Trends-in-Medicine

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By Lynne Peterson

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CARDIAC REVASCULARIZATION THERAPY 2003
Washington, DC
January 26-30, 2003

This meeting has become increasing important as a venue for researchers and the FDA to exchange information.

Restenosis Comparison

Trial	Bare Stent Restenosis	Drug-Eluting Stent Restenosis
TAXUS-2 moderate release	24%	9%
TAXUS-2 slow release	20%	5%
TAXUS-1	10%	0%
SIRUS	31%	9%
SCORE	26%	7%
RAVEL	26%	0%
ELUTES	21%	3%
ASPECT	27%	4%

In Europe, usage of drug-eluting stents ranges from 5% in some countries to as much as 60% in others. Dr. Patrick Serruys predicted that by the end of 2003, drug-eluting stents will be used in the majority of American patients, but Europe will remain "a missionary task," with usage trailing behind the U.S.

European Drug-Eluting Stent Penetration

Drug-Eluting Stent Usage	July 2002	December 2003
Overall use	6%	10%
>10% use	Ireland, Spain, Portugal	Norway, Sweden, Finland, Italy, UK, Denmark
<10% use	N/A	Belgium, Netherlands, Germany, France

Dr. Serruys' Thoraxcenter in Rotterdam, the Netherlands, converted to 100% use of drug-eluting stents when the Cypher was first approved in Europe, and Dr. Serruys is conducting his own cost-effectiveness study of drug-eluting stents. In practice, 79% of patients have gotten drug-eluting stents in his cath lab since April 2003. The reasons for not using a drug-eluting stent were: initial unavailability of

some diameters and lengths, enrollment in another study, and operator choice. So far, 914 patients have gotten a total of 1,918 stents (an average of 2.1 stents per patient): 7% in-stent restenosis (ISR), 2% ISR post-brachytherapy, 8% CTO, 16% small vessel (2.25 diameter), and 29% long lesions (>36 mm length).

Thoraxcenter Drug-Eluting Stent Experience

Measurement	Drug-Eluting Stents (n=563)	Control (n=806)
Treatment period	4-16-2002 to 10-16-2002	10-16-2001 to 4-15-2002
Stents per patient	2.2	1.9
Bifurcations	17%	7%
Death	1.4%	2.7%
Non-fatal MI	1.4%	2.7%
Repeat revascularization	1.2% (p=.01)	6.8%
Total MACE	5.7% (p=.01)	14.1%
Event-free survival (by Kaplan-Meier curve)	93.4%	85.9%
Non-Diabetic event free-survival	94.6%	86.3%
Diabetic event-free survival	89.1%	83.2%
AMI-free	88.9% (p=.01)	79.2%
SAT	N/A	0.4%

Drug-eluting stent failures, Dr. Serruys said, is due mainly to technical problems, "We intensively investigated with IVUS. In two-thirds of cases, we found a technical area – a gap between stents, etc…Then, there was a population that was able to develop true failure on drug-eluting stents, and those are diabetics, where we saw limited, focal restenosis inside the stent without any explanation. And then there was restenosis treated by brachytherapy and then by a drug-eluting stent, and in those patients, you don't get 100%, just 70%."

Interviews with leading interventional cardiologists and researchers yielded a few interesting tidbits:

- China has developed a rapamycin-eluting stent for use there.
- If Cypher is not approved by April 1 – and if, therefore, outpatient reimbursement does not begin until July 1, 2003, adoption initially may be slower than some analysts have predicted. A source said, "It might make people happy if CMS doesn't reimburse until July; it would be an excuse not to spend money on them right away. People might put a few drug-eluting stents in, but not many until there is reimbursement."
- There is a rumor Japan will set its reimbursement rate for drug-eluting stents as the average of the price in the U.S. and the price in Europe.
- Higher late loss rates (e.g., 0.35 in TAXUS-1 compared to 0.14with Cypher) may be a red flag. A source said, "There is little question that paclitaxel works, but there are now serious questions about whether the dose chosen is as potent as sirolimus, suggesting that TAXUS-4 may have trouble meeting its efficacy endpoint."
- Rapamycin (sirolimus) analogs are very different from rapamycin. A source said, "They were not developed to enhance local delivery proprieties, and actually may do the opposite. Rapamycin also may be more stable than the analogs."

Should drug-eluting stents be used in all patients and all lesions?

YES: Dr. Serruys warned that not using drug-eluting stents in all patients could negatively impact their ability to switch patients from CABG to stenting, "A selective and thus restrictive use of drug-eluting stents may mask, dilute and even erode their remarkable efficacy and their potential impact on the treatment of multivessel disease (and on CABG)…The ultimate effectiveness of drug-eluting stents should be viewed by their impact on bypass surgery."

NO: Several U.S. doctors attending the meeting said their hospitals will use a selective approach because they can't afford drug-eluting stents. A speaker commented, "TVF was only 14%-15% with the bare Penta in DELIVER, so do we really need drug-eluting stents?…I haven't seen anyone sued for not using brachytherapy for in-stent restenosis, so I think it is a myth (that we will be sued for not suing drug-eluting stents) as long as you are fair with the patients."

How long should patients get Sanofi's Plavix (clopidogrel)?

At least two months, speakers said – but longer in certain cases. One speaker said, "We heed to do a trial to figure out how long to give clopidogrel. Patients getting one stent up to 23 mm long gets it for two months. Then, difficult patients – main stem, main stem in combination with a bifurcation, CTO, stent >36 mm long – are given up to six months of clopidogrel. It is all arbitrary. And one group where we keep them on clopidogrel forever are the brachytherapy failures treated with a drug-eluting stent."

Following is a look at the drug-eluting stent programs of various manufacturers.

ABBOTT LABORATORIES and MEDTRONIC

There was no new news on ABT-578, but a speaker commented, "The Medtronic program is still in the development phase, so I'm focusing (in my talk) on the Abbott clinical program." Abbott has modified its DES program to use the DD stent with a micron thick coating against the vessel

wall to deliver the drug. Asked about the effect of the DELIVER results on the Abbott program, the speaker said, "This is not a polymer that allows sustained release over time. Granted, the elution may be more rapid than with some polymers, but I think there is still some sustained release."

JOHNSON & JOHNSON

Sources predicted that Cypher would not get FDA approval until April 2003 – at the earliest – and one doctor suggested it may be later than that. Several cardiologists who are generally considered knowledgeable suggested these reasons for the Cypher delay:

- Polymer problems. This is what we've heard before, and several sources cited this issue.
- Labeling. A source said he believes there continue to be labeling issues with the FDA over lengths.
- FDA 483 letters. A source said these manufacturing issues have not been resolved and believes J&J is still waiting for an FDA response to its answer to the 483s.
- The FDA's CDER still has labeling and other issues with Cypher. Several people brought up the idea that there are lingering issues with CDER.
- Storage issues. There were reports that some Cypher stents in India were affected by temperature.
- Inconsistent manufacturing.

