led to predictions that came true, it also led to predictions that did not come true.” “Any time you deviate from your preplanned attack on the

conduct of analysis of a trial, you weaken, to varying degrees, the precision of the estimate and the confidence you have in the data that you are looking at”.

- **REPLICATION ACROSS DRUG CLASS RATHER THAN INDIVIDUAL DRUG:** Dr. Nissen said that “an additional subtlety here” is that the committee is trying to assess the totality of the data for “a class of agents” and not just for “a single agent”, and trying to evaluate replication data occurs across different drugs. Dr. Packer said “that is why the process works best when there are human beings involved in the thinking process”. “In the absence of precision, you have got to do that. But don’t forget” that the data are imprecise.
- **SAFETY JUSTIFIES LESS STATISTICAL RIGOR:** *<The following is an extract from Dr. Fleming’s comments during the introductory statements by individuals and committees before Questions 1-3. It is provided in that document but also here because of its relevance to Dr. Packer’s paper.>* Dr. Fleming said that it is important to take into account, as Dr. Packer had said, multiplicity in testing individual safety parameters over time, and multiplicity in the actual safety parameters. However, “when you are looking at safety” it is less acceptable to apply conservative statistical procedures such as “monitoring boundaries” because there is a multiplicity of safety issues, and because you have to take into account both the “severity of those safety issues” and “benefit to risk”. Ultimately, the statistical procedures can “provide some

guidance” but “there has got to be

informed judgment”.

Discussion Text

DR. WOOD: Dr. D'Agostino?

DR. D'AGOSTINO: Thank you very much, Milt. I have a couple of questions that I think, I hope, are relevant to our deliberations. In terms of your sense of “large” and the idea of chasing after a safety event and making more out of it than one should, we have a study, APPROVe, where there was a serious up-front pre-stated deliberation to make sure they had good ascertainment and adjudication of cardiovascular events, and they come up with 45 versus 25 events, carefully collected. I am struck by that's being small, but I am also struck by the carefulness in which it was done, say, as opposed to the APC where they did an interim analysis that has those problems. Could you comment on, say, the APPROVe study?

DR. PACKER: I think that, when you have incomplete data, as you would if you have small-numbers events, you need to be a lot more careful about the thinking process. That doesn't mean you can't make judgments. It doesn't mean you can't incorporate a set of principles that would guide decision making by looking at the totality of the evidence and bringing to the process what you inherently believe. I think that is what the committee needs to do today. What I really wanted to address, however, is how hard this is and that the normal reliance -- as you know, clinical

investigators, because they don't understand p-values, rely on them. What I am trying to do is to explain that, in fact, we are less certain about what we know here than we, perhaps, should be.

DR. D'AGOSTINO: But that on the APPROVe study it was reasonable, too.

DR. PACKER: I think you need to take that in the totality of the carefulness in which it was done, the prospective nature of it. But, remember, in all the examples that I showed you, the trend seemed sometimes very striking trends in early pilot trials that were prespecified, adjudicated endpoints but, because they were small-number events with very imprecise estimates, the definitive trial was non-confirmatory. So just because it is up-front and predefined--

DR. D'AGOSTINO: That is my question, yes. That is my question. You still end up with small numbers. Let me have just a couple of other questions. The second question is really bothering me very much in terms of how we would recommend trials. If you decide--if the group decides and suggests to the FDA that there should be more trials, more randomized clinical trials, the sponsors are, then, going to have to go back and say, well, they are going to set up a trial saying the null hypothesis that the relative risk is 1.0 versus the relative risk

is not 1.0. Now, the best thing a sponsor can do is to run a very sloppy study and they will accept that null hypothesis because the confidence intervals will so wide and they will contain 1.0. The alternative is to sort of do a non-inferiority type idea that you end up the study, you end up with the confidence interval, and that confidence interval has to be below something like 1.3. Do you have advice for us if you did this sort of second approach? We are dealing with rates like 1 percent. Could we live with a 1.3 relative risk that you rule out, a 1.3 relative risk? People may be dying if you do that. So how do you respond to that?

