Guidance for Industry

Contents of a Product Development Protocol

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Draft Guidance – Not for Implementation

This guidance document is being distributed for comment purposes only.

U.S. Department Of Health And Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Office of Device Evaluation

Preface

Public Comment

Comments and suggestions regarding this draft document should be submitted by October 26, 1998 to Docket No. 98D-0563, Dockets Management Branch, Division of Management Systems and Policy, Office of Human Resources and Management Services, Food and Drug Administration, 5630 Fishers Lane, Room 1061, (HFA-305), Rockville, MD 20852

Additional Copies

World Wide Web/CDRH/ home page: http://www.fda.gov/cdrh/pdp/pdpguide.pdf, or CDRH Facts on Demand at 1-800-899-0381 or 301-827-0111, specify number 473 when prompted for the document shelf number.

Foreword

This document provides guidance on the content of product development protocol (PDP) applications, expected actions and time frames in the development of a product under a PDP, and how changes during the course of product development under a PDP should be handled. This guidance also provides a framework for interaction between FDA and the applicant, but, because of the wide range of devices that may be developed under the PDP authority, it is unlikely that every element addressed in the guidance will apply to any given device.

This guidance document represents the agency's current thinking on the Product Development Protocol process and the relative duties and responsibilities of the agency and the applicant.[1] It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable FDA statutes and regulations.

Section 515(f) of the Food, Drug, and Cosmetic Act provides an alternative to the IDE and PMA processes for class III devices subject to premarket approval. This alternative process, the product development protocol (PDP), was not implemented during the early years of FDA's medical device program because it was considered potentially complex and there was a need to focus attention on implementing the core provisions of the Medical Device Amendments of 1976 such as the IDE, PMA, 510(k), GMP, and problem reporting requirements.

The PDP process outlined in §515(f) consists of the following elements:

Class III devices subject to premarket approval may be approved through the PDP process. §515(f)(1).

Review of by an advisory panel when necessary. §515(f)(2).

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[1]FDA gratefully acknowledges the significant contributions of the following industry participants in the development of this guidance: Merry Lee Evans, MED Institute; Neal Fearnot, MED Institute; Steve Ferguson, Cook Group, Inc.; Peter Johnson, PTEI; William Pignato, Chiron Diagnostics Corporation; Janet Trunzo, HIMA; Donald Stone, McKenna & Cuneo; David Smith, Reed, Smith, and Shaw; Charles Swanson, Medtronic, Inc.; and Pamela Weagraff, Hewlett-Packard, Inc.

A proposed PDP must include:

> A description of the device and any changes that may be made.
>
> A description of any preclinical trials.
>
> A description of any clinical trials.
>
> A description of manufacturing methods, facilities, and controls.
>
> A description of any applicable performance standards.
>
> Proposed labeling.
>
> Any other information "relevant to the subject matter of the protocol" thought necessary by FDA. The advisory panel must concur in the need for this additional information.
>
> A requirement for progress reports to FDA and, when completed, records of the trials conducted under the protocol.

§515(f)(3).

A proposed PDP is to be approved or disapproved by FDA within 120 days unless the parties agree to an extension of time. §515(f)(4). Note that this provision does *not* provide that the PDP is deemed approved if FDA fails to meet the 120-day time frame, placing it in the same category as the 180-day requirement applicable to PMAs.

At any time after a PDP has been approved, the PDP holder may submit a "notice of completion" explaining how the protocol has been fulfilled and setting forth the results of the trials required by the protocol. §515(f)(5).

FDA may revoke an approved PDP prior to its completion if the protocol is not complied with, if the results of trials under the PDP differ substantially from required results, or the results of trials show the device presents an unreasonable risk to health and safety. §515(f)(6)(A).

Within 90 days of receipt of a notice of completion, FDA must either declare the protocol completed or declare it not completed. FDA may declare a protocol not completed only if the protocol is not complied with, if the results of trials under the PDP differ substantially from required results, or there has not been an adequate showing that the device is safe and effective as labeled. §515(f)(6)(B).

FDA has not promulgated regulations under the PDP authority. Until a regulation is promulgated, the statute and this guidance will serve as the primary expression of FDAís policies concerning the PDP process.

FDA believes the Product Development Protocol offers an extremely flexible framework for the development of new medical devices. It provides a streamlined

method through which an applicant and FDA can reach agreement concerning the criteria and data necessary to ensure the safety and effectiveness of a class III device prior to the start of preclinical and clinical trials. Devices approved through the PDP process may be modified within defined bounds without prior FDA approval.

Every class III device subject to premarket approval, irrespective of its stage of development, shall be eligible for review under the PDP process except for such devices as FDA specifically acts to exclude from the process. Class III devices which FDA excludes from the PDP process must be cleared through the PMA process. FDA will maintain a list of devices that it has determined to be ineligible for the PDP process; this list will be available though CDRH's Internet site (www.fda.gov/cdrh), by fax, and by mail. FDA may also periodically provide this information through the *Federal Register*, but publication in the *Federal Register* is not required for FDA to exclude a device from the PDP process.

When FDA acts under §515(b) to require submission of premarket approval applications for pre-Amendments class III devices, applicants may submit a PDP in lieu of a PMA unless FDA specifically acts to exclude particular device from the PDP process.

The existence of a Product Development Protocol will not be disclosed by FDA until one of the following conditions is met:

FDA has made a final determination concerning a Notice of Completion of the PDP;

The applicant has disclosed or otherwise confirmed the existence of the PDP; or

The applicant has failed to submit a Notice of Completion within the time set forth in the PDP.

No materials submitted to FDA will be disclosed until FDA has made a final determination concerning a Notice of Completion of the PDP or that the applicant has failed to submit a Notice of Completion within the time set forth in the PDP. At that time, all materials submitted to FDA will be subject to disclosure under the Freedom of Information Act to the same extent as equivalent information submitted under the investigational device exemption and premarket approval provisions of the FD&C Act.

For general information on the PDP process, or to comment on this guidance, please contact :

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INTRODUCTION

The 1976 Medical Device Amendments created a mechanism for the regulation of Class III medical devices that would allow a sponsor to come to early agreement with FDA as to what would be done to demonstrate the safety and effectiveness of a new device. It was recognized that early interaction in the development cycle of a device could allow a sponsor to address the concerns of the FDA before expensive and time consuming resources were expended. Many manufacturers already employ the concept of concurrent engineering, that is, they involve manufacturing and service personnel early in the design process to identify and address potential concerns. The Product Development Protocol (PDP, or Protocol) extends this concept to regulatory requirements. It is an attempt at "front loading" the approval process by considering all regulatory areas as well as product design and testing in the early concept and planning stages, since this will most efficiently solve most problems. Thereby, the regulatory oversight during product development is limited to administrative and conformance assessment.

The Protocol describes the agreed upon details of design and development activities, the outputs of these activities, and acceptance criteria for these outputs. It establishes reporting milestones that convey important information to the FDA as it is generated, where they can be reviewed and responded to in a timely manner. The sponsor would be able to execute their Protocol at their own pace, keeping FDA informed of their progress with these milestone reports.

As each device is unique, negotiations should be conducted to reach agreement as to what activities will be performed during the course of product development. This guidance document is designed to identify all potential areas for discussion of what the outputs of these activities will be and the acceptance criteria that can be used to assess these outputs. This "contract" establishes a predictable path to market with a potentially shorter review time frame when the device is ready for market. This document is intended to provides guidance throughout the life cycle of the device ("cradle-to-grave") on the engineering, preclinical, clinical, manufacturing and post-market content of the PDP contract.

The PDP process is initiated with an optional consultation with FDA to determine if the device is appropriate for review as a PDP, PMA, or other regulatory pathway. This phase is referred to as the Proposal. Its purpose is to establish that both FDA and the sponsor are willing to commit to activities, outputs, and acceptance criteria which would support regulatory approval of the described device. The sponsor would prepare a submission based on the guidance contained in Part I of this document. FDA has 30 days to review this information.

Once it has been determined that the appropriate regulatory mechanism for approval is the Product Development Protocol, the sponsor may submit the Detailed Contents of the Protocol. Guidance for the information necessary is described in Part II of this document.

The Protocol will come to consist of a table of contents, device requirements and description, details of proposed verification and validation activities, clinical trial data, quality systems and post-market information. It may have details and timing of milestones and reporting requirements, notices, and special requirements for Notice of Initiation of Clinical Trials and the last progress report before the Notice of Completion. FDA has 120 days to review the Detailed Contents during which time it can request additional information. Following this review, FDA can either accept the PDP or deny for lack of content.

