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by Lynne Peterson

SUMMARY

This one-day conference on ICD lead failure issues heard from academia, regulators (FDA), and industry. ♦ There was a call from some – but not all clinicians – for additional premarket clinical testing of ICDs, but industry, expectedly, and the FDA, perhaps unexpectedly, did not appear to be supporting the idea. Rather, the emphasis was on boosting post-market surveillance efforts. ♦ Proposals for a tougher stance on the approval process for new leads and for large premarket clinical trials didn't have any real support. ♦ The key point of agreement appeared to be that ICD lead failures need standard definitions in the manner of the ARC definitions of definite/probable/possible stent thrombosis for drug-eluting stents, and it is likely there will be collaborations/meetings to come up with standard definitions of failure. ♦ Overall, the meeting did not appear likely to change much of anything relating to ICD leads or lead manufacturers.

Trends-in-Medicine
Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

ICD Lead Performance Conference

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In the wake of the recall in October 2007 of Medtronic's Sprint Fidelis ICD lead, academicians, manufacturers, regulators, the Heart Rhythm Society, and prominent electrophysiologists met for a full day in Boston to discuss the problem of lead failures. The meeting was reminiscent of the conference held in September 2005 to discuss ICD pulse generator recall issues. The only significant party missing from the lead conference was managed care; there were no managed care speakers and no managed care officials in the audience.

The conference was on ICD leads, but participants agreed that it also should include pacemaker leads. Dr. Bruce Lindsay, president of the Heart Rhythm Society (HRS) and an electrophysiologist at Washington University School of Medicine, said, "This is called an 'ICD lead' conference. Should this have been a 'lead' conference? Those pacemaker leads are a smaller incidence, but it is a huge population."

Dr. William Maisel – co-chair of the conference and director of the Medical Device Safety Institute at Beth Israel Deaconess Medical Center in Boston – pointed out, "Striking a balance between getting devices to market and getting them there safely is key…For a person with a 70 bpm heart rate, that's 100,000 beats/day, 37 million beats/year, and 500 million beats over 13 years. We have perhaps unrealistic expectations for these devices (ICDs and leads)…You are more likely to be affected by an advisory (on safety) than to have your life saved."

ICD Statistics

Issue	Incidence per 100,000 ICDs implanted
Deaths due to ICD malfunction	6
ICD malfunctions	2,000
Lives saved by ICD	7,000
Advisories about ICD malfunctions	16,000

Dr. Maisel differentiated the device approval process from the FDA drug-approval process, "For drugs, the approval process is pretty much a cookie cutter from the FDA standpoint…If it takes an extra 6 months or a year to get a drug to market, it is not a big deal because it is likely to be on the market for many years…On the other hand, ICDs have changed tremendously through the years. There have been a number of advances that have benefited patients, including transvenous leads, true bipolar sensing, quadripolar, thinner leads, and steroid-eluting leads."

However, Dr. Maisel warned, "We need to do better. Surprisingly, we don't know as much as we should about defibrillator leads: How long they perform and how long they survive. A mix of products and manufacturers showed <90% five-year (lead) survival. The message is clear that there are a number of patients who are affected by defibrillator lead problems – whether they are called failures or performance issues. We need to do better."

One problem in tracking ICD lead problems is that, unlike malfunctioning generators which are usually returned to the manufacturer, leads are rarely returned, making it harder to get a handle on malfunction rates. He suggested that it is time to step back and think about how premarket lead evaluations are done. He urged:

1. Greater transparency in post-market surveillance, analysis, and reporting. Dr. Maisel said, "We have made strides in this area."
2. The establishment of a new system to identify malfunctioning devices more quickly.
3. Standardization of communication to physicians and patients from manufacturers.

The conference reviewed – sometimes rather repetitively – mechanistic, premarket, and post-market issues. Dr. Maisel summarized the findings:

On **mechanisms**, he said the meeting found:

- Lead failures are multifactorial and include design, physician, and patient factors.
- Malfunction mechanisms are well defined and understood.
- Standardized definitions are needed, and with the help of HRS, these may be able to be established relatively quickly.

Premarket findings were:

- Testing should include bench, animal, and human trials for new or unique platforms.
- Incremental lead change may not require extensive premarket testing, but "minor" changes should have a sound science and engineering rationale.
- Studies are needed to relate bench testing to clinical performance.
- New leads should be introduced to widespread use only with adequate reporting data. We have good, reliable leads, so new leads need to be reliable and with evidence to support it.

Post-market conclusions included:

- Post-market monitoring needs to be strengthened.
- Common definitions for post-marketing studies are needed.
- Barriers include HIPAA, underreporting, and cost.
- A number of mechanisms might be useful, such as NCDR, FDA's HeartNet, independent registries, Condition of Approval (COA) studies (prospective or remote monitoring) – and expected incidence needs to be determined.

On **clinical management and communication of ICD lead issues:**

- Improve the ability of manufacturers to provide resources for patients without considering it an "inducement."
- Develop a mechanism to support patients' financial needs, so patients don't fall through the cracks or have their devices turned off.
- Direct patient communication has been successfully implemented since the HRS Task Force document (on ICDs).
- Individualize risk:benefit decisions for recalls.
- Educate patients on expectations for device performance.

There were also a few extremely interesting comments by different speakers, including:

- Are smaller leads inherently more problematic?
- Lead failures tend to occur in clusters.
- The current failures are, in large part, things that could be picked up with appropriate simulations and fatigue testing. Mathematical models and simulation systems may be the next intermediate step beyond bench testing.
- The status quo appeared to be preferred by many speakers, but one electrophysiologist insisted new standards, not business as usual, are needed.
- Lead failures cannot be blamed entirely on operator error.
- A Canadian doctor accused the FDA and industry of "passing the carrot and stick back and forth" during the conference discussions.
- Pulse generators may be able to be re-designed to monitor lead performance.
- If HIPAA is impeding lead data collection, legislation should be introduced in Congress to lift that barrier.
- Medtronic has seen "a relatively small" number of Fidelis lead replacements so far.
- It may take a long time to restore cardiology, primary care, and patient trust in ICDs.

FDA officials indicated several areas that will get scrutiny or policy changes going forward:

- Development of reliable pediatric device products will be underlined over the next few years.
- The FDA views current bench and animal testing as limited in its predictive value.
- The FDA is looking to generate a lead test standard, though that will take time to accomplish.

- The Agency intends to work with standards groups to develop bench testing standards. And FDA officials believe "the biggest bang for the buck" will come from boosting both bench testing and post-market surveillance – not demanding more and larger premarket studies.
- A PMA – rather than a 510(k) application – is likely to be required for a fairly large lead modification – new fixation methods, a new drug component, a new patient population, or a new anatomical location for the lead.
- Most of what the FDA has been seeing in leads are small changes designed to improve reliability.
- In the short term, the FDA may be comfortable with new proposals for additional/larger post-marketing studies, but more attention has to be paid to the design of those studies.
- The FDA doesn't have the ability to respond as quickly as it would like to a lead failure.
- If manufacturers would come to the FDA earlier with lead problems, recalls might be able to be handled in a better way.
- The agency is interested in quickly finding ways to improve its risk:benefit decisions.
- Industry "should expect that requirements will change in the near future."
- Not every new lead will require a COA study, but the burden is shifting to the manufacturer to explain why a COA shouldn't be required.

FDA overview

Dr. Daniel Schultz, director of the FDA's Center for Devices and Radiological Health (CDRH), told attendees, "Medical device regulation must be aligned with the future of the medical device technology. We can't simply do what we've done in the past." He said that it is critical to have a strong post-marketing system that "lets us gather information quickly and feed it back into the next generation devices." He added, "There has been talk about the drug pipeline not being quite as fast and robust as we would like…From where we sit, that does not seem to be the case in devices. Companies seem to have no problem coming up with new things every single day, and, in fact, the pace of this seems to be accelerating almost on a daily basis."

FDA Device Applications

Application	2000	2003	2007
Original PMA	67	54	39
PMA supplements	546	666	581
Original IDEs	311	242	225
IDE supplements	4,388	4,415	4,376
510(k)	4,202	4,247	3,680

However, if you look at FDA applications over the past 7 years, there does not appear to be an increase; it is more flat to down.

Dr. Schultz noted that ICDs have been getting smaller, and so have leads for ICDs and pacemakers, "We need to understand what it means to have a smaller lead. How will that impact the different parts of the performance of that lead? That is what we are here to discuss."

CDRH faces a myriad of problems besides ICD lead malfunctions, Dr. Schultz pointed out, including how to deal with personalized medicine and a plethora of emerging technology trends, such as computer-related technology, molecular medicine, robotics, minimally invasive technologies, micro-electro-mechanical systems (MEMS), nanotechnology, organ replacements and assists, wireless systems, decentralized healthcare, and combination products. Dr. Schultz said that, in response, the FDA is working to ensure that its workforce mirrors this kind of technology by:

- Adding specific expertise with programs such as CDRH's medical device fellowship program.
- Boosting the FDA's research. He said, "We used to do a lot on mechanisms and other problems related to medical devices, and now we are moving more toward software and nanotechnology, etc., and we need to continue to do that."
- Issuing more guidance documents.
- Implementing strong quality systems regulations. He said, "We need to get to manufacturing facilities and make sure they are doing what they are supposed to do… but we need to do it differently. The idea that we will get to every site every so many years simply can't happen. We need to find ways to prioritize our field resources and focus them on areas where we've had or expect problems."
- Moving to an electronic reporting system for post-market surveillance.
- Creating the Matrix organization that coordinates across different parts of CDRH.
- Developing better metrics and methods for tracking post-marketing issues. He said, "We want devices to be 100% effective and 100% safe. We will probably never get there, but we want to move in that direction."

