SUMMARY OF PMA
P050023/S087
BUNDLED WITH P950037/S151, P980023/S072, P070008/S063 AND P000009/S063
PROMRI FULL BODY SCAN (FBS) ICD SYSTEM
BIOTRONIK

DESCRIPTION OF CHANGES/ REASON FOR SUPPLEMENT

With this PMA Supplement, BIOTRONIK requested approval to allow full body (MRI) scanning of their ProMRI ICD systems. The ProMRI ICD systems are comprised of the following BIOTRONIK legally marketed (non-MRI) devices:

The firm indicated (page 8, 12 and 13) that the Protego leads are identical to the Linox leads and that

ProMRI Compatible ICDs

Family Name	Model	Basic Description	PMA #	Approval Date
Iforia	Iforia 7 DR-T (DF-1)	Dual-chamber w/DF-1 header	P050023/S058	18-Mar-2013
	Iforia 7 DR-T (DF4)	Dual-chamber w/DF4 header		
	Iforia 7 VR-T DX (DF-1)	Single-chamber w/atrial diagnostics & DF-1 header		
Iperia	Iperia 7 DR-T (DF-1)	Dual-chamber w/DF-1 header	P050023/S079	10-Feb-2015
	Iperia 7 DR-T (DF4)	Dual-chamber w/DF4 header		
	Iperia 7 VR-T DX (DF-1)	Single-chamber w/atrial diagnostics & DF-1 header		
Inventra	Inventra 7 DR-T (DF-1)	Dual-chamber w/DF-1 header		
	Inventra 7 DR-T (DF4)	Dual-chamber w/DF4 header		
	Inventra 7 VR-T DX (DF-1)	Single-chamber w/atrial diagnostics & DF-1 header		

ProMRI Compatible Leads

Family Name	Model	PMA #	Approval Date
Pacing Leads			
Setrox	Setrox S 53	P950037/S042	14-Feb-2006
Safio	Safio S 53	P950037/S132	04-May-2014
ICD Leads			
Linox^{smart}	Linox^{smart} S 65	P980023/S043	28-Feb-2011
	Linox^{smart} SD 65/18	P980023/S038	17-Sep-2010
	Linox^{smart} S DX 65/15	P980023/S049	13-Feb-2013
	Linox^{smart} S DX 65/17		
Protego DF-1	Protego DF-1 S 65	Subject of this PMA (Protego DF-1 is an alternate trade name for Linox^{smart}; the lead families are identical.)	
	Protego DF-1 SD 65/18		
	Protego DF-1 S DX 65/15		
	Protego DF-1 S DX 65/17		
Protego	Protego S 65	P980023/S057	3-Jul-2014
	Protego S 75		
	Protego SD 65/16		
	Protego SD 65/18		
	Protego SD 75/18		

Tables 5 and 6 (page 18): Blue shaded cells indicate IPGs and leads included in Phase C of the ProMRI IDE trial.

Protego was introduced as an additional trade name for the Linox leads. The firm also indicated (page 19) that no changes to the current legally marketed ICDs or leads where necessary in order to be safe when operated under the MRI Conditions for Use (page 16 and 17).

It should be noted that the Safio S 53 lead is identical to the Setrox S 53 lead and the trade name Safio was introduced as part of the 180 day PMA supplement P950037/S132.

In addition to the above mentioned intend to label the listed ICDs and leads as MRI Conditionally Safe and the introduction of a new trade name for the Linox leads, the firm was also seeking approval for modifications to the ProMRI FBS system (section 17), minor updates to the MRI Conditions for Use (section 5.1) and an update to the programmer software (designated PSW 1503.U, section 12).

INDICATIONS FOR USE

Iforia 7 / Iperia / Inventra ICDs

The Iforia 7 / Iperia / Inventra Families of Implantable Cardioverter Defibrillators (ICDs) are intended to provide ventricular anti tachycardia pacing and ventricular defibrillation, for automated treatment of life-threatening ventricular arrhythmias. The VR-T DX ICDs are part of a system that includes both a BIOTRONIK DX ICD lead and an Iforia 7 DX / Iperia DX / Inventra DX ICD.

Linox / Protego DF-1 ICD Leads

The Linox / Protego DF-1 8F steroid-eluting, bipolar, IS-1 transvenous lead system is intended for use in the right ventricle of patients for whom implantable cardioverter defibrillators are indicated. The Linox S DX / Protego DF-1 S DX lead is indicated for use as a system that includes both the Linox S DX / Protego DF-1 S DX and a BIOTRONIK DX ICD.

Protego ICD Leads

The Protego 8F steroid-eluting, bipolar, DF4 transvenous lead system is intended for use in the right ventricle of patients for whom implantable cardioverter defibrillators are indicated.

Setrox S / Safio S Pacing Leads

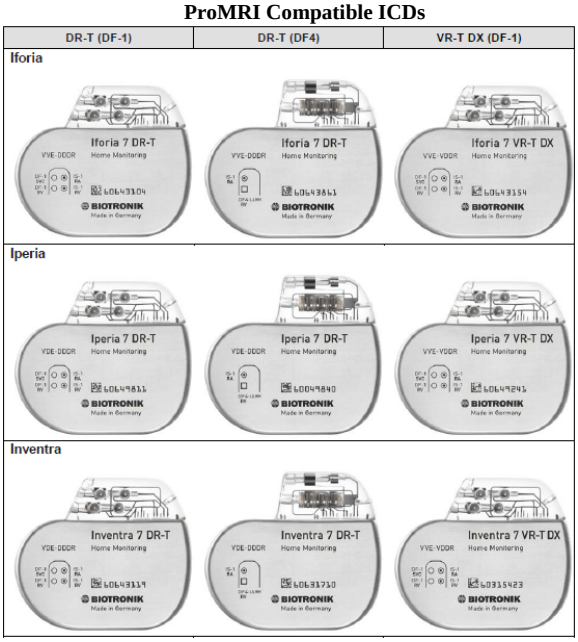
BIOTRONIK's Setrox S / Safio S transvenous, steroid-eluting, active fixation endocardial leads are indicated for permanent pacing and sensing. Active fixation pacing leads with a bipolar (BP) IS-1 connector configuration are designed for use in conjunction with implantable pulse generators with IS-1 headers. The leads may be used with single or dual chamber pacing systems, dual chamber ICDs, CRT-Ps and CRT-Ds. The Setrox S / Safio S lead models are intended for placement in either the right atrium or right ventricle.

DEVICE DESCRIPTION

PROMRI ICDS

The Iforia and Iperia / Inventra ICDs are identical to the devices included in P050023/S058 (approved March 18, 2013) and P050023/S079 (approved February 10, 2015), respectively. The only difference is in the labeling, which BIOTRONIK proposes to allow for full body MR scanning. No device changes were necessary to demonstrate the safety of the ICDs in a full body MR environment. Each ProMRI ICD family (Iforia, Iperia, and Inventra) consists of three variants: DR-T (DF-1), DR-T (DF4), and VR-T DX (DF-1).

ProMRI Compatible ICDs



- The DR-T variants provide dual-chamber rate adaptive bradycardia pacing support and use atrial and ventricular sensing/pacing leads to provide atrial and ventricular tachyarrhythmia discrimination. The two DR-T variants are identical, except for the header configuration – DF-1 vs. DF4.
- The VR-T DX variant provides ventricular rate adaptive bradycardia pacing support that can include atrial tracking with a single-pass ICD lead. The DX system uses a BIOTRONIK DX lead with two atrial sensing electrodes to provide enhanced atrial and ventricular tachyarrhythmia discrimination.

The Inventra ICDs have a maximum shock energy of 45 Joules, while the Iforia and Itrevia variants have a maximum shock energy of 40 Joules.

The ProMRI ICD system can be interrogated with one of BIOTRONIK's programmers, either the ICS 3000 (P950037/S035, dated May 18, 2005) or the Renamic (P950037/S089, dated April 15, 2011).

The ProMRI ICDs are Home Monitoring models and will be utilized with BIOTRONIK's currently approved CardioMessenger II and CardioMessenger II-S patient devices (P050023/S007, dated November 9, 2007 and P050023/S016, dated December 1, 2008) as well as the Home Monitoring Service Center (P950037/S066, dated November 21, 2008 and P950037/S137, dated November 17, 2014).

PROMRI LEADS

Leads included in the ProMRI ICD systems are shown in Table 6 (page 8) and again in Table 7 (page 48) and are indicated via a blue shading of the table entry.

All of the pacing leads (Setrox S, Safio S) that are part of the ProMRI system are active-fixation, transvenous, bipolar, endocardial leads designed for permanent atrial or ventricular stimulation and sensing. The inner and outer conductors consist of

Table 7: Protego DF-1 and Linox^{smart} Lead Model Designations[6]

Lead Type	Equivalent Protego DF-1 Lead Name (subject of this submission)	Protego DF-1 Order #s	Linox^{smart} Lead Name (approved)	PMA Supplement	FDA Approval Date
Active fixation, single coil	Protego DF-1 S 60	414018	Linox^{smart} S 60	P980023/S043	28-Feb-2011
	Protego DF-1 S 65	414028, 414062	Linox^{smart} S 65		
	Protego DF-1 S 75	414030	Linox^{smart} S 75		
Passive fixation, single coil	Protego DF-1 T 65	414056	Linox^{smart} T 65		
Active fixation, dual coil	Protego DF-1 SD 60/16	414014	Linox^{smart} SD 60/16	P980023/S038	17-Sep-2010
	Protego DF-1 SD 65/16	414015	Linox^{smart} SD 65/16		
	Protego DF-1 SD 65/18	414059; 414016	Linox^{smart} SD 65/18		
	Protego DF-1 SD 75/18	414017	Linox^{smart} SD 75/18		
Passive fixation, dual coil	Protego DF-1 TD 65/16	414033	Linox^{smart} TD 65/16		
	Protego DF-1 TD 65/18	414054	Linox^{smart} TD 65/18		
	Protego DF-1 TD 75/18	414055	Linox^{smart} TD 75/18		
Active fixation, single coil w/atrial sensing	Protego DF-1 S DX 65/15	414064; 414031	Linox^{smart} S DX 65/15	P980023/S049	13-Feb-2013
	Protego DF-1 S DX 65/17	414065; 414032	Linox^{smart} S DX 65/17		

Leads identified in blue are part of the ProMRI ICD system.
See also Table 5 and 6 above for cross reference.

quadruple wire coils.

