Report of Charles Swerdlow, MD

The Prizm 2 DR Electrical Overstress Failure: A Physicians' Perspective

March 6, 2007

Prepared for

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Background

Professional Experience

I am a cardiac electrophysiologist engaged in the practice of medicine, teaching, and research at Cedars Sinai Medical Center in Los Angeles, where I have worked for the last 16 years. I received my MD degree from the Harvard-MIT program in Health Science and Technology, performed my internship and residency at Los Angeles County Harbor - UCLA Medical Center, and received my Cardiology and Cardiac Electrophysiology training at Stanford University Medical Center. I was director of the Cardiac Clinical Electrophysiology Laboratory at Stanford University from 1984 – 1988. My present academic title is Clinical Professor of Medicine at UCLA. I am board certified in Internal Medicine, Cardiology, and Clinical Cardiac Electrophysiology.

As a cardiology fellow, I operated a data recorder during the world's second implantable defibrillator (AID) surgery in 1980; but I never dreamed I would have an interest in the technology. However, since the early 1990s, the principal focus of my research has been implantable cardioverter defibrillators (ICDs). My major, long-term projects include (1) design and testing of algorithms used by ICDs to detect atrial and ventricular tachyarrhythmias; (2) optimization of ICD defibrillation waveforms based on mathematical modeling of defibrillation; and (3) development and validation of a clinical method to determine the minimum shock strength that defibrillates the heart reliably without inducing ventricular fibrillation (VF).

In clinical practice, I have implanted 800 - 900 ICDs and worked in conjunction with a surgeon to implant 250 - 300 ICDs.

Previously, I have consulted regarding ICDs with both Medtronic and St. Jude. Presently, I consult primarily with Medtronic and to a lesser degree with St. Jude. I have received lecture honoraria from Medtronic, St. Jude, and Guidant.

My attached curriculum vitae includes the following work related to ICDs: 40 peer-reviewed original research manuscripts, 5 book chapters, 9 reviews or editorials, 61 abstracts, and 4 patents.

Materials Reviewed

I have reviewed the following documents: Report of the Independent Panel of Guidant Corporation, Report of the Heart Rhythm Society Task Force on Device Performance Policies and Guidelines, Proceedings of the Heart Rhythm Society – FDA Policy Conference on Pacemaker and ICD Performance, various internal Guidant documents, various depositions of current and former Guidant employees, and 2006 product performance reports for Guidant, Medtronic, and St. Jude.

I. Summary and Conclusions

The patient-physician relationship is based on trust. Informed consent is central to this trust. Thus, physicians must inform patients of known risks prior to recommending an ICD and update them promptly with new information that affects risk after an ICD is implanted.

In this context, physicians expect manufacturers to use reliable materials in assembling ICDs and to test these materials under conditions that accurately reproduce the stresses of ICD function in clinical use.

When an ICD manufacturer determines that a non-random, malfunction may have serious clinical consequences and that future similar failures are likely, physicians have

three key expectations: (1) the manufacturer should make a substantive effort to determine the likelihood of future failures, including an active audit and – if appropriate – accelerated laboratory testing; (2) the manufacturer should notify physicians promptly; (3) the manufacturer should act expeditiously to retrieve potentially-affected ICDs that have not been implanted.

In the case of electrical overstress arcing failures of the Prizm 2 DR (Model 1861) caused by shorting in the header, Guidant took none of these steps. Instead, it withheld information from physicians until the *New York Times* focused scrutiny on the company. In withholding this information, Guidant denied physicians the information necessary to provide patients with ongoing informed consent; it denied individual ICD patients the information necessary to decide, in consultation with their physicians, whether or not to explant at-risk ICDs; and it denied physicians information that they might reasonably use in deciding not to select Guidant ICDs for de novo implants. In my opinion, if Guidant had informed physicians about this malfunction, physicians would have taken some or all of the following actions: (1) discussed therapeutic risks, benefits, and alternatives (including explant) with patients implanted with pre-mitigation Prizm 2 DRs; (2) implanted no or few pre-mitigation Prizm 2 DRs; (3) explanted many pre-mitigation Prizm 2 DRs; (4) probably reduced utilization of Prizm 2 DRs; and (5) probably implanted fewer overall Guidant ICDs and more ICDs manufactured by Guidant's competitors.

II. Prizm 2 DR Electrical Overstress Failure: Summary of Events

A. Prior to Joshua Oukrop's death

Electrical overstress failure is a general term applied to semiconductor failure caused by application of extreme voltages or currents for a sufficient duration to cause a transistor to fail catastrophically. The first such failure of a Guidant Prizm 2 DR occurred in a patient on February 1, 2002. The ICD was explanted, returned to Guidant, and analyzed. Guidant engineers promptly identified the failure mechanism as arcing caused by a short circuit in the header that occurred while delivering a shock; and they determined the cause to be a preventable, systematic flaw in manufacturing. They recognized that this malfunction resulted in failure to deliver a potentially life-saving therapeutic shock and subsequent failure to provide pacing therapy.

Guidant introduced manufacturing changes to mitigate the problem on April 16, 2002. On June 14, 2002 Guidant completed a Risk Assessment in which it classified the likelihood of injury occurring from an event as "very likely" (5 – 10%) and the severity of such injury as "life-threatening." It concluded that failure to defibrillate as a result of this systematic malfunction could cause the death of a patient who would have been resuscitated by a normally-functioning ICD. The Risk Assessment does not mention the risk of failure of pacing function. This risk may be life-threatening in a pacemaker-dependent patient who receives either an appropriate ICD shock or an inappropriate shock delivered as a result of oversensing, self-terminating ventricular tachycardia (VT), or inaccurate discrimination of VT from supraventricular tachycardia. On November 13, 2002, Guidant made additional manufacturing changes with the goal of further mitigating this failure mode.