Dr. Marty Leon – who has been one of the strongest advocates of drug-eluting stents – discussed *Should We Treat the Vulnerable Plaque with Drug-Eluting Stents?* and the tone of the talk was surprisingly restrained. He cited some concerns with drug-eluting stents, including: persistent poor endothelialization, excessive thrombus, persistent fibrin with inflammation, claudification, and granulomas. He also commented, "(There's) only a small or moderate reduction in restenosis…and late incomplete apposition – I don't know what that means. It's probably benign, but it's there…If you look under the rug at SIRIUS, the results are not as pristine as have been suggested (suggesting people look at Cypher's 35% late loss in diabetics)…There was a patient from Brazil who maybe was late thrombosis…Can some of these drugs accelerate or promote late rupture?"

BOSTON SCIENTIFIC

The Express drug-eluting stent received a CE Mark, but it will not be available for use in Europe until March 1, 2003. A speaker said this was due to "some validation reason." Data from TAXUS-4, the U.S. pivotal trial, will be presented on September 11, 2003, at TCT.

Before the DELIVER data was presented, sources insisted there were no negative implications for the TAXUS program from DELIVER.

- The number of patients in the TAXUS program so far (~500) is sufficient to give sources confidence that this program will succeed.
- Sources all believe the TAXUS program is moving along just fine.
- The long-term animal data is good and raises no concerns.
- A speaker described Boston Scientific's polymer as "relatively inert" and "comparable to bare out to 180 days."

The TAXUS principal investigator, Dr. Gregg Stone, said, "Efforts to ascertain the relatively efficacy of these (various drug-eluting stent) agents across trials are hopelessly confounded by baseline differences in patients and lesions, differences in implantation techniques, core labs, definitions and analysis methods. How good is paclitaxel? There is no way to say if it is as good, better or not quite as good as sirolimus…DELIVER says to me that without some drug elution control, there were a lot of patients not getting the drug delivered to the lesion."

However, after the DELIVER data presentation, several sources changed began to worry that TAXUS-4 could fail to show efficacy – but not that it would prove unsafe. They pointed out that TAXUS-4 uses the Express stent but earlier TAXUS trials used the NIR Conformer stent, and there is growing concern among interventional cardiologists and the FDA that stent design is important to the performance of drug-eluting stents.

Among their concerns are:

- Express is considered a "better" stent than Nir Conformer, so there is a question whether TAXUS-4 will meet the primary endpoint of a 50% reduction in restenosis.
- The Express design could prove a wild card. If stent design matters, then paclitaxel may perform differently on the Express than it did on the Nir.
- Express was described as an open-cell stent, and a suggestion has been raised that open cell stents are inferior to closed cell stents for delivery of a drug.

Stent Cell Designs

Company	Open Cell	Closed Cell
Abbott	BiodivYsio	---
Boston Scientific	LP2, Express	Nir Conformer
Cook	V-Flex Plus Supra G	
Guidant	MultiLink Duet, Tetra, Penta, Achieve	---
Johnson & Johnson	---	Cypher
Medinol	---	NIRflex
Medtronic	beStent, S670	beStent-2

Other TAXUS trials, include:

- Boston Scientific has not yet finalized details for the TAXUS-V trial in de novo lesions. The company is still discussing with the FDA "how to enrich the subsets that will lead to labeling." This 1,108 patient trial will investigate lesions up to 46 mm, using stents with diameters of 2.25 to 4.0 and the Express 2 stent (same stent but new delivery system). Overlapping stents will be allowed. The primary endpoint is nine-month ischemic TVR and superiority.

- There will be data on the European TAXUS-VI moderate release program, probably at the American Heart Association 2003.

- A second, 528-patient TAXUS-V trial – this one in ISR – is due to start enrollment by late March/early April 2003, using slow release and Express-2, compared to VBT.

- In Italy, Dr. Antonio Colombo is starting (on January 28, 2003) a head-to-head trial of Cypher and the paclitaxel-eluting Express stent, but Dr. Stone commented, "A small randomized trial has two problems. It may miss differences that exist or find ones that don't exist…It will take a huge, randomized trial to tell us, and that would be very expensive, so don't hold your breath."

Peripheral Stents. Boston Scientific's Symbiott stent for SVGs was praised by several speakers. One said, "It is one of the best stents, self-expanding nitinol with an ultra-thin ePTFE 'sandwich' covering (2 layers of 16 microns) vs. a 200 micron covering for the Jomed stent…Symbiott is based on the Radius stent platform, and Boston Scientific has to be commended."

In a Phase II trial MACE at 30 days was 5.2% with Symbiott compared to 13.5% with the comparator (the Boston Scientific Wallstent) – a 61% reduction. A U.S. Phase III trial is underway.

GUIDANT

Paclitaxel. Guidant had earlier reported that the DELIVER trial failed, but details were available for the first time at this CRT meeting. There will be more DELIVER data at the American College of Cardiology in March 2003. As expected, the DELIVER data showed that the Achieve (Penta) stent spray-coated with paclitaxel was safe but not efficacious. Two reasons for this were suggested:

- The excellent performance of the bare Penta stent.
- The suggestion of weaker drug effect than expected.

Sources said the messages from DELIVER are:

- Surface volume of the stent may matter.
- Stent design -- including closed vs. open cell or the design itself -- may matter.
- Paclitaxel dosing matters.
- Length of trial may matter. The big different in ELUTES, ASPECT, PATENCY and DELIVER is the length of the trial, with DELIVER the longest.

DELIVER Results

Measurement	Achieve N=521	Control n=521
Diabetics in trial	30.7%	26.8
Insulin-dependent diabetics	8%	5%
Mean lesion length	11.7 mm	11.1 mm
One stent per patient	90.3%	87.1%
In-Hospital Events		
Death in hospital	0.2% (1 patient) *	0
MI in hospital	0.6%	0.2%
SAT in hospital	0	0
30-day Safety		
30 day death	0.2%	0.2%
30 day MI	0.8%	0.2%
30 day SAT	0.2%	0.2%
9 months death	1.0%	1.2%
170-day Efficacy		
TVF	11% - 12%	14% - 15%
Restenosis	16% - 17%	21% - 22%
270-day Safety		
MI	1.0%	1.0%
Stent thrombosis late	-0.2%	0.2%
All stent thrombosis	0.4%	0.4%
Residual dissection	0	0.2%
Major bleeding	4.8%	3.5%
CVA	0.6%	0.6%
Major vascular bleeding	1.9%	1.4%
IVUS findings		
Neointimal volume in stents <20 mm	26% (p<.05)	37%

* anaphylactic reaction to contrast dye

By IVUS, there was a statistically significant reduction in neotimal volume in DELIVER patients who got a stent <20 mm in length, but no difference between the drug-eluting stent and the bare stent when the stent length was >20 mm. There was no late incomplete apposition and no change in the in-segment vessel architecture. The drug appeared to be evenly distributed within the stent since IVUS found an even reduction in neointimal volume through the stents. The IVUS investigator said, "So, the drug gets there, but maybe it's not as efficacious in this technology. It looks like there simply is not enough drug…We can't tease out whether it was lack of polymer. It just looks like enough drug doesn't get there, but some does."