The Setrox/Safio leads are fixated using an electrically active, extendable/retractable fixation helix. Helix extension is accomplished by turning the connector pin with a fixation tool. The lead is insulated with silicone and has an IS-1 connector. The lead tip is equipped with a steroid collar containing 0.75mg dexamethasone acetate (DXA) in order to reduce potential tissue inflammation effects from the screw-in procedure. The active fixation helix has an active surface area of 4.5 mm^2. The lead has an isodiametric design with a diameter of 6.6 F, which allows the usage of a 7 F introducer. A picture of the Setrox S lead is provided in Figure 7. The Setrox S lead was approved on February 14, 2006 with P950037/S042 and has been legally marketed and commercially available in the US since that time. Safio S was approved as an alternate trade name for the Setrox S ProMRI leads on May 4, 2014 through P950037/S132. The Setrox S and Safio S leads are identical; the only difference is in the trade name and the associated labeling. Therefore, the Setrox S data is applicable to the Safio S leads.

Figure 10: Linox^{smart} S DX Lead

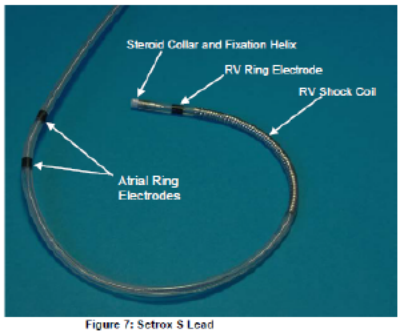
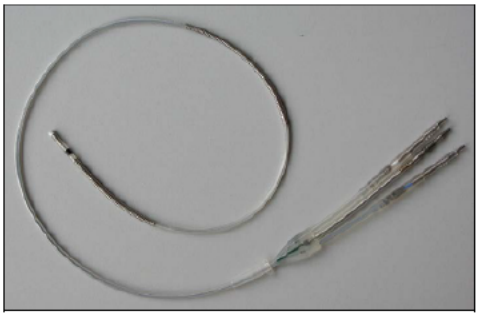


Figure 8: Linox^{smart} S Lead

Figure 7: Setrox S Lead

Figure 9: Linox^{smart} SD Lead



BIOTRONIK's legally marketed single- and dual-coil Linox (S/SD) and Protego (S/SD) ICD leads referenced in Table 6 are included in the ProMRI ICD system. The Linox and Protego ICD leads are active fixation, steroid-eluting leads for use with implantable cardioverter defibrillators (ICDs). The Linox and Protego leads, which are described below, are identical with the exception of the lead connector – Protego leads utilize a DF4 connector in place of separate DF-1 and IS-1 connectors on the Linox leads. The Linox S has one IS-1 bipolar sensing and pacing lead connector and one DF-1 defibrillation lead connector. The Linox SD has one IS-1 bipolar sensing and pacing lead connector and two DF-1 defibrillation lead connectors. The Linox S and Protego S leads are available in two lengths (65 and 75 cm) and have a single RV shock coil designed to be located in the right ventricle (RV), a ring electrode, and a helix electrode. The helix (the active pacing electrode) of both the Linox S and Protego S leads are identical and also identical to that of the Setrox S lead helix. A picture of the Linox S lead is provided in Figure 8. The Linox SD and Protego SD leads have two ventricular sensing / pacing electrodes (tip and ring) and two defibrillation / cardioversion shock coils designed to be located in the apex of the right ventricle (RV) and in the superior vena cava (SVC). The Linox SD and Protego SD leads are available in two lengths (65 and 75 cm) with a distance of 18 cm between the proximal coil and the tip electrode. The tip of Linox SD and Protego SD leads, including the helix (the active pacing electrode), is identical to the Linox S and Protego S leads. In addition, the RV shock coil of Linox SD and Protego SD leads is identical to the shock coil of the Linox S and Protego S leads. A picture of the Linox SD lead is provided in Figure 9. The Linox (S/SD) and Protego (S/SD) ICD leads include a steroid-eluting collar at the distal end, which elutes dexamethasone acetate (DXA) to the surrounding tissue after implantation. This steroid collar nominally contain (b) (4) [redacted]).

BIOTRONIK's legally marketed Linox S DX ICD leads (P980023/S049, approved February 13, 2013) are included in the ProMRI ICD system. The Linox S DX is a single-pass, active fixation, steroid-eluting, pentapolar ICD lead with two floating ring electrodes (dipole) in the atrium for sensing. When used with a

BIOTRONIK DX single-lead ICD system, the Linox S DX leads provides atrial and ventricular sensing, as well as ventricular rate adaptive bradycardia pacing and defibrillation shocks.

The Linox S DX ICD lead has two sensing/pacing electrodes (tip and ring), two floating atrial sensing electrodes, and one defibrillation and cardioversion shock coil, all of which are contained in a single lead. The tip and ring electrodes form the most distal portion of the lead and provide dedicated bipolar sensing and pacing in the right ventricle. The shock electrode is positioned in the right ventricle. Bipolar sensing in the atrium is possible by means of two floating ring electrodes. The lead utilizes an extendable/retractable fixation helix, which is identical to that utilized in the Setrox S, Linox S / SD, and Protego leads. The extendable/retractable fixation helix, which is controlled by an external fixation tool, is comprised of a (b) (4) proximal IS-1 connector pin with an external fixation tool extends or retracts the fixation helix. The ring electrode is composed of (b) (4) surface structure. The right ventricular shock coil has a flat wire profile and is made of a (b) (4) band with a tantalum core. The Linox S DX has one DF-1 defibrillation lead connector and two IS-1 bipolar sensing and pacing lead connectors. The Linox S DX includes a steroid-eluting collar at the distal end, which elutes (b) (4) (DXA) to the surrounding tissue after implantation. This steroid collar nominally contains (b) (4) is prepared with a carrier of (b) (4) (b) . The Linox S DX lead is available in one length of 65 cm and with two different distances between the center of the two floating ring electrodes and the tip (15 cm and 17 cm). A picture of the Linox S DX lead is provided in Figure 9.

With this PMA Supplement application, "Protego DF-1" is introduced as an additional trade name for the Linox leads. Table 7 includes the Protego DF-1 lead model designations and the corresponding Linox lead names. This change applies to all currently approved Linox leads (both active and passive). However, only the Linox and Protego DF-1 leads are part of the ProMRI ICD system. The Protego DF-1 leads are identical in design as compared to the corresponding Linox leads. The only differences are the accessories with which the leads are packaged.

- The Protego DF-1 leads are packaged with white suture sleeves (P980023/S060, approved September 16, 2014) mounted onto the lead. The white suture sleeves are currently approved as separately available accessories, and Linox leads are currently packaged with clear suture sleeves mounted onto the lead.
- The Protego DF-1 leads are packaged with one of each stylet type, whereas the Linox is packaged with two of each stylet type.

PROGRAMMER SOFTWARE

The ProMRI system also includes the programmer software (PSW 1503.U) for interrogation and programming of all BIOTRONIK devices, including ProMRI ICDs. The PSW 1503.U programmer software, which is based on PSW 1501.U (P950037/S148, approved April 9, 2015), is used to program the ProMRI ICDs to the "MRI Mode" before performing an MR scan, which sets the device to predetermined settings that are considered safe to use during an MR procedure. Programming of the MRI Mode is the same as compared to PSW 1501.U.

The PSW 1503.U programmer software supports the programmability of the ProMRI ICD system and the device programming necessary prior to an MR scan. Before an MR scan is performed, the medical professional must program the ProMRI ICD to "MRI Mode" that will automatically set the device to predetermined settings that are considered safe to use during an MR procedure. Programming of the MRI Mode is the same as compared to the current legally marketed PSW 1501.U programmer software. Additionally, the parameters set in the MRI Mode are identical in the ProMRI ICDs and ProMRI pacemakers, with the following two exceptions:

- Pulse amplitude: 5.0V for ICDs; 4.8V for pacemakers
- ICD therapy: Deactivated for ICDs; N/A for pacemakers
- Programming of an MRI System flag (indication whether the patient has an MRI system) on the patient data screen is no longer possible.

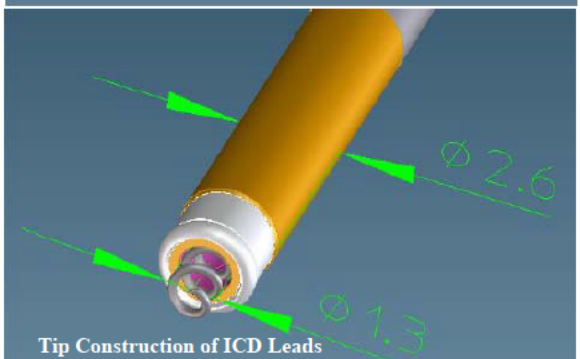
PRECLINICAL/BENCH

The firm did not modify the predecessor devices, non MRI IPGs and leads, in order to obtain MRI Conditionally Safe labeling, i.e., the submission is essentially an request to re-label market released devices and leads as MRI Conditionally Safe. Manufacturing processes, including packaging, sterilization, as well as quality control procedures and manufacturing sites are not changed as a result of this submission. Consequently, these areas did not require a review and were addressed via equivalence to the predecessor devices. Similarly, biocompatibility, electrical safety / EMC, with the exception of exposure to the MRI environment, as well as mechanical safety / performance did not have to be re-tested and were addressed via equivalency with the predecessor devices.