Things that still need to be done at CDRH include:

- A unique device identifier (UDI) system for medical devices.
- MedSun programs.
- Electronic MDR (medical device reporting).
- Updating the MAUDE system.
- Center/ORA/OCC interactions.
- Improved risk communication.

CDRH's HeartNet program is a targeted network designed to be an early warning system. It focuses on identifying, understanding, and solving problems with medical devices used in electrophysiology (EP) laboratories. Dr. Schultz said, "This is a two-way street. We will set up the system, but we need people to provide us with information. We need information from the user community on the devices of interest – ICDs, automatic external defibrillators (AEDs), pacemaker and ICD leads, low energy manual defibrillators, implantable pulse generators, EP basket catheters, RF (radiofrequency) ablation therapy devices, and ablation catheters and generators."

Dr. Schultz said that enhancing the understanding of pacemaker and ICD lead performance will require:

- Developing electronic monitoring systems for device surveillance. "This is something we've started to see used. It is an area that offers a lot of promise, specifically for these types of products where it may not be reasonable to use return product analysis."
- Acquiring data on specific products and product types through the HeartNet network.
- Pooling data from individual retrospective studies. "A lot of you do studies within your own institutions. We see these published as individual articles from individual sites. It would really be helpful if we could pool that data and analyze it."
- Developing data systems to prospectively monitor the complication rates for new leads.
- Standardizing adverse event terminology.
- Developing new bench and animal models.

Why is it such a problem for the FDA to identify a problem? Often the first inkling comes from outside the agency.

Dr. Schultz answered, "Part of the issue is the amount of data that comes into the Agency, how that data come to us, and the way in which we have traditionally looked at that data. There are a number of different parts of that question. Do we have a responsibility and role in problem identification? Yes. Do we have a role in analysis? Yes. Do we have a role in response? Yes. In terms of being able to identify problems, the MDR system that we traditionally use has challenges. As we see all these reports coming in, of variable quality, trying to make sense of that has been a challenge. That is why we are moving away from just relying on positive reports, to taking a more active and proactive approach to go out and work with users to see what is going on. But I make no apologies that we do rely on other signals coming from people like yourself and saying, 'Here, we see a problem.' And we keep up with the literature, and I think that is as critical and important a part of our signal detection system as anything we are doing internally."

What seems like a significant delay sometimes is the FDA putting their stamp on a recall or a product performance issue. What are the challenges the Agency faces, and is there any hope for shortening that time interval?

Dr. Schultz: "Yes, there is hope…However, this is the balance between responding the right way and getting the answer right and doing it quickly. Part of our due diligence in terms of handling a recall is going out…and making sure we can verify the data and make sure we understand…that all the information that we have is correct, and that we have done an appropriate analysis. Does it need to take as long as it sometimes has? Probably not. But we don't want to do a knee jerk. There needs to be a balance."

Where does the FDA's Sentinel network – a proposed system linking private- and public-sector post-marketing safety-monitoring systems to create a virtual integrated, interoperable nationwide medical product safety network – fit in?

Dr. Schultz: "The Sentinel network (needs) EMRs, unique identifiers, and methods to bring that information into the Agency...and (there are some legal and HIPAA issues. Ultimately, the idea of a Sentinel network that would instantaneously provide us with all the information out there on all the patients being treated with various medical devices is a very attractive prospect. Is it going to happen tomorrow? I don't think so. Should we be moving in that direction? Yes …There are a lot of steps we need to take between where we are today and where we want to be tomorrow."

Mechanisms of ICD Lead Failure and Definitions of Performance

Dr. Maisel said the consensus was that definitions need to be developed, perhaps under the guidance of HRS, with input from industry and the FDA, "This is the first step in reporting and measuring performance and deciding which devices are good. There are a lot of complex factors in this, but we need to do a better job on collecting that data."

Academic perspective

Dr. Bruce Wilkoff, director of Cardiac Pacing and Tachyarrhythmia Devices at the Cleveland Clinic, called for a consensus on definitions. The current definition of a documented lead failure, according to a North American Society of Pacing and Electrophysiology (now the Heart Rhythm Society) document prepared in 1990, is: A failure in pacing and/or sensing, documented at surgery to be consistent with conductor or insulation failure. He said, "Leads were an afterthought in that document. The definitions we provided at that time fit well in a general sense, but they don't fit very well for leads themselves…Every single device lead problem is multifactorial, and it is a combination of the lead, the way it was implanted, and the person it was implanted in. And I urge you to recognize that these things occur in clusters."

Industry perspective

Dr. Philip Tsung, senior director of Quality Assurance for St. Jude Medical, speaking on behalf of AdvaMed, the device industry trade association, said the information that industry gleans from lead failures helps to further improve the reliability of next generation leads, "The nature of failure analysis focuses on what goes wrong. It doesn't really do justice to what goes well."

Dr. Tsung said leads exist in relatively harsh environments and reminded attendees that there are unanticipated wear-out mechanisms such as insulation degradation, weld/crimp connections, and induced malfunctions. He noted that not all lead malfunctions have clinical manifestations (e.g., without compromised therapy), and many malfunctions share similar clinical manifestations. However, he cited two main mechanisms and causes for lead failure:

1. Insulation disruption (pocket abrasion and subclavian crush).
2. Conductive fracture (subclavian crush and fatigue/cycle stress).

Regulatory perspective

Mark Fellman, a scientific reviewer in the FDA's Pacing, Defibrillator and Leads Branch, CDRH, noted that the FDA adverse event reporting system is not a real-time system. It includes MDR reports, product performance reports, MedSun/HeartNet, sponsor registries, and institutional registries. He said, "Agreement on common terminology/ groups and modification of reporting vehicles to utilize this information would help characterize performance and improve future designs and reliability. It would also help the FDA do its job."

Fellman pointed out that there are "definitions of performance" problems, including:

- Vague terminology
- Groupings too general
- Missing key information
- Other problems – lack of narrative of clinical presentation/data used to diagnose a problem, and no descriptions of root cause, location, etc.

Mechanisms and Types of ICD Lead Failures

Mechanisms	Types of failures
Lead design: Mechanical weaknesses and biomechanical issues	**Mechanical breakage:** Insulation or conductor failure
Patient issues: Anatomy/disease and activity	**Degradation/loss of therapy:** Dislodgement
Surgical issues: Implant route and method/skill	**Undesirable effects:** Muscle stimulation or perforation
	Suspected failures: High/low impedance or high thresholds

Possible paths for improvement include:

- Unifying definitions, terminology, groupings of device, and clinical data documenting of suspected and verified failures.
- Incorporating unified coding into surveillance vehicles.
- Making reporting easier and strongly promoting reporting and product return.

Panel discussion

Have the mechanisms of lead failure changed over time?

- *Dr. Robert Hauser, a senior cardiologist at Minneapolis Heart Institute and co-chair of the conference:* "I feel the same failure modes are still in play. I would like to underscore a critical observation by Dr. Wilkoff: That lead failure can be in three categories – 1) implanting physician technique and the experience of the implanter, 2) the lead design and material, and 3) patient factors. All of these three main categories impact lead performance. I don't think that has changed over the years."

- *Mitchell Shein, an expert reviewer in the FDA's Pacing, Defibrillator and Leads Branch, CDRH:* "You have mechanical design – wires running through an insulated tube. We haven't seen huge advances in the leads. The fundamental wires running through don't have a lot of change…so I wouldn't expect a huge change in the nature of the failures."

- *Dr. Wilkoff:* "What changes is the matching up. You take the same design and materials, make it smaller, and change the technique…The problem is what we are doing is new combinations of materials, designs, size, and implant techniques, and what was not a problem with 9F may be a problem with a 7F lead. What was not a problem with silicone becomes a problem with polyurethane. What was not a problem with subclavian implantation becomes a problem with (a different approach). That is the problem…Then you have what I call cluster analysis…You have the same design, and for some reason a person finds the Achilles heel of a lead. They didn't do it on purpose. They are trying to improve things, and they find a problem."

What is being done to develop new animal and bench models?

- *Dr. Bram Zuckerman, director of the FDA's Division of Cardiovascular Devices in CDRH:* "With newer lead designs, boundary conditions are not well-characterized, and we can get into failure modes that bedevil us…I'd like to ask industry people if they are going to develop better computations and animal models as we go forward, so the industry can continue to evolve for this very challenging field."

- *Fellman, FDA:* "The failure mechanisms may evolve, and the testing we apply may not be exactly appropriate for newer models. We need to look at whether the testing we are doing is appropriate for newer designs."

What are the issues in establishing definitions and identifying lead problems?

