

Report
of the
**INDEPENDENT PANEL OF
GUIDANT CORPORATION**

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PREAMBLE

Implantable cardiovascular devices have evolved as a major class of medical products used for the management of cardiovascular disorders. This class of medical devices includes a broad range of categories, such as intravascular stents, artificial valves, hemodynamic support devices, as well as pacemakers, defibrillators, and their related lead systems. All categories of such devices are subject to the limitations inherent to any manufactured product, including unanticipated flaws in design, random errors during the manufacturing process, random component failures, and malfunctions acquired during the useful life of the devices. In the case of electrically active devices, programming errors also might result in malfunctions under certain circumstances. Such errors include both those that could not have been predicted and those that could have been predicted with a better understanding of the design, manufacturing, and device use. All of these categories of malfunctions and failures are superimposed upon the potential stresses of the human body environment, and in the case of electrically active systems, the expected battery depletion over time.

In order to effectively identify and manage device defects as part of their Quality Systems, manufacturers are required by the FDA to implement strategies for the design and manufacture of highly reliable devices and the surveillance of their products in the field. They must also develop methods for identifying and correcting defects that are potentially or manifestly hazardous. Policies for appropriate communication of information about defects to prescribing physicians and the relevant populations of patients are additional obligations. Under certain circumstances, the latter operate in parallel with, and in addition to, the regulatory requirements for reporting to the FDA and other regulatory bodies.

Beginning in May 2005, Guidant Corporation attracted a great deal of attention in the public media and medical community as a result of reports of a series of previously undisclosed defects in one category of their implantable products, namely pacemakers and defibrillators, manufactured by their Cardiac Rhythm Management (CRM) business. As information evolved, it became apparent that the CRM business of Guidant Corporation was aware of, evaluating, and mitigating the issues related to a number of these defects in a certain group of defibrillators during the period of more than three years from the point in time at which the first of this series of defects was recognized. In accordance with their procedures at that time, information about these defects had been reported to the FDA, as required by regulations, but had not been communicated to the Guidant Management Committee, to the public or

potentially affected patients.

The reported death of one individual attributed to a previously identified defect in a defibrillator, in conjunction with delayed visibility to the public, generated serious criticisms of Guidant Corporation in the public media, particularly in regard to failure to communicate in what was interpreted to be a timely fashion. Guidant's publicly stated position was that they had attempted to balance the benefit of disclosure against potentially negative consequences, and defended their position of non-disclosure as medically appropriate. This response was judged unacceptable by public media and some segments of the medical population, and negative commentaries about Guidant Corporation's policies and procedures in regard to defect reporting continued through the summer and fall of 2005.

In the wake of abruptly increasing criticism, Guidant Corporation announced in June 2005, that it intended to commission an Independent Panel charged with the responsibility of studying, analyzing and evaluating the Policies and Procedures of the CRM business, in regard to postmarket device performance, analysis of defects, surveillance of marketed devices, and communication of deviations to physicians, patients, and the general public. The mandate of the Independent Panel of Guidant Corporation was to carry out this review and analysis and provide recommendations for improving performance in regard to surveillance for low frequency events and communications to physicians and patients. The details of the history of the Independent Panel, including its creation, mission, charter, membership, procedures, and operations are provided in this Report. Among the commitments made by Guidant Corporation to the Independent Panel were unencumbered access to relevant corporate documents and personnel, and independence of function.

This document constitutes the Report of the findings and recommendations of the Independent Panel of Guidant Corporation. The design of the Report includes an initial summary of general observations and a series of problems requiring attention. These serve the function of an executive summary, providing focus on the major findings and recommendations. This is followed by a detailed description of observations of the multiple elements that the Independent Panel studied in all of the relevant segments of Guidant Corporation that deal with defibrillators and pacemakers. Detailed statements about the recommendations and their rationale follow, and are supported by the Independent Panel's findings. The next section cites relevant reference material that can provide detailed background information for the interested reader. Finally, the Appendix provides a series of technical descriptions of strategies for implementing the major recommendations.

We anticipate that implementation of the Independent Panel's recommendations, which are based upon the analysis and integration of the information made available to it, will provide better methods for identifying, mitigating, and communicating device malfunctions. Although many of the details of the recommendations are specific to Guidant Corporation, the general principles embodied in the statements will likely be applicable to the pacemaker and implantable defibrillator industry generally. Inherent to all the recommendations of the Independent Panel are three fundamental assumptions:

- Manufactured devices can never be 100 percent free of design or manufacturing flaws, but for products for which the consequence of a failure can be a fatal event, the design tolerances and postmarket surveillance strategies should be intended to move failure rates as close to zero as possible.
- Physicians have a need to know about the performance features of specific devices in a form that is understandable and clinically useful.
- Patients have a right to access such information in order to make informed decisions about risks and benefits, and to formulate expectations.

Our recommendations are generally intended to provide a smooth and effective interface between the manufacturer, prescriber, and recipient of these devices.

NOTE REGARDING TERMINOLOGY

Within the device industry generally, there are inconsistencies in the language used to address the problem of malfunctions and failures. For the purpose of this document, the Independent Panel has adopted a uniform language standard which may be at variance with some of the usages in other venues. The language variations include terms such as components versus devices, failure versus malfunction, and manifest versus potential risk. We have adopted the following language for use in this Report:

I. RELIABILITY

- A. DEVICE: The completed manufactured product, including all of its components (with the exception of its lead systems), in a physical form that is ready for implantation in a patient.
 - 1. Device Failure: The inability of the device to provide therapy that is intended for the survival or avoidance of major medical morbidities.
 - 2. Device Malfunction: A deviation from the intended function or response to a clinical event that the device is intended to provide. Malfunctions in the extreme may be device failures as defined above, or may be of lesser clinical significance but still requiring mitigation.
- B. COMPONENT: A manufactured element, or designed software, within a device, a failure or malfunction of which might lead to a device malfunction or failure.
 - 1. Component Design Flaw: A design feature of a component or components that creates a systematic risk of failure.
 - 2. Component Manufacturing Defect: A manufacturing error that can result in a component malfunction.
 - 3. Component Interaction Risk: A design feature that results in an interaction between components resulting in a malfunction, even though the components in isolation function properly.
- C. CATEGORIES OF COMPONENT OR DEVICE DEFECT
 - 1. Random: A defect unique to a specific component that causes non-repetitive malfunctions or failures. This may be due to manufacturing error during construction of a single device or a single defective component.
 - 2. Systematic: Repetitive malfunctions or failures due to a design flaw or inherent component defect.

D. CATEGORIES OF RISK

1. Manifest vs potential life-threatening events: “Manifest” refers to the occurrence of one or more actual fatal or near-miss events as a result of device failure or malfunction. “Potential” refers to a flaw or defect that creates a realistic potential for a fatal or near-miss event in the future, if not mitigated or replaced.
2. Population risk versus individual risk: Distinction between a statistical statement of risk probability among a defined universe of patients and risk consequences for an individual.

II. SURVEILLANCE

- A. VOLUNTARY REPORTING: Reporting of product variances at the option of physicians, patients, facilities, manufacturers, or distributors.
- B. MANDATORY REPORTING: Regulatory agency requirement for facilities, manufacturers, or distributors to report product variances.
- C. PASSIVE SURVEILLANCE: A process that relies upon information reported to a manufacturer or regulatory agency by a consumer or user, in the absence of a process that seeks disclosure.
- D. ACTIVE SURVEILLANCE: A policy or procedure that proactively tracks device performance and/or variances.

III. COMMUNICATION

- A. TRANSPARENCY: Availability of information to stakeholders regarding matters that affect their interests. For the mission of the Independent Panel of Guidant Corporation, stakeholders include the relevant health care providers, patients, family members, and regulatory agencies.
 1. Passive Transparency: Availability of information upon the volition of the stakeholder through public access sources. Examples pertinent the mission of the Independent Panel of Guidant Corporation include continuously updated postings on the Guidant web site and routine publishing of information in the product performance reports.
 2. Active Transparency: An active effort to direct relevant information to specific stakeholders. Directed communication of information to targeted audiences, such as physicians and patients, using methods such as press releases, “Dear Doctor” or “Dear Patient” letters, or specific performance postings on the web site.

3. Forced Transparency: Release of information by outside parties, such as regulators, activists, or the media, about an issue or concern of potential interest to the public or to other stakeholders.
- B. RELIABILITY AND PERFORMANCE COMMUNICATION: Techniques used to provide information to stakeholders about anticipated and actual product safety, reliability and performance, including deviations between projected and actual performance.
1. Proactive Communication Policy: An effort to provide information in anticipation of potential events of relevance to stakeholders. In the case of medical devices, this includes statements that any manufactured device may have a low rate of unexpected malfunctions or performance failures and the creation of a base of continuously updated performance information, accessible to stakeholders.
 2. Reactive Communication Policy: Information provided in response to an event internal or external to the institution. In the case of medical devices, this often involves reporting of previously undisclosed information, in response to circumstances that make disclosure mandatory.

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Section I

EXECUTIVE SUMMARY

A. Overview of Observations

1. CORPORATE STRUCTURE AND FUNCTION

Guidant Corporation consists of four core businesses in the biomedical industry (Cardiac Rhythm Management, Cardiac Surgery, Endovascular Solutions, and Vascular Intervention), and a combined sales organization, Guidant Sales Corporation. The four core businesses evolved from independently operating subsidiaries of Eli Lilly when Guidant Corporation was formed in 1994 and emerged from Eli Lilly as a separate corporation in 1995.

While they present themselves under the “Guidant” banner to the general public, including physicians, patients, and business stakeholders, the manufacturing and marketing activities of each of the core businesses function nearly independently, as do research and development and postmarket surveillance and communications. They are tied together at the corporate level by a structure intended to exert oversight, but little direct hands-on management. The oversight function is manifest through corporate officers, who meet with senior officers of each of the businesses regularly as the Guidant Management Committee. Generally, business communications at these meetings are informational in nature. Guidant Corporation’s management is overseen by its Board of Directors.

As is the case for each of the Guidant Corporation businesses, Cardiac Rhythm Management (CRM) functions as an independent unit. It has its own officers who retain the authority for decision-making for operations and internal policy, with limited requirements for reporting to senior corporate management. CRM remains physically located at its site of origin, Saint Paul, Minnesota, while Guidant Corporation headquarters is located in Indianapolis, Indiana.

The products of the CRM business, pacemakers, implantable defibrillators, and their related lead systems, are used for their symptom-control and life-saving potential in high-risk patients.

2. SURVEILLANCE OF PRODUCTS IN THE FIELD

Postmarket surveillance of performance and reliability of implantable medical devices is a challenge for the entire industry, in part because of the absence of uniform performance standards, consistent surveillance methods and effective reporting requirements. The category of products manufactured by the CRM business have a limited advantage in regard to surveillance, because of the clinical requirement for continuous field follow-up of performance and battery reserve by physicians and field technicians. In addition, the CRM business requires that all employees report any complaints or information concerning malfunctions that come to his/her attention from any source. Despite this corporate requirement, there is no existing system that ensures return of explanted devices to investigate their functional status and integrity – whether after a natural death unrelated to device function, following normal battery depletion, or due to a device malfunction. This is a limitation that confronts the entire implantable cardiac device industry.

3. EVALUATION OF PRODUCT PERFORMANCE

Complaints about product performance and other concerns enter the CRM business of Guidant Corporation through its Technical Services system. Technical Services receives communications from a variety of sources, including physicians, health care facilities, CRM's field representatives, and direct patient contacts. The Technical Services group has personnel with diverse background, including engineers, a few nurses, but no physicians.

Incoming complaints are first evaluated by the Technical Services group. If an incident is considered to suggest device malfunction and/or to be clinically relevant, it is assigned to a Product Performance Engineer who has the responsibility to evaluate and classify the complaint, integrate the hardware findings generated by a reliability engineer, and consult with others as needed to determine the relevance of the problem. In parallel with this, and in compliance with an FDA mandate for assessment of individual events, it is determined whether a formal Medical Device Report (MDR) report is required, and if so submission of that report occurs within 30 days of receipt of the observation, unless there is an exemption.

A group with multiple areas of expertise, referred to as a Cross-Functional Team, may be assembled to coordinate this activity and work with the Product Performance Engineer to determine whether the nature and frequency of the complaint warrants the generation of a trend analysis to follow the product performance. The Cross-Functional Teams are constructed informally, and are

established or terminated on an *ad hoc* basis.

The trend analysis is begun, usually at the discretion of the Product Performance Engineer, when a complaint reaches a predetermined threshold of frequency or is interpreted to threaten patient safety. The usual standard to open a trend is the occurrence of four events of a kind during a 12-month period. However, a Product Performance Engineer may open a trend after as few as one event if there are safety concerns.

Once established, the trend is presented to and followed by the CRM Product Performance Committee until the trend is closed, at which point new events continue to be monitored by the Product Performance Engineer for an ill-defined period of time. A trend can be reopened if the Product Performance Engineer (or Product Performance Committee) determines that the frequency or nature of events has reached a previously designated threshold, which is not consistently defined in CRM policy.

Each trend initiates a formal Health Risk Assessment (HRA). The HRA is designed to categorize the event as to both its probability of occurrence and its severity. Physician participation in the HRA process is limited

If a question of patient safety is suggested or identified by the information generated, the trend may be referred to a series of other committees (Performance Evaluation Committee and Officer Escalation Group). The Officer Escalation Group has the authority to recommend to senior leadership of CRM whether an identified problem warrants advisories or recalls, and/or communication to physicians, patients, or the general public. The CRM President reviews these recommendations.

Prior to recent changes in Guidant Corporation methods (subsequent to the PRIZM 2 DR and RENEWAL 1/2 recalls and prior to this Report), senior management of Guidant Corporation was not involved in this process until it reached at least the level of the Officer Escalation Group, at which point CRM leadership decided whether to communicate information to the Guidant Management Committee. Involvement of Guidant Corporation executives usually did not occur until a CRM decision was made to issue a public announcement.

4. INTERNAL FLOW OF INFORMATION

The flow of information about product reliability within the CRM business and Guidant Corporation, and between these two fundamental levels of corporate structure, is impeded by the lack of clearly-defined reporting

procedures. When a specific problem escalates to a level at which a systematic problem is observed to be occurring at a frequency that exceeds pre-defined limits, or is thought to be life-threatening, channels of communication open, and information is communicated to higher levels of business and corporate leadership. However, in dealing with a new problem, for which frequency and clinical relevance have not reached a threshold for concern as defined in the HRA process, information is retained at lower levels, usually with no or only limited physician input. Thus, a trend may be established by a Product Performance Engineer and followed by the Product Performance Committee, or a closed trend monitored only by a Product Performance Engineer without any knowledge of the event at higher levels of CRM business or Guidant Corporation authority.

5. PUBLIC COMMUNICATION

CRM has established two criteria for communication of a reliability deviation of one of its products to physicians and patients:

- a. “We act when predicted device performance does not achieve design or performance expectations.”

or

- b. “We act when we identify an opportunity to recommend to the clinical community a strategy for improved patient outcomes related to device function.”

The panel interpreted these quoted statements to mean that: 1) the frequency of a problem must fail to achieve design or performance reliability expectations; and 2) the root cause has been identified and a mitigation that can be communicated to the clinical community has been devised. These requirements are driven by the perspectives of engineering, the company’s commitment to continuous improvements, and FDA requirements. This is based upon long-standing CRM policies and procedures that place investigation, analysis, and recommendations to communicate device malfunctions or failures primarily in the hands of engineers. The input of physicians is limited, despite the company’s stated concern for reliability deviations that can harm patients. There is no general policy governing how the company crafts an announcement of product reliability deviations. The process appears to be both complex and largely *ad hoc*. CRM business personnel, Guidant corporate officers, and a variety of external communications advisors participate in the process. There is no Guidant Corporation policy that defines what should be communicated and how and

when it should be presented, as reflected in the case of the announcements of device malfunctions during the spring and summer of 2005.

6. GENESIS OF CURRENT PROBLEMS

In March of 2005, a death related to a low-frequency, but potentially dangerous defect in an implantable defibrillator product led to a stressed interaction between the external physicians involved in the patient's care and CRM representatives. The defect had originally been described, but not fully understood, and was believed to have been mitigated in April 2002, three years prior. It was subsequently determined that a second manufacturing change was required and a newly revised device was introduced in November 2002. The existing inventory of approximately 4,000 unmitigated devices continued to be implanted. This included 1,300 devices that were shipped from CRM's in-house inventory, and the remainder that were in possession of the CRM field sales force or in hospital inventories. CRM did not attempt to retrieve the unmitigated devices and the existence of the defect and subsequent manufacturing changes were not brought to the attention of physicians and patients because the communications criteria of CRM were not met. It was concluded by CRM that the risk of explant and replacement of older devices exceeded the risk of device failure.

At the center of the transparency issue was the long-standing restrictive external communication policy that resulted in physicians and patients feeling that they were not informed of relevant information about a potentially dangerous device malfunction, even after the first death occurred. After awareness of the problem came into the public domain via the news media, the consequences of the problem for Guidant were amplified by weak and conflict-ridden internal decision making processes used to respond to the issue. The combination of the product defect, a fatal event, and ineffective communication policies led to intense criticism of Guidant Corporation in the media. The public and physician reaction was magnified further by the subsequent announcement of a series of other low frequency defects in other devices, and FDA warnings and recalls. All of this was occurring against the backdrop of a highly publicized proposed purchase of the corporation.

7. RESPONSES TO ADVERSE NEWS REPORTS

There is no structure within Guidant Corporation or the CRM business that provides a uniform hierarchal approach to public communication when the following circumstances emerge:

- a. Adverse events that may threaten patient safety are observed but have not reached the pre-determined thresholds for consideration for public disclosure.
- b. An adverse event enters the public domain and generates a negative reaction to the corporate image because of the way it had been handled prior to public disclosure.
- c. There is a need to respond to adverse publicity with a uniform organized, and effective message.

To a large extent, responses emerge from the individual businesses, with no clear lines of authority between corporate level communications and those at the levels of the individual businesses. In the case at hand, conflicting approaches suggested by personnel in the individual businesses and by corporate communications personnel appear to have lead to friction between various levels of corporate structure and mixed messages entering the public domain.

8. POTENTIAL CONSEQUENCES OF THE CRM EVENTS OF 2005 ON GUIDANT CORPORATION

Guidant Corporation has determined that the greatest impact of the CRM events of 2005 was on the attitudes of physicians who are prescribers of the CRM products. A potential derivative of this effect is suggested in Guidant's recent financial reports, which demonstrate a decrease in 3rd quarter 2005 U. S. sales of its CRM products to \$331.2 million from \$469.0 million in the corresponding quarter of FY 2004, and a decrease in 4th quarter 2005 U. S. CRM sales to \$341.2 million from \$449.3 million in the corresponding quarter of FY 2004.

In addition, because the public views Guidant Corporation as a single entity, rather than a group of individual businesses, there exists the possibility that adverse reports from one business may have an effect on physician interactions with the other businesses, thus generating a more global influence on Guidant Corporation business.

9. CORPORATE ACTIONS TO PREVENT RECURRENT PROBLEMS

During the period of time that the Independent Panel was acquiring and analyzing information relevant to the issues defined by its Charter, Guidant Corporation had begun to make changes in Corporate and CRM business policies and procedures, intending to resolve some of its perceived problems in

a timely fashion. Its stated intent is to integrate the findings and recommendations of the Independent Panel into the matrix of changes made prior to the Panel's Report, seeking the best solutions to the problems identified.

10. PROBLEM RESOLUTION IN CONTEXT

There is a general perception by the members of the Panel that virtually all of the problems identified in the scope of its mission are correctable by appropriate actions by Guidant Corporation and its CRM business. The function and reliability of products manufactured by the CRM business have made it a respected leader in its industry. However, the Panel has identified two fundamental principles that apply to CRM's current problems and are likely to govern the implantable device industry practices in the next decade:

- a. Product quality alone is insufficient to protect and preserve business positions. The public demands greater transparency when product flaws are identified and mitigated.
- b. A high priority must be placed on avoiding preventable deaths that may result from a low frequency product malfunction. A malfunction that is identified as potentially life-threatening should take priority over the overall malfunction incidence, even if the latter is better than design expectations.

The challenge to Guidant Corporation is to implement systems that will meet these expectations, and restore the Corporation's eminent status in the field of implantable pacemakers and defibrillators.

B. Overview of Major Recommendations

Based upon the findings and conclusions of the Independent Panel of Guidant Corporation, the details of which are provided below, the Independent Panel makes the following major recommendations:

1. Guidant Corporation is strongly advised to establish an external committee of experts to evaluate product performance and risk assessment data in order to advise the corporation regarding the management of information flow, and actions to be taken in regard to device failures and malfunctions. The committee should include expertise in cardiac electrophysiology, and other disciplines such as engineering, statistics, risk assessment, and patient advocacy/ethics. The committee should operate at arm's length from the corporation, its deliberations linked to the corporation by an ombudsman who will carry information between internal committees and the external group.
2. Guidant Corporation is advised to designate or hire an in-house physician whose primary responsibility will be patient safety and whose job description will include participation in product performance analysis, health hazard analysis, internal communications, and external communication policies and procedures.
3. Guidant Corporation is advised to strengthen management links between itself and its CRM business. This could be achieved by either a reconfigured version of the Officer Escalation Group of the CRM business, a redefinition of the role and activities of the Quality System Assurance Team (QSAT), or a newly formed committee, any of which would include membership of Guidant Corporation leadership as well as CRM business leadership. The purpose is to ensure adequate information flow and oversight between the parent corporation and the CRM business regarding postmarket product performance, patient safety issues, and communication policies.
4. Guidant Corporation is advised to enforce the general policy of the CRM business on the primacy of patient safety by better integrating patient safety concerns into the factual and statistical analysis of product performance and performance failures. The Independent Panel strongly believes that under no circumstances should a potential or manifest risk of a preventable death be superseded by statistical analyses that indicate that performance remains within the general guidelines of estimated failure rates from either the premarket estimates or postmarket experience.

5. Guidant Corporation is advised to ensure that its CRM business, and the Corporation generally, implement and enforce policies of transparency of information regarding product performance and health hazard risk to physicians and to the general public as new information is emerging. It is the opinion of the Independent Panel that a more aggressive transparency policy will achieve three goals:
 - a. Discharge an implied obligation to physicians and patients
 - b. Allow for better understanding of, and an appropriate response to, a significant new event by providing an appropriate context of the event
 - c. Rebuild the trust and confidence in Guidant Corporation that was lost because of the dramatically increased flow of information that had not been shared prior to a major event.
6. Guidant Corporation, in general, and the CRM business in particular, should develop processes for more effective surveillance of marketed devices. This advice is given by the Independent Panel with the recognition that postmarket surveillance is a huge challenge that goes beyond the ability of Guidant Corporation, or any other business in the industry, to achieve alone. However, improvements can be made and should be sought.
7. Guidant Corporation is advised to re-visit the question of identifying a specific number of events that would serve as a trigger for initiating active notification of physicians about newly identified malfunctions or device failures. There was general agreement among the members of the Independent Panel that a *single event* that:
 - a. Is associated with risk of death or serious injury,
 - b. Has a suspected or defined basis for the malfunction or failure, and
 - c. Is likely to be systematic and to occur in other patients,

should be referred to the internal Guidant review body and the IRG for advice on active communications. In the absence of these qualifiers, a single event should *not* trigger active communication. However, such information should be made available passively in sources of information available to physicians, such as product performance reports.

The next consideration had to do with the question of specifying a number greater than one, or a defined event rate, that would warrant such activity. The main concern was whether any minimum number should serve a threshold function, independent of other considerations. After considerable discussion, the Panel *rejected* the notion of setting a minimum number of

events or event rate because considerations of this type have to be evaluated in the context of the nature of the defect, anticipation whether it is likely to repeat, the anticipated or actual rate of accumulation, indications of whether malfunctions or failures are related to time from implantation, and the potential clinical consequences of any specific malfunction or failure. Accordingly, such determination should be made on a case-by-case basis, with two qualifiers:

- a. Physician input regarding the question of potential clinical consequences must be an active part of the decision process; and
- b. The decision process should be handled in a fashion that reflects true independence from commercial considerations.

