Trends-in-Medicine

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by Lynne Peterson

SUMMARY

The FDA/HRS conference on ICD recalls didn't produce any consensus, but it opened a dialogue, and it gave all sides – electrophysiologists, FDA officials, the public, and device company executives – an opportunity to have a say. It was clear everyone wants to know what should trigger a recall and who should set that level, but finding a consensus may be difficult. The good news was that the process of discussion and negotiation is underway.

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ICD CONFERENCE: A LOT OF TALK, NO ACTION

Washington, DC
September 16, 2005

The FDA and the Heart Rhythm Society (HRS) held a joint conference at which nearly 300 physicians, patients, industry officials, and regulators discussed ways to improve the recall policy for implantable cardiac devices (ICDs). The goal was to improve the handling of ICD problems but keeping in mind that "these devices save lives every day."

The key issue all day was: what the trigger level for a recall should be, and who should set that trigger level. This was a question that came up early in the session but was never answered. Lisa Salabert, founder and president of the Hypertrophic Cardiomyopathy Association, urged that an outside third party make these determinations, and Dr. Douglas Zipes, editor-in-chief of the journal ***Heart Rhythm***, agreed, "With pre-market studies, there is a data safety monitoring board (DSMB) which is independent…I really don't see why post-market surveillance should be any different…While this would be laborious and expensive…I do think we need an independent route to analyze these data from the time of approval as post-market surveillance goes on…This is not to cast aspersions on industry, but they have an inherent conflict of interest." An FDA official on the panel declined to comment.

What did the meeting accomplish? Dr. Mark Carlson of Case School of Medicine, who chaired the meeting, called it a success. He said, "Everyone who walked out of that room knows more about the complexity of the process and expectations than they knew going in today…This meeting will build trust." He said participants learned:

- ICDs and pacemakers are very safe technology which has saved thousands of lives.
- There is a need to remove barriers.
- Improved surveillance is the key to timely and accurate information.
- Returning devices is important.
- Doctors differ in the level of information they want to receive.
- There are opportunities to standardize product performance reports.
- Databases can add value.
- There was a consensus on some aspect of communicating risk:benefit to patients and physicians.
- Patients want to know about device issues, primarily from their physician but also from the manufacturer and the FDA.

- Setting triggers for recalls needs to be worked on. Triggers were a key concern for attendees, but little progress was made on deciding what they would be or who would make the decision, except that there appears to be agreement that decisions have to be made about possible triggers. Dr. Stephen Hammill of the Mayo Clinic said, "I didn't hear anything specific for what is a trigger and how it is set…I heard some ideas…I heard the underwriter laboratory approach, the DSMB approach, and some type of external body. I think all of those need to be explored, and I think one of the most important next steps for HRS is to get people involved and decide how best we can determine what threshold is for a specific product problem and then where we go with it." HRS President Dr. Anne Curtis of the University of South Florida said, "Saying 1 in 10,000 or 1 in 2,000 is way too simplistic…It will be a complex process."

Asked on what the FDA will be focusing over the coming year, Dr. Daniel Schultz, Director of the FDA's Center for Devices and Radiologic Health (CDRH) said, "We (CDRH) are clearly committed to looking intensively at all post-market programs, including surveillance, inspection programs, and the way we handle annual reports…It is not about one specific office or function, but how we can better connect the dots between all the sources and all the data we take in… Obviously, we are committed to making sure devices continue to be reviewed in a timely fashion…But there needs to be greater emphasis on what happens to devices when they get to market, and that will be our focus for the next year or longer."

THE REGULATORY PERSPECTIVE

In an opening statement, FDA Deputy Commissioner Dr. Scott Gottlieb stressed that the FDA wants "to take new and additional steps to work especially hard to leverage our relationships with clinicians." His key comments included:

- "Over the next months, you'll be hearing more from FDA on precisely this goal: How we can take new steps to collaborate more with healthcare professionals and to work with medical professional groups."
- "Our ability to generate and share this (our) knowledge (about new medical devices) is only as good as the information we receive – and only as useful as our ability to translate it efficiently and effectively with the people who need it…We need your help in sending this raw information to us."
- "When we looked across the annual reports we receive about these products (ICDs, etc.), we have found some increasing trends for certain kinds of problems with some devices over time…Nobody is sure what these trends fully mean…It challenges industry to use this technology to make devices that are not only smarter and more beneficial but also safer."
- "It challenges those of us here at FDA to make sure we're asking the right questions about these products to get good data in."

