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Quick Pulse

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PREVIEW OF THE FDA ADVISORY COMMITTEE MEETING ON DRUG-ELUTING STENTS

Dr. Daniel Schultz, Director of the FDA's Center for Devices and Radiologic Health (CDRH), held a teleconference with reporters two days before the FDA's Circulatory System Devices Advisory Committee meeting December 7-8, 2006, on the safety of drug-eluting stents (DES).

HIGHLIGHTS

- The panel will discuss issues but not take any votes.
- Based on information from the American Heart Association, Dr. Schultz estimated that 2-3 million individuals have gotten a DES since they were first approved.
- There is no consensus yet on how the rate of stent thrombosis compares with DES vs. BMS.
- The experts on the panel were chosen because they had the expertise to understand the "very complex scientific and clinical issues" involved, and the FDA believes it is a well balanced panel that can give objective and non-biased information.
- There will be a discussion by the panel of off-label use of DES, but the FDA is walking a careful line. The Agency cannot interfere with the practice of medicine, and Dr. Schultz was careful here, but he made it clear that the FDA still can have influence on off-label use through the information it provides to doctors and patients.
- One of the panel questions is whether the risks of DES outweigh the benefits, and Dr. Schultz didn't rule out the possibility of pulling DES from the market, but he didn't leave the impression that this was a serious consideration by the FDA.
- There could be additional requirements for new DES seeking FDA approval after this panel.
- The FDA's key goals for this panel are:
  1. Provide the American public with the best current state of our knowledge with respect to the risks:benefits of these products.
  2. Define the appropriate populations in which these devices should or shouldn't be used.
  3. Define the appropriate adjuvant therapies – e.g., aspirin and Sanofi-Aventis's Plavix (clopidogrel).

- The Academic Research Consortium (ARC) definitions of stent thrombosis that were presented at TCT 2006 have been embraced by the FDA. While the FDA cannot impose the exclusive use of these definitions, the FDA will be looking at all data through those definitions and will ask companies for additional information (using the ARC definitions) if that information is not initially provided. And that includes companies seeking approval of new stents. However, the FDA ***could*** modify the ARC definition if the panel makes a strong push for that, though it appears it will take a very strong panel push for any change to be successful.
- It does not look like the FDA will make new DES companies do larger or longer studies.

DETAILS

In his opening statement, Dr. Schultz called late stent thrombosis with drug-eluting stents (DES) a "public health issue of great importance." He outlined the FDA's goal for this advisory panel: "Our goal in putting this meeting together was to look at a complex set of issues and try to balance the risks associated with the use of these products with their known benefit. There are a lot of sub-issues – the populations in whom they are being used, the adjunctive drug therapies used along with these devices, etc. Our goal is very simple. There are a lot of opinions and data circulating out there, and we need a coherent and understandable explanation of the risks and benefits associated with these products. We think that even though we may not have all the information at this time, this is **a public health issue of great importance,** and so we wanted to hold this meeting as soon as possible to get all the views on the table…Our goal is to provide the current status of the data we have, to look at the holes in the data, to look where we need to add new information and studies to get more information…and to try to provide physicians and patients with the best, most objective information we can."

He indicated that the DES panel may provide a guide for how the FDA handles other safety issues in the future: "We also recruited a set of panelists we think provides the necessary expertise and breadth of different views that will enable us to have the kind of discussion we want to have and to have a balanced overview on this topic. It is not unusual for us to have to deal with issues where there are real safety and effectiveness in a large number of patients but (where) we are still seeing signals in a relatively small number of patients. But ***these signals indicate the potential of a severe problem***. So, this is something we are increasingly getting used to seeing, and, hopefully, this meeting will provide a template for how we plan to deal with these issues in the future."

Are there any solid numbers on how many people have received a DES?

"We are estimating, based on information from the American Heart Association, that, since the time of introduction there have been approximately 900,000 per year. Since they were introduced in 2003/2004, I guess we are dealing with 2-3 million individuals."

Does clotting occur at the same rate as restenosis with bare metal stents (BMS)?

"We understand that the restenosis rates with DES are clearly reduced by a significant amount vs. BMS. The question we will be addressing at this meeting is what is the real rate of late stent thrombosis (LaST) of BMS vs. DES, and furthermore what are the consequences of those LaSTs. That is where the data start to get a little bit messy, partly because we've had in the past many studies using many different definitions, studies in different patient populations, studies with different uses of adjunctive therapies – and trying to sort through all that noise to get to that answer is what we will focus on."

So there is no consensus yet?

No

On conflict of interest waivers: There seems to be reasonable justifications for five panelists, but it may be hard for some to have confidence because the names of the firms with which they are associated were redacted. What is the harm in making that public? One panelist said (his conflict) has nothing to do with stents.

"The issue you raise is really a larger issue than this particular panel and this particular meeting. That is not to say it isn't an important question. Obviously, we are looking very, very closely at our panel process in general – the information, the way waivers are granted, and the information provided in those waivers. That is something the agency as a whole is taking a hard look at. I will assure you as far as this particular meeting is concerned, we recognized that it is extremely important for us to have: (1) a panel of experts who could give the necessary recommendations regarding what are very complex scientific and clinical issues, and (2) to make sure that the panel we put together, whether or not waivers were granted or not granted, that could give us objective, non-biased information. So the entire panel – and looking not at just those with waivers – if you look at that objectively you will see that I think we've done a pretty good job of achieving that goal."

Are you considering imposing restrictions on off-label use of DES?

