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Recommendations On The Development Of Guidance Governing The Submission Of Pre-Market Reports Pursuant To MDUFMA Section 302(c)

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INTRODUCTION

Boston Scientific Corporation respectfully submits these recommendations in support of the Food and Drug Administration's (FDA's) efforts to develop guidance governing the submission of Pre-Market Reports (PMRs) pursuant to Section 302(c) of the Medical Device User Fee and Modernization Act (MDUFMA). We believe that these recommendations will aid FDA in promulgating a guidance document that is consistent with the Congressional mandate underlying the enactment of MDUFMA Section 302(c): that manufacturers who reprocess single-use class III devices adequately demonstrate that such devices are safe and effective upon reuse.

The statutory language of MDUFMA Section 302(c) and the legislative history underlying its enactment require that PMRs be identical to Pre-Market Approvals (PMAs) in the information they require. The only difference – the one recognized by Congress – is the subset of the data required in PMA submissions, including information related to certain manufacturing processes and operating specifications, that generally is not available to manufacturers who reprocess single-use devices (Reprocessors). This information may belong to the original equipment manufacturer (OEM) and may not be publicly available. Therefore, Congress drafted the provisions governing the submission of PMRs with the intent that such information not be required.

However, it is equally clear that Congress intended that PMR submissions be reviewed according to the same benchmark as that established for PMAs; that is, that the PMR submission provide a reasonable assurance of the safety and effectiveness of the reprocessed, single-use Class III device. In order to provide a reasonable assurance of the reprocessed device's safety and effectiveness, Congress intended that Reprocessors submit data to compensate for the lack of OEM-internal design and manufacturing data. This conclusion is inarguable, for the type of data excluded from PMR submissions (*i.e.*, certain design control and manufacturing data) are necessary to properly assess the safety and effectiveness of a particular device upon reuse. Without this information, Reprocessors will be unable to demonstrate adequately the safety and effectiveness of reprocessed, single-use class III devices. Therefore, these recommendations identify the types of information that may properly be excluded from a PMR submission, as well as the nature and scope of data that should be submitted in lieu of that which is excluded from the PMR.

As an initial matter, several provisions of MDUFMA Section 302(c) mandate the submission of data, also required under a PMA submission, that are readily available to Reprocessors. We will not discuss these requirements in detail in these recommendations; instead, we urge FDA to promulgate guidance with respect to these subsets of data that is analogous to the guidance that FDA has issued with respect to PMA submissions (see Section II). These recommendations discuss the types of data – which may not be available to Reprocessors – that Boston Scientific believes are essential to an adequate review of the safety and effectiveness of reprocessed, single-use Class III devices.

I. THE STANDARDS AND SCOPE OF PRE-MARKET REPORTS AS COMPARED TO PRE-MARKET APPLICATIONS

Congress enacted Title III of MDUFMA in response to significant safety concerns regarding the reprocessing and reuse of devices that are cleared or approved by FDA for single-use only. Section 302 of MDUFMA requires Reprocessors to submit PMRs when seeking approval for a Class III device that is a reprocessed single-use device.[1] In developing guidance governing PMR submissions, FDA must require Reprocessors to include the same type of information and satisfy the same standard of safety and effectiveness that is required in the submission of a PMA. This is required for two reasons. First, the language of Title III clearly describes the information that must be provided in the PMR and expressly requires Reprocessors to demonstrate the safety and efficacy of the reprocessed device. Second, the legislative history of MDUFMA, found in debate regarding a precursor bills, clearly indicates that Congress intended that Reprocessors meet the same standard of safety and effectiveness as that applicable to PMAs.

A. Information Required In PMAs That Is Not Required In PMRs

Congress intended that the PMR for reprocessed devices be virtually identical in content and scope to the PMA. Section 515(c) of the Federal Food, Drug and Cosmetic Act (FFDCA)[2] sets forth the information that must be included in a PMA. The elements that Congress requires for inclusion in a PMA are nearly identical to those included in the list of required PMR elements in Section 302(c)(2)(A) of MDUFMA. The only significant information that Congress excluded from the PMR are very limited categories of information relating to the device components and the original manufacturing process. For instance, in the original PMA, the OEM must provide "a full statement of the components, ingredients, and properties and the principle or principles of operation of [the] device."[3] A Reprocessor must include in the PMR a "description of the device's components, ingredients, and properties,"[4] but is not specifically required to describe its principles of operation. Further, while a PMA must include a "full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and, when relevant, packing and installation of [the] device,"[5] a PMR must provide a "full description of the methods used in, and the facilities and controls used for, the reprocessing and packing of the device."[6] As a result, a Reprocessor need not include a description of the methods used in, and the controls used for, the "manufacture" of the device.