FDA's Dr. Thomas Gross, Director of the Office of Post-market Surveillance at CDRH noted:

- "Our threshold is very low for unique failures…but the reports we gather are many times incomplete."
- "A passive reporting system is necessary but not sufficient…and I think that will be a theme today. It (passive reporting) is not sufficient. There are other mechanisms that need to be put in place to help us gather the data we need."
- "The FDA can do a better job…We have to be smarter with resources we do have…We need to build complementary systems, and we need to start that today…There are gaps in the system, and the FDA recognizes them. FDA cannot do the job alone…It is an effort in which all stakeholders need to engage…It is a collaborative effort."

Joseph Levitt, a former FDA official, warned there is no quick fix: "It takes time, especially for the government, to reach a consensus on what needs to be done…and then, based on that, what is the method needed to do it. Do we need to issue new regulations, or can we do something through policy on our own? Is it something that needs funding? Does it have outside issues, outside of our control, that might need legislation?...It takes time…People should not expect the answers on Monday."

Dr. Timothy Ulatowski, FDA's Director of the Office of Compliance, CDRH, pointed out some of the problems with post-market analysis and reporting:

- "Most recalls are voluntary…Very, very few are instituted by FDA. We have mandatory recall authority, but it is rarely, rarely instituted."
- "Cooperation between FDA and industry has proven to be the quickest and most reliable means to remove potentially dangerous products from the market."

Dr. Brian Lewis, an electrophysiologist and FDA Medical Reviewer, Division of Cardiovascular Devices, provided the FDA perspective of what patients need and want to know about a recall:

- Different patients may have very different needs within a single recall.
- The most critical or timely device functions need the most attention when considering all recall patients as a group, but care of individual patients is considerably more complex.
- The recall of [a pacemaker lead] taught the agency that: not all recall devices require removal, removal may be associated with its own risk, and there is no substitute for long-term follow-up.

Dr. Steve Phurrough, Director of CMS's Coverage and Analysis Group, emphasized the value of the information that can be gleaned from large post-marketing registries. He also was enthusiastic about the prospects for combining Medicare claims data, health plan data, industry data, and clinical data. A basic CMS-HRS national ICD registry began in January 2005, and that data are now being transitioned to a new, more complete registry. He commented, "The real issue with Vioxx (Merck, rofecoxib) is the number of patients in the trials was too small to recognize the low incidence of serious adverse events. With this kind of (ICD) database, we believe we can assist in answering those kinds of questions."

Dr. Megan Mynahan, Chief of the FDA's Pacing, Defibrillators, and Leads Branch, discussed risk:benefit communication issues, and among the points she made were:

- As they are currently drafted, recall communications do not adequately inform physicians about what to do for patients whose at-risk devices have not failed.
- Recall Notifications are not designed to convey balanced information about device performance.
- A Health Hazard Evaluation (HHE) is more often skewed to Class I even if the probability of failure is very low because of the potential for death as an outcome.

THE PHYSICIAN PERSPECTIVE

Dr. William Maisel of Beth Israel Deaconess Medical Center, chaired a session on Technology, Performance, and Surveillance. He offered some interesting statistics from a study of FDA annual post-approval reports on ICD/pacemaker use from 1990-2002:

➢ Almost 300,000 pacemakers and ICDs are implanted in the U.S. annually.

➢ There were 17,323 pacemaker and ICD malfunctions (explants) in the period: 79.8% due to hardware, 3.6% for firmware, 11.8% miscellaneous, and 4.7% inconclusive.

➢ The malfunction replacement rate for ICDs was considerably higher than that for pacemakers. Per 1,000 devices, the replacement rate was 4.6% for pacemakers and 20.7% for ICDs.

➢ The number of pacemaker/ICD implants increased substantially during the period, with a total of ~2.67 million devices, including ~416,000 ICDs.