Therefore, it is the recommendation of the Panel that these decisions should be made by the *Internal Oversight Body* recommended in **SECTION III.A**, with independent review and input from the proposed external *Independent Review Group* (IRG) (see **Recommendation 1**, above). In effect, the IRG would serve a function analogous to a data safety monitoring board of a clinical trial, relying upon the judgment of an informed independent scientific group, rather than a threshold of numbers, to drive decision-making recommendations about when to actively communicate.

In the case of an event for which unacceptable patient risk is self-evident from the information available, CRM/Guidant should act immediately, and subsequently inform the IRG as soon as possible.

8. When a life-threatening defect has been identified and mitigated in a specific product line, Guidant Corporation and its CRM business should expedite review by the internal Guidant review body and the external IRG. These groups should consider appropriate actions, including ceasing shipments of unmitigated devices, and retrieving those in possession of the sales force or in hospital inventories. When such unmitigated devices have been implanted, the company should inform hospitals, implanting physicians, and patients about the nature and projected incidence of the problem. The internal and external review groups should determine when and how such communications should take place.

Section II

BACKGROUND

A. Overview of the Implantable Device Industry

1. RELEVANCE OF TECHNOLOGY

The implantable cardiac electronic device industry had its origins in the early 1960s with the invention of implantable cardiac pacemakers designed to support the heart beat in patients with conditions that caused too slow a heart rate. The pacemaker portion of this industry has grown steadily from then to the present. Beginning in the late 1960s and extending until 1980, another type of implantable cardiac electronic device was conceived of, developed, and tested clinically, namely the implantable cardioverter-defibrillator (ICD). This device is designed to shock the heart out of life-threatening heart rhythm disturbances, generally at very rapid rates, which may cause death if not interrupted by an electric discharge. During the time when the first device was implanted in 1980 to the present, the ICD industry grew slowly at first, and then very rapidly after publication of clinical trials supporting their benefit. The period of rapid growth began in the late 1990s and continues to the present. Therefore, the device technology addressed in this document has become an important part of clinical cardiac therapy and has important impact not only on patient management, but on health care economics.

2. EVOLUTION OF THE INDUSTRY

The implantable device industry began as small businesses growing into a business opportunity as pacemakers and ICDs were invented, determined to be of clinical value, and marketed. The industry began with corporations consisting of businesses focusing solely on this product line, and as those business opportunities grew, along with the development of other types of cardiac devices, including cardiac catheters and stents, the industry began to evolve into multi-business corporations having much more complex business models and management requirements. Today, what had begun as single business industries are now major components of the health care industry, and are seen to have very high value in the biomedical business world. The marked increase in unit sales, a reflection of the growth due to expanded indications for these devices, underpins some of the problems addressed in this Report. Low device malfunction rates, unrecognizable when unit numbers are small, become evident when sufficiently large numbers of units placed in the

population are followed for longer periods of time.

3. CORPORATE CHARACTERISTICS

a. Business Model

The implantable device industry is characterized by a hybrid business model that has some features of a consumer electronics business, a capital equipment business, and a service industry. The consumer electronics concept anticipates an “acceptable level of tolerance” for failure rates inherent to any manufacturing operation of that type. However, given the critical intent of their product, namely prolonging survival in high risk patients and improving the quality of life, levels of tolerance for failures should be targeted to approach zero, as are expected for unique capital equipment models such as NASA spacecraft or nuclear reactors, or clinical models such as expected level of safety of screening the blood supply for HIV (estimated failure rate ~1 per million units of blood). Acceptable rates of failure for conventional consumer products are significantly higher than acceptable rates for the life-saving devices. Accordingly, Guidant Corporation and the rest of the industry are placed in a position of having to achieve extraordinarily low failure rates for their manufactured products. Even having achieved that, the nature and intent of the products in the field require extraordinary contingency plans for dealing with real or potential component failures in individuals with implanted devices.

b. Customer Base

Another feature of this industry is its unusually complex customer base. The “customers” for the industry may be viewed as residing in three spheres: medical institutions/facilities, physicians, and patients. A medical institution is, in most instances, the actual purchaser of the devices, and deals with corporations on issues regarding pricing, inventories, and payment schedules. In that sense, they are the sales targets. In contrast, the marketing target is the physician/electrophysiologist who, with various levels of effectiveness, selects specific brands of preference in dealing with the institutions. Against this backdrop, the actual consumer is the patient who has little to do with brand selection and usually nothing to do with actual purchasing; but, nonetheless, is the end-user of the product.

Thus, in dealing with marketing, sales, and consumer issues, the corporation is in a complex relationship, in part because the user does not select or directly pay for the device. In these complex relationships, the

corporation has multiple levels of communication responsibility, which one could conceive of as being confusing, contorted, and uncomfortably indirect. This realm of communications is distinct from the Securities and Exchange Commission requirement to report “material issues” to the public.

c. Continuous Product Improvement/Short Product Life Cycle

A short product life cycle is a characteristic of the implantable cardiac device industry that impacts upon its strategies for surveillance and communication. Historically, the industry has focused on the desirability of continuously improving the features of its products for the purposes of generating wider scopes of therapeutic options, tailoring therapy to the needs of individual patients, and in a competitive sense, making devices smaller.

Whenever changes in structure or function of products are made, there exists the possibility that changes that are desirable for the purposes of the product will be accompanied by unanticipated potential for malfunction. For example, one of the theories about the arcing problems in PRIZM 2 DR and RENEWAL 1/2 products of Guidant/CRM is that the desire to make the device smaller resulted in shorter distances between critical components in the headers and/or cans of these devices, creating the spatial potential for arcing under circumstances in which it would not have occurred in prior designs. Accordingly, any strategy for surveillance must take into consideration the potential adverse impact of continuous product improvement, and the need to devise surveillance systems that will help to identify malfunctions as early as possible in the clinical setting.

This general concept is further reinforced by the product life cycle of implantable devices. It has been characteristic of the industry to generate new models with various platform changes over time, with such changes occurring over relatively short periods of time. Thus, the life cycle of any one product is relatively short and newly developed products, while theoretically sound, have the potential for unanticipated problems.

This entire spectrum of concern is different than its parallel in the pharmaceutical industry, in which new products generally have a fixed molecular content and formulation so that surveillance for unanticipated side effects or adverse events is carried out against the background of a stable product “design.” Even against this back drop, surveillance for low frequency events is problematic in that industry, a fact that serves to highlight the greater difficulties faced by the implantable device industry.

4. SURVEILLANCE OF ADVERSE EVENTS

The concept of surveillance can be separated into two categories: internal and external to the corporation. The problem of accurate and thorough external surveillance is not unique to Guidant or to the device industry generally. It calls for methodologies by which active processes could be used to identify adverse events with greater accuracy. It is unique to the device industry that the nature of the follow up of patients with implantable devices could make postmarket surveillance inherently less problematic than is the case in the pharmaceutical industry. Nonetheless, there are potential problems when the information enters the corporation. Judgments must be made about the significance of an adverse event or deviation from a performance standard. This process is challenged when evaluation methods do not routinely include more than technical input.

a. Premarket Evaluation of Product Reliability/Safety

Throughout the biomedical industry, including both device and pharmaceutical companies, premarket clinical trials have limited power to identify the potential for postmarket adverse events or failures. Even large clinical trials are small relative to most markets and are carried out for a short period of time relative to device life expectancy, and therefore, are very unlikely to identify low frequency adverse events. It is, therefore, not unexpected that low frequency adverse events appear only after a product is in general use. Since an attempt to solve the premarket identification of adverse events would involve trial design, it was not considered to be within the scope of the Independent Panel's mission.

b. Postmarket Surveillance of Adverse Events

Postmarket information enters the cardiac rhythm device manufacturing corporation by diverse and relatively unpredictable pathways. In the methodology used by Guidant Corporation, recognition of adverse events in the field by the technical staff, physicians and institutions constitute the majority of reports entering the company. The field technicians appear to be the largest source of such information. While this methodology is not anticipated to be anywhere near complete, it very likely exceeds the reporting rate of adverse events in the pharmaceutical industry by a large margin, where estimates of one percent or less of adverse events being reported are generally accepted. The device industry very likely receives notification of a high percentage of those adverse events that have occurred than does the pharmaceutical industry. Therefore, the device industry is more likely to have more data upon

which to act to improve their products. However, the precise reporting percentage for the device industry is unknown.

B. Business Goals and Business Ethics

1. OVERVIEW AND DISCUSSION

The ethical expectations placed on medical device and pharmaceutical manufacturers merge the demands of bioethics and of business ethics. As manufacturers and providers of products that users depend upon for their lifesaving potential – in an environment shaped by the conventional business requirements of a manufacturing industry – medical device and pharmaceutical firms are held responsible to both of these major fields of ethics. The fields of business ethics and bioethics raise similar but distinct issues, and this simultaneous distinctiveness is a source of both opportunity to excel and challenging moral conflicts.

To illustrate the differences between business ethics and bioethics, a for-profit, publicly-traded device manufacturer is widely understood as having duties to its customers and obligations to its shareholders. These duties include improving profits while improving products. However, they also include what have come to be seen in the world of business ethics as broader obligatory duties, including transparency to consumers, suppliers, regulators, investors, and others; veracity regarding communication to these same stakeholders; and equity, such that hiring, firing, promoting, monitoring and other functions are carried out in a fair and unbiased manner. A *medical* device maker has additional duties to the patients who are the ultimate recipients of these devices. A patient who uses a pharmaceutical product or a medical device is not a mere consumer. Rather, patients are located in a special world in which socially regulated experts – physicians – are involved in recommending the use of the drug or device. These distinctively medical duties are at the center of the constellation of issues addressed under the heading “bioethics.”

What follows from this is that drug and device makers must hew not only to business ethics standards; they must also attend to bioethical considerations, including those of informed or valid consent and patient-centeredness. As general principle, the values of life and patient safety are and should be elevated over those of profit and fiduciary duty to shareholders.

It is inherent to the nature of risk/benefit considerations and the efficacy of therapeutics in the context of the natural history of diseases that drugs, devices and other medical and surgical interventions will fail to save the lives of some finite number of users. Indeed, many people in industrialized societies die surrounded by biomedical instruments while receiving a vast array of

pharmaceutical products or after unsuccessful surgery. It is unusual for there to be significant controversy over product quality or reliability when this happens. Implantable medical devices, on the other hand and by their very nature, fail dramatically when they fail; this is especially – perhaps uniquely – true of implanted cardiac devices. When a defibrillator or pacemaker fails to do its job, and a patient dies, the effect is not only profound, it is *focused* and dramatic in way other failures are generally not. Cancer patients may die while receiving chemotherapeutic drugs; artificial joint failures tend not to cause or permit patients to die; were a ventilator to fail to deliver therapy, it would likely be in a critical care context, and the failure would be detected and a replacement installed. Were an external defibrillator to malfunction, the result would be most analogous to an implanted device, with the noteworthy exception that systematic correction of any flaw would not raise questions of surgical intervention to provide corrective action.

With extremely rare exceptions, implanted cardiac devices do not cause injury or death when they fail. Rather, they fail to deliver therapy that might have “saved” a patient from an underlying disease process. This is different from the failure mechanism and causal chain that precedes patient deaths in other contexts, including those involving medical error or adverse drug effects. A patient who dies *from* cancer drug toxicity, for instance, might have lived a little while longer but for the use of the drug. The defibrillator patient whose device fails, or whose heart rhythm disturbance does not respond to defibrillator therapy, would not have lived any longer without the device at all.

These factors point to a need for an exceptionally nuanced consent process both before cardiac devices are implanted, and afterward in cases in which new risks must be communicated and assessed. This process requires not only that patients consent to treatment after an adequate discussion of risks, benefits, alternatives, and other considerations, but also that they *subsequently* be informed of new information that might affect their willingness to continue on a particular course.^[1] The decision not to disclose PRIZM 2 DR failures to physicians and patients is seen as inconsistent with an appropriate informed consent process.

It should be uncontroversial that informed or valid consent and refusal is the cornerstone of contemporary bioethics. This is true of both clinical practice and human subject research. Valid consent has three components:

¹ The cognate phrase “affect willingness to participate” is drawn from the domain of human subjects research, where it is required that patients/subjects be told of risks (perhaps adverse events elsewhere) learned about after a clinical trial begins. When informed of such new risks, patients/subjects are free to withdraw from the trial. For this and other reasons, the standard is that consent should be viewed as a process and not an event. This standard should be applied in clinical contexts as well.

- Adequate information: Patients (or subjects; implied hereafter) must be given enough information about risks, benefits, alternatives, etc. to decide whether to agree to a treatment. This information must be presented before therapy, and updated as appropriate.
- Voluntariness: Patients must not be tricked, forced, coerced or otherwise compelled or pressured to accept or refuse a treatment.
- Capacity: Patients must be able (at the least) to understand and appreciate the likely consequences of any decision.

Assessing the adequacy of each of these components requires judgments which in some or many instances are unclear or vague. For instance, how should risks of accepting or refusing an implantable cardiac device be communicated? How should the risks of refusal be compared to the risks of acceptance? The responsibility for ensuring the adequacy of the consent process generally rests with physicians, who are especially challenged by varying degrees of patient education, risk acceptance/aversion and, especially, the inherently probabilistic nature of the risks.

Informed or valid consent content has taken on broader significance in view of the recent failure experience and unique business and ethical characteristics of the implantable cardiac device industry. In addition to conventional risk/benefit considerations about improved outcomes provided by devices contrasted to the risk of implantation and lead failures, the ICD/pacemaker candidate must be informed prior to implantation of the possibility of device malfunction or failure separate from expected battery depletion during the life of the device. This is an expanded concept of the informed consent process. This is a metric which has not previously been provided by industry to treating physicians, and accordingly has not been communicated to patients. Information available on the risk of no device vs. benefit of device vs. the risk of device failure in appropriate patients, although limited, certainly suggests that for the defined indications for ICDs and pacemakers, the benefits far outweigh either of these other categories of risk. Thus, information about risk should not dissuade the appropriate use of these devices, but it is information that physicians have a need to know and patients have a right to know.

It is quite important, therefore, that we not be sanguine about the best way to present or assess medical risks. These tasks are complex, and reasonable people might disagree with a particular decision despite being given precisely the same information. The importance of the consent process is made especially clear in the context of evidence-based practice, where even “gold standard evidence” is probabilistic and might require complex decisions under

uncertainty.^[1] It is a mistake to assume that physicians have special training or competence, let alone expertise, in theories probabilistic decision making or in communicating risk to patients on that basis. Even if physicians had more information sooner about the failure trends for any particular device, it may be difficult for them to provide a more robust consent process or provide patients with more nuanced or appropriate medical advice. This is especially true for low frequency events.

There are tensions among both Guidant Corporation/CRM (and likely other companies in the industry) and some physician groups regarding the process by which recommendations are made in regard to explanting devices having the potential to malfunction. The general view has been that the decision belongs in the hands of the treating physician, even though industry has not been forthcoming with risk information until recently. In contrast, some physicians believe that this represents a transfer of corporate responsibility to them, with obvious legal implications. In the opinion of the Independent Panel, it is no more appropriate to take clinical decision-making out of the hands of the physicians than it is for industry to withhold the informational tools required for physicians to make reasonable recommendations and communicate them effectively to patients. By analogy, physicians have always assumed the responsibility of applying the results of clinical trials in terms of risk versus benefit to their individual patients based upon consideration of the patient's circumstances. To do this properly, it is imperative that industry provide easily accessible and interpretable data on device malfunction risk so that this can be added to the overall equation.

Because physicians are responsible for the consent process, they need to be informed in a timely manner of information that bears on the validity of the patient's decision. While physicians might be inexpert about the logic of probabilistic decision making, only individual physicians are positioned to determine whether any bit of evidence is or is not significant for a particular patient. This criticism points to a further and larger obligation, however: physicians and patients must be given tools to assess evidence that bears on decisions related to low frequency events. It will not do, for instance, merely to suggest that the decision whether to replace an implanted cardiac device "must be made by the patient in consultation with his or her physician, based on the specific medical situation of the patient. Replacement of the device may pose some risk, so it is important that patients and physicians carefully discuss this matter before making a decision."^[2] That is to say, *of course* such decisions must be made thus – but without adequate decision support tools, the recommendation is without substance.

This line of reasoning points to the need for a comprehensive system to

assess and communicate risks associated with devices that experience low frequency failures. Put this way, we can see the vital intersection of business ethics and bioethics. A medical device manufacturer embracing the business value of transparency will simultaneously be contributing to the bioethics value of valid consent. One cannot ignore the one and somehow comply with the other.

Companies excel, as suggested earlier, by hewing to both values; we are in conflict if we believe that valid consent can be achieved without adequate transparency. It is now commonplace to observe of businesses that there is, in fact, no conflict at all – namely that good ethics *is* or *contributes to* good business. Firms that value transparency foster trust, which is good for business. It is shortsighted to suppose that withholding information from patients (or, in the extreme, to make false statements) can ever be good business. Indeed, the public will never – and arguably *should* never – consider it “good business” when information is withheld from patients and physicians.

It is often alleged that competitive pressures create a need for corporate opacity. While this is true of some information – trade secrets, for instance – it is almost always overstated.^[2] Tribulations that have their etiology in a competitive corporate environment are in many respects self-inflicted. Pressures to compete (including demands of secrecy, priority, and similar considerations) are relics of an economic system, not requirements of science or best practices. In the current social environment, it remains a question whether information impacting on saving lives and reducing suffering should be managed arbitrarily. Society must determine whether it is acceptable to keep such information secret in the interest of competitive advantage. If competition is truly the only way to drive progress – and this is not necessarily the case – then this is the high price society is apparently willing to pay. That it *is* paying this price is something that should be more widely recognized and debated.

It nevertheless remains the case that a business must protect its intellectual property. Suppose, then, that a medical device firm developed a better way to track or communicate risk of device failures. Should this be regarded as

² It could perhaps be argued that tribulations that have their etiology in a competitive corporate environment are in many respects self-inflicted. Pressures to compete (including demands of secrecy, priority, etc.) are features of an economic system, not requirements of science or best practices. It remains a challenge, if not a collective shame, that in the current environment, advances in saving lives and reducing suffering must be kept secret. If competition is truly the only way to drive progress – and this is not necessarily the case – then this is the high price society is apparently willing to pay. That it is paying this price is something should be more widely recognized.

proprietary? Do we really want to say that protecting patient safety should be subject to the same secrecy as innovative design or manufacturing methods? Here, the intersection of business ethics and bioethics is most palpable.

Harmonization of the values required in both domains should be a goal of all businesses that make pharmaceutical products or medical devices. Such harmonization will require adherence to the conviction that one can simultaneously “put patients first” *and* serve corporate shareholder interests. In the example being sketched here – a firm invents or discovers a better way to communicate risk – one could serve both business ethics and bioethics by making public the novel method while at the same time resolving to compete as aggressively as one liked by improving manufacturing techniques and quality. That is, there is an opportunity to compete on the basis of product quality and uniqueness, while escaping pressures that encourage concealing patient safety issues. Such an opportunity is evidence of the potential for harmonization and, in the current environment, an approach that would be embraced by society.

2. SUMMARY AND APPLICATIONS

The core lessons to be learned from low-frequency failures of implanted cardiac devices can be applied to Guidant/CRM, and the implantable device industry generally, as follows:

a. General

As a result of recent events centering on both public perception and reality of how the CRM business of Guidant Corporation handled adverse information, it is necessary for the Corporation to re-tool its internal product performance evaluation systems and its external communications policies and procedures to regain the trust of its customers. This *necessity* provides the Corporation with an *opportunity* to emerge from this episode in their corporate history as a leader in responses to the increasingly vocal societal demands for corporate transparency and ethical behavior.

b. Specific Points

- Medical device manufacturers wed considerations of business ethics and bioethics. The former teaches that “doing well” follows from “doing good.” The latter teaches that unfettered access to information usefully presented is key to the valid consent process. Responsibility for ensuring an adequate consent process generally rests with physicians, who are especially challenged by varying degrees of patient education, risk aversion and, the probabilistic nature of risk.

- Physicians and patients therefore need timely and reliable information to support a nuanced consent process. Such information is available only through a comprehensive system to assess and communicate risks associated with devices that experience low frequency failures.
- Adequate decision support tools are necessary for this process.
- Attention to ethics fosters business success. Firms that value transparency engender trust, which is good for business. Emphasis on corporate *compliance* is not a valid substitute for corporate social *responsibility*.
- Harmonization of the values required in business ethics and bioethics should be a goal of all businesses that make pharmaceutical products or medical devices.
- While corporate competition is unavoidable, medical device businesses should compete on the basis of *quality* and not on the basis of patient safety. For instance, information that can enhance patient safety, such as that improving the informed consent process, should be shared openly by all companies in the industry. To this end, it is desirable (although not necessarily achievable) that the various corporations competing in this industry agree to adhere to a general principle of this type.

These lessons are to be applied both narrowly – to individual industries and even businesses – as well as broadly. While some of these lessons might apply most directly to the implantable device industry, all apply in one way or another to medical business in general. Finally, moral rules sometimes permit exceptions in certain or extraordinary cases, such exceptions are and should be difficult to justify, and must always be applied sparingly.

Section References

1. Goodman KW. *Ethics and Evidence-Based Medicine: Fallibility and Responsibility in Clinical Science*. Cambridge: Cambridge University Press, 2003.
2. FDA News. FDA updates consumers on Guidant Corporation's implantable defibrillators. News release P05-37, July 1, 2005.

C. The Problem: Historical Perspective

Beginning in May 2005, Guidant Corporation came under extensive professional, regulatory, and media scrutiny and criticism after reports that it had failed to alert physicians about potential problems with one of its defibrillator models, the Ventak PRIZM 2 DR, manufactured by their Cardiac Rhythm Management (CRM). A 21-year-old college student, who had a congenital cardiac abnormality, died while mountain-biking in March 2005 when his defibrillator short-circuited and presumably failed to deliver a therapeutic shock.

According to a May 25, 2005 article in the *New York Times*, that quoted an expert in cardiomyopathy who was the young man's physician, Guidant did not tell doctors or patients for three years that this model defibrillator, manufactured by their Cardiac Rhythm Management (CRM) business and implanted in an estimated 24,000 people, contained a flaw that had caused a small number of those units to short-circuit and malfunction.

In a Physician Advisory, also issued on May 25, 2005, Guidant stated it was aware of 25 other events in which the PRIZM 2 DR Model devices, and specifically the subfamily of devices manufactured prior to April of 2002, had been affected by the same flaw. Guidant said it had changed its manufacturing processes three years ago to fix the problem. Guidant then recommended that, since this failure appeared to be random and had occurred at a very low frequency, implanted devices need not be replaced, although patients should be followed every three months, as indicated in the device instructions manual.

In June 2005, the company, working with the FDA, issued a device recall. The clinical issue in this Class I recall was that the device had failed to shock in response to a potentially fatal arrhythmia. The apparent cause of this failure was electrical arcing within the device. The recall indicated that this defect was associated with the death in a young man, and that Guidant had not communicated the very low but serious risk of this potential for a failure among the patient population with these devices for more than three years after it was first identified. During a period of approximately one year after the corrective action was taken in response to the observation of arcing, more than 4,000 of the pre-mitigated devices continued to be implanted, approximately 1,300 of which were shipped from CRM's in-house inventory and the remainder in the possession of the sales force and in hospital inventories. As mentioned, this event and lack of voluntary communication of the potential risk, precipitated considerable external concern and publicity, including an article in the *New York Times* at the end of May followed by other articles in the lay and

professional media. During the subsequent analyses and discussions with the FDA, the estimated rate of events actually changed and was understood to likely not be a stable rate over time.

A similar but not absolutely identical recall in June 2005 involved a group of ICDs, Contak RENEWAL 1/2, manufactured before August 2004. Again, the clinical risk was failure to shock if needed. There was one death. The cause again was electrical arcing.

A third recall in June 2005 involved a group of ICDs that could also deliver therapy to the atrium of the heart. In this case there was a software memory loop problem called latching, which basically meant that while the device was performing a certain function, it could get stuck there. This situation led to two separate but related actions. The first recommended mitigation was short term reprogramming to be done in the physician's office to be followed later by a permanent software correction. This was a Class II recall. However, very quickly it was recognized that the reprogramming advice was incorrect and could actually worsen the problem. This led to the second recall, Class I in this case, because Guidant had given incorrect mitigation advice in one of the software reprogramming options.