The scope and extent of the Detailed Contents submission should be carefully considered, as should the information contained in each milestone. Review of the milestone reports should be primarily administrative to ensure that the agreed upon activities were executed, that the outputs are as expected, and that the acceptance criteria have been met. Normally, FDA will have 30 days to review these reports. Milestone reports showing a deviation from the Protocol that may substantially impact safety and effectiveness may require additional negotiations with FDA to reach new agreements on impacted activities and acceptance criteria. Sponsors should have an established procedure for assessing this impact and determining if FDA should be consulted. A suggested matrix of modifications is contained as Appendix VI to this guidance document.

PART I: PROPOSAL

Part I is the Proposal for the submission which initiates the formal PDP process. The information in the Proposal should demonstrate that the intended use and indications for use are sufficiently developed for both the Agency and sponsor to commit to protocols, protocol outputs, and assessment criteria. It may serve to identify areas where discussions are needed prior to the submission of the full PDP.

1 SPONSOR IDENTIFICATION

1.1 COMPANY NAME AND ADDRESS

1.2 ESTABLISHMENT REGISTRATION NUMBER, IF AVAILABLE

1.3 COMPANY CONTACT PERSON, TELEPHONE NUMBER, FAX NUMBER AND E-MAIL ADDRESS

2 DEVICE INFORMATION

2.1 NOMENCLATURE (I.E., FOR PRODUCT AND COMPONENTS)

2.1.1 Common, generic, or usual name(s)

2.1.2 Proprietary name(s)

2.2 DEVICE DESCRIPTION

2.2.1 Sample, labeled diagram and/or photographs or video tape

2.2.2 Overview of theory/principles of operation

Describe how the device design relates to the clinical application and explain the underlying principles of operation

Overview of material, physical, chemical and/or biological composition

2.2.3 Summary of hazards identified or anticipated, their causes and associated risks, and proposed mitigating action.

2.3 DESCRIPTION OF INTENDED USE

2.3.1 Indications for use; description of indications, description of target population, claims and clinical utility (Blue Book Memorandum P91-1).

2.3.2 Description of intended use environment

3 BACKGROUND INFORMATION

3.1 Relevant regulatory submission numbers (e.g., IDEs, PMAs, 510(k)s, or master files) for components or related products and letters granting access where appropriate

3.2 Brief summary of all applicable clinical investigations or research conducted by the sponsor

3.3 Marketing history (foreign and in the United States).

Include such information as: the country where it was marketed; existence of a CE Mark or other recognized imprimatur; date of introduction; the quantity of product distributed; description of any experience reporting mechanism; a summary of the clinical experience; any adverse experiences reported; any information about withdrawals for any reason related to safety or effectiveness.

Device experience resulting in meeting presentations or publications.

3.4 Summary of development status

4 SUMMARY OF PLANNED MAJOR PRE-CLINICAL AND CLINICAL ACTIVITIES.

Outline of planned pre-clinical in-vitro, pre-clinical in-vivo evaluations. Outline of planned feasibility and clinical evaluation protocols. For novel technologies, greater detail of each test as well as the purpose may be provided.

5 PROTOCOL DEVELOPMENT RESOURCES.

List outside consultants, organizations, and individuals; their qualifications/experience

6 ANTICIPATED SUBMISSION DATE FOR THE FULL PDP.

PART II: DETAILED CONTENTS

This section contains the information that constitutes the details of the PDP submission. It should clearly describe the protocols and definitive evaluation criteria the sponsor and the FDA will commit to for the purpose of demonstrating safety and effectiveness. An application that is incomplete or that requires major additional submissions will not be accepted for review. FDA has 120 days to review this information.

1 TABLE OF CONTENTS

With volumes and page numbers for each item contained in the PDP.

2 DESIGN CONTROLS

Since early 1984, FDA has identified lack of design controls as one of the major causes of device recalls. The intrinsic quality of devices, including their safety and effectiveness, is established during the design phase. Unsafe and ineffective devices are often the result of informal development that does not ensure the proper establishment and assessment of design requirements which are necessary to develop a medical device that is safe and effective for the intended use of the device and that meets the needs of the user.

It is not the intent of the FDA to interfere with creativity and innovation, and it is not the intent of FDA to apply design control requirements to the early research stage. However, once a manufacturer decides that a design will be developed, a design control process with established procedures is required to ensure that the design that may eventually be released to production meets the approved design requirement.

FDA believes that a manufacturer has decided that a design will undergo some degree of development prior to any type of pre-market submission to the agency (i.e., PDP, IDE, Modular PMA, Standard PMA, Streamlined PMA, and 510(k)). Therefore, the FDA believes that a manufacturer would not be able to fulfill the requirements of the Quality System Regulation for that device if design control procedures for that device were not established in accordance with 21 CFR 820.30, prior to any type of pre-market submission.

FDA requires enough detail in pre-market submissions to obtain a sufficient level of assurance that an adequate design control process is in place. There are several places within this guidance that provides manufacturers the option to either submitted a particular procedure or to summarize that procedure. When this option is given, the manufacturer may choose whichever is most suitable for that particular situation. However, when the summary option is chosen, the manufacturer must assure that adequate details and information are in the summary in order for an FDA reviewer to assess compliance with the particular requirement and to assess whether an adequate procedure or process is in place. See Appendix VII for guidance on the content of this section.

3 DESIGN REQUIREMENTS

3.1 Design requirements that capture intended use, intended use environment, indications for use, description of indications, description of target population, claims and clinical utility (Blue Book Memorandum P91-1).

3.2 Discussion of known or anticipated hazards (failure modes), their associated risks and mitigating actions.

FDA needs to concur with the sponsors identification of appropriate hazards and with assessment of the risks associated with each hazard.

3.3 List of applicable guidance(s) and standard(s) intended to be used by the sponsor, including identity of relevant sections and intent to comply or deviate from same. Provide a description and justification for these deviations.

3.4 Copies of all published information directly relating to the device or device type and its uses; and a bibliography and summary of relevant published and unpublished works.

3.5 Identification of alternative practices and procedures for diagnosing, treating, preventing, curing, or mitigating the disease or condition for which the device is intended

4 DESIGN DETAILS

Expanded device description which demonstrates how the Design Requirements will be implemented. This section should amplify information in Part I: Device Description, not repeat it. Describe how the device design relates to the clinical application and explain the underlying principles of operation. Identify elements of the design that address significant hazards and implement the principal intended use(s). Include elements of the design that are essential for the proper clinical functioning of the device, especially details of material, physical, chemical and/or biological composition where they relate to the function of the device or come in contact with the patient. Please include an updated labeled diagram and/or photographs if changed from the Proposal.

Please identify the critical components and assemblies for the purpose of assessing the impact of changes on the protocols, outputs, and acceptance criteria.

This section should be updated with new information when it is available according to the modifications document (see Appendix VI).

Under 812.20(b)(3), the IDE Regulation, a sponsor must provide a description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient

detail so that a person generally familiar with good manufacturing practices can make a knowledgeable judgment about the quality control used in the manufacture of the device. This information is distinct from the information requested in the Quality System Manufacturing Dossier.

5 DESCRIPTION OF RISK MANAGEMENT ACTIVITIES AND RESULTS.

Please provide a detailed summary of the risk management activities that have been completed or are proposed that insure the device functions as intended. Examples of such activities include hazard analysis, risk assessment, fault tree and failure modes and effects analysis, and traceability analysis. Please identify all safety critical requirements and provide evidence that all safety related requirements are traceable back to the hazard analysis and forward to the detailed design specifications and test procedures. Sponsors should identify the activities, their outputs, and evaluation criteria for acceptance. Sponsors should make use of recognized risk management standards in their design process.

6 DESCRIPTION OF MAJOR PRE-CLINICAL TESTS, INSPECTIONS, AND ANALYSES WITH ACCEPTANCE CRITERIA

This section should identify the major areas of tests, inspections, and analyses that comprise the verification activities that influence safety and effectiveness. These activities should be presented with a rationale or purpose associated with a clinical requirement, the protocol or methodology used to evaluate it, and acceptance criteria. See Appendix I for a description of the information contained in preclinical protocols (bench and animal testing and activities).

Examples of testing that may be appropriate include: microbiological; toxicological; immunological; mechanical; electrical; shelf life/stability; specimen transport and storage stability (in vitro diagnostic devices or IVDs); analytical; software validation; biocompatibility; biostability; packaging; sterility; material characterization; environmental assessment under 21 CFR 25.22 (a)(18), unless the action qualifies for an exclusion (21 CFR 25.24(e)(4) or (5)), human factors (actual and simulated use) and safety testing.

7 DESCRIPTION OF CLINICAL EVALUATIONS WITH ACCEPTANCE CRITERIA

This section should identify the clinical studies and analytical methodology that comprise the validation activities which assure safety and effectiveness. This includes a description and rationale for the testing methodologies/protocols, acceptance criteria and analyses planned to validate the intended use of the product. See Appendix I for description of the information contained in clinical protocols.