According to the Report of the Independent Panel of Guidant Corporation (Independent Panel), Guidant continued to ship the approximately 1300 unmitigated ICDs in its in-house inventory and made no attempt to retrieve the approximately 2700 unmitigated but not yet implanted ICDs that had been shipped to its sales force or to hospitals. The company established an internal "trend" to monitor this failure mode. This trend was monitored intermittently based on the number of analyzed returned failures over the next two years (from May 20, 2002 to April 16, 2003 and November 5, 2004 to March 1, 2005).

B. After Oukrop's death: Role of physicians and press in Prizm 2 DR recall

Joshua Oukrop, a patient with a pre-mitigation Prizm 2 DR, died suddenly on March 14, 2005. His ICD was explanted post-mortem and confirmed to have failed from the known header short. The patient's physicians Drs. Barry Maron and Robert Hauser concluded that Oukrop died of VT or VF because his Prizm 2 DR failed to deliver a shock, and they asked Guidant to notify physicians about this failure mode about May 12, 2005. Guidant refused, but offered to work with the physicians to prepare a case report for an electrophysiology journal. Maron and Hauser declined the offer and submitted the case report to *Heart Rhythm*. In addition, they notified the *New York Times*.

On the evening of May 23, 2005 – the day before publication of the first *New York Times* article - Guidant sent a letter to physicians stating, "[a]s a result of recent communications from sources other than Guidant Corporation regarding the VENTAK PRIZM®2 DR ICD, we want to provide clarity and assure you that clinical performance of Guidant's PRIZM 2 DR ICD continues to exceed design expectations..." Over the next month,

the *New York Times* published a series of related articles, the FDA investigated the malfunction, and physicians questioned the reliability of pre-mitigation Prizm 2 DRs. On June 17, 2005, Guidant sent a second letter in which it indicated that the FDA would classify Guidant's safety notification regarding the Prizm 2 DR as a recall.

While not directly related to the subject matter of this report, Guidant's response to a similar electrical overstress malfunction in Contak RENEWAL 1 and 2 resynchronization ICDs was similar to its response to the Prizm 2 DR malfunction.

III. Physicians Depend on Manufacturers for Data Regarding Reliability of ICDs

Physicians typically rely on multiple sources of professional information, including medical journals, review courses, and meetings or publications from medical societies. But with regard to malfunctions of ICDs, physicians have no alternative other than to rely on the manufacturer to provide accurate, current, and actionable information. Physicians use this information to select the manufacturer and ICD model for new implants, to determine the need for special or intensified follow-up of implanted ICDs, and to determine if the risk of malfunction justifies explanting an ICD. ICD manufacturers have an obligation to provide physicians with such information.

According to the Heart Rhythm Society Task Force on Device Performance Policies and Guidelines (Task Force), accurate tracking of ICD performance is presently the responsibility of manufacturers. Usually, ICD malfunctions are first identified by analysis of returned products. Only manufacturers have the funding, infrastructure, and proprietary technology necessary to perform such analyses. Once a malfunction is identified, manufacturers are the only source of information regarding which specific devices are at

risk. Thus, physicians depend on direct notification from manufacturers for information regarding ICD malfunctions and have no practical, alternate sources of information to guide their practice.

Alternate sources include the MAUDE Database, manufacturers' product performance reports, and independent registries; but none serve as a basis for medical practice. The *FDA's Manufacturer and User Device Experience (MAUDE) Database* lists reports of adverse events involving medical devices. Search of the MAUDE Database results in reports of individual events submitted by physicians, user facilities (hospitals) and manufacturers. Based on my searches, most reports provide brief statements regarding the malfunction without clinical context. Summary statistics are not provided. The web site states, "MAUDE data is not intended to be used either to evaluate rates of adverse events or to compare adverse event occurrence rates across devices." Reports regarding device trade names may be submitted under different manufacturer names. For example, a search of the terms "Prizm 2 DR" and "Guidant" resulted in 46 records while a search of the terms "Prizm 2 DR" and "Cardiac Pacemakers" resulted in 599 records.

Manufacturers' product performance reports provide brief summary statistics. Prior to the conference establishing the Task Force, there was no standard method for reporting. Manufacturers typically provided single survival curves for pulse generators. Because these curves are dominated by the interval at which battery depletion occurs, they did not identify infrequent, systematic malfunctions and did not provide any information regarding clinical consequences of these malfunctions. The Independent Panel noted, "[l]ow-frequency, but clinically relevant, failure modes that may result in patient injury or death often cannot be detected on these curves."

Independent registries are based on voluntary reports from selected institutions or groups of physicians. Most physicians who care for ICD patients do not have direct access to information stored in these registries, and the registries do not routinely notify physicians regarding ICD malfunctions. Thus, physicians have no practical alternative but to depend on direct notification from manufacturers for information regarding ICD malfunctions.

IV. Physicians Expectations of Manufacturers vs. Guidant's Actions

Physicians expect manufacturers to use reliable materials in assembling life-saving ICDs and to test these materials under conditions that accurately reproduce the conditions of implanted ICDs.

