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# A Proposed Solution to the Notification Problem

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## I. INTRODUCTION

*A hard beginning hath a good ending.*
*- James Howell*

First, I want to acknowledge and thank the contributors who have invested significant time and effort to this project; their contributions have made this colloquy possible. This commentary will build upon the contributors' thoughts, identify the stakeholder objectives, review the current notification trigger proposals, and advance a new solution.

At its core, this is a debate about information. It is a debate over how information about device malfunctions should be gathered and when and how that information should be disseminated. There is manifest dissatisfaction with the current criteria for triggering a device malfunction notification. The colloquy contributors have demonstrated the complexity and multidisciplinary nature of these challenges, the strong need for a solution, and the absence of any simple solution. These challenges exist within a complex, congressionally mandated regulatory structure which must be honored. Any solution must combine legal and regulatory requirements, scientific, medical, and clinical considerations, statistical and analytical tools, communication expertise, and public policy. This commentary shall concentrate on the legal, regulatory, and public policy aspects of this problem with particular emphasis on the notification trigger issue.

The overall approach is to use, whenever possible, existing systems and regulatory structures. Generally, the analysis will be at the policy level. Specific implementation details, particularly technical matters, can be addressed after there is general agreement on the core policy issues. Once there is agreement on policy, the details, while important and complex, can be resolved.

## II. ANY PROPOSAL MUST ADDRESS STAKEHOLDER OBJECTIVES AND SATSIFY PUBLIC POLICY CONSIDERATIONS

*If you don't know where you're going, you might not get there.*
*- Yogi Berra*

### A. THE STAKEHOLDER OBJECTIVES

This colloquy has identified five core objectives: (1) protect and advance public health through both the dissemination of relevant device malfunction information and the promotion of lifesaving technologies such as implanted cardiac defibrillators (ICDs), (2) create and maintain trust among all the stakeholders, (3) maintain the primary role and responsibility of the physician for patient care, (4) maintain the integrity of the regulatory system, and (5) provide certainty for all stakeholders. These stakeholder objectives must both frame any proposed solutions and provide a yardstick against which proposals are to be measured.

#### 1. Advance Public Health

The overarching objective is to advance public health. This requires appropriate dissemination of device malfunction information and the appropriate use of lifesaving devices.[1] Three facts must be kept in mind in this quest to advance public health. First, devices such as ICDs have saved thousands of lives.[2] Second, a malfunctioning device can have fatal effects. Third, the lack of a device has killed innumerably more people than all defective devices combined.

#### 2. Establish Trust

Patients literally trust their lives to ICDs and, therefore, must have trust in the manufacturer and the regulatory

1. *See* Heart Rhythm Society & FDA, Proceedings Document from the Policy Conference on Pacemaker and ICD Performance 2 (Sept. 16, 2005) [hereinafter Proceedings], *available at* http://www.hrsonline.org/advocacyDocs/HRS-device_conference.pdf.

2. *See, e.g.*, Michael R. Bristow et al., *Cardiac-Resynchronization Therapy with or Without an Implantable Defibrillator in Advanced Chronic Heart Failure*, 350 NEW ENG. J. MED. 2140 (2004); Arthur J. Moss et al., *Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction*, 346 NEW ENG. J. MED. 877 (2002).

system.[3] Trust starts with communicating realistic expectations to the patient, including the fact that any device or medical procedure presents certain unavoidable risks. Trust also requires transparency, and that involves providing information even if the information may not be actionable or required. In the past, the patient often simply deferred decisions to the physician. Today, many patients play an active role in health care decisions and want, need, and have direct access to health care information.

3. Maintain the Role of the Physician

The physician has historically had the primary responsibility for the patients' medical care. Physicians, generally with the support of other stakeholders, feel the need to maintain that relationship. As such, any solution should not intrude into or replace the patient-physician relationship. Given this relationship, physicians generally want to be the first person to inform the patient of device issues.

4. Ensure Regulatory Integrity

FDA must maintain the integrity of the regulatory system. This is its statutory responsibility.[4] Industry has a parallel interest. For competitive reasons, industry wants a level playing field; this requires the consistent and predictable application of regulatory requirements.

5. Provide Certainty

Stakeholders in general and industry in particular want clearly defined rules. Otherwise, everyone faces post facto judging and public criticism. If the rules are clear and objective then companies will simply comply. In this context, certainty allows everyone to know when a safety alert will be triggered.

B. CONGRESS HAS ADDRESSED THIS POLICY ISSUE

The question of what should trigger a product notification is obviously a policy question. Congress is often the arbiter of

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3. *See* Dianne M. Bartels, *Disclosing Risks of New Technologies: Ethical Challenges for Physicians, Patients, and Companies*, 7 MINN. J.L. SCI. & TECH. 183 (2005); Lisa Salberg, *Heart Rythm* [sic] *Society and the FDA Hold Policy Conference on Pacemaker and ICD Performance*, HEART LINK ONLINE, Oct. 7, 2005, www.enewsbuilder.net/hypertrophic/e_article000468321.cfm?x=b11,0,w.

4. *See* 21 U.S.C. §§ 301-397 (2000).

such policy questions, and Congress has spoken on this issue. Subsections (a) and (e) of 21 U.S.C. § 360h describe in detail the criteria by which FDA should mandate either a notification to physicians or an actual device recall.

Under § 360h(a), FDA can mandate a product notification if a product "presents an unreasonable risk of substantial harm" and a physician notification is "necessary to eliminate the unreasonable risk of such harm."[5] Similarly, FDA can mandate a recall under § 360h(e) if there is "a reasonable probability that a device . . . would cause serious, adverse health consequences or death."[6]

Manufacturers also have the opportunity to provide product notification through voluntary recalls. Under 21 C.F.R. § 7.40, manufacturers perform such recalls in order to "carry out their responsibility to protect the public health and well-being from products that present a risk of injury or gross deception or are otherwise defective."[7]

Congress has an established policy that a physician notification of a device malfunction should occur based upon risk and probability. This same policy should apply whether FDA mandates a notification under § 360h or the manufacturer conducts a "voluntary" recall. In one case, FDA can mandate the notification, in the other, FDA can bring an enforcement action for the failure to notify.[8] In either case, the patient need is the same and there should be no meaningful legal or policy difference between these two paths to a physician notification.

I am not writing on a blank slate. Congress has spoken on this issue and that policy determination must shape any proposals to address malfunction notification issues. After identifying the key issue with the current system, I will propose improvements to the device notification system that will satisfy these objectives.

## III. WHAT IS WRONG WITH THE SYSTEM

*Where's the Beef?*

- *Wendy's television commercial*

5. 21 U.S.C. § 360h(a).
6. 21 U.S.C. § 360h(e).
7. 21 C.F.R. § 7.40 (2005).
8. *See* 21 U.S.C. § 331.

While there is agreement that the malfunction notification system must change, there is no consensus on where the system has failed. Someone has objected to every part of the process. A close examination, however, demonstrates that the decision as to whether to trigger a safety alert is the key issue. For example, in the Prizm 2 situation,[9] the event reporting and analysis process worked, and in 2005 the situation was presented for management decision whether to commence a physician notification.[10] It was that initial decision *not* to notify physicians that started the controversy.[11]

There is little or no data that suggests that the current event reporting and analysis system is the main problem. If there is a major gap in the event reporting and analysis process, then there must be some significant number of unknown device malfunction issues lurking out there. While one does not know what one does not know, there have been relatively few situations when years have passed during which devices malfunctioned without reports being made to the manufacturer or FDA. While these processes can and should be strengthened, that will not solve the problem.

Other commentators have identified weaknesses in the communication process. However, the fact is that once a safety alert decision has been made, information has gotten to the vast majority of physicians and patients in a relatively prompt fashion. Can the communications be made faster? Of course. Can the communications be more understandable? Of course. Was the Prizm 2 controversy the result of garbled communications? Of course not.

While I will address various aspects of the overall notification system, starting with the event reporting and analysis process, I will focus on the key trigger question.

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9. *See* Robert Steinbrook, *The Controversy over Guidant's Implantable Defibrillators*, 353 NEW ENG. J. MED. 221, 221-22 (2005); *see also* Ralph F. Hall, *To Recall or Not to Recall, That Is the Question: The Current Controversy over Medical Device Recalls*, 7 MINN. J.L. SCI. & TECH. 161, 161-62 (2005).