8 PLAN FOR SUBMITTING THE MANUFACTURING DOSSIER

8.1 Summarize or submit a copy of the plan for when the Manufacturing Dossier will be completed and submitted for FDA review. Guidance on the content of the Manufacturing Dossier can be found in Appendix VIII. Indicate at what milestone or projected date the submission is planned.

The summary or plan should show how the Manufacturing Dossier will be received at CDRH a **minimum of 90 calendar days prior to the PDP Notice of Completion (NOC)**. FDA requires the 90 days prior to the NOC for the following:

a) **30 days**: Office of Compliance (OC) performs initial review of the Manufacturing Dossier and prepares any necessary inspectional guidance.

b) **10 days**: OC coordinates with other CDRH Offices, and issues assignment(s) and any inspectional guidance to appropriate FDA Field Office(s).

c) **50 days**: FDA Field Office(s) performs and completes pre-approval inspection.

The acceptance criteria for this plan will be that the Manufacturing Dossier be submitted in accordance with the FDA guidance and no deficiency letter on the Manufacturing Dossier is necessary.

8.2 Submit an acknowledgment statement that recognizes that the FDA will require at a **minimum an additional 70 calendar days from the close of the pre-approval inspection until CDRH can reach the determination of Quality System regulation compliance.** FDA requires the 70 days after the close of the pre-approval inspection for the following:

a) **30 days**: FDA Field Office(s) writes the Establishment Inspection Report (EIR)

b) **10 days**: FDA Field Office(s) copies and sends completed EIR to OC

c) **30 days**: OC reviews the completed EIR and any FDA 483 response(s) from the manufacturer prior to the EIR being sent from the FDA Field Office(s). OC makes the determination of Quality System regulation compliance and issues a letter to the manufacturer stating the pre-approval inspection results.

The NOC should not be submitted with any outstanding Quality System issues as a result of the pre-approval inspection. An OC review of the pre-approval inspection EIR and any FDA 483 responses from the manufacturer that the FDA Field Office(s) received and reviewed prior to submitting the package to OC, in conjunction with the Field's recommendation, will determine if the Quality System regulation has been met. **Any FDA 483 response(s) from the**

manufacturer submitted after the FDA Field Office(s) has submitted the package to OC will lengthen the required review time. The successful completion of this entire process should occur before FDA can recommend approval of the PDP.

The manufacturer may submit the PDP NOC anytime after the completion of the pre-approval inspection but **should understand the risks** of submitting the PDP NOC prior to **OC's** determination of compliance with the Quality System regulation. If there are any open issues or concerns about compliance with the Quality System regulation at the close of the 90 days after the PDP NOC is submitted, FDA cannot recommend approval of the PDP.

9 ADMINISTRATIVE

9.1 Plan for submitting reports

Reports may include scheduled progress reports and/or information scheduled to be reported prior to proceeding with the development plan, e.g., a report of feasibility data prior to initiation of the next phase of a study (a Gantt Chart may be useful).

Discussions should include frequency of reporting and whether reports will be cumulative or for the period of time since the last report.

9.2 Plan with respect to modifications prior to notification of completion (see attached document Appendix VI: Modifications During the Course of Product Development Under a PDP).

9.3 Mechanism for request for modification to approved PDP that need prior FDA approval.

10 PRE-NOTICE OF COMPLETION REPORTING

10.1 SCHEDULED PROGRESS REPORT

These are reports of milestones (events or periodic) agreed upon in the PDP.

10.1.1 PDP number and report number.

10.1.2 Sponsor information, consistent with Proposal

10.1.3 Table of contents

10.1.4 Summary of milestones and testing completed to date and an update of planned milestones if changed from approved PDP.

10.1.5 Pre-clinical in vitro and in vivo test reports

a) Identification of test, referencing assigned number of the protocol/methodology in the approved PDP

b) Test results
Provide appropriate statistical analyses with confidence intervals and assumptions used as identified in the PDP protocol.

c) Comparison to success/failure criteria as defined in pre-clinical protocol, with an explanation of any differences and their clinical relevance

10.1.6 Clinical progress report

Information as described in the Suggested Format of Clinical Reports, Appendix III.

10.2 MODIFICATION SUMMARY REPORT

These are reports of modifications as negotiated in the agreed upon PDP to the protocols, outputs, and acceptance criteria that do not need immediate reporting to FDA.

10.2.1 PDP number and report number.

10.2.2 Sponsor information, consistent with Proposal

10.2.3 Table of contents

10.2.4 Summary of modifications and activities (testing, analyses, inspections) completed to date and an update of planned milestones if changed from approved PDP.

10.3 SPECIAL MODIFICATIONS REPORT

These are reports of modifications as negotiated in the agreed upon PDP to the protocols, outputs, and acceptance criteria that need immediate reporting to FDA with an FDA response of concurrence or questions within 30 days.

10.3.1 PDP number and report number.

10.3.2 Sponsor information, consistent with Proposal

10.3.3 Table of contents

10.3.4 Description of modification(s) and an analysis of its impact on the agreed upon protocols, outputs, and acceptance criteria and how the modifications may influence safety and effectiveness. Update of planned milestones.

10.4 LAST PROGRESS REPORT PRIOR TO INITIATION OF CLINICAL TRIALS

10.4.1 Provide updated description of device, including packaging, that will be undergoing clinical trials. This may be a Scheduled or Summary Report.

10.4.2 Draft of investigational labeling.

10.4.3 Draft of intended marketing labeling.

10.5 NOTICE OF INITIATION OF CLINICAL TRIALS

Should be submitted a minimum of 15 days before the initiation of clinical trials.

Identification of when the sponsor plans to begin clinical trials. Sponsor should certify that they have successfully completed those preclinical activities that were required to be completed before the clinical trials begin, and as previously agreed upon in the PDP. Reports containing the results of the testing should be provided according to the schedule agreed upon in the PDP.

Unless a sponsor hears otherwise from FDA, they may begin the clinical trials on the date specified.

A sample letter for sponsors to use in preparing this notice is provided in Appendix __.

10.6 LAST PROGRESS REPORT PRIOR TO NOTICE OF COMPLETION (NOC)

10.6.1 Provide complete Table of Contents for entire PDP, identifying date of submission of each portion of the PDP, providing cross-references for protocols, results, and analyses

10.6.2 All pre-clinical in vitro and pre-clinical in vivo reports not previously provided

10.6.3 Draft of the Summary of Safety and Effectiveness Data to be provided in the NOC

10.6.4 Draft of final labeling

11 NOTICE OF COMPLETION

11.1 Table of contents

11.2 Sponsor information, consistent with information above

11.3 Declaration of Completion by the sponsor

Requirements of PDP have been fulfilled

List all studies by number, cross-referencing protocols, endpoints, and analyses

11.4 Final clinical report (see attached Format for Clinical Reports)

11.5 Labeling (see current ODE policy)

11.6 Summary of safety and effectiveness data (see Appendix IV)

12 POST-NOC REPORTS

12.1 Time frame of submitting reports:

1-3 years, annually

4-7 years, every 2 years

after 7 years, every 4 years

Reporting obligations terminate with the periodic report following cessation of manufacture and/or marketing of the subject device

12.2 Contents of the report

Change in model number, name, or other identification (if any)

Contents as per the PMA periodic report (21 CFR 814.84)

APPENDIX I: PROTOCOLS AND METHODOLOGIES

The justifications requested below should be based on statistical and/or clinical and/or scientific rationale, as appropriate.

This information is to be provided for each test conducted or to be conducted in support of the safety and effectiveness of the device. For multiple tests within a category (e.g., pre-clinical in vitro tests, phases of clinical study), each test should be assigned an identifying number, such as 5.1(a), which will be referenced throughout the PDP process.

Protocols that have been previously recognized (e.g., through standards or guidances) may be used through reference. Deviations from recognized protocols should be explained and justified. Additional information may or may not be needed, as identified in discussions with FDA.

Examples of testing that may be appropriate include: microbiological; toxicological; immunological; mechanical; electrical; shelf life/stability; specimen transport and storage stability (IVDs); analytical; software validation; biocompatibility; biostability; packaging; sterility; material characterization; environmental assessment under 21 CFR 25.22 (a)(18), unless the action qualifies for an exclusion (21 CFR 25.24(e)(4) or (5)).

1 PRE-CLINICAL (IN VITRO AND IN VIVO)

1.1 Test facility

1.2 Purpose of test

1.3 Relevant parameters and variables/endpoints

1.4 Study hypothesis

1.5 Identify and justify devices to be tested (e.g., Sizes, models, configurations, and whether components or final finished devices, sterilized or unsterilized)

1.6 Describe test apparatus/instruments, including accuracy, precision, and calibration information

1.7 Describe test system used for the device or identify and justify animal model, including intended implant site, if applicable

1.8 Explain how the test system takes into account potential clinical conditions

1.9 Procedures for managing potential variables, including bias reduction measures

1.10 Detailed description of the test method or procedures, including procedural methodology and assessment methods for animal studies (with justification of assessment methods), and positive and negative controls used to monitor IVD functioning. Labeling assessment studies should also be described (e.g., for studies involving labeling evaluations for over-the-counter devices).

