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SUMMARY

An FDA advisory panel voted 8 to 0 on October 22, 2002, to recommend approval of the Cypher drug-eluting stents. The panel recommended only about one-fourth of the sizes that J&J requested, but label expansions will not require large, prospective trials. Brachytherapy is likely to be contraindicated in patients with a drug-eluting stent. The PDUFA date has been pushed back to April 21, 2002, because a Major Deficiency letter was issued on manufacturing issues, though the FDA is working with J&J to resolve this sooner. Final approval will depend upon resolution of several issues that may delay action on this product: a Major Deficiency letter, other manufacturing issues, shelf life and labeling (which an FDA official said the agency is "a fair ways away" from finalizing).

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DRUG ELUTING STENTS MOVE A STEP CLOSER

The first drug-eluting stent -- Johnson & Johnson's Cypher stent (a BX Velocity that elutes sirolimus) -- has been on the market in Europe since April 2002, and U.S. cardiologists are eagerly awaiting FDA approval for its introduction here. The Circulatory Systems Advisory Panel met on October 22, 2002, to consider the Cypher and voted unanimously (8 to 0) to recommend approval. However, the panel discussion revealed some issues – particularly with respect to manufacturing and labeling -- that indicate final approval may not come before the end of this year as many had hoped and expected.

In some ways, this was one of the less challenging FDA panel meetings. For instance, the acting chairman described the company presentation as "lovely," and there did not appear to be any real concerns that the trials did not prove safety and efficacy. However, the FDA asked the panel a long list of questions, many of which appeared to be over the heads of some of the panel members. The results was a vote in favor of approval – but for a much more limited range of sizes than J&J had sought.

J&J requested approval for use in patients with de novo native coronary artery lesions (length ≤ 30 mm) and reference vessel diameters ranging from 2.25 mm to 5.0 mm. The panel recommended approval in patients with de novo native coronary artery lesions (length≤ 30 mm) and reference vessel diameters ranging from 2.5 to 3.5.

The FDA raised questions about the ability to translate the SIRIUS and RAVEL data to larger vessels and smaller diameters because those sizes were not part of the study plan, a Bayesian analysis was performed, and the numbers of patients in each of those groups was small. An FDA official said, "The original intent of the (SIRIUS) trial was to try to design a real-world trial. That is why 2.5 mm - 3.5 mm diameter stents less than 30 mm were specified. A frequent criticism of the FDA previously is that in coronary stent trials we evolved into a situation where approved stents are in a range that only covers about half the patients treated in the U.S., which is not ideal. We can debate why that happens, but here was a chance to get more realistic data. The trade-off the FDA accepted was that in 2.5-3.0 mm diameters, the control and randomized trial would be a bare stent…There was never any intent from the FDA perspective for this type of trial then to result in a request from the sponsor to result in a labeling basically where the whole world of coronary artery disease could be stented."

However, FDA officials indicated that J&J probably can get other lengths approved using registry data. This should make it easier for the company to add shorter and longer lengths later.

Cypher Sizes Proposed (white) and Recommended (shaded blue)

Diameters (mm) for each length					
8 mm	**13 mm**	**18 mm**	**23 mm**	**28 mm**	**33 mm**
2.25	2.25	2.25	2.25	2.25	2.25
2.5	2.5	2.5	2.5	2.5	2.5
2.75	2.75	2.75	2.75	2.75	2.75
3.0	3.0	3.0	3.0	3.0	3.0
3.5	3.5	3.5	3.5	3.5	3.5
4.0	4.0	4.0	4.0	4.0	4.0
4.5	4.5	4.5	4.5	4.5	4.5
5.0	---	5.0	5.0	5.0	5.0

The most dramatic moment came when an FDA reviewer mentioned – almost in passing – that it had issued a Major Deficiency letter to J&J on September 18, 2002, and had gotten the company's response the day before the panel meeting and, thus, had not yet had time to review it. FDA officials later explained that the PDUFA clock stopped when the deficiency letter was issued. **A new 180-day clock started on October 21, 2002, moving the PDUFA data to April 21, 2002,** though officials were quick to emphasize that they did not need to take that long and would work with J&J toward a faster approval. A cardiologist on the panel commented, "This is the first time I've gotten a package with a major deficiency letter. That is a manufacturing issue and not our focus, so we will not discuss that, but obviously the ability to manufacture what was delivered in the trial is part of the assumption."

