Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry

Coronary Drug-Eluting Stents — Nonclinical and Clinical Studies

Companion Document

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

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For questions regarding this draft document contact (CDRH) Ashley Boam at 240-276-4222 or (CDER) Devi Kozeli at 301-796-2240.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)
March 2008
Combination Products

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1350 Piccard Drive (HFZ-220)
Rockville, MD 20850-4307 U.S.A.
http://www.fda.gov/cdrh/ggpmain.html
Email: dsmica@cdrh.fda.gov
Fax: 301.443.8818
(Tel) Manufacturers Assistance: 800.638.2041 or 301.443.6597
(Tel) International Staff Phone: 301.827.3993

or

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health (CDRH)
Center for Drug Evaluation and Research (CDER)
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Guidance for Industry[1]
Coronary Drug-Eluting Stents — Companion Document

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. 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 statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

INTRODUCTION

This guidance is intended to be used as a companion document to the guidance *Coronary Drug Eluting Stents — Nonclinical and Clinical Studies*, which provides recommendations to sponsors or applicants[2] planning to develop, or to submit to FDA, a marketing application for a coronary drug eluting stent (DES). This companion document provides additional and more detailed guidance on some of the recommendations in the *Coronary Drug Eluting Stents* guidance, including details on premarket approvals (PMAs), investigational device exemptions (IDEs), examples of various tables that may be submitted, and information on labeling a DES.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by a working group that included members of the Center for Devices and Radiological Health (CDRH), Center for Drug Evaluation and Research (CDER), and Office of Combination Products (OCP) in the Office of the Commissioner at the Food and Drug Administration.

[2] For purposes of this guidance, *sponsor* refers to any person who takes the responsibility for and initiates a clinical investigation; *applicant* refers to any person who submits an application, amendment, or supplement to obtain FDA approval of a new medical product or any other person who owns an approved application. *Sponsor* is used primarily in relation to investigational device exemption (IDE) submissions and *applicant* is used primarily in relation to premarket approval (PMA) submissions.

SUGGESTED ELEMENTS FOR AN IDE APPLICATION

The following elements should be provided within an original investigational device exemption (IDE) application for a DES:

- Executive summary of information provided in submission
- General overview
  - Name of the product (clearly indicate any differences between clinical builds and those used for nonclinical studies)
  - Product description, (identify all components)
  - Matrix of stent sizes intended for clinical study as well as future marketing application (by length and diameter, including drug dosage per size)
  - Description of drug distribution around struts and along length of stent
  - Proposed intended use
  - References to other regulatory submissions (including 'Right to reference' or other letters)
  - Prior communications with FDA (e.g., pre-submission meetings or teleconferences)
- Report of prior investigations, including any studies conducted outside the United States (OUS) (21 CFR 812.27)
- Master table(s), cross-referenced to the submission
- If necessary, appropriate 'bridging' documents that provide rationale/justification for the acceptability of prior investigations to the currently proposed study
- Supportive safety (and effectiveness) information
  - Drug Substance
    - Nonclinical systemic pharmacology and toxicology
    - Systemic clinical exposure
    - Chemistry, manufacturing and controls (CMC)
  - Finished DES
    - Nonclinical physical, chemical, and mechanical tests
    - Biocompatibility
    - Animal testing for safety and preliminary effectiveness
    - Pharmacokinetics/pharmacodynamics
    - Chemistry, manufacturing and controls
- Proposed clinical investigation plan (Required elements are described in 21 CFR 812.25. A suggested list, including both the required elements and other important information, follows.)
  - Purpose and objectives of study
  - Protocol synopsis
  - Identification of control group
  - Inclusion/Exclusion Criteria (patient population)
  - Clinical evaluations (including assessment intervals and tests to be performed)
  - Study endpoints and hypotheses
  - Study success criteria
  - Prospectively defined statistical analysis plan, including sample size justification, and randomization scheme (if applicable)

78 - Risk/benefit analysis
79 - Monitoring procedures
80 - Case report forms
81 • Informed consent document
82 • Investigational labeling, including product handling and storage information
83 • Investigator information
84 • Institutional review board (IRB) information
85 • Sales information
86 • Draft labeling (instructions for use, patient guide, and/or implant card)
87
88 *For general IDE requirements, sponsors should refer to CDRH's Device Advice*[3] *and 21 CFR*
89 *812. Sponsors are also reminded that as described 21 CFR 812, the regulations regarding*
90 *Design Controls in 21 CFR 820.30 also apply.*
91
92 *Note*: An identical electronic version of the entire IDE application should be provided
93 concurrently with the paper submission.[4]
94
95

[3] Refer to CDRH Device Advice, http://www.fda.gov/cdrh/devadvice/ide/index.shtml.

[4] See http://www.fda.gov/cdrh/elecsub.html for more information regarding the submission of electronic copies.

SUGGESTED ELEMENTS FOR A PMA APPLICATION

To adequately support the safety and effectiveness of the finished DES, an original premarket approval (PMA) application for a DES should contain the following elements: (Required elements are described in 21 CFR 814.20. A suggested list, including both the required elements and other important information, follows.)

- Name and address of applicant
- Table of contents
- Draft summary of safety and effectiveness data (SSED) [5]
  - Indications for use
  - Contraindications
  - Product description, with identification of critical active and inactive ingredients
  - Alternative practices
  - Warnings and precautions
  - Marketing history (in the United States as well as OUS)
  - Summary of studies (nonclinical and clinical)
  - Potential adverse events
  - Gender and/or other biases
  - Conclusions drawn from studies
- Executive summary with Master Table(s), which is cross-referenced to submission
- If necessary, appropriate 'bridging' documents to provide rationale/justification for the acceptability of prior investigations to currently proposed study
- Complete descriptions
  - Product, with all components identified
  - Chemical structures and engineering drawings
  - Matrix of stent sizes requested for marketing approval (clearly indicate the stents clinically studied in both the United States and OUS)
  - Principles of operation (mechanical and pharmacological)
- Chemistry, manufacturing, and controls for both drug substance and finished product
- Full description of the manufacturing methods, facilities, and controls in the context of the Quality System regulation (21 CFR 814.20) or the current Good Manufacturing Practice regulation (21 CFR 210, 211) [6]
- Conformance with any applicable standards
- Product evaluation (including executive summary, protocol, report, and supportive data for each test)
  - Nonclinical
  - Clinical, including any studies conducted OUS (21 CFR 814.20(b)(8)(iii))
- Bibliography
- Proposed labeling (instructions for use, patient guide, and implant card)
- Environmental assessment, unless the product qualified for a categorical exemption

[5] Please refer to the publicly available SSEDs for procode NIQ (coronary drug-eluting stents) on FDA's Web site for additional insight on the appropriate level of information to include within the proposed SSED.