DR. PACKER: I wish I knew the answer to that. I think that it depends on the type of adverse reaction. It depends on the particular drug. It depends on the vulnerability of the patient population. All of these need to be factored together with the actual feasibility of doing the study. The one thing I would say is that one learns very little by doing a lousy trial. So, doing a good trial is the only way to get a reasonable answer or reasonable estimate of the answer.

DR. D'AGOSTINO: Just one more. I will make it quick. In these trials, in many of these trials, people just won't stay in the trial. Can you give us some advice on how to deal with the drop-out--now, there are rules that you could say, the individual wants to leave, has decided to leave because the blood pressure is building up or because of G.I. problems building up. To say, we are only going to look at that individual for 14 more days after they leave, to me, is a problem because if the blood pressure is building up, they may be on their way and it may take two or three months before they get an M.I. and so forth. So

you have got the sort of dropouts, terminations, that are part of the protocol but you also have the individuals who just stop coming. And they could be substantial. So, any advice to us?

DR. PACKER: Gee, as you know, when we do trials for superiority, the effort that we put into adherence is extreme. We really want people to stay on treatment and we organize the trials to do everything we can to ethically and reasonably maintain adherence. I take your point that, if the trial were a non-inferiority trial, it is possible that the investigators and sponsor might be less motivated recognizing that poor adherence works in their favor. I think that there needs to be a reasonable effort--I mean, you can maintain adherence in most trials if you really, really want to.

DR. D'AGOSTINO: Thank you.

DR. WOOD: I suspect we are not going to solve that problem today. Dr. Shapiro?

DR. SHAPIRO: Just a comment on your comment. We all know, of course, that the Federal Regulations require that participants be allowed to withdraw and not be badgered into staying. But what I really wanted to talk about was your observations about how it is wrong to suggest that we should not chase safety quite as rigorously because we will, then, deprive ourselves and others of information and access to effective treatment. I don't think it is as simplistic as that, in that, when we are looking at potential harm or safety problems, we have to look not only at likelihood that it exists but prevalence and severity. So I think that your response to that approach

has to take account of those factors as well.

DR. PACKER: Let me try to reframe my response. You can't isolate benefit from risk. The judgment as to whether a drug should be used on an individual basis or on a population basis has to be the relative value of benefit to risk. You may decide that you don't even want to pursue a safety trend in a non-fatal event when you know the drug prolongs life. That would be a very reasonable judgment. On the other hand, you might want to vigorously pursue a very serious safety is in a drug for a symptomatic or cosmetic condition. So the risk-to-benefit relationship is the one that has to be vigorously defined.

DR. SHAPIRO: Right. I am sure you will agree with this; you also have to factor in prevalence of the condition and likely use of that drug in the population.

DR. PACKER: That's right. But it is always--it is risk to benefit. The goal here is not to say that the risk-to-benefit relationship can be altered, simply because you want to emphasize one part or another, has to be in the context of the clinical problem and looked at from the patient point of view.

DR. WOOD: Dr. Cush?

DR. CUSH: I have two questions. One, I need some education. You were frequently referring to very wide confidence intervals where it didn't seem so wide. It was only, like, 0.3 and 0.4 where, obviously, when it ranged from 1.0 to 8.0, that is very wide. But you used those terms in both situations. Could you explain the differences there?

DR. PACKER: Actually, I have used "wide" to refer to extremely wide, moderately wide and wide.

DR. CUSH: And narrow would be--

DR. PACKER: Narrow is less than wide.

DR. CUSH: Okay.

