SUMMARY MEMO P980023/S060, P950037/S138, AND P070008/S054
VARIOUS LEAD CHANGES

EXECUTIVE SUMMARY

With this PMA Supplement, BIOTRONIK is proposing the following changes:

1. A minor modification (addition of inner coating) of to the Linox^{smart} /VOLTA/Protego ICD leads (Section 4.1);
2. Modification of the current suture sleeve to create a White Suture Sleeve (Section 4.2);
3. PA 11 Adapter (Section 4.3);
4. Lead Technical Manual/Labeling updates (Section 4.4).

A detailed description of the changes is provided in a separate section of this memo. The changes appear to be minor in nature; however the firm has provided a complete suite of testing for each of the changes identified.

INDICATIONS FOR USE

The Indications for Use and Contraindications for all the products mentioned in this submission (Table 1 page 9 of 54) remain unchanged as compared to those currently approved.

DESCRIPTION OF CHANGES

Addition of Inner Coating to ICD Leads

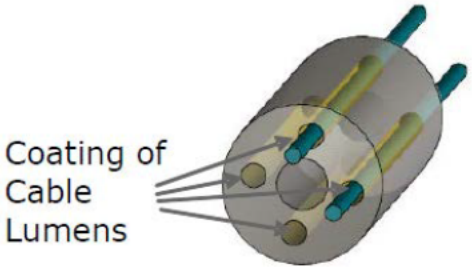
The first change consists of a coating that will be applied to the cable lumens inside the following ICD leads (table below) to further optimize the lead assembly process.

Table 3: Linox^{smart}, VOLTA and Protego ICD Leads

P980023 Supplement No.	Approval Date	Device Name	Lead Type
S038	September 17, 2010	Linox^{smart} SD 60/16 Linox^{smart} SD 65/16 Linox^{smart} SD 65/18 Linox^{smart} SD 75/18	Active fixation, dual coil
		Linox^{smart} TD 65/16 Linox^{smart} TD 65/18 Linox^{smart} TD 75/18	Passive fixation, dual coil
S043	February 28, 2011	Linox^{smart} S 60 Linox^{smart} S 65 Linox^{smart} S 75	Active fixation, single coil
		Linox^{smart} T 65	Passive fixation, single coil
S049	February 13, 2013	Linox^{smart} S DX 65/15 Linox^{smart} S DX 65/17	Active fixation, single coil, single-pass (A/V sensing)
S046	February 22, 2012	VOLTA 1CR 60 VOLTA 1CR 65 VOLTA 1CR 75	Active fixation, single coil

Table 3: Linox^{smart}, VOLTA and Protego ICD Leads			
P980023 Supplement No.	**Approval Date**	**Device Name**	**Lead Type**
		VOLTA 2CR 60/16 VOLTA 2CR 65/16 VOLTA 2CR 65/18 VOLTA 2CR 75/18	Active fixation, dual coil
		VOLTA 2CT 65/16 VOLTA 2CT 65/18 VOLTA 2CT 75/18	Passive fixation, dual coil
		VOLTA 1CT 65	Passive fixation, single coil
S057	July 3, 2014	Protego SD 60/16 Protego SD 65/16 Protego SD 65/18 Protego SD 75/18	Active Fixation, dual coil
		Protego S 60 Protego S 65 Protego S 75	Active Fixation, single coil
		Protego TD 65/16 Protego TD 65/18 Protego TD 75/18	Passive fixation, dual coil
		Protego T 65	Passive fixation, single coil

The image below shows a cross-section of the lead with five lumens, one center (conductor) lumen and four surrounding (cable) lumens (two lumens are illustrated with a cable inside). This general lead body design is the same for all of the Linox^{smart}/VOLTA and Protego lead models in this PMA Supplement.



(b)(4) TS/CCI As the same tubing is used for the lead body for all ICD lead variants referenced in this PMA Supplement, the coating is applied to all cable lumens regardless of which product variant the tube will be used. The coating is made of (b)(4) TS/CCI not in body contact and will only be applied to the inner surface of the cable lumens of the lead.

White Suture Sleeve

BIOTRONIK requests a minor modification to the White Suture Sleeve, in which the lead fixation sleeve will now be white in color.