10. Steinbrook, *supra* note 9, at 222; Barry Meier, *Maker of Heart Device Kept Flaw from Doctors*, N.Y. TIMES, May 24, 2005, at A1.

11. Guidant subsequently did commence a physician notification. *See* Hall, *supra* note 9, at 163.

## IV. EVENT REPORTING AND ANALYSIS

*The Plural of Anecdote Is Not Evidence*
- *Scott Ratzan*[12]

The fundamental purpose of the event reporting and analysis process is to identify device malfunction trends. These trends or issues are then presented to a decisionmaker, generally the manufacturer, to decide whether a product safety alert is needed.

Device performance data can come from two basic sources: (1) field experience and events, and (2) in-house investigations, bench testing, and analysis.

### A. FIELD EVENT REPORTING

Field performance data can be collected by two fundamental methods: (1) a "passive" system in which individual events are reported by a physician, and (2) an "active" surveillance or registry system that proactively collects data.

Passive systems, such as the Medical Device Reporting (MDR) system,[13] pose a number of limitations. First, underreporting is a recognized problem.[14] Particularly for low frequency events, every report is critical. There is a consensus that physicians need to improve reporting rates and completeness.[15] Second, passive systems provide only a raw number of events and not the incident rate; therefore, such a system may not provide a valid basis for medical decisions.[16] Without more information, mere reports of some field event may or may not mean something.

Paradoxically, another major weakness of the MDR system is that the system gets flooded with too many (generally

12. Scott Ratzan, *The Plural of Anecdote Is Not Evidence*, 7 J. HEALTH COMMC'NS 169 (2002).

13. *See* 21 C.F.R. pt. 803 (2005) (outlining MDR requirements).

14. *See* Steinbrook, *supra* note 9, at 223; Proceedings, *supra* note 1, at 5.

15. Bruce L. Wilkoff, *ICDs: Dealing with Less Than Perfect*, 16 J. CARDIOVASCULAR ELECTROPHYSIOLOGY 796, 796-97 (2005).

16. *See* Mark Carlson, *The Twin Pillars—Knowledge and Trust* , 7 MINN. J.L. SCI. & TECH. 177, 178 (2005); Robert G. Hauser & Barry J. Maron, *Lessons from the Failure and Recall of an Implantable Cardioverter-Defibrillator*, 112 CIRCULATION 2040, 2041-42 (2005).

unimportant) reports. In 2004, FDA received over 180,000 MDR reports, including several Prizm 2 reports.[17] Most MDR reports reflect known issues or adverse effects. Key data regarding new issues can get lost in this sea of irrelevant information. The lack of common terminology, staff shortages, and inconsistent reporting also add to the analytical challenges.

Eventually, MDR reports are entered into the publicly available Manufacturer and User Facility Device Experience (MAUDE) database. There are justifiable frustrations and complaints with the MAUDE database. The data is often incomplete, incorrect, or out-of-date.[18] The biggest weakness may well be the difficulty in using the MAUDE database to identify or analyze product malfunction trends or patterns. The system can be enhanced by improved physician reporting using common terminology and, to a lesser extent, manufacturer performance. Timeliness and accessibility are likewise data management challenges.

The other key data source is active surveillance systems or device registries. Some registries do not include "denominator" data (total device population or usage) and thus actual incident rates cannot be determined. Active surveillance systems must include large numbers of patients in order to have the statistical power to identify a low frequency event. This is a practical limitation on the current usefulness of such systems. Active surveillance systems can be time-consuming and expensive and so may not be practical in many situations. Some new approaches, such as using health insurance claims to identify device malfunctions, offer new avenues for data collection.

### B. MANUFACTURER DEVICE ANALYSIS RESPONSIBILITY

The manufacturer has the obligation to investigate any alleged device malfunction or event trends.[19] This process can include bench testing, failure analysis, analysis of returned devices, review of clinical information, trending, and statistical analysis.[20] These investigations are a key step in converting

17. *See* Proceedings, *supra* note 1, at 3.

18. *See* Salberg, *supra* note 3.

19. *See, e.g.*, 21 C.F.R. § 820.100 (2005) (describing the Corrective and Preventive Action requirements).

20. The specifics of these processes are beyond the scope of this colloquy.

isolated data points, such as a field report, into product trends, event frequencies, root causes, and corrective actions.

The fact that the manufacturer generally performs failure analysis and trending strikes some as a conflict of interest. If safety alerts are bad for the company, then will the manufacturer be less diligent in investigations and less willing to trigger a safety alert? Some have suggested using independent third parties to perform this task. However, for at least the foreseeable future, only the manufacturer can have the knowledge, equipment, personnel, or systems to fulfill this responsibility. Moreover, current regulations clearly place this responsibility on the manufacturer.[21] FDA routinely inspects a manufacturer's Corrective and Preventive Action (CAPA) system, complaint handling, and MDR systems to ensure compliance.[22]

In the end, information from all sources, internal and external, active and passive, must be combined to identify issues, determine ongoing investigation needs, and provide valid information to decisionmakers.

### C. THE DEFINITION OF MALFUNCTION MUST INCLUDE ALL CLINICALLY SIGNIFICANT EVENTS AND BE CONSISTENT WITH THE REMAINDER OF THE DEVICE REGULATORY SYSTEM.

Through this debate and this colloquy, commentators have generally discussed "device malfunctions" without any specific definition.[23] Surveillance systems are intended to collect information about device malfunctions. Everyone recognizes, however, that not all adverse device events are created equal. Some are life-threatening while others are simply inconveniences.

The malfunction definition must be clinically relevant and uniform across companies and device types. Rather than reinvent the wheel and create additional layers of complexity and confusion, I suggest using a preexisting and well-known (at

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Other groups, such as the Guidant Task Force, are working on enhancing these systems. *See* Press Release, Guidant, Guidant Independent Panel Recruited, Begins Deliberations (Aug. 29, 2005), www.guidant.com/news/500/web_release/nr_000573.shtml.

21. *See, e.g.*, 21 U.S.C. § 360j(f) (2000); 21 C.F.R. § 820.100 (2005).

22. *See, e.g.*, FDA, Quality System Inspections Technique, www.fda.gov/cdrh/comp/qsitpage.html (last updated Sept. 3, 2002) (specifying the process for inspections of these systems).

23. *See* Hauser & Maron, *supra* note 16, at 2042.

least to manufacturers) definition—the definition of a reportable event from the MDR regulations. The existing MDR regulations define reportable events as deaths, serious injuries, or device malfunctions that may lead to death or serious injury.[24] Clinically irrelevant events should be filtered out through the application of this definition.

While not perfect, this definition is uniform, well-known, and designed to capture all clinically relevant events.[25] This definition can even take into account normal end-of-life replacements of battery-operated devices.[26] In addition, by using this definition, the internal CAPA processes, the MDR system, and the MAUDE database are tied together with the device malfunction notification process. This allows for easier analysis, clearer communication, and fewer different systems.[27] If the MDR definition gets updated in the future, that new definition would simply roll into these other processes.

### D. CONCLUSION

The surveillance and analysis systems can and should continuously be improved. These efforts should be led from the scientific, engineering, medical, and clinical community with support from the legal and regulatory functions. A number of efforts are underway to do just that. For example, the Heart Rhythm Society (HRS) and the Guidant Independent Task Force are addressing certain of these issues. FDA and others

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24. The MDR regulations define "malfunction" as follows: "Malfunction means the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device." 21 C.F.R. § 803.3(n) (2005). "Serious injury" is defined as an injury or illness that: "(i) Is life-threatening, (ii) Results in permanent impairment of a body function or permanent damage to a body structure; or (iii) Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure." 21 C.F.R. § 803.3 (bb)(1) (2005).

25. Another option would be to use the definition of a "serious, adverse health consequence" in 21 C.F.R. § 810.2(i) (2005). This definition, however, is less well-known than the MDR definition and could be interpreted to exclude events otherwise included in the MDR definition. For example, "injuries that are nonlife-threatening and that are temporary and reasonably reversible" are excluded from the definition of "serious, adverse health consequence." *See id.*

26. *See* 21 C.F.R. § 803.3(i) (defining expected life).