Dr. Maisel made several points, including:

- "I think the real challenge will be in defining device performance. There are some novel challenges with some of the wireless technology. How do we tackle the device performance issues? How should we measure performance?"
- "This is somewhat akin to drug-eluting stents (DES), where they have suspected levels of stent thrombosis. A lead fracture is pretty straightforward. I think it is the suspected area that we struggle with. The 'suspected' failure is the issue. How precise should we be in defining performance and suspected performance?"
- "Does anyone have an issue where we call it definite, possible, probable? Is everyone in agreement with that concept?" No one objected.
- "However imperfect the definitions are, if they are used by everyone, it will allow comparisons and the identification of good and bad leads."

• *HRS's Dr. Lindsay:* "Just recently the NCDR ICD registry steering committee made the decision to expand the database to leads. This will allow us to track when leads are implanted, when they are replaced, and why. That will allow us to get a tripwire if issues are high with a specific lead. It won't give us a root-cause analysis, but it will allow us to identify leads that may be developing a problem earlier on than we have been able to do so far. We need to work on defining the definitions for the registry and design a registry so we can identify problems early. I can see an opportunity to do this that won't require a huge investment." Dr. Lindsay said that HRS will participate in creating robust definitions, "We certainly are interested in partnering with you to develop a manuscript (on definitions)."

• *Dr. Hauser:* "I think we need to be very specific. As long as we define failure, it makes things easier. In our registry, for a lead to have failed, we must have identified a problem in the lead – fracture, electrode dislocation, problem with extendable helix, etc. If we can't identify a specific cause, then it falls into a physiological failure category…So, I would argue we need to be very specific, and we also need to recognize there are some FUOs (fractures of unknown origin) that you simply are not able to categorize."

• *FDA's Dr. Zuckerman:* "It was not until we had some datasets to look at that the categorization of definite and possible was most useful (in stent thrombosis)…(We need) to come up with definitions, but are there people who would allow us to use datasets to see what sensitivity and specificity we can garner? Certainly the Agency would be very interested in participating in such an endeavor."

• *Dr. Wilkoff:* "I think we have a couple of issues: (1) initial identification of the problem and 2) how we manage it…We need two sets of definitions for two different purposes."

How does industry feel about definitions? Does it matter to you that much what the definitions are? If a group comes up with definitions, will industry use them? And what is industry's role?

• *Wolfgang Geistert PhD, vice president of Lead Development at Biotronik:* "A common language is good for all sides."

• *Industry official:* "There is an opportunity here to get something right – the definitions…But at the end of the day, there is a lot of uncertainty about what the mechanism is. Sometimes we can't tell if it is the lead, the patient, or another problem…If we do the wrong things with definitions, we may influence individuals to take actions that are not appropriate. We need to be extremely mindful of terminology. The definitions issue is even more important than the terminology issue…We need to be very thoughtful of the unintended consequences if we get the definitions wrong."

• *Dr. Lindsay:* "The NCDR ICD registry will be good for identifying high profile failures, but it won't get subclinical failures…It gives the big picture and acts as a tripwire...but industry has to be very involved with root-cause analysis, and I think they will."

What is the role of remote monitoring?

• *Dr. Charles Berul, a pediatric electrophysiologist at Children's Hospital in Boston:* "If you have daily monitoring with remote monitoring, you will pick up a variety of things that are at variance from daily performance but are difficult to classify."

• *Dr. Maisel:* "You will have tens of thousands of patients out there with remote monitoring. We need to figure out how to utilize that data."

• *Dr. Lindsay:* "That highlights the difference between a registry and a remote motioning system that is developed and monitored by a specific company, where they have specified impedance standards. There will always be a need for companies to have their own internal standards and methods of tracking."

• *Dr. Hauser:* "Remote monitoring will be useful too but we may also be creating a problem…by the fact that information will be generated that is not well-understood, and the action taken as a result of that information may not be in the patient's best interest…We need to work together to understand how to use these data and have a mechanism to rapidly communicate with our physicians."

How do we get a handle on the lead failure problem?

• *Dr. Hauser:* "One of the reasons this conference is needed is due to a general problem, the lack of information in this field, the lack of good research in this field. The failure, in many respects, on the part of medicine and the scientific community, in getting involved in understanding device performance. It reaches across a whole spectrum of issues, and one of them is underreporting. We have not, as a group, been willing to fire up the PC and submit MedWatch information…

If we asked our national society, I suspect very few have filled out a MedWatch form, and that is the heart of our problem. If HRS could do anything near term, it is to ask members to pay attention to MedWatch and submit their data."

- *Dr. Wilkoff:* "We tend to jump to conclusions as a community. We use a definition, and we extend it. The same thing with recalls, etc. I think the detection of a problem and the management of a problem are two entirely different things. Identify that there is an issue to deal with, and then, using that same definition…I really think that confirmed failures are important in order to help us identify where an issue is. Then, once we have confirmed failures, we need another set of definitions to manage that."

- *Dr. Maisel:* "I don't agree that they are different…ICD leads inevitably will have malfunctions over time, particularly if we are putting them in younger and younger patients... Identifying problems before they become a big problem will make advisory issues much more tolerable if we aren't waiting for the axe to fall."

What is the perception of current ICD lead performance? What is the likelihood a lead will be functional in 5 years? In 10 years?

- *Dr. Berul, pediatric EP:* "In our population we would be thrilled to have a 3% failure rate, which is what prompted the Fidelis recall, because the average rate in the pediatric population is ~15%. We combine a perfect storm of low volume implanters (pediatric EPs) with patient-specific factors of growth, playing sports, and living a long time…It is sort of the canary in the coal mine…The pediatric patients might be the ones to watch to see if they have early events."

- *Dr. Wilkoff:* "One of the interesting things with Fidelis is that it actually performs pretty well compared to historic data …I would say that up until this decade, expecting a percentage (1%) per year…is what you would expect. But then if you add in infection, which occurs at a fairly high rate, it is even higher than that. So, 5% at 5 years and 10% at 10 years is not unusual. Is that acceptable? Yes, if compared to a thoracotomy. I think we have over-estimated the performance of leads in general. There have been some good performers. And then part of the problem is also that we now have better diagnosis. We didn't used to be able to measure impedance…I think we have several problems."

- *FDA's Dr. Zuckerman:* "I think it goes back to what are the data…There are some questions being asked about ICD performance a year and a half ago. Could AdvaMed pool the industry data so we really get a better sense of what the current standards are now for adults? The Agency would also be very interested if there is a difference in pediatric device performance…Our continued interest in developing reliable pediatric device products will really be underlined over the next few years."

- *Dr. Geistert, Biotronik:* "I would say it is wrong to use one number for every lead…Trying to find a number as a threshold is not the right way."

- *Dr. Maisel:* "The idea of industry pooling data is a good idea...but the data we need are really not available. Mostly they have return product data, and we recognize that is greatly flawed in predicting rate of failure."

What is the regulatory view of raising the bar for lead performance? What about a lead that is not better than some leads already on the market but is better than others that have not been removed from the market?

The FDA's Dr. Zuckerman: "We are always interested in raising the bar, improving product performance, but I think… it really is important to understand the standards pre-approval – which is a reasonable assurance of safety and effectiveness. That has to be considered in the context of what changes, what we know about leads in this particular use."

Is there any way of improving imaging of leads *in vivo*?

- *Dr. Hauser:* "I was speaking to a lead engineer at one of the companies last week…and he said…we could very quickly fluoroscope the lead and do a high-speed cine along the body of the lead, perhaps in multiple views, to see if there are any abnormalities."

- *Warren Watson, vice president of Implantable Product Development for Medtronic:* "Many problems can't be detected unless there is patient movement…But we definitely need better imaging of patients and with movement."

What data are currently available relative to actual product analysis for leads that have been removed?

Dr. Tsung, St. Jude/AdvaMed: "We've seen figures of ~20% of explanted leads being returned. In high voltage leads it is higher than for low voltage leads. We've also looked at some data on known complaints – those that did result in MDRs – and for high voltage leads, that percentage is considerably higher, 50% or higher. Up to 60% - 70% of those are MDR known explants."

PREMARKET EVALUATION OF ICD LEADS

Academic perspective

The life expectancy of patients with an ICD today ranges from 5.88 to 11.75 years, and there is an increasing risk of lead failure as patients live longer with their ICD. Estimates of the risk of an ICD lead failure range from 1.2% - 7.3% at six years and from 6.9% - 10.4% at 10 years. Thus, more than one in every 10 ICD patients could have a lead failure in their lifetime – and that often leads to inappropriate shocks. It also has been estimated that the risk of ICD lead failure is 1,000 - 10,000 times greater than that of a generator failure.

The consequences of a lead failure include: inappropriate shocks, failure to pace, failure to deliver ICD therapy, and difficult extraction due to fibrosis. At the same time, leads have gotten more complex. Dr. Maisel said the goals of premarket testing are to identify the "good" and the "bad" leads before marketing, but "the reality is we fail to identify the 'bad' leads before device approval."

Industry perspective

Jon Brumbaugh, vice president of Regulatory Affairs and Compliance at Biotronik, said the goal of premarket evaluations is to confirm the safety, quality, reliability, and clinical performance of an ICD lead prior to market release. The premarket evaluations are complimentary, resulting in a comprehensive assessment of the product prior to market release. And there are continuous refinement of these elements. He pointed to limitations of both bench and animal testing:

- **Bench testing:** This may not anticipate all clinical variables and may not identify effects which only occur *in vivo*.
- **Animal studies:** For certain attributes, the animal experience is different than the human experience, and animal studies may not detect all long-term effects.