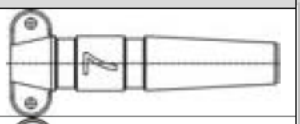
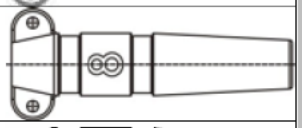
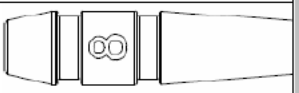
The main features for the white suture sleeves are:

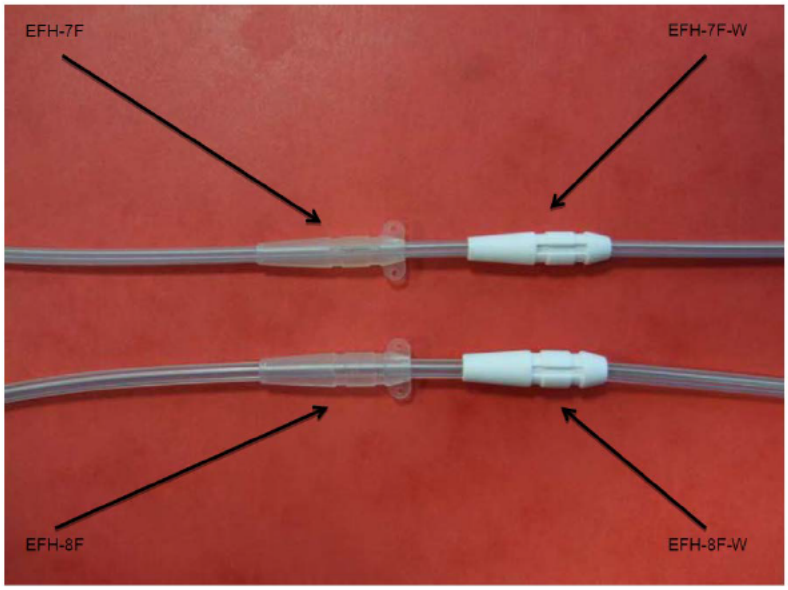
- White coloring
- No suture wings
- Available as a separate lead fixation sleeve, not pre-slit

Modified Lead Fixation Sleeve	Associated Lead	PMA No./ PMA Supplement	Combine /with
EFH-7F-W	Selox ST / JT	P950037/S38	Use with suitable BIOTRONIK leads with an outer diameter from 2.1 to 2.4 mm
	Setrox S	P950037/S42	
	Dextrus	P950037/S48	
	TILDA R/T/JT	P950037/S099	
EFH-8F-W	Linox^{smart} SD	P980023/S038	Use with suitable BIOTRONIK leads with an outer diameter from 2.5 to 2.7 mm
	Linox^{smart} TD	P980023/S038	
	Linox^{smart} S / T	P980023/S043	
	VOLTA 1CR/2CR/1CT/2CT	P980023/S046	

The physical dimensions of the white suture sleeves are nearly identical to the lead fixation sleeves pre-mounted on the current 7F and 8F leads (e.g. Linox^{smart} (2.6 mm lead body diameter) or Setrox S (2.1 mm lead body diameter)), only the height of the ligature groove is slightly enlarged (b)(4) TS/CCI to support reliable sutures.

The lead fixation sleeve modifications are presented below. The figure below shows photographs of the current transparent lead fixation sleeve, and the modified, white lead fixations sleeves. The White Suture Sleeve will not replace the transparent sleeve, but be available in addition to the transparent lead fixation sleeves. The materials used to construct the lead fixations sleeves are identical to the current sleeve, with the addition of (b)(4) TS/CCI (b)(4) TS/CCI.

Lead Fixation Sleeve	Image	Material	Nominal Inner Diameter (mm)	Length (mm)	Suitable for lead body diameter	Cut	Separately Available
EFH-7F		(b)(4) TS/CCI			7F	(b)(4) TS/CCI	No
EFH-8F					8F		No
EFH-7F-W					7F		Yes
EFH-8F-W					8F		Yes