Everolimus. The final design has not been determined for the SPIRIT FIRST trial, a feasibility study of 140 patients in Europe at 10-15 centers, but it will be a triple-blind, randomized trial, and the primary endpoint will be in-stent late loss at 180 days, powered for a .48 mm difference (from bare stent). After SPIRIT FIRST, there will be an EU approval study, then a separate, pivotal SPIRIT trial in the U.S. The first European trial is due to start soon, and if all goes well, Guidant could get CE Mark for this stent by April 2004.

Regulatory. Guidant is unlikely to get expedited FDA review for its drug-eluting stents, except for sizes or indications that J&J or Boston Scientific don't have at the time Guidant makes its final submission. However, FDA officials said they plan to handle all drug-eluting stents expeditiously. (*See The Regulatory Perspective below*)

Bare stents: There is a lot of enthusiasm for the new Vision stent, which is likely to capture much if not most of the stent market that doesn't go to drug-eluting stents. Binary restenosis with Guidant stents was cited as: 16% MultiLink, 19.7% Duet, 23.6%Tetra, 17.5% Penta, and ~10.8% Vision.

JOMED

The tacrolimus program appears sick but not dead. An investigator was asked whether the high restenosis rate is due to the drug, the stent or the platform, and he replied, "Initial data for the ceramic coating looked better in animals, so the company thought the high dose (in PRESENT-II) would counteract the inflammatory response of the ceramic coating. That didn't work out. Then, to really test tacrolimus only, they tried high and left the polymer out. Right now, it is clear Jomed dropped the ceramic coating and bonded the tacrolimus to the surface directly, but that is the last chance for the coating. If they have to further increase the dose, it won't be a winner either."

Tacrolimus Trials

	PRESENT-1	PRESENT-II	PRESENT-III	EVIDENT (SVG)
Drug Dose	Low (60 µg)	High	High (230 µg)	High (352 µg)
Coating	Ceramic	Ceramic	None	Stent graft
30-day MACE	0	N/A	N/A	N/A
6-month MACE	13.0% (all TLR)	36.4% (TLR 31.8%, TVR 4.5%)	N/A	36.4% (preliminary, with 27.3% TLR, 9.1% Q-wave, 9.1% death)
6-month restenosis	19%	32%	N/A	27%

BIOSENSOR

The expectation is that Guidant will do a deal with Biosensor, and a source said Biosensor currently is reviewing the term sheet. The source also indicted that Guidant is not expected to bring Biosensor's biodegradable everolimus-eluting stent to the U.S.

The preliminary data from the 36-patient FUTURE-1 trial was reviewed, but no new data presented. A Bio-sensor official said his company is reviewing the term sheet now, but it is almost a done deal. He thinks Guidant will choose to put their drug on a Guidant stent for US sales and use the biodegradable stent only outside the US if at all – because the regulatory hurdle is higher and harder for the combination of an unapproved stent and an unapproved drug.

The FUTURE-1 and FUTURE-2 principal investigator, Dr. Eberhard Grube, said Biosensors has done more animal studies than any of the big drug-eluting stent players. He said the data "looks good and safe so far."

The design of FUTURE-2 is: 90 patients, 1:1 randomization in a double-blind trial. So far 60 patients have been enrolled. The primary endpoints are: late loss at six months and freedom from MACE at 1 month, 6 months and 1 year. Six-month data is expected to be presented at American Heart Association 2003. Dr. Grube said enrollment was "going well" and should be finished soon.

MISCELLANEOUS

- A prominent interventional cardiologist said he is writing an editorial for the journal *Circulation* arguing that drug-eluting stents should ***not*** be used in all patients, that doctors should only use them in *labeled indications*.
- Biodegradable stents. A German researcher argued that these are the wave of the future, and he said a corrosive, magnesium (metal) stent that degrades is in development.
- A speaker warned, "VEGF- and DNA- eluting stents may have an interesting regulatory route." But he noted that the polymer being used for DNA-delivery "seems robust and does not delaminate."

VULNERABLE PLAQUE

Identifying vulnerable plaque continues to be gain interest, but the technology really isn't quite there. A speaker said GlaxoSmithKline, AstraZeneca and Novartis have taken the lead in pharmacology trials relating to vulnerable plaque.

Dr. Marty Leon sounded a cautionary note about drug-eluting stents for vulnerable plaque in coronary and non-coronary arteries, "Most of the drug-eluting stent systems being proposed for vulnerable plaque require the use of drugs or carrier vehicles which are simply too toxic…Even the best

drug-eluting stents have intrinsic toxicity…A kinder, gentler approach for vulnerable plaque may be stents that elute: BCP-671, VEGF, Estradiole, NO donors, or EPC…Are drug-eluting stents for vulnerable plaque even in the realm of the possible when we are still trying to pay for drug-eluting stents for restenosis?"

Among the vulnerable plaque technology worth watching (both positive and negative) is:

- **Optical Coherence Tomography** delivered by catheter. This also is becoming almost standard of care in ophthalmology.
- **CRP measurement**. This is the best marker right now, but it is likely to be only one of 4-6 markers in the future.
- **Thermography**, whether internal (by catheter) or external. There are a lot of unresolved issues with this technology, so while researchers are working with it, it is no where near read for prime time.
- **CT.** There is more interest in ultra-fast CT than MRI. 16-slice CT isn't ready to replace fluoroscopy, but it is very good, and the field is moving quickly. Siemens has a 32-slice CT machine in development that Dr. Patrick Serruys described as "very slick."

PHOTODYNAMIC THERAPY (PDT)

MIRAVANT – after failing to make a go of PDT in ophthalmology for AMD – is trying to find a role for it in the treatment of vulnerable plaque, but a researcher said this is far away, if it flies at all.

PHARMACYCLIC'S Antrin [motexafin lutetium (MLu)]. In a Phase I trial: no edge effect was seen, 91% of the drug was eliminated form plasma within 24 hours, and 20%-30% of patients got a rash. Phase II efficacy trials are planned.

Antrin 6-Month Results

Measurement	Overall Result
In-segment restenosis	33.8%
MLD	1.75
Late lumen loss	1.75

ORAL RESTENOSIS THERAPIES

Among the oral drugs in trials to treat restenosis are:

- **Rapamycin**. Researchers continue to explore this although preliminary safety data has not been good.
- **Cilostazol**. The CREST trial in ongoing and should be completed by the end of 2003.
- **Folates** (homocysteine-lowering therapy). Data on this to decrease restenosis will be available at a late breaker at the American College of Cardiology 2003.
- **Novartis's Lescol** (fluvastatin).

CRYOTHERAPY

A pilot trial of **CryoCath's** ICE trial using cyrotherapy (at –60°C delivered by catheter) showed the system was safe but did not reduce restenosis.

Cryovascular's approach (at -10°C delivered by balloon) appears somewhat more promising. In a Phase I trial of 102 patients, this N_2O cartridge system appeared safe and effective, and nine-month follow-up data will be available at TCT2003. The system is still too large, but it is undergoing continuous design changes and improvements. A European registry is ongoing with 30-40 patients enrolled now, and a goal of 150 patients. The company has a 510K for angioplasty in SFAs and popliteals.