However, premarket clinical trials also have limitations, Brumbaugh pointed out, including:

- Device conditions do not accelerate failure modes.
- The trials may not detect long-term effects.
- The trials cannot account for all implant conditions.

Regulatory perspective

Megan Moynahan, chief of the FDA's Pacing, Defibrillator and Leads Branch, CDRH, said, "Most of the changes we see are related to reliability…Some – but not most – changes are driven by a desire to improve manufacturability, reduce cost, meet customer preference, and make leads more consistent… The need for bench and animal testing is usually not a question, but I believe it is currently limited in its predictive value…FDA intends to work with standards groups to:

- Develop 'best practices' for obtaining lead failure information *in situ*.
- Develop and encourage 'safe practices' for returned product analysis.
- Identify ways to make bench testing more predictive of clinical performance."

Moynahan added, "On post-marketing clinical trial requirements: We will probably continue to use COA studies as the primary means of collection of post-marketing data. Industry's routine use of registries suggests they believe in the value of post-market data collection. The FDA will be refining its practices for requiring post-market clinical data."

Panel discussion

Should a new ICD lead ever be approved for widespread use without a substantial human clinical trial?

- *Dr. Douglas Zipes, an electrophysiologist from Indiana University School of Medicine and a Medtronic consultant:* "No. Frankly, I think that rigorous clinical testing is essential. There are leads with good track records, and it is not like we don't have something today. I would not want to put a device in or replace a lead I know is good in a patient at risk for sudden cardiac arrest…It may depend on the lead and the amount of change in that lead that determines how many patients and for how long…I would want some kind of 'vigorous' clinical testing in that situation because I know I have leads with good track records, and it is not like I am inventing something brand new…I tell my patients a failure here is not like your joint swells up because the anti-arthritis drug didn't work. The failure here could be death."

- *Dr. Jeffrey Brinker, an electrophysiologist from Johns Hopkins University:* "I'll take the devil's advocate view. What size trial would be necessary to detect the low incidence problems that have developed? Generally, the problems occur years after approval and only after thousands of patients. (Telectronics') Accufix – which was recalled in 1994 – was in 45,000 patients before there was any knowledge of the problem."

- *Dr. Paul Wang, director of the Cardiac Electrophysiology and Arrhythmia Service at Stanford University Medical Center:* "I think this will be a moving target…Until there are robust registries, official registries, with the ability to detect these phenomenon…there will be a role for significant design changes to undergo significant study…It depends on what we are looking for, what types of changes…If we are looking at design issues that might lead to perforation, a modest-size trial might pick up those things."

- *Dr. Maisel:* "What we are talking about here is a surrogate endpoint…What we are lacking is the science and the data… We can envision a time in the future where, when we gather bench and clinical data, we might not need big trials…I think we all agree we need additional data, but we differ on how much."

After a lead has been shown to have a defect, is it routine for the company to do repeat bench testing to see if they can detect whether or not that defect can be identified in that lead model?

Shantanu Reddy of Boston Scientific's Leads and Lead Delivery Systems: "As we monitor products in the field, we strive to understand the root cause and in some cases replicate …In one product, we realized our bench test was not sufficient to replicate the scenario…We spent a lot of time refining that bench test, and that will be used going forward for subsequent leads…So, that cycle of continuous refinement of bench testing just doesn't stop."

Are a company's findings communicated to all the other manufacturers or to the FDA?

- *FDA's Shein:* "We are looking to generate a lead test standard. That will take time to generate."

- *Moynahan, FDA:* "Every time we learn about failures, it helps us understand how the leads should have been designed."

How unique does a lead design need to be to warrant its own bench test?

- *Lonny Stormo, vice president of Therapy Delivery for Medtronic:* "We need to be careful that we don't set a base level of standards, and manufacturers don't go beyond that."

- *Dr. Wang:* "(Bench) standards have enormous value… There are mechanical design issues that really could have been picked up by bench testing…I think there is a large window of opportunity to create better systems that do that…What we are seeing (now), in large part, are things that could be picked up with appropriate simulations and fatigue testing."

- *Dr. Maisel:* "It is easy to say every new iteration needs a (clinical) trial…but the challenge is to say which changes don't require a human clinical trial."

- *Dr. Zipes:* "Clearly, the animal testing and bench testing are critical…but we do lots of animal studies, and at some point in each animal study, we say what is the ultimate test – that is in man…The ultimate is obviously in the human…and some sort of rigor has to be adapted for that kind of stage in the lead design…I agree that what we have is incredible technology… but we are looking to make it better…Are we smart enough to know that a small change really isn't meaningful?"

- *Fellman, FDA:* "Individual minor changes may not elevate (an application) to the level of a need for clinical data, but there can be a combination of small changes that makes us want more data."

FDA: Is anyone considering doing mathematical modeling, and would it be useful?

- *Dr. Wang:* "To have mathematical models and simulation systems really seems to be the next intermediary step beyond the current bench testing."

- *Reddy, Boston Scientific:* "The computer model is only as good as the input information, and all of that is only as good as the biomechanical studies, and that is only as good as the human data input…Computer modeling is currently a powerful tool, and it will continue to be powerful."

- *FDA's Moynahan:* "We already have a struggle between bench and clinical data…(What happens if) we add mathematical modeling in this…I think we get the biggest bang for the buck by making both bench testing and post-marketing surveillance more robust…If you look at what premarket clinical (data) give you, you won't get as much as from the combination of bench testing and post-market surveillance."

What studies have been published in peer-reviewed journals and are available to the FDA or industry that show definitively that non-human studies predict long-term lead performance?

No comments.

- *Dr. Hauser* then asked: "If we don't have this, how can we put so much emphasis on bench testing?"

- *Moynahan, FDA:* "(Industry does) have to explain to FDA why a certain bench test will (be) predictive…We have had IDEs that were stopped because they passed bench and animal testing, but in clinical trials they didn't pan out."

- *Chris Jenney, director of HV/LV Lead Development for St. Jude:* "We don't produce a lead we know has failures…(only those) that meet bench and animal criteria."

Is there a role for an independent association – perhaps MIT or the University of Minnesota – to assess bench testing and report it out?

No comments.

If a new ICD company wanted to get a lead approved tomorrow, what would it have to do to get its new ICD lead approved by the FDA?

- *Moynahan, FDA:* "We expect not only that you did bench testing, but we look at how you developed the bench testing …The same for animal testing…And you would have to do a clinical trial…For the first lead, we expect the full gamut of preclinical data and probably a post-marketing study…(A new PMA) is usually for a fairly large modification – a new fixation method, perhaps a new drug component, a new patient population, or if there is some new anatomical location for the lead."

- *Another FDA official added:* "Then, you can modify that lead, usually that's generational, evolutionary type of change."

What lessons are there from Medtronic's problems with the Sprint Fidelis lead?

- *Dr. Maisel:* "I think Fidelis is a perfect example of why premarket studies would not be that useful…You would have needed a (huge) trial to detect that problem."

What formal programs, if any, are in place to collect and evaluate leads that have been implanted in humans?

- *Stormo, Medtronic:* "We highly encourage always for the leads to come back…That is the best indication of the failure mechanisms. Post-marketing studies are great for trends, but getting leads back are the failure mechanisms that we can learn from and use to help improve our design and testing."

- *Dr. Zipes:* "We are here to do something different, and I am hearing a lot of support for the status quo...We have to set some sort of new standards instead of business as usual… What are we going to do differently?"

- *Dr. Maisel:* "We do need to do things differently…but there are some problems that can best be handled with post-market surveillance. There are other issues that can be determined premarket – like perforations. If we want to document long-term performance of a lead and have enough fidelity to determine a 1% - 2% incidence, that will be very costly and time consuming on the premarket side…I would rather see that on the post-market side and on the science of bench testing."

Do we all agree than human testing should be done on a new ICD lead model? That is, on a new model number which represents a change from any other model in that manufacturer's list of products – not just a new name but a legitimate new model?

There was no consensus on this.

- *Dr. Lindsay:* "I understand (the) concern…but we have to be careful we don't get what we ask for. If you reflect on where we were a decade ago, the FDA process was so slow, and we were clamoring to get lifesaving/morbidity-reducing technology through the FDA, and we felt there were impediments. Now, I think things are moving through better than they were. The challenge is identifying truly novel technology, so new technology needs to be done vs. smaller iterations where you don't need such a big scale trial. The discussion I hear among the panel is the difficulty in defining that difference."

- *Dr. Brinker:* "I think that goes to the point that a clinical trial is not sacrosanct…Unless it is powered enough and directed enough, it won't detect all the things you want it to detect."

If the incidence of an observation is projected to be low – in the 1% range – is it possible or advisable to identify a subgroup of patients who you hypothesize would be at higher risk for a certain abnormality – for example, might lead fractures occur more often in adults <50 who are more active?

- *Dr. Maisel:* "I think that is a good idea, but if I was industry I wouldn't do it. I wouldn't want my lead associated with a higher failure rate…The concern would be that information would be compared to a different failure rate in a different lead in a different population, and it might look worse than it is."