Like the PRIZM 2 DR and RENEWAL 1/2 situations, a defect involving a subfamily of the RENEWAL 3/4 devices resulted in a potential failure of the ICD to deliver a shock to abort a lethal heart rhythm. This recall occurred when no deaths or serious injuries whatsoever had occurred although the potential was there. Unlike the PRIZM 2 DR and Contak RENEWAL 1/2 recalls, the cause of the failure was not electrical arcing, but rather sticking of a magnetic switch that allows the electrophysiologist or other caregiver to temporarily literally put a magnet over the device to temporarily disable it. If this switch stuck, it could prevent the device from delivering a therapeutic shock. This situation was quite different from the defect in the pre-2002 PRIZM 2 DR devices for which the only clinical options were to either surgically remove and replace the device or leave the device in. With the RENEWAL 3/4 malfunction, however, there was the possibility for patients with this family of devices to go into the physician's office for a five-minute programming change to turn the enabled magnetic switch function to off. Although physicians could do that for already implanted devices, all shelf stock was recalled and returned to Guidant. These devices were not repaired and put back in the field. New devices with a different magnetic switch were manufactured. In other words, physicians were not permitted to simply reprogram a device prior to implantation due to FDA policy regarding device labeling. Many physicians were concerned because this was an active product line.

A subsequent Class I recall involved a set of older pacemakers. In this case, there were clusters of reported events that seemed clinically disparate and totally unrelated, but actually converged once the root cause was understood, namely, the very late and time dependent accumulation of some moisture in the hermetically sealed device.

The most recent Safety Advisories related to ICD and Pacemaker devices issued by Guidant are listed and summarized in **APPENDIX A**. This information was also communicated by Guidant via *Physician Letters* and *Patient Letters*, and to the general public via *Press Releases*.

Recent FDA regulatory communications and activities during this period are listed and summarized in **APPENDIX B**.

D. Charter and Function of the Panel

On June 22, 2005, Guidant announced its intention to establish an Independent Panel of experts to recommend guidelines for surveillance and assessment of malfunctions of its ICDs and pacemakers, and how and when to communicate safety-related information to physicians and patients.

Guidant proposed that this independent, blue-ribbon Panel would provide formal and specific recommendations regarding processes and methods to improve, among other things:

- Surveillance and understanding of infrequently occurring events among life-sustaining implantable devices that may affect physician decisions for their patients
- Assessment of benefit and risk to the patients
- Processes of communications to physicians and patients

On July 27, 2005, Guidant announced that Dr. Robert J. Myerburg Professor of Medicine and Physiology at the University of Miami had agreed to chair the Independent Panel.

1. CONCEPT OF INDEPENDENT REVIEW

The central theme governing the creation and function of the Independent Panel of Guidant Corporation was complete independence of the review process, analysis of information, and construction of its Report. Guidant Corporation agreed to provide the Panel members with all documents related to the mission of the Panel. This included documents disclosed by Guidant Corporation on its own volition at the start of the review process, and all additional specific information requested by the Panel during the course of its work. The agreement included freedom to independently interview Guidant employees and site visits to the headquarters of the CRM business in St. Paul, Minnesota. The Panel's deliberations were carried out in the absence of Guidant employees, officers, attorneys, or its facilitator, except as requested by the Panel for interviews of Guidant/CRM employees, and with the advice and counsel of the Panel's attorney.

Guidant Corporation agreed that none of the deliberations or conclusions would be provided for ongoing review prior to the generation of the Report, but that a near-final draft of the Report could be seen only by the Guidant facilitator and external attorney, solely for the purpose of a review limited to the

accuracy of factual statements related to regulatory and procedural issues. A penultimate draft subsequently would be submitted to the CEO of Guidant Corporation for comments or suggestions, but the Independent Panel retained the authority to accept or reject any suggestions, as it deemed appropriate. The final Report would be provided to the CEO and the Board of Directors of Guidant Corporation.

2. MISSION OF THE PANEL

As stated in the Charter (see **APPENDIX C**), the Mission of the Panel was to evaluate the current methods used by the Cardiac Rhythm Management (CRM) business unit of Guidant Corporation for postmarket surveillance and communication regarding the function and safety of life-sustaining implantable devices, and to develop recommendations and guidelines that will enhance:

- Early recognition of low-frequency events and trends
- Methods for evaluating the clinical relevance of such trends
- Methodology for disseminating safety information for the benefit of patients and treating physicians.

The Charter of the Panel required the preparation and delivery of a detailed Report of its deliberations and recommendations to be presented to the Chief Executive Officer and Board of Directors of Guidant Corporation. The target date for presentation of this Report was mid-to-late February 2006. The Report represents a consensus of the Panel, with individual Panel members having the right to add minority statements if there were points of disagreement with the majority.

3. GUIDING PRINCIPLES

The principles guiding the acquisition of information and deliberations in regard to conclusions and recommendations by the Independent Panel of Guidant Corporation included review of documents, interviews, and closed sessions for deliberation. The intent of the Panel was to acquire information from those sources and from visits to the site of the CRM business in St. Paul, Minnesota, as part of their fact finding responsibility. The Panel relied on Guidant to provide the relevant information in response to the Panel's requests and did not attempt to independently verify the completeness of the information provided or the authenticity of the documents reviewed. The Panel selected the persons to be interviewed and all persons selected were interviewed.

4. PANEL CONSTITUENCY

The Charter guaranteed that the Chair of the Panel would have full independence in final selection of Panel members. The general goal was to assemble a group consisting of members with expertise in disciplines relevant to the Panel's mission, including electrophysiology and general cardiology, epidemiology, statistical methodology, low frequency event prediction and recognition, professional/patient communications, ethics and patient advocacy, and regulatory affairs. The members of the Panel are listed in **Appendix D**.

5. INDEPENDENT PANEL ACTIVITIES

a. Overview

Based on the goals set forth in the charter, the Panel used a blend of sources of information to gain insight into the following aspects of Guidant's operations:

- Surveillance of product performance and adverse event recognition for marketed pacemakers and ICDs
- Internal evaluation of products after reported events - emphasis on root cause, trend, risk assessments, performance metrics, and mitigation
- Decision-making processes for evaluation of mitigation of identified root causes
- Determination of need to communicate reliability and mitigation issues to physicians, patients, and general public
- Methods and targets of communications

The Panel's deliberations focused on the following areas and issues regarding life-sustaining implantable devices marketed by the Cardiac Rhythm Management business unit of the Guidant Corporation:

- The processes and procedures regarding surveillance and interpretation of trends of reported low-frequency events that could affect safety and physician decisions for managing the devices.
- Device component failure analyses, and assessment/reassessment of benefit/risk to patients in light of new information on events and trends.

- Development of a more timely, transparent, understandable, and clinically useful communication processes that provide physicians and patients with the proper perspective regarding safety of the devices, including:
 - Triggers for communication
 - Timing of communication
 - Novel methods for communicating this information

In addition to six monthly, full group meetings, working subgroups focused on one of the following areas:

- Product performance and reliability
- Policies and procedures for surveillance
- Internal communications and decision-making
- Policies and processes, mechanisms, and appropriateness of communications with physicians and patients

In addition to review and discussion of requested documents and records, including relevant proprietary information on processes and procedures, the Panel interviewed key CRM management and line personnel in closed sessions. Two working subgroups of the Panel also made site visits to CRM facilities in St. Paul, Minnesota, to review processes and procedures and to interview key CRM staff.

In order to maintain independence and credibility, the deliberations of the Panel, during both the full group and subgroup meetings, were maintained under strict confidentiality, with no communication of these deliberations with Guidant personnel, or outside parties including the press, media, and financial analysts.

b. Activities of the Independent Panel

Dr. Robert J. Myerburg agreed to Chair the Independent Panel on July 27, 2005, subsequent to which he recruited the Panel members, a Counsel to the Panel, and a writer to assist editing and formatting of the document. Recruitment was completed on August 17, 2005. The constituency of the Panel is provided in **APPENDIX D**.

The Independent Panel held its first meeting on August 30 and 31, 2005, in Coral Gables, Florida. During that meeting and all subsequent meetings, the

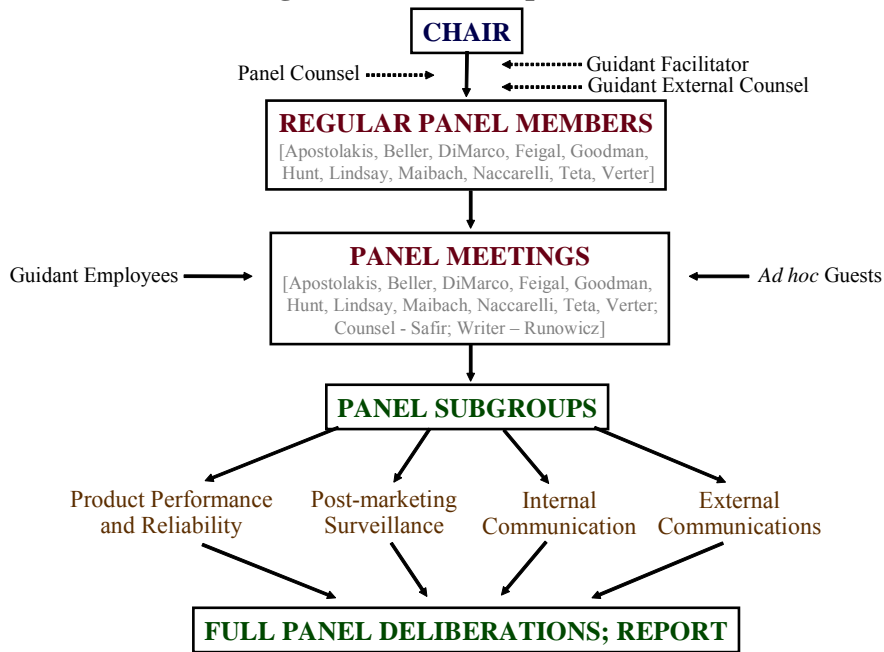
Panel held closed sessions. In addition, sessions were held with personnel of the CRM business of Guidant Corporation and Guidant Corporation officers for information gathering. Personnel were asked to make formal presentations on the structure and function of the CRM business, and their perception of the problems that evolved between 2002 and 2005; they were also interviewed by Panel members. Most interviews were conducted using a format in which a single individual was interviewed by the full Panel; but in a few sessions, when it was felt to be appropriate, multiple individuals were interviewed simultaneously. The Guidant Corporation facilitator for the Panel (Dr. Beverly Lorell), and a Guidant Corporation external attorney (Edward Basile, Esq.) were on site at all of the meetings. These individuals were not present during the interviews of other Guidant employees or during closed Panel deliberations.

Prior to the first meeting of the Panel, Guidant Corporation had provided documents on the operations of the CRM business generally, and in specific reference to product performance evaluation methods and communications policies and procedures. Additional documents were provided for the Panel at the August 2005 meeting, and yet more documents were requested by the Panel as a result of the presentations at the meeting and were delivered subsequently in a timely fashion.

One of the items on the agenda of the August 2005 meeting was a series of three invited presentations by authorities in the field of clinical cardiac electrophysiology, Dr. Douglas Zipes of Indiana University, Dr. David Cannom from Los Angeles, California, and Dr. Ronald Berger of Johns Hopkins University. Each provided the Panel with his opinion on appropriate policies for communication of low frequency adverse events to physicians and patients, and the basis for these opinions. These invited guests did not participate in the deliberations of the Panel beyond the questions and answers related to their individual presentations.

After the first meeting, the Independent Panel held a conference call on September 26, 2005, to analyze the information provided in submitted documents and at the first meeting, and to plan its subsequent activities. The second meeting was held on October 16 and 17, 2005, in Tyson's Corner, Virginia. The purpose of this meeting was to gather more information, interview additional CRM and Guidant personnel, and continue deliberations on the issues at hand.

Organization of Independent Panel



In addition to the activities of the full Panel, four subgroups were established to carry out in-depth evaluations and generation of initial documents on the topics of: (1) product performance and reliability; (2) postmarket surveillance; (3) internal communications and decision-making within CRM and between CRM and Guidant Corporation leadership; and (4) policies for external communications between the CRM business, Guidant Corporation, physicians and patients, and consider recommendations for the future. These subgroups held a series of conference calls to plan their information-gathering, analysis, and reporting.

The next meeting of the full Panel was held on November 20, 2005. The format of this and subsequent meetings remained the same, with fewer employees being interviewed and more time devoted to deliberations as the process continued.

During the November 20, 2005 meeting, the Panel finalized plans for site visits to the CRM business facility in St. Paul, Minnesota, which had been discussed previously. Site visits were set up for December 12, 2005 and December 20, 2005, the second to be followed by the next regular Panel meeting on December 21, 2005, in Tyson's Corner, Virginia. The purpose of the December 12, 2005, site visit was to interview employees, and explore policies, procedures, and processes for product performance evaluation and

quality assurance by the CRM business. The mission of the second site visit was to explore policies, procedures, processes, and interview internal and external individuals in groups involved in internal and external communications by the CRM business and Guidant Corporation. At the December 21, 2005, Panel meeting, the results of the two site visits were discussed with the full Panel, since only 6 to 8 members of the full Panel went to each of the two site visits, with the Chair attending both. The next full Panel meeting occurred on January 25, 2006, with the major mission for that meeting being the coordination of writing of the Panel's Report. The final meeting of the Panel was held on February 23, 2006, for the purpose of carrying out additional edits of the Report.

Between each of the meetings cited above, there were *ad hoc* conference calls of the full Panel to discuss specific issues and/or general progress, in addition to a series of telephone conferences among the four subgroups of the Independent Panel for the purpose of analyzing and creating documents on their specific assignments. One additional meeting was held in Washington, DC on January 19, 2006. This was a meeting of the Product Performance and Reliability subgroup for the purpose of addressing specific issues in their section of the document.

During the entire process of fact-finding and writing, the Panel did not meet with Guidant or CRM employees outside of the venues where formal presentations and interviews took place. Communications with Guidant outside of the formal meetings were limited to communications between the Chair of the Panel and the Guidant facilitator or between the Guidant external counsel and counsel for the Panel for the purpose of session planning, requests for additional documents or information, or interpretation of the Charter.

The Chair of the Panel met with the CEO of Guidant Corporation, Mr. Ronald Dollens, in Miami, Florida, immediately prior to accepting the position of Panel Chair. Both Mr. Dollens and Dr. Myerburg felt that a face-to-face meeting prior to formalizing this agreement was necessary and appropriate. Subsequent to Mr. Dollens' retirement from the position of CEO of Guidant Corporation in December 2005, Mr. James Cornelius, Chairman of the Board of Directors of Guidant Corporation assumed the added responsibility of Interim CEO of Guidant Corporation, and met with the Chair of the Panel in Miami, Florida, on December 10, 2005, to discuss his intent for corporate governance and offer his support for the ongoing work of the Independent Panel. At no time during this meeting, or discussion with any other Guidant officers or personnel, was any form of interim report on the findings and/or recommendations of the Independent Panel disclosed to Guidant. As indicated

in the Charter, no interim reports were required before the final report was to be presented to the CEO and Board of Directors of Guidant Corporation.

Section III

PANEL OBSERVATIONS, CONCLUSIONS, AND RECOMMENDATIONS

A. Corporate Structure and Function

1. GENERAL BACKGROUND AND THE CARDIAC DEVICE INDUSTRY

Corporate business models range from single business entities to those having a multiplicity of businesses in a single general category or a range of business interests unrelated to each other. The latter structure results in a diversity of business goals and strategies that may challenge the coordination of corporate function and management. In the latter corporate model, individual businesses may function semi-autonomously, impeding uniformity of corporate governance and problem-solving.

The implantable cardiac device industry had its origins as small, single business corporations, when pacemakers and their related lead systems, and subsequently implantable defibrillators and their lead systems, were emerging as new business opportunities. As these businesses matured with increasing growth of the implantable electronic cardiac device industry, two business patterns emerged. In one, a device manufacturer became a subsidiary of a larger and more diverse corporation, only to emerge later as part of a newly formed corporation with business interests focused on various types of devices. In another, a device manufacturer broadened its business horizons by adding other medical device businesses, both related and unrelated to the original core businesses. In both cases, multi-business structures emerged, creating the need to develop complex management and oversight functions.

2. OBSERVATIONS REGARDING GUIDANT

Guidant Corporation was formed as a public corporation from a group of cardiac device-related businesses owned by Eli Lilly Corporation in 1994. It emerged from Eli Lilly as a fully separate and independent corporation in 1995. Guidant Corporation now consists of four core businesses in the biomedical industry (Cardiac Rhythm Management, Cardiac Surgery, Endovascular Solutions, and Vascular Intervention), and a combined sales organization, Guidant Sales Corporation.

While they present themselves under the “Guidant” banner to the general

public, including physicians, patients, and business stakeholders, the manufacturing and marketing activities of each of the core businesses function nearly independently, as do research and development and postmarket surveillance and communications. They are tied together at the corporate level by a structure intended to exert oversight, but little direct hands-on management. Oversight for compliance with regulatory policies rests with a corporate Compliance Officer, and oversight for legal matters rests with a corporate General Counsel. The business oversight function is manifest through corporate officers, who meet with senior officers of each of the businesses regularly as the Guidant Management Committee. Generally, business communications at these meetings are informational in nature. Its corporate Board of Directors has the responsibility and authority to oversee Guidant's management.

As is the case for each of the Guidant Corporation businesses, Cardiac Rhythm Management (CRM) functions as an independent business unit. It has its own officers who retain the authority for decision-making for operations and internal policy, with limited requirements for reporting to senior corporate management. CRM remains physically located at its site of origin, Saint Paul, Minnesota, while Guidant Corporation is located in Indianapolis, Indiana. The products of the CRM business, pacemakers, implantable defibrillators, and their related lead systems, are used for their symptom-control and life-saving potential in high-risk patients.

3. CONCLUSIONS: THE GUIDANT-CRM BUSINESS MODEL

As part of its mission, the Independent Panel of Guidant Corporation has reviewed the organization structure of Guidant Corporation and its CRM business, largely in the context of postmarket surveillance of product reliability, corporate oversight of quality control, and internal and external communications policies. The assessments are based upon review of corporate documents and interviews of personnel. The Panel evaluated interactive functions in these three realms of business activities between the various levels within the CRM business, and between CRM and Guidant Corporation management.

Based upon its analysis of information acquired from the review process, the Panel has reached the following conclusions about processes that had been in place at the time of the events relevant to the Independent Panel's mission:

- a. Within the CRM business, a Corrective and Preventive Action (CAPA) system had been designed with provision for escalating serious problems

to higher corporate levels (see **SECTION III.B**). While the technical expertise and processes for determining root causes of device malfunctions were adequate, CAPA's function has been impaired by subjectively applied procedures for decision-making and communication with limited oversight by the CRM business or Guidant Corporation.

- b. Neither the CRM business nor Guidant Corporation has in place a process for comprehensive internal (see **SECTION III.D**) or external (see **SECTION III.E**) medical review of the clinical impact of product malfunction. Such a medical review process would be intended to provide guidance for the CRM business or parent Corporation on the potential implications of product reliability deviations related to patient health hazards.
- c. Information that has the potential for serious consequences may be delayed in reaching CRM business or Guidant Corporate leadership levels because of inadequate internal reporting requirements.
- d. During public emergence of product performance issues beginning in May 2005, there was lack of uniformity and internal strife concerning methods and content of public disclosure (see **SECTION III.E**). These problems impacted the timing and uniformity of public statements, and likely were detrimental to Guidant Corporation's relationship with its customer base and the general public.
- e. Guidant Corporation has internal communication and decision-making policies that appear effective as written, but are not adhered to uniformly or efficiently.

4. RECOMMENDATIONS

- a. Guidant Corporation and its CRM business should jointly develop a system of oversight methods for monitoring the effectiveness of product reliability evaluation, health hazard assessment, and communication policies for its CRM business. Oversight should be carried out at both the business and corporate levels, and should be both internal and external. The following specific models are recommended:
 - 1) Internal Oversight: A modification of the Officer Escalation Group can be designed to fulfill this need. The Officer Escalation Group as currently comprised, with the addition of two or more members from Corporate leadership, would provide a communication conduit between the business and the corporation. They would receive

- information from CAPA regarding event patterns of concern, and provide dialogs and agreement on management strategies prior to escalation of critical circumstances.
- 2) External Oversight: A new Corporate function, tentatively named the *Independent Review Group* (IRG), should be established. The IRG, as described in **APPENDIX E**, is envisioned as a permanent body analogous to a DSMB (Data and Safety Monitoring Board in a clinical trial) but with important differences. The primary role of the IRG will serve both monitoring and advisory functions, independently advising the Corporation on the clinical relevance, including health hazards, and need to communicate product performance events.
- b. Guidant Corporation is advised to designate or hire a physician whose primary responsibility should be patient safety and whose job description should include participation in product performance analysis, health hazard analysis, internal communications, and external communication policies and procedures.
- c. Guidant Corporation should establish clear lines of communication between the CRM business and Guidant Corporate leadership that will foster the flow of information regarding product performance or patient safety (see **SECTION III.D** and **SECTION III.E**).
- d. A clear line of authority should be established describing decision-making responsibility for the timing and content of information regarding product performance or patient safety to physicians, patients and the general public.

B. Product Performance Evaluation

1. OVERVIEW/DISCUSSION

Implantable devices for cardiac rhythm management have become an integral part of cardiovascular therapy. Implantable pacemakers for patients with bradycardia were introduced more than 40 years ago and the first implantable cardioverter-defibrillator (ICD) was implanted in 1980. Subsequent approval for clinical use by the FDA in 1985, and by Medicare in 1986, was followed by a series of large scale randomized clinical trials for both secondary prevention of recurrent cardiac arrest and/or ventricular tachycardia and primary prevention of for a first life-threatening arrhythmic event in subjects at high risk. The outcomes of these trials of ICD therapy have, in most cases, demonstrated a reduction in both arrhythmic and total mortality, with relative risk reductions for total mortality typically in the 20-30% range.^[1,2] Subsequently, specialized pacemakers, called cardiac resynchronization devices that improve the mechanical function of the heart, often combined with ICD capability, were introduced for patients with heart failure. As a result of these demonstrated benefits, there has been explosive growth in ICD prescriptions. There are now, in just the United States, well over 1,000,000 individuals living with an implanted cardiac rhythm device and this number is increasing rapidly.^[3]

Pacemakers and defibrillators have benefited from the explosion in electronic technology, material science and manufacturing capability that has occurred in the decades since the initial models were developed. Current rhythm management devices are smaller and more effective, last longer, and have many added diagnostic and therapeutic functions. They are safer and more reliable than earlier models. A contemporary model ICD may contain more than 70 individual components. It will be expected to provide pacing capability in 1-3 cardiac chambers, monitor for dangerous ventricular, and in some cases, supraventricular rhythms, deliver pacing or high voltage therapy according to programmed parameters, store diagnostic data, and perform automatic maintenance functions and self checks. All these functions must be contained in a can sealed against biological fluids that is small enough to fit comfortably in a subcutaneous pocket below the clavicle. The progressive miniaturization of devices that has been driven by clinical considerations and the pattern of rapid introduction of new product models in a competitive market environment has placed enormous pressures on manufacturers' ability to maintain and enhance the reliability of devices. Given the complexity of the devices and the sophisticated tasks they must perform, it is not surprising that malfunctions occur, as is the case for any manufactured product across all

industries. There is currently no general consensus on appropriate reliability standards within the implantable cardiac rhythm device industry.

Device failures can lead to injury and deaths, and it is therefore necessary that manufacturers have in place surveillance methods for identifying malfunctioning devices and quality assurance techniques for finding and correcting root causes. The Safe Medical Devices Act of 1990 and the Medical Device Amendment of 1992 require manufacturers to report to the FDA any device malfunction that causes, or has the potential to cause, significant patient injury or death. Limitations of the current postmarket surveillance system are discussed in **Section C** of this Report.