BRACHYTHERAPY

A speaker said that vascular brachytherapy (VBT) currently is used in nearly 500 cath labs in the U.S., and that >40,000 patients were treated with VBT in 2002. However, he noted that usage at his lab has been relatively stable since 2000. Once drug-eluting stents are available in the U.S., he predicted there would still be a role for VBT, particularly for (1) insulin-dependent diabetics where the Cypher restenosis rate in SIRIUS was 35%, and (2) in-stent restenosis in drug-eluting stents, (3) fem-pops, and (4) in-stent restenosis of renal arteries. He also predicted VBT would be approved for use in SFA by the end of the year. His conclusion: "Radiation will stay in the cath lab as long as restenosis exists or something better comes to replace it."

Dr. Renu Virmani of the Armed Forces Institute of Pathology compared drug-eluting stents and brachytherapy, and concluded, "I think drug-eluting stents are more benign than brachytherapy." But she warned against using a drug-eluting stent in a patient who has had brachytherapy, "If you've given brachytherapy first, then a drug-eluting stent is a bad combination and shouldn't be tried."

Comparison of Drug-Eluting Stents (DES) and Vascular Brachytherapy (VBT)

DES	VBT
Delayed healing	Delayed healing persists longer than with DES
Mild to moderate delay in endothelialization	Persistent lack of endothelialization
May cause medial necrosis and inflammation, depending on drug toxicity and dose	Induces inflammation and atherosclerosis long-term
Edge effects no worse than bare stent	Edge effects much worse than bare stents
Will only result in neointimal growth equivalent to control, if drug not toxic	Eventually will lead to aggressive and severe restenosis

FDA: THE REGULATORY PERSPECTIVE

The FDA participated in four sessions at this meeting instead of the usual one. A senior FDA official said the goal was to convey that the FDA wants "good science," implying that this is not what the agency has been getting generally in the drug-eluting stent area. Among the messages for interventional cardiologists:

1. Sponsors must have the science to support device approvals.
2. Post-market surveillance of cardiovascular devices has to improve.
3. Evidence-based trials are necessary not only for FDA approval but also for CMS reimbursement. An official said, "The agency is working very interactively with Medicare, and we have a very good working relationship, but it is Medicare that has a certain set of standards…Correct clinical trial design can be very important for CMS reimbursement approval."

An official also made an oblique reference to the upcoming CMS decisions on reimbursement for ICDs and LVADs. "Over the next several months, important trials will be discussed by CMS with potentially very important implications for reimbursement in cardiology which underlines the need for appropriate clinical and preclinical data in evidence-based medicine."

At one session, seven FDA officials answered questions submitted in advance via the CRT website. Among the most interesting answers – and their implications -- were:

- ✓ Guidant, Medtronic and Abbott will not be able to cut time corners with their drug-eluting stent programs. That is, they will not (1) be able to do shorter animal studies, (2) skip a phase even if their drug is a sirolimus analog – and probably not for any other reason, or (3) get expedited review unless it is for a size or indication for which Cypher is not approved. Everolimus and ABT-578 both will be treated as NMEs.
- ✓ The FDA will consider accepting more OUS data, but it will have to be a very carefully designed trial, probably with FDA input in that design.
- ✓ The FDA currently believes that stent design can affect how a drug-eluting stent performs; it is not assuming that the same drug will perform the same way on another stent.
- ✓ The FDA does not appear willing to grant J&J broader lengths and diameters for Cypher than the Advisory Panel recommended. An official said, "The Advisory Panel opinion was that, in general, approval should be limited to the studied population, and thus far, we tend to agree with that."
- ✓ Post-marketing data can be supportive but are not sufficient, on their own, to expand an indication.
- ✓ The FDA does not appear to feel pressured to approve Cypher. Rather, FD officials emphasized that sponsors have the option of making investigational stents and other devices available to patients through two programs: "compassionate use" and "continued access registries."
- ✓ The initial drug-eluting stents (Cypher, etc.) are likely to have a warning that there is lack of data about their use in drug-eluting stent failures and brachytherapy failures.
- ✓ The FDA will not consider registries sufficient for approval of a new drug-eluting stent for the near future, but a registry could be used to expand labeling for an approved drug-eluting stent.
- ✓ After Cypher is approved, the FDA might accept a trial design that uses a combination of QCA and a clinical endpoint in lieu of a head-to-head trial with Cypher, but officials assume a bare stent comparator trial will be difficult or impossible to conduct because drug-eluting stents will be "standard of care."
- ✓ The FDA is concerned about stent malapposition and companies will have to convince the FDA there is no safety issue when malapposition appears in a trial.

Following is more detail on the questions and answers from this session, for readers interested in those details.

Can a Phase I trial be initiated with only 30-day animal studies?

FDA official: "No, unless there is substantial, quality OUS data – four- to six-month angiography and follow-up on a significant cohort. Even if the drug already is approved (for some indication), from the CDER perspective none are approved yet in coronary or peripheral vessels. We feel three month animal data is more predictive before we start thinking about human trials."

How much animal data do you need to move from Phase I to Phase II or Phase II to Phase III?

FDA official #1: "What we are asking for is, in the ideal situation, as much long-term data as you have, and, ideally, you should have six-month data. If the three month data looks really good, we might consider letting you go forward, but we would still expect you to be collecting the (longer-term) animal data."

FDA official #2: "Even if we allowed initiation of a pivotal trial with just three month animal data, we would want to make sure -- before we allow full enrollment -- that you have a DSMB who could stop the trial if necessary, have reporting to the agency so we are kept abreast if any safety issues or unusual anomalies surface. And for approval you would still be required to submit that (longer animal) information – not only on the intended dosing but also on overdosing."

Is a First in Man trial essential, or would the FDA allow OUS data for a pivotal trial?

FDA official: "When dealing with drugs with which we have little experience, I think our answer at this time is a first in man trial is essential. We also would accept OUS data, but we urge you to have the trial design as similar as possible. There are differences in demographics and regimens overseas, and you need to take them into account in trial design. Also be sure that your feasibility study appropriately addresses appropriate safety information – largest potential drug dose, multiple indications, etc."

Does an analog of an approved drug require different studies in comparison to an approved drug?

FDA official: "If it is an analog, it is considered an NME (new molecular entity), so it has to go through the new drug approval process, which requires animal studies, PK studies, etc."

Would a clinical study be different for a drug-eluting stent with an NME vs. an. approved drug?

FDA official #1: "The answer depends on the safety information…If there are no safety considerations, we would expect the clinical study to be similar to the approved drug on a stent."

FDA official #2: "For peripheral devices with an NME, the size of the study may be slightly larger...If you are doing a peripheral study with an NME, there may be safety issues that we may need to look for."

What about the combination of a new stent design and a new drug?