- *Reddy, Boston Scientific:* "I don't think we can…because often it is a confluence of factors that lead to a lead issue…To set up a study to distinguish between different products you would need control of all those factors…and you are dealing with a confluence of various factors."

- *Dr. Maisel:* "There are other clinical trials on the premarket side that could be done to alleviate some of the concern… There are non-inferiority designs. There are FDA objective performance criteria...You could set a failure rate bar."

- *Dr. Wang:* "You can identify those patients, I would argue."

- *Dr. Zipes:* "I can't accept that response. I think this is a very reasonable suggestion, and to then say we are not going to do that because my lead would look bad...The whole purpose is to find the weaknesses of a new lead. The FDA requires a new lead to be tested in patient populations with 4-10 times the dose of a drug to uncover just those things…So, why wouldn't you want to enrich your population by patients who are more susceptible to failure?...If Fidelis were used in a 120-year-old, would the fracture cycle be uncovered, and we wouldn't be where we are now?"

- *Stormo, Medtronic:* "If we knew the projected rate of failure, we wouldn't have released that lead. We never release a lead we expect to fail in 15%. That is just not the way it works."

- *Dr. Zipes:* "No one is questioning your (Medtronic's) credibility…If you found failure in animal or bench testing, you would change it…But once the lead has been through all of your rigorous testing – bench, computer, animals, whatever – then consider a population where the lead might be most likely to be at failure…and study that population to try to demonstrate it will fail, and then correct it."

- *Fellman, FDA:* "Now, you've added another leg – the patient population. How do we dial in what the physician is doing? And how do we design a trial that takes all of that into account?"

- *Dr. Zipes:* "You can't always do that...(With a drug), you do the best you can with all the testing before a drug is released, and I would think you would want to do the same thing with a lead."

We have good leads from all the manufacturers. If that is true, why are we in such a rush to approve new leads without very cautious step-by-step testing from preclinical all the way through to the clinical phase? Is it innovation? Something new for patient comfort or safety?

- *Dr. Maisel:* "I think it is striking the balance between getting new technologies and products to market vs. safety. There was a lot of interest in thinner leads when they came out. We can look back and say it is not a big deal now…There are times when they are forced to make changes to leads because a supplier changes…I think there are practical issues …I think we are saying we want more clinical data, especially in certain situations…I agree we have good leads, and there is no urgency to get new leads on the market…but there are major changes that will occur, for example, wireless."

- *Dr. Tsung, St. Jude:* "Some of our changes are intended to address the issues with a low incidence but are something we want to address in the future…Downsizing is good for some patients…Features are one thing, but safety and reliability are the main things we are interested in with most of our changes."

- *Brumbaugh, Biotronik:* "From a competitive standpoint there is pressure for our leads to be as small (as competitors' leads)…We are not rushing. We do more animal and bench testing today than ever in the past…We are always trying to rush the FDA…So, the urgency to get it out there is true, but we aren't short-cutting testing to get there."

- *Dr. Brinker:* "I don't think we should stifle innovation…Baby steps shouldn't be encumbered so much that it isn't worth it to the manufacturers…but large changes deserve the attention that is being directed at them…The biggest issue still is the early detection of a problem even in a large population."

- *Dr. Wilkoff:* "The Cleveland Clinic failure rate is 1%, and others have a failure rate of 5%-7%...The issue isn't so much the lead construction…The (leads) have Achilles heels, but we have to watch for the big problem, the implanter."

Dr. Wilcoff made a statement that the No. 1 variable in lead performance is the implanting physician. How do you account for that in premarket testing?

Dr. Andrew Krahn, University of Western Ontario, Canada: "We found four complaining centers (in Canada about the Fidelis lead)…Among the 75 failures in our Canadian database, in only one case was a single operator responsible for more than one failure, so it says there are other components besides the operator."

Why is there such a rush to get products to market?

- *Moynahan, FDA:* "It reflects industry pressure as well as market competition…but I think FDA is not driving the need for innovation…In fact, most of what we see are small changes designed to improve reliability. And from the bench testing, you can see they will achieve that…FDA doesn't play a role in driving innovation…We see small changes over the lifetime of a lead."

- *Reddy, Boston Scientific:* "I would hesitate to say there is a rush…The reality is if you dig deep into the product development cycle, minor changes are in development for many years…and a new platform for 7-8 years."

POST-MARKET MONITORING OF ICD LEAD PERFORMANCE

Academic perspective

Dr. Jeptha Curtis of Yale University School of Medicine provided an overview of the ongoing ACC-NCDR (National Cardiovascular Data Registry): Currently, >160,000 approved records are included – 23% single chamber devices, 39% dual chamber devices, and 37% biventricular ICDs – and this is 280,000 leads. NCDR has been the only CMS-approved data repository since April 2006, and it is mandatory for all CMS primary prevention implants, but discretionary for all other indications. He said 71% of hospitals report all implants, accounting for >80% of total implants.

Version 1 of NCDR does not include any lead information, but there is the capacity to capture device information, including make, model, and serial number as well as information in explants. He said, "Can we leverage this information? In the present ICD registry, we cannot. But we have the capacity to capture device information…Adding lead elements is a high priority for the ICD Registry steering committee, and Version 2 will contain lead information, but the exact format is still to be determined."

Dr. William Hauser pointed out that registries are not studies, "The utility of a registry is directly proportional to the new knowledge it generates." However, he recommended that independent registries be encouraged and supported. And it was his registry that first reported the Fidelis problem.

Industry perspective

Ms. Reggie Groves, vice president of Quality and Regulatory for Medtronic, explained that monitoring leads post-market is a little different from monitoring devices:

- It is a little more difficult to correlate between accelerated bench testing and survival rates *in vivo*.
- Performance impact for the environment is different. The can (pulse generator) is hermetically sealed.
- The rate of return is more limited for leads.
- Damage (to leads) can be caused by explantation.

Returned Product Analysis (RPA) complaints have the potential for underreporting and inaccurate reporting. She said, "It is a broad way to get information, but there isn't necessarily documentation."

All the major manufacturers have systems to capture some or all of the information in their devices via remote monitoring, but remote monitoring is designed primarily to provide patient information, not post-market surveillance. She explained Medtronic's experience with the Fidelis lead, "In that case we created an algorithm (for our remote monitoring system, CareLink) that we thought could identify a patient having a problem…We looked at >25,000 patients with a Fidelis lead. The benefits were the large sample size and reporting bias was limited. Patient record data were enormously helpful to see what happened before the fracture…but false positives were a risk."

Groves also cited several limitations to remote monitoring, including: "Non-lead performance causes may be included, false negatives are possible, it requires significant manual effort, and the survival curve may be system- or problem-specific…Expanding post-market monitoring methods to include either/both remote monitoring and prospective clinical studies will enhance understanding of lead survival rates…The manufacturers are in the best position to combine datasets and look at performance."

Lead Surveillance Sources

Issue	RPA	Complaints	Post-approval clinical studies	Other surveillance	Remote monitoring
Overview	U.S. DRS data joined with RPA reports	U.S. DRS data and RPA data joined with complaints	Leads enrolled in prospective clinical studies	MAUDE, registries, center-based reporting	Patient alerts and device data from remote monitoring systems
Event assumption	Confirmed events on returned U.S. DRS registered leads	Events reported and coded by complaint category	An event reported and adjudicated as a complication	Various	Assumed events are confirmed by independent data source
Sample size	Large	Very large	Small	Varies	Medium
Benefits	Failure mechanism understanding	Breadth of input	Truest numerator and denominator	Independence	Combination of sample size and accuracy
Limitations	Return rate	Numerator accuracy	Sample size varies	Denominator accuracy; not integrated	Lack of automation; accuracy

Regulatory perspective

Dr. Thomas Gross, director of the FDA's Division of Post-market Surveillance, CDRH, said the Agency has had ~8,000 lead adverse event reports from 2005 to the present, with an approximate doubling of reports every year. He said the strengths of the NCDR registry include: It is nationwide, reports come in from various sources, and it is relatively inexpensive and potentially useful for "unexpected" events. On the other hand, it also has weaknesses, such as incomplete and non-validated data, report "rates" that are not true incidence rates, and it is subject to reporting bias. He said this makes the data less useful for "expected" events where incidence is of prime concern, "We are swamped with passive surveillance data…So, we turn to data-mining as an aid to finding device-event associations. CDER (FDA's Center for Drug Evaluation and Research) has developed a system using Bayesian algorithms, which dampen the noise in the system...We've done some exploratory analysis, looking at coronary stents and thrombosis…We need manufacturers to help us connect the dots. They are aware earlier than we are in terms of trends in failures. It would be useful for manufacturers to share some of that trend information with the FDA on a routine basis."

The FDA also has HeartNet, a subnetwork of MedSun – an FDA-sponsored targeted surveillance network of 350 hospitals from across the country – that can help monitor ICD lead problems. Terrie Reed, a project manager, Patient Safety Staff, FDA, explained how HeartNet works, "The ideal is…for an EP lab experiencing a new and unusual event to report it to HeartNet. A HeartNet team reviews the report and assesses the potential safety signaling. If there is a potential signal, the HeartNet team sends out a reported event and requests feedback from the HeartNet participants. All HeartNet participants review the event and respond to FDA with their own reported events and/or anecdotal data. FDA staff determine further action to determine extent of safety issue."