1.11 Specify and justify number of each type of device to be evaluated and number of animals, as appropriate

1.12 Specify and justify number of tests to be performed for each device, as appropriate

1.13 Identify and justify data to be collected, including frequency (assessment intervals) and documentation, for each parameter and variable

1.14 Autopsy and explant retrieval and analysis protocol, as appropriate

1.15 Pass/fail or acceptance/rejection criteria (with tolerances, if applicable) include a justification for the criteria based on anticipated in vivo or in use conditions or on comparison to legally marketed products used under similar physiologic conditions

1.16 Explain use of applicable guidance(s) or standard(s) and planned conformance to Good Laboratory Practices (GLPs)

1.17 Identify anticipated changes to test objectives, protocol, acceptance criteria, and analysis. Describe rationale for each change (e.g., associated device change, test equipment change) and describe the effect on device safety and effectiveness.

2 CLINICAL

IDE regulations apply to all clinical investigations and are not reiterated here, however, some specific information to be included in the PDP submission is requested under section 5.2.10. Approval of a PDP satisfies the requirement of needing an approved IDE.

An overview of the clinical evaluation plan should be provided. This plan should include identification of study phases and the purpose of each phase.

The following information is needed for each phase, as appropriate:

2.1 PURPOSE

2.1.1 Device name

2.1.2 Intended use

2.1.3 Overview of study design

2.2 CLINICAL STUDY POPULATION

2.2.1 Device/treatment

a) Identify and justify devices to be evaluated (e.g., Sizes, models, configurations)

b) Identify and justify control (comparison) group for the comparative study

2.2.2 Subjects

a) Identify and justify

b) Clearly specify inclusion and exclusion criteria

c) Describe demographics

2.3 STUDY DESIGN/STATISTICAL INFORMATION

Describe in detail what statistical methods will be used to evaluate study data. Provide example calculations if possible.

2.3.1 Identify study design and justify that the study design meets the study objectives and the proposed indication(s) for use

2.3.2 State study hypothesis and present rationale

2.3.3 Identify whether superiority or equivalency study

2.3.4 Specify and justify number of each type of device to be evaluated; include a sample size calculation and a justification of the choice of any clinical parameters in the determination. Describe a plan for adjustment of factors used in calculations vary from anticipated performance.

Note: such a calculation will depend on the planned statistical analysis of the primary endpoint(s)

2.3.5 Specify number of sites and minimum number of subjects to be studied by each investigator

2.3.6 As appropriate, describe procedures for managing potential variables, including bias reduction measures to include:

a) Randomization: describe what procedure will be employed for any random allocation of treatments to subjects

b) Masking techniques: who of the subjects, physician, healthcare professional and assessor will be masked to the assignment of the device

c) Stratified statistical design and/or analysis of patient demographics or characteristics, investigators, sites or surgical techniques

d) Describe the plan of how to investigate whether the data can be pooled, for example, across centers in a multicenter study. What will be done if data cannot be pooled?

e) Description of how drop outs and crossovers will be avoided/handled and analyzed

f) Describe conditions which would dictate a study participants removal from the study, and how issues of potential bias will be resolved

g) Process for protocol deviations

2.4 ENDPOINTS AND CLINICAL METHODOLOGY

2.4.1 Identify and justify clinically relevant, measurable endpoints and any surrogate endpoints, including appropriate case definitions for IVDs, and identify primary endpoint

2.4.2 Summary of the primary endpoints by demographic categories

2.4.3 Identify and justify assessment intervals and length of study period

2.4.4 Identify and justify assessment parameters and methods of assessment for each interval

2.4.5 Provide a detailed description of the procedural methodology

2.4.6 Identify data to be collected, including frequency and documentation, for each parameter and variable at each assessment interval

2.4.7 Success/failure criteria for each endpoint or for IVDs a definition of true positive and true negative

a) Identify and justify based on historical information, potential alternative treatment, device, diagnosis, etc.

b) Discuss how the data and information from the study will constitute valid scientific evidence within the meaning of ß860.7 (determining safety and effectiveness) and will provide reasonable assurance that the device is safe and effective for its intended use.

c) Define success for a patient

d) Define success of the study

2.4.8 Case report forms, including informed consent document (see 21 CFR 50.25(a)), and investigator agreement

2.4.9 Definitions of complications

2.5 EXPLANT RETRIEVAL AND ANALYSIS PROTOCOL, AS APPROPRIATE

2.6 RISK/BENEFIT ANALYSIS

Description of risks and benefits

Manner in which risks will be minimized

2.7 INVESTIGATORS/SITES

Identify all clinical investigators, cites, institutional review boards (IRB), and contract research organizations (CRO), as applicable

Note: this information may be incorporated as it becomes available as per the specific PDP agreement.

Discuss training program for investigators, as appropriate

2.8 DATA ANALYSIS

Interim analysis protocol; specify any plan for interim examination of the data and an independent committee or board to do this

Describe statistical analysis, and provide a sample of the data analysis (describe how data will be presented)

Describe all statistical procedures that are to be used, providing references where necessary

Describe how any assumptions required in the statistical analysis will be validated

Patient data spreadsheet; provide a method for tracking and displaying all subjects entered into the study, including patient status (i.e., Pre-device use or pre-treatment, device use or treatment, post-device use or post-treatment) at any point in time

Patient spreadsheet; a database of the primary raw data that are analyzed in the marketing application (listed separately for each patient enrolled in the clinical study)/patient tree chart; a flowchart diagram that visually describes the patient cohorts of a clinical study

Data auditing plan

2.9 EXPLAIN USE OF APPLICABLE GUIDANCE(S) AND STANDARD(S) AND FOR IVDs PLANNED CONFORMANCE TO GLPS

2.10 SPECIFIC IDE REQUIREMENTS

Labeling for investigational device (21 CFR 812.5)

Investigational site, IRB, sales, environmental assessment, and informed consent information (812.20 (b) (4-9) and (11))

Monitoring (812.25 (e) and 812.46 (a-c))

2.11 IDENTIFY ANTICIPATED CHANGES
to study hypotheses, protocol, patient population, endpoints, data analysis, etc. Describe the rationale for each change (e.g., Associated device changes, addition/deletion of proposed labeling claims) and describe the effect on device safety and effectiveness.

2.12 OTHER RELEVANT PROTOCOLS/METHODOLOGIES

APPENDIX II: GUIDANCE DOCUMENTS

1 AVAILABLE THROUGH DSMA

phone: (800) 638-2041 or (301) 443-7491:

PMA Review Statistical Checklist (#84)

2 LABELING REUSABLE MEDICAL DEVICES FOR REPROCESSING IN HEALTH CARE FACILITIES:

FDA Reviewer Guidance (#198)

Product Development Protocol Guidelines (#420)

Guidelines on General Principles of Process Validation (#425)

Do It by Design - An Introduction to Human Factors in Medical Devices (#995)

3 CDRH BLUE BOOK MEMORANDA:

Device Labeling Guidance (#G91-1)

ISO-10993 (Biocompatibility) (#G95-1)

Clinical Utility and Premarket Approval (#P91-1)

4 STANDARDS:

Electrical Safety (IEC 60601-1)

5 REGULATIONS:

In Vitro Device Labeling (21 CFR Part 809.10)

Design Controls (21 CFR Part 820.30)

Good Laboratory Practices (21 CFR Part 58)

6 INTERNET (http://www.fda.gov/cdrh):

General Principles of Software Validation; Draft Guidance (7/28/97)

Guidance (Final) on Design Controls: go to
http://www.fda.gov/cdrh/cgmphome.html

7 OTHER:

Draft Guidance on Statistics (call Division of Biostatistics at (301) 594-0616)

APPENDIX III: CONTENTS OF A CLINICAL REPORT

1 BASICS

Date of Report

PDP Number

Device name and indication for use

Sponsor's name, address and phone number

Contact person

Date of most recent previous progress report (if any)

Investigational site limits in approved PDP

Dates of reaching investigational site limits

Dates of all new IRB approvals

Number of subjects enrolled (by indication or model)

Dates of reaching subject limits

2 TYPE OF REPORT

Progress - To be filed at predetermined intervals as agreed to in PDP contract or upon completion of a significant component of the investigational plan

Final - To be filed upon completion of the investigational plan

3 STATUS OF STUDY

Data from beginning of the study should be reported, unless otherwise indicated

Description of overall study progress in relation to approved investigational plan

Cumulative listing of all changes to approved PDP investigational plan including those initiated by sponsor, IRB, or FDA

4 STUDY RESULTS

Summary of results, including results of any interim analyses and number of subjects who have prematurely discontinued participation. (Include patient tree

and spread sheets to provide full accounting of all study subjects including controls and drop-outs)

Description of events potentially affecting study success (e.g., difficulties enrolling patients; changes in key personnel; discontinuation of participation by subjects and investigators)

Summary of anticipated and unanticipated adverse effects

Description of any deviations from the investigational plan by investigators (since last progress report)

Statistical analyses as per approved PDP

Comparison of results to approved success/failure criteria

Conclusions drawn from study

5 RISK ANALYSIS

Summary of all adverse device events (ADE) including any new adverse information (since last progress report) that may affect the risk analysis, including preclinical data, animal studies, foreign data, clinical studies, etc.