27. There are certain aspects of the MDR regulations that are not relevant for notification purposes. For example, the obligation to report events before investigation is complete is important for MDR reporting but not particularly relevant for malfunction notification. Overall, however, the MDR reporting structure works well for notification purposes.

are exploring new ways to access data from health insurance claims databases. While many issues still remain open, including who pays for these changes, these improvement efforts should be encouraged, coordinated, and supported.

To improve the surveillance and analysis systems, key recommendations include:

- Improve the rate of physician reporting of device malfunctions;
- Include complete information in individual event reports;
- Filter reports of known issues so that truly new events are more visible;
- Increase rates of physicians returning devices for evaluation and interrogating devices;
- Improve the robustness, timeliness, and accessibility of the MAUDE database;
- Use common terminology and coding;
- Improve registries and active surveillance systems;
- Use health claims databases for event detection; and
- Ensure ongoing FDA oversight of manufacturers' compliance with event reporting and analysis requirements.

As the surveillance systems improve, more low and ultra-low frequency events will be found. As such, the decision on what triggers a physician notification will only become more important.

## V. A NEW APPROACH IS NEEDED AS THE PROPOSED NOTIFICATION TRIGGERS DO NOT SATISFY STAKEHOLDER OBJECTIVES

> *There is always an easy answer to every human problem – neat, plausible and wrong.*
> - *Mencken's Law*

As previously stated, the key question is under what circumstances should a manufacturer notify physicians of device malfunctions. Answer this question correctly and the physicians and patients needs are met, and industry has the certainty it seeks. Any viable trigger must satisfy four criteria: (1) it must be objective, (2) it must be clinically relevant, (3) it

must be consistent with FDA's statutory and regulatory structure, and (4) it must be applicable to all medical devices.

### A. THE CRITERIA FOR TRIGGERING A PRODUCT SAFETY ALERT MUST BE LINKED TO PHYSICIANS' NEEDS

Physicians need information that will assist them in providing patient care. This includes new information regarding previously unknown or unanticipated device malfunctions.[28]

The physician should be charged with knowing the content of the device labeling at the time of the implant and the device performance information that is otherwise already publicly available. Flooding the physician with redundant information adds no benefit and risks important new information being lost or ignored.[29] Consensus on this point is critical as it drives the solution.

Physicians need information that modifies or changes the previously assessed risk/benefit ratio, reduces the risk of a malfunction, or modifies how to detect or mitigate the effects of a malfunction in devices currently in use. Physicians also need actual information, not simply individual event reports or masses of unanalyzed data.

There is risk in providing "too much" or inappropriate information. Unwise product notices can trigger inappropriate medical decisions, lead to patient anxiety, and mask other, more important issues. As Dr. Bruce Wilkoff stated in reference to a particular ICD recall: "I am certain that many more people have been harmed than helped by our collective response and will even die instead of being alive due to the removal and replacement of these devices."[30] Other reports exist of unfortunate medical intervention (sometimes at the insistence of the patient) due to device notifications. One physician has reported that "while Accufix . . . active-fixation pacing leads were prone to fracture, more people were harmed by extracting normally functioning leads then were harmed by the retention wire fracture itself."[31] A New York Times article describes a patient who decided to have a device explanted and

28. *See* Carlson, *supra* note 16, at 177.

29. *See* Proceedings, *supra* note 1, at 18.

30. Wilkoff, *supra* note 15, at 796.

31. William H. Maisel, *Physician Management of Pacemaker and Implantable Cardioverter Defibrillator Advisories*, 27 PACE 437, 441 (2004).

replaced because of press reports regarding a series of product recalls.[32] Of course this is ultimately the patient's decision. However, public pronouncements can certainly (and sometimes inappropriately) influence these decisions.

Likewise, inappropriate notifications undermine the agreed objective of encouraging appropriate device usage. Continual exposure to minor product notifications that do not involve any real-life patient risk can dissuade physicians and patients from using lifesaving device therapies.

It is always easy to say more data should be given. However, the risks of excessive notification must be recognized and addressed. It is this concern that renders the trigger issue so complex. The right balance between over- and under–notification must be struck.

### B. THE CURRENT PROPOSED APPROACHES FAIL TO MEET PHYSICIANS' NEEDS

Five approaches to the trigger question have been advanced.

#### Option 1: Notify Physicians of Every Device Malfunction

The first approach is to simply inform the physician of every event even if it involves a known issue.[33] In one sense, the current MDR and MAUDE systems start to do just this. Under the MDR system, any death, serious injury, or malfunction that could result in a death or serious injury related to the device is to be reported to FDA.[34] At some point, MDR reports become publicly available to physicians via the online MAUDE database.

But the physician needs information, not simply raw data. In order to transform this raw event data into actionable information, each physician would need to continually review data from multiple sources including the MAUDE database, conduct ongoing analyses of possible trends, perform additional investigations, and then derive some consistent, medically relevant conclusion. Logic and recent events, however,

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32. *See* Barry Meier, *Repeated Defect in Heart Devices Exposes a History of Problems,* N.Y. TIMES, October 20, 2005, at A1.

33. *See* William H. Maisel, *Safety Issues Involving Medical Devices: Implications of Recent Implantable Cardioverter-Defibrillator Malfunctions*, 294 J. AM. MED. ASS'N 955, 956 (2005).

34. *See* 21 C.F.R. § 803.30 (2005).

demonstrate that this is not realistic. [35]

The weaknesses in this approach are easily seen in the Prizm 2 situation. According to public reports, all of the Prizm 2 incidents were reported to FDA via the MDR process and some of the event reports were on the MAUDE database when that controversy erupted.[36] Despite these public filings, doctors and FDA were honestly surprised by the Prizm 2 situation. Simply having the Prizm 2 MDR reports available to each physician was pointless. Any potential patient harm caused by excessive or inappropriate communication is maximized by this approach.

This approach is also inconsistent with the risk/benefit and probability-based criteria for FDA-mandated notifications in 21 U.S.C. §360h. Overall, this approach fails to satisfy the stakeholders' objectives and so should not be implemented.

Option 2: Establish a Trigger Based on a Specific Number of Device Malfunctions

Under this approach, FDA would simply establish a specific number of events and whenever that number is hit, a product alert would be sent out. For example, a product alert could be required whenever ten events of one type have occurred.

The first question is whether society will require a safety alert when just one malfunction occurs regardless of the total device population or event rate. In other words, is it acceptable as a policy matter that a certain number of malfunctions occur before there is a physician notification? The first possible answer is a flat no—if there is a single event it must be communicated. This is simply Option 1 discussed and rejected above. The second possible answer is yes, there is some number of events, regardless of incident rate, that should trigger a product alert.

The reality is that the media, lawyers, and Congress often get excited about the raw number of events. It makes for

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35. Placing this responsibility on each individual physician actually increases the liability risks of the physician. For example, a physician could well be criticized for failing to identify some trend from the mass of individual case reports sent to the physician or available via MAUDE. Similarly, questions can easily arise if physicians come to different conclusions about risks and patient care.

36. This fact did not prevent Guidant from being subject to extensive criticism. *See* Hauser & Maron, *supra* note 16, at 2040-41.

sensational press and often has a predictable emotional impact. However, emotional reactions and sensational press should not drive policy. A raw number can be incredibly misleading. Ten malfunctions out of 100 devices is a critical issue. Ten events out of 1,000,000 devices is a very different thing.

Using a raw event number as the trigger flies in the face of FDA's overall regulatory policies. It is illogical to suddenly shift policy when evaluating post-approval device events. FDA explicitly considers probability of benefit and harm when determining whether to approve a Premarket Approval application (PMA). For example, when considering a PMA, FDA weighs "the probable benefit to health from the use of the device weighed against any probable injury or illness."[37] This and similar provisions[38] clearly demonstrate that FDA uses (and must use) a risk/benefit calculation in device approval decisions and explicitly considers the probable injury or illness. The raw number of events provides only a numerator and is not capable of providing the probability of injury or illness. Product labeling generally provides event frequency rates rather than absolute event numbers as part of the risk/benefit analysis. Stakeholders have the same patient welfare and risk/benefit considerations in the premarket approval stage as they do postmarket approval. As such, the same policies should exist.