[6] Please see Section VIII.A. of the main guidance document for further discussion.

- Financial disclosure
- Postapproval study protocol

For general PMA requirements, sponsors and applicants should refer to CDRH's Device Advice, Premarket Approval Manual, and CFR 814.20.[7]

Note: Although pertinent information contained in applications previously submitted to FDA may be incorporated into a PMA application by reference, for ease of FDA review, the prior submission should be appropriately cross-referenced (including page numbers) within the current application. The sponsor should clearly indicate whether this information is the same as previously provided. If there are any changes, these modifications should be explicitly identified and an appropriate justification provided to the applicability of the information. FDA also requests an identical electronic version of the entire PMA application be provided concurrently with the paper submission.[8]

MASTER TABLE

Sponsors/applicants should provide a summary listing in tabular form (referred to as a 'Master Table') of the nonclinical and clinical testing performed on a DES. For ease of review, for each test report listed in the master table, the sponsor/applicant should provide a cross-reference to the location of the test reports in either the IDE or PMA application.

As part of the test article column, the sponsor/applicant should disclose any differences between the DES tested and the DES intended for use within the proposed clinical studies (for IDE) or intended for commercialization (for PMA). Such differences might include different delivery systems, modifications to the stent substrate, or differences in manufacturing methods (e.g., processing aids, coating deposition method, sterilization parameters). The sponsor should also provide a rationale for the amount of drug per stent to be studied as part of the clinical study.

The sponsor should use these tables to support the position that sufficient nonclinical safety information has been collected before requesting to initiate human exposure to the DES. If there are clinical data from studies conducted outside the United States (OUS) at the time of submission of a U.S. IDE application, this information should also be included in the table. In addition, the table should be updated to include up-to-date clinical information with the PMA application. When summarizing clinical information, the applicant should clearly differentiate which studies are considered feasibility, supportive, or pivotal study cohorts for the PMA application.

Please see the next page for an example of a Master Table.

[7] Refer to CDRH Device Advice, http://www.fda.gov/cdrh/devadvice/pma/ and CDRH Premarket Approval Manual, http://www.fda.gov/cdrh/devadvice/pma/printer.html.

[8] See Footnote 4.

178
179
180 Example of a Master Table
181

Test &/or Study Name	Test Article	Stent Size (diameter & length) and number of stents (if applicable)	Stent Surface Area (mm^2)	Total Drug / Stent & Total Carrier / Stent (µg)	Dose Density (µg/mm^2) & Formulation	Vessel Location	Release: Rate, Duration, Amount &/or Residual Drug on Stent	Drug Systemic and Tissue Levels	Evaluation Time Points	Testing Summary &/or Objective
Engineering Studies										
Animal Studies										
Biocompatibility										
Clinical Studies										
Feasibility/First-in-Man (OUS or US)										
Supportive (OUS or US)										
Proposed or Completed Pivotal Trial (US or OUS)										

EXAMPLE DES CLINICAL STUDY SUMMARY

In addition to study protocols and final study reports, as appropriate, the sponsor/applicant should provide a summary for each of the clinical studies conducted in support of the IDE or PMA application. This information can be presented using a one- to two-page summary for each study conducted or proposed. PMA applicants should clearly differentiate which studies are considered to be feasibility, supportive, or pivotal study cohorts for the PMA application. The summary should address the following study parameters. A suggested format is also provided below.

- Design of the study, including any randomization, blinding, and the control or controls used
- Number of patients enrolled
- Number of investigational sites, identifying whether study is solely conducted outside the United States
- Significant inclusion/exclusion criteria, including lesion characteristics
- Safety and efficacy endpoints and hypotheses
- Amount of follow-up currently available and total planned follow-up
- Other relevant issues that differentiate feasibility or supportive studies from the proposed pivotal study cohort.

Proposed DES Name
Study name

Product Description/Indications for Use:

- Intended Use Statement
- Brief description of product (1 or 2 sentences) including delivery system(s) used
- Drug name and supplier (if applicable, reference IND/NDA/DMF)
- Carrier name and supplier (if applicable, reference MAF)
- Matrix of DES stent sizes available in study, including the drug and carrier dose per stent size
- Maximum number of stents per patient

Patient Population:

Significant inclusion and exclusion criteria should be described. For example:

- De novo target lesion located within one or two native coronary vessels
- Reference vessel diameter (RVD) is $\geq$ 2.5mm and $\leq$ 3.5mm
- Cumulative target lesion length is 28mm

Study Design:

Important elements of the study design should be provided. For example:

- Number of study arms: 1 / 2 / 3
- Type of control: None / Concurrent / Historical / Patient-as-own / Performance goal
- Control arm, if applicable

- Randomized? Yes / No (1:1, 2:1, etc.)
  - Randomization stratified by?
- Blinded? Patient only/ Physician only/ Both / None
- Sample size/Number of sites/Location of sites (US/OUS)
- Length and type of follow-up
- Duration for which patients were consented
- Is there a pre-specified interim analysis plan? Yes / No
- Dual anti-platelet regimen
  - Peri-procedure
  - Post-procedure

Primary Endpoints and Sample Size:

- Primary Safety Endpoint(s)
- Primary Effectiveness Endpoint(s)
- Study success defined by multiple endpoints? If yes, please describe.
- Null Hypotheses – please specify alpha, power (1-beta), and null hypothesis stated using standard mathematical notation

Definitions for outcomes specified in the primary study endpoints should be provided.