Reprints of any articles published from data collected from this study since last progress report

Reprints of any articles on similar devices published by others since last progress report

New risk analysis, if necessary, based on new information and on study progress

6 FUTURE PLANS

Progress toward product approval, with projected date of PDP completion

Any plans to change investigation, e.g., to expand study size or indications, to discontinue portions of the investigation or to change manufacturing practices (NOTE: Actual proposals for change should be made in a separate PDP report)

7 DEVICE LABELING

APPENDIX IV: SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1 GENERAL INFORMATION

1.1 Device generic name

1.2 Device trade name

1.3 Applicant's name and address

1.4 PDP number

1.5 Chronology of PDP

a) Date of PDP summary submission

b) Date of FDA approval of summary

c) Date of submission of PDP

d) Date of panel meeting

e) Date of FDA approval of PDP

f) Date of submission of notification of completion

g) Date of FDA approval

2 INDICATION FOR USE

3 DEVICE DESCRIPTION

4 ADVERSE EFFECTS

5 ALTERNATIVE PRACTICES AND PROCEDURES

6 MARKETING HISTORY

7 SUMMARY OF STUDIES AND RESULTS

7.1 Pre-clinical in-vitro

7.2 Pre-clinical in-vivo

7.3 Clinical

a) Subject selection and exclusion criteria
b) Study population/demographics
c) Study period
d) Safety and effectiveness data
e) Adverse reactions and complications
f) Patient complaints
g) Device failures and replacements
h) Patient accountability
i) Statistical analyses
j) Other information, as appropriate

7.4 Abstract of other data, information or report described in PDP which relates to safety and effectiveness

8 CONCLUSIONS DRAWN FROM STUDIES

8.1 Discussion of valid scientific evidence

8.2 Discussion of data on safety and effectiveness

8.3 Risk/benefit analysis

9 SUMMARY OF VERIFICATION RESULTS AND VALIDATION RESULTS

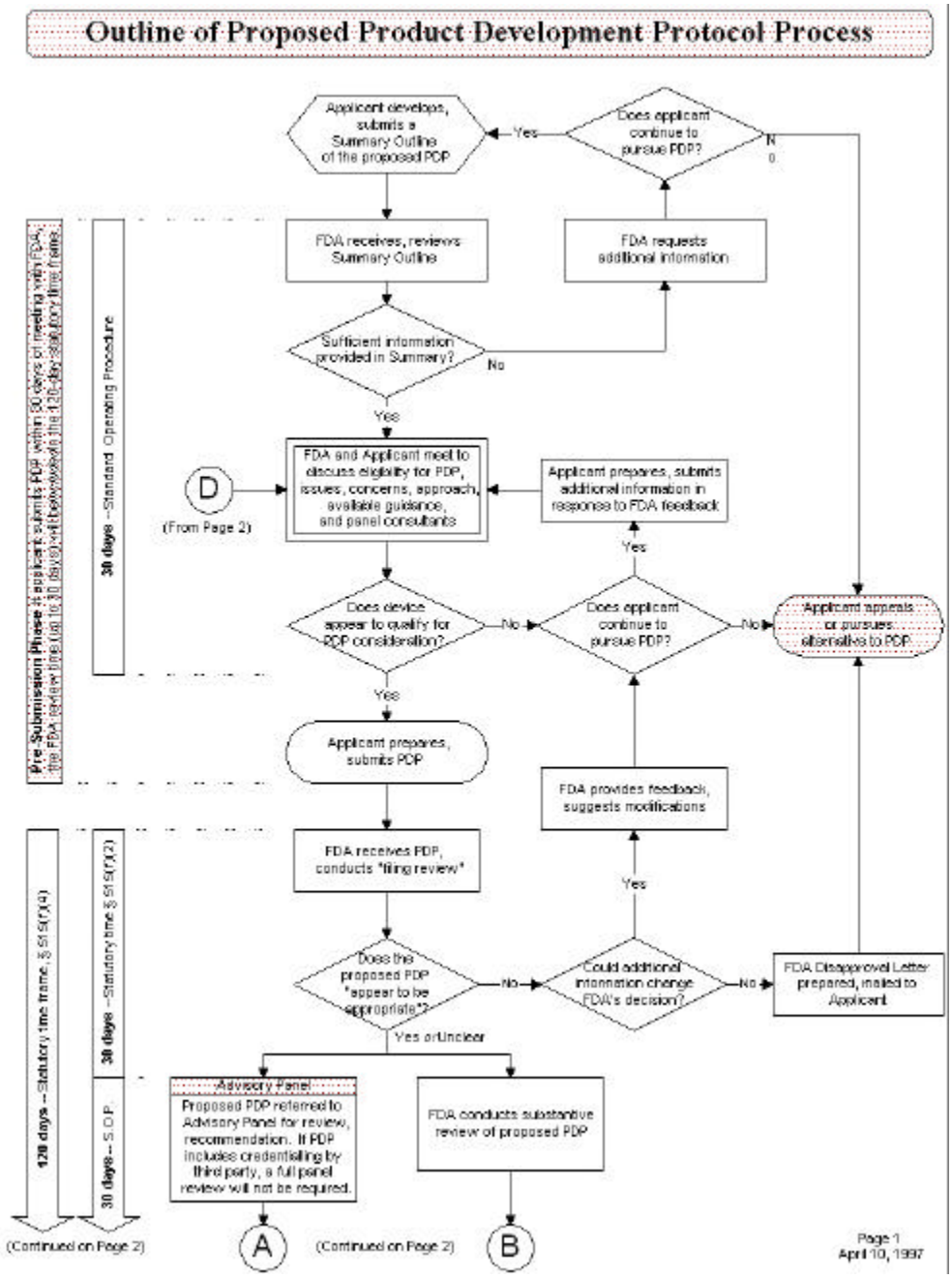
10 SUMMARY OF RISK ANALYSIS ACTIVITIES THAT ESTABLISH RISK HAS BEEN ADDRESSED AND ADEQUATELY MITIGATED