The FDA receives approximately 180,000 Medical Device Reports (MDR) per year describing clinical and product related problems related to medical devices. The FDA Manufacturers And User Facility Device Experience (MAUDE) database currently contains over 20,000 MDRs just on pacemakers and defibrillators.^[1-2] Most of these MDRs are either not caused by a product malfunction or are of minor significance but some identify important issues that have affected, or could potentially affect, patient safety. Maisel reported that between 1990 and early 2005, there have been 29 safety alerts and recalls involving 337,000 ICDs from all manufacturers.^[4, 5] These totals have increased substantially since Maisel collected these data.

Despite this system and the numerous safety alerts, it is still difficult to determine the reliability of any individual ICD or pacemaker model. Manufacturers have traditionally published reports on performance and reliability of their products that describe estimated device survival, but the survival curves and tables are dominated by the interval of time at which battery depletion is expected and observed. Unless battery depletion is sudden and unexpected, an uncommon battery failure mode, it is only rarely an important safety issue. Although several manufacturers may provide additional data in their reports, there is not an industry standard format for the presentation of reliability data beyond these curves. Low-frequency, but clinically relevant, failure modes that may result in patient injury or death often cannot be detected on these curves. Even if normal and premature but gradual battery failures are excluded in the manufacturer's report, it may be difficult to distinguish malfunctions which may prevent delivery of life-saving or life-sustaining therapy from malfunctions of only minor clinical importance.

Product recalls generated in response to systematic failures are extremely expensive and damaging to the manufacturer. Each manufacturer therefore maintains a quality program designed to improve the reliability of their devices yet failures continue to occur. Selected data about reported total failures from

the two leading manufacturers' current Product Performance Reports are shown in **TABLE III.B.1** below. It is recognized throughout biomedical industries, including both pharmaceuticals and devices, that the reported numbers of adverse events underestimates true rates since events will accumulate over time as long as products are in use and not all adverse events will be recognized and/or reported. These data illustrate that confirmed device malfunctions or failures, as described by the manufacturers, while not common, are a consistent feature and have been noted in every device manufactured.

TABLE III.B.1: SELECTED DATA ON REPORTED TOTAL FAILURES* IN THE UNITED STATES FROM PRODUCT PERFORMANCE REPORTS FROM THE TWO LEADING MANUFACTURERS

| Manufacturer | Model - Model # | # of US Implants | Confirmed Failures (%) |
|---------------------|------------------------|-------------------------|-------------------------------|
| Guidant | RENEWAL - H135 | 10,000 | 33 (0.33) |
| | Vitality 2 DR - T165 | 6,000 | 5 (0.08) |
| | Vitality AVT - 135 | 7,000 | 16 (0.23) |
| | PRIZM 2 DR - 1861 | 43,000 | 124 (0.27) |
| | PRIZM DR - 1851-1856 | 13,000 | 254 (1.95) |
| Medtronic | Gem III DR - 7275 | 19,000 | 93 (0.48) |
| | Gem II DR - 7272 | 15,000 | 130 (0.86) |
| | Gem DR - 7271 | 19,000 | 618 (3.2) |

*From Guidant Product Performance Report, December 2005; Medtronic Product Performance Report, First Edition, July 5, 2005.

2. THE CRM SYSTEM

Product failures with PRIZM DR 2 and RENEWAL 1/2 drew attention to the problem of postmarket product performance assessment that is not unique to Guidant's CRM business unit. Their products are extremely reliable; however, like any manufactured device, they may fail unexpectedly at a very low frequency. The result of these failures may be catastrophic, but in some cases, may be preventable, if signals of a systematic failure are detected early.

The CRM business of Guidant Corporation evaluates product performance at two stages in the life cycle of devices: 1) during the design phase, and 2)

after the product has been marketed, including after explantation of a device if it is returned to CRM. Product lifetime reliability is evaluated using a variety of statistical metrics based on predicted and observed failure rates. The failure rate is simply the ratio of the observed failures over the number of implant months (or in some cases, the number of implanted devices). These measures are compared to established *reliability standards* for product families that define the minimum acceptable reliability over a product's lifetime and *reliability goals* for each new product design that, if met, would result in Guidant being the industry leader.

During the design phase, a predicted failure rate is calculated for a new product based on data from field performance of similar products in the U.S. An estimate of the expected failure rate of the device is produced using past experience with similar devices, whose failure rates are modified to account for differences with the new product. If there are "n" failure modes (such as design, process, user, components) with failure rates λ_i , $i= 1, \dots, n$, the predicted failure rate of the new device is estimated as follows

$$\lambda_{\text{predicted}} = \text{mod}_1 * \lambda_1 + \text{mod}_2 * \lambda_2 + \dots + \text{mod}_n * \lambda_n$$

The relevance of past failure modes to the product under development are reflected in the "modifiers," mod_i . These are numbers between 0.0 and 1.0 and are estimated by CRM engineers, taking into account the similarity of past products and components to the new product and the effectiveness of manufacturing changes that were intended to eliminate past problems.

The predicted failure rate, using the exponential distribution below, is the basis for comparison with CRM standards for lifetime reliability for new products:

$$R(T_{\text{life}}) = R(0) * e^{-(\lambda * T_{\text{life}})}$$

where "R(0) = 1, if λ is averaged over the entire life of the product

$$= [1 - U(0)], \text{ if infant mortality (unreliability at time 0) is segregated}"$$

In this equation, a constant failure rate is assumed.

The predicted failure rate is then compared to two metrics used to monitor performance within a device family: 1) a lifetime reliability standard which must be met by all devices in the family; 2) a reliability goal, which if met by the family would make them the industry leader. The reliability standard for the PRIZM family, based on decreased observed failure rates, has been made

more stringent between 1997 (0.200% failures/month over a three year period) and 2005 (0.065% failures/month over a five year period). In 2005 the five year reliability goal was 0.032% failures/month. In June 2005 the observed failure rate for PRIZM 2 DR was lower than the reliability goal.

The predicted failure rate and the lifetime reliability standard estimates do not include normal battery depletion. The cumulative device survival curves in the Product Performance Reports issued by Guidant for each of its products do include normal battery depletion. However, the first few years of the curves are not influenced by battery depletion, and reflect other malfunctions.

Guidant is using a product performance evaluation system designed to identify and evaluate postmarket product performance of implantable cardiac devices. The system includes a passive surveillance component and therefore relies on voluntary reports from patients, physicians, Guidant field representatives, and others to identify problems and complaints (events) with devices that occur after implant. The system, while having some limitations, appears to function well, especially for those devices implanted and used in the U.S. The system is referred to as the Corrective and Preventative Action (CAPA) system. This system is designed to meet the current FDA regulations to identify, correct and/or prevent serious malfunctions of implantable cardiac devices that cause, or have the potential to cause, significant injury to a patient.

The initial contact within CRM for a problem or complaint (ie, “A product malfunction, allegation of malfunction, or other issue requiring intervention occurring during clinical use.”) is a technician who enters the details into an electronic database (MERLIN). Such reports are classified, and a decision is made, as to whether the problem or complaint requires a Medical Device Report (MDR), or needs to be reviewed by a Product Performance Engineer. If the information warrants generation of an MDR, it must be submitted to the FDA within 30 days. In parallel, the Product Performance Engineer becomes the “owner” of the event and makes critical decisions as to what, if any, additional investigations or tests may be needed and makes assignments accordingly. The results of any additional investigations and tests are provided to the Product Performance Engineer. After reviewing these results, the Product Performance Engineer decides whether an event requires initiating a trend analysis, and therefore, review by the Product Performance Committee, as specified in the CAPA procedures.

A root cause analysis is triggered by any event characterized by a malfunction. In the case in which a number of reported events appear to have the same failure mechanism, the Product Performance Engineer may declare it

as a “trend.” A trend must be declared if four similar events occur during a period of twelve consecutive months, although trends have been opened by knowledgeable Product Performance Engineers with fewer events (eg, the PRIZM 2 DR trend was initiated after two events). Alternatively, there is a second criterion for opening a trend - a failure rate that exceeds design expectations (reliability standard). When a trend is opened, an *ad hoc* “cross-functional” team is usually assembled to investigate the trend, and to participate in characterizing the root cause and proposing a corrective action.

Opening of a trend also initiates a process of risk assessment regardless of the severity of the event or events prior to this step. If it is judged that the health risk is not negligible, a formal Health Risk Assessment (HRA) is performed. The HRA is designed to grade events associated with the trend, as to both the probability of occurrence and their severity.

For each HRA, the Product Performance Engineer is required to assess the occurrence index, using the worldwide observed probability of the occurrence of the event, and the severity index (health impact) to place the trend into one of three risk review zones (red = high risk; yellow = medium risk; green = low risk).

The occurrence index has six levels for the observed probability of the occurrence of an event, as follows:

1. Remote (<0.001%)
2. Rare ($\geq 0.001\%$, <0.01%)
3. Sporadic ($\geq 0.01\%$, <0.1%)
4. Occasional ($\geq 0.1\%$, <1.0%)
5. Frequent ($\geq 1.0\%$, <10.0%)
6. Continuous ($\geq 10\%$)

The severity index has five levels as follows:

1. Limited (Transient or minor injury)
2. Moderate (Neither impairment nor treatment is severe)
3. Severe (Impairment or treatment can result in serious injury)
4. Life Threatening (Impairment or treatment could result in death)
5. Death (Death has occurred)

The system is color-coded. The following matrix shows the three colors: red,

yellow, and green. The vertical axis shows the occurrence index and the horizontal axis the severity index. A malfunction that is judged to be life-threatening, or one in which a death has occurred, is placed in the “red” zone, regardless of its probability level.

| | | | | | |
|---|---|---|---|---|---|
| 6 | R | R | R | R | R |
| 5 | Y | R | R | R | R |
| 4 | Y | Y | R | R | R |
| 3 | G | Y | Y | R | R |
| 2 | G | G | Y | R | R |
| 1 | G | G | Y | R | R |
| | 1 | 2 | 3 | 4 | 5 |

There are three relevant committees in the CAPA system (see **APPENDIX F**). The Product Performance Committee reviews all trends periodically to ensure consistency of methods and the appropriateness of the corrective actions. The Product Evaluation Committee reviews all new devices before the first human use, and all “red” zone HRAs. The Officer Escalation Group reviews all trends elevated to the level requiring consideration of field notification and/or action. All “Yellow” HRA results are reviewed by the chair of the PEC for possible review by the full PEC. All “Green” HRA results are reviewed by the Performance Evaluation Committee chair.

3. OBSERVATIONS

- a. The system relies heavily on Product Performance Engineers to process information, decide when additional tests are needed, when to request input from other sources, open trends, and monitor open and closed trends. The demands on the Product Performance Engineers in terms of workload and expertise, given their high level of responsibility and decision making, may at times be excessive. For further details on the Product Performance Engineer functions, see **SECTION III.D**.
- b. The Product Performance Engineer positions have been chronically understaffed. At times only one of the three positions designated for ICD reviews was filled. It seems to be difficult to recruit Product Performance Engineers. Although their role is critical, they may be under appreciated and inadequately compensated for the level of responsibilities that they are assigned and assume.

- c. Individuals with medical training are not sufficiently involved in the CAPA process. For example, medical personnel with clinical training and experience with implantable cardiac devices are not involved in obtaining relevant clinical information related to reported events. The Product Performance Engineers are not required to have, and document, formal discussions with medical personnel. As a result, personnel without appropriate medical background or sufficient acquired expertise make severity determinations in the HRA process.
- d. The method for long-term tracking of events with potentially serious patient outcomes is inadequate. There is no mandated review of Product Performance Committee and Performance Evaluation Committee decisions by CRM senior management. Although there are formal rules for the Performance Evaluation Committee chair to review HRA results, there are no such formal rules for the Officer Escalation Group chair to review Product Performance Committee and Performance Evaluation Committee decisions. A large number of Guidant personnel received reports, known as the “Red Book,” summarizing trends. It is unclear what they were to do with these reports. This may have created a climate of reassurance (eg, in the case of PRIZM 2 DR) within the company since a large number of personnel were receiving the reports in the Red Book, in addition to the Product Performance Engineer and the committees, and no concern was being passed on to CRM senior management. In fact, CRM senior management was on the distribution list of these reports, but do not participate in active evaluations. The reports are poorly designed for those receiving them to efficiently monitor malfunctions with potential or actual life-threatening events.
- e. There are a variety of statistical performance evaluation metrics, each of which has utility in certain circumstances. The survival curves, for example, include battery depletion and provide overall reassurance of product reliability and life expectancy. However, there is no metric or presentation that permits a comparison for a single specific life-threatening trend over time, irrespective of whether the overall failure rate of the device meets design expectations.
- f. There is insufficient attention paid to uncertainties. Uncertainties in the estimation of failure rates during the design phase are not treated explicitly. For example, the estimated effectiveness of design changes to mitigate past failure modes observed in components used in previous devices, are included in the “modifiers,” which themselves are uncertain. It is unclear whether the possibility of previously unobserved failure modes (ie, due to the new design features) are included in the modifiers.

For postmarket evaluations, confidence bounds on failure rates are derived using the observed statistical data. The system appears to have worked well from the point of view of the estimated failure rates during the design phase and the eventual observed values. However, uncertainties in the evidence itself (eg, the under-reporting of events) are not considered when calculating either rate.

- g. The basis for CRM reliability standards and goals, while stringent, are unclear. For example, there is no evidence that the uncertainties noted above are considered. Making a decision as to whether there is a systematic or random failure is difficult after the first event of a kind has been identified. In the Guidant CRM evaluations, repeated events are too readily accepted as random, even after replication of the failure and root cause has been determined.
- h. The limitations of many of the non-U.S. surveillance systems makes performance evaluation of devices sold outside the U.S. very limited and incomplete.
- i. During the production of devices, CRM strives for continuous improvements in quality, reliability, and manufacturing efficiency. During the life-cycle of a single model, there are normally many changes in manufacturing processes, components, or product testing. Many of these changes have no effect on safety and reliability, although rarely (eg, the PRIZM 2 DR "mitigations") they may. At present, Guidant reports these to the FDA, but previously did not routinely report any of these changes to either physicians, patients, or the public, except as part of a Product Advisory.

4. RECOMMENDATIONS

- a. The responsibilities, workload, and training of the Product Performance Engineers should be reviewed and appropriate action taken to optimize their performance as part of the CAPA system. This should include additional numbers of Product Performance Engineers, with additional expertise and/or training. They should also have formal access to individuals with higher levels of medical expertise
- b. Individuals with relevant clinical training and experience should work closely with the Product Performance Engineers in all phases of the CAPA process, including early data gathering, analysis of the information obtained and conducting the HRA. Guidant CRM should appoint a

medical safety officer who would take responsibility for medical input and analysis throughout the CAPA process.

- c. CRM/Guidant should review the current interactions between the Product Performance Engineers, the Product Performance Committee, the Performance Evaluation Committee, and the Officer Escalation Group. Changes should be implemented to assure that senior management of CRM or Guidant Corporation, as appropriate, is informed of all decisions made by these individuals or groups that involve malfunctions that have been classified as life-threatening or were associated with a single death.
- d. CRM/Guidant should establish multiple ways for the Officer Escalation Group to be informed of important trend issues. Guidant should undertake a review of which personnel receive reports of trends, what their responsibilities are after receiving the reports, and the format of the reports. Since there are usually a very large number of trends in these reports, a format needs to be developed that will allow for efficient identification of trends that need further internal, and potentially external, communication. Using this information, the chair of the Officer Escalation Group should review these reports on a monthly basis to identify important issues to bring to the attention of the full Officer Escalation Group.
- e. The chairs of the Product Performance Committee and Performance Evaluation Committee should attend quarterly meetings of the Officer Escalation Group and review all red zone HRAs.
- f. The Medical Safety Officer should be a regular member of the Officer Escalation Group.
- g. The criteria for establishing a trend should formally include greater weighting of severity (ie, clinical implications) independent of the number of events or failure rate.
- h. Product performance reviews should include a graphical presentation of events over time that permits identification of life threatening trends, irrespective of whether the rates meet design expectation (Kaplan-Meier plot with the axes appropriately scaled).
- i. CRM should undertake a critical review of all metrics and quantitative models used during the design phase and the post-implant product performance evaluation process. This might include a formal review and

advice from external advisors. As part of this, a review of the currently used assumptions needs to be critically performed. Alternative metrics and models developed for low-frequency, high consequence events (eg, Fault-Tree Analysis, Bayesian methods) should be considered (See **REFERENCES 6-8**). For example, the development of the predicted failure rate uses point estimates of the rates λ_i . In a Bayesian framework, one would develop probability distributions for $\lambda_1, \lambda_2, \dots$ and then develop a probability distribution for $\lambda_{\text{predicted}}$ by taking the weighted average of these distributions (rather than of the failure rates themselves) or combining the distributions in some other way. We acknowledge that no method is perfect. The point is that predicting future failure rates is better done by acknowledging the subjective nature of the exercise, being explicit about the uncertainties, and doing sensitivity studies on the assumptions.

- j. The technical bases for CRM's reliability standards, definition of goals, analysis of event numbers, frequency, and trending patterns, and conclusions regarding clinical relevance of malfunction modes, all should be subject to external review. The creation of an Independent Review Group (IRG), recommended elsewhere in this Report and described in **APPENDIX E**, would achieve these goals.
- k. CRM should work in collaboration with regulatory agencies, AdvaMed, and professional societies, to develop uniform industry standards pertaining to processes and procedures that enhance patient safety.
- l. Continuous quality improvement is a practice that should be encouraged. The effectiveness of each improvement should be monitored as completely as possible both before shipment of the product and during clinical follow-up. If an improvement introduced in the middle of a product's life cycle is shown to result in enhanced patient safety and involves a high risk issue, Guidant should note this in their Product Performance Report and, if un-implanted, pre-mitigation devices still exist, notify potential users. If the magnitude of safety enhancement is uncertain, the data should be presented to the Independent Review Group for advice in a timely manner.
- m. The use of the term 'random' in connection with a device failure should be discouraged. The phrase "low frequency event" is recommended. The addition of the phrase "of unknown cause" may be added, if the root cause has not been identified.

- n. Observations regarding malfunctions, such as those noted in **TABLE III.B.1** above, should be considered in the context of the cohorts from which the data are collected and any variation in the quality and or completeness of the data collection process. There are two specific categories of concern:
- 1) The denominators in some reports include the number of devices used worldwide, while in others are limited to U.S. only. Since the reporting of malfunctions is not quantitative, and likely differs between devices sold in the U.S. and those sold outside of the U.S., summary statistics from U.S. and non-U.S. experiences should not be merged.
 - 2) If a statistic is to track the incidence of a specific malfunction, and at some point in time there is a manufacturing change which is believed to mitigate the malfunction, two statistics should be calculated; one based on the number of devices manufactured and failed pre-mitigation and one on the numbers post-mitigation.
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C. Postmarket Surveillance

1. BACKGROUND

All manufacturers selling finished medical devices or ready for use components are required to monitor and identify significant adverse events involving medical devices in order to detect and correct problems in a timely manner.^[1] Events which must be reported include device related deaths, serious injuries, and reportable malfunctions. The FDA requires a report "... when a manufacturer becomes aware of information that reasonably suggests that one of their marketed devices has or may have caused or contributed to a death, serious injury, or has malfunctioned and that the device or a similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur."^[2] (See **APPENDIX G** for a brief discussion of FDA definitions and reporting requirements.) This formal report to the FDA, a Medical Device Report (MDR), must be submitted by industry within 30 days of receipt of the information unless there is an exemption, and becomes part of MAUDE, the FDA public database.

Postmarket surveillance is the process of reporting and evaluating clinical adverse events and product malfunction. Most systems are passive collection systems since there is no well-defined population being actively assessed as would happen in a cohort study or clinical trial. The objective of the voluntary reports is to identify signals of potential new problems that can be evaluated further with appropriate methods. Under-reporting of adverse events is virtually unavoidable with passive surveillance methods. This can both underestimate occurrence rates and can delay detection.

Pacemaker and ICD manufacturers have potential advantages for effectiveness of postmarket surveillance systems for several reasons. Patients with implanted pacemakers and ICDs are actively followed, the model and serial numbers are usually documented, the devices are interrogated at regular intervals to assure proper function, and they can be reprogrammed. In addition, when they are removed because of malfunction, they are commonly returned to the manufacturer for evaluation. They may also be returned after replacement for normal battery depletion. This provides many features of active surveillance methods. In contrast, there are malfunctions that are not recognized because they cannot be detected by device interrogation, because the malfunction only occurs after delivering a defibrillation shock, or because the patient died and the device was not suspected or the device was not recovered. Nonetheless, the surveillance system for cardiac electronic devices offers many more opportunities for detecting and evaluating product

malfunctions than most other medical devices and pharmaceuticals.

2. OPPORTUNITIES TO STRENGTHEN SURVEILLANCE

Pacemakers and ICDs are devices that change incrementally and within a single manufacturer may be thought of as products grouped in multigenerational families of technology. As such, premarket trials of a new family member are opportunities for active surveillance of problems that may span many of the older products.

Due to the complexity of setting up a comprehensive active surveillance system and the large number of patients and clinicians involved, it may be more feasible to establish an active surveillance system for a subset of patients. Consideration could be given to sampling techniques that would capture the experiences of a large number of patients who would be followed longitudinally. These strategies could be derived from multiple large practices, hospital clinics, Medicare databases, and/or shared data from registries or companies in the device industry. In any case, care must be taken to avoid unintended selection biases. By having complete data on a subset of patients it would be possible to estimate underreporting in the broader surveillance population.

Key elements for an active surveillance system would include a well designed data collection protocol, training for clinicians in reporting methods, standardization of the definitions of outcome events, case report forms that characterize relevant patient characteristics at baseline, identification of the device model and serial number, prospectively planned follow-up and analysis plans that would identify clusters of new events and estimate malfunction and failure rates. For each of these categories, attention must be paid to HIPPA requirements for patient confidentiality. (For a more extended discussion of these issues see **APPENDIX H** and **APPENDIX I**).

3. GUIDANT PRACTICES

Guidant's CRM Division has all of the elements of the postmarket surveillance system required by FDA and the regulatory systems of other countries. All employees are trained and mandated to identify and report complaints. There are written procedures and training programs. Complaints which are MDR reportable events are identified and reported and the MedWatch 3500A forms (FDA's mandatory reporting form) were made available for review by the Panel. Malfunctions identified in returned pacemakers are also reported as required. The complaint and MDR systems are part of the CAPA system which has been evaluated by FDA on field inspections. FDA has

not identified problems with the postmarket surveillance system at Guidant.

a. Malfunctions

Guidant's approach to device malfunctions appears to be based on the FDA approach to malfunctions. To again quote from FDA regulations:

"A malfunction [§803.3(m)] is a failure of the device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device."

Although a device is not intended to fail, Guidant's evaluation of a malfunction is heavily influenced by their expectation of the product's performance. Since the performance specifications include estimates of random component failures, for example, a device failure, although clearly a malfunction in the plain-English meaning of the word, may be viewed as a problem that does not necessarily cause the product to fail to meet its performance specifications. While Guidant reports individual malfunctions to FDA, they conceptually think of making changes that further reduce a low failure rate as part of "continuous improvement" of a product with a low failure rate, rather than thinking of the devices as having a correctable defect that causes malfunctions.

b. Passive Postmarket Surveillance

Guidant's postmarket surveillance system is passive in the sense that physicians, field representatives and patients voluntarily report events and device malfunctions to them. As discussed above, the surveillance system has more active follow-up, required for clinical patient care, and better documentation of the identity of the pacemaker than most medical devices. Nonetheless, the ascertainment of device malfunctions is incomplete, the magnitude of which is unknown. Guidant tracks patients who have had devices implanted for a mortality benefit, but does not have access to causes of death unless individuals who die are voluntarily reported to them. In calculating their failure rates, Guidant uses the incomplete number of failures divided by an estimated number of implant months or "at risk" device months. The "at risk" denominator is adjusted by an estimation of the death rate in pacemaker users. No adjustments are made to account for underreporting or from missed opportunities to assess potential failures in patients who have died or in devices removed for battery depletion that are not returned to Guidant. There do not seem to be industry-wide methods in place to estimate the degree of underreporting.