Secondary Endpoints:

Endpoints for which a hypothesis has been prespecified or that may provide important additional information about the investigational treatment should be outlined.

Status/Other Comments:

Other important information about the study should be provided. For example:

- Dates of enrollment or initiation of enrollment or current number of patients enrolled
- Major adverse event update with clinical narratives

EXAMPLE COMMITMENT TABLE

Following the review of a DES submission, a letter to the study sponsor may include a substantial number of deficiencies or questions, even if adequate preliminary evidence of safety to initiate the clinical study has been provided. Given the wide variety of issues that may be identified, we recognize that certain tests or information may take longer to develop and provide in response to such a letter. To allow the clinical study to progress in a timely manner and to encourage the submission of information as it is available without losing track of pieces of information requested by FDA, we suggest the use of a tabular format to summarize all of the deficiencies and the status of the response to such deficiencies.

The sample table below includes reference to the submission number in addition to the date of FDA's deficiency letter. FDA recommends including a column outlining the "current supplement" that indicates the issues that are being addressed in a particular submission. Deficiencies resulting from responses to deficiencies from previous submissions should be tracked in the same rows across the table. Sponsors may also want to include a column with a rationale for any delay in answering a particular deficiency. The sponsor should track deficiencies starting from the original submission and reference subsequent submissions to track which deficiencies are outstanding or were only partially addressed in the responses. This deficiency tracking document should be inclusive and provided with every submission.

Original IDE (letter date)	**S1 (letter date) Response to S0**	**S2 (letter date) Response to S1 & New Issue (ex. Change in materials)**	**Current Supplement Response to Sxx**	**Justification for any delayed submissions (to include reason & expected date of submission)**
Q1				
Q2	Q1	Q1	Delayed	Submission expected: x/xx/xx Ex: Animal data not available until x/xx/xx
Q3				
Q4	Q2	Q2a-c	Addressed here	
Q5	Q3	Q2d	Addressed here	
		New Q3	Addressed here	
		New Q4	Delayed	Future PMA Concern to be addressed in marketing application
	For deficiencies that have been fully addressed, and where no questions remain from the Agency, it is helpful to shade subsequent boxes across a specific row, so it is clear that this deficiency is no longer open.			

GENERAL BIOCOMPATIBILITY CONSIDERATIONS

The following are common biocompatibility issues that should be considered when conducting biocompatibility testing for a DES and delivery systems.

- It is important to understand how the test samples compare to the final sterilized product (including the drug substance). The test article certification (the stand alone document) could be used to detail how any differences may or may not affect biocompatibility of the final product. If a coated coupon is to be used as the test sample, data should be provided to demonstrate that the drug, carrier, and substrate materials elute drug and chemical leachants (from both the carrier and substrate materials) of the same type and quantity using exhaustive extraction techniques. For example, FDA has not accepted the use of coupons for biocompatibility testing for drug-eluting stents where the stent is manufactured from Nitinol. This is because changes in manufacturing of a Nitinol product could change the final surface properties of the Nitinol substrate material thereby potentially affecting the amount of nickel (a known sensitizer) released from the stent.
- Sponsors should consider whether carrier-only samples should be tested (e.g., if the drug has the potential to mask a toxic response to the drug-eluted carrier system).
- For bioabsorbable materials, test sample preparation should take into consideration starting, intermediate, and final degradation products so that the toxicity of all can be assessed.
- For extraction testing, sponsors should consider the following.
    - It is important to conduct short-term extraction tests on the stent and the delivery system separately. If the delivery system and the stent are combined into a single test sample, this will dilute the amount of implanted stent materials being presented to the test system and may not identify potentially toxic agents that would have been found if the stent was tested separately from the delivery system. We think this is especially important to consider as a DES is a permanent implant that typically incorporates novel polymer/drug combinations where biocompatibility should be assessed carefully. The extensive vascular implantation testing that is conducted for these types of products is either unable to determine some of the toxicity issues assessed by these extraction screening tests or is not as sensitive as some of the extraction screening tests. The stent and delivery system should be evaluated separately in the following tests, if performed:
        + cytotoxicity
        + sensitization
        + intracutaneous reactivity
        + acute systemic toxicity
        + material mediated pyrogenicity
        + hemolysis (extract test only; the direct contact test may be performed on the stent alone)

322 + complement activation
323 + subchronic and chronic toxicity (stent alone)
324 + traditional muscle implant (stent alone)
325 + genotoxicity (stent alone; delivery system should be tested separately if new
326 materials are included that have never been previously used in blood-contacting
327 devices or implants)
328 + carcinogenicity (stent alone)

329 - Final, sterilized stents that include any coating and/or carrier materials and the drug
330 should be used for extraction testing.

331 - Surface area to extract volume, according to ISO 10993-12, should be used to
332 calculate the amount of product being sampled. Weight per extract volume
333 calculations should only be used in the event that the surface area cannot be
334 calculated (which likely will not be the case for the stent). Where there are concerns
335 about numbers of samples needed for extractions, one can consider using
336 concentrated extraction techniques to meet surface area recommendations.

337 - Both polar and nonpolar extracts should be used.

338 - If extraction samples are not used immediately, they should be stored according to
339 ISO 10993-12.

340 - Test reports should include information on the condition of the extraction vehicle
341 (e.g., color, presence of any particles) and any changes in the postextraction vehicle
342 from pre-extraction should be explained. Details regarding storage conditions should
343 be described. If the samples are stored prior to use, the sponsor should discuss why
344 storage would not affect the test results.

345 - For cytotoxicity testing, extraction vehicles should include MEM and 5 percent serum
346 as these materials will allow for extraction of both polar and nonpolar constituents
347 from the test sample.