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1 MDUFMA § 302(c)(2)(A).

2 21 U.S.C. § 360e(c).

3 *Id.* at § 360e(c)(1)(B).

4 MDUFMA § 302(c)(2)(A)(vi).

5 21 U.S.C. § 360e(c)(1)(C).

6 MDUFMA § 302(c)(2)(A)(vii).

B. Information Required In PMRs That Is Not Required In PMAs

In drafting the provisions excepting certain information from inclusion in PMRs, Congress recognized that discreet information relating to the manufacture of the original device and its principles of operation may belong to the OEM and may therefore not be accessible to the Reprocessor. The legislative history on H.R. 3580, a precursor to MDUFMA, reflects this recognition, stating in pertinent part:

> The information required to be submitted in [a PMR] tracks the information required to be submitted in a PMA, except that the manufacturer need not supply certain information about the manufacture and operation of the original device. It is the inability to provide this information (because it is available only from the original equipment manufacturer) that has made it difficult for reprocessing manufacturers to get PMA approval.[7]

This legislative history also makes clear that the PMR must "track" the PMA in all other respects. Moreover, in recognition of the safety and effectiveness concerns associated with reprocessing and reuse of single-use devices, MDUFMA provides that the PMR must contain "[a]ny additional data and information, including information of the type required [for a PMA] application . . . that the Secretary determines is necessary to determine whether there is a reasonable assurance of safety and effectiveness of the device."[8] For instance, Congress explicitly requires that the PMR must include "validation data . . . that demonstrates that the reasonable assurance of the safety or effectiveness of the device will remain after the maximum number of times the device is reprocessed as intended by the person submitting [the PMR]."[9] This validation data must be included in addition to, not instead of, all of the clinical and preclinical data that are required to demonstrate the safety and effectiveness of the reprocessed device. Further, MDUFMA also requires Reprocessors to certify that, to the best of the applicant's knowledge, all of the data and information submitted in the PMR are truthful and accurate and no material fact was omitted.[10] No such certification is required in PMA submissions. Therefore, notwithstanding the exclusion of limited manufacturing and operations information, Congress clearly intended that the PMR contain all of the information needed to demonstrate the safety and effectiveness of the reprocessed device, including information that may not otherwise be required in PMA submissions.

C. The Standard of Review Applicable To PMRs

As discussed above, PMR submissions must establish the "safety and effectiveness" of the used, reprocessed device. The legislative history of MDUFMA makes clear that the "safety and effectiveness" standard applicable to PMRs is the same "safety and effectiveness" standard required for PMA submissions. The Report on H.R. 3580 states:

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7 H.R. REP. NO. 107-728, at 46 (2002).

8 MDUFMA § 302(c)(2)(A)(xi).

9 *Id.* at § 302(c)(2)(A)(xii).

10 *Id.* at § 302(c)(2)(A)(x).

> FDA still is able to require all or some of the other information needed to establish a reasonable assurance of safety and effectiveness that would have been required in a PMA, including clinical data. . . . The Committee intends that the standard for approval of a pre-market report be identical to the standard for PMA approval under section 515: a reasonable assurance of safety and effectiveness. Nothing in this section is to be construed as lowering this standard.[11]

Clearly, Congress intended that FDA require the submission of information in a PMR that "tracks" the information submitted in a PMA and that satisfies the same safety and effectiveness standard necessary for PMA approval. The only substantive difference between the requirements of a PMA and PMR is certain manufacturing and operating information produced and held by OEMs that is not available to Reprocessors. However, Congress explicitly requires the submission of extensive validation data and has authorized FDA to require the submission of any additional data – including information beyond that required in a PMA submission – that is needed to demonstrate that the reprocessed device satisfies the same standard of safety and effectiveness applicable to the original PMA. PMRs are not meant to be "PMAs minus one;" they are meant to be the same in all substantive respects.