DR. PACKER: Let me try. All the examples that I showed you that I characterized as wide truly reflected estimates that had a high degree of uncertainty associated with it. On the benefit side, benefits that range from an 80 percent reduction in risk on the high side to a 20 percent reduction in risk--remember, and I guess I should emphasize this and I guess Tom would reinforce this dramatically, the concept of how these curves looked like in terms of the width is not symmetrical on both sides of 1.0. The lowest you can go below 1.0 is 0. So wide confidence intervals below 1.0 can be 0.2 to 0.8. Those would be wide confidence intervals. There is no limit for estimates greater than 1.0, so you can have 1.0 to 24 on the adverse side of this. So you have to sort of think about what is wide differently when you are looking at estimates below 1.0 than when you are looking at estimates above 1.0. Maybe that would be helpful.

DR. CUSH: That does help. Secondly, you have told us that when we are dealing with low-numbers adverse events and that being very imprecise and hard to make conclusions from, is it even less valid or even greater error to, then, take that data derived in one situation, like in an Alzheimer's trial, and then try to generalize that to the general population?

DR. PACKER: But we do that all the time. There is a general sense that efficacy is not extrapolatable across diseases but safety that is not disease-specific is extrapolatable. Let me put it this way. If we didn't do that, the problem that I put forward would be really impossible, really impossible. So I actually feel comfortable extrapolating safety data across indications as long as the safety item is not disease-specific.

DR. WOOD: Dr. Shafer?

DR. SHAFER: Thanks. That was actually a very informative presentation and I can confirm the distance from Washington to California. There are really two questions here that I think we need to bifurcate. One of them involves the scientific question of getting at the truth, whatever that is. I appreciate everything you say and, prior to a drug being approved, at least ideally, there would be adequate time and resources to do exactly what you are proposing. But there is a second question which is how to inform clinical and regulatory decision making based on imprecise information following approval because, in that setting, a daily decision is being made by patients and their physicians as to whether or not they need to take the drug. One question about how to approach these sorts of imprecise data when, in fact, a daily decision is occurring, is can you take the confidence bounds for both the risk and the benefit and integrate those over the public-health hazard and the public-health benefit to try to incorporate the entire-- both the point estimates but also the uncertainty about them into the regulatory decision-making process?

DR. PACKER: Oh, wow. Just a couple of comments. One, the precision of the estimates on efficacy is almost always more precise, much more precise, than the estimates on safety. So you have this very precise estimate on efficacy. You have this very imprecise estimate, in general, on safety. And you try to sort of integrate them and you have to now weigh them because it could be that the efficacy thing you are looking at is really important and the safety is sort of not very important. Or it could be other way around, the efficacy is sort of very small--the efficacy is small, but the safety is a big risk.

DR. SHAFER: That is exactly the question.

DR. PACKER: You might think that someone in the world might be clever to create a statistical model that would allow that to take place. I am actually much more comfortable with people doing that than statistical models doing that. Somehow, people have the ability to integrate all of this, especially a group of people have an ability to integrate this, much better than any mathematical model. I would be very uncomfortable if someone were actually to propose a mathematical model that replaced the human, very important human, element here.

DR. WOOD: Dr. Farrar.

DR. FARRAR: Every example that I have seen to date in looking at the risks in over-interpreting data seem to go from being a positive study to a negative study. I wonder about the other way around and whether there are any inherent differences in thinking about it the other way around, the bottom line

being that if you have ten studies that show no safety issue with a well-measured process, whether you can then say, well, maybe the 11th study is going to show it somehow.

DR. PACKER: I think you need to find out how much information there is in each study, how easily or how appropriate it is to combine the data across the studies to determine how precise the estimates, after you have collected and integrated all of the data, and put that into a judgment as to how much data you actually need to be confident about the precision of the estimate. So there isn't a uniform way of thinking about it. It is not like you will know it when you see it. There is some guidance, some mathematical guidance, that needs to be incorporated into the thinking process.

DR. WOOD: Dr. Domanski.