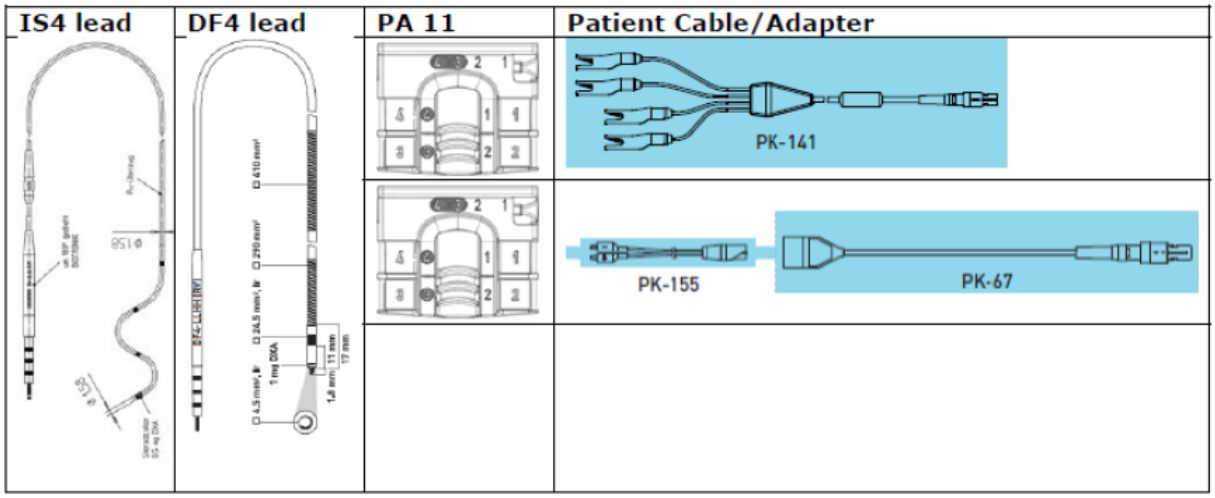
The white suture sleeves EFH-7F-W and EFH-8F-W do not have silicone wings. BIOTRONIK has already started providing some of their leads with lead fixation sleeves without suture wings (e.g. Corox leads – P070008, approved May 12, 2008 and P070008/S015, approved December 23, 2010).

Since most recently approved leads are typically isodiametric, the new white suture sleeve can be simply pushed over the lead tip without the need for a longitudinal slit in the sleeve. Therefore, the new white suture sleeves do not include a slit.

PA 11 Adapter

BIOTRONIK's PA 11 is similar to the PA 10, which was approved through P050023/S076 dated July 3, 2014. The adapters only differ in the number of connectable alligator clips. Whereas PA 10 could only be connected to DF4 leads, PA 11 is compatible to IS4 and DF4 connectors. The two additional surfaces are used to contact the new IS4 or DF4 leads through

the PA 11 adapter and a cable to an external device. The PA 11 adapter does not have any body contact. The PA 11 is used to connect a lead with IS4 or DF4 connector to the alligator clips on one of the following BIOTRONIK patient cables.



Lead Manual Updates

BIOTRONIK made minor updates to the lead manuals (Kainox, Corox (Celerity), Selox ST/JT (Tilda T/JT), Setrox S (Tilda R, Dextrus), Solox, Linoxsmart (VOLTA) and Protego). Refer to the labeling section of this memo for more information.

REASONS FOR THE CHANGES

Addition of Inner Coating to ICD Leads

This change is being implemented in order to optimize the assembly process. Due to the length and flexibility of the conductor cables and lead body and the tight fit between the cables and lumen, is often difficult to thread the cables through the narrow lumens; friction occurs between the cables and the lumen surface resulting in tedious advancement of the cables.

White Suture Sleeve

The reason for this change is to improve visibility of the suture sleeve during surgery.

PA 11 Adapter

The PA 11 was created to be compatible with both IS4 and DF4 connectors. The predecessor was only able to be connected to DF4 connectors.