348 • For material-mediated pyrogenicity testing, methods such as those outlined in the current
349 USP <151> Rabbit Pyrogen Test can be used, except that traditional biocompatibility
350 extraction methods should be used, (e.g., 50°C for 72 hours; 70°C for 24 hours; or 120°C
351 for 2 hours) or an equivalent method.

352 • If overlapping stents could be used clinically, should be explained why biocompatibility
353 testing will provide information on toxicity at the overlapped stent segment.

354 • For cytotoxicity testing, both direct contact and elution methods should be considered.

355 • For guinea pig maximization sensitization testing, historical positive control testing is not
356 sufficient to determine whether the animal model continues to be capable of detecting a
357 positive sensitization response. We recommend running either concurrent controls, or
358 periodic test laboratory controls within 3 months of the evaluation of the test samples.
359 Protocols and results from positive control testing with a minimum of 5 animals should

be provided with the application to confirm that the same methods were used for both the positive control testing and the test samples.

- For guinea pig maximization sensitization testing, test reports should confirm that none of the female animals used in the testing is pregnant, as pregnancy can reduce the ability of a female animal to detect a sensitization response.

- For sensitization testing, FDA will also accept local lymph node assay (LLNA) testing as an alternative to guinea pig maximization testing, if appropriate methods are used.

- For hemocompatibility testing, hemolysis, complement activation, and in vivo thromboresistance should be considered. Complement activation should be addressed either by testing with both C3a and SC5b-9, or with a scientific justification for the omission of testing. Sponsors may also assess in vivo thrombogenicity in the vascular animal implantation testing in lieu of a separate canine in vivo thrombogenicity test.

- Muscle implant studies should be performed even when vascular implant studies are performed. When new materials/chemicals are used in a medical device, FDA traditionally requests both the muscle implant study as well as studies of the device implanted at the proposed anatomical site. The muscle implant study is used as a screening test to look at local toxicities. Because the muscle implants tend to form a fibrous capsule around the implant, any materials eluted over time from the test article will be contained within the capsule, and therefore might result in an exaggerated response that might not necessarily be observed in the vascular implant study. We believe that both tests are informative to the overall toxicity assessment of both the material components of the product and the final product when used in its intended anatomical location.

- For implantation testing of products including biodegradable materials, tests should be conducted to determine the length of degradation and/or absorption time (i.e., until the material has completely disappeared) and to assess whether tissue healing occurs once the material is gone.

- For materials that have not been used previously as implant materials (e.g., new base materials and/or materials with altered formulations), additional toxicity testing (e.g., reproductive toxicity, additional immunotoxicity) not normally performed for products in contact with cardiovascular tissue and circulating blood may be called for.

- A risk assessment should be conducted to determine the necessity of carcinogenicity testing. This assessment should include the following elements:

  – The complete chemical formulations for all components of the DES (drug, coating materials, metals, additives, and processing agents). The sponsor should identify how much would theoretically be present in an individual stent (assume worst case, i.e., largest stent) as well as per patient (assume a worst case situation where a patient might receive multiple stents).

  – The potential breakdown products and descriptions of the mechanism by which the breakdown products, drug, and/or other compounds of concern are formed during the degradation process should be evaluated. Because certain constituents may be

present upon degradation that were not included as original materials or processing agents, these constituents should be evaluated as well. Assessments should also include the effects of all processing agents (e.g., adhesives, mold cleaning agents, mold releasing agents, sterilization chemicals) that come into contact with the stent and delivery system materials during processing (including contact with other material components of the final product).

– A thorough literature review should be provided to include search terms and an analysis of the toxicity of the materials and breakdown products. If potential carcinogens exist in the materials and/or in the intermediate or breakdown products, the sponsor should identify and quantify these components and determine how much of the potential carcinogen would be available in a single product (i.e., assume all breakdown product precursors are converted into the potential chemical of concern, and that all of this material is available to the tissue environment). A risk assessment should also be provided with literature evidence to demonstrate that the amount of the potential carcinogen available in one stent does not pose a carcinogenic risk. This analysis should also be provided assuming a maximum number of stents likely to be implanted in a single patient (worst case analysis). This overall carcinogenicity risk assessment should be considered in conjunction with genotoxicity testing on the final product.

EXAMPLE TEST ARTICLE CERTIFICATION

In certain instances, a sponsor may choose not to perform certain tests, based on the fact that the current product is the same as a previously tested product. If such a device is made, the following example statements may be helpful to demonstrate that the test article is identical to the final, sterilized product,

Component Certification

For each component and any joining processes/materials (e.g., adhesives, sintering processes, etc.), the following statement can be provided:

> "The **[polymer/metal/ceramic/composite name] [component name]** of the test article is identical to the **[component name]** of the final sterilized product in formulation, processing, sterilization, and geometry, and no other chemicals have been added (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents, etc.)."

Product Certification

If the above statement is true for all of the fabrication material formulations, processes, and sterilization methods, the following general statement can be provided:

> "The test article is identical to the final sterilized product in formulation, processing, sterilization, and geometry and no other chemicals have been added (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents, etc.)."

New Processing/Sterilization Changes

If there are any processing or sterilization changes that the sponsor believe will ***not*** alter the performance of the final, sterilized product, the sponsor should use the component certification, and include the following qualifier:

> "…with the exception of **[identify change]**. Exhibit **[#]**, page **[#]**, submitted on **[date**], provides scientifically valid information to demonstrate that the **[processing/sterilization]** change does not alter the chemical or physical properties of the final sterilized product, and therefore, results from the test article can be applied to the final sterilized product."
>
> NOTE: The information provided to support a claim that processing and sterilization changes will not affect chemical or physical properties of the final sterilized product should be provided in sufficient detail for FDA to make an independent assessment, and arrive at the same conclusion.
>
> NOTE: Surface alterations due to nanotechnology processing could result in "nanogeometries" or chemical changes at the surface that could result in a toxic response (even if the base material has a long history of safe use in similar applications).