ANIMAL STUDIES

BIOTRONIK proposed the use of the results from the initial Entovis (pacemaker) ProMRI animal study submitted with the Original IDE G120226 and with IDE Supplement G120226/S012 for the Iforia ICD system with full body scan to support this PMA Supplement for the ProMRI FBS ICD system. The firm asserted that the it is appropriate to use the results from the Entovis ProMRI animal study, because the Setrox leads used in that study and all of the leads included in this submission have the exact same helix electrode, and the goal of the animal study was to demonstrate how much power can be safely dissipated by the helix electrode without damaging tissue.

Tip Construction of Pacing Leads
Setrox S



Tip Construction of ICD Leads
Linoxsmart, Protego DF-1 & Protego

Reviewer's Comments

Even though the helix is identical (see figure 3), the tip diameter is not. A larger or smaller diameter of the tip in the immediate vicinity of the helix potentially impacts the ability to dissipate thermal energy into the surrounding tissue. It is not clear if this change will increase or decrease the tissue temperature and therefore the potential degree of damage to the tissue near the helix. The firm should provide some data, maybe temperature profiles obtained from simulations, to show that the nearly 15 percent change in diameter has no substantial impact on the temperature rise near the helix. This is important since the ICD leads seem to be depositing higher amounts of power than the Setrox S 53 lead. The reviewers concern was expressed in Deficiency 1 of FDA's Major Deficiency Letter dated July 15, 2015:

FDA Deficiency 1

(b) (4)

[redacted]

(b) (4)

[redacted]

SOFTWARE/FIRMWARE

The firm indicates on page 100 that there are no changes to the IPG firmware. The IPG programmer is being updated to version PSW 1503.U.

PSW 1503.U is based on programmer software version 1501.U (P950037/S148, approved April 9, 2015). PSW 1503.U is similar to the programmer software currently utilized in the ProMRI IDE study (PSW 1303.U). The 1503.U programmer software implemented the following:

- Configure Iforia, Iperia, and Inventra ICD applications as MRI devices.

- Support interrogation/programming of the Itrevia/Iperia/Inventra HF-T QP ICD device models (P050023/S085, approved June 19, 2015) and associated LV pacing/sensing parameters.
- Global Programmer Component Updates.
  - IRSplus renamed as I-Opt: ON (nominal setting)
  - The UDI for PSW 1503.U is: (01)04035479150211 and will be shown on the hardware label of the PSW.
- Pacemaker Application Updates
  - New battery measurement for Philos II and Cylos (50% pacing for the first 4 months):OFF
  - EASY AV delay is not available (Entovis)
  - MRI attribute is no longer located on the Bradycardia => Patient menu.

The PSW 1503.U programmer software will be used with the Renamic and ICS 3000 programmers for interrogation and programming of all currently distributed BIOTRONIK devices approved under P050023, P950037, P000009, and P070008 (for details see Table 33 on page 103 and 104).

The software and firmware changes were reviewed according to the "Guidance for Industry and FDA Staff -Guidance for the Content of Premarket Submissions for Software Contained in Medical Device, May 11 2005". The results of the review are summarized in the table below. Green indicates that the guidance was followed and the reviewer agrees with the firm, yellow indicates some deviation and potential need for additional information and red indicates missing information and a potential deficiency. The table summarizes the review, i.e., a deviation may be either creates by the software or the firmware aspect of the submission.

SOFTWARE DOCUMENTATION	MINOR CONCERN	MODERATE CONCERN	MAJOR CONCERN
Level of Concern	A statement indicating the Level of Concern and a description of the rationale for that level.		
Software Description	A summary overview of the features and software operating environment.		
Device Hazard Analysis	Tabular description of identified hardware and software hazards, including severity assessment and mitigations.		
Software Requirements Specification (SRS)	Summary of functional requirements from SRS.	The complete SRS document.	
Architecture Design Chart	No documentation is necessary in the submission.	Detailed depiction of functional units and software modules. May include state diagrams as well as flow charts.	
Software Design Specification (SDS)	No documentation is necessary in the submission.	Software design specification document.	
Traceability Analysis	Traceability among requirements, specifications, identified hazards and mitigations, and Verification and Validation testing.		
Software Development Environment Description	No documentation is necessary in the submission.	Summary of software life cycle development plan, including a summary of the configuration management and maintenance activities.	Summary of software life cycle development plan. Annotated list of control documents generated during development process. Include the configuration management and maintenance plan documents.
Verification and Validation Documentation	Software functional test plan, pass / fail criteria, and results.	Description of V&V activities at the unit, integration, and system level. System level test protocol, including pass/fail criteria, and tests results.	Description of V&V activities at the unit, integration, and system level. Unit, integration and system level test protocols,

			including pass/fail criteria, test report, summary, and tests results.
Revision Level History	Revision history log, including release version number and date.		
Unresolved Anomalies (Bugs or Defects)	No documentation is necessary in the submission.	List of remaining software anomalies, annotated with an explanation of the impact on safety or effectiveness, including operator usage and human factors.	

Level of Concern: The updated software was determined to be of Major Level of Concern since the programmer and programmer software are accessories to a medical device that has a Major Level of Concern. Both control the delivery of therapy such that an error or malfunction could result in death or serious injury.

Software Description: A detailed description of the software is provided in section 12.2 of the submission.

Device Hazard Analysis: A brief description of the device Hazard Analysis is provided in Section 12.3 of the submission. This section links back to Table 32, which list various Risk Analysis Documents provided as Appendices to the submission. A review of these Appendices (2, 82, 83 and 84) showed that a sufficient Hazard Analysis was performed.

Software Requirement Specifications: Software requirement specifications were provided in Appendices 85 and 86 of the submission and are sufficient.

Architecture Design Chart: The firm indicates on page 105 (section 12.5) that the software architecture is the same as that of previously approved software version(s). Regardless of this fact, the firm provided software architecture documentation in Appendix 81, 87, 88 and 89.

Software Design Specification (SDS): The software design specifications are summarized in BIOTRONIK's software detailed design documents (SDD). All software design specifications that were used in the development of PSW 1503.U are listed in DSP-138-041, which is provided in Appendix 81. The firm states that detailed design documents (SDD) are available upon request. The firm should be asked to provide the documents (Deficiency 2).

FDA Deficiency 2
You indicated that software design specifications are summarized in your software detailed design documents (SDD). All software design specifications that were used in the development of PSW 1503.U are listed in DSP-138-041, which is provided in Appendix 81. In Appendix 81, you stated that detailed design documents (SDD) are available upon request. Please provide these documents for review.

Firm's Response
The relevant software detailed design specifications (SDD) from DSP-138-041 are those pertaining to Iforia, Iperia, and Inventra. These SDD documents are listed in Table 3 (A001) and are provided in the referenced appendix.

Review of the Firm's Response
Table 3 (A001) provided list of the SDD documents; the documents were provided in Appendix 3-19 (A001) and were reviewed. The documents provided were sufficient to address the noted deficiency and no further information is required.

Traceability Analysis: A traceability analysis for the software is provided in Appendix 83 and 84 and is sufficient.

Software Development Environment Description: The programmer software Development Environment Descriptions is provided in section 12.8 and is sufficient.

Revision Level History: Programmer revision history is provided on page 111. Software revisions generated during the course of product development are documented in Appendix 92. Revision History has been reviewed and is sufficient.

Unresolved Anomalies (Bugs or Defects): The firm provided the Table 36 of known anomalies for PSW 1503.U. The firm indicates that these are the same anomalies that were reported, and accepted by FDA, as part of the previous software revision 1501.U. Consequently, since no additional adverse information has surfaced, the unresolved anomaly is acceptable.

Table 36: List of New Known Anomalies for PSW 1503.U

Issue ID	Summary	Consequences and Justification for Acceptance	Concerned Items	Significance
587161	Pace Impedance Measurement in AAI mode does not provide valid measurement results if ventricular events are absent	Diagnostic Data Issue (Interrogation, Display, Printout): Display/printout of missing diagnostic information may impede diagnosis Justification Of Acceptance Behavior accepted as is due to acceptable residual risk resulting from medium severity and low probability of occurrence. Product safety and performance are only insignificantly affected.	ICS_Programmer Application TachNXT, Tach70	low

Verification and Validation Documentation: Summaries of the validation testing for PSW 1503.U are provided in Table 35. The firm indicates that the PSW 1503.U programmer software has passed all in-vitro laboratory validation tests, and all test reports may be found in the referenced appendices. Each test report details the testing performed, equipment used, specification(s) followed and the actual test results. The individual Appendices were reviewed and found sufficient to address verification and validation testing.

Table 35: Summary of Validation Testing for PSW 1503.U

#	Test	Test Conditions/Specifications	Test Report
1.	Automatic Tests	(b) (4)	
2.	Release comparison PSW 1503.U		
3.	Identification & Analysis of the product media – 1503.U		
4.	Software Configuration Test – 1503.U		
5.	AIMDD 90-385-EEC - Active Implantable Medical Devices Directive – 1503.U		
6.	Check of Unique Identifier - Labeling and GUI – 1503.U		
7.	Installation and Labeling Check (UDI-Code, US) - 1503.U		

MRI SPECIFIC REVIEW

The firm indicates that MRI specific testing was performed on the IPGs, leads and IPG/Lead systems following the ISO 10974:2012 (E) Technical Specification addressing the following potential hazards:

Table 21: Potential Patient Hazards and Corresponding Test Requirements		
General Hazards to the Patient	**Test Requirement**	**Clause**
Heat	RF field-induced heating of the AIMD	10
	Gradient field-induced device heating	11
Vibration	Gradient field-induced vibration	12
Force	B_0-induced force	13
Torque	B_0-induced torque	14
Extrinsic electric potential	Gradient field-induced lead voltage	16
Rectification	RF field-induced rectified lead voltage	17
Malfunction	B_0 field-induced device malfunction	18
	RF field-induced device malfunction	19
	Gradient field-induced device malfunction[a]	20
[a] Device malfunction due to eddy current heating of internal components is covered in Clause 11. Device malfunction due to vibration of internal components is covered in Clause 12.		