Among the other interesting findings that came out of the panel meeting were:

- **Dose.** The sirolimus dose with Cypher is 180 µg per stent. For a 3.5mm x18 mm stent, this translates to 140 µg/cm^2. For a 15 mm stent, the total drug on the stent would be 1500 µg, evenly distributed in the polymer on the stent, inside and outside. A J&J expert said, "The main issue is not the total dose but that the dose per cm^2 is constant, no matter what diameter or length. Compared to systemic doses, it (the Cypher dose) is significantly lower and the tissue in direct contact with the drug-eluting stent is the tissue getting the highest exposure."

- **The polymer.** A panel member commented, "When the drug is gone, all that's left is the polymer, and we have no data except from joints and lenses on the impact of the polymer on the vessel wall. You can't divorce carrier and drug." An FDA official said, "We have concerns about the non-erodable polymer, and we want more preclinical data. I would re-emphasize that we asked J&J for information on dose response…It is hard to separate the issue (of the polymer and the drug…The polymer is there as a carrier, but they are combined and both need to be addressed. We want chronic, preclinical data on the polymer alone." A J&J expert responded, "We looked at the polymer in dogs…and found canines were not different in their response. In the pig, we observed a difference in sensitivity – greater inflammation -- at a higher (three-fold) dose. The concern long-term is any leaching of the polymer…and we have 180 day data in pigs with no deaths and no thrombotic events...even when the stents are oversized 20% in pigs."

- **Incomplete apposition.** The journal *Circulation* reported a 4.4% rate of late incomplete apposition with bare stents, all of which had positive remodeling and no clinical events.

- **Elution time.** The slow-release Cypher formulation releases 80% of the drug over 28 days, and is undetectable by six weeks.

- **MACE.** An FDA statistician concluded that the probability of MACE with Cypher is considerably less than with a balloon in any one of the historical studies used for comparison. He said, "There is a 98% probability that the MACE rate is less with Cypher than with a balloon."

- **Longer term follow-up.** J&J plans to follow the SIRIUS patients electronically for five years to collect long-term data. A J&J official explained, "We will identify centers, enroll consecutive patients, and do electronic case report forms. There will be no fixed monitoring."

QUESTIONS RAISED BY THE FDA AND THE PANEL

The influence of angiography on the clinical meaningfulness of TVF. FDA officials pointed out that there may have been some effect on revascularization from the angiographic findings.

Antiplatelet therapy. Post-PCI, patients received Sanofi/ Bristol-Myers Squibb's Plavix (clopidogrel) for three months in SIRIUS and for two months in RAVEL, but FDA officials indicated the length of antiplatelet therapy probably will not be specified by the FDA. One official commented, "There is a regulatory issue here. Plavix and Ticlid (Sanofi, ticlopidine) are not indicated in the PDR (Physicians Desk Reference) for stents. We'll just describe what was done in the trial but not mandate anything."

Trial blinding. The FDA raised questions about whether SIRIUS was properly blinded. An official said, "If even one patient was unblinded, there is a potential for the entire study to be unblinded. Both (SIRIUS and RAVEL) used an A-B scheme…The quality of the blinding is unknown. I don't mean to imply it wasn't blinded, but we can't assess the quality of the blinding."

Interaction with brachytherapy. Dr. Jeff Moses, the SIRIUS principle investigator, said, "There is no evidence there is safety or efficacy with that. Personally, I wouldn't recommend it (brachytherapy after a drug-eluting stent) at this point." Asked if he would caution against it, Dr. Moses responded, "Until there is evidence, I wouldn't recommend it.

Another J&J expert said, "The dose in brachytherapy is far lower than the dose required to chemically alter the polymer, so it appears from a theoretical standpoint that the brachytherapy dose is not high enough to alter the polymer, so the company doesn't have any data that cautions against use, but there also is no data on (Cypher) performance after brachytherapy."