Likewise, if one examines FDA's mandatory recall authority under 21 U.S.C. § 360h(a), it is apparent that risk/benefit or probability concepts are an explicit part of the statutory structure. FDA can mandate a notification to health care providers if a device "presents an unreasonable risk of substantial harm to the public health."[39] If FDA considers event probability for FDA-mandated recalls, it should apply the same concepts to the "voluntary" safety alerts performed by industry.[40] Again, using a simple number of events as the

37. 21 C.F.R. § 860.7(b)(3) (2005); *see* 21 U.S.C. § 360(e) (2000).

38. *See, e.g.*, 21 C.F.R. § 860.7(d)(1); 21 C.F.R. § 814 (2005).

39. 21 U.S.C. § 360h(a) (2000).

40. While technically the recalls or safety alerts that are the subject of this commentary are voluntary industry actions, there is substantial direct and indirect FDA oversight and pressure. *See, e.g.*, 21 C.F.R. §§ 7.40-.59 (2005); 21 C.F.R. § 806 (2005) (establishing procedures and obligations for manufacturer initiated safety alerts). If a company fails to conduct a field action, FDA has a variety of formal and informal remedies available to it, including Form 483 observations. For example, one observation in a recent Guidant Form FDA-483 was that Guidant's quality system was deficient

trigger for a safety alert would result in an unjustifiable policy inconsistency.

Similarly, physicians also make decisions based upon probability or frequency rate-based risk/benefit assessment. Without a frequency rate or probabilities, the physician and patient cannot make any rational risk/benefit decision. For these reasons, product safety alerts almost always include frequency rates and probabilities.

Using just an arbitrary number of events as the trigger creates a key gap. Sometimes the manufacturer can identify an issue that has not actually caused a field malfunction but rather increases the risk of a future malfunction. In that case, there is no event against which to apply the trigger. Relying only on actual events as the trigger ignores this crucial risk prevention or mitigation function of the notification system.

Finally, there is no logical or policy basis to differentiate one number from another. If we say notify whenever there are ten events, why not nine or eleven?

A trigger based upon the raw number of events will not be that helpful for physicians, patients, or policymakers. Here, FDA and all other stakeholders need to take a stand that raw event numbers are not an appropriate basis upon which to base critical patient care decisions. This approach is also inconsistent with the risk/benefit and probability based criteria for FDA-mandated notifications in 21 U.S.C. § 360h. While this approach would give industry certainty, it does not advance the needs of physicians and patients.

Option 3: Establish a Trigger Based on the Frequency or Rate of Events

The next option is to define an objective trigger based upon some frequency or event rate. For example, one could set a trigger for a safety alert at a 1/5,000 or 1/1,000 event rate. This approach addresses some of the key weaknesses of Option 2 while still providing industry with certainty. It is more consistent with other FDA policies. As such, it merits closer scrutiny.

Several difficult issues exist with this option. First, what

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because physicians had not been notified of several product issues. *See* FDA, Form FDA-483 (Sept. 1, 2005), *available at* http://www.fda.gov/ora/frequent/483s/2124215_guidant/MINDOGuidantCorpFD483_20050901.pdf.

should the line be? The clinical relevance of a particular event rate will vary among devices and among individual physicians. As demonstrated by the presentation of Dr. Michael Barber, there are significant differences in what event rate physicians consider relevant for ICDs.[41] The value of incident rates as a tool for medical decisionmaking was likewise challenged at the HRS Policy Conference. "[O]ne panelist noted that the rate of incidents is meaningless unless put in the context of a specific patient."[42] Dr. William Maisel's work also establishes that different physicians view the importance of certain levels of malfunction probability very differently. "Physician consensus exists regarding the management of some device advisories but substantial differences of opinion are present regarding the management of many others."[43] Some would act with risks of 1/10,000 while others would be comfortable up to a 1/100 risk. The level of acceptable risk will also vary by device type.

Second, how should situations be handled in which the trend in question is under the anticipated incident rate of the device? For example, assume that the device in question has an anticipated and labeled malfunction rate of 0.1%. The actual performance rate is 0.07%, but the notification trigger is 0.05%. Would it benefit anyone to take the time and effort to notify the physician that the device is performing as well or better than anticipated? If we are consistent in our position that physicians should be provided with new information, then this approach falls short. Moreover, notification about clinically irrelevant events can also create unnecessary anxiety among current patients and can adversely impact the willingness of new patients to use devices.

One could modify this approach and use a frequency rate as a trigger for only "new events." This requires everyone to agree to what is an "old" event and what is a "new" event. Current product labeling is certainly of no help as it generally does not describe component or process specific failure risk. Rate-based triggers also ignore the cumulative impact of multiple malfunctions and event severity. It is practically impossible to create different trigger levels for different combinations or types of adverse events. There are multiple types of adverse events and often we are concerned with future

41. *See* Proceedings, *supra* note 1, at 12.
42. Proceedings, *supra* note 1, at 14.
43. Maisel, *supra* note 31, at 442.

events for which there is either a large span of possible effects or even unknown effects.

This approach also relies upon the accuracy of both past event reporting and future anticipated malfunction event rates. Everyone recognizes that underreporting is a real issue. Use of a frequency-based trigger increases the reliance on the robustness of a system everyone questions and on the accuracy of future event rate projections.

In addition, as discussed earlier, there is no logical or policy basis to differentiate one number from another. If we say notify whenever the frequency is 0.1%, why not 0.09% or 0.11%? Appropriate risk and patient needs vary tremendously between devices. This approach ignores this key fact. A certain malfunction rate may be acceptable for a Class I or Class II device, but may not be acceptable for an implantable Class III device.

This approach is also inconsistent with the criteria for FDA-mandated notifications under 21 U.S.C. § 360h. This provision compels a broader analysis than simply rate. It requires consideration of "unreasonable" risk and potential for patient harm. These considerations are more complex than a mere percentage.

While more enticing than the other options discussed above, this option still fails to satisfy the need to provide the physician with actionable information or "new" information. It also lacks agreed clinical relevance and can discourage additional use of device-based therapy.

Option 4: Provide Information Deemed Relevant to Patient Care Decisions

This approach proposes a subjective standard—tell the physician if it is important. It requires the manufacturer to make a subjective medical judgment. As such, it fails to provide certainty and forces the manufacturer into making medical judgments.

There are multiple problems with this approach. First, as with any subjective standard, there is the challenge of different opinions and second-guessing. Arguably, this is what happened in the Prizm 2 situation. Guidant made the initial assessment that notifying physicians of the Prizm 2 situation was not appropriate or required. Others strongly disagreed. Similarly, the lack of objective criteria or certainty would make FDA and public oversight difficult.

Some have expressed concern that vesting this decision in the manufacturer creates an unavoidable conflict of interest. At the same time, delegating this task to a private body such as HRS or a physician committee raises a host of issues including makeup of that body, oversight, and conflict of interest. It also may be an impermissible delegation of a government function.[44] FDA itself has historically avoided making such specific medical judgments.

Overall, the approach lacks clarity and certainty and may not provide physicians with information that is truly needed. This proposal simply repackages many aspects of the current system. A better solution is needed.

Option 5: Keep the Old System

Few, if any, advocate keeping the current system unchanged. The current system does not establish any objective trigger[45] and, for a variety of reasons, has not met stakeholder needs. Under the current system, companies are to "carry out their responsibility to protect the public health and well-being from products that present a risk of injury or gross deception or are otherwise deceptive"[46] in making recall decisions. One can argue that this is equivalent to the subjective standard of Option 4. In order to add some certainty and objectivity, most manufacturers have created their own criteria for initiating a recall, often through the use of health hazard evaluations (HHE).[47] In many ways, this is similar to the HHE concept used by FDA to evaluate industry-initiated recalls in the current system.[48] However, because each manufacturer can have a separate HHE, there is no assurance of uniformity. Companies that might "push the envelope" may feel "rewarded" by having to conduct fewer safety alerts.

In addition, current FDA regulations generally link recalls with violations of FDA requirements. "Recall is an effective

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44. *See* United States v. An Article of Drug . . . Ova II, 414 F. Supp 660, 665 (D.N.J. 1975), *aff'd without opinion*, 535 F.2d. 1248 (3d Cir. 1976).

45. *See* Barry Meier, *Implants with Flaws: Disclosure or Delay*, N.Y. TIMES, June 14, 2005, at C1 ("'You have to make judgment calls, and there is no hard-and-fast rule,' said Dr. Susan Alert, the chief quality and regulatory officer at Medtronic . . . . 'Different companies might come out differently.'" ).