➢ The ICD malfunction replacement rate appears to be increasing.

➢ There were 61 confirmed deaths due to device malfunctions (30 in pacemaker patients and 31 in ICD patients).

➢ Potential limitations in assessing the rate of device malfunctions and their resultant effects include:

- Potential under-reporting of malfunctions.
- Change in reporting frequency.
- Assumptions.
- Unreported time from implant to failure.
- All malfunctions considered the "same."

Other speakers urged caution in interpreting Dr. Maisel's data. The FDA's Dr. Schultz said, "This is an area where we need to put some time and energy to try to figure out why this is happening." Dr. Hammill warned: "Be very careful interpreting the Maisel data…I think there was an average 2% failure rate…that includes early battery depletion and things we will detect in routine surveillance."

Dr. Rachel Lampert, Associate Professor of Medicine, Yale University School of Medicine, outlined the limitations of current ***passive*** surveillance systems, which include:

➢ Not all malfunctions may be detected.

➢ Not all detected/suspected malfunctions may be reported.

A potential ***active*** surveillance system could:

- Require all explanted devices to be returned to the manufacturer instead of just potential malfunctions as is currently done.
- Require interrogation of any devices in a sudden/unexpected death instead of only sporadic interrogation/removal in highly suspicious cases.
- Be limited by cost and family attitudes. Additional reimbursement for post-mortem device interrogation or generator removal would help.
- Be aided by systematic cooperative agreements between industry and mortician groups.

Dr. Michael Barber, Director of Pacemaker and Arrhythmia Services, Centura Health/Penrose Hospital Healthcare System in Colorado Springs CO, presented a survey of electrophysiologists about how they wanted to be notified about device failures. The survey was sent to 100 random physicians, academic and private practice, high volume and low volume implanters. The survey found doctors had a relatively high threshold for device failure before they want notification, and there was no significant difference in approach to device notification based on the type of practice they were in. A Class I recall means death or serious illness is likely; a Class II recall means it is a serious injury that is reversible.

Physician Preferred Level for Recall Notification

Failure rate	In the future, at which device failure rate would you like to be notified for a:			
	Potential Class I recall		Potential Class II recall	
	Academic	Private practice	Academic	Private practice
1:5,000	3	6	2	6
1:2,000	3	3	6	5
1:1,000	7	5	6	4
<1:1,000	4	4	4	2
Other	1	1	0	2
Total	**18**	**19**	**18**	**19**

Dr. Barber said patients want:

- **To hear risks and problems directly from their device company manufacturer and physician,** not read about them in the newspaper.
- **To be completely informed** – not misinformed, over-informed, or under-informed. They want to know the current extent of the problem, the predicted/projected extent, the guidelines or recommendations for handling it, and that their problem is important to their physician and the device manufacturer.
- **To have the same information that other physicians and patients have** – not more or less. All patients, he said, should get the same letter sent ***by the company***, so they feel they are receiving upfront information. The letter should outline the extent and severity of the problem but leave the specifics of what to do to be discussed with the physician.

Survey of Experienced Physicians about Recent Guidant Device Recalls

Measurement	Guidant Prizm-2 DR ICD Class I recall		Guidant Renewal and Renewal 2 CRT-D Class I recall		Guidant Pulsar/ Discovery/etc. Pacemaker Class I recall	
	Academic n=18	Private practice n=18	Academic n=18	Private practice n=18	Academic n=18	Private practice n=18
Mean explanted	14%	40%	15%	33%	30%	47%
Minimum explanted	0	0	0	0	0	0
Maximum explanted	65%	100%	90%	100%	100%	100%
Usual reason for explant						
Patient safety	56%	50%	50%	59%	65%	67%
Patient request	22%	50%	11%	29%	6%	11%
Battery near ERI	6%	17%	0	18%	12%	39%
Medical/legal	6%	6%	6%	6%	12%	11%
Recall class	17%	17%	17%	18%	12%	17%

Dr. Eric Prystowsky, Editor in Chief of the ***Journal of Cardiovascular Electrophysiology***, and Director of the Clinical Electrophysiology Laboratory at St. Vincent Hospital in Indianapolis, and a former president of the Heart Rhythm Society/North American Society of Pacing and Electrophysiology (NASPE), urged earlier notification, "Once a company has figured out something that is not a usual, expected failure – something different that they didn't count on, that has come up repeatedly – and they now have a handle on it (physicians should be notified). The problem is they (companies) have their own voluntary system on when they think they should let us know…I think they should let us be part of that decision… It is their product but our patient, and we should be part of that process…We would like doctors who deal with patients in the loop somewhere because what we perceive needs intervention may be at a different point from industry."