Deployment issues. *A panel member pointed out that, in SIRIUS, 75% of the bare stents but only 25% of the drug-coated stents were properly deployed.* A J&J official responded, "We assume that was due to the ability of the operator and the types of lesions treated. It could be somewhat related to the type of lesions. We have looked at pooled data, and we don't find any evidence the data can't be pooled, so we think it is more related to technical issues at the centers…In bench (testing), there was no difference in performance, expansion, deployment and device success."

Deregistration. An FDA official said ~4% were "deregistered" in SIRIUS. That is, they didn't get a stent and so were not followed. He commented, "The review appears to indicate they didn't meet eligibility, but there are other patients who stayed in the study who didn't meet the criteria." A cardiologist testifying for J&J said, "Deregistered patients happen in every trial…They never got therapy. They did not have restenosis (but we didn't discover that until they were randomized)."

Drug-drug interaction. *Panel members were concerned about a lack of warnings about drug-drug interactions, particularly with drugs such as cyclosporine or drugs using the CYP3A pathway.* A Wyeth official said, "There is a higher rate of non-specific rash in patients treated with (systemic) sirolimus which generally disappears when they continue on the drug, so we are not worried about it. In our (systemic) trials, we saw a few clearly documented true cases of hypersensitivity, but these patients also were on cyclosporine and steroids. In our (Rapamune) post-marketing reports from the field -- which frequently aren't well-documented -- there have been some other cases of allergic events, but there is not enough data to say they are related and not enough data to say they are truly idiosyncratic either…With a 1500 µg (stent) dose, there is a peak of 6 ng/mL, but that is only for one hour. The target levels of Rapamune are steady state levels, but the stent is a moving target, constantly changing. It looks steady state in the terminal region, but it is not; it is constantly decreasing. It would take, I guess, six or seven half-lives to get rid of it entirely…(but) by five half-lives you can no longer measure the drug…This momentary (peak) is not a problem…We did not find any single dose peak problems, which is essentially what a stent is…I don't think it is important to compare the steady state trough and the peak. It is important how significant that peak is to toxicity, and it really isn't." FDA officials indicated that small (6-12 patient) PK studies would be sufficient to answer this CYP3A question.

Interaction with IIb/IIIa inhibitors. A J&J expert, "We have extensive analysis on that. So far, there has been no effect on restenosis with IIb/IIIas -- on acute complications or any other factor…We simply can't say we saw any synergistic effect. Doctors tend to use IIb/IIIas for the highest risk patients, so the most important analysis of this is to be sure nothing funny is happening and there is no negative synergism."

Labeling. *A panel member was very concerned that the label should include all the information available on oral Rapamune and should be more readable.* She said, "We are dealing with a drug that has never been approved for atherosclerosis, plaque reduction, or injury except T-cells or B-cells in transplant patients...Here we are putting a drug on the vessel, yet we hear very little about the chemistry of these patients, very little about the side effects of the drug. This is not a totally benign drug…Here we are approving a drug for a purpose the drug was not approved for." An FDA official responded, "The hard part, and what we are not finished grappling with is the description of the drug part of the drug/device application. I share your concerns about the description of the drug part of this. For the drug, we have to make decisions on the consequences of known systemic effects, drug-drug interactions, monitoring, a black box warning. How many of those pieces need to be in this label?…I think we are a fair ways away from finalizing that discussion." Another FDA official said, "Right now, I'm hearing the device label doesn't say enough about the drug, per this panel. So now the issue is how much of the PDR (for Rapamune) needs to go in the label, and it sounds like most of it." A panel member commented, "This is a drug that most interventional cardiologists know little about."

Manufacturing issues. The FDA said it still had not validated consistency in the manufactured product. An official said, "The applicant (J&J) needs to verify that the testing product is the same as the commercial product. We are assessing the need for additional testing on this."

Margin effect. *A panel member wanted to know if there was geographic miss in this study.* A J&J expert said, "We looked at pre- and post-dilatation balloons to see if they caused injury at the margins and didn't find a consistent relationship. We will present that data at the American Heart Association meeting in November 2002. Even though there is efficacy at the edges, why is the restenosis rate there higher? One reason is that we were not stenting normal to normal. If we systematically put in longer stents, we would have gotten away form some of that edge phenomena. We did not protect the margins against balloon injury. Everywhere we injure the atherosclerotic vessel, we want to make sure we have adequate coverage with a drug-eluting stent."