46. 21 C.F.R. § 7.40 (2005).

47. Manufacturers are expected to have a "written contingency plan for use in initiating and effecting a recall." 21 C.F.R. § 7.59 (2005).

48. *See* 21 C.F.R. § 7.41 (2005).

method of removing or correcting consumer products that are in violation of laws administered by the Food and Drug Administration . . . ."[49] There may well be situations in which the product is not violative, but additional or new safety information should be made available to physicians. Linking safety alerts with violations of law confuses quality and compliance and can create a strong disincentive against initiating safety alerts.

Given the overwhelming dissatisfaction with the current system and its lack of objective and meaningful criteria, it seems clear that the existing system has not met the needs or objectives of the stakeholders.

### C. A NEW APPROACH: LINK THE NOTIFICATION TRIGGER TO THE PRODUCT LABELING

Given these issues with current approaches, the challenge is to identify a realistic alternative approach that satisfies the various stakeholder objectives. This commentary now offers such a proposal for consideration. The basic concept is to link the approval process, product labeling,[50] and event reporting systems with the product notification process. This proposal also differentiates quality improvements from non-compliance or a failure to meet product specifications.

#### 1. Overview

The core of this proposal is to include in the product labeling the total "all cause" predicted malfunction rate for the specific device.[51] Actual device performance, including both actual and predicted malfunctions, would be compared to that labeled rate throughout the life of the product. In this context, actual device performance rates would include both actual failures and anticipated or predicted failures. If at any point the actual malfunction rate is higher than the predicted malfunction rate, then a product safety alert would be

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49. 21 CFR § 7.40(a); *see also* FDA, Guidance for Industry: Product Recalls, Including Removals and Corrections, http://www.fda.gov/ora/compliance_ref/recalls/ggp_recall.htm (last updated Nov. 3, 2003).

50. This commentary uses the term "labeling" in the broad sense as defined in 21 U.S.C § 321(m) (2000). Thus labeling includes the physician's manual or instructions for use for the device. *See id.*

51. *See* Proceedings, *supra* note 1, at 14 ("One of the things I'd like to see . . . is what the expected failure rate should be.").

required.[52] This approach uses the actual product labeling for each product as the unique, device-specific trigger for product safety alerts.[53]

There is also a recognized need to periodically update the physician and patient about the performance of an already implanted device even if it is performing as specified.[54] To address this need, the physician's manual or a product performance report would be periodically updated with information about device performance even in situations in which the device was performing better than the total predicted malfunction rate. Whether one uses the annual report process as the jurisdictional basis or an obligation to update the labeling as a condition of approval, the result is the same.[55] The physician would have access to new information and a periodic performance affirmation.

This approach also differentiates compliance and quality. Compliance sets minimum standards, in this case a malfunction rate. Compliance is binary. One is either in compliance or out of compliance. Quality, on the other hand, is aspirational. Quality can and should always be improved. The failure to meet the labeled malfunction specification is a compliance issue. Acting to improve device safety or efficacy when the device is already meeting labeled requirements is quality improvement.

2. Implementation

The first step in this process is for manufacturers to include the total anticipated malfunction rate in the product labeling. This would be an "all cause" predicted malfunction rate. This rate would be reviewed and approved by FDA as a required part of the device labeling before product approval and marketing.

In addition to its use for product safety alert purposes, the

52. There may be a degree of uncertainty about a predicted malfunction rate given incomplete information. If the predicted rate range straddles the trigger point, at least the product performance report can be updated pending more information and certainty.

53. Any unique requirements such as the notification requirements for certain electronic products would remain applicable. *See* 21 C.F.R. § 1003 (2005).

54. *See* Salberg, *supra* note 3.

55. *See, e.g.*, 21 C.F.R. § 814 (2005) (providing additional information on the labeling and annual report requirements).

malfunction rate has the additional benefit of providing the physician with key information at the time of the implant. As discussed by several commentators, the total predicted malfunction rate should be a vital part of the risk/benefit analysis and product selection at the time of implant.[56]

This approach also allows FDA and physicians to compare device performance across time, manufacturer, and feature sets.[57] Because all companies would have to include an overall malfunction rate in their product labeling, quality and reliability would truly become transparent and a basis for competition.

Under this approach, the labeled malfunction rate becomes the trigger for safety alerts. As long as the device is performing at a level equal to or better than the labeled rate, the initial positive risk benefit conclusion remains valid and the device is performing as expected. So, for example, if a product has an expected malfunction rate of 0.5% and the actual malfunction rate is 0.2%, the physician and patient should be satisfied with the original risk benefit analysis and decision. No product safety alert would be required unless and until the malfunction rate exceeds 0.5%.

One key advantage to this approach is that it takes into account the overall performance of the device, not just one trend. Under this approach, a product alert can be triggered by one event that exceeds the labeled rate. However, unlike the other approaches, a product alert can also be triggered by the aggregate impact of multiple trends. For example, a number of small issues might, in aggregate, exceed the expected "all cause" malfunction rate when no one issue separately would do so. The initial implant decision is based on aggregate device reliability. If that level is exceeded, the physician should be notified.

One could challenge this approach for failing to differentiate between types of malfunctions or their implications. However, this approach offers the flexibility to deal with such differences. If the manufacturer or FDA believes that it would be useful to include a more detailed

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56. *See* Hauser & Maron, *supra* note 16, at 2042; Proceedings, *supra* note 1, at 20, 25.

57. Commentators have urged that quality become a marketing tool. *See* Maisel, *supra* note 33, at 956 ("Public reporting would make safety a market force.").

breakdown by malfunction type or patient impact, then that information can simply be included in the labeling along with the total predicted malfunction rate. A safety alert would then be required whenever (a) the total malfunction rate was exceeded, or (b) a more specific malfunction rate was exceeded. This allows labeling flexibility based upon the specific risks, characteristics, and usage of different devices.

One might also object to this approach because of weaknesses in event reporting systems. However, using total projected reliability as the trigger, actual event reporting variations should have minimal impact.[58] The methodology used to predict performance when the product is developed and approved should be the same methodology used to update the predicted malfunction rate. As such, data reporting variability should be neutralized. This approach also focuses on trends, not single events.

Actual performance from the MAUDE database, registries, or other information sources would be available as both an input into the predicted malfunction rate and as a public check on actual performance and accuracy of the predictions. Furthermore, FDA routinely inspects the manufacturer's systems that are the input into the predicted performance rates, resulting in a built-in check on company performance.

Including a total anticipated malfunction rate in product labeling is well within FDA's authority. FDA can require companies to include that overall malfunction rate in PMA and Supplemental Premarket Approval (SPMA) submissions and to include that rate in the product labeling.[59] Of course, similar methodologies are needed for cross-company comparisons. If there are not already acceptable industry standards, FDA can develop guidance documents (with stakeholder input) to establish a common methodology for various device classes. FDA's approval and inspection processes should ensure consistent application of these standards.

The final question is whether this concept is consistent with FDA's mandatory notification powers. It is. Devices are

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58. Any impact of low reporting rates also applies to other suggested approaches. For example, using a raw number of events or an actual frequency rate as the trigger depends upon robust reporting. Here, engineering analysis can be used to calculate the predicted failure rate and thus compensate for any low reporting issues.

59. *See* 21 C.F.R. §§ 814.20, 814.39 (2005); 21 C.F.R. § 860.7(b), (d) (2005).

approved and labeled to reflect a risk/benefit balance.[60] Using the labeled predicted malfunction rate as the trigger incorporates this risk/benefit consideration and is consistent with the risk based criteria in 21 U.S.C. § 360h.

3. This Concept Works for All Factual Situations

Once the total projected malfunction rate has been established, any malfunction trend falls logically into one of four categories. A detailed review of each category demonstrates that this approach satisfies the various stakeholder objectives and can be reasonably implemented.

a. Group 1

In this first category, the malfunction trend in question is known and by itself or in combination with all other malfunctions is within the labeled predicted malfunction rate. In this case, the devices are performing as predicted and intended. By definition, the performance of these devices is equal to or better than the information used to make the initial risk/benefit decision to implant the device.