Dr. Prystowsky presented the findings of a survey of physicians who implant a high volume of pacemakers and ICDs.

Physician Survey About Recent Device Recalls

Device	Recall class	Average % of ICDs and pacemakers explanted after recalls
Medtronic Marquis ICD	Class II	31%
Medtronic Marquis CRT-D	Class II	33%
Guidant Prizm-2 DR ICD	Class I	27%
Guidant Contak Renewal CRT-D	Class I	24%
Guidant pacemakers	Class I	39%

Survey of Experienced Physicians About Recent Medtronic Device Recalls

Measurement	Academic n=18	Private practice n=18
Medtronic Marquis ICD Class II recall		
Mean explanted	28%	33%
Minimum explanted	5%	3%
Maximum explanted	95%	100%
Usual reason for explant		
Patient safety	78%	78%
Patient request	6%	44%
Battery near ERI	6%	11%
Medical/legal	6%	11%
Recall class	11%	11%
Medtronic Marquis CRT-D Class II recall		
Mean explanted	32%	33%
Minimum explanted	5%	0
Maximum explanted	100%	100%
Usual reason for explant		
Patient safety	82%	61%
Patient request	6%	28%
Battery near ERI	6%	6%
Medical/legal	6%	17%
Recall class	12%	0

Dr. Leslie Saxon, Director of Cardiac Electrophysiology at the University of Southern California (USC), said standardizing advisory communications has both advantages and disadvantages:

- **Advantages** include providing physicians with clinical information to facilitate patient communication and clinical action, objectify information, and is easily referenced and subject to updates.
- **Disadvantages** include more complexity requiring more oversight, all key information is not communicated, and there are legal implications.

Dr. Robert Hauser of the Minneapolis Heart Institute reported on a physician volunteer post-marketing database begun six years ago in the U.S. and Canada to track failure data on pacemakers, ICDs, and leads. Failures were defined as devices that didn't function as expected or were removed because of a recall. The database collected information on >4,500 devices, including >1,350 ICDs.

Dr. Hauser provided a brief look at data to be reported soon from this registry:

- Average device life was 4.1 years.
- Average device life with recalls excluded was 4.4 years.
- Only 73% of ICDs function >3 years and are replaced for battery depletion.
- 52% of ICDs function >4 years and are replaced for battery depletion.
- ~82% of ICDs had battery depletion, and 9% with premature battery depletion.
- 8% had electronic, housing, or mysterious failures.
- 10% were recalled.

Europe has more experience with ICD databases, and Dr. Lucas Kappenberger, head of the Division of Cardiology at the University Hospital of Canton de Vaud, Switzerland, said European registries have had the same difficulties as U.S. registries. The best, he pointed out, is the Danish registry because reimbursement requires participation, and that has resulted in 99.5% documentation. France, in contrast, has an old and very basic system that he described as "like hunting stories." The U.S. is not far from the French system, he concluded.

Dr. Chris Simpson, President of the Canadian Heart Rhythm Society, and an Associate Professor of Medicine at Queen's University in Ontario, Canada, pointed out, "If we all have the same information, it is okay if we make different decisions. But we all need the same information. We should get the same technical information, but a difference in response to that information doesn't necessarily mean the whole process is invalid."

Dr. Bruce Lindsay, Vice President of the Heart Rhythm Society, said he would like industry to set expected failure rates for products. Gabe Kohanyi, Vice President of Quality Assurance at St. Jude Medical Cardiac Rhythm Management Division, responded, "The rate of incidence…is meaningless unless we talk about the specifics…Because a rate of 1 in 5,000 of an incident that has a relatively low severity, little clinical impact, is different than a rate of 1 in 5,000 of an incident in which the device malfunction may have caused a serious injury."