Given the complexity of RF induced heating, it will be reviewed last.

Gradient field-induced device heating

The firm provides test methods in Appendix 14 (pre and post electrical testing of the device) and Appendix 26 (gradient field induced temperature rise). Test exposure limits were established in GTR-12-0279-B and can be found in Appendix A of Appendix 49 in G120226/S010.

The maximum dB/dt established in the referenced document appears to be reasonable and is comparable to values used by other manufacturers. The firm also establishes a maximum exposure time of 80 seconds based o a conservative estimate of number of slices, resolution, etc. The firm does however not account for back to back scanning. It is not clear to the reviewer what impact this might have on the actual exposure time, i.e., is the 80 seconds quoted by the firm conservative or an under estimate? Furthermore, as can be seen from the figure to the right, the temperature rise on the surface of the device (here an Evia Pacemaker, graph from GTR-12-0279-B) is very rapid and has not stabilized. Therefore, small changes in exposure time could result in relatively large changes in temperature. The firm did not provide an equivalent time temperature graph for the ICD but only provides the temperature measurement after 80 seconds; which is reported to be 2.25 °C, including uncertainty. The maximum temperature reported for the pacemaker was 1.62 °C, including uncertainty. The numbers confirm that ICDs are predicted to heat more than pacemakers (see ISO 10974 page 28) due to the larger surface area. Even though the temperature increases are likely to be below a tissue damage threshold the may reach the on-set of "warming sensation" and less likely pain; the onset off both is a function of temperature and exposed area. In the opinion of the reviewer, labeling may be required to inform the patient of this possibility.

(b) (4)

Gradient induced vibration-Device Malfunction / Tissue Injury

The firm provides test methods in Appendix 14 (pre and post electrical testing of the device) and Appendix 29 (vibration induced via shaker table). The firm indicated that the test limits were established via TSP 461-200 (Appendix 32); which closely follows the methodology outlined in the ISO 10974 Technical Specification. The accepted limit of 10 g is argued for based on the referenced paper by Allen ["Acceleration perturbations of daily living. A comparison to 'whiplash'". Spine (Philadelphia, Pa. 1976) (0362-2436), 19 (11), p. 1285. PMID: 8073323]. The paper fundamentally discusses single, relatively short term events and it is not clear how it would apply to the nearly periodic vibration experienced during an MRI scan. The maximum vibration

force measured was 7.4 times the gravitational force. It should be noted that the maximum vibration force on the Entovis pacemaker was 9.6 times the gravitational force. However, since ICDs are substantially heavier than the pacemakers the force on the ICD is greater. Based on the information provided, it is not clear to the reviewer what the potential risk to the patient is. Other companies have used similar criteria and the Joint Working Group for the Technical Specification 10974 does not consider gradient field induced vibrations a significant issue. Given the lack of information on this topic, the reviewer is of the opinion that the labeling should contain some information about potential discomfort due to device vibrations.

B0 Induced Force

The firm indicates that the test was performed according to ISO/TS 10974: 2012 (E) §13. The quoted paragraph generically points to ASTM F2052 but does not specify the revision level. Based on images shown in Appendix 33, the test method as described in ASTM F2052 – 14 was utilized. The firm did measure the maximum magnetically induced force and results are summarized in Table 1 of Appendix 33. Even though the forces measured are less than the self-imposed 1 N, the limit is not rationalized. Furthermore, the force is measured along the center line of the bore. It is known that this is not the location of the maximum force on the device accessible to the patient. ASTM F2052 – 14 (pages 6 and 7) states that the maximum force on non-saturated materials is proportional to the product of magnetic field and magnetic field gradient. It furthermore indicates that the force on saturated materials is proportional to the magnetic field gradient. The standard provides typical values for 1.5 T system to be 19 T/m (field gradient) and $41T^2/m$ (field x field gradient). The firm should provide force estimates for devices exposure at these values (whichever is higher) and provide a rationale why these forces will not cause injury.

B0 Induced Torque

The firm indicates that the torque measurements were performed according to ISO/TS 10974: 2012 (E) §14 and ASTM F2052. The Test Specification generically points ASTM F2213 not F2052. The pass fail criterion is based on a combination of the 1 N force multiplied by the devices maximum dimension of 0.064 m. It should be noted that the device weight appear to be between 81 and 85 gram (see Table 1, Appendix 33). This would result in a weight times length product of 0.005184 to 0.00544 Nm. This would place the magnetically induced torque reported in Table 1 of Appendix 35 at the limit of the gravitational torque. Even though these values are acceptable and no further information is required, it might be useful to remind the firm that information could be presented in an easier format.

Gradient Induced Extrinsic Potential

The firm states that the test was performed according to ISO/TS 10974: 2012 (E) §16 Annex T, EN 45502-2-1:2003, and EN 45502-2-2:2008. The test methods are provided in TSP-461-196 (Appendix 39). The text in section 7.2 of the Appendix indicates an error. A new document without this error should be submitted. The test results presented in Appendix 37 and 38 indicated that there is no risk of unwanted cardiac stimulation.

B0 Field- Induced Device Malfunction

The test was conducted by placing Iforia devices in DOO pacing mode in a 1.5 T MRI scanner for at least one hour in each of the three orthogonal orientations. Pre and post device functional testing was conducted via TSP-111-042(Appendix 14). The devices passed required tests. Documentation provided is sufficient.

RF Field- Induced Device Malfunction and Rectification

The firm indicated that the test was conducted in order to determine the relationship between the RF field strength and the voltages that may be induced in the leads that will return to the ICD. The new tier 3 approach (from ISO 10974 Draft 2nd Edition), similar to RF lead heating approach, was used. A Local Element Model for the Reverse Transfer Function model (energy injection from the lead into the device) was generated and used with the human body models and trajectories to determine the 95th percentile worst case induced voltage, which was used for injection. The firm provided a test method description in TSP-461-202 (Appendix 45). Test limits were derived using the methodology presented TSP-461-201 (Appendix 16). This appendix briefly outlines the various parameters used in the electric field simulations but does not discuss the lead transfer function. The “reverse lead transfer functions” are discussed in detail in

appendices to Appendix 42. Even though the methodology used by the firm is not the traditional method seen by other manufacturers, the firm has provided a substantial amount of validation data. At this point in time, the reviewer has not been able to identify any flaws with the methodology and given the validation data presented will accept the test results as sufficient. The firm should however be asked if fluid ingress has any impact on the transfer function.

Gradient Injected Immunity
The firm indicates that the test was performed according to ISO 10974 Technical Specification. Detailed test methods were provided in Appendix 48 and result were provided in Appendix 46 and 47. The method and results are acceptable.

Gradient Radiated Immunity
The firm indicates that the test was performed according to ISO/TS 10974: 2012 (E) §20.3, IEC 60601-2-33, EN 45502-2-1:2003, and ANSI/AAMI PC69: 2007. The test methods are provided in Appendix 51 and results are presented in Appendix 49 and 50. The method and results are acceptable.

Image Artifact
The firm indicates that the test was performed according to ISO/TS 10974: 2012 (E) §15, ASTM F2119-07: 2013, and ASTM F2182-11a. Details of the test method are provided in Appendix 54 and results are presented in Appendix 52 and 53. The method and results are acceptable.
In addition to the ISO 10974 evaluation, the firm also incorporated image evaluation as part of the clinical study and reports the results on pages 1295-1297 of this submission. The report indicates that image artifacts are not an issue and are well recognized by the radiologists.

Combined Fields
The firm indicates that the test was performed according to ISO/TS 10974: 2012 (E) §21. The Technical Specification only provides a generic statement that combined testing should be performed. The firm references VTD-111-1130 as the test methodology document in Appendix 55-57 but did not provide the referenced document. The firm should be asked to provide the document in order to fully evaluate the combined field test results.

RF Induced Heating near the Implant
The firm indicates that testing (including simulations) was performed utilizing the methodologies outlined in Appendix 16, 20-23 with results presented in Appendix 17-19. The following was noted during the review of the cited Appendices:

1. Appendix 16 "Numerical Evaluation of MRI Induced RF Energy of AIMD Lead and Device in Human Body". The Appendix essentially presents the electromagnetic field calculation methodology used with various body types, positions in the birdcage coil, etc. It is noted that the firm expanded the set of body coils from 1 to 5, a positive change. The transmit coils in MR systems have an RF shield, the dimensions of these shields are not provided. The firm should be asked to do so. The firm also needs to confirm if the simulations were performed using shielded coils or not. Furthermore, the firm indicates on page 37 that the elliptical scanners are acceptable, yet only circular body coils have been modeled. The electromagnetic field distribution is expected to be different for circular vs. elliptical body transmit coils. The firm should provide data to support the elliptical scanner claim. It is clear from Figure 3 b of Appendix 16 that the E-field of a highpass birdcage coil is different from that of a lowpass birdcage coil. In the latter, the electric field is stronger in towards z=0. One may want to ask the firm if low pass birdcage coils should be included in the simulation.
2. The firm measures the input impedance as a function of header / device platform in Appendix 17. This measurement is critical to extent the simulation results from a limited number of transfer functions to the full set of devices submitted. Based on the review of the data submitted, the reviewer accepts the equivalence of the transfer functions. The firm should be asked to submit the validation data.
3. Appendix 18 reports the predicted power dissipation at the helix of the Linox^{Smart} S65, Linox^{Smart} SD65/18 and Setrox S53 leads when utilized with the Iforia 7 DR-T IPG. Utilizing only one version of IPG is acceptable as shown in Appendix 17. The firm indicates that the lead transfer functions were validated in the report "IT'IS 457&485

Technical Report: "(b) (4)
The reviewer was not able to locate the report in the submission. The firm also provided the fluid filled transfer functions for the indicated leads. However, it is not clear from the Appendix if the fluid filled transfer functions were validated or not. (b) (4)

Labeling – MRI Specific

ProMRI System (Technical) Manual

All the information, required to perform the MRI scan safely is provided within the manual. However, the lead reviewer beliefs that flow of the manual is sub-optimal considering that the workflow requires the ICD system to be place into an MRI mode prior to the MR scan and needs to be manually re-programmed to pre-MRI parameters once the scan has been performed. The need to do so is indicated but there is a sense of not having emphasized this point strongly enough. The workflow probably should be part of a Post Approval Study to monitor adherence to the workflow under lesser control than found in an IDE clinical trial.