New Formulation Changes

If there are any formulation changes the sponsor believes will ***not*** alter the performance of the final, sterilized product, you should use the component certification, and include the following qualifier:

> "…with the exception of **[identify change]**. Exhibit **[#]**, page **[#]**, submitted on **[date]**, provides scientifically valid information to demonstrate that the formulation change does not alter the chemical or physical properties of the final sterilized product, and therefore, testing on the test article can be applied to the final sterilized product."
>
> NOTE: The information provided to support a claim that formulation changes will not affect performance should be in sufficient detail for FDA to make an independent assessment and arrive at the same conclusion. FDA requests that the following be included:
>
> a. formulation of the test article
> b. formulation of the final sterilized product

AND

> c. a discussion of why the differences would not require additional testing

GENERAL GUIDELINES REGARDING GOOD ANIMAL HUSBANDRY

Issue: When lesions appear in histological samples, the FDA must determine the device causality of potentially confounding variables. It is important to control for all factors that might contribute to the presence of unexplained lesions when conducting animal studies. This section includes study controls that may be used to rule out contributing factors to foci of infectious and noninfectious etiology. Unless we minimize the possibility of contributing influences to the development of such lesions, interpretation of etiologic cause becomes more difficult. Animal husbandry processes should be sound and ensure that procedures for the monitoring of infectious agents or the effects of infectious background agents on normal tissue are in place whenever possible**.**

Background: Swine are commonly used for preclinical research to illustrate the safety of a device in the cardiovascular system. This species has well-documented similarities to the human and represents the standard of preclinical evidence due to this similarity. Little has been mentioned to date regarding the expectations that we have related to GLP work associated with the use of swine. However, the FDA wishes to reduce the number of study-related confounders that can come from infection and to encourage the detailing of methods used during studies so that infection can be monitored and minimized.

Regrettably, domestic-reared pigs often carry enzootic diseases that may confound the interpretation of contributors to lesion formation. Most commonly in adult pigs, these are agents associated with enzootic pneumonia (*Actinobacillus pluropneumonia, Pasturella multocida, Mycoplasma hypopneumoniae, Haemophilus parasuis,* and *Bordetella bronchiseptica*). Diseases spread through ulceration of the feet are also not uncommon in domestic pigs and can be carried into the research setting if modern housing practices are not followed. The FDA seeks to articulate practices that may reduce these confounders. Such confounders can be associated with the source herd, husbandry practices, technical procedures, and necropsy method.

Source: Animals used for nonclinical studies must be free of any disease or condition that might interfere with the purpose or conduct of the study (21 CFR 58.90(c)). Swine can be purchased as purpose-bred research animals; either specific pathogen free, minimally pathogen loaded, or farm-raised domestic stock. It is widely accepted that conventionally derived swine stock often have enzootic bacterial pneumonia. However, it is also the standard of care at reputable research facilities that this incidence is minimized either through source-controls or active clean-up procedures. The latter is less likely to produce a clean result than starting with a clean source. This is important because background infectious processes can elevate circulating fibrinogen and other acute phase proteins that can contribute indirectly to granulomatous formations or in rarer cases can embolize to form niduses of inflammation on implanted devices.

Sponsors should consider purchasing or generating pigs from SPF-accredited sources to mitigate subclinical infectious processes. SPF or axenic pigs may be produced free of specific enzootic agents by derivation from cesarean followed by routine conventional rearing or they may be maintained as a secondary closed SPF herd that originally came from a cesarean derivation but

has been bred and maintained as a closed herd with no introduction of pigs from non-SPF stock. There are also true gnotobiotic pigs that are injected with known flora. The latter are generally custom-generated and not practical for the studies of devices. SPF-conventionally reared pigs can be purchased by contacting an accredited vendor through the National SPF agency. The National Academies of Science Institute for Laboratory Animal Resources has formerly discussed the differences between conventionally reared and germ-free of Axenic pigs.[9] The National Pork Producers may be able to help identify SPF Swine Herds (515-223-2600).

Husbandry: The FDA has observed the following issues as contributors to poor outcomes or research unknowns, which may be considered as husbandry related.

- No description of shipping methods and whether or not the animals are in air conditioned trucks, single or group containers, and whether any national policies or regulations were followed to minimize transportation stress
- A shipping experience that is within the first week following surgery
- No description of housing or a description of housing that indicates crowding, lack of raised floor surfaces, possible sore feet
- No description of diet (note that FDA is interested in whether the vendors and sponsors have included screening for unacceptable feed additives such as melamine and other more recently discovered contaminants of swine food)
- No description of, or an overly short acclimation period
- No description of socialization or companionship
- Description of crowding or isolation in the research facility
- No description of bedding and bedding changes

Shipping and housing stress can elevate endogenous steroid release, slow healing, and can decrease host defenses. Similarly, insufficient bedding or uncomfortable flooring in ungulates has been associated with foot-borne or decubital ulceration leading to bacterial migration. Efforts should be made to keep pigs as clean and comfortable as possible. These efforts should be described in the study protocol so that the FDA can reasonably exclude these possible contributions to unexplained lesions. If pigs originated at one source, were shipped to the operative location and were shipped again, their shipping details should be provided. Likewise, if the diet was one type at the vendor site and different at the study location, this should also be discussed. The standard of care at GLP research facilities is housing for at least the first postoperative week on raised polyvinyl-coated flooring to minimize contact of the incision with feces and urine. We would prefer to know the flooring conditions were and the sanitization schedule for the pig studies we review.

Procedural Confounders: The sources of stress or contamination in procedures related to swine handling, husbandry, and study include but are not limited to:

- Vaccination stress; usually vaccinating too closely in time to the study implant

[9] Safron, Joe, Gonder, Jan. 1997. "The SPF Pig in Research," ILAR Journal V38(1)1997.