The Public's Perspective

Public Citizen was not on the agenda and was not speaking at this meeting, but Dr. Peter Lurie, Deputy Director of Public Citizen, distributed a press release on the petition Public Citizen filed on September 14, 2005, with the FDA asking the agency to establish tighter regulations over the review and recall of medical devices. Dr. Lurie cited the case of a patient who got a St. Jude replacement pacemaker (for an original St. Jude pacemaker that failed prematurely) that had a known defect but was allowed to be sold and used anyway. Public Citizen wants the FDA to issue a new rule that lets the agency "withdraw approval for an approved medical device that has caused patient harm, or that raises a substantial likelihood of causing harm, when another device is on the market that is equally or more effective for the same use but poses less risk."

Panel and audience suggestions for improvements in reporting, included:

- Networking.
- Physician education about reporting methods.
- Simplified forms to accompany returned devices.
- Standardized definitions and coding.
- An outside, independent testing agency to examine devices that are explanted due to a suspected malfunction.
- More feedback to people who file a report about a device problem to the FDA.

A nurse who suffered worsening in her cardiac condition due to a device malfunction said, "The recent corporate behavior has made many of us feel like ticking time bombs."

Richard Brown, President of the Sudden Cardiac Arrest Network, told attendees that patients want to hear about recalls from their physician, "They want to hear from the manufacturer, but they really want to hear from their physician. That is where the level of trust is." Salabert of the Hypertrophic Cardiomyopathy Association agreed, and she predicted there would be new notification legislation – which she would like to see after Joshua Orcutt – the young man who died due to the failure of a Guidant ICD that was later recalled.

However, Ralph Hall, Visiting Associate Professor of Law at the University of Minnesota Law School, warned that this is not practical, "We will never have a situation where patients hear first from their physician…If a recall is potentially material, then the company will have SEC (Securities and Exchange Commission) disclosure obligations…With the explosion of technology – yahoo message boards, blogs, emails – once a part of the country hears about something, it spreads quickly."

The Industry Perspective

The Advanced Medical Technology Association (Advamed) offered these critiques of Dr. Maisel's study:

- The analysis treats all malfunctions as being of equal importance.

- The 1999-2001 malfunction increase does not establish a negative trend; rates rose in 1999, 2000, and 2001, but dropped again in 2002. The failures in Dr. Maisel's data are from earlier generations of devices.
- The FDA post-market monitoring and reporting system functioned effectively to minimize harm to patients.
- The study does not demonstrate a link between the 31 deaths due to device malfunctions and the increased malfunctions observed from 1999-2001.
- ICDs saved an estimated 30,000 lives during the time of the study.
- There is enormous under use of lifesaving ICDs.

Dr. Stan Myrum, Cardiac Rhythm Management (CRM) Vice President of Quality and Operations at Medtronic, noted that one area that has to be resolved is the definitions to be used:

- ***FDA definition of a device malfunction:*** A failure of a device to meet performance specifications or otherwise perform as intended. Performance specifications include all claims in the labeling of the device.
- ***Device performance definition:*** A measure of how well a device meets the user expectations that not only include specific device failures but also perceived quality, usability, robustness, and conformance to applicable labeling.
- ***Device failure:*** A device that does not perform its intended function as a result of a specific hardware and/or software failure.
- ***Anticipated failures:*** Manufacturers perform device reliability modeling to establish specific component, interconnect, software, and overall device predicted failure rates that are anticipated over the life of the device.
- ***Non-anticipated device failures:***
  - Specific component, interconnect, software, or overall device failure rates above predicted values.
  - A higher than predicted failure rate that is isolated to a specific subset of the total device or patient population.
  - A new failure mechanism not previously observed.
  - Device failures caused by exposure to a new source of external environment stress (e.g., MRI).
- ***Random component failure:*** Inherent failure of electronic components and certain manufacturing processes due to unavoidable imperfections in materials and processes (e.g., random defects on integrated circuit silicon or random coating defects in transformer wires).