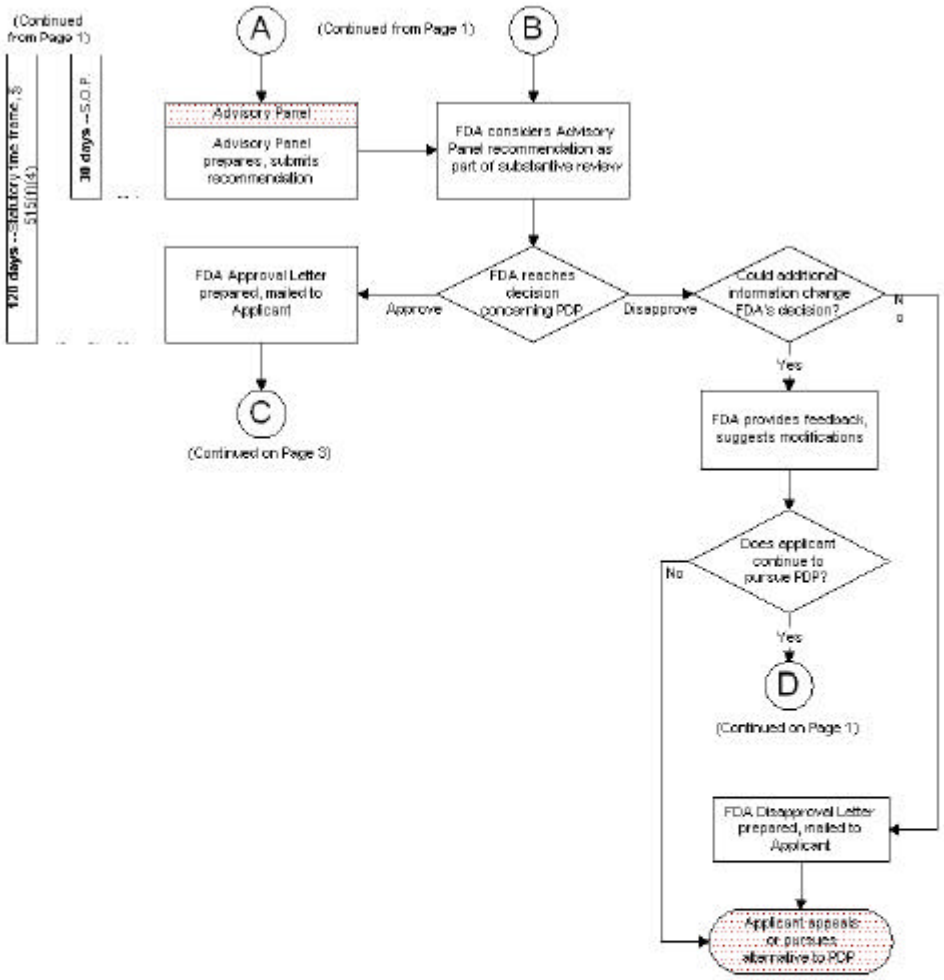
11 PANEL RECOMMENDATIONS

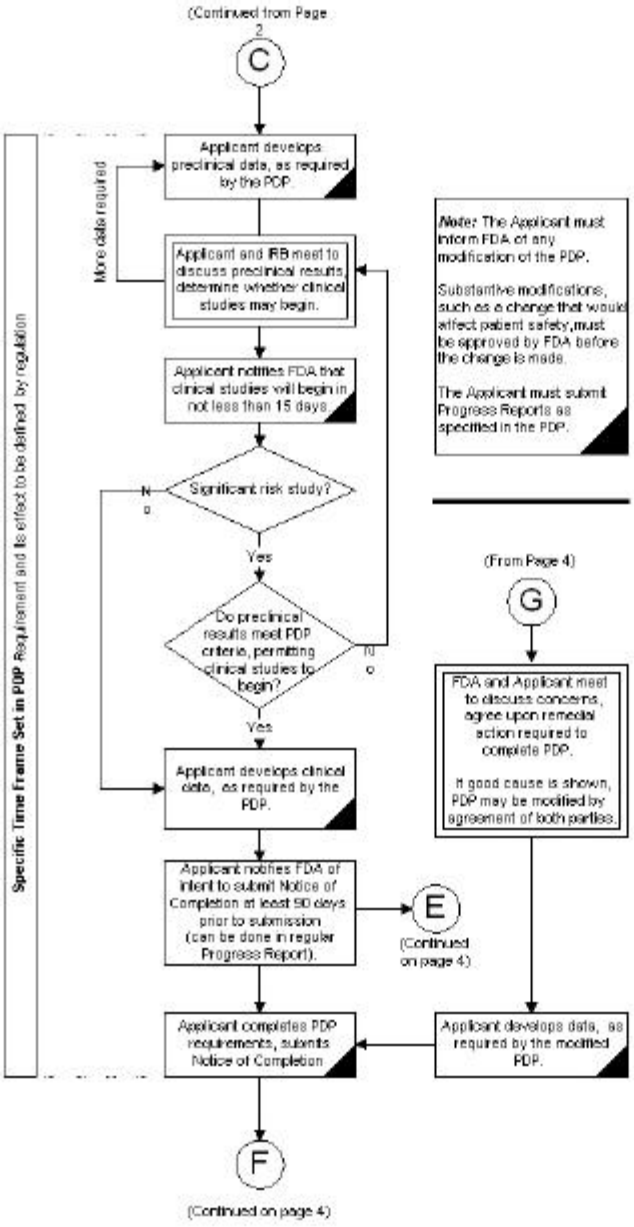
12 FDA DECISION ON PDP

13 PROPOSED DEVICE LABEL

APPENDIX V: PDP FLOW CHART




(Continued from Page 1)
A
(Continued from Page 1)
B
120 days --statutory time frame; § 515(d)(4)
30 days -- S.O.P.
Advisory Panel
Advisory Panel prepares, submits recommendation
FDA considers Advisory Panel recommendation as part of substantive review
FDA Approval Letter prepared, mailed to Applicant
Approve
FDA reaches decision concerning PDP
Disapprove
Could additional information change FDA's decision?
No
Yes
C
(Continued on Page 3)
FDA provides feedback, suggests modifications
Does applicant continue to pursue PDP?
No
Yes
D
(Continued on Page 1)
FDA Disapproval Letter prepared, mailed to Applicant
Applicant appeals or pursues alternative to PDP



Page 3
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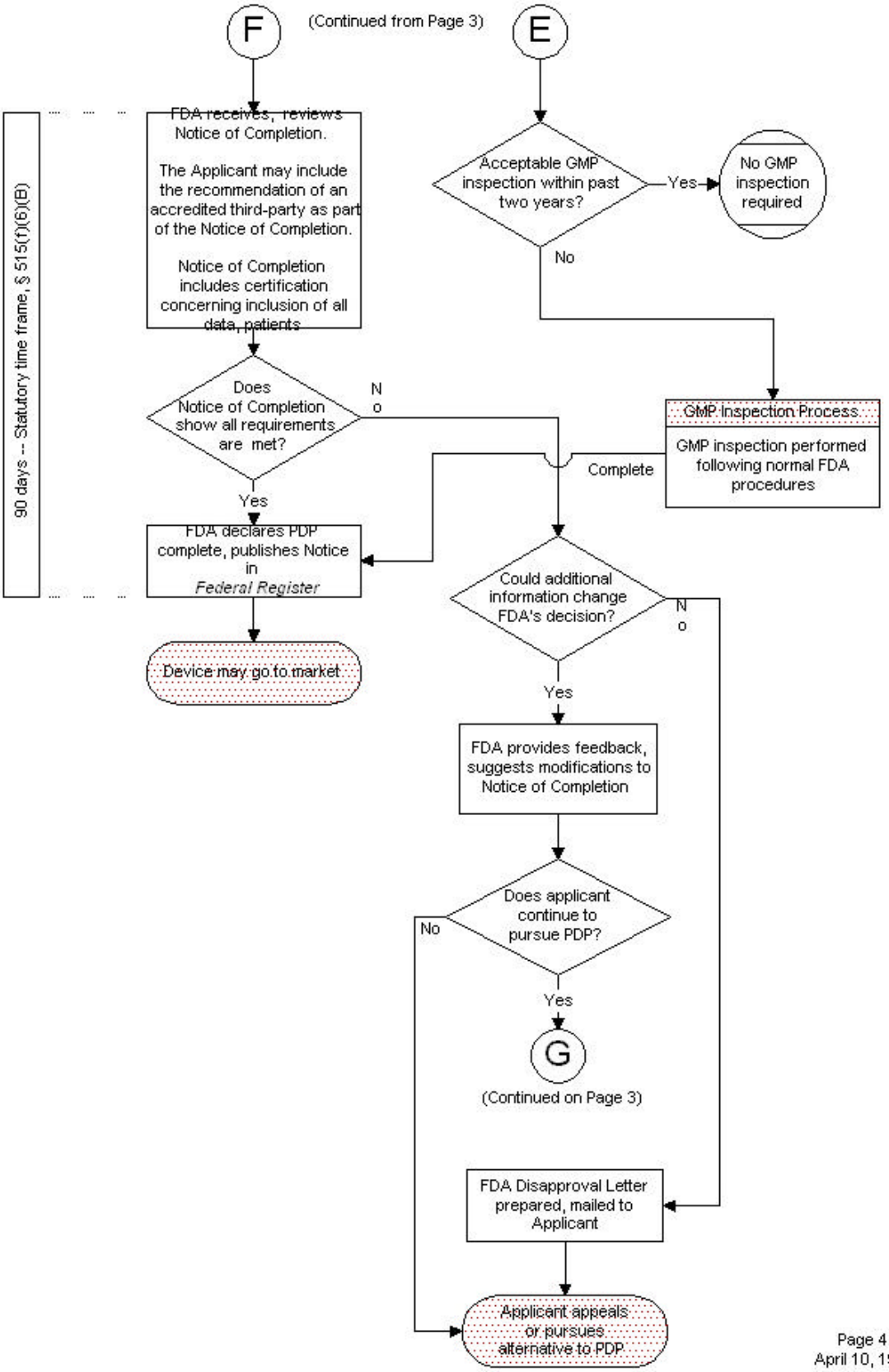

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APPENDIX VI: MODIFICATIONS CHANGE MATRIX

1 PDP Modifications Reporting Guidance

This Modifications Reporting Guidance can broadly apply to most PDPs, and should provide a starting point for drafting a PDP.