Panel discussion

Is there anyone who thinks the current system is satisfactory and no changes need to be made?

No answers.

What needs to be done to make the current system better?

- *Dr. Wilkoff:* "I think we have a lot of the components we need. What is happening now is a huge improvement over the past. What we did two years ago (by holding a similar conference on ICD recalls) is positively impacting what we are doing now…We (still) have some barriers, and they have to do with confidentiality issues in terms of HIPAA...but we have some opportunities. The remote monitoring is an opportunity, but it doesn't have all the information. It doesn't have patient identifiers, surgical information, etc…We have ACC-NCDR, which has surgical information but no patient identifiers or follow-up information…and no clinical follow-up, the deep information that is in an EMR (electronic medical record)…I think we are in the perfect situation to leverage those motivations by pulling together things like remote monitoring and NCDR and hospital records. What is required is to overcome the hurdles of communication…And there will be clusters (of lead failures), and we need to find out why there are these 'outbreaks,' what made the lead vulnerable for that situation."

- *Reynold Russie, director of Quality Trend Management and Reporting for Boston Scientific:* "Within the industry, one of the first steps we took was to disseminate the data we already had…We have noticed an increase in return rates and phone call rates from the physician community…We, as an industry, have made a commitment to remote monitoring technology."

- *Dr. Lindsay:* "I think remote monitoring will be a key element…One of the things that concerns me is I think we need to ultimately link that to the NCDR registry, but each company has a different platform…And right now if we sit down and talk about how to link it to NCDR, conversation tends to focus on why it can't be done. I think we need to change to how to do it."

- *Dr. Maisel:* "Are you suggesting industry is now committed to doing post-marketing clinical studies on every new lead and if so, how quickly can they be started after approval, how large, and how long?...Medtronic has been on the leading edge of prospective studies on post-market monitoring, and the other companies are doing that as well. With Fidelis, there were not many patients enrolled and not very quickly – 100 patients at the 30 month period. Can you provide more details

on how many patients you think it might take to answer the questions we are concerned about?"

• *Groves*, *Medtronic:* "I'll speak for myself/Medtronic…We are already doing that. Every new lead goes into a post-marketing study…We are learning about the rate at which we enroll...but we are definitely committed and have been…The design of a system longevity study on lead performance was not originally designed for rapid identification of the emerging issues. It was designed for long-term performance and performance over time. It never had as criteria the speed with which we enrolled. It had criteria on the number of centers, with 1,000 leads for each model. There was a perfect storm with Fidelis…We are going back to look at the design (of the post-marketing study) to look at the speed with which we get to the 1,000 patients."

• *Kathy Chester*, *vice president of Quality Assurance and Regulatory Affairs for St. Jude:* "St. Jude has several post-marketing approval studies underway...And in September we started a new active-monitoring SCORE study for all CRMS studies. We are enrolling all patients at 40 sites over time for an indefinite period…As leads are approved, they will be added to this post-marketing study…SCORE is indefinite follow-up. It is hard to say how many of each model will be enrolled...but anyone implanted with a St. Jude device at any of those centers will be enrolled."

• *Brumbaugh, Biotronik:* "The question is how to incorporate home monitoring into that study…so we don't have the costs and expenses of following these patients in the office...That is what we are struggling with – determining what we can do remotely."

• *FDA's Dr. Zuckerman*: "I think we need to look at short-term solutions and longer term technological solutions. In the short term for the Agency to be comfortable with these newer post-marketing studies, I think there needs to be more appreciation of the actual details, and those would include:

- √ Can the industry as a whole agree to this common definitional database?
- √ Is the industry – similar to what they nicely did with the ICD situation – willing to potentially pool their data so we can establish realistic performance estimates (OPCs) for key parameters that we can follow over time?
- √ In a general sense, this willingness for the industry to do more post-marketing studies is kind of news to me today. I am very happy to hear it. But in terms of establishing the pre/post-market balance…for the Agency to be comfortable with the new registry protocols, we need to see them as soon as possible, so we can really impact what data are being collected."

• *Russie, Boston Scientific:* "We plan to start a study in 1Q08 …The challenge is length of time to get enough patients with enough months to have usable data…So, we are trying to augment that with data from our Latitude patient monitoring system."

How precise do we need to be in the definitions? What confidence intervals, and at what time point, should be used?

• *Dr. Curtis:* "It depends if it is really a tripwire or something greater. It has the capability, especially if we come to integration with home monitoring, that it could set the bar for all other devices. The problem is funding…I heard four different company reps talk about four different studies…For the greater good, is it potentially better putting them to augmenting NCDR?"

• *Dr. Maisel:* "We need a sense of what the ideal post-marketing study looks like? I haven't heard any numbers how fine we need to look, what confidence intervals, what number we need to see…If we study a certain number of patients, the narrower the confidence index gets, how confident do we need to be in that measure of performance – 0.2%, 2%, 5%?...The point of a definition is you have performance – definite, probable, suspect…I think we need an overall sense of how a lead is behaving."

• *Dr. Wilkoff:* "We had a hard time on pulse generators with this…I can't say what the tripwire is for saying it is a real problem…but the surveillance we need to have has to be very sensitive to pick up potential, suspected problems, and then you need an investigative team or rules for doing that…I don't know what the numbers are, but we have to understand there is no perfection. Every lead is going to fail…We can't say 1% or a period of time…We could not come up with a number for generators; I don't think we will come up with a number for this."

• *Russie, Boston Scientific:* "Even that question is complicated because not all lead failures are equal. Some can lead to patient death virtually immediately. Those are rare, thankfully. Others may lead to failure to deliver therapy when needed. Some are detectable at follow-up, and some aren't. In some cases, the lead may have to be abandoned, and in other cases perhaps some changes (need to be made) to the device program…It is difficult to define a general study that can detect all those problems to the sensitivity you want."

Do we have a system in place where this type of event (Fidelis) won't happen again?

• *Dr. Gross*, *FDA:* He said the adverse events reported to the FDA "in no way reflects true incidences," adding, "If we detected a signal on a model related to fracture, I would still have to go back to the company and say, 'What data do you have?'…And there are significant problems with RPA – but unless I can turn to something else that is closer to true incidence, I am sort of stuck with that…Even if I could generate a signal, I would have to go to some other data source to verify what I might be looking at…It could happen next week that we generate a signal, but I would be in the same position …That is why I keep emphasizing that we need additional infrastructure to address – and to have the ability to determine – unanticipated events. I think we are hamstrung in our ability to take quick action…With unexpected events, we can take

effective action, but for things that need incidence rates, we are all sort of stuck…I support HeartNet…the intent can be delivered quite quickly...if we get a dozen or so major hospitals and key clinicians there…to detect signals in real time that we can amplify in a network situation…Hospital A detects something peculiar, we share with the network, other institutions have had the same problem…that amplifies the signal in real time…These efforts can be implemented quite soon. They don't have to wait for major funding. We are ready to go. We just need senior champions who can advocate on behalf of their patients and in partnership with the FDA to detect these signals…Then, we can go back to the manufacturers to discuss the signal."

- *Dr. Hauser:* "I would think the medical community would respond if the FDA came and said, 'This is what we need, very specifically.'"

- *Kimber Richter, deputy director of medical affairs for the FDA's Office of Compliance:* "There is a role for the medical community, not only in notifying firms when they have a problem with a product…The earlier firms come to us with possible issues, the earlier we can help a recall perhaps roll out in a different way than the recent ones have gone."

- *Chester, St. Jude:* "It makes sense to come together as an industry. Through the standards committee, we will look for ways to standardize testing. We should also look to standardize some design issues…There are certain things about welding, etc., that we know we should and shouldn't do…we should harmonize."

- *Dr. Maisel:* "We've heard a lot about surveillance methods and how to improve monitoring – through HeartNet, Dr. Hauser's registry, etc. How do we decide where to invest? Dr. Hauser is the only one who has found problems that turned out to be real problems."

- *Dr. Lindsay:* "Do we have everything in place today? "This is a step forward…NCDR is a key step…and remote monitoring is key. But I think there will be a need for the professional societies like HRS and ACC (American College of Cardiology) to work with industry and the FDA to bring this all together…I don't think we have all the parts in place, but we have the potential."

- *Dr. Krahn, Canada:* "I can't help but sit here and listen and think the FDA and industry are passing the carrot and stick back and forth…I ask myself if this information exists that we want. Yes, we are collecting it at bedside all the time, but we are not generating the information and some kind of response that is standardized and dispersed properly…So, while I think it makes sense to externalize it, I also think it works if…it becomes a part of our clinical care…So, it becomes a standard thing to do."

- *Dr. Wilkoff:* "What happened this time (with Fidelis): We had a suspicion from the Hauser registry…We went to Medtronic…What gave Medtronic the courage to do what they did were data from CareLink…Of course, it then required some intensive work…So, I don't think there is one answer…I think it is the combination…This will happen again…There will be a next time…And if it is this order of magnitude, it will take a while to figure out…I think if we try to have it just HeartNet or just remote monitoring or just small studies, I don't think it will work…I think you need all those components…There is a sensitivity and specificity part of this problem…And the stakes are high because the morbidity of even talking about this creates real harm."