FDA official: "Yes, you could do that, with caution. Currently, we are in a paradigm where we are doing superiority trials, comparing bare stents -- whether or not approved -- to the proposed drug-eluting stent…Once the first product is approved, in the realistic world we would like a three-arm trial, but we know that is not the most realistic thing, so we are really going to be inventive…(but) stent design can have an impact."

What is the variability of drug elution for a drug-eluting stent?

FDA official #1: "It depends whether it is pre- or post-approval. Post-approval, it should be as close as possible, depending on manufacturing limitations…It is advantageous to study variable elution rates to see if they are effective, but once something is approved, you want to minimize variation as much as possible."

FDA official #2: "Depending on the drug, the rate of elution may be more or less of a factor in efficacy. So, if you are manufacturing lots with a wide range of elutions, you may see a difference in your clinical study results. So, this requires some thought and planning. Maybe you should look at that in your FIM studies."

How should a sponsor evaluate the efficacy of a drug-eluting stent that uses a stent not already approved for SFA? What would the appropriate trial design be?

FDA official #1: "In the ideal world, we would like to know the effect of the drug over the stent, so we always encourage a trial design with as many arms as needed to answer these questions. If you add a drug to a stent, we want to know if it is superior, so we want superiority. If you are willing to include a bare arm, a drug arm and a PTA control, that would tell us how well you do in long-lesions. But if you don't choose to study bare stent, we are willing to listen."

FDA official #2: "We are willing to think creatively on design even though it may not sound like that, for example, looking at alternatives to randomization schemes."

FDA official #3: "The problem with the SFA field is that there is only one approved stent which is not perhaps the most commonly used stent. There is lot of off-label use of biliary stents (for SFA). Given that, it wouldn't necessarily be required to do a DES vs. bare vs. PTA, though that would be a desirable design given that the manufacturer could potentially get both the bare and the coated stent approved in one trial. We would consider a trial of a drug-eluting stent vs. provisional PTA, where in the control arm, you start with PTA and, if result is not felt to be acceptable based on objective criteria such as the presence of a long dissection or flow-limiting lesions, one could put in a bare metal stent. It is that thinking that is potentially negotiable with the FDA. This is a difficult area to get going in, and our recommendation is for early action with the agency on trial designs."

Does the FDA require long-term animal studies prior to institution of a peripheral stent trial if the same drug already is used in coronaries?

FDA official: "The problem in leveraging coronary data for peripheral use is that often times the stent design is so different that, beyond the drug issues, there are actual stent issues. Often the platform uses different materials which require a different polymer. And it may be larger stents, so the total drug dose may be much larger, and that raises safety issues that need to be studied before clinical trials. So, while we are willing to think of how to use coronary data, it is often difficult for us to do so."

If the sponsor wants labeling approval for multiple vessels in the same patient, does this require additional study?

FDA official: "In the stainless steel stent era, that was not a big deal to make the leap after a single stent trial to multivessel use. In the drug-eluting stent era -- with really some remaining issues about pharmacology, local concentrations, and systemic concentrations – the idea of multiple stenting with drug-eluting stents is still a question mark. We still want to see some registry data to better convince us of the potential safety…(Manufacturers) need to recognize the immediate safety concerns we have at this point in time."

Does the FDA view stent malapposition without sequelae to be a problem?

FDA official: "It is clear from the data presented so far that with drug-eluting stents, like brachytherapy, we have an abnormal arterial wall remodeling process or an altered process that is different from the stainless stent era. The question of malapposition is an important issue to examine in detail. That's why, in addition to the usual nine-month TVF primary endpoint, the October advisory panel meeting said it was important to: (1) have longer term data, and (2) use IVUS as one mechanism for convincing the FDA that this isn't a significant safety problem. We can't ignore this type of arterial remodeling when putting together our risk:benefit assessment."

Will the FDA be willing to expand indications beyond a pivotal study?

FDA official: "The Advisory Panel opinion was that, in general, approval should be limited to the studied population, and thus far, we tend to agree with that."

Can data from post-marketing surveillance studies of off-label use support a label expansion?

FDA official: "They can be supportive, but generally these are not sufficient on their own to exp and an indication."

Will FDA allow broad compassionate use of drug-eluting stents before marketing approval?

FDA official: "It is granted on a patient-by-patient basis…We have a continued access provision that allows investigators to continue to use a device while the marketing application is under review. We encourage sponsors to set up continued access registries."

Once the first drug eluting stent is approved, will other drug-eluting stents be subject to expedited review?

FDA official #1: "In general, if a drug-eluting stent is coming with a new indication, it probably would be eligible for expedited review. If not, it probably would not be eligible – unless in some other way it represented a major therapeutic advance. Otherwise, the timeline depends on: (1) the quality of the interaction between the sponsor and the agency, (2) the quality of the submission itself and how it is organized, and (3) the responsiveness of the sponsor to our questions and requests for additional information."

FDA official #2: "You would have to show you address an unmet medical need, and you would have to show how you do this. If it is a different indication where there is no alternative, that very likely would qualify."

After the first drug-eluting stent, would the FDA consider registries for new drug-eluting stents?

FDA official #1: "No, a registry is probably not sufficient – at least for a while."

FDA official #2: "With drug-eluting stents we are looking for a clear risk:benefit profile that shows the drug adds something positive. The addition of a drug can have negative factors, and we want to be sure the risk:benefit is appropriate, so that won't fly."

Could you use a registry of an approved drug-eluting stent to expand labeling?

FDA official: "Yes. Say the trial was designed for 2.5-3.5 mm diameters, and you want to expand to smaller and larger diameters, then that is a situation where we would consider a registry-type of approach…If you wanted to study it in a different indication or a different patient population, such as diabetics or in-stent restenosis, that is where we want randomized trials."

Once the first drug-eluting stent is approved, would the FDA accept IVUS or QCA as an endpoint?

FDA official: "Potentially. The bottom line is that we are interested in clinically-relevant results that shows a risk:benefit profile that is appropriate…When drug-eluting stents become the standard of care, and we will have significantly lower event rates, so to use our usual clinical endpoint of TVF with the delta extremely narrow, would require a trial size not seen in device trials. What we do know from device trials over the last decade is that the use of QCA as a surrogate is usually a powerful variable. There is a potential to design an equivalence trial with co-primary endpoints – one QCA and the other TVF with a moderate-sized delta -- so the sample size would not be 10,000 patients…(BUT there are some) caveats to utilization of QCA as a key primary endpoint. Angiographic follow-up has (historically) been less than ideal. There have been even more problems, in some cases, getting QCA follow-up on subgroups…This also applies to IVUS, which is an important secondary variable. We will need to get more confidence in the use of IVUS as a key secondary endpoint. The main problems (with IVUS) are: difficulty in getting the required follow-up, problems with the quality of studies done at certain sites, and the standard deviation for IVUS at most core labs is not as favorable as for QCA. So, you probably are better off proposing a combination of QCA and a clinical endpoint to the FDA."

What if a drug is already approved by one company on its stent and you want to use that same drug?