There is no need for any safety alert as the physician has had the necessary information since the time of implant and has already been able to take it into account in making health care recommendations to the patient. MDR reporting, failure analysis, and trending would still be required, and individual events would still be entered into the MAUDE database. This level of reporting will satisfy the regulatory requirements and ensure that there is adequate information for trending and analysis. These information sources also operate as a confirmation of device performance. To the extent that an individual physician wants to see individual events, that information will be available from the MAUDE database. Periodic product performance reports can reflect that the device is performing as intended.

This approach is aligned with the product approval and labeling processes. It promotes transparency, and it ensures that physicians will not receive redundant or unnecessary communications and current and future patients are not unnecessarily alarmed. Finally, it is consistent with current regulatory structures.

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60. *See* 21 U.S.C. § 360e (2000); 21 C.F.R. pt. 814 (2005); 21 CFR § 860.7 (2005).

b. Group 2

In this category, the malfunction rate by itself or in combination with all other malfunction causes exceeds the predicted and labeled rate. It does not matter whether the particular problem was known or unknown. The patient is not getting what the patient expected and what was represented to the physician and FDA. This product may well be at least technically adulterated or misbranded.[61] The physician should be notified of these events through a product safety alert.[62] The safety alert should describe the issue, its frequency, any possible detection or mitigation steps, the new overall predicted malfunction rate, and any other relevant information. Once publicly available, the new malfunction rate then would become the new standard against which any future device issues get measured.

In one sense, the predicted malfunction rate can be viewed as analogous to a contractual warranty. The warranty provides that the device will not malfunction for whatever reason at more that a specified rate. If the device is malfunctioning at a higher rate than "warranted," the physician is notified.

This approach provides the physician with new patient care or risk/benefit information. It promotes transparency and should help build or restore trust in the system. It provides FDA with updated information and the opportunity to assess any issue or set of issues on an ongoing basis. Finally, it gives industry and other stakeholders certainty.

c. Group 3:

In the third category, a new event or trend is discovered and the overall malfunction frequency rate or severity from all causes, including the new event, is less than or equal to the predicted malfunction rate. The labeling already correctly identifies the failure rate and includes any relevant malfunction detection or mitigation information.[63] As such, the current product labeling informs the physician of all necessary and appropriate information. Given the continuing accuracy of the labeling, nothing new needs to be communicated to the

61. *See* 21 U.S.C. §§ 351, 352 (2000).

62. Generally speaking, the requirements of 21 C.F.R. §§ 7.40-.59 and 21 C.F.R. pt. 806 would be applicable to this situation.

63. For our purposes, mitigation includes decreasing either the risk or severity of the event.

physician for patient care purposes. No safety alert is required. Nothing more should be required from a compliance perspective.

However, quality, trust, and transparency goals encourage more communication. Patients live with these devices and so have an ongoing desire for information.[64] As such, information about these trends, even though arguably offering nothing new for patient care, can easily be made available to physicians via Internet-based product performance reports or publicly available physician manuals. This update can also include an affirmation that the existing predicted malfunction rate remains correct. Throughout this process, the manufacturer's obligations for MDR reporting, event analysis, and trending would remain.

New information of this type should not be considered by the agency or the public as evidence of non-compliance. As is the situation today, updates to product performance reports should not be treated as labeling changes subject to FDA review and approval.[65] To do so would build delays into informing the physician, burden FDA, and convert quality initiatives into compliance matters. Since the device is still performing better than labeled or warranted, this is a quality initiative. Manufacturers should not be punished, penalized, or criticized for quality initiatives.

d. Group 4

The fourth and final group includes device issues (old or new) which occur at a rate less than the labeled malfunction rate but for which additional detection or mitigation information now exists. Detection or mitigation information in this context means information that is different from what is already publicly available to the physician and that would enhance the physician's ability to selectively detect this particular malfunction or to reduce or eliminate the potential health impact of the malfunction.

This group presents a more complex situation. From one perspective, the device is continuing to satisfy the product labeling, including its specified malfunction rate. The

64. *See* Bartels, *supra* note 3, at 184-85; Salberg, *supra* note 3.

65. One detail to be addressed upon implementation of this concept is whether any provisions of 21 C.F.R. pt. 814 need to be modified to permit changes to product performance reports without FDA review and approval.

risk/benefit calculation that supported the initial implant decision remains unchanged. Given that, the device may not be considered legally adulterated or misbranded. However, the fact remains that additional information can improve patient outcomes or device performance. In this situation, the product should be considered compliant, but the product quality can be improved. Quality improvement opportunities can exist without the product being in violation of any FDA regulation. If we mutate quality improvement opportunities into "recalls" and non-compliance, we will discourage and penalize quality improvements and risk misleading consumers about the nature of the issue.

At the same time, we should not ignore this information. From the patient and physician perspective, quality considerations predominate, and the manufacturer should make this new information available. The product performance updates can be used to promptly communicate this information. Again, such updates would involve established trends,[66] not random events. The only difference would be in timing. Rather than waiting for an annual update or revision to a product performance report, the update would take place promptly. The dividing line between a product performance update and a product safety alert is whether the product is performing as well or better than its specifications. This is the difference between a quality improvement and violative product.

Reserving the safety alert process for situations involving risks greater than those set forth in the labeling enhances communication clarity, avoids diluting the impact of actual safety alerts, reduces inappropriate patient reaction, provides a consistent linkage between the product labeling and the original risk/benefit calculation, and does not inappropriately discourage use of lifesaving therapy.

So, is there precedent or support for this approach? First, issuing safety alerts for products out of specification that pose some patient health risk is consistent with current FDA practice.[67] The proposed total predicted malfunction rate is simply another device specification. Second, the product performance reports are essentially equivalent to how medical information, apart from drug or device issues, is already

66. The definition of a "trend" should be device-specific, part of the Quality System of the manufacturer, and subject to FDA review.

67. *See* 21 C.F.R. §§ 7.40-.59 (2005).

communicated to physicians. The physician currently has the duty to keep abreast of developments in his or her field. This continuing education process relies on physicians reading the medical literature and attending medical meetings. For example, if one physician learns of a better way to perform a particular surgical technique, that information is communicated through medical literature and medical meetings. This approach to device quality improvement information uses the same communication process. If it is acceptable and usable for physicians in the surgical technique situation, it should work here.

If we incorporate an overall malfunction rate in the product labeling and use that rate as the notification trigger, then defining what constitutes a malfunction is critical. First, the labeled malfunction rate should include anticipated or potential malfunctions, not just the rate of past events. The risk being assessed by the physician and the patient is the risk of a future event, not just what has already happened. Second, as discussed earlier, it should use the MDR definition of deaths, serious injuries, or malfunctions.[68] This approach allows comparison of data across systems and provides an overall quality indicator for the consumer. The traditional adverse event descriptions, warning, and contraindications in the product labeling would remain. This concept simply adds new information, namely the overall "all cause" predicted malfunction rate as well as any subsets deemed appropriate, to the labeling.

4. Various Regulatory and Market Forces Should Drive Manufacturers to Be Accurate in Calculating the Total Predicted Malfunction Rate

Any new regulatory approach should be reviewed with a cynical eye. Is there a way to "game" this new system? Here, the initial predicted malfunction rate in the labeling is the key trigger point. So, would a company seek to game the system and simply publish a high malfunction rate and thus minimize or eliminate the risk of formal product recalls?

Two mechanisms should prevent this. The first is the marketplace. Every competitor will also be publishing overall malfunction rates. In this environment, reliability becomes a basis of competition. Companies with lower malfunction rates

68. *See* 21 C.F.R. § 803.3 (2005).

should garner a competitive advantage. Public awareness would reinforce the market pressures. By making overall malfunction rates transparent and comparable, we use market forces to drive higher reliability and prevent "sandbagging."

The second check on artificially high malfunction rates is the FDA itself. By making overall malfunction rates part of the submission and approval process, FDA will be able to consider that rate in device approval decisions. FDA certainly should question a manufacturer's submission if there is any significant increase in malfunction rates over previous generations or over competitor's products. FDA's inspection process, including pre-PMA inspections, can also review the accuracy of the manufacturer's predicted malfunction rate.