Note that page 3555 (page 7 of the manual) allows cylindrical as well as elliptical bore scanners. As previously noted, the electromagnetic field in elliptical bore scanners is different from that of the cylindrical bore scanners. No data have been provided for ellipitcal scanners.

ProMRI Patient ID Cards

The ID cards appear to have sufficient information to ensure that technologist performing the MRI scan since they are directed towards the firm's website www.biotronikusa.com/promri. The website has the technical manual available for download.

ProMRI Checklist and Quick Reference Guide

The MRI conditions shown on page 3627 are not consistent with the once shown on page 3555, i.e., in the latter elliptical scanners are permitted whereas here they are not. In addition, the reviewer has the same sense with respect to workflow as expressed in the comments about the ProMRI System (Technical) Manual. The need to program into and out of the MRI mode seems "drown" in the quantity of information provided.

Iforia, Iperia, Iventra, Protego and Linox Technical Manual

Each of the manuals identifies the IPG/leads as MRI conditional and appropriately points towards the firm's website www.biotronikusa.com/promri for additional information regarding the MRI conditions of use. The manuals appear to be sufficient.

ProMRI Device Box Label
Reviewer did not see a reference to the company's website (www.biotronikusa.com/promri) and would suggest adding it to the labeling.

Summary of the MRI Specific Review

The firm has provided substantial documentation towards the safety and effectiveness of their device when used in an MRI environment as outlined in their MRI Conditions for Use. A detailed review has however raised several questions as well as suggestions for the firm that should be addressed prior to approval of the system.

1 (b) (4)

FDA Deficiency 3

(b) (4)

Firm's Response

The time-temperature curve is provided in (b) (4) test condition represents the worst case.

(b) (4)

This worst-case condition for gradient induced heating was evaluated using manufacturer provided data for representative MRI scanners, analysis of clinically used MRI pulse sequences and limits set by IEC 60601-2-33. Details for this analysis are included in GTR-12-0279-B, which was provided in Appendix 39 of P950037/S142 and is also re-submitted as Appendix 20 for FDA's convenience.

The following section was added to the ProMRI System manual (Appendix 21) to advise the MR technicians to monitor patients during an MR scan and provide recommended actions in case of potential warming during an MRI.

"4.2.3 Patient monitoring during the MR scan The patient should be continuously monitored during the entire MR scan, including maintaining visual and verbal contact with the patient and monitoring of blood oxygen saturation, blood pressure or ECG. Emergency equipment for resuscitation must be kept at hand and properly certified staff must be available.

If the patient exhibits signs of discomfort (i.e., warming is noted) or hemodynamic function appears to be compromised at any point during the scan, discontinue the scan and remove the patient from the MRI scanner."

Review of Firm's Response
The firm provided the requested graph and additional information justifying the (b) test time. Given the fact that one could double the test time and the hot spot still would remain under the (b) limit addresses this deficiency. The firm also added the requested statement to the manual; again, the deficiency has been addressed sufficiently.

2. The firm established test limits for the gradient field induced IPG vibrations in Appendix 32 of this submission and provided the paper by Allen ["Acceleration perturbations of daily living. A comparison to 'whiplash'". Spine (Philadelphia, Pa. 1976) (0362-2436), 19 (11), p. 1285. PMID: 8073323] as a rationale. The paper fundamentally discusses single, relatively short term events and it is not clear how it would apply to the nearly periodic vibration experienced during an MRI scan. Even though FDA agrees with the firm that tissue damage caused by device vibrations during the MRI examination is unlikely the firm is encouraged to provide additional rationale for the test limits. Furthermore, the firm is encouraged to add a note to their labeling (for example the ProMRI Technical Manual) to raise awareness of potential discomfort.

FDA Deficiency 12
You established test limits for the gradient field induced IPG vibrations in Appendix 32 of this submission and provided the paper by Allen ["Acceleration perturbations of daily living. A comparison to 'whiplash'". Spine (Philadelphia, Pa. 1976) (0362-2436), 19 (11), p. 1285. PMID: 8073323] as a rationale. The paper fundamentally discusses single, relatively short term events and it is not clear how it would apply to the nearly periodic vibration experienced during an MRI scan. Please provide a rationale for your vibration levels other than the paper by Allen or a rationale why the paper should apply. Furthermore, a note to the labeling (for example in the ProMRI Technical Manual) should be added to raise awareness of potential discomfort.

Firm's Response
BIOTRONIK agrees that the short term limit discussed in the Allen paper is not a perfect fit with the nearly periodic vibrations experienced during an MRI scan. However, this is the only publication discovered addressing vibration limits for vibration-induced damage of tissue.

Note that it is planned to remove this test from the upcoming 2nd edition of ISO 10974, which is currently in draft and is scheduled to be published in early 2016. It was removed because the subject matter experts on the ISO 10974 committee do not believe that vibration-induced tissue damage from an AIMD is a risk in actual clinical situations.

Additionally, the vibration measurements were on the order of (b), with the worst case of (b) including uncertainty. These test results are significantly below the limit of (b) Therefore, BIOTRONIK believes that the results are adequate to support approval of the proposed MRI conditional systems.

Furthermore, the following section was added to the ProMRI System manual (Appendix 21) to raise awareness of potential discomfort.

"4.2.3 Patient monitoring during the MR scan The patient should be continuously monitored during the entire MR scan, including maintaining visual and verbal contact with the patient and monitoring of blood oxygen saturation, blood pressure or ECG. Emergency equipment for resuscitation must be kept at hand and properly certified staff must be available.

If the patient exhibits signs of discomfort (i.e., warming is noted) or hemodynamic function appears to be compromised at any point during the scan, discontinue the scan and remove the patient from the MRI scanner."

Review of Firm's Response

The reviewer is aware of the ISO/TS 10974 Joint Working Group's decision to remove the vibration test with regards to patient discomfort and has accepted similar arguments from other sponsors. The firm's response is therefore sufficient.

(b) (4)

environment. ASTM F2052–14 indicates that typical values for the field gradient and the field / field gradient product for 1.5 T MRI systems are 19 T/m and 41 T^2/m, respectively. The firm should provide a rationale why it is safe to exposure the patient to these field values or should provide limits for which it is safe. In the latter scenario the labeling should be amended.

FDA Deficiency 4

You provided test data concerning the magnetically induced force on IPGs. (b) (4) ASTM F2052–14 indicates that typical values for the field gradient and the field / field gradient product for 1.5 T MRI systems are 19 T/m and 41 T2/m, respectively. You should provide a rationale for why it is safe to expose the patient to these field values or should provide limits for which fields it is safe to expose patients to. In the latter scenario the labeling should be amended.

Firm's Response

The main source of force on Ilesto ICDs results from the ferromagnetic materials that are used on the ICD charging inductor as well as nickel plating of component terminals. All of these materials have magnetic saturation points that are well below (b) For this reason, the force is linearly proportional to the spatial gradient of the static magnetic field. Furthermore, in saturation, the field / field gradient product does not contribute to force. More details are included in GTR-14-0381-0A, which was provided in Appendix 24 of P950037/S142 and is also re-submitted as Appendix 22 for FDA's convenience. Although GTR-14-0381-0A addresses pacemakers, the same principles also apply to ICDs.

The force test was performed at (b). According to ASTM F2052-14, the worst-case spatial gradient on a (b) scanner is (b) (4) The location of this uncommonly high spatial gradient is at the magnet cover of GE Optima MR450W (b) scanners, to which an implanted device is not normally exposed. Other fielded MR scanners have much lower maximum static magnetic field spatial gradient.

Scaling our measurement for the maximum spatial gradient, the maximum pressure becomes:

(b) (4)

well below the safety limit of 2 N/cm^2.

Review of Firm's Response

The overall rationale appears to be reasonable; however, it is not quite clear to the reviewer where the N/cm2 specification arrives from since the ASTM standard calls out for force not for force per area. This was a typographical error.

In Appendices 19, 39, 85(Error!....) various references are not found / equation(s) are missing, etc. The firm should provide the named documents without these errors and corrected links, equations, references.

FDA Deficiency 5

You In Appendices 19 (page 709), 39 (page 855) and 85 (numerous pages) various references are not found / equation(s) are missing, etc. and an error message is displayed instead. Please provide the named documents without these errors and corrected links, equations and references.

Firm's Response

Appendices 19, 39, and 85 from P050023/S087 have been updated and are included in the appendices referenced in Table 4.

Review of Firm's Response

The firm updated the documents and the updated documents were reviewed. The firm sufficiently addressed the deficiency.

The firm referenced VTD-111-1130 as the test methodology document in Appendix 55-57 but did not provide the document itself. The firm should provide VTD-111-1130 for review.

FDA Deficiency 6

You referenced VTD-111-1130 as the test methodology document in Appendix 55-57 but did not provide the document itself. Please provide VTD-111-1130 for review.

Firm's Response

VTD-111-1130 is provided in Appendix 26.

Review of Firm's Response

Appendix 26 was reviewed. The provided document is sufficient to address the deficiency.