FDA official #1: "If the same sponsor wants to come in and use same drug and polymer on a different platform, where the sponsor has the drug and wants to change the stent platform, then we are looking at a different trial design...If a sponsor want to leverage public information with the same drug, using a different stent or polymer, then there are a lot of variables to consider – differences in stent design, polymer thickness, manufacturing issues, elution characteristics, drug distribution in tissue, etc. Those can all lead to differences in clinical outcome, so this is not an easy question to answer."

FDA official #2: "When sponsors do a feasibility outside the US with a different design, and then want to come to the U.S. with a pivotal trial, they need to address safety issues looking at the clinical dose and overdosing. Make sure the stent area theoretically has the same drug dose…This is an area where it pays to talk to us early."

What will the FDA recommend on the safety of drug-eluting stents for DES failures and brachytherapy failures?

FDA official: "This is a difficult situation…I expect the initial label will have a warning that indicates the lack of data right now. Our main concern would be to try to motivate investigators and industry to develop appropriate trials to find out better treatment strategies for these difficult patients."

What would you tell patients today about deferring a procedure to wait for a drug-eluting stent?

FDA official: "There is a potential for a continued access registry to be set up by the sponsor, and a compassionate use program. So the real person to talk to is the sponsor. From our perspective, this is a device that qualifies for both of these programs."

FDA Town Hall Meeting

At a two-day FDA Town Hall meeting, Duke University interventional cardiologist Dr. Mitchell Krucoff provided a postmortem of the FDA Advisory Committee meeting on Johnson & Johnson's Cypher stent. He said patient and physician demand is strong and described Cypher as "clearly breakthrough technology." He added, "(Cypher) showed a 59% treatment effect (reduction in TVF). We usually see around a 15% effect, so that is pretty substantial."

Dr. Krucoff said the panel's safety concerns with Cypher were:

1. **Porcine histology.** Post-elution polymer inflammation led to restenosis in pigs. He said, "Once the drug has eluted form the stent, there is clearly an ongoing inflammatory reaction surrounding the polymer."
2. **IVUS substudy.** There was a finding in a small percentage of patients of negative remodeling and late malapposition.

Other Cypher panel concerns included:

- **Lesion length.** SIRIUS average lesion length was 14.4 which was shorter than lower end of enrollment criteria, which Dr. Krucoff thought was probably due to visual measurements by the investigator vs. QCA data. He added, "What we focused on was lesion length rather than stent length -- not whether the FDA should approve different length stents."
- **Labeling**. The panel felt there was a lack of information on the drug itself and a proximity of an explanation of what a drug-eluting stent is to the explanation of what brachytherapy is. He said, "The concern was how we tell doctors and patients about this product."
- **Off-label use.** "Practice of medicine" is likely to lead to off-label use patterns. He said, "Just weeks before…I was at an Egyptian cardiology meeting where we watched a live demonstration put 10 Cypher stents in one human."
- **Long-term human data.** Although the panel felt nine-month data was enough to move forward with Cypher, there was a concern that problems might not manifest for years.

The FDA Town Meeting was chaired by Dr. Robert Califf, a clinical cardiologist also from Duke. He said, "It looks like Cypher is a winner, and the majority (of other drug-eluting stents) are losers. It looks like the biggest win is in totally disrupting the bypass surgery industry." He also commented later in the meeting, "I'm shocked and concerned by some of the things I've heard here today."

Among the points that Dr. Califf made about drug-eluting stents and stent trials during the first session that captured the tone of the meeting were:

1. Insufficient data. "I would argue that one or two clinical trials does not give the data consumers and payors need."

2. Impact of rising cardiovascular spending. "The impact of this (drug-eluting stents, ICDs and LVADs) is likely to be a marked reduction in services to those who already can't pay. We can't just say suck it up and spend more money on cardiology. There isn't any more money. The increase in CMS is only half the money; the rest will come from other areas where patient groups are not as strong, like psychiatry…(and it isn't only drug-eluting stents), it's also ICDs and LVADs…We just calculated that to take care of all the patients we have whom we know qualify for an ICD – and for whom we have addresses and phone numbers – we need to hire seven full-time electrophysiologists for a year to catch up with the implants that need to be done."

Dr. Califf stressed that there is not enough money in the U.S. healthcare system to pay for all the drugs and devices – particularly cardiovascular devices -- being developed. He said, "Psychiatrists are told now they can't see patients and do psychotherapy because they'll lose money. There are individual heroic acts like Dr. Patrick Serruys who got five million euros from his institution for drug-eluting stents, but that is rare…I think this time it is for real; we actually are out of money."

3. Human experimentation. "We have to keep remembering when we are talking about device development that we are talking about human experimentation."

Other issues raised by participants included:

Patient selection for drug-eluting stents. *Should drug-eluting stents be used for all patients?* In the Netherlands, Dr. Serruys is using drug-eluting stents for 100% of his patients and has an eight-week waiting list for PTCA, but most other interventional cardiologists who spoke at the meeting – U.S. and European -- argued that drug-eluting stents should be reserved for selected patients, and it appears that FDA labeling may be the determinant for many hospitals and doctors. One cardiologist said, "I don't think we can put drug-eluting stents in all our patients. I'm troubled by the potential for more broad use than we have data for." Another said, "I was in Miami giving a talk and all of the cardiologists said, 'This is Miami. We have to put them in or we will be sued.' I don't believe that for a minute…There will be a competition to see who is first on the block to offer them, and some people may use them as a loss leader…so the pressures (to use them) are out there)…We can't afford to put them in everyone. Just like a triage in wartime where you take the people you can help, we need to find where can have the biggest impact…We are not in a crisis; our patients are not dying…if I had to keep using bare stents for another six to 12 months in some subset of patients, I don't feel that would jeopardize my patients. I feel differently about ICDs…but they save a life and a drug-eluting stent only saves a procedure."

More studies needed. There is a need for more independent studies (e.g., NIH studies) but not just a bunch of small, investigator or site-specific studies as Dr. Serruys is doing in the Netherlands and Dr. Antonio Colombo is doing in Italy, one participant said. An interventional cardiologist said, "Once a (drug-eluting stent) is approved, then the ability of the FDA to help keep watch on the device or expand indications is limited, so…it falls to NIH to do studies, where there is more confidence in the (the findings)."

Registries. The FDA is willing to consider the use of registries in certain situations, but some cardiologists emphasized their limitations. An official said he wasn't a proponent of registries (for a lot of reasons), but if they are going to be used he offered some recommendations, including use of propensity score analyses and sensitivity analyses.

Animal studies. Can and should be relied on more heavily for safety data, but they need to be longer – at least 90 days. A researcher said, "Had we done that with actinomycin-D and some of the Taxol stents, we might not be sitting here with some of these (failed) trials."

Greater CDER involvement in stent approvals. CDER, the drug side of the FDA is getting more and more involved in approval of drug-eluting stents, and, as a result, it appears that the approval process may get more difficult, not easier. The moderator said, "The device industry is now two-thirds as large as the drug industry in terms of dollars so crying poor may not hold up any more."