Labeling Updates

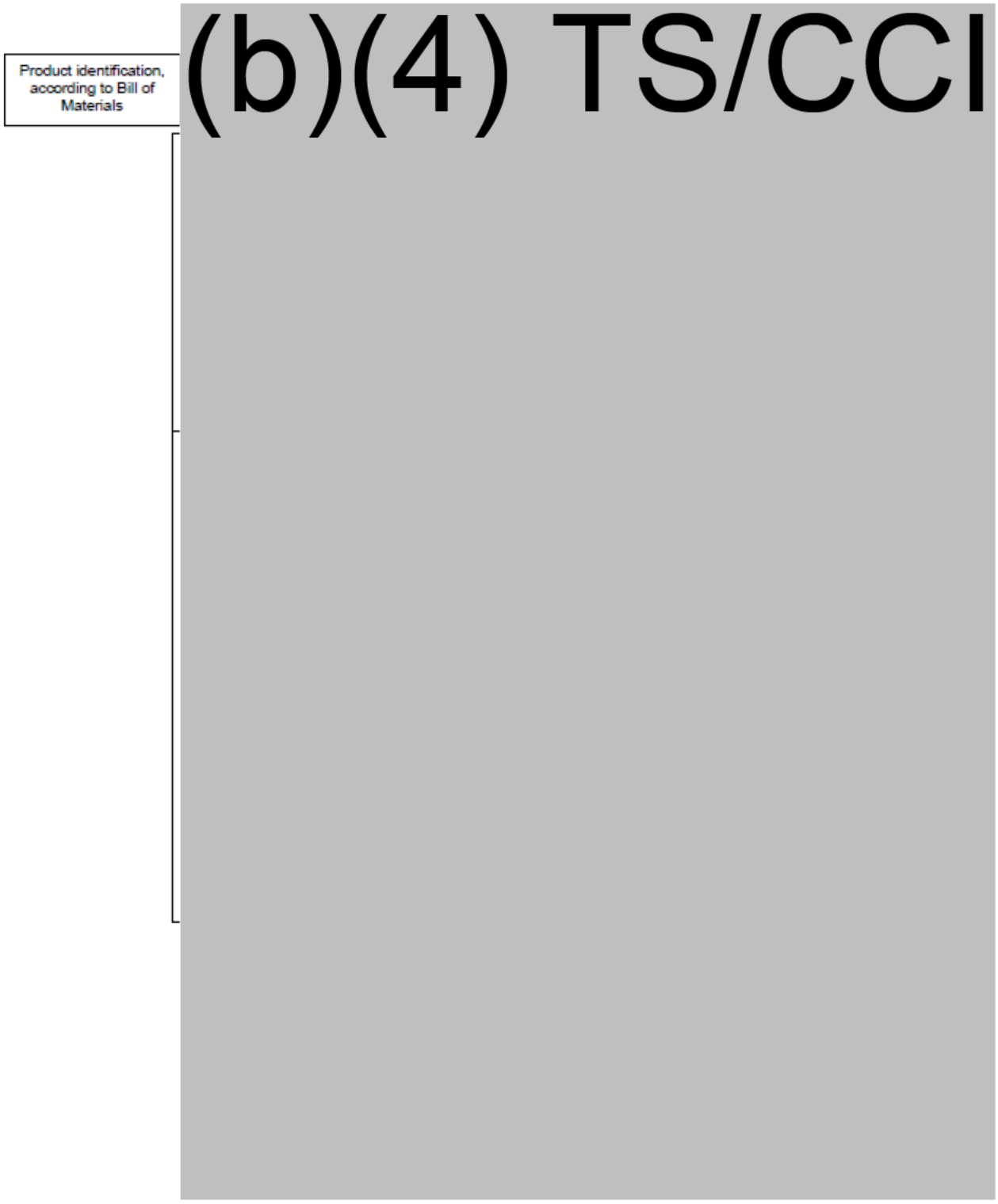
These manuals are largely based on the OUS manual. For all manuals, there are minor language changes that do not alter the content of the manuals. In addition, several sections of the manual, including warnings and precautions, were updated for clarity and for consistency with manuals used outside the US.

VALIDATION AND VERIFICATION TESTING

Addition of Inner Coating to ICD Leads

The Linox^{smart} / VOLTA/ Protego ICD leads validation testing was conducted to demonstrate the addition of the lumen coating had no negative effect on the product performance. Testing focused on the lead body and its long-term stability. This change affects a large number of leads. Therefore the firm selected samples that were considered the worst-case devices and are representative of comparable leads.

All testing samples were preconditioned (b)(4) TS/CCI sterilization cycle(s) that are identical to the normal manufacturing process (same steps as distributed leads in standard packaging), prior to being subjected to environmental preconditioning, which includes temperature, pressure and moisture changes, transportation test, and drop test. All tests (mechanical and electrical tests) are further preceded by appropriate mechanical preconditioning. The mechanical preconditioning included multiple repetitions of acute bending, offset insertion, and securing ligature on the suture sleeve, in order to simulate the most challenging venous pathways that a lead would have to navigate during a typical implantation procedure and the worst case connector insertion. The order of the testing is shown in the figure on the following page.