When a manufacturer identifies an ICD malfunction, the company takes several actions: it determines the root cause; it determines whether the malfunction is a random event or due to a systematic failure; and it performs a hazard analysis to determine the potential clinical consequences for the patient – both the consequences of not delivering appropriate pacing or shock therapy to treat arrhythmias and any consequences that the malfunction might pose directly to the patient in the absence of arrhythmias. (In this context, a systematic failure may be a design flaw, a manufacturing flaw, or inherent component defect independent of its observed frequency.)

If the malfunction may be associated with serious clinical consequences, physicians expect the manufacturer to make a substantive effort to determine both the present prevalence of failures and the future likelihood of failures. These efforts should include an active audit and, if appropriate, accelerated laboratory testing. Unless the malfunction is determined to be a random failure, the manufacturer should both notify physicians

promptly and act expeditiously to retrieve potentially-affected ICDs that have not been implanted.

A. Materials and components: polyimide insulation

1. Physician expectations and rationale

Physicians expect manufacturers to make a substantive effort to review public information that relates to safety of materials used in ICDs, especially those materials subjected to environmental, physical, or electrical stress. They further expect manufacturers to use materials of known reliability under expected operating conditions when assembling life-saving medical devices. If reliability data are insufficient, physicians expect manufacturers to test these materials under conditions that accurately reproduce the stresses of ICD function in clinical practice. Mission-critical components exposed to the body should undergo testing to ensure reliable function in a in a biological environment. In some cases, the time course of failures over the service life of an ICD can be estimated using accelerated testing, such as testing at a higher temperature.

2. Guidant's actions

According to a 2002 General Accounting Office report on aviation safety, serious arcing failures caused by degradation of polyimide insulation had been reported in the public domain in the 1980s and 1990s. The report states that cracks in polyimide insulation occur most commonly when wiring is exposed to a humid environment and subjected to mechanical stress. The report further states that resultant arcing caused in-flight fires on helicopters and that the largest aircraft U.S. manufacturer (Boeing) discontinued use of uncoated polyimide as an insulator in 1993.

Guidant changed the insulation on defibrillation feedthrough wires from silicone rubber to uncoated polyimide in 1992. The Company did not adequately test for degradation of polyimide in a biological environment before making this change. In the late 1990s,

several models of "hot can" Guidant ICDs experienced catastrophic failures caused by electrical overstress arcing.

Because the header of the Prizm 2 DR ICD is not hermetically sealed, its components are exposed to the body's humid environment. Additionally, the DF- feedthrough wire in the Prizm 2 DR makes a tight bend in the header, resulting in mechanical stress. Thus the polyimide insulation on the Prizm 2 DR feedthrough wire is exposed to the precise conditions known to cause arcing failures.

Guidant selected polyimide to insulate the DF- feedthrough wire in the Prizm 2 DR header in or about 1999. By that time, the Company should have been aware that the aviation industry had abandoned uncoated polyimide because of arcing failures under the conditions in which the Guidant intended to use it. Despite catastrophic header arcing in earlier ICDs, Guidant did not perform adequate testing of the Prizm 2 DR to assess the integrity of the uncoated polyimide insulation in its expected service environment.

B. Efforts to identify malfunctions

1. Physicians' expectations and rationale

To advise patients about replacing a potentially-faulty ICD, physicians must be informed both of the known probability that a complication will occur at replacement surgery and the initially unknown probability that the implanted ICD will malfunction. Thus physicians expect the manufacturer to make substantive efforts to determine the likelihood of future failures if the malfunction may have serious consequences for the patient. These efforts may include bench testing of potentially affected ICDs and must include an active audit ("active surveillance").

ICD failures are under-reported. See Section IV.C.1. Thus a passive surveillance method such as analysis of returned products substantially underestimates the incidence

and prevalence of ICD malfunctions. Active surveillance methods proactively track ICD performance and malfunctions. The resultant active audits can be used to estimate the degree of under-reporting associated with passive surveillance methods. The International Standards Organization (ISO) has accepted active audits. Because the confidence intervals associated with an active audit are inversely related to the number of faulty ICDs identified, an audit of a rare malfunction usually must include many patients to provide an accurate estimate of the malfunction's incidence and prevalence. Thus, a large, active audit is required to provide a meaningful estimate of the true frequency of ICD malfunctions.

Active surveillance can provide an accurate estimate of future failure rates only if the rate of failure is constant over time. However, if the likelihood of failure increases with time, all surveillance methods underestimate the expected rate of future failures.

Once the component(s) responsible for a failure mode have been identified, manufacturers should use accelerated laboratory testing to estimate the likelihood of component failure whenever possible. This testing may be particularly useful for malfunctions that occur during shocks. In laboratory testing, each ICD may be programmed to deliver many shocks in a short period after testing that simulates varying durations of clinical use. In contrast, most implanted ICDs deliver less than one shock per year. Thus the likelihood of a malfunction that occurs only during a shock can be estimated more rapidly by laboratory testing than clinical observation. Further, for failures such as polyimide degradation, the increasing rate of failures over time can be estimated by accelerated laboratory testing. However, laboratory testing is not a substitute for active surveillance because differences between laboratory and clinical conditions may result in different occurrence rates of some malfunctions. Both laboratory testing and active

surveillance usually are required to provide a meaningful estimate of the likelihood of future malfunctions.