Stent design. There is a growing consensus that stent design does affect performance of a drug-eluting stent. A speaker said, "Everyone thought stent design doesn't make a difference if the drug works. But why is overlapping stents in SIRIUS bad for neointima? Everyone can speculate why that is happening, but I don't know…(and) In torturous vessels, the stent design possibly makes a difference – and that was not looked at much in trials."

More independent safety monitoring boards. FDA official expressed confidence in DSMBs, but some doctors complained that safety monitoring in the U.S. is not as good – or as independent -- as it should be. The moderator said, "I don't think there is any reason the industry, because it is young or for any other reason, should be allowed to do human experimentation without safety oversight." A researcher said, "I've done more than one trial where the DSMB had no opportunity for input. I've decided to being on those boards."

Dosing. In light of the DELIVER findings, dosing may need to be viewed differently. An expert suggested setting a uniform standard dose, "If you look at ASPECT, DELIVER, ELUTES and normalize the dose to the surface area, the total dose in terms of the volume of that stent may be five-fold or more, simply because of critical differences in stent surface areas. That doesn't seem to me to be most logical approach to drug dosing. We need to think perhaps more in terms of the tissue volume potentially exposed (to the drug) or the stent volume, and then define the maximum drug dose based on the volume of the expanded stent." (NOTE: The FDA took notes on this.)

Among the insights into FDA thinking that came out at the meeting were:

Regulatory approvals may take longer. Dr. Bram Zuckerman, head of Cardiovascular Devices at the FDA's CDRH, compared drug-eluting stent approvals to brachytherapy approvals, noting that industry was told nine-month data was sufficient for brachytherapy approvals, and then the FDA decided longer data was needed but accepted OUS data.

IVUS needs to be reviewed at a core lab.

Post-marketing surveillance will increase. At CRT, FDA officials repeatedly referred to an editorial in the New England Journal of Medicine recently by new FDA Commissioner Mark McClellan on post-market surveillance, particularly: (1) complying with existing law, and (2) improving things in the near future.

Off-label use should be done more responsibly. FDA officials continue to be disturbed by off-label use. An official urged interventional cardiologists to deal with drug-eluting stents "in a professionally responsible way…which means actually looking at the label."

Trials may need to be larger. An official pointed out that there have been a series of results that haven't panned out in larger trials, "Even though a trial is randomized, it doesn't mean the randomization works in a small population, and errors can occur in QCA."

First-in-Man trials are – and will remain -- a requirement.

Data from outside the U.S. (OUS data) can speed up an FDA approval. Cardiologists and FDA officials have some trouble with use of OUS clinical trial data obtained prior to sufficient animal data, but the FDA officials indicated that the regulations allow it. One said, "We may not personally agree…but that's the way it is."

Drug-eluting stents that don't qualify for expedited review may still see a speedy approval process. An FDA official said, "We expect to do them quickly because they are an advance that the clinical community wants. The timeline is not so much dependent on whether it is official expedited but the quality of the submission and the responsiveness of the sponsor."

Multiple endpoints may be required for future drug-eluting stent trials. As with drug trials, the FDA would like to see future device trials (at least stent trials) with multiple (two or, preferably, three) endpoints.

The data the FDA has been getting does not appear to be as good as the agency would like, and this was a point brought home several times during the CRT meeting. Dr. Jonette Foy of CDRH pointed to several areas where submissions have been falling short, including:

Failure to complete the matrix (chart).

Manufacturing issues. She said, "When reviewing IDEs, we try to take into account the manufacturing issues earlier rather than later (at the PMA stage) because we found modifications to manufacturing can have a huge impact on the product…One of the things that will be a requirement if you get expedited review will be to have the facilities ready for inspection when the PMA comes in…(and) Something we are doing for drug-eluting stents that we have not done in the past is setting up pre-PMA meetings to fine tune issues we will be looking for."

Bench evaluation issues such as inadequate:

- Inadequate stent platform testing.
- Analysis of surface variations.
- Coating integrity and durability information, including particulate analysis, drug content and chemical stability of the drug component. Dr. Foy said, "Spray coatings are notorious for causing pinholes…A lot of these products are not simply coatings; they are like functional grade composites and if you have a layer structure, the base needs appropriate adhesion."

Incomplete in vitro PK data. She said, "We are seeing very incomplete PK data coming in. This is a big problem. And we really need this information at the IDE stage, not just the PMA stage."

CMC (Chemistry, Manufacturing and Control) issues inadequately addressed, such as:

- Impact of sterilization.
- Toxicity of leachants/residual solvents.
- Stability/shelf life. She said, "We are in a new paradigm on shelf-life. When using an approved drug, we can fall back on the NDA information, but we don't have that with an NME."

Inadequate reports to assess safety, such as:

- Lacks evaluation of clinically intended doses and or overdose at appropriate times.
- Lacks evaluation of serial sections of myocardium.
- Lacks description of arterial histopathology.
- Lacks necropsy reports (especially important for unexpected deaths).

Dr. Foy also outlined some clinical evaluation issues that have come up:

- **Quality, duration and or application of feasibility**, especially if OUS data is being used. She said, "Quality means what kind of follow-up. Thirty-day MACE won't buy you a lot to get an IDE up and running, but four- to six-month angiography with an IVUS subset gets you further."
- **Omission of dose-ranging studies.** She said, "We want to see some basic science that may keep patients from being subjected to ineffective products – like dose ranging studies, testing different doses to see which is the most effective – and we are open to altered trial designs."
- **Failure to give full consideration to the pharmacologic aspect of the product.**
- **Failure to provide complete and comprehensive clinical data.** She said, "This is not just related to drug-eluting stents, but to all applications we get."

An NME on an unapproved stent is the toughest hurdle, FDA officials said. Dr. Foy said, "If the company has no aspirations to market the drug separately, then an IDE and a PMA is the route, but if there is no information on the drug, you will need to do single/multiple dosing studies in the U.S., and that would require an IND. We are struggling with that issue, but a lot of these drugs, as drugs, don't fall under the CardioRenal Division. If single and IV dosing is done OUS, then a PMA is the route."

In December 2002, a new Office of Combination Products was created. It is in the office of the Commissioner of the FDA, above both CDER and CDRH, and is headed by Dr. Mark Kramer. A CDRH official said, "Dr. Kramer has been very involved in our working groups. The point of this office

is to be an umbrella to provide oversight and potentially an outlet if there are issues that need to be raised…It is more policy and overview…They don't have a staff right now; they are waiting for user fees to come in."

PERIPHERAL DRUG-ELUTING STENTS

Dr. Andrew Farb of the Armed Forces Institute of Pathology offered several reasons why pre-clinical testing for SFA is different from coronary stent studies. He explained that there are several differences between peripheral arteries and coronary arteries, including:

- Different flow rates in specific arterial bed
- Effects of limb movement and strut fracture
- SFA is elastic artery and coronary is muscular artery

Some of the problems Dr. Farb and others said they don't expect to be an issue with peripheral drug-eluting stents include: stent thrombosis and edge effects. Strut fracture also may not be clinically significant if it occurs after the stent has been incorporated into the vessel.