II. CONTENT OF PRE-MARKET REVIEW APPLICATIONS

FDA has promulgated extensive regulations and guidance documents implementing the PMA requirements of Section 515 of the FFDCA. These regulations and guidance documents clearly articulate the specific information, data and format that must be included in a PMA to satisfy the statutory requirements.[12] According to FDA's PMA regulations and guidance documents, a PMA must include the following sections:

- General information, including the device name, submitter's name and address, and manufacturing sites and addresses;
- Table of contents;
- Summary of safety and effectiveness;
- Device description, including engineering drawings, functional components or ingredients, device properties, principles of operations, draft labeling and draft operators manual;
- Manufacturing information in accordance with the QSR;

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11 H.R. REP. NO. 107-728, at 46-47 (2002).

12 The information that must be included in a PMA is set forth at 21 C.F.R. § 814.20 and incorporate the Quality System Regulation at 21 C.F.R. § 820. Guidance documents that outline the sections needed to complete a PMA include the "Premarket Review Manual," HHS Publication FDA 97-4214 (January 1998) and FDA's "Guidance for Industry on PMA Shell Development and Modular Review" (Nov. 6, 1998).

- Certification of conformance with performance standards;
- Non-clinical laboratory studies, including product testing, biological testing, useful life, animal testing of finished device, other appropriate animal testing, statement of Good Laboratory Practice (GLP) compliance and environmental assessment;
- Clinical studies, including a description of the device's intended use, clinical protocols, and safety and effectiveness data;
- Bibliography and references;
- Operations and instructions manual; and
- Applicable post-marketing studies.

FDA should also require that each of these components also be included in a PMR for a Class III reprocessed single-use device. The PMR guidance would differ from the PMA requirements in several notable respects. First, like a PMA, the PMR must include detailed information, including composition, diagrams, functions and characteristics of the device's components, ingredients and properties. It need not, however, provide information regarding their specific principles of operation that must be included in a PMA. The PMR submitter must nonetheless include adequate information regarding the function and operation of device components to ensure that their safety and effectiveness are not compromised by reprocessing and reuse.

Second, although the Reprocessor is not required to provide detailed information regarding the OEM manufacturing process, it must nonetheless provide detailed design and reprocessing information to demonstrate its compliance with the Quality System Regulation (QSR) at 21 C.F.R. Part 820, including validation data demonstrating the safety and effectiveness of the reprocessed device up to the maximum number of times the device is reprocessed.

Third, the PMR must include a statement affirming the completeness, truth and accuracy of the information provided. Finally, the PMR must include labels and advertising information that adequately describe the reprocessed device, its intended use, and its directions for use such that the reprocessed device is not misbranded.

The recommendations below focus on three key aspects of the PMR submission for reprocessed single-use devices: (1) compliance with QSR requirements for reprocessed devices; (2) clinical and non-clinical studies for reprocessed devices; and (3) labeling of reprocessed devices.

III. APPLICATION OF THE QUALITY SYSTEM REGULATION TO REPROCESSED DEVICES

MDUFMA requires that a PMR for a reprocessed, single-use device include a "full description of the methods used in, and the facilities and controls used for, the reprocessing and

packing of the device."[13] As with the manufacture of single-use devices, the reprocessing of a device for reuse must comply with the QSR requirements at 21 C.F.R. Part 820 and in FDA's recently-issued Quality System Information guidance document applicable to PMA reviews.[14] The QSR requirements apply to all "manufacturers of finished medical devices,"[15] including persons who "process" or "remanufacture" a finished device.[16] Reprocessors must therefore demonstrate in the PMR their compliance with the applicable QSR requirements. As a result, the PMA QSR Guidance provides the most appropriate starting point for determining the type of information that Reprocessors need to include in their PMRs to demonstrate that they satisfy the requirements of the QSR.

The recommendations outlined below follow the approach outlined in FDA's QSR Guidance to identify the QSR information that must be included in a PMR. As presented in the QSR Guidance, the PMR must include both "Design Control" and "Manufacturing" (or, in this case, reprocessing) information. In addition, the PMR must contain validation data establishing the maximum number of times the device can be reprocessed. Each of these categories of information and their particular components are discussed below. Where particular design or manufacturing information is unavailable to the Reprocessor, these recommendations address the types of data that must be included in PMR submissions to demonstrate the safety and effectiveness of the reprocessed device.

A. Design Control Information

The QSR Guidance requires that PMAs include extensive design control information, including: (1) design and development planning; (2) design input; (3) design output; (4) design review; (5) design verification; (6) design validation; (7) design transfer; (8) design changes; and (9) design history.