2. Guidant's actions

In its letter of May 23, 2005, Guidant informed physicians that failures had been documented in approximately one in a thousand Prizm 2 Drs (0.01%) and estimated the likelihood of failure at *a constant value* of .002% per month. This estimate (to the best of my ability to determine) was based on analysis of returned products with at most minor corrections for under-reporting.

After the Prizm 2 DR was recalled, Guidant perfomed laboratory testing on 4682 pre-mitigation ICDs. Of these, 26 (0.55%) failed testing. Guidant provided these data in the fine print of the annual Product Performance Report.The corresponding 95% binomial confidence intervals are 0.4% – 0.8%.[1] This was a large sample (about 30% of at-risk ICDs); and it approximates a random sample with respect to the likelihood of failure of Prizm 2 DRs in *living* patients *at the time the ICDs were explanted.* The alternative would imply bias by Guidant in providing some physicians or patients with defective Prizm 2 DRs. However, these data likely underestimate the true failure rate both because the risk of failure may increase with time and because devices from patients who died of Prizm 2 DR failures prior to explant in 2005 were not analyzed.

Guidant studied the endurance of the polyimide insulation in the Contak Renewal header using accelerated laboratory testing in 2004. To the best of my knowledge, no

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[1] Guidant states that this is a "non-random" sample. According to Renold Russie, Guidant's Director of Product Performance Reporting, the sample is non-random with respect to physicians because some physicians explanted a higher fraction of at-risk Prizm 2 DRs than others. Probably, it was also not random with respect to patients because some patients were more likely to request device explant than others.

comparable testing was performed for the Prizm 2 DR. Accelerated testing demonstrated arcing failures when polyimide insulation was placed in a humid environment and shaped in a tight bend. According to the FDA, failures occurred in 31% - 45% of headers exposed to testing that corresponded to between twenty and forty-two months of clinical service.

The aggregate implication of these results is that the polyimide insulation on the feedthrough wire often fails during the expected service life of ICDs. Guidant did not inform physicians or the FDA of the results of these tests until mid 2005.

3. Guidant's inaction

Between the time Guidant redesigned the Prizm 2 DR header to mitigate the arcing malfunction in April 2002 and the time it became aware of Hauser and Maron's intention to report the failure mode in April or May of 2005, Guidant (to the best of my knowledge) did not perfrom an active audit of the Prizm 2 DR arcing failure.

In fact, Guidant was engaged in active surveillance of Prizm 2 DRs at 128 implanting centers in a study titled "Synergistic Effects of Risk Factors for Sudden Cardiac Death (SERF)." This study followed 1703 ICD patients including approximately 1250 patients implanted with Prizm 2 DRs.[2] The first enrollment occurred on January 31, 2001, the final enrollment occurred on December 6, 2002, and the last patient follow-up was performed on March 3, 2004. The period of prospective data collection substantially overlaps with the period during which Guidant was following the Prizm 2 DR electrical overstress failures. Overall, 289 SERF patients (17%) were withdrawn from the study. Of the remaining 1414

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[2] There are two versions of the Guidant Final Report of the SERF study, both dated January 31, 2005. CPI 503 000084863 lists the number of Prizm 2 DRs as 1250. ROSS 1 00000119 lists the number as 1251. Note also that CPI 503 000084863 lists the number of withdrawn patients as 449 and ROSS 1 00000119 lists the number as 289.

patients, 167 (12%) died during the follow-up period. According to the Guidant study scientist Rocco Rossinni, this mortality rate was higher than the expected value of 5 - 7% predicted by Guidant based on other ICD populationss. Despite this higher than expected mortality rate, none of the personnel involved in the study, including Rossinni, were informed that Guidant was tracking a Prizm 2 DR malfunction that could result in catastrophic failure to deliver a shock. Of the deaths that occurred in Prizm 2 DR study patients, 9 were classified as "cardiac:arrhythmic," 5 as "cardiac:unknown," and 58 as "unknown." Many of these 72 deaths (43%) could have been caused by the known arcing malfunction. After the Prizm 2 DR failure mode became public in May 2005, Rossinni recommended that the study data be reexamined to determine how many of the deaths were likely caused by ICD malfunction; but Guidant management overruled this recommendation.

In summary, while Guidant was following the Prizm 2 DR failures by analysis of returned products, it had access to a large, ongoing, active-surveillance study; but it made no effort to analyze these data to provide an accurate estimate of the likelihood of Prizm 2 DR malfunctions.

C. Efforts to estimate the probability that an ICD will fail

1. Under-reporting of ICD failures

ICD failures are under-reported. Physicians expect a manufacturer to make a credible estimate of the rates of under-reporting caused by patient deaths and failure of explanted ICDs to be analyzed at Guidant. Physicians further expect the manufacturer to account for the higher frequency of arcing with increasing age of the pulse generator.

Under-reporting due to patients' deaths. Because post-mortem interrogation of ICDs is performed rarely, analysis of returned products may result in the greatest underestimates

for malfunctions associated with patient death. A rigorous valid analysis of under-reporting due to patient deaths requries formal statistical techniques. But a "back-of-the envelope" estimate can provide a reasonable approximation: About one third of shocks are "inappropriate," delivered in response to abnormal sensing signals (oversensing) or arrhythmais such as supraventricular tachycardia that rarely cause death. The remaining two-thirds of shocks are appropriate, delivered in response to VT/VF. About half of these appropriate shocks (one third of all shocks) are delivered for VT/VF that would have been fatal without the shock.