Guidant bases many evaluations and decision-making on trends that are dependent on postmarketing surveillance. There appear to be rules, such as the rule that four events of the same type occurring within a year period require that a trend be opened, which rely, at a minimum, on a constant rate of problem underreporting. There do not seem to be methods in place to estimate the degree of underreporting.

4. CONCLUSIONS

- a. Guidant Corporation has written procedures, training, and clearly identified responsibilities to identify and evaluate malfunctions, identify and report FDA required MDR's that comply with FDA Quality System regulations.
- b. Guidant Corporation's postmarket surveillance identifies malfunctions, only a small number of which cause injuries and even less frequently deaths. Their postmarket surveillance detected the malfunctions for the PRIZM 2 DR and Contak RENEWAL 1/2.
- c. The MDR system is not an effective surveillance system.
- d. Guidant and the implantable cardiac device industry in general, do not have methods to estimate the extent of under-reporting which likely results in underestimation of malfunction rates.
- e. Hospitals are required to report implant data, but there is no requirement for subsequent ambulatory office follow-up. The fundamental problem is that once the device is implanted, it belongs to the patient and industry has no inherent right to retrieve it, even if it fails. It would require legislation to mandate post-mortem retrieval. However, if patient deaths were tracked, suspected failed devices may be more easily retrievable. The limitation is the fact that physicians often learn about patients deaths only after burial.
- f. Each device manufacturer works on postmarket surveillance in isolation making identification of common problems more difficult and creating disincentives for a single company to improve under-reporting or to detect rare malfunctions that may occur across company product lines.

5. RECOMMENDATIONS

- a. In addition to current procedures, it would be helpful in periodic reports, such as the Product Performance Report, to link events to the actions taken to mitigate malfunctions.

- b. Evaluation of MDRs by experienced clinicians may improve the identification of problems that could potentially be life-threatening.
 - c. Guidant Corporation, in conjunction with the device industry, the FDA, and professional societies (eg, HRS, ACC-NCDR) should explore active surveillance methods to supplement the MDR system. Benefits would include better information about trends, and additional opportunities (eg, consent to explant devices post-mortem, training morticians to correctly remove and return devices) to obtain information early. However, because industry-wide surveillance and data evaluation systems are challenging to individual corporate concerns about protecting trade secrets and proprietary information, such cooperative efforts are not likely to be developed in the short term. Until such efforts are agreed upon, Guidant (and the others in the industry) should proceed with individual efforts to develop better surveillance systems internally.
 - d. If evaluation of product problems continues to rely on trends, there should be scientifically valid criteria to open or close trends and methods for data collection.
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Section References

1. Safe Medical Device Act, 1990 and the Medical Devices Amendments of 1992, amending section 519 of the Food Drug and Cosmetic Act.
2. <http://www.fda.gov/cdrh/mdrovrw.pdf>

D. Internal Communications and Strategic Management Decisions

1. GENERAL BACKGROUND

Corporate structure requires carefully designed methods for internal communication in order for its multiple interests and oversight needs to be met. Medical device companies are characterized by multi-disciplinary expertise. This includes engineering and product development, post-market surveillance, medical applications, trial design, sales and marketing. Because of the diversity of expertise required for these disciplines, it is incumbent on these companies to integrate and coordinate the activities of these business components for clinical effectiveness and safety. This necessitates carefully thought out policies and procedures for internal communication leading to an informed consensus for strategic decisions.

Concerns about internal corporate communication are not unique to the implantable cardiac rhythm device industry generally or to Guidant Corporation and its CRM business in particular. However, this device industry is confronted by challenges that create a unique demand on communication issues. There are links between internal communication and patterns and content of external communication, and between adequacy of quality assurance and its communication to a customer base that is particularly relevant to a business that manufactures and markets life-sustaining products. A corporate reputation for both business ethics and bioethics (see **SECTION II.B**), and trust for transparency, begins with an organized and consistent approach to appropriate corporate behavior. The latter requires coordination that can only be achieved by effective and appropriate internal communications.

2. CRM'S INTERNAL COMMUNICATIONS AND DEVELOPMENT OF STRATEGIC DECISIONS

a. Description of Internal Communications

The operational independence of Guidant Corporation's businesses, including CRM, affects internal communication both within the CRM division and between CRM and Corporate headquarters. CRM bases critical product management decisions on a chain of internal communications from Field Engineers and Representatives who report product failures, analysis of incoming data by Product Performance Engineers, investigations of product

failures by the engineers who perform bench testing, Health Risk Analysis of product malfunctions, and review of these reports by the Product Performance Committee, the Product Evaluation Committee, and the Officer Escalation Group.

Internal guidelines channel the flow of information to senior executives only after certain thresholds are reached (or recognized), and there is considerable latitude at each step that may delay or interrupt the flow of information. Employees who follow trends may decide independently to withhold or delay transmission of critical information to more senior management. Cross-functional teams are created to improve the transfer of information and facilitate collaboration and consensus development among groups with different expertise. These teams are created “*ad hoc*” without clear guidelines to establish, disband, or reconstitute them. Medical oversight by physicians with clinical expertise appears to be a secondary priority. In fact, no physicians have primary responsibility for this critical function related to safety, nor does Guidant make appropriate use of external advisory Panels to provide important clinical insights when life-threatening product failures are identified. In some cases, senior management may not learn about key product failures until it becomes a matter of public interest.

b. Development of Strategic Management Decisions

FIGURE III.D.1 illustrates the delay that occurred between the time the critical flaw was identified with PRIZM 2 DR and review of this problem by CRM senior management, which followed the death of a patient widely publicized in the *New York Times*. The three year delay in transmitting this information to CRM senior management reflected the independent function and policies of the Product Performance Committee and Performance Evaluation Committee that did not obligate reporting these issues to the Officer Escalation Group. This reflects the culture of internal communications within CRM during this period.

CUMULATIVE PRIZM 2 DR ARCING FAILURES

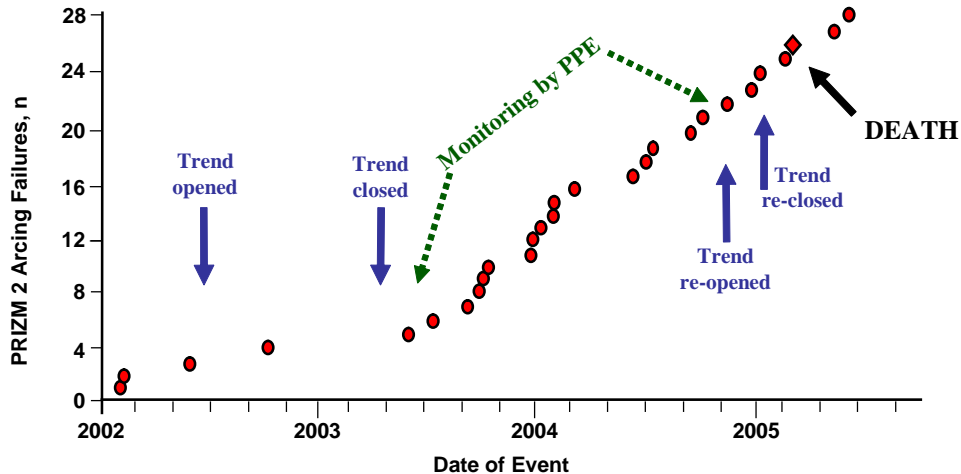


Figure III.D.1. Cumulative PRIZM 2 DR Arcing Failures

In the case of PRIZM 2 DR, the trend was opened May 20, 2002 and closed on April 16, 2003. It was reopened November 5, 2004 after 21 cumulative failures had been identified. CRM’s Chief Medical Officer was unaware that this problem existed while it was under discussion by the Product Performance Committee and Performance Evaluation Committee. The Officer Escalation Group met to discuss public management of this problem only after it was about to be disclosed by the *New York Times* on May 23, 2005. There was very little communication between CRM’s senior management and Guidant Corporate Headquarters prior to this revelation.

In the case of the RENEWAL 1/2 malfunctions, the root cause of arcing was recognized and mitigated relatively early (**FIGURE III.D.2**). The health risk was recognized and carefully considered. The information was analyzed and brought to the attention of CRM senior management more effectively than was the case with PRIZM 2 DR. The incidence of product failures and associated deaths were higher for RENEWAL 1/2, yet in the early stages, the Product Performance Committee struggled to decide the best course of action.[³] Several

³ On July 2, 2004, a patient in Spain died when a RENEWAL ICD failed to terminate a lethal arrhythmia. Subsequent analysis of the device identified arcing as the cause of the failure, but

months later, when mounting RENEWAL 1/2 failures forced the Product Performance Committee to provide guidance to the Officer Escalation Group, CRM was confronted with the dilemma that a faulty product design had been identified, and that many of these products had already been sold to hospitals and were awaiting implantation in uninformed patients. On August 26, 2004, CRM stopped shipping products at risk to its customers.

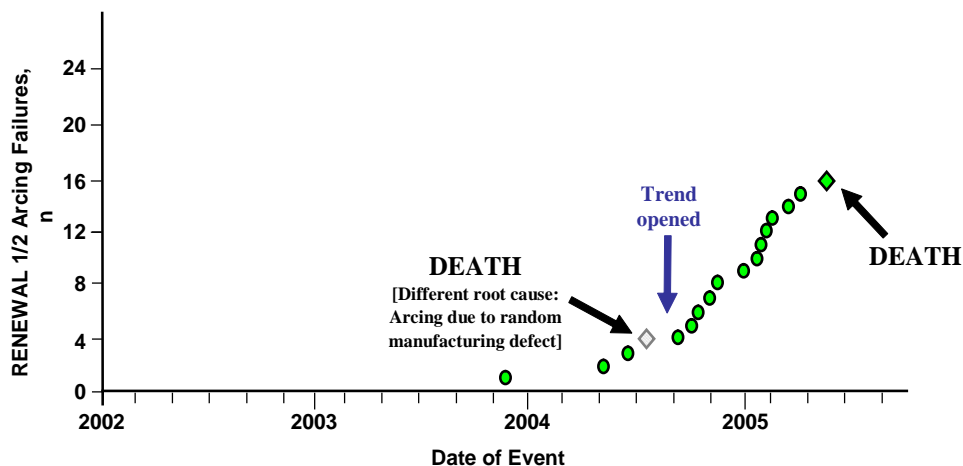


Figure III.D.2. Cumulative RENEWAL 1/2 Arcing Failures

On September 7, 2004 the Product Performance Committee recommended that CRM should not pull back the field inventory, and on September 30 the Product Performance Committee recommended that implants should continue. The inventory in the field was 283 devices with an additional consignment of 85 devices. On September 29, 2004, the Product Performance Committee recommended to the Officer Escalation Group that finished goods within the

the specific mechanism for arcing appeared to differ from other RENEWAL cases. Analysis of the device led to the conclusion that arcing was caused by a miss-feed of the wire in the ICD header, which was a random manufacturing flaw. A defect in the polyimide insulation was also present, but not determined to be the primary cause. The failure and analysis was reported to the Spanish authorities and to the United States FDA. CRM decided to include this failure in its Health Risk Analysis of the RENEWAL arcing problem, but it did not include it in statistical projections of future failures because it was a unique mode of failure. The FDA concurred with this decision.

manufacturing facility should not be shipped because there were “large error bars” around the model’s predicted rates. In the same meeting, the Product Performance Committee recommended that CRM continue to sell the inventory of products at risk of failure that it had already shipped to hospitals because the event rates were consistent with reliability predictions and these rates did not warrant a field action. The logic behind these decisions seems inconsistent. A different decision might have been reached if input had been obtained from senior management and medical experts within CRM and Guidant Corporation when the problem was first characterized.

One can argue that there is no consensus regarding an acceptable failure rate when the mode of failure is life-threatening, but deliberations by the Product Performance Committee and Officer Escalation Group seemingly dismissed the need to inform physicians that a product flaw had been identified. Even when the decision was made to stop shipping products, the Officer Escalation Group review of September 2, 2004 seems to focus on the field inventory of 1-2 months and the need to manage back-orders by moving inventory to the site in need. In its meeting on August 30, 2004 the Product Performance Committee proposed response for its sales force was “backorders are due to a manufacturing process/yield issue that is being worked.” There appeared to be a fundamental belief at CRM that notification of physicians would lead to unnecessary explantation and replacement of the ICDs that had already been implanted. There is no evidence that further discussion of this issue occurred with a panel of qualified medical experts.

On January 11, 2005 the Product Performance Committee considered withdrawal of RENEWAL 1/2 from the market versus the following alternative to early withdrawal: “Even if implanting pre-fix devices turns out to pose a clinical risk, by the time statistical surety is reached, most or all pre-fix devices will have been implanted, making the issue of pre-implant recall moot”. It is not clear that CRM senior management was involved in this discussion or its implications.

Product failures with PRIZM 2 DR and RENEWAL 1/2 devices draw attention to a problem that is not unique to Guidant’s CRM business or its competitors. These industries face the challenge of managing product failures that occur with extremely low rates, but the implications of isolated failures can be catastrophic. In the absence of industry standards, the discussions within CRM illuminate its own uncertainties. The lack of standards within industry at large contributed substantially to decisions that can be regarded as arbitrary and flawed.

In summary, the events of 2002 through 2005 reveal flawed internal

communications and development of appropriate strategic decisions. Specific conclusions and recommendations focus on the following areas pertaining to internal communications for development of improved consensus-based strategic decisions:

- 1) Product Performance Engineers
- 2) Improved Use of Cross-Functional Teams
- 3) Medical Oversight
- 4) Trend identification and Management
- 5) Physician Expectations and Education
- 6) Engagement of Senior Management
- 7) Relationship between Guidant Corporation and CRM

3. CONCLUSIONS

a. Regarding Product Performance Engineers

- 1) The CRM business of Guidant is extremely dependent on decisions that are made by the Product Performance Engineers. These individuals examine trends and prioritize them based on the frequency of events and the relative health risk posed by the nature of the events. Trends are established when devices malfunction with a frequency that is higher than expected (approximately 0.065% per month) or if four device failures are identified over an interval of 12 months. A Product Performance Engineer has the prerogative to open a trend if the level of health risk associated with a device malfunction is judged to be extremely high, even if only one or two failures have been identified. Despite the fact that a Cross-Functional Team may be assigned to work with the Product Performance Engineer (and usually is) and the Product Performance Engineer may informally consult with others in the reliability section, *the Product Performance Engineer is not required to report findings to other levels of the business hierarchy until a trend is opened and may monitor a closed trend alone.*
- 2) Even after a trend is established and information escalated to committees in the CRM business that deal with product reliability evaluation (eg, Product Performance Committee and Performance Evaluation Committee), *senior officers of CRM may remain isolated from the decisions made by these committees, and Guidant Corporation headquarters may not be informed about important decisions that are*

made by the Product Performance Committee or the Performance Evaluation Committee.

- 3) Product Performance Engineers appear to have diverse educational backgrounds. The job requires significant insights about engineering principles, statistical analysis, and health risk assessment. Although they have some training in these areas, it is likely that no Product Performance Engineer will have a high degree of expertise in all relevant fields. This creates a need for closer oversight, peer review, consultation, and communication between different disciplines that seems to be lacking or inadequate.
 - a) Experienced Product Performance Engineers may leave the job and pass responsibility for a trend to a new and relatively inexperienced Product Performance Engineer who may lack the judgment or insight required to assess the health risk of a specific defect. For example, communication between the Product Performance Engineers during transfer of the PRIZM 2 DR trend data seems to have been inadequate.
 - b) Trends are also passed from one Product Performance Engineer to another depending on the load that a specific Product Performance Engineer is carrying or the need for that individual to assume responsibility for new trends. When responsibility for a specific trend is passed on to a new Product Performance Engineer, he or she may not appreciate the priority assigned to that trend, particularly if the trend had been closed prior to assuming responsibility for it.
- 4) The criteria that were used to open a trend or reopen a closed trend provided a great deal of latitude to the Product Performance Engineer. When the PRIZM 2 DR short circuit trend was being monitored, the Product Performance Engineer chose not to reopen the trend because the problem had already been mitigated. This decision failed to take into consideration that the unmitigated devices had already been implanted in a large number of patients and they remained at risk. This decision was never brought to the attention of CRM management at a higher level. Thus, with this degree of latitude, CRM's senior management was at risk of being uninformed if the Product Performance Engineer made a decision that later proves questionable.
- 5) Although Product Performance Engineers have access to other opinions and advice prior to opening a trend, they are not necessarily

required to seek these opinions. Internal communication appears to be informal, which increases the risk to patients, CRM and Guidant Corporation if the Product Performance Engineer makes a poor judgment.

b. Cross Functional Teams

- 1) The Cross-Functional Team concept provides strong support for the mission of evaluating and mitigating product performance issues arising out of observed malfunctions.
- 2) CRM lacked clear guidelines for developing cross-functional teams to analyze product malfunctions and relate these problems to health risk assessment.
- 3) The use of cross-functional teams that facilitate the exchange of information between individuals with different expertise would reduce the risk of ignoring important trends.

c. Medical Oversight

- 1) A striking inconsistency between the perception about medical oversight by the physicians employed by CRM and nonphysician employees is apparent. The design engineers, Product Performance Engineers, Health Risk Assessment Committee, Product Performance Committee, and Performance Evaluation Committee feel that they have ready access to medical expertise from:
 - a) A consultant to CRM who is primarily concerned with trial design
 - b) The Chief Medical Officer of CRM who believes his primary responsibility is physician education and his role as the liaison to practicing physicians
 - c) A veterinarian whose primary responsibility is in the animal laboratory

In fact, none of these individuals has the specific responsibility to serve as the primary advocate for patient safety.

- 2) Engineering teams at CRM do not seem to fully appreciate their lack of medical oversight or the importance of medical oversight pertaining to deliberations when life-threatening product malfunctions are identified.

- 3) Guidant Corporation has medical advisory boards that focus primarily on clinical trials and marketing. There are no advisory boards that serve primarily as advocates for quality and patient safety.

d. Engagement of Senior Management

- 1) The flow of information is designed to allow engineers to weigh risks and make changes in the product line without undue influence from marketing interests. Moreover, there were no clear guidelines to alert the Officer Escalation Group when life-threatening product failures were identified or to engage the Officer Escalation Group in early decisions that critically influence the management of these problems. One consequence of the separation of this structure is that senior management and the Medical Officers of CRM and Guidant Corporation may not be informed about important decisions that are made by the Product Performance Committee or Performance Evaluation Committee that affect clinical outcomes.
 - a) The isolation of the Product Performance Committee and Performance Evaluation Committee from medical oversight is illustrated by the fact that CRM's Chief Medical Officer learned about the PRIZM 2 DR failures during a casual conversation with a Guidant sales representative at the Annual Scientific Sessions of the American College of Cardiology in March 2004.
 - b) Other senior officers of CRM appear to have been equally isolated from the decisions made by the Product Performance Committee and Performance Evaluation Committee.

e. Relationship Between Guidant Corporate and CRM

- 1) Guidant Corporation has four autonomous business enterprises. CRM has a quality control system that is proprietary. When the product failures were identified, there appears to have been a broad failure to communicate between CRM, which identified the problem, and Guidant Corporate which bears ultimate responsibility to its shareholders and the public at large.
- 2) As was the case for CRM, the Chief Medical Officer for Guidant Corporation was focused on research and development and medical policy. Neither Guidant Corporation nor CRM had a physician who served as the primary advocate for patient safety. CRM promoted the concept that every employee is committed to the safety and quality of

its products, yet it did not provide effective physician oversight of decisions that affected the safety of patients who received these products.

Since the crisis of June 2005 PRIZM 2 DR and RENEWAL 1/2 recalls, the primary focus of the Chief Medical and Technical Officer of Guidant Corporation has been advocacy and oversight for patient safety.

Within the corporate structure of Guidant Corporation, there was inadequate formal communication and reporting structure between the Chief Medical Officers of CRM and Corporate Headquarters pertaining to the risk of product malfunctions and public disclosure. These discussions were initiated after public disclosure in the media. The delineation of roles between the Chief Medical Officer at CRM and the Chief Medical Officer at Guidant Corporation in Indianapolis was not well defined and communication between them was nonexistent during the events culminating in the *New York Times* article. In the case of PRIZM 2 DR, the CRM Medical Officer met with the physicians of the young man who died after failure of his device to deliver therapy. A full and clear picture of the events leading to the *New York Times* inquiry was never conveyed to senior officers at Guidant Corporate headquarters, nor were they aware of the meeting with the treating physicians or the tenor of the conversation. As a result of the communications policies within Guidant Corporation, CRM or other subsidiaries could reject centralized advice rendered by Guidant headquarters. In fact, it appears that senior management at CRM did not feel compelled to elicit advice or develop a consensus of opinion with Guidant headquarters. CRM's insular approach reflected a firm conviction that they could manage the problem alone. Subsequent difficulties with communicating information to physicians, the press, and employees cast doubt on the wisdom of this decision.

4. RECOMMENDATIONS

a. Communications Between Product Performance Engineers and Other CRM CAPA Entities

- 1) CRM's policies and guidelines for Product Performance Engineers should be revised to require timely communication of life-threatening trends to CRM's senior management and personnel with medical expertise. Conversely CRM's senior management should be required

to review decisions made by a Product Performance Engineer that have important implications for exposing patients to additional risk. All potential barriers between Product Performance Engineers and other experts at CRM should be eliminated and consultation for troublesome trends should be required.

- 2) CRM's policies should also require improved communication between the Product Performance Engineers. It is preferable for a Product Performance Engineer to retain a trend once it has been established. Greater collaboration and oversight is needed if it is absolutely necessary to pass the trend to another Product Performance Engineer. This is particularly important if the Product Performance Engineer who receives the trend lacks the same level of experience, a frequent occurrence in these positions.

b. Cross-functional Teams

- 1) Cross-functional teams should be required to analyze and monitor all potentially life-threatening product malfunctions. Results should be prioritized and communicated to senior management expeditiously.
- 2) Trends that have been deactivated should be reviewed periodically by the cross-functional team to confirm that there is no reason to reactivate the trend. These decisions should be transparent to senior management and medical experts.
- 3) Guidelines to disband or reestablish cross-functional teams require clarification.

c. Medical Oversight

- 1) CRM should identify a Medical Officer whose primary role is to serve as an advocate for patient safety, risk assessment, and post market surveillance.
 - a) The Medical Officer must be informed promptly of any potentially life-threatening trends.
 - b) The Medical Officer, in turn, should be obliged to advise senior management and the Chief Medical Officer at Guidant Headquarters when further review of a life-threatening trends should be undertaken by an independent review group that would function akin to a data safety monitoring board.

d. Engagement of CRM's Senior Management

- 1) The criteria for alerting CRM's senior management about life-threatening product failures must be reviewed and revised. CRM's senior management should be alerted promptly when life-threatening product malfunctions are first identified.
- 2) Improved criteria should be established to accelerate communications to the Officer Escalation Group by the Product Performance Committee and Performance Evaluation Committee about their deliberations on serious product malfunctions.

e. Relationship Between Guidant Corporate and CRM

- 1) It is critical for Guidant Corporation to establish stronger oversight and communication with CRM. There appears to be a need for uniform corporate wide processes for quality control, corrective actions, risk assessment, risk management, and public communications.
- 2) It is also critical that CRM communicate more openly and promptly to Guidant Headquarters when quality issues regarding product flaws that may adversely affect patient safety are identified.
- 3) CRM and Guidant Corporation should collaborate closely when formulating a response to the public media. This requires improved internal communications between CRM and Guidant Corporation.
- 4) Guidant Corporation has a responsibility to work with its competitors, AdvaMed and the medical professional societies (Heart Rhythm Society and American College of Cardiology) to establish uniform reliability standards that would influence management decisions when product flaws are identified.

E. External Communication Policies and Methods

1. BACKGROUND

Pacemakers and ICDs are designed and proven effective for preventing sudden cardiac death in appropriate candidates and improving symptoms and significant morbidities. As described elsewhere in this document, these devices are subject to the same limitations as any other manufactured product, namely their susceptibility to random or systematic malfunction or failure to function due to manufacturing flaws or unanticipated design errors.

In general, the failure rates of these devices are quite low. Nonetheless, when unanticipated problems come to light, the manufacturer is confronted with the decision of when and how to make the flaw visible to the public, primarily treating physicians and patients. At the regulatory level, reporting requirements to the FDA are straightforward, but the information is difficult to access and interpret by the public stakeholders. Therefore, effective public communication requires a level of transparency that demands corporate intent and initiative.