Reprocessors must provide design information for each type or brand of single-use Class III device that they intend to reprocess, and for each component of that device. As a result, a Reprocessor must be required to submit a separate PMR for each device model it reprocesses. Although Reprocessors may not have access to the OEM's design history for a particular device, it is essential that, in order to ensure the safety and effectiveness of reprocessed single-use Class III devices, Reprocessors develop and submit precise and comprehensive design data in order to identify, characterize, verify and validate all relevant design inputs and outputs and to account for and address any design changes. Single-use devices are not designed for reprocessing and, as such, the manufacturer of the device (the OEM) does not account for multiple uses in its design control procedures.

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13 MDUFMA § 302(c)(2)(A)(vii).

14 *See* FDA, "Quality System Information for Certain Premarket Application Reviews; Guidance for Industry and FDA Staff," U.S. Food and Drug Association, Center for Devices and Radiological Health (February 2003) (QSR Guidance).

15 21 C.F.R. § 820.1.

16 *Id.* at § 820.3(o).

Indeed, the specifications relating to the design, materials, durability, and other characteristics of a single-use device frequently reflect the OEM's intention that the device be disposed of after a single-use (and not be reprocessed). Therefore, the Reprocessor must identify and develop design controls applicable to the reprocessed, single-use device. These must assess not only the characteristics, composition, materials and performance of the original single-use device, but also must consider the variable conditions of use, misuse, handling, preprocessing and reprocessing of the device. In effect, the single-use device intended for reprocessing must be evaluated as though it is a different, *new* device for purposes of promulgating design control procedures.

Further, even if Reprocessors have access to OEM design control and performance specifications, they must still account in their design control system for the stresses and effects of use and reprocessing on the device, as well as the characteristics of the device that may be relevant to reprocessing that may not have been relevant to its safety and effectiveness for a single use. The Reprocessor must therefore define and validate specifications for the used device to ensure that it performs as intended upon reprocessing and reuse.

These requirements, which are necessary to ensure the safety and effectiveness of reprocessed, single-use Class III devices, are summarized below.

1. General

As for PMAs submitted by the OEM, Reprocessors must include in PMRs an explanation of the application of their design control processes to each used, reprocessed device.

2. Design and Development Planning

Reprocessors must develop and submit in their PMR a comprehensive Design and Development Plan comparable to that submitted in the PMA. The Plan must include consideration of design inputs, outputs, review, verification, validation, transfer, changes and history for the used, reprocessed device. Risks associated with used, reprocessed devices may be different in magnitude and nature than those of the single-use counterpart. Reprocessors must therefore incorporate and explain their risk management activities in their Design and Development Plan.

3. Design Input

The QSR Guidance requires manufacturers to provide a copy of the procedures used to identify and control design input for the device under review. This information must also be included in a PMR. The design control procedures must address incomplete, ambiguous or conflicting input requirements, and must explain the documentation, review and approval of design inputs. Potentially relevant aspects that must be considered include, among others:

- Intended use;
- Performance characteristics;
- Safety requirements;

- Safety and performance parameters;
- Toxicity;
- Bio-compatibility;
- Compatibility with accessories and the use environment;
- Electromagnetic interference (EMI);
- Clinical reports;
- Physical/chemical characteristics; and
- Labeling and packaging.

For each used, single-use Class III device to be reprocessed, the PMR must identify the performance characteristics and design specifications of each component of that device. These specifications should be defined on a component-specific basis, depending on the nature of the device. A Reprocessor must have controls in place to account for various attributes of the device, such as compatibility with disinfection and sterilization, component composition, sterility and cleanliness, tensile strength, flexibility, trackability, electronic parameters, shelf life, and ageing. The Reprocessor must develop device-specific input specifications based on the intended use, design characterization, and safety and performance requirements and parameters for the reprocessed device. The design inputs should identify and consider all potential and emerging risks associated with the reprocessing and reuse of the used device, including, for example, the risk of prion infection.

4. Design Output and Design Reviews

The QSR Guidance requires that manufacturers provide a copy of the procedures used to define and document design output in terms that permit an adequate and measurable evaluation of conformance to design input requirements for the device. Reprocessors must develop and identify design outputs sufficient to ensure the proper function of the used, reprocessed device, including output acceptance criteria and mechanisms for identifying essential design outputs for each device model and manufacturer. Reprocessors must also develop and submit procedures for design reviews.

5. Design Verification and Validation

The QSR Guidance requires manufacturers to describe the process that confirms the design outputs meet the design input requirements. Manufacturers must also provide the procedures used to verify or validate the design for the device under review. The procedure should include:

- Validation/verification results;
- Identification of the design;

- Validation/verification methods;
- Dates; and
- Individuals performing the validation/verification.