Of course, this then raises the opposite issue. Will companies seek to publish excessively low malfunction rates as a way to gain a competitive edge? Several control mechanisms should prevent such actions. First, if the labeling understates the actual malfunction rate, the product could be considered adulterated or misbranded.[69] As such, shipments of those products expose the company and individuals to significant enforcement actions.[70] During inspections, FDA can easily compare complaint and MDR information against stated failure rates to assess compliance. FDA also has access to information from sources other than the manufacturer, including the MDR and MAUDE databases, published medical literature, and active surveillance systems such as MedSun. Second, if one understates the malfunction rate, one is then exposed to additional formal product safety alerts and relabeling requirements.

Pressures to game the system in either direction are negated or balanced by market dynamics and the regulatory system. Here, market forces and regulatory requirements are aligned to drive accuracy and compliance. Consumers will now be able to compare real safety alert rates and respond in the marketplace. As a result, manufacturers have every incentive to make labeled malfunction rates as accurate as possible.

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69. *See* 21 U.S.C. §§ 331, 351, 352 (2000).

70. *See* United States v. Park, 421 U.S. 658 (1975) (reaffirming criminal liability for corporate executives even in the absence of intent); *see also* 21 U.S.C. §§ 332-34 (2000) (describing FDA enforcement options).

5. The System Must Address the Distribution of Other Non-Compliant Devices

To date, the entire discussion has revolved around determining the criteria for triggering a product safety alert related to patient safety. For the sake of completeness, we must address product issues that do not involve safety or efficacy issues.

First, there are products which do not meet specifications or are otherwise non-compliant but present no safety or efficacy concerns. These products may be considered "technically" adulterated. The question is whether a product safety alert should be initiated for these product issues. Given the need to both avoid unnecessary consumer concern and to ensure that the importance of safety alerts are not diluted, it seems clear that it would not be appropriate to use the safety alert mechanisms discussed above. "Safety Alerts" should be reserved for safety issues.

FDA has access to a number of enforcement tools to address these issues. These can range from inspections and "483" observations to seizures and criminal prosecution.[71] Use of these processes rather than safety alerts preserves the integrity of the safety alert system while giving FDA its full panoply of enforcement tools. Under these circumstances, if FDA wants to pull products from the distribution chain, it can use its seizure powers.[72]

There are some circumstances in which devices are being marketed or distributed without FDA approval. Because these products have not gone through the safety review process under the PMA regulations or the investigational device exemption (IDE) regulations,[73] it is difficult to determine whether these devices pose a health risk. In this situation, logic dictates that safety alerts and actual product recalls may well be appropriate in addition to the usual enforcement mechanisms.

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71. *See, e.g.*, 21 U.S.C. §§ 332-34 (establishing injunctive relief, penalties, and seizure as possible enforcement options).

72. FDA can also use its enforcement powers in addition to a safety alert in instances involving a violative product that presents a risk to health. For example, the seizure provisions specifically cover products that are "dangerous to health." 21 U.S.C. § 334(a)(1)(B).

73. *See* 21 C.F.R. pt. 814 (2005) (establishing premarket approval requirements); 21 C.F.R. § 860.7 (2005); 21 C.F.R. pt. 812 (2005) (outlining IDE requirements).

D. SUMMARY AND RECOMMENDATION

The proposed approach to health-based product issues can be visualized as follows:

| | Group 1 | Group 2 | Group 3 | Group 4 |
|---|---|---|---|---|
| Product Performance | Performance better than labeling | Events exceed predictions | New event; performance better than labeling; no mitigation | New event; performance better than labeling; no mitigation |
| Complaint Handling Obligations | Yes | Yes | Yes | Yes |
| Update to Physicians Manual | No | Yes | No | Yes |
| Product Performance Report Update | Reconfirmed at next publication | Yes | Updated at next publication | Yes, prompt product performance update |
| Product Safety Alert | No | Yes | No | No |
| Actual Physical Recall | No | Yes, if needed to protect patients | No | Yes, if needed to protect patients |

Few changes need to be made in either the regulatory systems or current manufacturer or physician practices in order to implement this new approach. This approach is consistent with current regulatory processes including device reporting and surveillance requirements under 21 U.S.C. § 360i and 21 C.F.R. part 821 and FDA's mandatory recall rights under 21 U.S.C. § 360l. FDA already has the authority to consider device reliability, including total malfunction rates.[74] As such, only the following general actions would be needed to implement this proposal:

- Product labeling (including physician manuals)

74. *See* 21 C.F.R. § 860.7(b)(4) (specifically stating that in considering the safety and efficacy of a PMA device, FDA will consider "[t]he reliability of the device").

must include an overall malfunction rate. This rate can be added to current product labeling either over a defined time or when the next labeling update occurs.

- The regulations need to provide for mandatory safety alerts when the total malfunction rate (including known and new events) exceeds the labeled rate. This could require amending certain provisions in 21 C.F.R. §§ 7.40-.59 and 21 C.F.R. part 806.
- Product performance reports would be used to provide the physician access to any additional or new information about trends within the anticipated failure rate. These can be required either by regulation or via the Conditions of Approval for a PMA device.

This approach satisfies the stakeholder objectives and links the various parts of the device regulatory system together. It protects public health, maintains the role of the physician, enhances trust, uses the regulatory system, and provides certainty. It also differentiates compliance issues from quality improvement initiatives. The required updates to the product performance report ensure transparency and provide access to quality improvement information. Anyone can follow up on the new information as desired.

This approach also satisfies the criteria for an effective trigger. It is objective and clinically relevant as it is based on a device-specific safety and efficacy analysis. It is not only consistent with FDA's current statutory and regulatory system,[75] but it actually goes further and links many key parts of the device regulatory process. Finally, it is applicable to all devices and results in a uniform system with device-specific triggers.

Making this information public does carry with it some risk. Safety alerts must be made public in order to protect public health. There is the risk of patient overreaction or adverse psychological impacts when the product is performing as well or better than predicted. By making information on these products available in the product performance report, we are minimizing the risk and making a conscious policy decision

75. As discussed above, this approach is entirely consistent with FDA's risk-based notification criteria in 21 USC § 360h.

that the value of the information in that form, even if not actionable, outweighs the risk.

## VI. A PLEA FOR PREEMPTION

Assuming that FDA does indeed establish a trigger mechanism—as it is encouraged the agency does—that trigger must be national and uniform in application. This requires preemption.

Patient and physician needs are identical from Maine to California. Having different explicit or implicit trigger points is simply unworkable. It is medically, ethically, and politically impossible to defend notifying patients and physicians in one state and not another. Modern communication systems such as email, blogs, and message boards result in any safety alert being at least national in scope. In addition, companies post product information and safety alerts on websites and issue press releases due to SEC considerations and FDA issues such as Class I recalls. Safety alerts follow products across state lines. As such, safety alerts have an unavoidable national scope. Therefore, the rules determining when there should be a safety alert must be national in scope as well.

One can create a de facto trigger through legal channels other than FDA. Private class actions based on a failure to notify physicians or patients of a product malfunction trend or state actions based on similar grounds will create trigger or notification requirements that are inconsistent with FDA and potentially inconsistent among the states. This is not an idle concern. For example, at the time of this article, the New York Attorney General has recently filed an action against Guidant for failure to issue a safety alert or recall for Prizm 2.[76]

The obvious response to this preemption plea is that a state may be permitted to establish different, non-conflicting standards. Here, however, any rule that sets a different standard than FDA's is conflicting. The notification trigger actually makes two policy decisions. The first decision is when a safety alert is needed. The second implicit but equally

76. *See* Press Release, Offices of New York State Attorney General Eliot Spitzer, Medical Device Maker Sued for Hiding Defibrillator Defect (Nov. 3, 2005), www.oag.state.ny.us/press/2005/nov/nov03a_05.html. I offer no opinion as to the legal or factual merits of this action. The point is simply that in the future if a manufacturer has complied with the FDA trigger requirements, such a state action would be inconsistent with established national policy.

important policy decision is that in the defined circumstances, a physician or patient notification not only is not required but will have a negative impact on the consumer. It is this policy decision that demands preemption. If a state requires notification in a situation in which FDA does not, that state is overriding FDA's determination that such a notification may actually be inimical to the patients' interests.

Once FDA establishes a trigger mechanism, compliance with that trigger requirement must shield manufacturers from different national, state, or private standards or requirements for instituting product alerts. It is unfair and undercuts national policy as expressed in the Food Drug and Cosmetic Act for a manufacturer to be subjected to such inconsistent requirements.