According to the FDA letter of June 16, 2005, approximately 24 Prizm 2 DRs had been reported to develop arcing failures during shocks that occurred outside the hospital. But only one resulted in a patient's death. Why is only one known death related to these 24 arcing failures? The likely reason is that ICD arcing failure during treatment of VT/VF results in deaths that are not recognized as related to the ICD and thus under-reported. For the purpose of illustration, suppose that none (zero) of 20 reported out-of-hospital failures caused death. If 1/3 of the events are fatal and the observed fatality rate is 0/20, we need to add 10 unrecognized fatal events to both the numerator and denominator to determine the true event rate. Then there will be 10 fatal events out of a total of 30 events. In this hypothetical case, one third of events are under reported, and the total number of out-of-hospital failures is 50% higher than the observed value of 20 failures. Using the actual values (1 fatal event in 24 total events), the expected rate of under-reporting for shocks occurring outside the hospital is 44%, assuming one third of shocks are delivered for VT/VF that would be fatal if untreated.

Under-reporting due to failure to analyze explanted ICDs. Physician reporting is voluntary, and return of products by manufacturers' representatives is inconsistent. There

are no accurate estimates of under-reporting of faulty ICDs in clinical practice, but there are several reasons that an explanted faulty ICD may not be be analyzed: (1) If a Guidant ICD is replaced by one from another other manufacturer, Guidant may not know the ICD was replaced. (2) Even if it is replaced by a Guidant ICD, Guidant may not be informed that the explant occurred. (3) Guidant may be informed that the explant occurred, but not that the ICD failed unexpectedly. ICDs explanted for expected battery depletion are not returned to the manufacturer. (4) Guidant field representatives focus on customer support. Prior to May 2005, Guidant representatives had no reason to consider Prizm 2 DR failures as anything but random events. Returning these units to St. Paul required effort that did not contribute to customer support. Thus, some ICDs presumed to have had random component failures may have been discarded. (5) Guidant had no system to ensure that ICDs explanted in hospitals were received by the group that analyzed returned products. There is no way to know how many explanted ICDs were lost between operating rooms and the Guidant lab where returned products are analyzed. My personal estimate is that the rate of under-reporting of explanted faulty ICDs in the absence of a recall is 25% - 50%.

Increasing failure rate with time. Physicians expect the manufacturer to provide a meaningful estimate of the cumulative probability of header arcing during a shock. Based on the substantial increase in frequency of arcing with age in accelerated testing, the probability of failure probably increases with service time, at least until the polyimide is totally degraded.

2. Guidant's actions

Once the Prizm 2 DR arcing failure became public, the Company seems to have used a post hoc justification for its estimate that under-reporting of the Prizm 2 DR malfunction was about 10 - 15%. To the best of my knowledge, Guidant made no effort to determine the actual rate of under-reporting of failures caused by patient deaths. The Company also

estimated a constant rate of failues over time, even though its own accelerated testing demonstrated an increasing rate of failues over time.

When asked about this under-reporting, Guidant's Director of Product Performance Reporting/Quality Assurance Renold Russie replied in an e-mail of June 1, 2005, "[i]t's hard to argue that some device related deaths couldn't go undiscovered. Here's the best data we have: a few years ago, we did a study comparing our device records with actual patient files at three centers."

This "SEARCH Study" requested chart reviews of 822 patients at three large implanting centers and succeeded in reviewing charts of 587 active patients (71%). The study, reported in March 2001, found an overall rate of under-reporting of approximately 10% for variety of ICD-related events. However, this study is not applicable to the issue of under-reporting for the Prizm 2 DR arcing failure for several reasons. First, charts of deceased patients were not reviewed. Thus any device-related deaths were systematically excluded. Second, *the report makes no mention of any ICDs returned to Guidant for analysis*. ICD explants were not analyzed. Guidant ICDs that had been explanted and replaced by ICDs from other manufacturers might not have been included. Third, the under-reporting rate in this study probably is less than the rate in clinical practice: The study was performed at large implanting centers for Guidant ICDs. These institutions typically receive the highest level of field service from Guidant and have a well-developed reporting infrastructure. These features increase the likelihood of accurate reporting. In contrast, reports of malfunctions are likely to be less consistent at small institutions or those less well served by Guidant, ones with less-developed reporting infrastructure, and ones with no incentive to perform accurate reporting. Fourth, SEARCH included no or few patients with Prizm 2 DRs.

In summary, Guidant based its estimates of the likelihood of catastrophic Prizm 2 DR arcing failures on returned products, with minimal and inadequate corrections for under-reporting. The Company should have known that this method substantially underestimated the true failure rate. This underestimate was demonstrated by subsequent analysis of a reperesentative sample of Prizm 2 DRs in surviving patients, despite the fact that this latter analysis excludes failures that resulted in death and failures that would have occurred if the ICDs had not been explanted.

D. Threshold for notifying physicians about ICD malfunctions

1. Informed consent in the patient-physician relationship

The patient-physician relationship is based on trust. Central to this trust is the concept of informed consent. Before initiating any therapy, physicians are required to communicate its risks and benefits as well as the risks and benefits of alternative therapies. Patients trust physicians to provide this information accurately. As applied to ICD therapy, patients at risk for life-threatening cardiac arrhythmias trust their physicians to inform them of known risks prior to recommending an ICD and to update them promptly with any new information that affects risk after an ICD is implanted. Bioethicists consider both elements necessary to the ongoing process of informed consent. Both are essential to the process of empowering patients to participate in decisions regarding their medical care. At the joint Heart Rhythm Society - FDA Policy Conference on Pacemaker and ICD Performance (Policy Conference), Dr. Brian Lewis of the FDA focused on medical decisions after ICD recalls. He stressed that the FDA "recognizes and supports an individual patient's right to make informed decisions" with the guidance of expert physician advice. Dr. Michael Barber's comment at the same conference is apt, "[i]n the end it only matters that the 'patient, not the doctor, sleeps better at night' with their decision."