For used, reprocessed devices, MDUFMA requires "validation data that . . . demonstrates that the reasonable assurance of the safety or effectiveness of the device will remain after the maximum number of times the device is reprocessed as intended by the person submitting [the PMR]."[17] Boston Scientific Corporation submitted extensive recommendations to FDA on January 21, 2003 outlining the minimal validation program that must be in place to ensure reprocessed versions of single-use devices remain both safe and effective prior to reuse.[18] Boston Scientific urges FDA to adopt those recommendations when promulgating PMR guidance. Some pertinent aspects of those recommendations are discussed below.

As discussed above, single-use medical devices are designed and manufactured for one use only. The OEM selects the device design and materials necessary for effective first-use performance, functionality and cost-effectiveness, not for long-term durability or tolerance to repeat sterilization. Differences in device design and materials may significantly affect a device's compatibility with cleaning and sterilization processes. Therefore, data must be developed to validate the cleaning, disinfection, sterilization and functional performance of each model or make of the device and for each time the device is to be reprocessed. Extensive up-front information regarding device characteristics and design input and output parameters is required to demonstrate that, for each type of device reprocessed, the device's materials are compatible with reprocessing (*i.e.*, with disinfecting and sterilizing agents), that the design specifications relating to the functionality, integrity, and critical performance characteristics of the device are not adversely impacted by prior use and reprocessing, and that the surfaces and crevices of the device can be adequately cleaned, disinfected and sterilized (including inner surfaces and lumens).

The cleaning and sterilization processes must be validated to demonstrate that the established processes are effective and reproducible. As discussed in greater detail in the attached validation comments, this must include equipment and installation qualification, operational and performance qualification, review and approval of validation, as well as validation of microbiocidal effectiveness and pyrogen testing. In addition, sterilization processes must be validated and controlled in accordance with recognized standards. However, it should not be assumed that such standards are effective in inactivating prions, which are believed to be the causative agents of spongiform encephalopathies such as Creutzfeld-Jakob disease.

Reprocessors also must validate procedures governing bioburden and particulate testing. Once the cleaning, decontamination and disinfection processes have been validated, the Reprocessor should conduct baseline testing to determine the level of bioburden on the reprocessed devices. The Reprocessor should then institute and document a program of

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17 MDUFMA § 302(c)(2)(A)(xii).

18 A copy of Boston Scientific's validation comments are submitted with these comments as Attachment A.

bioburden and particulate monitoring to ensure that a consistent level of bioburden is achieved on the reprocessed devices pursuant to the established baseline. This validation data should also demonstrate the effectiveness of test methods for recovery of bioburden and particulate.

Finally, the Reprocessor should include information demonstrating compliance with ISO 10993 – Biological Evaluation of Medical Devices – Part I: Evaluation and Testing. This information should demonstrate that leachable substances, including cleaning and disinfection chemicals, do not adversely affect the safety and biocompatibility of the device. Due to the variability of chemical and material interactions, the Reprocessor should test each individual device model to ensure compliance with design input requirements and ISO 10993.

6. Design Transfer

Reprocessors should submit a copy of the procedure used to transfer the design output to reprocessing procedures for the device. The procedure should detail how the Reprocessor conducts final review and approval of design and development activities.

7. Design Changes

Manufacturers are required in the QSR Guidance to document their procedures for handling design changes in the original device, and must describe when it uses verification instead of validation. In the PMR, Reprocessors must similarly account for changes made to their reprocessing procedures. In addition, the Reprocessor must account for design changes made to the device by the OEM, indicated by the filing of a new PMA by the OEM or otherwise. Design changes made by the OEM must be addressed by the Reprocessor's design control process described in a PMR. Reprocessors must ensure that their "raw materials" – the used, single-use devices intended for reprocessing – continue to satisfy the design input and output specifications for the particular device model and manufacturer. Reprocessors must file a new PMR describing the revised design control procedures each time the OEM files a new PMA or supplement for a particular device.

B. Manufacturing (Reprocessing) Information

MDUFMA requires that the PMR include "a full description of the methods used in, and the facilities and controls used for the reprocessing and packing the device."[19] Reprocessing procedures for a single-use Class III device must be designed, characterized and validated in the same way as the manufacturing process instituted by an OEM. Thus, PMRs should include the same quantity and quality of information relating to the reprocessing and packing operations as that which is required regarding manufacture in a PMA submission. Indeed, as discussed above, single-use devices are designed and manufactured for one use only; the device, after its first use, becomes a "raw material" in the hands of the Reprocessor. The used device may have been subject to varying levels of stress, wear, soil or contamination and may pose potential risks to health that are not readily apparent. Therefore, in order to ensure the safety and effectiveness of Class III devices, Reprocessors must generate data on each original device model and

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[19] MDUFMA § 302(c)(2)(A)(vii).

manufacturer, characterize the methods of reprocessing, and validate the performance of these methods.