If both FDA and the applicant agree that a particular modification is adequately addressed here, the PDP does not need to explicitly address that modification. Alternatively, if either FDA or the applicant prefers, a different approach to handling a particular modification can be negotiated and included in the PDP. It is extremely unlikely that every type of modification described here is possible for any given device, and it is not necessary to address modifications that are not expected to occur.

The following four reporting categories are used in this guidance:

- Company files -- Modifications that are to be documented in company files consistent with FDA's Quality System Regulation, 21 CFR Part 820. No additional reporting to FDA is required.

- Modification Summary Report -- Modifications that are to be summarized in a periodic report to FDA, following a schedule specified in the PDP. This report may provide a complete, current description of the device being developed under the PDP or a complete summary describing each individual modification made to date. A Modification Summary Report may be submitted as a clearly delineated section in a Regular Progress Report.

- Special Modification Report -- Modifications that are to be reported to FDA concurrent with the change. FDA will respond to the modification within 30 days; if FDA does not respond within 30 days, the modification is deemed approved. Modifications reported in a Special Modification Report are at the risk of the PDP sponsor from implementation until 30 days after reporting or FDA's approval of the change, whichever comes first.

- Prior FDA Approval -- Modifications that are not to be made without prior approval from FDA. FDA will approve or deny the proposed modification within 30 days, unless an extension of time is agreed to by the applicant.

In addition to the reporting required by this guidance, PDP sponsors should also submit regular Progress Reports in accordance with specific requirements included in the PDP; Progress Reports can be triggered by the occurrence of a specified event, such as completion of

preclinical trials and a decision to move forward to clinical trials, or by the passage of time, such as an annual report.

This guidance applies only to changes made prior to the Notice of Completion.

All device design changes after NOC will be subject to the same requirements as PMA

PDP Modifications Chart - Listing of Requirements

Description of Change (Terms in SMALL CAPS are defined terms.)	Reporting Required			
	Company Files	Mod. Summary Report	Special Mod. Report (30 day)	Prior FDA approval
A. Device Design Changes (Preclinical) - 515(f)(3)(i)				
1. Any change that affects safety and effectiveness determination and which is not addressed in the PDP or this guidance.				X
2. FORMULATION change or change to type of RAW MATERIAL (e.g., plastic in lieu of metal). Changes are within range of criteria set in approved PDP. Critical Component Non-Critical Component	X		X	
3. Change in vendor / supplier or RAW MATERIALS (including CRITICAL RAW MATERIALS) or COMPONENTS without any change in FORMULATION or SPECIFICATIONS.	X			
4. Change in sterile packaging or packaging in immediate contact with the device (other than labeling changes). Exception : Implant		X	X	
5. Change in expiration dating within range of criteria set in approved PDP.	X			
6. SOFTWARE/FIRMWARE changes that do not affect intended use, and do not result in performance changes outside the range of criteria set in approved PDP.	X			

7. Change in OPERATING PRINCIPLE -				X
8. Change in PERFORMANCE CHARACTERISTICS Affects safety and effectiveness Does not affect safety and effectiveness			 X	X
9. Change in INTENDED USE or INDICATIONS FOR USE. *Exception*: A reduction or limitation			X	X

Description of Change (Terms in SMALL CAPS are defined terms.)	Reporting Required			
	Company Files	Mod. Summary Report	Special Mod. Report (30 day)	Prior FDA approval
B. **Preclinical Testing Changes - 515(f)(3)(ii)**				
1. Any change that affects safety and effectiveness and which is not addressed in the PDP or this guidance.				X
2. Expansion of preclinical trials; no change to SPECIFICATIONS.		X		
3. Increase in SAMPLE SIZE.		X		
4. Change in preclinical trial SPECIFICATIONS; no effect on clinical trials or device design.			X	
5. New TEST DESIGN or TEST ARCHITECTURE (change to test regimen, not the device - IVD).			X	
6. Change to study success / failure criteria.				X
7. Additional testing to ensure safety or conformance with device or component SPECIFICATIONS.	X			
8. Reduction in preclinical testing.			X	
9. Change to test plan that cannot be validated as comparable.			X	

Description of Change (Terms in SMALL CAPS are defined terms.)	Reporting Required			
	Company Files	Mod. Summary Report	Special Mod. Report (30 day)	Prior FDA approval
C. Device Design Changes (During Clinical Trial) - 515(f)(3)(i)				
1. Any change that affects safety and effectiveness determination and which is not addressed in the PDP or this guidance.				X
2. FORMULATION change or change to type of RAW MATERIAL (e.g., plastic in lieu of metal). Changes are within range of criteria set in approved PDP. Critical Component Non-Critical Component			 X	 X
3. Change in vendor / supplier or RAW MATERIALS (including CRITICAL RAW MATERIALS) or COMPONENTS without any change in FORMULATION or SPECIFICATIONS.	X			
4. Change in sterile packaging or packaging in immediate contact with the device (other than labeling changes). *Exception*: IMPLANT		X	X	
5. Change in expiration dating within range of criteria set in approved PDP.	X			
6. SOFTWARE/FIRMWARE changes that do not affect intended use, and do not result in performance changes outside the range of criteria set in approved PDP.	X			
7. Change in OPERATING PRINCIPLE				X

8. Change in PERFORMANCE CHARACTERISTICS May affect safety and effectiveness Addresses safety issue Does not affect safety and effectiveness			 X	 X X
9. Change in INTENDED USE or INDICATIONS FOR USE. *Exception*: A reduction or limitation			 X	X
10. Changes made after initiation of the clinical trial as a result of an unexpected adverse event or increase in adverse event rate.				X

Description of Change (Terms in SMALL CAPS are defined terms.)	Reporting Required			
	Company Files	Mod. Summary Report	Special Mod. Report (30 day)	Prior FDA approval
D. Clinical Trial Changes - 515(f)(3)(iii)				
1. Any change that affects safety and effectiveness and which is not addressed in the PDP or this guidance.				X
2. Change that poses additional risk to patients. Change due to unexpected adverse event or event rate in clinical experience.				X
3. Administrative Changes with no effect on safety.	X			
4. Additional COMPARATIVE TEST, MEASURES or MONITORING. Directly Effects Patient Safety No Effect On Patient Safety		X		X
5. Modification of COMPARATIVE TEST, within range of criteria set in approved PDP.			X	
6. Change in number of patients in trial outside agreed range of patients necessary to establish safety and effectiveness or exceeding maximum number permitted in the study.				X
7. Clarification of instructions for use.		X		
8. Reduction in follow-up time.				X
9. Change in clinical plan to demonstrate conformance to newly established standard.			X	

10. Change in ENDPOINT MEASURES provides less safety and effectiveness information.				X

Description of Change (Terms in SMALL CAPS are defined terms.)	Reporting Required			
	Company Files	Mod. Summary Report	Special Mod. Report (30 day)	Prior FDA approval
E. Manufacturing Changes - 515(f)(3)(iv)				
1. Any change that affects safety and effectiveness and which is not addressed in the PDP or this guidance.				X
2. Deletion of manufacturing facility with no change in procedures.		X		
Addition of new manufacturing site Significant Risk Device			X	X
Non-Significant Risk Device				
3. Expand existing facility to increase capacity.	X			
4. Moving equipment within facility.	X			
5. Replacement of existing manufacturing equipment with new equivalent equipment.	X			
6. New owner / operator.		X		
7. Change from manual to automated manufacturing.		X		
8. Significant change in the manufacturing process.			X	
9. Change in COMPONENT assembly steps.		X		
10. Change to incoming, in-process, or final testing methods with no effect on product performance.		X		

11. Change to incoming, in-process, or final acceptance SPECIFICATIONS with no effect on device safety or effectiveness. Critical Specifications should be identified in the PDP. Critical Specifications Non-Critical Specifications	X		X	
12. Additional testing as part of quality control procedures.	X			
13. Reduction in quality control testing validated by appropriate statistical rationale.			X	
14. Change from one method of sterilization to another.				X

Description of Change (Terms in SMALL CAPS are defined terms.)	Reporting Required			
	Company Files	Mod. Summary Report	Special Mod. Report (30 day)	Prior FDA approval
F. Labeling Changes - 515(f)(3)(vi)				
1. Any change that affects safety and effectiveness and which is not addressed in the PDP or this guidance.				X
2. Change to indications for use.				X
3. Deletion of warning or precaution.				X
4. Additional warning or precaution.			X	

APPENDIX VII: QUALITY SYSTEM DESIGN CONTROL DOSSIER

The following is guidance on what should be submitted or what should be readily available at the time of a pre-market submission with respect to the design control requirements of the Quality System Regulation:

1 820.30(a) GENERAL

1.1 Explain at what stage in the design and development effort design controls were applied. (Note, if the design and development effort was initiated prior to June 1, 1997, identify the date the design effort was initiated.)

1.2 Describe how risk management or risk analysis will be used throughout the design and development of the device. Summarize the methods used and at what stages of design and development they will be employed.