I think the firm went above and beyond with the testing to support this change. The testing identified above mimic what would be expected of a new or substantially modified lead. For this change I do not consider these leads to be new or substantially modified. Never the less the result of the testing showed that all leads samples passed the validation testing. I believe the firm used appropriate preconditioning and adequate testing to support the change. The testing

demonstrates that the coating does not negatively influence the lead body stability and long term performance of the lead.

White Suture Sleeve

The white suture sleeve validation testing was conducted to validate the dimensional changes and demonstrate that there is no negative effect on the product performance with the addition of the white, (b)(4) TS/CCI coloring. Testing included:

- Patricualate Matter
- Correction Factor and Microbial Load (Bioburden)
- Tests for Inhibitors and Activators, Endotoxin Test
- Labeling
- Environmental preconditioning
- Visual Inspection and Geometric Control of White Suture Sleeves
- Bending Test under Suture Sleeve and Visual Inspection for Inner Abrasion
- Tests after Accelerated Aging of 25 simulated months

A review of the results showed that all requirements were met and the test passed. The major concern for this change, I believe, is verifying new dimensions as well as biocompatibility (next section). Overall, I do not believe this change would have an effect of mechanical performance. (b)(4) TS/CCI a common colorant for suture sleeves. The above testing appears adequate and appropriate for supporting the change. The firm provided a rational for the sample sizes used as well as appropriate acceptance criteria. There are no additional concerns with the testing provided. Please refer to the next section of this memo for the biocompatibility review.

PA 11 Adapter

PA 11 validation testing was conducted to validate the additional surfaces for alligator clips and demonstrate that there is no negative effect on the product performance with the addition of the additional surfaces used to contact the new IS4 or DF4 leads through the PA 11 adapter. The following testing was conducted:

- Transportation and Storage
- Packaging
- Correct markings on the sales and sterile packaging labels
- Mechanical Requirements
- Compatibility to the leads
- Compatibility to cables and adapters
- Labeling of the Product
- Visual Inspection of the Manual
- Handling of the Product
- Overview of Fulfillment of Standards
- Identification of Materials (Biocompatibility – See next sections)
- Connection of the lead
- Connection of the patient cables
- Electrical measurements

- Inspection of Usability File
- Usability Tests
- Functional test after accelerated aging
- Validation of Sterilization with ETO (See Sterilization Section)

A review of the testing concluded that all requirements were met. The testing above is similar to that conducted for the approved PA 10 Adapter. That being said the main concern with this testing is to demonstrate the added connections function as intended. The testing above appears adequate and appropriate. The firms provided a suitable rationale for samples sizes as well as appropriate acceptance criteria. The testing demonstrates that the new adapted is compatible with both DF4 and IS4 leads. The adapter is non patient contacting. Overall, there are no concerns with this testing.

Biocompatibility

Addition of Inner Coating to ICD Leads

With the exception of the material used for the lumen coating (b)(4) TS/CCI all materials used in the construction of the ICD leads that are the subject of this PMA Supplement are the same as those used in the current FDA approved Linox^{smart} / VOLTA / Protego ICD leads. (b)(4) TS/CCI not in body contact and will only be applied to the cable lumens of the lead. As the material is non-patient contacting no biocompatibility testing was provided in the submission. There are no additional concerns with this change as it pertains to biocompatibility.

White Suture Sleeve

The silicone material used for the white suture sleeve remains unchanged compared to the currently FDA approved lead fixation sleeves. The proposed change includes the addition of (b)(4) TS/CCI to achieve the white coloring of the suture sleeve. A mixture of (b)(4) TS/CCI (b)(4) TS/CCI is used. BIOTRONIK performed biocompatibility tests with this material using material samples which were fully processed in the same way as the white suture sleeves. To determine the biocompatibility risk of this change, I spoke with and expert in biocompatibility during a curbside consult. She stated that the addition (b)(4) TS/CCI as a colorant was very common. She cautioned me to confirm the (b)(4) TS/CCI particle size as certain size particle (b)(4) TS/CCI be toxic. The firm provided that (b)(4) TS/CCI particles are below (b)(4) TS/CCI The cut-off for smallest (b)(4) TS/CCI about (b)(4) TS/CCI I have reviewed this with the reviewer who stated this was acceptable. She had no further concerns with this change.

PA 11 Adapter

The PA 11 adapter has no patient contact. Therefore I agree no biocompatibility testing is warranted for these accessories.