1. Quality System Procedures

Reprocessors must promulgate and provide a copy of its quality system procedures. The procedures must contain the same information required in a PMA submission (described in the QSR Guidance), including quality or internal audit procedures, management review procedures and the structure of the quality system documentation.

2. Production Flow

Just as an OEM must provide a production flow diagram in its PMA that identifies the steps involved in the manufacture of a device, the Reprocessor must similarly provide a flow diagram that identifies the steps of its reprocessing process. This diagram should include all the pertinent steps of the process, including used product design characterization and specifications; reprocessing methods, equipment and materials; standards for device performance, cleanliness and sterility; and product review and approval procedures.

In order to adequately characterize and design its cleaning and sterilization process, the Reprocessor must assess, among other things: (1) the longest time interval between the first use of a device and reprocessing; (2) the compatibility of selected cleaning, disinfecting and sterilization agents with the device design, materials and components; (3) the factors that affect microbiocidal effectiveness in the sterilization process; (4) the effects of sterilizing agents on materials, device performance, personnel safety and environmental protection; and (5) specifications for the number of sterilization cycles allowed for each particular device model and OEM.

In addition, Reprocessors must account for any differences in the sterilization method(s) they employ versus those employed by the OEM. OEM's choose raw materials for their products based on first-use performance and cost-effectiveness, not long-term durability or sterilization tolerance. For example, OEMs may choose raw materials that may not be stable when exposed to repeated sterilization. On the other hand, Reprocessors choose reprocessing methods based on effectiveness and cost. Thus, for example, Reprocessors may favor radiation over ethylene oxide or steam sterilization because the latter is more costly. Because the effects of different sterilization methods vary for different materials, Reprocessors must evaluate and validate the effects of a particular reprocessing method on a particular device based on the characteristics and tolerances of the materials from which they are made. The Reprocessor must demonstrate, not only that the material comprising a particular device is compatible with its sterilization and cleaning processes, but also, as in the case of gamma sterilization, that material stability and performance are not diminished up to the total acceptable dose of radiation to which the device will be exposed up to the maximum number of times the device is reprocessed.

With respect to microbiocidal effectiveness, the Reprocessor must demonstrate the adequacy of the chosen sterilizing agent with respect to the contamination expected to be on the device, based on worst-case conditions. The Reprocessor must also (1) identify the process variables and document physical and/or chemical interactions that may adversely affect the

effectiveness of the chosen sterilizing agent; and (2) identify the processing steps used to remove residues from the device after sterilization and the procedures for testing and approving the reprocessed device.

3. Purchasing Controls

As the QS Guidance recognizes, purchasing controls are particularly important if a manufacturer uses a contract design service or contract manufacturer for a device. It is suggested that manufacturers provide:

- Description of the manufacturer's supplier evaluation process and a description of how the manufacturer determines the type and extent of control that it exerts of suppliers;
- Description of how the manufacturer maintains records of suitable suppliers and how it addresses the purchasing approval process; and
- Explanation of how the manufacturer balances purchasing control and receiving acceptance activities to ensure that the product is acceptable for its intended use.

These same considerations are even more important in the PMR context, where Reprocessors exert *no* control over the original equipment design or the conditions of use to which the used device has been subjected. Even for identical models and makes, used devices are sure to vary within each batch, and among batches, due to variable conditions of use (or misuse) resulting in variable levels of stress, wear, contamination, or bioburden. Therefore, it is essential that the Reprocessor describe the procedures it has implemented to ensure that each device it reprocesses meets the design specifications it has established for the particular model and manufacturer.

4. Production and Process Controls

Reprocessors must provide copies of the procedures for controlling the extent of environmental and contamination effects on the device, as is required in the QSR Guidance.