"The issue of off-label use and what kinds of information is provided in the label, and how people should make those decisions is really something we will focus on during the course of this meeting. We need to be careful in how we talk about what goes on between an individual patient and an individual doctor, and we need to make sure patients and doctors have the ability to do what is best for those

individuals. We, as a public health organization, have the responsibility to make sure that as much information as possible is provided to those doctors and patients to allow them to make those individual decisions using the best possible information."

Might safety outweigh the benefits of DES? One of the questions to the panel asks whether the stent thrombosis risk of DES outweighs the benefits. Is there a real possibility that DES could be withdrawn from the market? Is this a real possibility that the FDA is seriously entertaining?

"Obviously, we are putting a very straightforward and somewhat provocative question on the table. This will give this very distinguished group of individuals an opportunity to tell us what they really think. Depending on what they say and how they say it, we will have to take that information and opinions and analyze it very carefully to see what, if any, actions are needed."

What is the role of the advisory committee with no vote, just opinions being requested?

"All of our panels are defined as advisory panels, so even where there is a formal vote, the advice of those panels is still subject to the review of the agency, and final determinations on any regulatory decisions are still the responsibility of the FDA. So, whether there is a formal vote vs. listening intently to all the different members is secondary to the importance we place on the opinions of those individuals."

What does this panel mean for the approval process for new DES in development?

"When we evaluate these kinds of products, we are constantly learning and using information from the first approval to make the second approval that much better, and the third and fourth approval, etc. Clearly, one of the goals of this process as well as our entire post-marketing process is to learn things and feed it back into the review process. In some cases, we identify questions that we no longer need to ask, and it streamlines the process. In some cases, we get new information that tells us we may not have all the information we should have in making those decisions. Clearly, as with any other scientific process, you can't just stop at a certain point and say this is how we are always going to do things. You have to learn as you go along to improve the process and make these devices as safe as possible."

What is the single most important or broadest thing the FDA would like to get out of this panel?

"The single most important thing is to provide the American public with the best current state of our knowledge with respect to the risks and benefits of these products. Under that broad heading, there are a number of subtests, which include: the appropriate populations in which these devices should or shouldn't be used, and appropriate adjuvant therapies with these devices."

Does the FDA have any reason to believe there is a differential between Johnson & Johnson's Cypher and Boston Scientific's Taxus on LaST risk?

"What we've seen so far is a lot of data, some of which looked at one stent, some at another stent, some looked at combinations of stents in different populations, and part of the reason for this meeting is to look at all of the data to see if we can get a unified picture of what is going on. I really can't answer your question. I'm sure part of the discussions will touch on that, but it is premature to predict how that is going to go."

At TCT 2006, a new definition of stent thrombosis was put forth, the Academic Research Consortium (ARC) definitions with Dr. Cutlip as the first author. Please comment on redefining the definition of stent thrombosis, and whether you will go forward with that definition.

"As we started looking at this issue – and we didn't just start looking at this yesterday – what became clearer and clearer is that in all the different datasets we were examining, one of the most difficult aspects of analyzing and making sense out of all the different studies was the fact that people were using different definitions. So, getting the companies and academic groups together with the Agency to try to agree on a common set of definitions was really a key step for all of us in trying to get a better handle on what is actually going on here…When you say we are re-defining it, I'm not sure it was ever defined in the first place, so we are trying to get a common language."

At TCT, it was said that you would use this definition for this panel, but will it be "the" definition in the future?

"We see them (the definitions) as not only a way of analyzing the data already collected but of analyzing data going forward as well. There may be additional discussions at this meeting that may add or modify our thoughts on that, but we believe we need a common set of definitions so that we can enhance our – and the public's – understanding of how these devices are performing."

So, is it likely this definition will be applied to stents going forward looking for approval?

"We would like to see everyone move toward a common definition of the performance properties for these stents. In terms of how those definitions would be used, we will encourage all people to do that. We can't mandate that someone writing an article use our definitions. And we can't mandate that every company in all of their communications use exactly the same definitions, but our goal is to work toward a common set of definitions that would allow us to better analyze the data. When we don't have that common set of definitions, it may require additional information to be provided for us to

better understand how companies or others are presenting their data…We think it is in everyone's interest to move toward a common set of definitions."

Is the FDA looking at requiring longer and larger trials for DES or requiring risk stratification data for appropriateness of off-label use?

"You are talking about specific study requirements and specific pieces of information that we may or may not require in the future. What we would like to do now is try to understand what information is missing, what information we need to try to collect, and then the next step is how best to achieve that. Obviously, the size of studies, the length of studies, the type of studies, the type of endpoints we look at all contribute to our understanding of how these products function, and simply saying we need bigger or longer trials or this or that endpoint may not be the complete answer…One of the reasons for getting all these experts together is trying to understand, for these products, what it is we are missing, and what is the best way to get that moving forward."

The FDA did not review the company data analyses prior to sending panel members the briefing package. Did you do an independent analysis that the panel will have access to? How unusual is it not to be able to do an analysis before the panel meeting?

"One of the unusual things about this panel, is that in most cases when we convene a panel, we convene it with enough time ahead to really allow us to get all the information that will be presented and do a complete review of all the information that will be presented at that meeting…We are treading on new ground in a way. We really believe this is a public health issue of such importance that we didn't want to wait for every last piece of information and have the chance to review and analyze every piece of information. We thought it was important enough to hold this meeting as quickly as possible to at least get whatever information we could to try to provide some sense of better understanding of how these devices are functioning This is a little departure from our normal way of putting a panel together, but we think that departure is justified by the nature of the problem."

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