The firm provided an overview of their modeling framework, in particular the electromagnetic field simulation aspect, in Appendix 16 of this submission. The firm indicated only the use of circular

(b) (4)

FDA Deficiency 7

(b) (4)

Firm's Response

To be consistent with the testing that has been conducted, elliptical bore MRI scanners will not be included in the MRI Conditions for Use. Therefore, the ProMRI System manual (Appendix 21) has been updated accordingly.

Review of the Firm's Response

The firm has taken out the reference to elliptical scanner in the manual. This is sufficient to address the deficiency.

The firm provided validation data for the lead transfer function in Appendix 19. The reviewer was only able to locate validation data the Protego S 75 lead. The lead transfer function is a function of lead construction; including length and wire conductor arrangement, as well as fluid ingress. The firm should provide transfer functions and validation data for all leads submitted for approval.

Furthermore, there appeared to be some inconsistency with respect to the uncertainty scale factor. On page 712 and 713 it appeared that the Protego S 75 has an uncertainty factor of (b) (4) yet on page 715 the value is (b) (4) is used. The firm needs to clarify which value applies and why. Additionally, the firm only provided fluid ingress modeling for (b) (4) fluid ingress. Since fluid ingress alters the electrical length and heating can be a strong function of this length, the firm should provide data showing that there is no resonance effect as a function of fluid ingress. Finally, in order to allow an industry wide comparison, the firm should provide the 99th percentile power levels.

FDA Deficiency 8

You provided validation data for the lead transfer function in Appendix 19. FDA was only able to locate validation data for the Protego S 75 lead. The lead transfer function is a function of lead construction; including length and wire conductor arrangement, as well as fluid ingress. Please provide transfer functions and validation data for all leads submitted for approval.
Furthermore, there appeared to be some inconsistency with respect to the uncertainty scale factor. On page 712 and 713 it appeared that the Protego S 75 has an uncertainty factor of (b) (4), yet on page 715 the value used is (b) (4) Please clarify which value applies and why.
Additionally, you only provided fluid ingress modeling for (b) (4) fluid ingress. Since fluid ingress alters the electrical length and heating can be a strong function of this length, please provide data showing that there is no resonance effect as a function of fluid ingress.
Finally, in order to allow a complete assessment of safety, please provide the 99th percentile power levels (without uncertainty correction) predicted from your electromagnetic modeling.

Firm's Response

BIOTRONIK's RF heating analyses involve the generation and validation of lead transfer function models. This process is detailed in TSP-461-241 (Appendix 23 of P050023/S087 and Appendix 32) and involves validation of the methodology of generating lead transfer functions subject to the entire set of Transfer Function Models (TFMs) being generated within a reasonable time frame, using the same apparatus and media. This includes a full validation of the electrode with the highest induced surface RF power density for each lead family. In addition, every lead is subject to a subset of the full validation test cases to verify that the transfer function generation process remains valid.
For RA and RV leads, the tip electrode is the most critical Lead Electrode Under Test (LEUT), since it is in the most intimate contact with cardiac tissue. Hence, in compliance with the ISO/TS 10974: 2012 (E) §10 recommendations, the tip electrode with the highest induced surface RF power density in a lead family and any other LEUT that exhibits deposited surface power density greater than such tip electrode shall be the focus of validation. This strategy was further detailed in GTR-15-0135-0A §7.1 (Appendix 23).
Full validation of the Setrox S 53 lead was completed by the (b) (4) (b) (4) and is detailed in IT'IS Report 351, submitted in Appendix 14-2 of IDE G120226. Validation data from Tables 15 through 22 of that document are reproduced below (Reviewers Note: Please refer to pages 23-29 of the amendment A001).

Similarly, full validation of the Linoxsmart S 65 and Linoxsmart SD 65/18 leads were completed by the (b) (4)) and are detailed in IT'IS Reports 457 and 485, which are referenced in GTR-15-0136-0A (Appendix 18 of P050023/S087). Validation data from Tables 23 through 28 of that document are reproduced below (Reviewers Note: Please refer to pages 30-34 of the amendment A001).

Full validation of the Linoxsmart S DX leads was completed by BIOTRONIK and submitted in VER-461-14-0008 (Appendix 27).

The uncertainty factors are referenced in GTR-15-0135-0A, which is Appendix 19 of P050023/S087 and is also re-submitted as Appendix 23 for FDA's convenience.
The uncertainty factor of (b) (4) as indicated on page 720 of P050023/S087) refers to the total (b) (4)

powers.

As indicated on pages 712 and 713 of P050023/S087, the uncertainty factor of 5.16 dB refers to [redacted]

(b) (4)

and represents the validation criterion.

Several design elements are incorporated in BIOTRONIK leads to avoid penetration of fluid in the lead. As shown in the figure below, all BIOTRONIK leads have a sealing gasket at the distal tip, where the pin connects to the fixation helix, which is designed to prevent fluid from entering the lead. The material used for the sealing gasket is silicone, which is the same sealing material used in the IS-1 connectors of all BIOTRONIK leads to prevent fluids from entering the header cavity of the implanted device. Therefore, even under extreme implant conditions, fluid does not penetrate the inner lumen of the leads.

BIOTRONIK routinely conducts validation testing to ensure that the leads are leak-proof. In addition, a 100% test during production evaluates the leak tightness of th lead. [redacted]

(b) (4)

In terms of the RF behavior of leads, it is well known that the phase transfer function strongly influences the resonance response of the lead electrode. As seen in Figure 2, the Protego, Linoxsmart S and Setrox leads exhibit resonance response in the empty state. The resonance response occurs where there is a sharp change in the phase characteristic. Lead electrode models of the Protego, Linoxsmart S and Setrox S families of leads have been validated under resonant conditions (validation cases using foldbacks to alter the lead's electrical length) as reported in (IT'IS reports and GTRs).

Notwithstanding the above-stated, BIOTRONIK generated transfer functions for the tip electrode of the Protego S 75 lead (highest heating electrode among all leads reported in Appendix 19 of P050023/S087) with the central lumen of the lead filled with saline at different fill percentages. This analysis, documented in GTR-15-0444 (Appendix 29), concludes the following two points:

(b) (4)

[redacted]

(b) (4)

Review of the Firm's Response

The firm appropriately addressed the need for transfer functions for all submitted lead. Even though not ideal, not all transfer function were fully validated but only partial validation utilizing path ways that the firm considered most challenging to the model were used in all cases but the "hottest lead" per lead family. This approach is, even though barely, acceptable.

The firm also explained the difference in scaling factors resulting from various error analysis. The response is sufficient and no further information is required with regards to the scaling factor.

(b) (4)

[redacted] (b) (4)

Considering the conservative estimate provided by the scaling factor, the reviewer believes that the lead can be approved. However, the upper limit certainly has been reached.

CLINICAL DATA

A summary of the clinical trial results are provided in Section 10 of the submission and a detailed final study report is provided in Appendix 65. A shortened version of the study summary is provided in the following:

The Phase C of the ProMRI prospective, single-arm, multi-center, non-randomized study enrolled subjects implanted with an ICD System consisting of an Iforia DR-T and Linox^{smart} S 65 or Linox^{smart} SD 65/18 ICD lead with a Setrox S 53 atrial lead, or Iforia VR-T DX and Linox^{smart} S DX 65/15 or Linox^{smart} S DX 65/17 ICD lead, and were willing to undergo an MRI scan.

A total of 170 subjects were provisionally enrolled at 39 sites as of March 17, 2015. At the time of this report, there were 16 subjects that did not meet the MRI criteria or were exited prior to the MRI procedure. The remaining 154 subjects were fully enrolled and had a cumulative implant duration at the time of enrollment of 34.0 years (average implant duration of 0.22 ± 0.14 years). At the time of this data analysis, 154 patients were programmed into the MRI mode at their MRI visit and 150 had completed their 1-month follow-up (3 subjects had a missed visit and 1 visit was pending). The average subject is a 60-year old male who weighs 200.9 pounds and is 68.3 inches in height. The patient follow-up compliance rate was 98.8% out of 245 required follow-ups.

All endpoints were analyzed as per-protocol (PP) and intent-to-treat (ITT). In general, the per-protocol population is defined as all subjects who fulfill the requirements of the protocol and have no major protocol deviations. The intent-to-treat population consists of all enrolled subjects who were programmed to the MRI mode and had endpoint data available from follow-up or missing data imputed by Home Monitoring. An additional sensitivity analysis was performed on all subjects who were programmed to the MRI mode and assumed failure for missing endpoint data.

The pre-specified protocol sample size requirements for assessments of the three primary endpoints in the ITT population were met: SADE-free rate evaluated in 54 subjects, ventricular pacing threshold evaluated in 145 subjects, and R-wave sensing attenuation evaluated in 154 subjects.

Information about spontaneous VT/VF episodes was collected to determine irregularities in detection or conversion of VT/VF. Investigators were encouraged to program a VT monitoring zone and conduct defibrillation threshold testing (DFT) following the MRI procedure. Table 28 provides a summary of all VT/VF episodes detected from the date of baseline through the pre-MRI procedure and post-MRI through study exit as reported in the EDC system and transmitted by Home Monitoring. As of March 17, 2015, there have been no post-MRI DFT tests conducted on any study subject as reported in the EDC system. There were no adverse events reported during the study related to inadequate or delayed ICD detection or cardiac arrhythmias. No reports of over or undersensing were noted.