5. Inspection, Measuring, and Test Equipment

Reprocessors must provide a copy of procedures describing how inspection, measuring, and test equipment is calibrated, inspected, checked, and maintained. Reprocessors must also demonstrate the extent to which their means of reprocessing, *e.g.,* cleaning and sterilization, are monitored. Specifically, Reprocessors should establish and document the complete specifications of all equipment used to clean or sterilize the device, including any ancillary items, as well as equipment used to package, test or inspect the reprocessed device prior to approval and release. The Reprocessor should also include the established operating procedures for the equipment, and should document instructions for installation and monitoring of such equipment.

6. Process Validation

Reprocessors must describe in the PMR the validation procedures and plans it has implemented using objective and measurable acceptance criteria. The Reprocessor should describe how appropriate statistical methods for data collection and analysis are used. Specifically, the Reprocessor should generate data demonstrating the attainment of defined physical, chemical and/or microbial conditions within specified tolerances, and should confirm that the product meets the specified requirements for safety and performance following the application of the defined process at the upper and lower tolerances of the process parameters.

The Reprocessor must also document the criteria used for designating an individual process used for a particular device model or OEM. Further, the Reprocessor should provide the procedures for monitoring and process controls that it has established to ensure that the specified cleaning and sterilization process has been properly applied to the reprocessed device. This may include recorded measurements, supplemented as necessary by biological or chemical indicators, which demonstrate that the sterilization process was applied to the device within the specified parameters, and data demonstrating the attainment of the process parameters.

7. Receiving Acceptance Activities

Reprocessors must provide a copy of the procedures for receiving or incoming acceptance activities. This is particularly important in the context of reprocessed medical devices, where the "raw material" accepted by a Reprocessor is the used, single-use device intended to be reprocessed. It is essential to demonstrate that the used device, which will have been subjected to unknown conditions of use, meets appropriate specifications and is suitable for reprocessing. As outlined in the QSR Guidance, the PMR should describe the Reprocessor's assessment techniques, including the nature of inspection and tests, supplier audits, a history of a particular device model's compliance with design input controls, and the risks associated with reprocessing the product as identified in a risk management program.

Additionally, the PMR should outline the Reprocessor's acceptance and rejection criteria, describe how rejected devices are disposed, and identify how and when nonconforming devices are reworked, accepted, regraded, scrapped, or returned. Finally, documentation of acceptance activities should be included in the PMR, especially with respect to how the Reprocessor conducts acceptance activities (through material analysis or otherwise).

8. Final Acceptance Activities

Reprocessors must identify specific release criteria, based on valid scientific methods. The Reprocessor must ensure that the reprocessed single-use Class III devices meet established design control output requirements and performance specifications, including, but not limited to, sterility, cleaning, and functionality criteria. This is necessary to adequately ensure that the reprocessed device will be safe and effective for its intended use after each time that it is reprocessed, up to the maximum number of reuses.

9. Nonconforming Products

As discussed in the QSR Guidance, a Reprocessor must document, through Corrective and Preventive Action (CAPA) procedures or otherwise, how nonconforming products are handled. In the PMR, the Reprocessor should address identification, documentation, evaluation, segregation, and disposition of nonconforming products.

10. Corrective And Preventive Action

Reprocessors should include in their PMRs a copy of their CAPA procedures. The procedures should address analysis of multiple data inputs from the Reprocessor's quality control system. The procedure should clarify the information included in such analyses and the mechanisms for justifying when data are not included. The procedures should also identify:

- Method for determining verification or validation;
- Implementation planning to include recording changes in methods and procedures; and
- Method for disseminating information on the quality problem of non-conforming product to those responsible.

This section of the PMR should explain, among other things, how design changes made under the Reprocessor's CAPA program interact with the Reprocessors design change control system and risk management program.

11. Complaint Files

Reprocessors should provide a copy of the procedures for handling complaints. The procedure should identify the criteria used to determine whether a complaint merits investigation, how such decisions are documented, and how the procedure is coordinated with the procedure for handling nonconforming products.

In addition to the requirements outlined in the QS Guidance, the Reprocessor must also provide documentation identifying controls for determining the number of times a particular device has been reprocessed if a complaint is made. Additionally, any complaint that represents an event which must be reported to FDA under 21 C.F.R. Part 803 or 804 should be maintained in a separate portion of the complaint file. The record of investigation conducted for these complaints should include (1) whether the device failed to meet specifications; (2) whether the device was being used for treatment or diagnosis; (3) the relationship, if any, of the device to the reported incident or adverse event; and (4) the number of times the device had previously been used and reprocessed. The Reprocessor must create and maintain performance trending data demonstrating the efficacy of a reprocessed, single-use device after each use up to the maximum number of uses.