Last year HRS recommended certain changes to the MAUDE database, especially a special form created for CRM products, so defibrillators would be tailored to be more specific and have definite data fields. Is that being considered?

Reed, FDA: "It is part of future directions."

Underreporting and post-mortem interrogation of devices and retrieval of explanted leads, how big a problem are these, and what can we do to deal with that problem?

- *Brumbaugh, Biotronik:* "The number of leads we receive back is <20% of the complaints we get…It is miniscule even compared to the number of pulse generators we get back."

- *Dr. Krahn:* "Why don't you (industry) lease it (the lead) to patients? So they don't get a new one unless they return it?"

- *Dr. Wilkoff:* "I try not to damage the lead during explantation…but we do explantation analysis the same way as when we started…Or maybe we do it worse today…I'm not sure getting the leads back is the right thing to do…I don't think all the leads should be extracted, but I do think there should be a standard for testing the leads…When there is a hole in a (oil) pipeline in Alaska, they have ways to figure out exactly where that hole is…And I'm told by engineers there are other ways to find defects…Do we need better ways of testing (leads)?…When I send back a lead, I cut it, break it…I sit down with engineers afterward and try to piece it together, but you don't get the whole story…You (should) test the lead *in situ*…Some of these things might even be able to be put in the pulse generator."

Could funeral homes be more helpful in retrieving devices and leads? Is that practical? And what about privacy issues?

- *Groves, Medtronic:* "Through AdvaMed, we have begun working with funeral homes to see if we can do a better job of what they will get when a patient comes in with an implanted lead, what their options are for de-planting them…And we are doing more training of our personnel (sales reps) who are not always present at death…but we need to be a little careful with …going after every single patient who dies with a device…These are sick folks who die of many causes."

- *Dr. Maisel:* "One hurdle is the device is owned by the patient so family consent is needed."

- *Dr. Wilkoff:* "Patient confidentially is extremely important, but to handle this particular problem, we have compelling

reasons to pull together clinical identifiers and clinical information…but divorced from the rest, it just gives us trends…We have to hook it up the rest of the way…There is a difference between what HIPAA requires and the perception of what HIPAA requires…I think we worry more than the reality itself."

- *Dr. Lindsay:* "HIPAA is an important point. I don't think it was ever the intent to stand in the way of issues like this. Perhaps one of the legislative issues we need is to work on that…If HIPAA is really keeping us from tracking patients and saving lives, we need to change that. Perhaps one of the things coming out of this meeting is a recognition that we have to work on this…The lung cancer registry has the same problem with HIPAA, and they came to compromise that patients have indefinite consent – a sort of hybrid (consent)… Clearly, there is room to maneuver and overcome the barriers."

How would the FDA view a large registry?

- *Dr. Zuckerman, FDA:* "Are we doing things differently now? Is there any better protection for the American public? …Certainly, the organization of the FDA is difficult with a critical problem like this where we need to follow a device through the entire product life cycle...In a situation like this, we would consult with our post-marketing colleagues quickly (Dr. Gross's division)."

- *Dr. Maisel:* "Suppose if the post-marketing study for a lead going forward were a condition of approval. Is there a way to do that?"

- *Dr. Gross, FDA Postmarket Surveillance:* "We need a clear idea internally of what questions we want the post-marketing study to address…It makes relatively no difference if it is in a remote monitoring system or a registry as long as we are convinced it will give us data in a timely manner to address the questions we have…There are systems in place for things like vaccines that link 8-10 very large HMOs that survey (patients and doctors) continuously…They overcame any HIPAA issues…so HIPAA is more a conceptual problem than a real problem."

What will prevent a similar thing (to Fidelis) from happening at other companies?

- *Brumbaugh, Biotronik:* "Just the nature that there was an issue and that we all understand what happened is big reason it won't happen again. That can't prevent a lead out there from having a similar issue…But the problem is we've learned from the Medtronic experience, and we know certain things we won't do with our leads…but there isn't a lot to stop it today that wasn't there two years ago."

- *Chester, St. Jude:* "I'm not sure what we can do in the short term, but there are many things we can do (longer term). Rate of returns could be improved – maybe through returns or through making leads easier to explant – and sponsoring industry registries, harmonizing the definition of failure, enhance and standardizing bench testing, and working toward expected levels of performance."

- *Groves, Medtronic:* "On lessons learned: A fair number of mechanisms that were presented educated us on new ways to monitor for failures…Modeling will continue to evolve and get better...On post-marketing: We are taking lessons away for role of our longevity study…We dabbled in the use of remote monitoring for the first time and learned a ton about that and will continue to explore ways to do that more effectively…At a more industry-wide level and in partnership with the FDA: Better definitions of what we mean by failure, how to categorize those failures, and better ways to monitor all leads so one can compare and make a risk:benefit from one lead model to another and knowing relative performance."

- *Russie, Boston Scientific:* "We, as a company, have reviewed our processes top to bottom, with much greater emphasis on prevention…to try to catch any potential problems early on…(There have been) improvements in bench testing, simulations, and we have tried very hard to improve our surveillance system so if anything escapes, we can take it and feed it back."

If FDA approves a new ICD lead today with significant design changes, would the FDA require a premarket clinical study? What will happen when a new lead comes out?

FDA's Dr. Zuckerman: "The agency on its clearance side, before post-approval, has to make an appropriate risk:benefit decision such that there is a reasonable assurance of risk:benefit…Certainly, based on current data, the Agency is very quickly interested in seeing what changes we can make to improve our risk:benefit decision...What should the industry realistically expect? The industry should be expecting that requirements will change in the near future, and it is very heartening to hear that people have come together (here)... There is a spirit of collaboration and science, and the sooner we raise the level of the water in the dam, everyone will benefit…We are suggesting beefing up preclinical testing and studies prior to approval, and now we are talking about post-marketing studies. From a realistic perspective, that is where we can get the biggest bang for the buck. It is for us to really seriously examine our preclinical/animal studies and what we are requiring in the post-approval realm. I'm not saying that every lead would require a COA study, but it would be incumbent on the manufacturer to explain why it shouldn't… The decisions in this field are complex, and the Agency needs to huddle post this conference."

Is the message that to achieve significant change, we need to have better data collection, starting with device approval in a large enough number of patients to get a reliable estimate of device performance?

- *Groves, Medtronic:* "On Fidelis, the data are not statistically different on the leading edge, so there is not anything the FDA could have required in the post-marketing study that would have led to different results."

• *Dr. Maisel:* "There was a significant amount of time (between the first Fidelis reports in March 2007 and the recall in October 2007)…And there was a lack of understanding in the clinical community about what the device performance was…So, having the information as soon as possible seems prudent and something we could do easily and quickly."

• *Dr. Wilkoff:* "The problem is where do you make a decision …Only compared to Quattro (the previous-generation Medtronic lead) is the Fidelis a less good lead…All their other leads are (inferior)…so are most of the other manufacturers' leads…and most of them have not been recalled or withdrawn, and there is no safety alert on them. The problem is information without being able to do something about it creates anxiety without action…We have a problem, but I think what happened was impressive because action was taken before there were statistically significant results…We have to learn how to predict, before things are statistically significant…I don't think that will ever happen from a premarket situation."

• *Dr. Hauser:* "I advocate there is a significant role for (independent, multicenter studies), conducted by institutions willing to collect and analyze the data in a very consistent way."

Clinical Management and Communication of ICD Lead Performance Issues

Academic perspective

Dr. Rachel Lampert of Yale reviewed the consequences of:

- **Replacing a lead** – death, inappropriate shocks, no shocks. This is recommended for patients who are pacemaker-dependent and have an ICD for secondary prophylaxis or as primary prophylaxis in patients who have received appropriate therapy – but only when the risk of replacement is not substantially greater than the risk of malfunction.
- **Leaving it alone** – infection, pain, death. This is recommended for patients who are not pacemaker-dependent, who have an ICD for primary prevention with a low probability of future therapy, or where the rate of malfunction is low (<1:1,000).

Industry perspective

Dr. Richard Fogoros, a medical advisor for Boston Scientific, emphasized that industry recognizes the importance of timely, clinically importunate information about leads, but gathering and analyzing lead data present special challenges. He pointed out that making a clinical decision on whether or not a device subject to a potential malfunction should be replaced requires knowing:

- The risk associated with the replacement procedure.
- The underlying risk associated with the proposed replacement device.
- Adequate characterization of the malfunction. Clinically-useful information includes; root cause, pattern, incident, predictability, consequences, mitigation, and impact of the malfunction.
- Leads, he noted, present a special challenge because:
  - √ Performance is multifactorial.
  - √ They are subject to constant, long-term wear-and-tear.
  - √ Clinically important data on leads are inherently difficult to obtain.

Regulatory perspective

Dr. Brian Lewis, arrhythmia cardiologist and medical review officer for the FDA, explained that assuring continued safety and effectiveness of a lead involves: freedom from complications, stable position, stable insulation and conductors, and good electrical performance.

What can physicians do to help with post-market surveillance? He suggested:

- Participate in post-market data collection.
- Contribute data to the FDA (MDR, HeartNet, etc.).
- Participate in post-mortem data collection.
- Provide information to the NCDR ICD registry.