The clinical section was primarily reviewed by Dr. Lewis and Dr. Huang. Dr. Lewis's review concludes that the submission provides, from a regulatory perspective, a reasonable assurance of safety and effectiveness of the system in the MR environment under the recommended MR Conditions of Use; the Conditions of Use are appropriate and the Instructions for Use and Labeling are adequate and appropriate. He does, however, have some deficiencies that, even though do not alter his regulatory recommendation, should be addressed before the system is approved or should be addressed in a Post Approval Study. Key points are:

The firm was asked to include 24 reviewable VF episodes; however, included only 16 episodes spread over 9 patients. It was also not clear if these episodes would qualify as true VF episodes and we would like to have access to the EGMs for review. Since true VF episodes are rare, the team is willing to move the collection and review of post MRI VF episodes into a post approval study. Similar to PASs requested by other firms we would recommend that the Biotronik collects and evaluates post MRI VF episodes from 25 patients with respect to potential treatment delay and impact on treatment effectiveness. The

firm will have to clearly specify what is considered an undue therapy delay based EGMs and experiences with their devices that have not been exposed to MRI scans. Such definition was lacking or not reported in the study protocol / report. The team is open to consider the use the firm's home monitoring features to a) Determine if an MRI occurred and b) determine if there were subsequent VF episodes. The firm should update the clinical manual and IDE report results if data becomes more complete (Deficiency 10).

FDA Deficiency 9

You were asked to include 24 reviewable VF episodes as part of your clinical study; however, included only 16 episodes in 9 patients. Please address the following.

a. It was not clear if these episodes would qualify as true VF episodes since true VF episodes are rare. Please provide the EGMs for review.

Firm's Response

Table 27 of the ProMRI Clinical Study Report included data from VF episodes detected during the study follow-up period. The Post-MRI Procedure columns specifically included episodes detected post-MRI through study completion (3-Month visit), or through the report data cut-off date for subjects that had not yet completed the study. There were 16 VF episodes in 9 subjects during this time period.

In addition, BIOTRONIK continued to collect VF episodes for study subjects after the 3-Month visit via Home Monitoring (HM). Cumulative post-MRI VF episode data (episodes collected during the study plus episodes collected after study completion via HM) were included in Section 10.8, Table 30, of the PMA Supplement. At the time of the submission, there were 93 cumulative VF episodes detected in 19 subjects. IEGMs were available for 47 VF episodes and were provided in Appendix 72 of the PMA Supplement. Appendix 72 of the PMA Supplement included individual case reports for subjects with VF episodes in the following format*:

- Cover sheet
- Subject summary sheet (subject demographics, list of VF episodes and timing relative to study visits, list of available IEGMs, etc.)
- Recordings – Shocks (list of shocks from last available study visit from device interrogation)
- Recordings – Counters (count of detections per zone since implant from device interrogation)
- Recordings – Episodes (list of detections and relevant details since implant)
- IEGMs (from device interrogation or HM)

Some subjects may have slightly different formats depending on type of data available. Since the PMA Supplement was prepared, there have been 27 additional VF episodes detected in the Phase C study subjects. Seven subjects that had not previously had a VF episode had a total of 20 episodes. Four subjects that previously had a VF episode had seven additional episodes. In total, 120 episodes of VF in 26 subjects were detected after MRI procedures. All available IEGMS are provided. One ProMRI Phase C subject had 59 VF episodes with 14 IEGMs available via Home Monitoring, one ProMRI Phase C subject had 6 VF episodes with 2 IEGMs available via Home Monitoring, and two ProMRI Proven subjects had 2 VF episodes with 1 IEGM available and 5 VF episodes with 4 IEGMS available, respectively, resulting in 69 total VF episodes post-MRI with available IEGMs. Table 30 of the PMA Supplement has been updated with the current information and is provided below in Table 17.

Table 17: VF Episodes Detected Post-MRI – Updated July 2015

	Number of Subjects with VF Episodes Post-MRI	Number of VF Episodes Post-MRI	Number of VF Episodes Post-MRI with IEGMs Available
ProMRI Phase C	18	103	54
ProMRI PROVEN	8	17	15
Total	**26**	**120**	**69**

The VF episodes discussed here are defined as detections in the VF zone based on programmed device settings. BIOTRONIK acknowledges that detected VF episodes may actually be true VF, VT and/or SVT arrhythmias meeting the programmed VF detection criteria.

Appendix 28 includes all previously submitted individual case report summaries as well as the new individual case reports including all available EGMs for FDA's review.

Clinical Reviewer's Comments

The clinical reviewer reviewed the submitted episode data and found:

- There is a mix of patients with episodes that are and are not VF, including non-sustained and treated, sustained VF. Most of the submitted episodes are not VF.
- The firm has not made clear how many they believe are VF. For this reason, the clinical reviewer reviewed the EGMs and found:
    - ONLY 6 OF THE EPISODES INCLUDE VF
    - This excludes repeat episodes for single patients and episodes which lack VF.
- However the firm HAS DONE ANALYSIS EXAMINING FOR VF SENSING PROBLEMS. The clinical reviewer does not believe FDA could reasonable do this analysis themselves. The reviewer indicated that it is difficult seeing all details in the submitted tracings clearly. But it appeared grossly that there were no delay to therapy and that provided the firm's analysis is acceptable – for the 6 VF episodes. The SIX specific episodes are:
  Subject (b) (6) .

b. Since true VF episodes are rare, FDA is willing to move the collection and review of post MRI VF episodes into a Post Approval Study. Please provide a PAS protocol for review in which you collect and evaluate post MRI VF episodes from 25 patients with respect to potential treatment delay and impact on treatment effectiveness. You should clearly specify what is considered an undue therapy delay based on available EGMs. Such definition was lacking or not reported in the study protocol / report. FDA is open to consider the use of your Home Monitoring capabilities to i) Determine if an MRI occurred and ii) determine if there were subsequent VF episodes. Once you have collected the data, you should update the clinical manual and IDE report results.

Firm's Response

There were no sensing, detection, or delayed therapy issues noted for any post-MRI VF episode. No clinically significant adverse effects of the MRI scan were reported affecting the subsequent ability of the system to detect VF. Study results demonstrate that the ProMRI® ICD System provides appropriate detection of ventricular arrhythmias after MR exposure. During Phase C of the IDE, there were no sensing attenuations > 50% of the pre-MRI R-wave values.

One-hundred-forty-six Phase C subjects with ventricular leads completed the study MRI procedure (with matching sensing polarities measured pre- and post-MRI). Sixty-six (45.2%) subjects experienced a slight R-wave decrease between pre-MRI and post-MRI, mean decrease -1.453 +/- 1.659 mV (mean percentage decrease -8.7%). The largest percentage R-wave decrease experienced pre-/post-MRI was 24.2 to 14 mV (-42.2%). Despite some R-wave decreases post-MRI, the signal amplitudes are well above the minimal sensing threshold of the ICD. These results are consistent with Phase A, Phase B, and the overall study results summarized in Table 18 (Reviewer: refer to Amendment).

The clinical experience with BIOTRONIK's ProMRI pacemaker/ICD systems characterize the effect of MRI on R-wave sensing which is also supported by literature.
Prior literature describing R-wave sensing immediately after MRI; Nazarian et al. (Ann Intern Med, 2011) compares R-waves pre- and post-MRI of 461 subjects with pacemakers and ICDs. The median percentage change post-MRI compared to baseline was 0% (-7 to 0% IQR). Post-MRI, 94.8% of R-wave measurements either increased from pre-MRI or decreased ≤ 20% from pre-MRI. No subject experienced a post-MRI R-wave decrease greater than 40% (Reviewer: Refer to Amendment).

Further information about spontaneous VT/VF episodes was analyzed to determine irregularities in detection or conversion of VT/VF. Investigators were encouraged to program a VT monitoring zone and conduct defibrillation threshold testing (DFT) following the MRI procedure. Table 21 provides a summary of all VT/VF episodes detected from the date of baseline through the pre-MRI procedure and post-MRI through study exit as reported in the EDC system. There was no post-MRI DFT tests conducted on any study subject as reported in the EDC system.
Table 22 provides a summary and subsequent success of each post-MRI VT and VF ventricular therapy sequence. There were 9 episodes in 5 subjects that are excluded from Table 22 due to detections of AF with rapid ventricular response in the VT/VF therapy zone. An additional 12 episodes were excluded due to no IEGMs available for success determination.

There were no adverse events reported during the study related to inadequate or delayed ICD detection or cardiac arrhythmias. No reports of over or undersensing were noted.
All episode detections and therapies delivered for VT/VF episodes post-MRI (35/35, 100%) indicate that there was no delayed VT/VF detection due to the MRI procedure. Results demonstrate that the

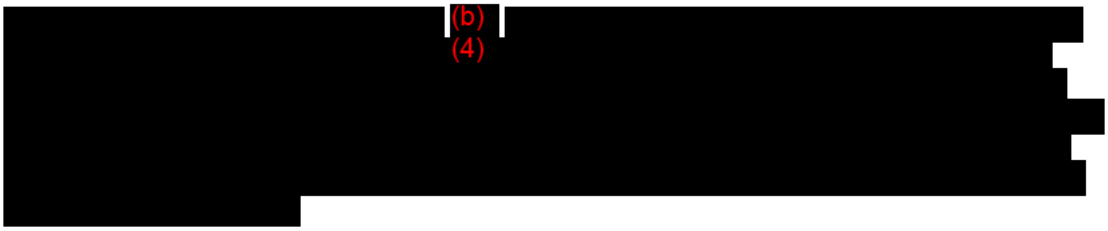
ProMRI ICD System provides appropriate detection and effective therapy for the treatment of ventricular arrhythmias post-MRI.

(b) (4)

Clinical Reviewer's Comments

The clinical reviewer examined the firm's response and disagrees with their conclusion that VF testing is not needed through a PAS. Due to the collection of only 6 VF episodes in the study (see previous deficiency a)) the reviewer recommends that the firm collect 18 more episodes (being careful to exclude both multiple episodes in given single patients, which would not be informative, and excluding non-VF episodes) to fulfill the original FDA request for assurance that VF sensing is not impaired by MR exposure.