DR. DOMANSKI: You know, I am not nearly as sophisticated, really, Milton, as you are about this sort of thing nor about some of the people in the room, but I am a little bit concerned about some of the examples. I will give you one. I don't think ISIS 4 was a definitive trial of magnesium, because I know something about that. We did the MAGIC study which was a very large study. Like ISIS 4, it was negative, but ISIS 4 was substantially different methodologically in terms of when that was given. I think that example actually, to be honest, is fairly misleading as a result. I think it is an example of a stopped clock is right twice a day. But, yeah; it came out right. But I am worried if that is the basis for this--that kind of thing is the basis for this discussion across more of the landscape.

DR. PACKER: Let me emphasize, Mike, that I knew that if I picked one study and gave you an example of one study that I would be at great risk because everyone knows something about these studies more than what I know about these studies although some of the studies I actually mentioned were studies I was personally involved with and think that I know a little more about them. So I just wanted to--I would not overemphasize--and, in fact, one might appropriately underemphasize -- the magnesium example. But the other examples, time and time and time and time again. It is just like reaching conclusions during a very early part of a study based on interim monitoring. When you have small numbers of events, the estimates are very imprecise and may not reflect what happens at the end of a complete experiment. That is just a general principle. I take your point about ISIS 4 but the number of examples here is just overwhelming.

DR. WOOD: It is important, Milton, to remember, we have replication for two of these drugs and these safety signals here. So it is not just single studies. Dr. Furberg.

DR. FURBERG: Milton, I think that was a great presentation. I think, for balance, it would be nice if you can have examples showing the other side, how trends in smaller studies were confirmed in definitive trials. And I know plenty of those.

DR. PACKER: Oh, yes.

DR. FURBERG: That was never discussed. You are painting a dark picture saying you can't trust smaller

studies. You are right. You never know where you are going to end up and you need to be careful. But don't say that you can't rely on those.

DR. WOOD: I was actually on the advisory committee that turned down Vesnarinone, that looked at that study. There were lots of issues that came up at that time that led us to do that. So it wasn't just that there was a study that was compelling and that people went with that. Dr. Nissen?

DR. PACKER: Curt, let me just say that -- I think your point is very, very important. What I have not done is shown many, many examples of interim monitoring in trials where the early results were reflective of the endpoint. I have not shown a whole host, probably more than I could think of, of all of the pilot trials where the initial trends encouraged someone to pursue it and that the second study was, in fact, very confirmatory. Let me just make my point clear. It is just not as reliable as we think it is. It is not that it is worthless. I do not want to say that. If I have implied that, then I do not want to imply that. I just want to say that the risk of error early when you have small-number events is much, much greater than when you have a much more precise estimate at the end of the trial. My plea here is that when you don't know, the best thing you can do is say, "I don't know." And that is my only plea.

DR. WOOD: Milt, when you have two trials that replicate one another, with a p-value of less than 0.05, if that was an efficacy endpoint, we would approve on the basis of that; correct?

DR. PACKER: That's right.

DR. WOOD: But you are telling us that, when it is a safety endpoint, we should not act on that. I think it is counterintuitive.

DR. PACKER: No, no, no.

DR. WOOD: Hang on. That seems to me counterintuitive. We have, for two of these drugs, two randomized trials that replicate the outcome. In three of the four trials, the outcome was predefined, adjudicated and so on. That is about as good as any drug that has been approved on the U.S. market that I can think of.

DR. PACKER: Let me just add one dimension, Alastair, to the thinking process and that is that when you have a p less than 0.05 on two trials, on the primary endpoint because it is efficacy, you have two trials that were designed for the endpoint and have fairly narrow confidence intervals and precise estimates. That is not the same concept as having a p less than 0.05 on two imprecise estimates which are combined together.

DR. WOOD: No; I understand that very well. I think we all do. The issue here is both of the second trials--both of the second trials--were designed to test the safety issue that was in the first trial even though they were efficacy studies. So it is not like they were just two trials that fell on the ground from Mars that arrived with something. These were designed, at least according to the sponsors, to check for that outcome. So I think you are overselling the point a bit. Let's move on. Dr. Jenkins?