Panel discussion

Under what criteria will industry pay for things? How is industry dealing with added cost of safety advisories?

• *Dr. Fogoros, Boston Scientific:* "I believe financial support has come forward in the past, at least when device replacements were done…but I can't speak for industry on what they should be spending."

• *Carlson, St. Jude:* "Guidelines is one idea worth exploring …And there may be some commonalties that may lead to general recommendations...but it is like hospitals and pricing in medicine – if you've seen one, you've seen one…I'm not sure there is one answer…These are not easy issues…They need to be brought up and discussed and negotiated for every single malfunction that comes up…For every instance you have to decide who gets compensated and who doesn't…I agree there are problems that real people are facing, and it can be better. I'm not sure what the right way is."

• *Dr. David Steinhaus, vice president and medical director for Medtronic:* "There are a lot of legal issues…I don't think it is a bad idea to have some guidelines…We've tried to help as much as we can (with Fidelis)…to have our reps available in clinics…If you set up early reprogramming, we will pay for that – pay the patient co-pay for that…And we have the warranty…If a physician feels it is imperative that a lead be replaced…we will give our warranty service for that as well… This is a tiny, tiny problem compared to all the patients out there who don't get healthcare because they can't afford it…It is kind of how you view healthcare: 1) Healthcare is any other

consumer product – if there is a problem, you fix it or replace it; or (2) We healthcare providers do the best we can to help people…but what tends to happen is not guaranteed. Just like a doctor doesn't guarantee that there isn't an infection or any other adverse event, and how the same medications given to the same population will help some, not help some, and hurt some. We all recognize that. It is part of the risk we take when we take medications...You could change that, but you have to change the model. We would have to accrue enough money to self-insure…but where would that money come from? By charging more for products. You have to add the cost somewhere, and that's okay, but right now that's not where we are."

- *Lisa Salberg, CEO and founder of the Hypertrophic Cardiomyopathy Association*, made several points, including:
  - √ "Why is a medical device different from every other product patients can buy in this country…The cost of the recall basically falls on the patients. They can get a device or a lead but can't get it implanted…I think we have a huge problem with that…I asked industry what to do (about a patient who couldn't afford the Fidelis replacement cost)…I was told to have the patient call charity care…Is it their (the patients') responsibility for a recalled device? I don't think so."
  - √ "I think we need to come up with something new, like the National Vaccine Injury Compensation Club… Vaccines are inherently beneficial to the community… that model might give us clues on how to set up a system (for ICD and pacemaker leads)…No one has to admit liability or guilt. We know we will have failures and recalls. Maybe we can come up with a better system."

- *Dr. Daniel Kramer of Massachusetts General Hospital:* "Industry feels caught between legal obligations and a sense that they want to do the right things for patients…Hopefully, legislation can address this…and find a way for industry to acknowledge recalls and provide for the means to financially manage that without opening them up to a liability that would make it impossible for them to participate."

- *Dr. Zipes:* "I suggested an independent group…They could then rule on who got reimbursed…If you wait for government, forget it…There is no way that a manufacturer can guarantee something is 100% working, but one expects someone to stand behind it if there is a defect. This is different than an uninsured or broken healthcare system. We are talking about product reliability and who stands behind it."

- *Dr. Maisel:* "I'd rather err on the side of notifying patients than not notifying them."

It is easier to recall a generator than a lead, but how do you assess the risk at your institution of a replacement – whether a lead or pulse generator? Or the risk of not replacing it? Is there a database in your center? Do you rely on the literature? What source of information do you use on not replacing it?

- *Dr. Maisel:* "The (ICD) task force suggested physicians understand the complication rate at their own institutions…We know it varies from center to center…I heard (here) that the malfunction rate can vary from center to center…It isn't as easy as monitoring the complication rate…(HRS) did a survey, and 30% (of electrophysiologists) said they would replace a lead with a failure rate of 1:10,000…And we know the failure rates are below that…So, we have failed to provide patients with realistic expectations…It is a lot easier to have a discussion with a patient on replacing a device than not replacing it."

- *Dr. Lampert:* "There are two levels of warning before a catastrophic event…impedance monitoring and inappropriate shocks, which are terribly distressing but not life threatening for the vast majority of cases. With those two levels of warning, we have time to wait, with no push for prophylactic replacement."

- *Dr. N. A. Estes III, Tufts-New England Medical Center:* "Certainly, there are selected patients we all know – pace-maker-dependent patients – where the consequences of failure (are high), where (the devices are) used for primary prevention …Beyond all those factors, there is also the quality of life and psychological issues that come to the forefront. We had an extremely low risk patient with a Marquis (Medtronic InSync defibrillator, which was recalled in 2005), but she insisted it be removed because she just couldn't live with it in. What's right for one individual might not be right for another. You really have to individualize these decisions on a case-by-case basis."

- *Dr. Zipes:* "That is one of the good things that came from the ICD conference – that there is now widespread education on how to handle these issues…Many physicians had never faced the issue…We've all learned a whole lot on how to handle these issues."

When the Fidelis announcement came out, there was a concerted effort to educate physicians. Does Medtronic have any sense of how many prophylactic replacements have been made?

Dr. Steinhaus, Medtronic: "There have been some…mostly in pacemaker-dependent patients, and in some patients who can't stand having a lead with any type of issue...I think it has been relatively small so far, but there have been some."

What is the role of HRS in the Fidelis recall?

- *HRS president Dr. Lindsay:* "I can't say I've gotten uniform feedback…I've had scattered calls…My patients have been pretty low key about it…Some of it has to do with our education of patients, telling them that there can be problems, so it hasn't been an overwhelming problem for us. I got a call about a week ago from a physician whose fracture rate with Fidelis is 10%. Our fracture rate with it is <1%...He wasn't hostile, but he wanted to know, 'If I have a rate of 10%, whether right or wrong, do the recommendations still apply to me?' He wanted to extract prophylactically all Fidelis leads...I advised him I thought that would be a great mistake...that the recommendations still applied to him. But to my knowledge we haven't gotten a huge influx of calls at HRS about this. The (Medtronic) conference call was very helpful; it was clinically very useful and helped manage the issue."

- *Patient advocate:* "You have to inform hundreds of patients …Why not fill a room with a group meeting and educate 50-100 patients at a clip. Patients don't mind hearing in that manner."

What has FDA heard from patients?

- *Dr. Kim Selzman, FDA:* "I don't think we have heard from a lot of patients. As a practicing physician in North Carolina, we contacted all our patients. They had all received a letter from Medtronic on the Fidelis recall, and I think patients pretty well received the information. Very few patients were demanding lead extraction. But in terms of the FDA, I'm not sure there was a lot of direct-to-FDA contact."

- *Another FDA official:* "Sometimes you tend to hear at FDA the more basic questions...'I have a St. Jude lead, is that a Fidelis?' I think it is our responsibility for all of us to talk people down from the ledge."

In the last two years there has been an issue of loss of trust and quite a lot of pushback from patients who say, "Doctor, do I really need this device (ICD)?" What does industry have to do to restore or regain the trust of patients or the referring community?

- *Dr. Maisel:* "No matter how much information there is, there will be people who don't think it is accurate or timely… but being in front of the story, having Medtronic issuing the press release and making the story, it was Medtronic working with the FDA and HRS. That goes a long way to making patients more comfortable. All the ducks were in a row. It wasn't piece by piece…It has been handled, I think, well."

- *Dr. Murray Malin, medical officer in the FDA's Office of Compliance:* "Patients in this particular recall looked at the industry website…and that is where they are going more than to clinicians (for information)."

- *Carlson, St. Jude:* "We have to keep our eye on the ball… This is an important problem, but, on the other hand, we have a huge number of patients out there who are not getting therapy…One of these problems is actually affecting the other."

- *Dr. Estes:* "We have a passive monitoring system…We need more robust systems and to do something about patients who can't pay for these things, to fundamentally re-establish that trust, not just in devices, but in so many other areas of medicine. Right now, I think it is a system issue more than an individual issue. It is fundamentally a systems problem."

- *Patient advocate:* "I know everyone in the room has the idea that the patient comes first. That is not what comes through to the patient…The patient thinks investors come before the patient…That is how they feel when they hear that we are not paying for this or that…To put out some type of system that says to a patient, 'We are here with you. We are a partner.' You can build trust back with that…The other piece is to continue the transparency. I am so happy to see the changes there…We will get better at that…Remote monitoring is wonderful. We need more patients using that."

- *Dr. Fogoros, Boston Scientific:* "Speaking for myself, not Boston Scientific, I am fairly cynical on primary care doctors referring for ICDs...They are punished for referring for an ICD. Their cost profile with the HMO goes south…That's No. 1. No. 2, I don't know how they can live with the constraints they are under…They are limited to 7.5 minutes per patient encounter…Now, today, through pay-for-performance (P4P) the insurers and the government are dictating to them what exactly they can and can't talk about during that 7.5 minutes…So, when events like the last two years occur (ICD and lead recalls)…we are basically giving those who are disinclined to have this discussion a great excuse not to have the discussion with the patient…I believe primary care doctors are taking the advantage to move on to something else with their patients…I think it will take a long time to recover from that damage."

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