- Bleeding stress: this can be minimized by chemical restraint and sling acclimation for scheduled bleeding procedures
- Lack of baseline and serial clinical chemistry and hemogram
- Lack of baseline and serial fibrinogen measurement
- Lack of baseline and serial weight monitoring
- No description of aseptic technique for bleeding procedures or surgical preparation.
- Indwelling catheters left in more than 24 hours. Such use should be avoided in DES studies or should be supported with an adequate justification due to the risk of infection or the need for long-term antibiotics. Use of indwelling catheters for longer than 24 hours or non-periprocedural antibiotic use should be noted in the study report.
- Hypothermia or lack of controls describing homeostasis
- Oversizing of the stent (initial placement in swine with vessels that are subject to high radial stress)
- Undersizing of the stent (placement in rapidly growing domestic swine or already overly large swine)
- No description in the study protocol of surgical recovery monitoring and controls

Procedural stress and procedural contamination can significantly contribute to unexplained lesions due to circulating endogenous steroids that can cause immunosuppression and lead to opportunistic infections. Once a remote infection is established, fibrinogen and other acute phase proteins may increase in circulation, and bacteria can seed implanted devices. Routine monitoring of clinical chemistry values, serum fibrinogen and hemograms should be conducted to rule out these possible contributors. At the same time, body temperature should be recorded in conjunction with these observations. Additionally, sponsors should identify the aseptic techniques used for phlebotomy and surgical procedures as well as incisional care and inspection following surgery. Any prophylactic antibiotics used and any antibiotic use required to mitigate infections during the chronic study period should also be detailed (e.g., dose, frequency). Since bleeding sites are relatively limited in swine, we would encourage the use of immobilizing agents such as ketamine and xylazine for bleeding procedures to minimize handling stress and facilitate accurate placement of needles for venipuncture. We do not consider the frequency of tranquilization by intramuscular routes a significant confounder in device-associated studies.

Study confounders associated with the collection of samples following animal death (either planned or unplanned):

- Source animal incidence of opportunistic or enzootic flora not identified (*what is the baseline pathogen status?*). A cytological and microbiological evaluation of a tracheal wash (perimortem) may be good practice to rule out subclinical respiratory infections. Bacterial count and differential cytology are acceptable tools for this purpose.
- Failure to identify or characterize lung lesions
- Failure to describe normal or abnormal findings in other organs than the organ or tissue of study

A pathologist should evaluate gross and histologic findings. Digital photos should be taken at time of necropsy under GLP defined conditions. A thorough postmortem examination should be carried out on study animals; this examination is particularly useful in the evaluation of potential

study confounders. Lesions should be fully characterized and there should be an explanation as to why the lesion is or is not device related. Statements regarding normal background incidence of pathogens should be supported by baseline data as well as data collected during the in-life period to demonstrate that confounders related to infection were excluded as possibilities. We encourage a description of the necropsy procedure. We would also encourage practices at harvest that rule out blood-borne bacterial processes as opposed to pre-existing processes. Lesions can be aseptically cultured before fixation.

The bullets below are summary suggestions that have aided in the minimization of infectious processes in swine cardiovascular research:

- Acquire swine from an SPF-accredited source
- Reduce the possibility for vaccination and shipping stress
- Use raised flooring for research swine housing to minimize contact with feces. (Cleaning frequency should be defined.)
- Document changes in housing
- Screen baseline hemograms, serum fibrinogen, weight general exam at baseline and other key time points during the study
- Document operative and postoperative conditions
- Pay attention to the feet and legs for sores or lameness. (Please note that lameness or sores should be recorded in the animal records. Treatment plans for changes in health status should be considered protocol deviations that require appropriate reporting to the IACUC.)
- Use chemical restraint and humane swine slings to minimize handling stress (for example, Panepento slings)
- Use a sterile approach at necropsy: Cultures of gross lesions along with cultures taken of the device area would be helpful. If the device area cannot be accessed without physical disruption of the area, then left ventricle blood cultures could be used to assess infection in cardiac tissue.
- Bacterial Cultures: Infections of Staph. aureus would indicate infections of animal origin; Staph. epidermidis would indicate infection of human origin.
- Choice of surgical scrub: Betadine scrub followed by alcohol is preferable over chlorhexidine. Do not dip in and out of the same moist gauze container. (*Chlorhexadine scrubs have occasionally been contaminated this way.*)
- Pay attention to necropsy technique: The use of a tranquilization, anesthesia, and termination process that allows for the minimization of thrombi and opportunity to cleanly collect blood and tissue.
- Manipulation of the device: Document any manipulation of the devices during surgery that could influence the study due to the introduction of either contaminants or microorganisms, that may be present confounding issues.
- Collection of the device post-euthanasia. Storage conditions and tissue fixation methods should be clearly defined.

FACTORS AFFECTING POOLABILITY BETWEEN U.S. AND OUS (Outside the U.S.) STUDIES

Patient Demographics/Clinical Characteristics

- Race/ethnicity
- Diabetes
- Smoking
- Hyperlipidemia
- Hypertension
- Obesity
- Age
- Sex

Procedural/System Related Differences

- Concomitant medication use/availability (clopidogrel, IIb/IIIa inhibitors, direct thrombin inhibitors)
- Adherence to study protocols
- Regional differences in standard of care
- Patient educational level, ability to understand informed consent, follow-up instructions
- Cultural differences in symptom manifestation

Protocol Factors

- Inclusion/exclusion criteria
- Procedural characteristics
- Lesion characteristics
- Test material used (products with different coating process, different source materials, delivery systems, etc.)

GUIDANCE ON LABELING FOR A DES

General labeling requirements for medical devices are described in 21 CFR Part 801. Additional information can be obtained from "Device Advice."[10] All proposed labeling (e.g., instructions for use (IFU), patient guide and stent implant card) should be provided in the IDE and PMA application (21 CFR 814.20(b)(10)).