Shelf Life/Sterilization/Packaging

Shelf Life

The shelf-life for the Linox^{smart} / VOLTA /Protego leads, White Suture Sleeve, and the PA 11 is 24 months which is identical to all of BIOTRONIK's other legally marketed leads and accessories. Overall, I do not believe that the changes noted in this submission would impact the shelf life for the above mentions devices. The PA 11 has minor change from the approved PA 10 that would not impact device shelf life. There are no changes to the device sterile packaging. Therefore, I agree that no further testing is required to support the device shelf life.

Sterilization

The sterility and sterilization process of the Linox^{smart} / VOLTA / Protego leads does not appear to be affected by the addition of the inner lumen coating, and remains unchanged. There are no concerns with sterilizations with regard to this change.

The sterility and sterilization process of the white suture sleeves remain unchanged as compared to the currently approved transparent suture sleeves. I do not believe the addition of (b)(4) TS/CCI influences the sterility of the product.

All adapters are sterilized at BIOTRONIK SE & Co. KG, Woermannkehre 1, 12359 Berlin, with ethylene oxide. An assessment of the PA 11 adapter with comparison to 'worst case product' was provided by the firm.

The comparison showed:

- The materials and design of PA 11 154 adapter relevant for sterilization are comparable as for the representative worst case product (b)(4) TS/CCI
- Both products are open and easy to penetrate for moisture and ethylene oxide
- The sterilization process and process parameters are identical for both products
- The sterilization load configuration for PA 11 IS4 adapter and (b)(4) TS/CCI the same

It was demonstrated that the products are sterilized with a sterility assurance level (SAL) of 10-6. There are not further concerns regarding sterilization.

Packaging

There are no changes to the approved packaging for any of the changes noted in this submission. The packaging for the updated Linox^{smart} / VOLTA / Protego leads is identical to that currently approved and remains unchanged. White Suture Sleeves are packed in two pouches made (b)(4) TS/CCI and (b)(4) TS/CCI foil as the currently approved transparent BIOTRONIK lead fixation sleeves. There are no changes to the packaging or packaging process. I do not believe the changes proposed in this submission would impact the overl packaging. There are no further concerns with this section of the review.

Clinical Impacts

Addition of Inner Coating to ICD Leads

The firm states there is no clinical impact with this change. There are no changes to the assembly process and no other changes to the lead design. BIOTRONIK is only proposing the addition of coating the lumen surface of the silicone tubing prior to assembling the leads. An evaluation of the change was conducted, including an analysis of associated risks. It was concluded that the addition of the coating does not create additional risks to the patient. BIOTRONIK conducted several mechanical and electrical validation tests to show that the coating does not negatively influence lead body stability or long term performance of the lead. Additionally, there are no changes to the labeling as a result of this change. With this change, there are no changes to the intended use, basic functionality, contraindications, precautions, or warnings. Therefore, I agree there is no clinical ramification introduced with the addition of the lumen coating.

White Suture Sleeve

No clinical impact. There are no added clinical ramifications for the use of the white suture sleeve. Due to the current approved use of the transparent lead fixation sleeve and the successful completion of the white suture sleeve biocompatibility testing and reports, there is no additional risk of use in clinical environments.

PA 11 Adapter

BIOTRONIK's PA 11 is similar to the legally marketed PA 10 where the adapters only differ in number of connectable alligator clips. The two additional surfaces are used to contact the new IS4 or DF4 leads through the PA 11 adapter and a cable to an external device.

Labeling

The package labels for the leads included in this PMA Supplement remain unchanged.
The firm made minor updates to the lead manuals (Kainox, Corox (Celerity), Selox ST/JT (Tilda T/JT), Setrox S (Tilda R, Dextrus), Solox, Linoxsmart (VOLTA) and Protego). The table below provides an overview of the changes and the affected lead manuals.

Change	Affected Lead Manuals						
	Kainox VCS	Corox (Celerity)	Selox ST/JT (Tilda T/JT)	Setrox S (Dextrus, Tilda R)	Solox	Linox^{smart} (VOLTA)	Protego
Removal of the "unipolar (UP), and Corox OTW UP Steroid" language and any associated product		X					
Minor language changes that does not alter the content of the manual		X	X	X			
Removal of OVID clinical study (OUS) and COSMO Post Approval Study (US)		X					
Warnings and Precautions section added (referring to Table 21 for more information)	X	X	X	X	X	X	
Removal of Kainox : A+, RV, RV-S, SL, and VCS wording	X						
Removal of Selox SR wording			X				
Addition of cautionary statements and notes						X	
Removal of Lead Positioning wording						X	
Removal of PA 10 warning							X

In the Protego technical manual, a cautionary statement that informs users to not contact the DF4 connectors directly with alligator clips is proposed to be removed. An investigation report, provided in Appendix 79, was conducted, and concluded that no damages or changes in the geometry, surface finishes, or electrical performances of the connectors was observed when the DF4 connectors were connected directly to the alligator clips. Based on a review of this report I believe that the cautionary statement can be removed.