IV. CLINICAL TRIALS

MDUFMA requires that Reprocessors include in the PMR "full reports of all information . . . known to the applicant concerning investigations which have been made to show whether or not the device is safe or effective."[20] As Congress recognized, the safety and effectiveness standard for PMR approval is "identical to the standard for PMA approval," and FDA can require all of the information "that would have been required in a PMA, including clinical data."[21] To satisfy the standard, Reprocessors must develop and submit clinical data sufficient to ensure the safety and effectiveness of the reprocessed device. Clinical data must be developed for each reuse up to the maximum number of reuses specified by the Reprocessor. This data should be specific to each device model and OEM, and to the specified design control and reprocessing parameters developed for the devices.

Clinical data demonstrating the safety and effectiveness of the unused, single-use device are not adequate to demonstrate the safety and effectiveness of the reprocessed device. Clinical data must be developed on the used, reprocessed device after each reuse because it is not otherwise possible to identify, control for and validate all aspects of design and reprocessing parameters given the large numbers of variables that may impact the safety and effectiveness of the reprocessed device, including the conditions of original use (or misuse), device soil and contamination, material degradation, degradation of critical bonds and seals, handling characteristics, and materials integrity and properties.

Nor are design and process validation and controls alone sufficient to reasonably assure the safety and effectiveness of the reprocessed device. A reprocessed single-use device is not like a drug with a common chemical moiety, where a second manufacturer can reasonably be assured of the drug's safety and effectiveness even in the absence of new clinical data. For reprocessed devices, design data generated after the first use or reuse will not be sufficient to demonstrate the safety and effectiveness of the device after the next reuse. Each new reprocessing and reuse results in a new device because, on each use, the device will be manipulated and subjected to stresses in variable ways. Clinical data must therefore be developed to account both for the effects of each use as well as for the cumulative effect of all prior uses and reprocessing.

Clinical studies must be conducted on devices which have been subjected to reprocessing and conditioning in a manner that provides an assurance of safety and effectiveness after each use (*i.e.,* clinical studies demonstrating user handling equivalency in a typical clinical setting). Under Section 302(c), Reprocessors must independently establish and present adequate evidence to support the assertion that the reprocessed device is safe and effective after each individual use up to the maximum number of uses. In order for FDA to make this finding and for the Reprocessor to meet this high threshold, Reprocessors should include in PMR submissions adequate clinical data from testing of reprocessed devices supporting the conclusion that they are safe and effective each time they are reused and reprocessed.

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[20] MDUFMA § 302(c)(2)(A)(v).

[21] H.R. Rep. No. 107-728, at 46-47 (2002).

V. LABELING

Reprocessors must include in their PMR, "proposed labels, labeling and advertising, sufficient to describe the device, its intended use and directions for reuse."[22] Appropriate labels and labeling are essential to ensure that the device is safe and effective and not misbranded.

Reprocessors must develop labeling that is consistent with the design specifications developed for the particular single-use device intended to be reprocessed. OEMs may label and package single-use devices in ways that may not be appropriate for reprocessed devices. Therefore, Reprocessors should include in their PMR submissions the labeling and packaging design they have developed to reflect the specific design control parameters that have been established for each device model and manufacturer. The labeling must include, for example, appropriate shelf-life information for both product shelf-life and sterile package shelf-life. It must also include instructions relating to use of the reprocessed device and handling of the used device prior to shipment for reprocessing. In addition, labeling and packaging controls must include information sufficient to indicate how many times the device has been reprocessed, in order to ensure that the device is removed from the market after the maximum number of uses.

CONCLUSION

Boston Scientific appreciates this opportunity to submit comments in support of FDA's promulgation of guidance applicable to the submission of PMRs. We believe that PMR Guidance should require the same type and quantity of information as that required in PMA submissions, with the exception of certain specified design and manufacturing data that are not available to Reprocessors. With respect to such information, Reprocessors should submit data equivalent to that in the QSR guidance for PMAs, tailored to the context of a PMR for reprocessed, single-use devices. In addition, Reprocessors should submit clinical data demonstrating that the reprocessed, single-use device will be safe and effective upon each reuse up to the maximum number of reuses. Guidance issued in this fashion, and adopting the recommendations outlined above, would provide a reasonable assurance of safety and effectiveness of reprocessed, single-use Class III devices. Boston Scientific is willing to work with FDA in developing PMR Guidance, and urges FDA to contact us with any questions or comments.

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[22] MDUFMA § 302(c)(2)(A)(iv).