Types of failures include:

- Non-device failure malfunctions, such as early battery depletion.
- Device failure malfunctions, such as:
  - Memory byte errors that can be re-set by re-programming, component failures resulting in high current drain, and premature battery depletion.
  - Gradual loss of device therapy, easily detected by routine follow-up.
  - Sudden loss of device therapy detection, patient "alert" triggered.
  - Sudden, undetected loss of device therapies.

Dr. Myrum's conclusions were that:

- There is a need for standardized nomenclature.
- A specific device failure rate would not be an appropriate "trigger" for clinician notification as other considerations are warranted to more thoroughly assess patient risk.
- Overall device reliability has remained constant or has improved, despite significant advances in device therapy and diagnostic clinical value.

Kathy Lundberg, Guidant's Chief Compliance Officer, commented that in 1995, new products introduced had about a 95% three-year reliability, compared to >99% for more recent (2003) devices – "and these occurred while battery longevity is improving as well as overall reliability." She said her goals at this meeting were to:

- Identify what types of communication would be more useful for physicians and patients.
- Establish clear definitions for each communication.
- Establish criteria for triggering special communications – when, the content, format, and best vehicle.

Tim Samsel, Vice President for Regulatory Affairs for Medtronic's CRM business, provided the industry perspective of what patients want and need to know about a recall:

- Patient communication should come from physicians.
- Affected devices can be quickly identified and communicated to physicians.
- Coordination of world-wide advisory communication is important.
- Public communication of advisories has an adverse impact on unaffected patients and potential patients.
- The term "recall" is commonly misunderstood by patients with implantable devices as requiring explantation.

POST-CONFERENCE UPDATE

Less than a month after the conference, the Heart Rhythm Society announced a 14-member task force of leading electrophysiologists and other experts in the field to draft public policy recommendations to improve the post-market surveillance system for pacemakers and ICDs. The task force

also will write clinical guidelines to respond to device advisories, alerts, and recalls. The task force is hoping to have the public policy recommendations available for public comment by May 1, 2006. Developing the clinical guidelines is expected to take 9-12 months.

The task force members are:

- *Chair:* Dr. Mark Carlson, Case School of Medicine
- Dr. Michael Cain, Washington University School of Medicine
- Elizabeth Ching, RN, Cleveland Clinic
- Dr. Anne Curtis, University of South Florida
- Dr. Wyn Davis, St. Mary's Hospital, U.K.
- Dr. Kenneth Ellenbogen, Virginia Commonwealth University Medical Center
- Dr. Stephen Hammill, Mayo Clinic
- Dr. Robert Hauser, Minneapolis Heart Institute
- Dr. Rachel Lampert, Yale University School of Medicine
- Dr. William Maisel, Beth Israel Deaconess Medical Center
- Dr. Eric Prystowsky, St. Vincent Hospital, Indianapolis
- Dr. Leslie Saxon, USC University Hospital
- Dr. Bruce Wilkoff, Cleveland Clinic
- Dr. Douglas Zipes, Krannert Institute of Cardiology in Indianapolis

On October 27, 2005, CMS announced that it will work with the American College of Cardiology (ACC) to collect data nationwide on ICDs implanted in Medicare patients. Beginning April 1, 2006, the ACC's National Cardiovascular Data Registry's (ACC-NCDR's) **ICD Registry** will become the data repository for information from >1,300 hospitals nationwide. The registry is a partnership of the ACC and HRS, with support from the ICD industry, private health plans and payers, and hospital groups.

CMS hopes the ICD Registry will help answer questions such as:

- Are the indications for ICD implantation in the Medicare population similar to the patients who received ICDs in the SCD-HeFT and other clinical trials?
- How frequently do ICDs stabilize the electrical activity of the heart in different subgroups of patients?
- Do cardiac morbidity and mortality differ among patients based on clinical characteristics, device characteristics, the facility and/or the physician who implants the device?

Currently CMS is collecting ICD information through the Quality Network Exchange ICD Abstract Tool (QNET), but the transition to the ICD Registry must be completed by April 1, 2006. Hospitals must contact ACC-NCDR no later than January 1, 2006, to begin the enrollment process.

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