(b) (4)



The review of histograms included in the submission to show frequency of specific values of PCT change, R-wave sensing change and impedance changes across MRI exposure (including visit and home monitoring data) found the data overall favorable and reassuring for approval. It appears that MR-related significant changes in these parameters were overall very uncommon by visit monitoring. However, FDA found that histograms of ventricular sensing change showed differences comparing data from visits vs home monitoring. The home monitor data suggests more decreases in R-wave voltage occurred after MRI than the data from visits. FDA asks that you provide your perspective on why this apparent difference in sensing particular to home monitoring occurred and whether this observed difference is significant or concerning.

FDA Deficiency 13

The review of histograms included in the submission to show frequency of specific values of PCT change, R-wave sensing change and impedance changes across MRI exposure (including visit and home monitoring data) found the data overall favorable and reassuring for approval. It appears that MR-related significant changes in these parameters were overall very uncommon by visit monitoring. However, FDA found that histograms of ventricular sensing change showed differences comparing data from visits vs home monitoring. The home monitor data suggests more decreases in R-wave voltage occurred after MRI than the data from visits. Please provide a rationale for the observed difference and why it should not be significant or concerning.

Firm's Response

Further analysis of the Home Monitoring versus in-office visit data for ventricular (R-wave) sensing was conducted to provide an explanation for the observed difference in measurements reported in the histogram references in FDA's question.

There are a couple of differences between in the method of R-wave measurement of the values reported on Home Monitoring and those acquired during the in-office sensing test:

1. Home Monitoring reported ventricular sensing values are capped at 20 mV whereas the device and the in-office sensing test is capable of measuring values of up to 25 mV.
2. Home Monitoring reported ventricular sensing values are an average of 4 values measured through the automatic sensing test prior to the time of the Home Monitoring transmission. The inoffice test measures a one-time, current R-wave amplitude.
3. In order to measure the R-waves, the automatic sensing test extends the AV-delay to 300 ms. If no intrinsic R-waves are measured during the automatic test and the ventricle remains paced, the test would report an R-wave <2mV. The in-office sensing test allows for a change in pacing mode during the test, which could result in R-waves being measured in case of an AV-delay > 300ms.

In general, these measurement differences between the Home Monitoring and in-office methods result in lower ventricular sensing amplitudes reported on Home Monitoring compared to the in-office measurement. Figure 7 (Reviewer: Refer to Amendment) shows a comparison between the Home Monitoring ventricular sensing values and the in-office ventricular sensing value obtained on the same day and demonstrates that the Home Monitoring value is lower in most cases.

Additionally, Figure 8 (Reviewer: Refer to Amendment) shows a comparison between the in-office ventricular sensing value obtained at Pre-MRI, the 1 –month follow-up and the 3-month follow-up. Figure 9 (Reviewer: Refer to Amendment) shows a comparison between the Home Monitoring ventricular sensing value obtained at Pre-MRI, the 1 –month follow-up and the 3-month follow-up, if Home Monitoring data was available in a window of +/- 3 days around the in-office follow-up.

Note that not all subjects had Home Monitoring data available. The similarity between the two graphs and the values presented demonstrate stable R-wave amplitudes over the course of the study, regardless of what method is used (In-Office or Home Monitoring) to obtain the R-wave amplitudes.

BIOTRONIK believes that the above data and the explanation of the differences in measurement techniques for Home Monitoring versus in-office follow-ups clearly show that the referenced differences are not attributable to the MRI.

Clinical Reviewer's Comment

The firm's explanation that the differences are an artifact of method makes sense, and the larger picture supports no change in the tissue interface from MR exposure, but the differences are hard to incorporate specifically into the analysis, i.e. they appear unpredictable on a per patient level.

This analysis should be included in the PMA clinical section and FDA should be aware of this issue moving forward with other similar reviews. I do not think this raises a safety concern for this device, however.

No experience with multiple and clinically indicated MRI scans were reported in the IDE and it is not clear if any occurred. The firm should clarify if such information was collected. Regardless, the team would like to see an assessment of multiple MRI scan exposure as part of the PAS. Again, such assessment may utilize the home monitoring feature if it has the ability to determine if an MRI scan was conducted.

FDA Deficiency 13

No experience with multiple and clinically indicated MRI scans were reported in the IDE and it is not clear if any occurred. Since the additional scans may impact the safety and performance of the system, please clarify if such information was collected (specifically for the ProMRI ICD). FDA will need to see an assessment of multiple MRI scan exposure, but is willing to include this as part of the PAS. Again, please provide a PAS protocol including this element and note that such assessment may utilize the Home Monitoring capabilities if it has the ability to determine multiple MRI scan were conducted.

Firm's Response

Each successive phase of the ProMRI protocol has collected data on subjects who underwent multiple MRI scans. There were four subjects in Phase C of ProMRI and five ICD subjects in the ProMRI Proven Master Study who received a clinically indicated scan in addition to their study MRI scan. Three subjects completed their clinical scan first, and six subjects first underwent their protocol required MRI scan. These ProMRI and Proven subjects and their MRI scan dates are summarized in Table 23 and Table 27, respectively. The post-MRI procedure and three month follow-up procedure were completed on the same day for two ProMRI Phase C subjects.

For the subjects receiving multiple MRI procedures, Table 24, Table 25, and Table 26 display each ProMRI Phase C subject's ventricular sensing, threshold, and impedance values at the study and clinical MRI procedures and 3-Month follow-up. In this analysis, the clinical and study MRI scans are labeled as MRI1 and MRI2 based on chronological order.

In the ProMRI Proven Master study (Appendices 78 and 79 of the PMA Supplement), device testing data was not collected immediately prior to and after the clinical MRI scan. Therefore, testing that occurred prior to both scans and the latest available follow-up after both scans was used in this analysis. Table 27 summarizes visit dates and Table 28 summarizes ventricular testing data from Proven subjects for follow-up visits prior to both MRI scans and the latest available follow-up visits after both MRI scans.

Table 29 summarizes the difference in ventricular pacing threshold, R-wave sensing amplitude, and ventricular pacing impedance between device testing measurements prior to MRI1 and after MRI2 for the nine total ProMRI Phase C and ProMRI Proven subjects.

Clinical Reviewer's Comments

MEDICALLY INDICATED SCANS: Based on the firm's and the clinician's review of all the pre- and post- MRI comparison R-wave amplitudes, PCT and impedances from the nine subjects with medically indicated MR scans there are no concerns about MR toxicity to the leads. The analyses should be included in the labeling.

MULTIPLE SCANS: Based on the firm's and the clinician's review of all the pre- and post- MRI comparison R-wave amplitudes, PCT and impedances from the many subjects with multiple MR scans there are no concerns about MR toxicity to the leads. The analyses should be included in the labeling.

(b)
(4)

Unlikely other systems currently under IDE studies or approved systems the Biotronik ProMRI system does not include an automatic timeout feature for the MRI mode. Specifically, all systems studied or approved suspend the ICD therapy during MRI. The primary reason for this suspension is the thought that electromagnetic interference during the MRI scan may trigger inappropriate shocks. However, suspension of ICD therapy beyond the time period of the MRI presents a risk to the patient. The firm indicated that there were no issues with this workflow during the IDE study. However, a study of the workflow under less controlled, real world conditions should be made part of the Post Approval Study.

FDA Deficiency 11

Your ProMRI systems do not include an automatic timeout feature for the MRI mode which suspends ICD therapy during MRI. The primary reason for this suspension is the thought that electromagnetic interference during the MRI scan may trigger inappropriate shocks. However, suspension of ICD therapy beyond the time period of the MRI presents a risk to the patient and your workflow mandates that the ICD system is programmed to its pre-MRI values once the MRI is completed or aborted. You indicated in your submission that there were no issues with this workflow during the IDE study. However, a study of the workflow under less controlled, real world conditions should be made part of the Post Approval Study. Please incorporate evaluation of the work flow into a proposed PAS protocol for FDA review. Furthermore, please update your labeling to draw more attention to this specific work flow.

Firm's Response

The following updates were made to the ProMRI System manual (Appendix 21) to draw attention to the fact that the device remains in the MRI mode until it is reprogrammed after the MR scan.

- Updated Section 4.1.3 (Performing an MR Scan and Programming the MRI Mode)
  The second paragraph of Step 8 was updated to the following.
  "Several device functions may be deactivated in the MRI mode. Therefore, make sure that the patient can be scheduled for a follow-up immediately after completion of the MR scan in order to reprogram the device back to the permanent parameters as defined by the patient's physician."
- Updated Section 5 (Post MR Scan Requirements)
  The following Note was added.

"The device parameters during activation of the MRI mode are maintained until the MRI program is set to OFF after the MR scan."

Clinical Reviewer's Comments
The firm has not addressed FDA's request for data collection in the PAS to document whether MRI mode programming is restored in a timely manner. The firm should provide this response.

(b) (4)

The statistical review conducted by Dr. Huang concludes and all three primary endpoints of the study appear to have been met except some minor questions concerning subject enrollment and accountability. These questions are:

1. It appears that the ITT analysis for Primary Endpoint #1 was based on 153 fully subjects (Page 1277 of 4486). However, according to the definition of the ITT population, it should include a total of 154 fully subjects (please refer to Figure 3 in Page 1272 of 4486). The firm should address the discrepancy (Deficiency 13)
2. The tables in Page 1305 of 4486 presented the subject distributions among (b) (4) . The firm should address this issue.

These questions were addressed in the firm's response to the July 15th deficiency letter and the response did not change the final conclusion that the clinical trial met all endpoints.

CONCLUSION

The firm has shown substantial evidence of safety and efficacy of the ProMRI ICD system when used in an MRI environment as defined in the MRI Conditions of Use. Since the firm has agreed to perform a Post Approval Study similar to the one currently (b) (4) the reviewer recommends that the PMA supplement be approved with the condition that the final PAS protocol by submitted within 30 days of approval.

OAI Firm & Corporate-wide Warning List was checked on April 20th, 2015 and the document was found to be clear. A subsequent check on December 14, 2015 gave the same result.