In any corporation in this industry, the decision-making process for transparency and external communication of low frequency events, independent of FDA reporting requirements, invites cross-currents between perceived responsibility to patients and physicians, business and marketing concerns, corporate ethics, and risk-benefit considerations. To place these conflicting considerations in proper perspective to one-another, and develop policies that are in the best interests of both the customers and the business, a corporation must have carefully thought out and clearly defined policies on information dissemination and transparency.

The concept of transparency of device performance can include several corporate strategies, having different implications and impact. When being passively transparent, a corporation makes relevant information available in a manner that allows interested stakeholders to find and access it. Passive transparency assumes that interested stakeholders will seek out and correctly interpret the information on their own volition. Examples include general postings on a web site and routine publishing of information in Product Performance Reports. When being actively transparent, a corporation makes active efforts to provide relevant information to specific stakeholders in a manner that is useful to them. Active transparency is premised on the belief that better outcomes will result when stakeholders are aware of, and understand, information held by the corporation, and therefore all reasonable

efforts should be made to share that information. This involves directed communication of information to targeted audiences, such as physicians and patients, in a variety of ways, often including methods such as press releases, letters, and specific performance postings on the web site. The final approach to transparency, forced transparency, results when information is released by parties outside of the corporation, such as regulators, activists, or the media, about an issue or concern of potential interest to other stakeholders.

Both passive and active approaches to transparency can be used to *proactively communicate* information to help stakeholders form appropriate expectations, by providing them with clear useful information about relevant risks and benefits, in advance of their decisions that could incur risk. In the case of medical devices, this should include information about the anticipated and/or actual risks and benefits associated with specific devices, and general statements that help explain the inherent potential for unexpected failure in any manufactured device. Proactive communication places a corporation in the desirable position of having adopted a positive role in its interactions with stakeholders.

Forced transparency, by its very nature, invokes *reactive communication*, placing the corporation in the position of responding to an event internal or external to the institution. In the case of medical devices, this often involves reporting of previously undisclosed information, in response to circumstances that make disclosure mandatory, an inherently undesirable position from which to be communicating.

It is axiomatic that some level of risk of device malfunction or failure after implantation, unanticipated at the time of design and manufacture, is inherent to the deployment of cardiac devices. The issue at hand concerns events that occur at a frequency so low that they do not significantly distort pre-production performance estimates or field experience, but may nonetheless have life-threatening implications for a small number of patients. The mortality potential of such events, however low, places a special communication burden upon the corporation.

The general principles of informed consent respond to the desire of most patients to be fully informed about both the benefits and the potential risks associated with treatment options, even rare risks, and the ethical and legal obligations of physicians to provide that information. Informed consent generally focuses on the balance between therapeutic risk and clinical benefit, but the question of device failure has been generally ignored in this communications formulation, in part because the device industry has not focused on this as a general concept in its patient and physician information,

or made information of this type easily accessible through available sources.

By its very nature, effective risk management depends on effective communication among all parties involved. Effective risk management-oriented communication in the context of medical devices has several attributes: (a) the parties responsible for managing the risk (i.e., the manufacturer and the treating physicians) must make every reasonable effort to communicate all relevant information about the nature of the risk to the patients; (b) the process of providing information should involve at least enough dialogue to ensure that the risk information is properly understood; and (c) the parties who are subjected to the risk (i.e., the physicians and patients) should have an opportunity to express their wishes regarding how to manage the risk.

2. OBSERVATIONS

a. General

There is an implicit social contract between medical device manufacturers, health care providers, and patients: while each party is anticipated to advance its interests through its actions, no action on the part of any party should in any way be detrimental to the patient's well-being. Given this social contract, almost by definition, no party will benefit from the situation when there is a needless loss of trust between a medical device manufacturer, health care professionals, and the patients who benefit from the medical device.

All medical device manufacturers should strive to achieve genuine active and passive transparency with health care provider and patients. Although almost certainly operating within the norms of their industry, the communication policies and procedures of the CRM business of Guidant Corporation, and the parent Corporation, are characterized by both a perceived and real lack of active transparency and only limited passive transparency, leaving the Corporation to have to respond by reactive communications to forced transparency. The CRM business' decisions to communicate are based on a policy to actively communicate only when "device performance does not achieve design or performance expectations" or "an opportunity to recommend to the medical community a strategy for improved patient outcome related to device function" is identified. This approach for management of safety information runs contrary to the policy that patient safety is the first priority for evaluation, and managing device malfunction. First, life-threatening performance deviations can be hidden in accepted overall performance statistics and not enter the public domain.

The current process for communication allows engineers, with limited (if any) medical review or input, to make initial judgments as to whether there is a need for communication to physicians, patients, and senior Guidant personnel with corporate decision-making authority. Even very low frequency but serious health risks, if preventable, need to be communicated. Second, inherent in their second criterion is the presumption that CRM can determine both the societal and individual patient benefits and risks. In the case of the PRIZM 2 DR experience, this communication policy appears to have served, at least in part, as the basis for continued implants of unmitigated devices, after corrective action addressing the arcing problem. In addition to the fact that the existence of the defect and subsequent manufacturing changes were not brought to the attention of physicians and patients because the communications criteria of CRM were not met, the existing inventory of approximately 4,000 unmitigated devices continued to be implanted. These included approximately 1,300 devices that were shipped from CRM's in-house inventory, and the remainder that were in possession of the CRM field sales force or in hospital inventories. CRM did not attempt to retrieve the unmitigated devices. It was also concluded by CRM that the risk of explant and replacement of older devices exceeded the risk of device failure. Even though the risks are small, failure to make them known and clearly understood impinges on patients' safety rights, and can lead to -- and in the PRIZM 2 DR case appears to have led to -- a sense of betrayal by physicians and patients.

At the corporate level, Guidant has not paid adequate attention to the challenges associated with communicating the risks that evolved in the CRM business, however small, to patients, family members, and physicians. In part, this appears to result from the absence of corporate oversight of the CRM business generally, as well as to the absence of adequate communications links between the corporation and its businesses in regard to product performance and health hazard analysis, internal communications, and external communications to physicians and patients.

b. Explants and Information

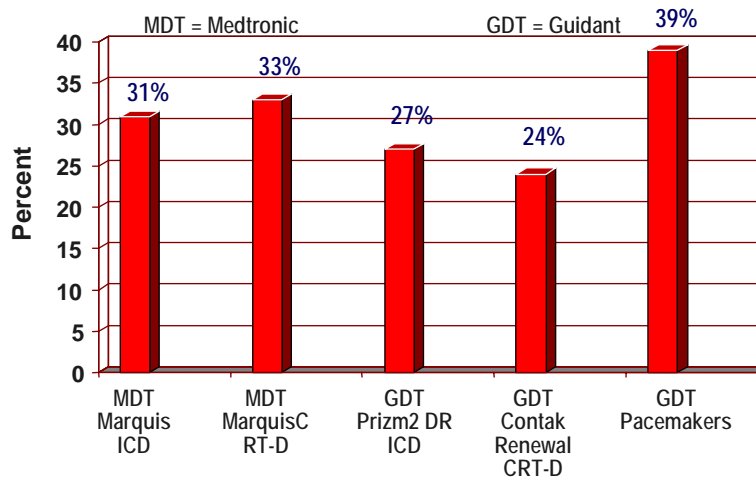
Decisions to explant devices that have an identified potential for malfunction or failure to deliver therapy require insight into risk/benefit considerations that are somewhat different than those generally used in clinical practice. Physicians understand risk/benefit ratios for drugs, devices, or surgical procedures when they are related to the proven or anticipated benefit of a therapy compared to the risk of a procedure or long-

term drug therapy. The recent experience in the implantable cardiac device industry brings another variable to the risk/benefit formula, namely the recognition that device malfunctions or failures may occur and the determination of how to deal with the risk once it has been identified.

In a recent survey of heart rhythm specialists, up to 30 percent of those responding recommended replacement of ICDs if the malfunction rate was one in ten thousand (0.01%).⁽¹⁾ This finding highlights the fact that experienced practitioners expect a very high degree of reliability of implantable devices. The same survey also reported that physicians used appropriate criteria for recommending explantation of a device. These criteria included replacements in patients who had already had a cardiac arrest (secondary prevention), those who had had prior ICD shocks, and circumstances in which device malfunction rates were higher. The survey further suggests that both physicians and industry need to develop a consensus for dealing with the reality of malfunctions in manufactured devices.

The experience with a low-frequency rate of malfunctions, in the setting of defined clinical benefits of the therapy, creates a broad range of dilemmas. The major conflict is between the financial impact of an aggressive replacement policy on corporate business and the fiscal status of the health care system and the ethical drive to preserve a single life, in accordance with individual patient preferences. Despite the low probability of manifest adverse events, the **Figure** below demonstrates that high replacement rates occurred as a result of potential device malfunctions for a number of devices recently reported by device manufacturers. These numbers speak to the absence of a baseline of information that would provide clinicians with a balanced insight into the entire scope of the issue, in the context of risk/benefit ratios. It is likely that clinical judgment would drive the numbers of device replacements down, with appropriate physician awareness and education on actual risk.

ICDs and Pacemakers Explanted After Recalls
 [Mean Percent of Subject Products Explanted after Recalls]



[These data are based on the reported experience of 37 implanting physicians who responded to a survey on this question, and may not reflect general experience or that subsequent to the survey. Modified from Prystowsky E: Device recalls: What patients need and want to know from their physicians - Clinician perspective. Presented at the HRS/FDA Policy Conference on Pacemaker and ICD Performance, Washington, DC, September 16, 2005. Reproduced with permission from Eric Prystowsky, MD]

3. CONCLUSIONS

- a. The recent issues surrounding recalled devices demonstrate that the communication policies used by Guidant – policies that had seemed to work well when the industry was smaller and had a less important role in the overall medical enterprise – have significant flaws in the context of the industry today, including new societal demands for openness and transparency by all industries. In the case of PRIZM 2 DR, the criteria used to trigger external communication would not have triggered either a “Dear Dr.” letter or an FDA recall if not for the *New York Times* article. This strongly suggests the need for a revised approach to external communication. The revised approach should shift from delivering the device performance information that Guidant believes is important, to delivering the device risk, benefit and performance information that Guidant, and its physician and patient customers see as important, and have a right to know, in order to make appropriate medical choices. Individual patient safety must be the guiding principle for communication. In the end, clear patient safety oriented communications is the only ethical choice and ultimately the best business choice (see **SECTION I.A.8**).
- b. The nature of medical device manufacturing is complex. This includes challenges associated with identifying, diagnosing, and remediating

devices that have, or might, malfunction. Guidant, and the device industry as a whole, have demonstrated a historical lack of transparency. This historical lack of transparency made it difficult for Guidant to effectively explain to stakeholders its actions associated with the PRIZM DR and RENEWAL 1/2 ICD devices when there was a pressing need to do so. Public understanding, and acceptance, of reactive communication is typically limited by the extent and effectiveness of the proactive communication that preceded it.

- c. By being actively transparent, a company can better manage its stakeholders' expectations, facilitate good decisions on the part of its stakeholders, and ultimately minimizes the odds of placing itself in a defensive position. Proactive communication to help physicians, patients and family members better understand the risks and benefits associated with implantable devices will enhance Guidant's ability to effectively respond to newly identified implantable device malfunctions in the future. In this context, when reactive communication becomes necessary, an open, balanced, and appropriately contrite, response is likely to be helpful to, and well-received by, external stakeholders.

The risks and benefits associated with implantable devices can only be accurately understood in the context of the risks versus benefits associated with *all* available options. For example, the risk associated with a potential device failure must be considered in context of the known risks associated with explantation and reimplantation with another device. There is a growing understanding in the field of risk communication regarding how best to present risk information in a manner that facilitates informed decision-making and appropriate response.

4. RECOMMENDATIONS:

- a. Guidant should establish new policies and procedures intended to increase its transparency to external stakeholders. The objective should be full and complete disclosure, in the most useful format possible, of all information with the potential to have an influence on patient safety. To this end, Guidant should embrace the challenge of enhancing its risk management procedures by creating and/or facilitating communication processes as follows:
 - 1) Reasonable and thorough efforts should be made to communicate all relevant information about the nature of implantable device risks to physicians, patients and family members. This will require significant

revisions of Guidant's approaches to physician and patient education. In addition – because it is the duty of the prescribing and implanting physicians to discuss the risks and benefits of device therapy with their patients, so that patients can make informed decisions about their treatment — Guidant should make reasonable efforts to make sure this task is routinely and effectively accomplished during patient counseling and informed consent processes. Guidant should work with the Heart Rhythm Society to establish a routine and effective approach to patient counseling and informed consent as an important element in standard of care for all patients receiving implantable cardiac devices.

- 2) The effectiveness of Guidant's educational efforts with physicians and patients should periodically be rigorously evaluated. If physicians' and patients' understanding of risks and limitations associated with implantable devices is not adequate, more active educational efforts may be required. A similar type of company-managed, mandated training program is already required for certain drugs. Dofetilide, an antiarrhythmic drug with a potential for proarrhythmia, can only be prescribed by physicians who have completed a company supervised training course which stresses how to manage the drugs potential for toxicity. The acne treatment drug, isotretinoin, which is associated with embryopathy when used during pregnancy, has an even more extensive, required educational program (iPledge). This program requires training of distributors, prescribers and patients in the proper use of this effective, yet potentially toxic, agent.
- 3) Patients should have the opportunity and be encouraged to express their wishes regarding how to manage implant-associated risks. At a minimum, patients should formally acknowledge in writing that they understand the potential risks and benefits of therapy with an implantable device. *When patients receive their warranty documents, they should be given the opportunity to accept or decline post implant safety communications from Guidant Corporation.* The Panel advises direct to patient communication about important post-implant safety concerns when these concerns are conveyed to the patient's physician.
- 4) As part of their educational efforts, Guidant should develop and include a *glossary of definitions* for all relevant safety-related terms that stakeholders may encounter in Guidant and FDA materials, and in the media (eg, recalls, alerts, manufacturer change orders, reliability, performance, malfunction, device failure, etc.). The relevant

definitions should be included in any written material where they are explicitly used.

- b. The Independent Panel considered the question of identifying a specific number of events that would serve as a trigger for initiating active notification of physicians about newly identified malfunctions or device failures. *There was general agreement that a single event with identified root cause for the malfunction or device failure that is likely to be systematic and to occur in other patients should be referred to the IRG for advice on active communications.* In the absence of these qualifiers, a single event should *not* trigger active communication. However, such information should be made available passively in sources of information available to physicians, such as product performance reports.

The next consideration had to do with the question of specifying a number greater than one, or a defined event rate, that would warrant such activity. The main concern was whether any minimum number should serve a threshold function, independent of other considerations. After considerable discussion, the Panel *rejected* the notion of setting a minimum number of events or event rate because considerations of this type have to be evaluated in the context of the nature of the defect, anticipation whether it is likely to repeat, the anticipated or actual rate of accumulation, indications of whether malfunctions or failures are related to time from implantation, and the potential clinical consequences of any specific malfunction or failure. Accordingly, such determination should be made on a case-by-case basis, with two qualifiers:

- 1) Physician input regarding the question of potential clinical consequences must be an active part of the decision process; and
- 2) The decision process should be handled in a fashion that reflects true independence from commercial considerations.

Accordingly, it is the recommendation of the Panel that these decisions should be made by the Internal Oversight Body recommended in **SECTION III.A**, with independent review and input from the proposed external Independent Review Group (IRG). In effect, the IRG would serve a function analogous to a data safety monitoring board of a clinical trial, relying upon the judgment of an informed independent scientific group, rather than a threshold of numbers, to drive decision-making recommendations about when to actively communicate. *In the case of a product failure that CRM/Guidant Corporation has determined, from available information, to pose an extraordinary patient risk, the company should act immediately. The IRG should be notified as soon as possible,*

but action by CRM/Guidant Corporation should not be delayed while awaiting IRG input in this specific circumstance.

- c. Guidant should modify its criteria that trigger communication with external stakeholders about product performance. Any one of the following three criteria should trigger communication with external stakeholders about device performance:
 - 1) when a systematic device performance deviation creates a potential for a life-threatening event, an active communication strategy should be triggered as guided by the IRG;
 - 2) when device performance does not achieve design or performance expectations, active or passive communication strategies should be triggered depending upon the nature of the defect;
 - 3) when a strategy for improved patient outcome related to device function has been identified, active or passive communication strategies should be triggered, as appropriate.

This communication should, in all cases, be directed to all relevant implanting and monitoring physicians. It should also be directed to all relevant patients (or at least those patients who have indicated a desire to be provided with such information) unless there is a compelling reason to communicate only with their physicians.

- e. Guidant Corporation should retain expert support to synthesize the medical education, patient education, and especially the risk communication literatures for the purpose of developing science-based “best practices” for communicating a balanced understanding of risks and benefits associated with the implantable devices to physicians, patients and family members. This should include best practices for achieving informed consent among prospective ICD patients. These best practices should be used to revise Guidant’s current patient education and physician education materials and courses (see Recommendation a1 above), and to develop a patient education “tool kit” that physicians can use to effectively educate their patients who are candidates for an implantable device. **APPENDIX J** provides a brief review of the literature for this purpose. Moreover, to maximize the transparency of this effort, and to further enhance its value to society, Guidant should partner with an appropriate professional society, standards organization, or trade association, and with the FDA on this best practices development

activity.

As part of this process, it may be necessary to refine current estimates about risks associated with explantation of an implantable device. These risks are highly germane to making an informed risk-benefit decision about explanting a potentially defective device and implanting an alternative device.

- f. To prevent further loss of trust, and to rebuild trust, Guidant should pay careful attention to the factors that influence stakeholders' perceptions of credibility and trust in them. By enhancing its approaches to physician and patient education and active transparency as suggested above, Guidant will earn the highest levels of credibility and trust from its stakeholders.

Furthermore, Guidant is advised to systematically and continuously monitor stakeholders' perceptions of their credibility and trust because doing so will serve as an important early warning signal regarding the need to further improve the company's approach to risk management. To enhance the validity and reliability of such monitoring, Guidant should use a previously validated survey instrument. The Meyer's Credibility Index instrument may be ideal for this purpose.^[1,2]

- g. Guidant should work with FDA, AdvaMED, HRS, and ACC, and other cardiac rhythm device manufacturers to seek effective ways to communicate updated product performance information, advisories, and other new information about product reliability. The public should be able to expect that all companies in the field will divulge data about the safety and reliability of the devices in a standardized format. There should not be any opportunity for competitive advantage to be gained by differences in disclosure policies.
- h. Guidant is advised to participate in the education and dissemination of information in regard to the need for physicians to understand the risk paradigms that drive decisions to explant devices with demonstrated potential to malfunction. The following points pertain:
 - 1) The industry should report malfunctions and improve reporting mechanisms as discussed elsewhere in this report.
 - 2) Industry should work with HRS and other organizations to develop an educational program for physicians based on newly developing evidenced-based guidelines for device management.

- 3) The independent review group (IRG) should help Guidant review the seriousness and appropriate action of communication for device malfunctions and failures. The review of device malfunctions by the IRG may help physicians choose the best course of action for patients who have a recalled device.
 - 4) Industry should facilitate the analysis and interrogation of devices which are explanted for end-of-life indicators, for less clear reasons, or are in place at the time of death.
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Section References

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F. Guidant Initiatives from July 2005 to February 2006

The Independent Panel of Guidant Corporation has been carrying out its mission of evaluating the policies and processes of the CRM business, and related Guidant Corporation functions, since its formation and first meeting in August 2005. The scope of the Panel's activities has included review of surveillance, evaluation, and communication of low frequency device and component malfunction, and formulation of recommendations based upon the findings. During this period of time, Guidant Corporation and its CRM business have been evaluating their policies and procedures internally and making changes that they felt were needed and appropriate. The following is a series of changes made known to the Independent Panel during the course of its deliberations, with commentaries on how the actions may be further improved.

1. PRODUCT PERFORMANCE REPORT

The CRM business of Guidant Corporation began publishing a Product Performance Report for public dissemination as early as 1979, and has published it regularly since 1988. In its early iterations, the content focused largely on cumulative performance statistics based on predicted reliability, in which the reader was unable to separate the function of normal battery depletion from mechanical and electronic malfunctions. No separate listing of potentially life-threatening malfunctions was made available in these reports. In two modifications of the Product Performance Report format and content in September and December 2005, additions of significant new information, specific to the question of malfunction unrelated to the expected battery performance of the devices, have been provided. It is now possible for the reader to access specific details of the type and number of malfunctions experienced for each of CRM's active products, and to see these listings in the context of the denominator of number of devices in service.

a. Evaluation and Recommendations

The new content in the current version of the Product Performance Report is a major improvement over past versions. This action is a form of proactive communication, providing passive transparency of malfunction information as discussed in **SECTION III.E** of this Report. However, there remains room for improvement. The Product Performance Report still does not provide a risk assessment value on the specific defects. For example, the Table on page 107 of the December 2005 version cites accurately the number of events in the

PRIZM 2 DR incident, but does not highlight the fact that this defect has life-threatening implications. This led to the conclusion that, for all defects, some metric of risk potential should accompany the raw data. In addition, the reader should be provided a highlight at the very beginning of the document, citing those devices and/or malfunctions that are of potential interest or concern to physicians and patients. This can be done in the format of a “black box” that leads the reader to specific sections of the report.

2. CAPA SYSTEM MODIFICATIONS

The CRM business of Guidant Corporation has begun a systematic review of its entire CAPA (Corrective and Preventive Action) program, and has implemented a number of changes. It has established a committee to regularly review signals of product malfunction that may require modifications in manufacturing or design. It plans to implement a new system to track and follow-up low frequency events and respond with internal corrective actions. In addition, it has hired 38 new employees to focus on product performance, analysis, and corrective actions.

a. Evaluation and Recommendations:

The initiative to modify the CAPA system is viewed as appropriate and necessary by the Independent Panel. While the specific plans for changes to date are not available to the Independent Panel, the general concept is in accord with the conclusions reached by the Panel. It is recommended that Guidant Corporation and the CRM business integrate the specific recommendations made by the Panel for improvement in strategies to identify and manage product malfunctions.

3. DESIGN FOR RELIABILITY PANEL

CRM has appointed a Design for Reliability Panel, an independent external team, to study and develop recommendations for device reliability based upon design and manufacturing principles. This front-end initiative is complementary to the mission of the Independent Panel, which is evaluating postmarket surveillance, low frequency events, and communications.

a. Evaluation and Recommendations

This activity, which is complementary to the activities of the Independent Panel of Guidant Corporation, addresses a different issue than those in the mission of the Independent Panel. It is an important parallel to the activities of the Independent Panel, and the findings and recommendations of the Design

for Reliability Panel should be carefully evaluated and where possible, integrated with the findings of the Independent Panel.

4. INFORMATION MANAGEMENT AND DECISION ESCALATION POLICIES

The CRM business has begun modification of its information management and decision escalation policies and procedures. These plans address such issues as trend monitoring and reopening of closed trends, regular review of high level health hazard analysis by the Officer Escalation Group, quarterly updating of the Productive Performance Report and implementation of new advisory updates, including future risk projections and clinical recommendations for follow up to physicians. This appears to be an expanded version of the QSAT program that was designed to evaluate product performance policies and procedures, but not individual performance problems.

a. Evaluation and Recommendations:

This initiative has an important counterpart in the observations, conclusions, and recommendations of the Independent Panel. Guidant Corporation and the CRM business should integrate the recommendations of the Independent Panel with this initiative.