There was some discussion about how investigators and sites should be chosen. Doctors expressed concern that corporate marketing departments were too involved in selecting investigators. Dr. Califf commented, "It is not the FDA's job to do site selection. That is a professional issue."

One interesting suggestion was for cardiologists to form a peripheral vascular disease consortium to run clinical trials, much as oncologists have done with SWOG and ECOG to test chemotherapy drugs. Dr. Califf said, "To do oncology clinical trials you have to be certified that you have a fundamental understanding of what randomization is. A lot of doctors think randomization means arbitrary. I hear that all the time among people who haven't done clinical trials….And there are a set of standards that everyone understands that the investigator is not working for a company; even if he is paid by the company, his primary responsibility is to the patient…And if you did trials through this network…you might answer a lot of questions quickly at a reasonable cost."

Dr. Neal Fearnot, President of Cook, provided the industry view. He cited several key issues, including:

Issue 1: How to apply drug regulations to drug-eluting stents. Which device and which drug regulations apply? "I think an additional effort is required by the scientific and regulatory community to sort out the pharmaceutical requirements vs. drug-eluting stents. We have been challenged with inspectors coming in saying, 'You didn't follow drug regulations, and you have drugs in your facility,' even though you are a device manufacturer. Drug and device regulations don't always agree with each other, in fact sometimes they compete with each other." He cited differences in shelf-life testing for drugs and devices and urged the FDA to appropriately distinguish drug-eluting stents from pharmaceuticals in the regulatory process.

Issue 2: Lack of clear guidance for bench or animal testing of drug-eluting stents. He said progress is being made on this but that questions remain as to the appropriate animal model, the meaning of histological findings, preclinical testing endpoints and the linkage between animal and human responses. He complained that testing may take longer than a product's life cycle, and he urged the FDA to provide guidance for drug-eluting stents in general and for peripheral drug-eluting stents in particular.

FDA officials agreed there is a need for guidance documents but said they currently don't have the time to create them. A CDER official said, "Right now, our priority is on the documents on our desk. I hope eventually to have the additional resources to work on guidance documents, but at this point we can't spend the time we would like to."

Issue 3: Lack of global harmonization of regulatory requirements that creates redundant and wasteful efforts. He called for:

- *Internationally-recognized standards*, saying: "We are a long way from having any harmonization among countries where what is important to one government is the same as what's important to another government."
- *Consistent categorization*, noting: "Some countries right now request information as if a drug-eluting stent is a drug and have classified it as a drug, not a device, and others have it under device regulations."
- *Streamlined and consistent regulations.*

Issue 4: Short lifecycle products (~18 months) with long term questions that yield obsolete information. He called for accelerated analytical methods to assess long term performance, such as latent drug and polymer effects, and a better understanding and use of surrogate endpoints. He said, "What is the appropriate test to assure that the five and 10 year effects of a drug and a polymer are acceptable? We don't have an answer for that because of the liability that faces industry long-term."

The FDA and some researchers called for patience on the part of industry. A researcher said, "We need to approach this disruptive technology with more patience. We now have products with a half life more like a drug…We won't have a new drug-eluting stent from every manufacturer every six months…These will be three- to five-year life cycles, so some of the burdens we face will be a very different world…We all have to learn to live with these devices longer than before." Dr. Fearnot responded that three- to five-year lifecycles have stifled innovation in other product lines, "As the incentive for coming up with the next generation improvement or even re-looking at potential improvements or evolution, as incentives for that go away, you have less innovation and that extends the life cycle, making the first shot at a product the only shot. I'm not sure first generation products are worthy necessarily of being there three to five years." Dr. Ron Waksman, of Washington Hospital Center, said, "Three weeks ago I would

have said a one-year trial was enough, but now I've seen data showing a benefit at nine-months, but at 18 months it was neutral. That was a smalls study, but it raises questions." A researcher added, "There is no way to cut corners."

Issue 5: Lack of consensus on the clinical and preclinical endpoints for safety, efficacy and reimbursement complicating clinical trial design. He said, "Reimbursement is a haunting issue in the U.S. and worldwide and may undermine the desires of industry to treat many of these diseases as we find the challenges before us on reimbursement for evolving technology becomes more and more difficult." He called for consensus guidance on acceptable clinical endpoints for approval and for reimbursement and a better understanding of measurement methods. Dr. Califf reiterated the concerns he expressed during the first day of the FDA Town Hall meeting about human experimentation: I'm very worried that humans are being exposed to experimentation, and I don't know how to balance that against device innovation…I think linking reimbursement to proof of benefit has to be part of the plan. There is no way to afford all this expensive (healthcare) technology, and balancing that with innovation is difficult…My conclusion is there is no substitute for clinical outcomes. Surrogates simply don't work. It is valiant to keep trying and to use them for screening, and maybe there are things in animals that could tell you when to stop." An industry consultant said, "I think it is responsible to go to surrogate endpoints, but I think it is too early now." Cook's Dr. Fearnot agreed, "It's too early."

Conducting clinical trials of peripheral drug-eluting stents is more difficult than trials of coronary drug-eluting stents, several speakers pointed out. Dr. James Zidar, an interventional cardiologist at Duke University, commented, "The peripheral field is more fragmented than the coronary field, with interventional radiologists, vascular surgeons and cardiologists all doing it (peripheral stenting)…There has been a push for clinical trials, but it is a more fragmented market so there is a bigger challenge for enrollment and a lot of pushback from surgeons who like the status quo."

The FDA's Dr. Zuckerman indicated endpoints could be different in peripheral drug-eluting stent trials. He said, "We traditionally utilize TVF at 9 months…but with SFA we would not require angiographic follow-up on all patients – (just) an IVUS or QCA subset." An investigator asked about using a crossover trial design, and Dr. Zuckerman said, "The problem with crossover trials in the past has been that the crossover needs to be independently reviewed by a CEC before it becomes a true crossover or it will be abused." Dr. Zidar estimated that provisional stenting would occur in 40% of focal lesions and close to 70% of longer lesions.

Dr. Zuckerman reiterated his recommendation that peripheral (SFA) clinical trials have three arms: (1) provisional stenting, (2) an uncoated stent, and (3) a drug-eluting stent. He said, "We think possibly that drug-eluting stents won't work and at least you could get an uncoated stent approved…There is a lot for industry to win at in a three-arm trial if the device is any good. I suspect with a lot of the first SFA stent trials, the drug-eluting stent will not be the winner, and this is a way to get an uncoated stent approved." Dr. Kenneth Rosenfield, an interventional cardiologist at Massachusetts General Hospital in Boston, said, "Conceptually that is a very good, well-thought out approach. I think that would fly and would get people to enroll. As long as there is an option for a provisional stent, not just a plain balloon, it might fly. I would enroll patients in such a trial….(and) whenever a crossover is done, that case could automatically be reviewed by CED, and if someone violated the spirit of the investigation, they would be reprimanded or dropped." Dr. Zidar suggested that sites or doctors who abuse the crossover option should get one free pass: "One is a technical foul; two, you are out of the game."