2 820.30(b) DESIGN AND DEVELOPMENT PLANNING

2.1 Submit or summarize the design and development plan. If a written procedure was established to control or describe the overall design process, submit a copy.

The submitted plan or summary should describe or reference, and assign responsibility for the implementation of each of the following:

a) Risk Analysis
b) Design Input
c) Design Output
d) Design Review
e) Design Verification
f) Design Validation
g) Design Transfer
h) Design Changes
i) Interfaces

The submitted plan or summary should have provisions for the review, update, and approval of the plan as design and development evolves.

The submitted plan should include information on the timing and chronology of the development strategy (e.g., Gantt Chart). Outline timing strategy (i.e., initiation, completion, and analysis) for all testing, with specification and justification of data needed prior to subsequent studies contained or referenced in the plan. The plan should contain specific deliverables of each stage and criteria

for initiation and completion. The plan should identify critical milestones that should be completed before initiation of successful tasks.

3 820.30(c) DESIGN INPUT

3.1 Submit a copy of the written procedure(s) for identification and control of design input.

The submitted procedure should cover relevant aspects such as:

a) intended use
b) user/patient/clinical
c) performance characteristics
d) safety
e) limits and tolerances
f) risk analysis
g) toxicity and biocompatibility
h) electromagnet compatibility (EMC)
i) compatibility with accessories/auxiliary device
j) compatibility with the environment of intended use
k) human factors
l) physical/chemical characteristics
m) labeling/packaging
n) reliability
o) statutory and regulatory requirements
p) voluntary standards
q) manufacturing processes
r) sterility
s) MDRs/complaints/failures and other historical data
t) design history files (DHFs)

The submitted procedure should describe the process or mechanism for addressing incomplete, ambiguous, or conflicting requirements.

The submitted procedure should have provisions for how design inputs are documented, reviewed and approved.

3.2 Summarize how the manufacturer considers and addresses user interface and other human factor issues in the design input.

3.3 For electrically powered devices, summarize how the manufacturer considers and addresses EMC issues in the design inputs.

4 820.30(d) DESIGN OUTPUT

Submit a copy of the written procedure(s) for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements.

The submitted procedure should contain or make reference to acceptance criteria.

The submitted procedure should contain or make reference to the process or mechanism for identifying the design outputs that are essential for the proper functioning of the device.

5 820.30(e) DESIGN REVIEW

Submit a copy of the written procedure(s) that defines and controls formal design reviews.

The submitted procedure should describe how the manufacturer plans formal design reviews and how the manufacturer defines the appropriate stages of the deviceís design development to conduct formal design reviews.

The submitted procedure should contain or make reference to the process or mechanism to assure that formal design reviews are comprehensive, systematic, and that participants at each design review include representatives of all functions concerned with the design stage being reviewed.

The submitted procedure should contain or make reference to the process or mechanism by which the manufacturer ensures that an individual(s) who does not have direct responsibility for the design stage being reviewed, as well as any specialists needed are included in the formal design reviews.

The submitted procedure should have provisions for the results of design reviews to be documented in the design history file, along with the date, and the individual(s) involved.

6 820.30(f) DESIGN VERIFICATION

6.1 Submit a copy of the written procedure(s) for verifying the device design.

The submitted procedure should have provisions for the documentation of the results of design verification, including identification of the design, method(s), date, and individual(s) performing the verification.

The submitted procedure should contain or make reference to a process or mechanism for resolving any discrepancy between design output and design input.

6.2 Summarize the method or mechanism used to trace and confirm that the design output meets the design input requirements.

7 820.30(g) DESIGN VALIDATION

7.1 Submit a copy of the written procedure(s) for validating the device design.

The submitted procedure should have provisions for the documentation of the results of design validation, including identification of the design, method(s), date, and individual(s) performing the validation.

7.2 If validation activities are to be performed or were performed on non-production devices, summarize the process or scientific method that will be used or was used to prove equivalence to production devices.

7.3 Summarize how the clinical evaluations planned will ensure that the device design meets defined user needs and intended uses.

7.4 If the device is automated with computer software, describe how the software validation will be completed by the completion of the overall design validation.

8 820.30(h) DESIGN TRANSFER

Submit a copy of the written procedure(s) for transferring the design output from design and development to manufacturing.

The submitted procedure should have provisions for ensuring that there is some final review and approval of the design and development activities (i.e., the approval of the device master record) being correctly transferred to manufacturing.

9 820.30(i) DESIGN CHANGES

9.1 Submit a copy of the written procedure(s) for design change control.

The submitted procedure should clearly define when in the design process the manufacturer begins control of design changes.

The submitted procedure should describe when verification of changes is sufficient in lieu of validation of changes and how this will be documented. It will not be acceptable for the procedure to simply state ìvalidation or where appropriate verification.î The ìwhere appropriateî should be clearly defined or the procedure should provide a process for such decision making.

The submitted procedure should ensure that changes are validated or where appropriate verified, reviewed, and approved prior to implementation of the design change.

9.2 Describe how design changes to the device or the manufacturing process (to include test methodology) will be handled after the device has been transferred to manufacturing. Describe how these types of changes will go through design controls.

10 820.30(j) DESIGN HISTORY FILE (DHF)

Submit a copy of the written procedure(s) for maintaining and retaining the contents of the DHF.

If more than one device shares a common DHF, the submitted procedure should describe how the manufacturer identifies each device within the family or group having common design characteristics.

APPENDIX VIII: QUALITY SYSTEM MANUFACTURING DOSSIER

The following is guidance on what should be submitted or what should be readily available at the time of a pre-market submission with respect to the manufacturing requirements of the Quality System Regulation:

1 QUALITY MANUAL

Submit a copy of the quality manual for the manufacturing facility that will be responsible for the PDP device.

The quality manual should be consistent with ISO 10013-1995 "Guidelines for Developing Quality Manuals". The quality manual should contain:

a) title, scope, and field of application
b) table of contents
c) introductory pages about the organization concerned and the quality manual itself
d) the quality policy and objectives of the organization
e) a description of the organizational structure, responsibilities, and authorities
f) a description of the elements of the quality system and any references to documented quality system procedures
g) a definitions section, if appropriate
h) a guide to the quality manual, if appropriate
i) an appendix for supportive data, if appropriate

21 CFR 820.20(e) Quality system procedures states, "Each manufacturer shall establish quality system procedures and instructions. An outline of the structure of the documentation used in the quality system shall be established where appropriate." FDA believes that such an outline is appropriate for high risk devices such as those that require PDP or PMA approval. Therefore, the development of a quality manual according to the above recommendation would satisfy this quality system requirement.

Note, ISO 10013 section 4.2.4, "Any quality manual should identify the management functions, address or reference the documented quality system and procedures, and briefly cover all the applicable requirements of the quality system standard selected by the organization."

2 MANUFACTURING PROCESS

Submit a description or preferably a flow diagram identifying the steps involved in the manufacturing process.

3 VALIDATION MASTER PLAN

Submit a copy of the Validation Master Plan or a description of which manufacturing processes will be validated.

Identify any processes that will be validated, where the manufacturer has never performed a similar type of validation at that manufacturing site. This notation will help FDA recognize where a particular manufacturing site has experience in similar validation activities.

For example, a manufacturer may need to perform a sterilization validation for this PDP device. If the design specifications call for ETO sterilization and the manufacturer has never performed sterilization validation or has only performed a different type of sterilization validation (i.e., gamma sterilization), then this process should be identified in the submission. If a manufacturer has performed similar ETO sterilization validations for other products, then the sterilization validation does not require any special notation.

The manufacturer should validate processes where the results of a process cannot be fully verified by subsequent inspection and test, in accordance with 21 CFR 820.75. If the manufacturer chooses to validate a process that can be fully verified by subsequent inspection and test, for business or economic reasons, the manufacturer by choice then subjects these processes to the requirements of 21 CFR 820.75.

A Validation Master Plan is a convenient method of quality planning (21 CFR 820.20(d)) for process validations required in the manufacturing of the PDP device.

4 VALIDATION PROCEDURE(S)

Submit a copy of the validation procedure(s) for each process that will be validated.

The validation procedure(s) should contain or make reference to objective and measurable acceptance criteria.

Appropriate statistical methodology for data collection and analysis should be employed. The validation procedure(s) should define or reference the statistical methodology.

The validation procedure(s) should also contain the criteria for revalidation.

5 FINAL ACCEPTANCE ACTIVITIES

Submit a copy of the Final Acceptance Activities procedure(s), required under 21 CFR 820.80(d) for this PDP device.

6 CORRECTIVE AND PREVENTIVE ACTIONS

Submit a copy of the corrective and preventive action procedure(s), required under 21 CFR 820.100.