Investigational Labeling

FDA acknowledges that it may not be appropriate at the time of the IDE submission to disclose certain aspects of the DES (e.g., polymer components); however, the purpose of the labeling at the IDE stage is to provide the reader with an appropriate level of information to make an informed decision about participation/inclusion within a clinical study using an investigational product. According to 21 CFR 812.5, an investigational product or its immediate package must bear a label with the following minimal information:

- The name and place of business of the manufacturer, packer, or distributor
- The quantity of contents

and

- As appropriate, the statement "CAUTION – Investigational Product (drug and device). Limited by Federal (or United States) law to investigational use."

The label must also describe all relevant contraindications, hazards, adverse effects, interfering substances or products, warnings, and precautions. Claims that have not been substantiated by clinical evidence should not be included in labeling for an investigational DES as part of an IDE submission. For example, the labeling should not state that the investigational product is safe and effective. The FDA strongly recommends working with the appropriate review division to reach consensus on an acceptable version of the labeling prior to trial initiation.

It is also critical that the patient guide capture fairly and at an appropriate reader comprehension level the potential risks and/or benefits associated with implantation of a DES system.

Labeling for a Marketed Product

As part of the final labeling for a DES, the following statement should be included:

> **Caution: Federal (USA) law restricts this product to sale by or on the order of a physician.**

If an applicant intends to use electronic labeling for a DES, the most up-to-date version of the labeling must be available for physicians, patients, and FDA review.

[10] See CDRH Device Advice, http://www.fda.gov/cdrh/devadvice/ide/index.shtml.

Recommendations for Coronary DES Labeling

Labeling for a coronary DES should include the sections described below. These recommendations reflect the information that the Agency considers appropriate for inclusion and is consistent with labeling of currently marketed coronary DESs. The appropriate divisions in the Agency are available to discuss specific labeling questions for DESs and their indications.

1. Product description

The components of the product, such as the stent, stent delivery catheter, drug substance, and inactive ingredients (polymers) should be briefly described. For the drug substance and inactive ingredients, the chemical structures and names should be included. A table with the following attributes, as appropriate should also be included:

- Available stent diameters and lengths
- Stent material and geometry
- Drug component
- Guiding catheter compatibility
- Deployment and rated burst pressure(s)

2. Indications for use

Proposed labeling should reflect the precise indications for use statement that is the subject of the application. The general statement of the "Indications for Use" identifies the target population in which sufficient valid scientific evidence demonstrating that the product, used as labeled, will provide clinically beneficial results and at the same time does not present an unreasonable risk of illness or injury.

3. Contraindications

Contraindications specific to DES implantation as well as to coronary artery stenting in general should be included. Contraindications describe situations in which the product should not be used because the risk of use clearly outweighs any possible benefit. For example, inclusion of the following contraindication should be considered:

- Patients who cannot receive recommended antiplatelet and/or anticoagulation therapy.

4. Warnings

An appropriate warning should be included if there is reasonable evidence of an association of a serious hazard with the use of the DES. A causal relationship need not have been proved. We believe a warning is also appropriate when the DES is commonly used for a disease or condition for which there is a lack of valid scientific evidence of effectiveness for that disease or condition,

and use of the DES is associated with a serious risk or hazard. For example, the following warnings should be considered:

- "Patients who are unlikely to comply with recommended antiplatelet therapy should not receive this product."
- "The inner package should not be opened or damaged prior to use to maintain sterility."
- "The use of this DES carries the risks associated with coronary artery stenting, including subacute thrombosis, vascular complications, and/or bleeding events."
- "Patients with known hypersensitivity to the product components (stent substrate, polymer(s), drug substance) may suffer an allergic reaction to this implant."

5. Precautions

Precautions information should include any special care physicians or others should exercise for the safe and effective use of the DES. In addition, labeling should include any limitations on the use of a product for reasons including, but not limited to:

- Lack of long-term safety and effectiveness data
- Lack of safety and effectiveness data for special patient populations
- Need for appropriate physician training
- Anatomical or physiological limitations on the effectiveness of the DES

Inclusion of precautions that fall into the following categories should also be considered.

- General precautions
- Pre- and postprocedure antiplatelet therapy recommendations
- Use of multiple stents
- Use in conjunction with other procedures (e.g., brachytherapy, atherectomy)
- Use in special populations, such as:
  - Pregnancy
  - Lactation
  - Gender
  - Ethnicity
  - Pediatric
  - Geriatric
- Lesion/vessel characteristics
- Drug interaction
- MRI (see Note below)
- Stent handling
- Stent placement
- Stent system removal
- Postprocedure precautions

Note: FDA strongly recommends that a DES be tested using the methods described in the guidance *Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems*[11] for MRI compatibility rather than assessing compatibility based on a literature review. Also, see the guidance for additional recommendations for language to be included in the labeling.

6. Drug information

Labeling should include pertinent information about the action and potential toxicities of the drug substance as incorporated in the DES. The following items should be addressed:

- Mechanism of Action
- Pharmacokinetics
- Drug Interactions
- Mutagenesis, Carcinogenicity and Reproductive Toxicity
- Pregnancy and Lactation

7. Overview of clinical studies

A narrative description of the pivotal study or studies and any supporting or feasibility studies relevant to the DES should be provided. The narrative should be concise and include the following information for each study followed by results in a tabular format:

- Whether the study was a pivotal, supporting, or feasibility study
- The design of the study, including any randomization, blinding, and the control or controls used
- The number of patients enrolled
- The specific lesion criteria
- The products used
- The primary study endpoint or endpoints
- The number of investigational sites both inside the U.S. and OUS (outside the U.S.)
- The antiplatelet therapy used
- The amount of available follow-up
- The total planned follow-up.

8. Adverse events

a. Observed adverse events

A brief narrative statement about the source or sources of the adverse event experience should be provided, followed by results in a tabular format. In the table, adverse events should be presented using a *completed case,* or *evaluable* approach, specifically defined as follows:

In this approach, the numerator consists of:

[11] Available at http://www.fda.gov/cdrh/ode/guidance/1545.pdf.