5. SPECIAL LEADERSHIP TEAM

Guidant Corporation has established a special team led by the Chairman of the Board and Interim CEO, James Cornelius. The team consists of six members of the Guidant Management Committee and Board of Directors. This is an *ad hoc* group intended to prepare the Corporation to evaluate and implement the recommendations of the Independent Panel of Guidant Corporation. While awaiting the Report, it has begun considering modifications and information flow, and decision escalation. Once changes are in place, this committee is not intended to become a standing committee of the Corporation.

a. Evaluation and Recommendations:

The Independent Panel views this initiative as an important action by Guidant Corporation, in that it provides an enabling mechanism for its stated intent to implement changes that the Independent Panel views as important for improving systems to assure patient safety and reversing injury to the corporate image. This intent is consistent with a general perception by the members of the Panel that virtually all of the problems identified through the scope of its work are correctable by appropriate changes. Guidant Corporation

and the CRM business manufacture products that are inherently among the best in the industry, in terms of both function and reliability. That being the case, the challenge to Guidant Corporation now is to put in place systems to correct the problems that led to the current circumstances and restore the Corporation to its former pre-eminence.

Section IV

APPENDICES

- A. SAFETY ADVISORIES ISSUED BY GUIDANT
- B. REGULATORY COMMUNICATIONS AND ACTIVITY
- C. THE PANEL CHARTER
- D. PANEL CONSTITUENCY
- E. CREATION AND FUNCTION OF THE INDEPENDENT REVIEW GROUP
- F. THE PRODUCT PERFORMANCE COMMITTEE, PRODUCT EVALUATION COMMITTEE,
AND THE OFFICER ESCALATION GROUP
- G. FDA REPORTING REQUIREMENTS
- H. Features of an Active Surveillance System
- I. EXPECTED NUMBERS OF EVENTS – ACTIVE SURVEILLANCE
- J. IMPROVING COMMUNICATION ABOUT ICDS: RELEVANCE OF THE RISK
COMMUNICATION LITERATURE
- K. NEW FDA POSTMARKET SAFETY INITIATIVES

APPENDIX A

Safety Advisories Issued By Guidant Since June 2005

VENTAK PRIZM 2 DR

JUNE 17, 2005: VOLUNTARY PHYSICIAN ADVISORY

- Short circuiting due to deterioration of in a wire insulator within the lead connector block resulting in potential failure to deliver an appropriate therapeutic shock.
- Twenty-eight reported failures, including one death, worldwide from approximately 26,000 devices built prior to the April 2002 manufacturing change.
- No such failures observed in devices built after April 2002.
- Recommendation: No need for immediate explant; normal patient follow up.

SEPTEMBER 12, 2005: ADVISORY UPDATE

- No additional failures reported as of August 31, 2005
- Between June 17 and August 31, 2005, testing of a non-random sample of 1,005 returned devices built on or before April 16, 2002 provoked 4 failures (0.40%).
- The reported clinical failure rate of the ~14,000 VENTAK PRIZM 2 DR devices built prior to April 16, 2002 that remained implanted as of August 31, 2005, is projected to range between 0.10% and 0.24%, with an increasing failure rate as the devices age.
- No changes to initial recommendations.

DECEMBER 20, 2005: ADVISORY UPDATE

- *Devices manufactured on or before April 16, 2002:*
 - Four (4) additional failures worldwide, including one (1) associated with patient death, have been confirmed between September 1, 2005 and December 13, 2005.
 - A total of 32 clinical failures of this type (including 2 patient deaths)

represent 0.12% of ~26,000 devices distributed worldwide.

- Laboratory testing of a non-random sample of 3,279 returned devices built on or before April 16, 2002 provoked 19 (0.58%) failures.
- Modeling of the projected occurrence rate for the ~11,000 of this population of devices that remained implanted as of December 13, 2005 suggests an increasing failure rate as devices age. The predicted failure rate remains within the range of 0.10% and 0.24% as reported in the September 12, 2005 *Advisory Update*.
- *Devices manufactured after April 16, 2002 but before November 13, 2002:*
 - One clinical failure of this type was detected during device interrogation and resulted in no clinical injury.
 - This single failure represents 0.009% of the 11,000 devices in this non-advisory population, of which ~7,300 remain implanted worldwide.
 - Laboratory testing of a nonrandom sample of 607 returned devices from this population resulted in zero (0.0%) failures.
- *Devices manufactured after November 13, 2002:*
 - There have been zero (0) failures of this type reported out of ~18,000 devices built after November 13, 2002.
 - Recommendations remain unchanged from those stated in the *Safety Advisory* of June 17, 2005 and the *Advisory Update* of September 12, 2005.

CONTAK RENEWAL/CONTAK RENEWAL 2

JUNE 17, 2005: VOLUNTARY PHYSICIAN ADVISORY

- Short circuiting due to deterioration of a wire insulator within the lead connector block resulting in potential failure to deliver an appropriate therapeutic shock.
- Fifteen confirmed reports of failure, including one associated with patient death, in approximately 16,000 devices manufactured on or before August 26, 2004, implanted worldwide.
- Reported rate of failures may increase to between 0.20% and 0.59% over the device family lifetime.
- Recommendation: No need for immediate explant; normal follow up.

SEPTEMBER 5, 2005: ADVISORY UPDATE

- Six additional reported clinical failures (for a total of 21) worldwide. Three of these failures were associated with patient death.
- Between June 17 and August 31, 2005, testing of a non-random sample of 429 returned devices built on or before August 26, 2004 provoked 5 failures (1.17%).
- The reported clinical failure rate of the ~10,500 RENEWAL devices built prior to August 26, 2004 that remained implanted as of August 31, 2005, is projected to range between 0.72% and 1.83%.
- No changes to initial recommendations.

DECEMBER 21, 2005: ADVISORY UPDATE

- Fourteen (14) additional clinical failures worldwide, four (4) of which were induced by physician-commanded shocks, and including two (2) associated with patient death, have been confirmed between September 1, 2005 and December 13, 2005.
- A total of 35 clinical failures of this type (including 5 associated with patient death) represent 0.22% of ~16,000 devices distributed worldwide.
- Laboratory testing of a non-random sample of 2,063 returned devices of this population provoked 25 (1.21%) failures.
- Modeling of the projected occurrence rate for the ~8,400 devices of this population that remained implanted as of December 13, 2005 suggests an increasing failure rate as devices age. The predicted failure rate remains within the range of 0.72% and 1.83%, as reported in the September 12, 2005 *Advisory Update*.
- Recommendations remain unchanged from those stated in the *Safety Advisory* of June 17, 2005 and the *Advisory Update* of September 12, 2005.

VENTAK PRIZM AVT, VITALITY AVT, and CONTAK RENEWAL AVT

JUNE 17, 2005 VOLUNTARY PHYSICIAN ADVISORY

- A memory error may cause a functional “latching” that limits available atrial therapy (AVT) and affect battery life in subgroups of certain ICD and CRT-D product families. This issue does not impact standard ICDs and CRT-Ds in these product families.

- Two occurrences have been confirmed out of approximately 20,950 implanted devices.
- Recommendations: (1) device replacement is required if latching occurs; (2) schedule a patient office visit to program Atrial Tachy Episode Data Storage to 0%.

JULY 22, 2005 ADVISORY UPDATE

- On July 11, 2005, a third AVT latching event was reported in the U.S. Analysis determined that this event occurred despite programming of Atrial Tachy Episode Data Storage to 0%. This resulted in a latched state of continuous atrial pacing at approximately 120 pulses per minute. This third event, similar to the first two events, resulted in no apparent patient injury beyond device replacement. Additional events, including a possible injury, are being investigated.
- It has been determined that one of the original recommendations – namely programming Atrial Tachy Episode Data Storage to 0% – can cause latching in a subset of AVT devices that have previously stored atrial episode data. This newly observed latching pathway can have a significantly higher probability of occurrence (estimated at 0.086% per month).
- A non-invasive software solution for this anomaly is being developed and may be available in early fourth quarter, pending regulatory approval.
- Revised recommendations:
 - Schedule a patient follow-up visit:
 - As soon as possible for patients with devices reprogrammed to 0% as per the June 17th recommendation any patient with Atrial Episode Data Storage programmed to less than 20%
 - Per normal schedule if Atrial Episode Data Storage is at the nominal of 50% or is programmed to 20% or more.
 - At this visit:
 - Verify normal device function using routine clinical follow-up procedures
 - Program Atrial Episode Data Storage to 20%
 - Review the provided rate of occurrence estimates (provided) to evaluate the additional risk reduction benefits of programming ATP therapy to OFF

JANUARY 6, 2006 ADVISORY UPDATE

- There have been thirty (30) additional failures since the July 22, 2005 communication. A total of thirty-three (33) clinical failures have been confirmed out of approximately 21,800 implanted devices.
 - Three (3) failures (0.01%) are as described in the original June 17, 2005 advisory.
 - Thirty (30) failures are related to programming Atrial Tachy Episode Data Storage to 0% in a device that has previously stored atrial episode data; none have been reported since November 2005.
- There have been no patient deaths.
- Recommendation: remain unchanged from those provided in the July 22, 2005 communication.

CONTAK and CONTAK RENEWAL 3/4 Family

JUNE 23, 2005: VOLUNTARY PHYSICIAN ADVISORY

- A magnetic switch may stick in the closed position, potentially inhibiting tachyarrhythmia (but not bradyarrhythmia) pacing, and also affecting battery life.
- Recommendations: (1) Consider programming switch to “OFF;” (2) patients should immediately go to their physicians or ED if tones are heard coming from the device; (3) a programmer software application is being developed and distributed

AUGUST 1, 2005: ADVISORY UPDATE

- Four confirmed occurrences out of ~46,000 devices sold worldwide, and a fifth is suspected but the device was not returned for confirmation.
- No additional failures identified since the June 23, 2005 advisory.
- Products incorporating a new switch component have been approved by the FDA and are available on the market.
- No changes to initial recommendations.

PULSAR, DISCOVERY, MERIDIAN, CONTAK Subfamily of Pacemakers

JULY 18, 2005: VOLUNTARY PHYSICIAN ADVISORY

- Hermetic sealing compound in a subset of pacemakers manufacturer

between October 27, 1997 and October 26, 2000 may experience gradual deterioration resulting in increased moisture content within the pacemaker case later in the device's service life, possibly resulting in a two major clinical behaviors, including loss of pacing therapy and accelerometer dysfunction resulting in inappropriate sustained rapid pacing and development of heart failure.

- These products have not been sold or implanted for the last four years.
- As of July 18, 2005, 69 devices were identified possibly exhibiting this failure mode, 52 of such failures out of 78,000 distributed worldwide were confirmed.
- Recommendations: (1) consider replacing the device in pacemaker-dependent patients; (2) advise patients to seek attention immediately if they notice a prolonged rapid heart rate; (3) select a suitable Maximal Sinus Rate (MSR) setting to prevent inappropriate sustained pacing; (4) consider increasing the frequency of programmer/transtelephonic monitoring.

JANUARY 23, 2006: ADVISORY UPDATE

- *Advisory population update:*
 - As of January 9, 2006, there have been a total of 145 reported incidents, which represents an occurrence rate of 0.19%.
 - Approximately 16,000 devices of this population remain implanted worldwide as of January 9, 2006.
 - The projected rate of occurrence rate for reported events within the remaining lifetime of active devices is now estimated to be between 0.31% and 0.88%, which has increased from the July 18, 2005 estimate of 0.17% and 0.51%.
 - Initial recommendations remain unchanged.
- *Second population:*
 - Since July 18, 2005, a second population of 54,000 devices manufactured between October 19, 1998 and December 5, 2000 that are at risk of hermetic seal degradation has been identified.
 - At the time the devices in this second population were manufactured, hermetic sealing components susceptible to gradual deterioration were mistakenly mixed with a much larger group of non-susceptible components, therefore, the rate of failure in this second population

although at a much lower rate than the previous advisory population.

- Within this population of 54,000 devices, ~2,500 have been identified by model number and date-of-manufacture with susceptible components, but further identification of susceptible devices by serial number has not been possible.
- As of January 9, 2006, a total of five (5) reported incidents out of 54,000 devices and represents a projected occurrence rate of 0.009%. Degradation of the hermetic seal was confirmed in 2 of the 5 reports. Approximately 19,300 devices in this population remain implanted worldwide.
- Because devices with a susceptible component cannot be specifically identified and are distributed among the 54,000 devices in the second population, the projected occurrence rate reported events within the second population is substantially lower than rate in the original advisory population.
- The projected occurrence rate in the second population is estimated to be between 0.02% and 0.06% for the remaining lifetime of active devices.
- Recommendation: Consider the much lower projected occurrence rate and the needs of the individual patient, including pacemaker dependency, when make patient management decisions for patients with second population devices.

INSIGNIA and NEXUS Family of Pacemakers

SEPTEMBER 22, 2005: VOLUNTARY PHYSICIAN ADVISORY

- Two separate failure modes have been identified that may result in intermittent or permanent loss of pacing output without warning, loss of telemetry, and or reversion to VVI mode, or appearance of a reset warning message upon interrogation.
- The root cause of the first failure mode is foreign material within the crystal timing component. The root cause of the second failure mode has not yet been determined: analysis is ongoing.
- *Failure mode 1:*
 - As of September 6, 2005, 36 failures (0.073%) have been confirmed out of a subset of 49,500 devices distributed worldwide.
 - This failure mode was associated with three (3) reports of syncope and six (6) reports of bradycardia or heart block.

- The majority of failures occurred early in device life (mean implant time 7 months). This failure mode demonstrates a failure rate that increases with implant time, but no failures have been reported beyond 22 months of service.
- First failure mode: Field experience and statistical modeling predicts the failure rate in the 41,000 active device population to be between 0.017% and 0.037% over the remaining device life.
- Shipping of devices susceptible to “Failure Mode 1” from manufacturing facilities was discontinued in March of 2004
- The supplier of this crystal component has corrected the problem, and no failures have been reported in any device shipped after March 12, 2004.
- *Failure mode 2:* As of September 6, 2005, 16 failures (0.0047%) have been confirmed out of 341,000 devices distributed worldwide. All 16 devices exhibited a “no output” condition at the implant procedure or during pre-implant testing. There have been no clinical consequences or patient deaths.
- Recommendations:
 - *Failure mode 1:* (1) normal follow up; (2) advise patients to seek immediate attention if they experience syncope or lightheadedness.
 - *Failure mode 2:* verify pacemaker operation in the packaging prior to implantation.

DECEMBER 12, 2005: ADVISORY UPDATE

- *Failure mode 1:*
 - As of November 30, 2005, one (1) additional “Mode 1” failure was confirmed, for a total of 37 (0.075%) out of the subset of 49,500 devices distributed worldwide.
 - The projected failure rate for the active device population of 40,000 remains between 0.17% and 0.37%, as reported in the September 22, 2005 *Advisory*.
 - No additional clinical consequences have been reported as on November 30, 2005.
- *Failure mode 2:*
 - Root cause for “Failure Mode 2” has been identified as a microscopic particle within the crystal timing component used in a subset of 257,000 devices. Although devices with manufactured with this

component passed all manufacturing tests prior to distribution, in rare instances, mechanical shock, such as during shipping, have caused the particle to relocate to a point where it interferes with the crystal.

- As of November 30, 2005, one (1) additional “Mode 2” failure for a total of 17 (0.0066%) failures out of the subset of 257,000 devices manufactured and distributed worldwide that utilize the crystal timing component susceptible to this failure mode.
- All 17 failures were identified before or during the implant procedure. There have been no reports of a “Mode 2” failure in over 3.8 million months of the accumulated service life after implantation.
- *Update of Recommendations:* normal monitoring of the patient as per device labeling for **all** implanted INSIGNIA and NEXUS pacemakers.

APPENDIX B

Regulatory Communications and Activity

I. Pre-2005 FDA Activity

In the decade prior to 2005, Guidant CRM had had between one and three voluntary safety advisories per year. A total of sixteen of these safety advisories were subject to FDA's recall classification, while the others were either not classified or occurred in geographies outside of the United States. Only one of these sixteen advisories was classified as a "Class I" recall by FDA. This recall occurred in 1998.

Prior to 2003, Guidant CRM's St. Paul, Minnesota, facility received three FDA Forms 483. These FDA Forms 483 were issued in 1995, 1998 and 2001, and each consisted of one observation. Guidant CRM's manufacturing facilities in other locations also received three FDA Forms 483 in 1995, 1998, and 2005, consisting of twenty-one, one and two observations respectively. Between 2003 and mid-2005, the St. Paul, Minnesota, CRM facility was inspected 7 times with no 483 observations.

II. FDA Activity in 2005-2006

A. FDA PRELIMINARY PUBLIC HEALTH NOTIFICATIONS

- ***July 14, 2005: FDA Announces Class I Recalls of Guidant Corporation's Implantable Defibrillators***

In this public communication, the FDA listed and explained the voluntary Class I recalls of the PRIZM 2 DR, RENEWAL, and RENEWAL 2 devices, described the causes and potential clinical consequences of the device malfunctions, and summarized Guidant's recommended actions for patients.

- ***July 22, 2005: FDA Announces Guidant's Class I Pacemaker Recall***

In this public communication, the FDA listed and explained the voluntary Class I recalls of the PULSAR, DISCOVERY, MERIDIAN and other groups of pacemakers, described the causes and potential clinical consequences of the device malfunctions, and summarized Guidant's recommended actions for patients.

- ***October 13, 2005: FDA Updates Its July 14, 2005 Notification***

In this public communication, the FDA informed the public of 6 additional device failures for the RENEWAL 1/2 devices, bringing the total number of device failures to 21, including three (3) patient deaths as of October 7, 2005.

The FDA noted that no additional failures have been reported for the PRIZM 2 DR since the July 14, 2005 notification.

The FDA stated that its previous management recommendations for the PRIZM 2 DR remain unchanged.

B. FDA INSPECTIONS AND RESPONSES

- ***FDA Inspection***

As often is the case following product recalls, the FDA initiated an inspection of Guidant Cardiac Rhythm Management's St. Paul, Minnesota, facility on August 22, 2005. The inspection was concluded on September 1, 2005. A FDA Form-483 listing the inspectional observations was then delivered to Guidant.

- ***Guidant Responses to Form-483***

On September 15, 2005, Guidant provided a full written response to the 483. Additional written progress reports were provided to FDA on October 5, October 18, November 17, and December 15, 2005. In addition, on October 27, 2005, Guidant published its responses to Form-483 by providing a transcript of the responses on the Corporation's website.

- ***FDA Warning Letter***

On December 22, 2005, the FDA sent a warning letter stating that the actions taken to address the Form-483 Inspectional Observations described in the Guidant responses of September 15, October 5, October 18, November 17, and December 15, 2005 did not satisfactorily address all of the observations listed in Form-483. As result, this letter noted that failure to promptly correct these deviations may result in regulatory action without further notice. A response was required within 15 working days.

- ***Follow-Up to the Warning Letter***

On January 5, 2006, the FDA sent a follow-up to the Warning letter of December 22, 2005, listing a few remaining concerns, and noting that, while

most of the corrective actions have been completed on schedule, a few have not yet been completed. However, these were not scheduled to be completed until June 2006. The company filed a complete response to the December 22, 2005 warning letter and to the January 25, 2006 follow-up letter.

It also stated that a follow-up inspection will be necessary.

C. ADMINISTRATIVE SUBPOENAS

On October 25, 2005, Guidant announced that it had received administrative subpoenas from the United States Department of Justice U.S. Attorney's offices in Boston and Minneapolis issued under the Health Insurance Portability and Accountability Act of 1996.

The subpoena from the U.S. Attorney's office in Boston requested documents concerning pacemakers, ICDs, leads and related products. The subpoena from the U.S. Attorney's office in Minneapolis requested documents relating to Guidant's VENTAK PRIZM 2 DR and CONTAK RENEWAL 1/2 devices.

APPENDIX C

The Panel Charter

The final Mission and Charter, reproduced below, were approved by Ronald Dollens, CEO of Guidant Corporation, and Dr. Robert Myerburg on July 11, 2005.

Mission of the Panel

The first commitment of Guidant Corporation is the safety and health of patients. To this end, this Independent Panel is convened with the following mission:

The Mission of the Panel is to evaluate the current methods used by Guidant Corporation for postmarket surveillance and communication regarding the function and safety of life-sustaining implantable devices, and to develop recommendations and guidelines that will enhance:

- early recognition of low-frequency events and trends;
- methods for evaluating the clinical relevance of such trends; and
- methodology for disseminating safety information for the benefit of patients and treating physicians.”

Relationship of the Work of the Panel to Activities by other Organizations

The Panel will be an independently functioning body, whose focus is on issues of identifying and reporting adverse events that occur with implantable life-sustaining technology. Its mission is oriented to both the physician and patient community, using Guidant Corporation systems for direction. In addition and separately from this Panel, Guidant will also actively work with FDA, other regulatory agencies, physician societies – including the Heart Rhythm Society – and other industries. Guidant will participate in future activities with these stakeholders in establishing broad and general principles to communicate and take appropriate action when new safety information arises. By examining current issues in the context of specific Guidant products and methods, the Panel’s recommendations will enrich Guidant’s understanding of the broader principles of dealing with new safety information, at the same time contributing to the broader base of knowledge in the field. Thus, the completed work of this Panel will complement, and not replace, such endeavors by other organizations.

Focus of the Panel

The overarching goal of the Panel is to develop principles, processes, and guidelines which may be applicable to implantable life-sustaining devices. *To this end, the predominant focus of this Panel will be implanted cardiac rhythm management devices and low-frequency events and trends associated with such marketed devices.* The Panel will be constituted to have the necessary expertise in clinical medicine, manufacturing controls and quality systems, safety surveillance and risk communication required to achieve these goals.

Charter

The Panel will be expected to first review and analyze, and then provide specific recommendations to Guidant Corporation as well as the broader medical device industry and public regarding four core questions.

In conformance with FDA and regulatory guidelines, and using both internal information from Guidant Corporation and other sources, in what ways can Guidant Corporation and other medical device industries further enhance capabilities in detection and understanding:

- Surveillance and interpretation of low-frequency trends among life-sustaining implantable devices that may affect patient safety and physician decisions for device management;
- Reassessment of benefit and risk to patients in light of new information about marketed devices;
- Device component failure analysis and estimation of its frequency;
- Development of more transparent, understandable and clinically-useful communication processes to physicians and patients, including triggers for communication, timing, and novel methods of transferring information.

Independence of the Panel

A. CREATION AND OPERATION OF THE PANEL. The Panel will be established by the Chief Executive Officer (CEO) of Guidant Corporation.

B. ACCESS TO INTERNAL INFORMATION OF GUIDANT CORPORATION. The Chair and Panel members will work under formal nondisclosure agreements with the

firm. To facilitate the work of the Panel, Guidant Corporation will provide internal information, as well consultation with Guidant employees and officers, as needed, under formal nondisclosure agreement with all Panel members to protect Guidant's proprietary interests.

C. INDEPENDENCE OF THE PANEL. The Chair of the Panel will have full independence in final selection of Panel members, finalization of the work charter for the Panel, work procedures, and the format and content of the final report of recommendations.

D. SUBMISSION OF THE REPORT OF THE PANEL. Timely execution of the work of the Panel is expected. The Panel will provide a written Report of its recommendations to the CEO of Guidant Corporation, and to the Board of Directors of the Corporation. Recommendations regarding principles and guidelines for enhancing surveillance techniques, interpretation of accumulated data, and the notification and communication of information to patients and physicians will be made available to the public.

E. MANAGEMENT OF POTENTIAL OR PERCEIVED CONFLICT OF INTEREST (COI). It is the intent of Guidant Corporation that this Panel functions with full independence and without constraint of real or perceived conflict of interest. Prior to initiating its work, all potential Panelists will be asked to report with confidentiality and transparency any potential conflicts of interest regarding Guidant, related industries, and consultations on intellectual property or product liability. A template similar to that employed by potential participants in FDA review Panels will be used. This information will be disclosed only to the Chair, and a designated external attorney, to determine if reasonable freedom from perceived conflict of interest is present. Any changes in COI will be disclosed in writing to the Chair during the work of the Panel.