Re-endothelialization. *A panel member wanted to know whether re-endothelialization is delayed with these stents.* A J&J expert said, "No, we think it starts by 14 days and is

complete by 30 days. Pre-clinical studies indicate that, and there is no sign of clinical delay.

Concerns about the effect in patients on statins. *This appears to be a real concern with the CDER (as opposed to CDRH) officials.* A CDER official said, "We need to talk to the sponsor more about hyperlipidemia). A J&J official said, "I wouldn't expect to have any long-term increased lipids. And when dosing stops, lipids return." A Wyeth official said, "We have a drug study of sirolimus and Lipitor (Pfizer's atorvastatin), and we found interaction."

Shelf life. J&J officials appeared to avoid discussing this issue, except that one commented that the shelf life in the CE Mark is 12 months. An FDA reviewer said that J&J's limited data doesn't support its shelf life claim at this time, and the agency has not been able to establish an expiration date.

Effect of sterilization on the finished product. An FDA official said, "The agency can't ascertain if there is an effect of sterilization on the finished product."

Effect on surgery. *A panel member wanted to know what would happen if a patient had to go to surgery after a Cypher stent had been implanted.* A J&J expert said, "I would treat it just like a bare stent. After six weeks, there should be no difference from a bare stent. In the shorter term, if bypass is done in that time period, the rate of re-endothelialization seems the same as a bare stent."

SIRIUS Final Results

Measurement	Full Cohort	
	Cypher with sirolimus n=349 of 556	Bare Bx Velocity n=353 of 545
In-Stent		
Restenosis	**3.2%**	**35.4%**
MLD	2.5	1.68
% DS	10.5	40.1
Late loss	**0.17**	**1.00**
% volume obstruction	2.6	34.2
Loss index	0.,15	0.54
In-Segment		
Restenosis	**8.9%**	**36.3%**
MLD	2.15	1.60
Late loss	**.24**	**.81**
Proximal Margin		
Late loss	0.17	0.33
Restenosis	5.8%	7.1%
Distal Margin		
Late loss	0.04	0.24
Restenosis	2.0	5.5%
Restenosis by Vessel Size		
Small vessels	18.6%	42.9%
Medium vessels	3.2%	18.3%
Large vessels	1.8%	12.0%

SIRIUS Final Safety Results

Measurement	Cypher n=533	Control n=525
MACE	7.1%	18.9%
TVR	7.3%	21.4%
TLR	4.1%	16.6%
TLR-CABG	0.6%	1.5%
TLR-PCI	3.8%	15.8%
In hospital MI	2.3%	1.5%
Out of hospital MI	0.4% 0.2% non-Q	0.4% Q 1.3% non-Q
Death	**0.8%**	0.6%
Acute thrombosis ≤24 hours	0	0
SAT (1-30 days)	0.2%	0.2%
Late thrombosis (31-270 days)	0.2%	0.6%
Total thrombosis	0.4%	0.8%
TVF (primary endpoint)	8.6%	21.0%
Survival free from TVF	92.7%	80.7%
Aneurysms	0.6% (2 patients)	1.1% (4 patients)
Incomplete apposition	8.7% (7 patients)	0

SIRIUS Subgroup Analyses

Measurement	Cypher n=349 of 556	Bare stent n=353 of 545
Diabetics		
In-stent restenosis	8.3%	48.5%
In-segment restenosis	17.6%	50.5%
TLR	6.9%	22.3%
MACE	9.2%	25.0%
In-stent late loss	0.29	1.2
In-segment late-loss	0.4	1.00
LAD patients		
In-stent restenosis	2.0%	41.6%
In-segment restenosis	10.1%	41.6%
TLR	5.1%	19.7%
MACE	85.%	22.4%
In-stent late loss	0.2	1.4
In-segment late-loss	0.26	0.81
Overlapped Stents		
In-stent restenosis	7.1%	42.7%
In-segment restenosis	8.8%	41.7%
In-hospital MACE	4.5%	4.2%
In-stent late loss	0.23	1.14
In-segment late-loss	0.2	0.93