The technical manuals are largely based on the OUS manual. For all manuals, there are minor language changes that do not alter the content of the manuals. In addition, several sections of the manual, including warnings and precautions, were updated for clarity and for consistency with manuals used outside the US. The proposed warnings and precautions are described on the following page.

Topic	Warning and Precaution
Lithotripsy	Lithotripsy treatment should be avoided since electrical and/or mechanical interference with the pacemaker or ICD is possible. If this procedure must be used, the greatest possible distance from the point of electrical and mechanical strain should be chosen in order to minimize a potential interference with the implant.
Medical Procedures	For any medical procedures that may affect the device (e.g., therapeutic ultrasound, external defibrillation, electrophysiological ablation, HF surgery, lithotripsy), perform a complete follow-up after the procedure.
Therapeutic Ultrasound	Therapeutic ultrasound is not recommended due to possible heating effects of the device at the implant site. If therapeutic ultrasound must be considered, it should not be applied in the immediate vicinity of the implant.
Transcutaneous Electrical Nerve Stimulation (TENS)	Transcutaneous Electrical Nerve Stimulation should be avoided, as it may lead to unintended heart stimulation.
Excessive Pressure	Excessive pressure and hyperbaric oxygen therapy should be avoided, as it may cause damage to the implant.
Intrusion of Blood	Avoid intrusion of blood into the lead lumen.
Lead Positioning	If the ICD or pacemaker is implanted underneath the pectoral muscle, ensure that no parts of the lead lie between the ribs and clavicle or between the housing of the implant and the ribs/clavicle. Chafing and pressure on the lead between the housing of the implant and the ribs/clavicle could damage the lead's insulation and thus cause premature failure.
Stylet Compatibility	To ensure compatibility, use only the stylets that are packaged with the lead. Other stylet types may result damage to the lead and/or patient injury.

BIOTRONIK is applying these changes to the US OEM manuals (Dextrus, Tilda, VOLTA, and Celerity) and plans to include the manuals in the Final Labeling Amendment. The above warnings and precaution appear appropriate. There are no further concerns with the labeling updates.

Manufacturing

All manufacturing/quality control procedures, including packaging and sterilization of the Linox^{smart} / VOLTA / Protego leads, White Suture Sleeves, and the PA 11 are performed at the following facilities:

MANUFACTURER:	CONTRACT MANUFACTURER:	(b)(4) TS/CCI
BIOTRONIK SE & Co. KG Woermannkehre 1 D-12359 Berlin Germany	BIOTRONIK AG Ackerstrasse 6 8180 Bülach Switzerland	

The facilities named above are the same facilities employed in the manufacture of all leads and accessories currently distributed by BIOTRONIK, Inc. in the United States. FDA inspected

BIOTRONIK SE & Co. KG's facility on August 12 – 15, 2013 for a routine FDA inspection of the manufacturing facility and processes. A FDA Form 483 was issued during this inspection, to which BIOTRONIK responded in September 2013. The changes identified in the submission have minor impacts to the overall manufacturing process. I believe that the verification and validation testing submitted for these changes support the manufacturing process used.

Recommendation
Approval – APPR in CTS

With this PMA Supplement, BIOTRONIK is proposed the following changes:

1. A minor modification (addition of inner coating) of to the Linoxsmart /VOLTA/Protego ICD leads (Section 4.1);
2. Modification of the current suture sleeve to create a White Suture Sleeve (Section 4.2);
3. PA 11 Adapter (Section 4.3);
4. Lead Technical Manual/Labeling updates (Section 4.4).

The firm has provided adequate and appropriate testing to support changes 1 -3 above. The lead technical manual updates all appear to be minor updates for consistency in the device manuals. The updates to the warnings and precautions also appear appropriate and were not cause for concerns. There are not outstanding concerns with this submission, therefore, I recommend approval.