APPENDIX D

Panel Constituency

ELECTROPHYSIOLOGY

JOHN P. DIMARCO, MD, PhD
Professor of Medicine University of Virginia Health System
Charlottesville, VA

BRUCE D. LINDSAY, MD
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ROBERT J. MYERBURG, MD (*Chair*)
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Bernard Trabin Chair in Cardiology
Professor of Medicine
Chief, Division of Cardiology
Penn State University College of Medicine
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STATISTICS

JOEL I. VERTER, PhD
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Statistics Collaborative, Inc.
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RISK ASSESSMENT AND MANAGEMENT

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COMMUNICATIONS EXPERTISE

EDWARD W. MAIBACH PhD, MPH
Professor and Director of the Public Health Communications & Marketing
Program
School of Public Health and Health Services
The George Washington University
Washington, DC

ETHICS AND PATIENT ADVOCACY

KENNETH W. GOODMAN, PhD
Associate Professor of Medicine and Philosophy
Director, Bioethics Program
University of Miami Ethics Program

Miami, FL

REGULATORY PERSPECTIVE

DAVID W. FEIGAL, MD, MPH
Former Medical Deputy Director (1992-1999) and Director (1999-2004)
Center for Devices and Radiologic Health
Federal Drug Administration
Phoenix, AZ

COUNSEL TO THE PANEL

PETER O. SAFIR, Esq
Covington & Burling
Washington DC

APPENDIX E

Independent Review Group

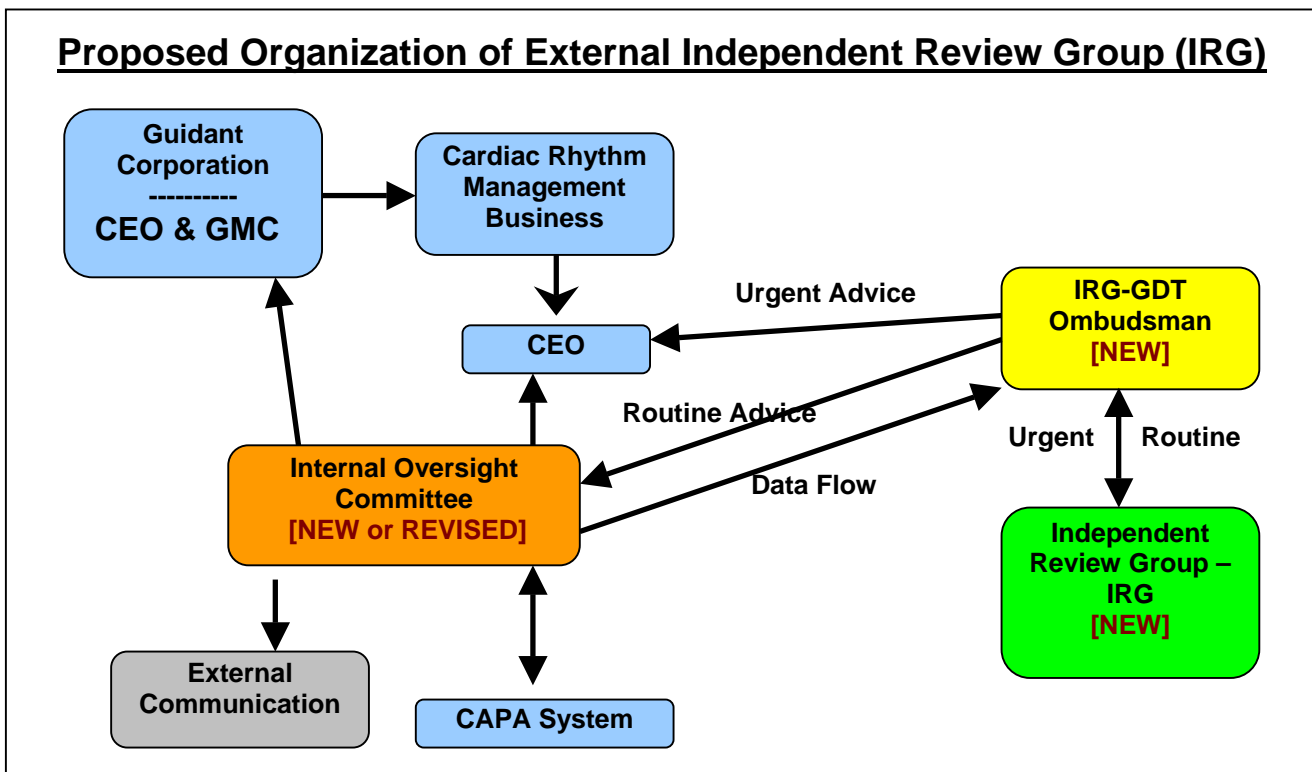
The Independent Panel recommends that Guidant Corporation establish an external Independent Review Group (IRG) for its CRM business. The intent is to provide unbiased independent evaluations, interpretations, and recommendations concerning Guidant's internal review and actions on matters of specific device or component malfunctions or failures, or the risk thereof. The primary orientation of the IRG should be patient-safety, including evaluation of the clinical significance of malfunctions or device failures and issues of communication and transparency.

The function of the IRG will be analogous to a Data Safety Monitoring Board for a clinical trial. However, this is proposed as an ongoing *advisory* function, serving as an objective resource that will provide oversight and independent recommendations of the management of device malfunctions or failures, including surveillance, risk analysis, trending, mitigation, and communication. The IRG is viewed as operating in parallel with, and not as a replacement for, the recommended internal review and oversight body that the Panel recommends in **SECTION I.B.3** and **SECTION III.D.4**. The technical considerations in the development of such a program are complex because they involve not only the need for objectivity and confidentiality, but also a sensitivity to the global considerations of corporate activities, including manufacturing surveillance, and communication. To achieve an effective advisory function, the IRG must receive continuing and visible support from senior leadership of Guidant Corporation

It is recommended that the IRG should be provided all relevant information regarding actual or possible device failures due to component or device malfunctions and evaluate patient-risk and opportunities for mitigation, with its conclusions not driven by marketing considerations. The IRG membership should include expertise in electrophysiology, and other areas of expertise, such as patient advocacy/ethics, engineering, statistics, and risk assessment. Membership should be staggered, with terms of service of at least two years. In order to maintain objectivity, considering person-to-person interactions that may develop during dialogues between corporate personnel and IRG members, it is recommended that the IRG function through an ombudsman who will serve as a nexus between the internal corporate structure and the IRG.

The IRG members should receive information from the corporation through an oversight structure that serves as a clearinghouse for initial internal

evaluation of the significance of reported deviations (see **Section III.D: Internal Communication and Decision-Making**). The conduit between the corporation’s internal structure and the IRG will be the ombudsman. At its discretion, the IRG may interview corporate personnel for information gathering purposes, but there should not be corporate membership on the IRG in order to avoid the creation or perception of unintended influences or biases through collegial working relationships.



The IRG should be an ongoing function, with its membership funded by Guidant Corporation with the ombudsmen being the only person carrying out dialogues with the Corporation in regard to funding questions.

The group should hold face-to-face meetings regularly (for example, every three months), but will convene conference calls on an *ad hoc* basis in a timely fashion for each product deviation that, in the judgment of the Chair, requires immediate attention. It will not be within the scope of the activities of the IRG to review every report or complaint coming into Guidant Corporation because of sheer numbers. In addition, many complaints are not relevant to patient safety or communication issues. However, the IRG should review all reported

actual or potential malfunctions or device failures that are determined by Guidant's Internal Oversight Committee to have life-threatening or serious morbidity implications. A summary of those incidents not determined to be in the life-threatening or major morbidity classification will be reviewed at the semiannual meetings of the IRG.

The IRG should report through the ombudsman directly to both the Chief Executive Officer of the Cardiac Rhythm Management business and the Internal Oversight Committee (either a new committee or a revised Officer Escalation Group – see **Section III.D: Internal Communications and Decision-Making**) on matters it considers urgent, and the CEO should then delegate responsibility for action and decision-making on these recommendations, according to the internal operating structure of the Corporation. For matters of a more routine nature, the reporting line will be through the ombudsman to the Internal Oversight Committee. The responsibilities of the IRG should include analyses and recommendations concerning specific problems and how information should be disseminated to physicians, patients, and the general public. The IRG should not have either the responsibility or the authority to make such information public on its own. Rather, the recommendations by the IRG should be made public by Guidant Corporation or its CRM business, using guidelines for external communications and transparency cited elsewhere in this Report.

APPENDIX F

The Product Performance Committee, Product Evaluation Committee, and the Officer Escalation Group

PRODUCT PERFORMANCE COMMITTEE

According to CRM's CAPA system, the Product Performance Committee is charged to improve customer satisfaction by prioritizing, approving, and monitoring corrective actions for product performance and customer satisfaction issues.

Regular Members:

- Director of Reliability Engineering/Device Analysis (*Chair*)
- Director of Product and Program Management
- Director of Hardware Engineering
- Director of Product Performance Reporting/Quality Assurance
- Director of Leads Design
- R&D Medical Advisor
- Representative of Legal
- Director of Compliance
- Manager Bradycardia Marketing
- Manager Tachycardia Marketing
- Director of Heart Failure Marketing
- Japan Marketing Authorization Holder Representative

Ad Hoc Members:

- Director, Manufacturing and Operations, Guidant Puerto Rico
- Director of Manufacturing
- Director, Manufacturing and Operations, Guidant Clonmel
- Chief Medical Officer

PRODUCT EVALUATION COMMITTEE

According to CRM's CAPA system, the Performance Evaluation Committee is charged to perform independent, objective assessment of newly developed products, proposed human clinical trials, and ongoing product performance to assure the protection of patients' safety and health.

Regular Members:

- Director of Product Performance Reporting/Quality Assurance (*Chair*)
- Director of Product and Program Management
- Director of Hardware Engineering
- Director, Reliability Engineering
- R&D Medical Advisor
- R&D Clinical Advisor
- Director, Regulatory
- Director, Research and Technology Advancement Center
- Manager, Clinical Research
- Advisor, Clinical Research
- Japan Regulatory Representative

OFFICER ESCALATION GROUP

The Officer Escalation Group was officially constituted in January 2004, when the Charter (Procedure 006415) describing this body was released. Prior to that date, this group met periodically as an informally recognized body during 2003, starting in February. It was first referred to as the Officer Escalation Group in July 2003.

In general, the Charter charges the Officer Escalation Group to improve customer satisfaction by either approving or rejecting, and provide guidance on, those items and issues elevated to it by the Product Performance Committee. The requirement to periodically review trends where "the potential for serious injury or death exists" was added to the Officer Escalation Group Charter in September 2005. However, it first met to review such trends during July and August of 2005.

Regular members:

- Vice President of Product Engineering (*Chair*)
- Vice President of R&D
- Vice President of Regulatory Affairs
- Vice President of Reliability & Quality Assurance
- Vice President of Marketing
- Chief Medical Officer
- General Counsel

Ad Hoc Members:

- Vice President of Manufacturing
- Vice President Regulatory/Clinical/Quality & Vigilance, Guidant Japan

APPENDIX G

FDA Reporting Requirements

REPORTABLE MALFUNCTIONS

The FDA requirements for reporting malfunctions are of particular relevance to postmarket monitoring of pacemaker problems:

A malfunction [§803.3(n)] refers to 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. The intended performance of the device refers to the intended use for which the device is labeled or marketed, as defined in section 801.4.

[21CFR§803.50(a)(2)] defines when a malfunction is reportable. This section requires a report any time a malfunction “would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur.”

A malfunction is also reportable when a manufacturer takes or would be required to take action under section 518 [notification of health professionals of a device risk] or 519(f) [corrective action or removal of device to remove risk to health] of the FD&C Act as a result of the malfunction of the device or other similar devices.

Reporters do not need to assess the likelihood that a malfunction will recur. The regulation presumes that the malfunction will recur. Furthermore, FDA believes that once a malfunction has caused or contributed to a death or serious injury, a presumption that the malfunction is likely to cause or contribute to a death or serious injury has been established.

MDR LIMITATIONS

It is recognized that although manufacturers are required to report all known deaths and serious injuries, only a fraction of adverse events associated with medical devices are reported in the MDR system. Some events are more likely to be reported than others: unusual events, problems with a newly implanted device, clusters of events (which often occur by chance), and publicized device problems. Unfortunately, although it is known that the degree of underreporting varies widely, it is not known what the degree of reporting is, even for a single device, making it difficult to interpret trends.

MDR information is frequently incomplete and may not even include enough data to identify the model of the medical device, or even the manufacturer even though this information is required on the MDR form (FDA Form 3500A). In addition, reports are often missing key details that would help assess the relationship between a device malfunction and injury. MDR reports themselves have a disclaimer that submission of the report does not necessarily reflect a conclusion that the device caused or contributed to the event. By casting a broad net, they hope not to miss signals of new problems, even if initially they are not recognized as caused by the device.

APPENDIX H

Features of an Active Surveillance System

An active surveillance system requires a very detailed protocol that must be defined before implementing such a system. Consideration should be given to inviting experts to help design the system, which might be preceded by a pilot program to test feasibility and utility. Opportunities to train a cohort of hospitals and clinicians in reporting methods, such as have been employed in FDA's MedSuN program, may provide opportunities to get more accurate trend estimates.

Other opportunities provided by active surveillance include:

- STANDARDIZATION: Any monitoring system for events must be based on a precise common vocabulary for both events and outcomes. For example, how might we define device failure modes for implantable cardioverter defibrillators (ICDs)? While clinicians might resist "box checking" in the sense of placing events into predefined categories, this is better than the rather idiosyncratic "clinical impressions" that one sometimes encounters in medical charts. A good model here is the cancer grading systems used in the National Cancer Institute's SEER (Surveillance Epidemiology and End Results) program— which shows how one can categorize diverse phenomena in a systematic way.

Note that training is a key issue. Even with the best standardized collection instrument, trained physicians or nurses are necessary to use it in a consistent manner.

- PATIENT CHARACTERIZATION: Baseline data on patient characteristics is an important component of an active surveillance system. That is, some patients may be more likely to respond better to a specific device, or for whom it may be easier to program the device. If a particularly good device (eg, perhaps with an exceptionally wide range of adjustment options) tends to be used for difficult patients it might appear to have a high failure rate because, while it is doing well relative to the patient pool it is used in, it might look worse compared to the general patient pool. These sorts of selection bias phenomena are seen in outcomes research where the best hospitals may have relatively high mortality rates because they attract sicker patients. The issue of patient characteristics needs to be carefully evaluated and if there are different sub-populations, these need to be considered in any analysis of device failure.

- DEVICE CHARACTERIZATION: Another issue concerns the age of a device. That is, some devices may “fail” because their batteries ran down, while others may experience actual device failure. Older implants are certainly more prone to battery failure, but may be more prone to other failure modes as well. The important point here is that when a device was installed is a major covariate. This is rather obvious, but is also critical to any evaluation of failure rates.

We also assume that ICDs have serial numbers or other individual identifiers. Collecting this information would be important because one might have a set of devices manufactured in a finite period that share a common failure mode – which in turn might help identify manufacturing issues that result in defective devices. This issue appears less challenging for Guidant, given the detailed electronic information routinely collected on implanted devices.

- ROUTINE FOLLOW UP: One of the most challenging aspects of an active surveillance system of this type is ensuring that important patient information is captured in a timely fashion. Various elements to ensuring complete event identification include committed physician and patient participation in the surveillance program, participation incentives, routine communication and information sharing. Field representatives might be a valuable asset in patient follow up.
- DATA ANALYSIS OPPORTUNITIES: Given that the company has an accurate “roster” of devices that have been installed which includes the time of installation for each device and the characteristics of the patient who was its recipient, the challenge is collection of data on failure events. As noted earlier, an aggressive active surveillance system is best. An ideal data stream would include “events” that did not result in device removal, events that did result in device removal, severity of the “event”, whether therapy was delivered, malfunction mode, and terminal events where the device functioned correctly up until the time of the patient’s death from unrelated causes. Of course one could and should calculate malfunction rates from such data, but a more pressing issue is identification of event clusters that indicate problems with a particular device of device/patient type combination. The exact form of such analyses cannot be specified a-priori but some of the recent work with Bayesian modeling of disease cluster data would seem to offer promising leads.

APPENDIX I

Expected Numbers of Events – Active Surveillance

The value of an active surveillance system would be lost if it did not increase the number of reported events.

A number of assumptions are necessary to define the feasibility of such a system:

1. Active surveillance systems should be developed for defined geographic regions. For example, a system developed for devices implanted in the U.S. should be developed according to U. S. regulatory issues, physician attitudes, and patients' access and wishes. These variables may differ in Europe and the Far East, and modified methods should be devised in consideration of these variations
2. The example below (**TABLE 1** and **TABLE 2**) uses data for the PRIZM 2 DR model 1861 case and limits the number of devices to those implanted by April 16, 2002. We were told this was about 24,000 devices;
3. This exercise assumes a 10% annual all-cause mortality;
4. The failures of interest are limited to the arcing events. Other failures that result in the loss of therapy can be added later.
5. There were 26 failures reported prior to the "recall," 25 of which were in devices implanted in the U.S.
6. A uniform failure incidence for each of the first four years post-implant is assumed. Although there are some data to suggest that the risk of a failure increases overtime, and that this can be built into the model, we do not think it will have a major impact on the results
7. The results are presented for various assumptions about the incidence of failure in those who died.
8. An actuarial model is assumed for this exercise since the exact dates of the failures were not known. Again, the model could be refined with this information, however, it should not have a major impact on the results.

TABLE 1. ACTUARIAL CALCULATION OF THE PROBABILITY OF ARCING, BY YEAR POST-IMPLANT

| Post-Implant Year | Number with Device on January 1 of Indicated Year | Number of Observed Failures in the Indicated Year | Number of Deaths in the Indicated Year | Probability of a Failure in the Indicated Year |
|-------------------|---|---|--|--|
| Year 1 | 24,000 | 6 | 2400 | 0.000263 |
| Year 2 | 21,594 | 6 | 2159 | 0.000292 |
| Year 3 | 19,429 | 6 | 1943 | 0.000325 |
| Year 4 | 17,480 | 7 | 1748 | 0.000422 |

TABLE 2. EXPECTED NUMBERS OF FAILURES FOUND POST-MORTEM

| Probability of Arcing Failure: Year 1 | 100% of Devices Recovered Post-Mortem (DRPM) | 50% of DROM | 33% of DRPM | 25% of DRPM |
|---------------------------------------|--|-------------|-------------|-------------|
| 0.000263 | 0.6 | 0.3 | 0.2 | 0.2 |
| 0.000526 | 1.3 | 0.6 | 0.4 | 0.3 |
| 0.001315 | 3.2 | 1.6 | 1.0 | 0.8 |
| 0.002630 | 6.0 | 3.0 | 2.0 | 1.5 |

The first column, first row, in **TABLE 1** presents the probability of an arcing failure. The probabilities in rows 2-4 of column 1 assume failure incidences of 2X, 5X and 10X, what was observed. We observe that in the first post-implant year even if 100% of the devices were recovered post-mortem, few devices would be identified as having failed due to the arcing mode. It is only when the probability of an arcing failure in a deceased individual is 5-10 times higher (rows three and four) than in a person who did not die, that 3-6 events might be identified. If only 25%-33% are recovered two or fewer failures would be found.

The total number of events identified post-mortem would be approximately four times each of the numbers in **TABLE 2**.

APPENDIX J

Improving Communication about ICDs: Relevance of the Risk Communication Literature

Effective communication about risks associated with medical interventions, particularly when rendered in the context of patient-provider interactions, has many positive benefits for patients.^[1]

These benefits include:

- Enabling patients to make informed choices.
 - Physicians are ethically obligated – and increasingly legally obligated – to help patients make informed choices.^[2] The same is likely true for medical device manufacturers.
- Helping patients to better understand the risks, make better decisions, and improve their odds of a good health outcome.
 - Improved understanding of risk typically leads to improved decisions, which in turn, increases the odds of better health outcomes.
- Increasing the odds that patients will experience positive affective outcomes.
 - These include enhanced satisfaction with the information provided, with the decision-making process, and increased feelings of certainty that the best option was chosen;^[3,4] reduced negative reactions to risk information,^[5] and helping people put their fears in perspective.^[6]
- Although the science of risk communication is still young, and consensus has not yet emerged on how best to communicate various risks to various people in various situations, the following principles appear to be emerging:
 - The way in which risk information is presented can have a powerful impact on subsequent decisions by people who process that risk information. This has considerable ethical implications for information providers if manipulation is to be avoided.^[7]
 - People, even highly trained professionals, have a difficult time interpreting numbers. It is therefore helpful to use a combination of quantitative (ie, numeric) *and* qualitative (ie, verbal) descriptors of risks and benefits.^[8,9]

- Any uncertainty about risk and benefit information should be acknowledged and its key components should be explained in qualitative terms.
- Visual representations may substantially improve comprehension of risk, in part, by “debiasing” overestimations of risk that result from exclusively word-based descriptions of risk.^[8-13]
- Efforts should be taken to “de-bias” risk information presentation whenever possible.^[14]
 - Patients often prefer statements frame in terms of relative risk, however, such rates bias perceptions toward overestimation of risk.
 - Presenting risk information in absolute terms rather than relative risk terms is more effective in helping people make decisions that are consistent with maximizing their expected utility (ie, improved odds).^[13,15]
 - People find using information in frequency format (1 in 100) easier than using information presented in percentage format (1%), and when risk data are presented in frequency format they make less biased judgments of risk.^[16]
 - Single event probabilities – eg, 0.1%, or 1 person out of 1,000 – tend to be better understood when they are presented as frequency statements (ie, 1 person out of 1,000 people who have an implant will experience X).^[13]
 - Presenting data as natural frequencies (versus conditional probabilities) improves comprehension.^[13]
- Framing effects can also bias risk presentations. Framing on success, or positive outcomes (eg, 99% chance of a good outcome) tends to lead to a higher preference for an intervention than framing on risk, or negative outcomes (eg, 1% chance of a bad outcome).^[17]
 - Presenting both frames may be the best way to de-bias risk information of framing effects.^[18]
- Decision-aids are another useful tool for debiasing risk information in a clinical context:
 - When physicians use decision aids in their consultations, the focus of the consultations is sharpened, and physicians and patients are both more likely to report that *decisions* are actually being made.^[19]

- A Cochrane Collaborative review showed that decision aids improved by 40% the proportion of patients with realistic perceptions of the chances of benefit and harms.^[20]
- Risk communication that references a standardized system for classifying medical options according to strength of the scientific evidence and magnitude of benefit to harm – such as the US Preventive Services Task Force or Chalmers – can provide important missing context.^[21]

Some other important “best practices” in risk communication as suggested by Covello^[22] include:

- Disclose risk information as soon as possible; fill information vacuums.
- If information is evolving or incomplete, emphasize appropriate reservations about its reliability.
- If in doubt, lean toward sharing more information, not less.
- Discuss data and information uncertainties, strengths and weaknesses.
- Identify worst-case estimates as such, and cite ranges of risk estimates, when appropriate.
- Do not minimize or exaggerate the level of risk; do not over-reassure.
- If errors are made, correct them quickly.

Lastly, it is important to note that physicians and other health care professionals also have a hard time understanding probabilistic terminology. All of the risk communication suggestions above are equally pertinent to physicians and patients.

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APPENDIX K

New FDA Postmarket Safety Initiatives

The Center for Devices has recently announced efforts to improve the MDR system. The five main areas they highlighted are:

- Working toward an electronic reporting system for adverse medical device events;
- Unique ways to identify medical devices including standardized and globally accepted names;
- Ways to improve device information in patient records;
- Improved internal collaboration on post market safety issues; and
- Identifying opportunities to improve the safety of medical devices through collaborative efforts with professional organizations and the medical device industry.

The first initiative is designed to improve both the timely acquisition of reports at FDA and to allow better cross-manufacturer evaluation of emerging signals. In the pacemaker manufacturing community this could allow earlier detection of problems than any single manufacturer could accomplish. As companies automate they may improve their internal capacity to evaluate new problems. FDA is not only interested in an improved MDR and MAUDE system, but is also interested in making company annual reports more useful.

The second and third initiatives are less of a problem with pacemakers than with many other medical devices. It is unusual for a patient record not to include the model and serial number of the pacemaker, and MDR reports from manufacturers can usually identify the pacemaker model.

The fourth initiative is an internal FDA effort, although it may change the way that the premarket staff evaluate applications for new products. Manufacturers may need to systematically describe their postmarketing experience with older approved products that use some of the same technology.

The fifth initiative emphasizes the need to solve many problems across a whole group of manufacturers, even though the tendency historically has been to focus on the company where a problem is first identified. The FDA will welcome continued efforts by the Heart Rhythm Society to work with pacemaker manufacturers to find opportunities to improve the quality of

medical devices.