2. Physician expectations and rationale

The Task Force and Independent Panel agree that manufacturers should provide information about product performance if a physician might reasonably take that information into consideration when making a clinical decision. The Independent Panel states, "[t]he general view has been that the decision belongs in the hands of the treating physician... 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."

Physicians expect to be provided with such information in a timely manner to consult with patients in making decisions about their care. The Task Force emphasizes this point, "[p]hysicians and patients need timely, accurate, and understandable information regarding device performance in order to make appropriate decisions regarding medical care." Although this report was written after the Prizm 2 DR recall, it reflects long-held expectations of the medical community which are also expressed by the Independent Panel. Indeed, Guidant reached this same conclusion in the March 2001 report of the SEARCH Study, "[o]ur physician customers believe that reporting product performance issues in a timely manner is critical to ensure appropriate patient management."

To determine the threshold at which physicians wished to be notified of systematic ICD malfunctions, the Heart Rhythm Society performed a survey of 100 randomly-selected implanting electrophysiologists. Of 37 respondents, 27 (73%) wished to be notified if the probability exceeded 0.1% over the service life of the ICD. The best conservative estimates for the Prizm 2 DR arcing failure exceed this prevalence.

However, the Task Force rejected the concept that a threshold for notification should necessarily require any fixed percentage of malfunctions. Instead, it recommended that the

threshold depend on the clinical significance of the malfunction: "[a] *single event*, if it is associated with a significant risk for death or serious injury, is due to a systematic problem, and for which there is reason to suspect that it could occur in other patients" (emphasis added) merits a risk review by experts independent of the manufacturer.

2. Guidant's actions

To the best of my knowledge, Guidant made its decisions not to communicate the Prizm 2 DR arcing failure without consulting any physician. It did not inform its Chief Medical Officer Dr. Joseph Smith, who learned of the Prizm 2 DR problem independently, and it did not consult its Medical Advisory Board until after Smith learned of the problem.

Guidant's stated policy regarding communicating malfunctions to physicians was, "We act when predicted device performance does not achieve design or performance expectations" *or* "we act when we identify an opportunity to recommend to the clinical community a strategy for improved patient outcomes related to device function." The Independent Panel interpreted this to mean: "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."

The first criterion is inconsistent with the recommendations of the Task Force regarding notification based on a fixed percentage of malfunctions as well as the recommendations of the Independent Panel: "[e]ven though the risks are small, failure to make them known and clearly understood impinges on patients' safety rights."

The first criterion also appears to give equal weight to all deviations from performance expectations without regard to the severity of the clinical consequences. According to the Independent Panel, battery depletion effects dominate ICD survival curves

if this criterion is applied. However, failures caused by battery depletion are typically gradual and thus *rarely* constitute a safety issue. In contrast, the Prizm 2 DR electrical overstress failure is *often* life-threatening. Thus overall survival curves obscure the effect of less frequent systematic, preventable, and catastrophic failures.

The second criterion presumes that Guidant officers and employees without professional medical training are qualified to determine strategies that improve patient outcomes without consulting any physicians. This criterion is at odds with the previously cited view of the Independent Panel, the Task Force, and – in my opinion – with the perspective of an overwhelming majority of physicians: Medical decisions should be made by treating physicians in conjunction with informed patients, not by non-medical industry personnel who have substantive conflicts of interest. The Task Force states, "[t]he impact of a particular device malfunction may vary greatly among patients depending on individual clinical circumstances, and it is generally agreed that clinical decisions should rest ultimately with the patient and the physician."

Guidant's decision to withhold information about Prizm 2 DR failures was criticized widely in the medical community. Many prominent physicians disagreed, including six of seven Guidant Medical Advisory Board members (two of whom are former presidents of the Heart Rhythm Society, Drs. David Cannom and Eric Prystowsky); and Dr. Douglas Zipes, President of the American College of Cardiology. The Independent Panel said it "appears to have led to a sense of betrayal by physicians and patients." Dr. Richard Fogoros, a Guidant consultant, understood the developing attitudes of the medical community. In a May 15, 2005 memorandum, he wrote, "[o]ur reluctance to communicate, however, is not viewed as reflecting our concern for patients, but instead is viewed as our concern for our own image and bottom line. Our explanation for this reluctance (i.e. that docs will behave

inappropriately) is further viewed as paternalistic and insulting to our physician customers." Echoing this sentiment in an unusual Perspective article in the *New England Journal of Medicine*, Dr. Robert Steinbrook wrote, "[t]he fallout from the potentially preventable death of Joshua Oukrop has triggered a broad discussion about the propriety of Guidant's actions..."

The specific implementation of Guidant's general notification guidelines in the case of the Prizm 2 DR is described in an e-mail written by Product Manager of Arrhythmia Marketing Michael Marcroft on May 16, 2005, four days after Guidant's meeting with Maron:

> The current plan of action is as follows:...
> We will track the Prizm 2 failure related calls through the contact center.
> If one of the following 4 triggers occurs, we will move forward with vmxs/conference calls to the field:
>
> 1) We see a dramatic influx of calls relate to this issue
> 2) We determine that Medtronic/St. Jude has obtained a photocopy of the Dr. Hauser email.
> 3) We determine that knowledge of this incident has escaped outside of the physicians notified by the Hauser email
> 4) We receive inquiries on the issue from the FDA.
>
> If none of these triggers occur, we will not pursue a field communication.