The legal authority for preemption exists; 21 U.S.C. § 360k expressly provides for preemption for certain device requirements. This provides that no state or other political subdivision may have in effect any requirement: "1) which is different from, or in addition to, any requirement applicable under this Act to a device, and 2) which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to a device under this Act."[77]

Both required elements of § 360k are present. As discussed above, a different rule would be either "different from or in addition to" FDA's regulations, and the notification rules, by definition, relate to safety.[78] As such, FDA has the authority to create a trigger that preempts any inconsistent public or private trigger or any effort to penalize a company for complying with the FDA-mandated trigger.[79] FDA must exercise this power to preempt once it determines the appropriate trigger policy. Anything less eviscerates FDA's policy and its responsibilities.

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77. 21 U.S.C. § 360k (2000).

78. *See, e.g.*, 21 U.S.C. § 360h (2000); 21 C.F.R. §§ 7.40-.59 (2005) (establishing criteria for triggering a device notification).

79. Other legal theories or causes of action may still exist. For example, there may well still be a standard product liability action for marketing an allegedly defective product. The issues of preemption for these types of actions are governed by cases such as Medtronic v.Lohr, 518 U.S. 470 (1996), and Kemp v. Medtronic, 231 F.3d 216 (6th Cir. 2001). A full analysis of preemption issues including the issues surrounding preemption of product liability suits in a Class III medical device context is outside the scope of this commentary.

## VII. COMMUNICATION PROCESSES

*Success always occurs in private and failure in full view.*
*- Anonymous*

### A. PHYSICIANS, NOT MANUFACTURERS SHOULD HAVE THE RESPONSIBILITY TO COMMUNICATE SAFETY ALERTS TO PATIENTS

Historically, information about device malfunction issues has gone from the manufacturer to the physician and then from the physician to the patient. Several commentators have suggested that the manufacturer communicate device malfunction information directly to the patient in addition to providing the information to the physician.[80]

There are several reasons why this concept is not prudent. First, such a communication could interfere with the patient-physician relationship. Only the physician is in a position to customize the general information to the specific needs and desires of the individual patient. Multiple communications to the same person about the same issue invites confusion, particularly when dealing with issues and concepts as necessarily complex as product safety alert information.[81]

This is not to say that patients are incapable of understanding such information. The goal is to provide clear, consistent information that is relevant to the specific circumstances of that patient. The most effective method for doing so focuses on the one source—the physician—who has the relationship with the patient and understands the particular needs of that person. The physician can answer specific medical questions and make medical recommendations.

The manufacturer can be a resource for the physician and should be willing to provide additional information at the request of the physician. The manufacturer has a separate obligation to ensure that the physician communication is clear and accurate.

Before we mandate direct manufacturer to patient communications, we must remember that some patients may not want to have direct contact with the manufacturer or to receive certain information. Given that it is impossible to

80. *See, e.g.*, Maisel, *supra* note 33, at 957.

81. In essence, I assert that the criteria set forth in 21 U.S.C. § 360h(a)(2) regarding notifications to physicians rather than patients have been satisfied for safety alerts for products such as ICDs. Exceptions for unusual circumstances can always be made.

determine in advance who has what preferences, the physician must be the link to the patient.

### B. TIMING

Many physicians want the opportunity to communicate to the patient before the information becomes public. That is probably an impossible goal. Often the manufacturer and FDA will immediately issue a press release about the product issue that echoes the content of the actual physician notification. The actual physician communication is usually available on the company or FDA website. Public disclosure of recalls also may be required by SEC. Any press release will become public before the physician has received the information and had an opportunity to communicate with every patient.

In addition, email, message boards, and blogs speed information around the globe. While we can debate the accuracy or value of such communication tools, they are real. As such, the patient may well have significant information before the physician can contact the person. It is impossible to control these various information sources until physicians can communicate with each patient. This is the new reality of the information age, and physicians must be prepared to reeducate patients who have gotten questionable information from one of these sources.

### C. TERMINOLOGY

Multiple commentators have expressed concerns over the lack of clarity in the current recall terminology. The most common example is the use of the term "recall."[82] Whether intended or not, this term communicates the actual, physical removal of a product. In most recalls, this is simply not the case. As a result, patients can be unnecessarily upset and confused.

The term "safety alert" should be the universal term for a physician notification of situations in which the device is not meeting its labeling. This term is accurate and does not mislead the lay public. The term "recall" would be included in a safety alert if the recommendation is that the product actually be physically removed from a patient. Otherwise the term creates too much confusion and apprehension,

82. *See* 21 C.F.R. §§ 7.40-.59 (2005).

particularly among patients.

The current "recall" classification system can work as long as the definitions are used consistently. This requires an accurate assessment of the risk and a consistent application of risk analysis methodologies including the use of the actual device risk. This is the total risk to the patient (risk of malfunction multiplied by the risk of injury in the event of malfunction) rather than the risk to the patient if the device actually malfunctions.[83] The latter approach is not consistent with the actual classification language. More importantly, it miscommunicates the real situation to the physician and patient.[84] In order to accurately communicate risk, the classification system must consider both the risk of device malfunction and the risk to the patient in the event that the specific device malfunctions.

FDA must exercise discipline when making classification decisions. Objective criteria need to be established and followed. Even if the issue involves an implantable device, if the risk is less than the frequency requirements for a Class I designation, so be it. "Overclassification" weakens the system, unduly alarms patients, and results in true safety alerts getting less attention than deserved.

Other terminology questions may also need to be addressed once the overall system has been established.

### D. SUMMARY AND RECOMMENDATIONS

The communication process and dissemination of product information has caused anxiety and confusion. Risk communication specialists could be a great help in crafting accurate, understandable, and non-alarming messages. The key objective is to communicate accurately and to avoid unnecessary alarm. The following conclusions or actions should be considered:

- Product safety alerts should go to physicians, not directly to patients.

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83. This is a major difference. For example, a product may have a 1/5000 chance of malfunctioning, but if it does malfunction, there is a 1/10 risk of patient harm. Historically, the risk of malfunction is the product of the two elements, or a 1/50,000 risk in our example. If we look only at the second part of the risk equation, the "risk" is 1/10.

84. A related issue is that many physicians are simply unaware of the meaning of the various classifications. *See* Proceedings, *supra* note 1, at 12.

- The physician is responsible to communicate with the patient. Manufacturers and FDA should be available to support that effort.
- Communication specialists should be enlisted to help craft understandable and accurate messages.
- The system cannot ensure that physicians have a chance to communicate with patients before information becomes public.
- Terminology such as "recall" should be revised to enhance clarity.

FDA's recall classification system should be reviewed and updated. FDA must apply those classifications in an objective, consistent manner. In part this means that individual FDA officials cannot allow personal views about the significance of some event to affect the objective classification process.

## VIII. CONCLUSION

*A conclusion is the place where you got tired of thinking.*
*- Arthur Bloch*

The key to this proposal is linking the product labeling to the device malfunction notification system. An overall or "total" malfunction rate provides the trigger point for determining whether a physician notification is required. Different devices can and should have different trigger points based upon product reliability, risk, and usage. Once the trigger point is exceeded, a prompt, complete, and understandable safety alert must be sent to physicians. Product performance reports provide the mechanism for physician updates of product trends that do not exceed the labeled performance specifications.

Is this approach perfect? Of course not. Any notification policy requires policy tradeoffs. Any line is arbitrary. No definition of "malfunction" is perfect. Industry compliance and FDA oversight is always required. However, this approach does link together various parts of the regulatory system. It allows the trigger to be set in advance, in the public view, and in a device-specific manner. It also encourages quality initiatives without branding such actions as examples of non-compliance.

The final test is to determine whether this proposal meets the objectives set by our commentators. I believe that it does.

Public health is protected because physicians are promptly notified of important new information. The consumer gets information whenever the product exceeds predicted and public malfunction rates. This approach also reduces the dangers of overnotification and therefore does not create unnecessary anxiety among patients. It also does not discourage the appropriate use of device therapies. There is transparency because product labeling sets forth malfunction rates, safety alerts are triggered whenever that rate is exceeded, and product performance reports contain overall trends even if the product overall is performing better than specified. The approach is consistent with the current statutory and regulatory systems, and the patient-physician relationship is maintained. Finally, industry and all other stakeholders get certainty.

Let the debate begin.