DR. JENKINS: I found the presentation very interesting and I wanted to probe a

little bit further on the APPROVe study because that is the one that I think we were feeling very comfortable with the finding in APPROVe. Yet, I went back to Merck's presentation, and their prospective plan was actually to combine three studies that were going to be placebo versus rofecoxib in three different populations. Their plan was to have 25,000 patients to evaluate the cardiovascular signal. Now, in APPROVe, presumably, they had stopping rules that the Data Safety Monitoring Committee saw an extreme effect that met those criteria so they stopped the study. But I am just interested in hearing your thoughts about how should we interpret APPROVe where the stopping rule is met for an individual study when the prespecified plan was to have three studies combined for 25,000 patients.

DR. PACKER: Gee, I must say that I am delighted to have everyone ask me the hard questions for this afternoon. I sort of think that this is what this committee has to do. I only wanted to add a dimension to the thinking process here. I don't come with any answers on how to put all of the data together. All of the points on how to synthesize these data, I am very comfortable with the human process of doing so, as long as the human process incorporates an understanding of how difficult and imprecise this is, and the fact that, in the past, although it has led to predictions that came true, it also led to predictions that did not come true.

DR. JENKINS: I think, more specifically, the point I was trying to get you to comment on is not the overall interpretation of the rofecoxib data but the fact that there was a plan for 25,000

patients in three studies. What I am trying to understand is how should we, then, interpret a finding from one of those three studies where an interim analysis crossed the stopping boundary and met the criteria for stopping the study. What weight should we give to that finding in that single study?

DR. PACKER: I don't think there is a precise answer to that. Any time you deviate from your preplanned attack on the conduct of analysis of a trial, you weaken, to varying degrees, the precision of the estimate and the confidence you have in the data that you are looking at.

DR. WOOD: Dr. Nissen?

DR. NISSEN: Milt, there is an additional subtlety here. Let me see if I can drill down with you on it. What we have here is a class of drugs where we have multiple trials within the class. So what we are asked to do is not necessarily, in some respects, for each individual drug, say, well, do we have replication or not. But if we take the position that this is a class effect, then we have got four, or perhaps, five trials. This came up once before. It was kind of controversial. I think you may have been on the committee at the time when we had the angiotensin-receptor blockers for renal protection. What the two companies did with two different drugs is they stipulated that the other could use the data from the other company's trials as supportive. So the reason that this is really much harder is that we have a lot of trials here. We may not have reached all the evidence in an individual drug, but we have trials across the class of drugs. I wonder if you have any thoughts about this because it is obviously a

difference between studying a single agent and studying a class of agents.

DR. PACKER: I think that, Steve--I mean, that is why the process works best when there are human beings involved in the thinking process. There is no predetermined sense that one should bring to the process -- that you confine the analysis only to one drug. What you should allow yourself to do is look at the data with one drug, look at the data with drugs that you think are related. If there are data that you think are in a drug that really isn't related, you might want to analyze that separately or do it both ways to see if it is consistent. There is no statistical formula that can guide the very important human process here. My major point is that the precision that most clinical investigators think exists here isn't as precise as we think it is. But that doesn't mean that you -- and Curt would emphasize this -- that doesn't mean that you can't put together your own picture of the totality of the data and bring to it a sense of whether it reaches some critical level of concern. In the absence of precision, you have got to do that. But don't forget inherently that the data are imprecise.

DR. WOOD: Curt, do you want to say something else? No. Then let's move on. The next speaker is Bob Temple who we are going to confine to his seat.

DR. TEMPLE: Alastair, I have a question. What am I supposed to do about my slides? Can someone show them for me? I will delete many of them.

DR. WOOD: Okay. You can come up here if you do it quickly.

DR. TEMPLE: I don't care where I'm from. I really don't.

DR. WOOD: Then Kimberly will work the slides for you.

DR. TEMPLE: Okay; if Kimberly will do that.