In summary, Guidant's stated criteria for communication were established by personnel who had no professional medical training. They assigned equal weight to failure modes that resulted in widely-different risks to patients. Much of the medical community judged that Guidant's application of these criteria denied patients – in consultation with their physicians – the right to make important medical decisions in an informed and timely manner. In the end, Guidant's May 23, 2005 communication regarding the Prizm 2 DR arcing failure was not a proactive effort to provide physicians and patients with information

necessary to make medical decisions. Rather, it was a reactive response: News of this malfunction had "escaped" beyond a limited number of physicians, and the medical community and public at large were about to be informed by a third party with a large audience - the *New York Times*.

E. Retrieval of at-risk ICDs that have not yet been implanted

1. Physicians' expectations

At-risk ICDs should not be implanted. This expectation is explicit in both the reports of the Independent Panel and the Task Force. The Independent Panel recommends, "ceasing shipments of unmitigated devices, and retrieving those in possession of the sales force or in hospital inventories." The Task Force states: "[i]n the case of a malfunction that is associated with significant risk for patient harm, devices that are not implanted and in which the malfunction has not been corrected or addressed adequately should be retrieved from the sales force and from hospital inventories."

2. Guidant's actions

Guidant continued to ship the approximately 1300 unmitigated ICDs in its in-house inventory and made no attempt to retrieve the approximately 2700 unmitigated but not yet implanted ICDs that had been shipped to its sales force or hospitals. Dr. Joseph Smith, Guidant's Chief Medical Officer, justified this action by arguing that Guidant was not certain the April 2002 mitigation would improve performance of the Prizm 2 DR. If he meant uncertainty that the mitigation would improve overall performance measured primarily by battery depletion, this is the wrong metric. If he meant uncertainty that it would not prevent catastrophic electrical overstress failures, Guidant should have withdrawn the Prizm 2 DR from the market until it had confidence in the mitigation. As Steinbrook wrote in his *New England Journal of Medicine* Perspective, "[f]or more than three years, Guidant kept

quiet about the serious malfunctions of some of its ICDs and continued to sell defective devices after it made manufacturing changes to fix the defects. The company will have to regain the trust of physicians and patients."

V. How Physicians Use Information Regarding ICD Malfunctions

Once provided with timely, accurate, and understandable information regarding device performance, physicians use this information in three ways: to counsel patients, to minimize risk to patients with potentially affected ICDs, and to determine which ICDs to implant in other patients.

A. Counseling individual patients

As noted above, the doctrine of informed consent is central to the physician-patient relationship. Once a potentially-affected ICD is identified, most patients or their responsible family members want to understand the alternative approaches and the risks and benefits of each approach. Physicians must have sufficient information to counsel patients and their families in an informed and timely manner.

In the session titled, "What Patients Need and Want to Know From Their Physicians" at the Policy Conference, both the FDA representative Dr. Brian Lewis, and the physician representative Dr. Eric Prystowsky were in broad agreement that each patient is unique and that each patient's unique medical condition and preferences must be considered in deciding upon a course of action. Dr. Lewis emphasized that one patient may have substantially different needs from another within the context of a single recall and that decision-making for a single patient may be more complex than that for the group of patients affected by a recall.

If Guidant had provided timely and informative communications to physicians about the Prizm 2 DR malfunction, it is likely that physicians would have counseled individual patients based on this information. It is also likely that physician experts would have addressed the issue in medical journals sooner and that the Heart Rhythm Society would have provided guidance sooner. Both occurred after Guidant was forced to disclose the malfunction.

B. Minimizing risk in implanted ICDs

In general, physicians consider various steps for minimizing risk in patients with ICDs affected by safety alerts and recalls. These include intensified follow-up or home monitoring, reprogramming, testing in the electrophysiology laboratory, or explant. The following considerations apply to the case of the Prizm 2 DR failure:

1. Intensified follow-up

Quarterly follow-up is usually recommended for ICDs, but not all patients comply and not all physicians follow this recommendation. If Guidant had provided earlier communications, in my opinion most, if not all, patients with at-risk Prizm 2 DRs would have been monitored consistently on a quarterly basis. High-risk patients (pacemaker-dependent patients or those with prior VT or VF) may have been monitored more frequently. Nearly all patients would have been evaluated promptly after receiving a shock, and the risks and benefits of explant would have been reassessed after each shock.

2. Testing in the electrophysiology laboratory

Some physicians may have elected to deliver commanded shocks to their patients. In its June 17, 2005 letter to physicians, Guidant described this testing as optional for patients who had not received a recent shock.

C. The decision to explant of ICDs

1. Task Force Recommendations

The Task Force provided specific recommendations regarding which patients should undergo explant:

1. Consider device/lead replacement if:
   a. the mechanism of malfunction is known and is potentially recurrent,
   b. the risk of malfunction is likely to lead to patient death or serious harm, and
   c. the risk of replacement is less than or at least not substantially greater than the risk of device malfunction.