- The number of patients who experienced an adverse event during or before the analysis window

The denominator consists of:

- The number of patients evaluated during the analysis window, plus

- Any patients not evaluated during the analysis window, but that had the specified adverse event between treatment and the analysis window

An adverse events table that captures data through the longest available follow-up for the study should be included. Protocol definitions for adverse events should be provided as footnotes, or a reference to definitions included with the Principal Safety and Effectiveness Table.

We have provided a list of suggested elements for inclusion, below. Additional elements may also be appropriate given the outcomes from the study(ies).

In-hospital events should be separated from out-of-hospital events (through X days or months), for categories such as:

- Target Lesion Failure (TLF), which includes:
  - Cardiac death
  - Target vessel Q-wave or non-Q wave Myocardial Infarction (MI) (i.e., Q-wave MI that cannot be attributed to a non-target vessel)
  - Emergent Coronary Artery Bypass Grafting (CABG)
  - Target Lesion Revascularization (TLR)

- All death
- All MI
- Target vessel failure (TVF)
- Target vessel revascularization (TVR)
- TVR, non-TLR
- Stent thrombosis (acute, subacute, late, very late)
- Cerebro-vascular accident (CVA)
- Bleeding complications
- Vascular complications

b. Potential adverse events with the stent placement and drug component

Potential adverse events associated with stenting of the intended coronary vessel or vessels and potential adverse events associated with the drug substance should be included.

9. Clinical Studies

Additional specific information about the clinical studies described in the section titled "Overview of Clinical Studies," above should be included. We suggest the following format:

c. Study name

The name of the study should be given and whether it was a pivotal or a supportive study should be stated.

d. Purpose/objective

The intent of the study, including the primary endpoint or endpoints should be given.

e. Conclusions

The study outcome or outcomes should be briefly stated.

f. Design

The study design should be described. The following is a partial list of elements that may be appropriate to the design:

- Whether the design is randomized or nonrandomized
- Which type of controls were used
- If the study results were compared to a performance goal
- How any performance goals were derived

The success criteria for the trial should be described (i.e., superiority or noninferiority when compared to the control).

A brief description of patient entry criteria should be included, such as:

- Vessel location
- Vessel size
- Vessel type, (i.e., *de novo* or restenotic)
- Type of evaluations (clinical, telephone, angiographic/intravascular ultrasound follow-up).

g. Demographics

For the treated patient population, demographic information and rates of important risk factors that could affect the results of the study should be included, including:

- Age
- Race
- Sex
- Smokers

- Dyslipidemia
- Previous MI
- Previous coronary revascularization
- Hypertension
- Diabetes
- Any other important covariates.

h. Methods

Any use of a Clinical Events Committee, a Data and Safety Monitoring Board, and/or a core laboratory for adverse event adjudication should be described, as appropriate.

i. Results

The results of the study, including whether the primary endpoint or endpoints were met should be described, for example:

> The X stent demonstrated a lower rate of TLF as compared to the control group (X% vs. Y%, $P<0.001$).

The Principal Safety and Effectiveness Table, described below, should be used.

10. Principal safety and effectiveness table

The clinical outcomes should be presented in a tabular format as "effectiveness measures" and "safety measures," separately or combined. Your data presentation should follow the same approach used for adverse event reporting, discussed earlier. Protocol definitions for terms used in the table should be included.

Kaplan-Meier estimates for relevant endpoints in safety and effectiveness table should be provided. These may include, but are not limited to:

- TLF-free survival
- TVF-free survival
- TVR-free survival
- TLR-free survival

In some instances, it may be appropriate to provide a graphical presentation of the most appropriate Kaplan-Meier survival endpoints (see examples of these endpoints below) and accompanying life tables. We believe that statistical comparisons between groups are only appropriate for randomized trials. The Interventional Cardiology Devices Branch is available to advise you on this issue.

a. Examples of Kaplan-Meier survival endpoints

If a survival graph is provided, it should include confidence intervals that estimate a standard error (SE) of ± 1.5. The scale should either begin on the y-axis at a value greater than zero – we recommend using a value around 50 to 60 percent – or indicating a break in the scale to illustrate the differences in survival curves, if applicable.

b. Updates to principal safety and effectiveness table

For a coronary DES, updating the Principal Safety and Effectiveness Table to reflect additional clinical follow-up beyond the primary follow-up interval has been identified as a condition of PMA approval. Once information is available, the updated labeling should be submitted as a PMA supplement.

In the event an update is not listed as a condition of approval, the updated labeling can be provided in the annual report, as long as the updated information is based on the endpoints and follow-up schedule prospectively defined in the clinical study protocol. For updates that relate to new indications, see 21 CFR 814.39.

If clinical results in the updates raise a safety or effectiveness concern when compared to the initial results of your study, the labeling should be updated to reflect this new information.

12. Patient selection and treatment

This section should provide information related to individualization of treatment.

13. Patient counseling information

This section should include any particular issues the treating physician should consider in counseling the patient prior to the procedure.

14. Directions for use (Operator's Manual)

Directions for proper preparation and use of the DES should be included in this section of the labeling. If multiple delivery systems are available, differences specific to the stent delivery system should be clearly indicated. An example would be to indicate the difference(s) between an over-the-wire (OTW) and a rapid exchange (RX) stent delivery system.

15. Compliance chart (Balloon Expandable Stents Only)

A compliance chart that provides the average stent inner diameter following deployment at various pressures derived from engineering testing should be provided, displaying the data as determined from testing. However, if the data are rounded, this should be indicated in a footnote to the chart. We recommend the format presented in Table 5 in *Section VII.C.4*. of the guidance entitled *Non-Clinical Tests And Recommended Labeling For Intravascular Stents And Associated Delivery Systems*.[12]

[12] Available at http://www.fda.gov/cdrh/ode/guidance/1545.pdf.

16. Patient materials

Examples of patient materials, such as the patient guide and implant card should be provided. See also *Guidance on Medical Device Patient Labeling.*[13]

[13] See http://www.fda.gov/cdrh/ohip/guidance/1128.pdf.