2. Consider device/lead replacement in:
   a. patients who are pacemaker-dependent,
   b. patients with an ICD for secondary prevention of sudden death, and
   c. patients with an ICD for primary prevention of sudden death who have received appropriate device therapy for a ventricular arrhythmia

The Task Force further offered the more general guideline of balancing the risk of explant in an individual patient against the risk of the malfunction in that individual patient, "[r]eplacement of the device/lead should be considered strongly if malfunction of the device/lead could result in patient death or serious harm, and if the risk of replacement is not substantially greater than the risk of device/lead failure."

While these recommendations were published after publication of the Prizm 2 DR malfunction, in my opinion they accurately reflect a consensus that applied during the time Guidant was monitoring the Prizm 2 DR failures.

2. Application of recommendations for replacement to Prizm 2 DR failures

The Prizm 2 DR malfunction meets both recommendations 1(a) and 1(b): The mechanism of malfunction is known to be recurrent (1a), and it is likely to lead to patient death or serious harm (1b).

Application of recommendation 1(c) requires that the physician have a working estimate of the risks of both ICD replacement and continued therapy with the Prizm 2 DR. I consider four principal factors: (1) the risk that a Prizm 2 DR will fail during its service life, (2) surgical risks of explant at a specific hospital, (3) the patient's arrhythmia condition, and (4) comorbidities that influence surgical risk or life expectancy.

To me, the most reasonable starting basis for estimating the likelihood of Prizm 2 DR failure is the value of 0.55% (confidence intervals 0.4% - 0.8%) determined by analysis of a large sample of explanted ICDs in living patients. This value must be corrected for at least two sources of underestimation. (A) ICD failures that resulted in patient deaths were excluded from this analysis. (B) Some ICDs that were functioning at the time of explant would have malfunctioned during their remaining period of service.

The precise failure rate of Prizm 2 DR cannot be known with certainty. But physicians must make clinical decisions in the face of such uncertainty. From a "big picture" perspective, I would estimate the probability of Prizm 2 DR failure at closer to 1% than to 0.1% or 10%. It is also reasonable to estimate that, if an appropriate shock is delivered for VT or VF, an arcing failure will be associated with patient death in about 50% of clinical episodes; and significant morbidity will occur in most of the remaining episodes.

The principal surgical risk is that of infection requiring re-operation, which varies widely, depending on institutional and patient-specific factors. In the report of the Canadian Heart Rhythm Society Working Group on Device Advisories, the risk was 1.9%. I think a reasonable estimate on the national level is about 2%. The risk of death from an ICD

infection is less than 1% if experienced operators perform lead extraction. The other common complication of ICD replacement is local bleeding, which requires re-operation in 2% of patients, but is never fatal.

Patients at high risk for death or morbidity as a consequence of arcing failure include those who are pacemaker-dependent, those whose ICDs were implanted for secondary prevention of VT/VF, and those whose ICDs were implanted for primary prevention of VT/VF but have since received appropriate therapy. In the first group, arcing failures during either appropriate or inappropriate shocks will likely result in pacemaker failure and either death or significant morbidity. The second and third groups have a greater than 50% chance of subsequent appropriate shocks for VT/VF, and an arcing failue is likely to result in death in about 50% of such clinical episodes.

Few ICD patients have comorbidities, such as development of a new, rapidly-fatal illness that would contraindicate ICD replacement. Patients whose anticoagulants cannot be stopped safely have a greater than usual risk for non-fatal, postoperative bleeding.

Based on these considerations, most high-risk patients with pre-mitigation Prizm 2 DRs would have undergone earlier, appropriate explants if Guidant had communicated the Prizm 2 DR failure sooner. The risk/benefit trade-off for explanting ICDs in patients who did not meet one of these specific high-risk criteria is less certain. For these patients, physicians must consider the surgical risk for a specific patient at a specific institution as well as the patient's preference.

3. Patient preference

When other factors do not provide strong guidance, physicians should give substantial weight to the patient's preference, particularly if the patient experiences the possibility of having a faulty ICD as a major psychological burden. With this consideration in

mind, earlier disclosure also might have resulted in replacement of fewer Prizm 2 DRs. As predicted by Fogoros and noted by Steinbrook, Guidant's response resulted in widespread loss of trust in the Company among patients and physicians. Several patients (and physicians) expressed this sentiment to me: "I want the ICD explanted (or I plan to explant the ICD) because I don't know what else Guidant is hiding."

D. Selection of new and replacment ICDs.

If Guidant had communicated the Prizm 2 DR failure sooner, in my opinion physicians would have implanted no or few pre-mitigation Prizm 2 DRs, consistent with the recommendations of the Independent Panel and Task Force noted above. Physicians also might have implanted fewer overall Guidant ICDs and correspondingly more ICDs manufactured by Guidant's competitors. However, the latter effect might have been small if Guidant had communicated earlier and thereby retained the trust of its physician customers.

In summary, if Guidant had communicated earlier about the likelihood and clinical consequences of the Prizm 2 DR arcing failure, it is my opinion that physicians would have counseled most, if not all, patients based on this information, followed some patients more closely, and explanted many of these ICDs. Physicians would have stopped implanting pre-mitigation Prizm 2 DRs and may have implanted fewer overall Guidant ICDs.

Rule 26 Requirements

Depositions and Court Testimony in Past 4 Years: None

Expert Consultation Rates

Consultation and Expert Review: $750 per hour

Deposition and Trial Testimony: $7500 per day or $3750 per half day

Publications 1996 – 2006

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I reserve the right to amend this report if I learn of new, relevant information.

Charles Swerdlow

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March 6, 2007