Guidance for Industry

Coronary Drug-Eluting Stents—Nonclinical and Clinical Studies

DRAFT GUIDANCE

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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)
March 2008
Combination Products

Contains Nonbinding Recommendations

Draft — Not for Implementation

Guidance for Industry

Coronary Drug-Eluting Stents

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U.S. Department of Health and Human Services
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Coronary Drug-Eluting Stents —Nonclinical and Clinical Studies

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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.

I. INTRODUCTION

This guidance is intended to provide recommendations to sponsors or applicants[2] planning to develop, or to submit to FDA, a marketing application for a coronary drug eluting stent (DES). The guidance discusses the data and clinical studies needed to support such an application. This guidance does not discuss noncoronary DESs (e.g., peripheral drug-eluting, nonvascular biliary stents) or stents that contain biological product components such as cell or gene therapy or therapeutic biological products such as monoclonal antibodies. The guidance makes recommendations for stents made from metallic stent substrates, but does not provide complete information for degradable stents or stents made from other material substrates (e.g., polymer or ceramics).

The associated companion document provides additional information that may be useful, including suggested contents of investigational and premarket approval applications; various examples (e.g., example of a DES clinical study summary, a commitment table, test article certification); information on good animal husbandry, biocompatibility considerations, and issues related to U.S. and OUS (outside the U.S.) studies; and labeling recommendations. The companion document is intended to be used together with this guidance.

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

[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) applications and *applicant* is used primarily in relation to premarket approval (PMA) submissions.

use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Coronary stents are implantable devices that are placed percutaneously in one or more coronary arteries to maintain patency. DESs incorporate a pharmacologically active agent (drug) that is delivered at the site of stent deployment and is intended to reduce the incidence of restenosis due to neointimal hyperplasia associated with bare metal stenting. In many cases, the drug is incorporated into and released from a polymeric coating of sufficient capacity to accommodate the selected dose and to modulate its delivery at the intended site of action and for the intended duration. The chemical, physical, and mechanical attributes of the polymer coating system are important for stent deployment, biocompatibility, and stability. To perform a regulatory assessment of a DES, FDA would review data from a comprehensive evaluation of individual components (drug, polymer, and stent), as well as from a comprehensive evaluation of the finished drug-device combination product.

After briefly discussing some general FDA jurisdictional considerations related to this drug-device combination product, the guidance clarifies a number of issues related to the development of DESs including the following:

- How to characterize the drug substance, including chemistry, nonclinical systemic and local tissue pharmacology and toxicology, and how to evaluate the potential for and consequences of systemic clinical exposure
- How to characterize the drug-device combination product, including the chemical/physical/mechanical properties of the DES, the nonclinical local vascular and regional myocardial toxicology, and the clinical performance of the drug-stent combination
- Regulatory considerations that are unique to DES combination products

We encourage sponsors and applicants to consult closely with FDA during development of a DES.

A. Regulatory Basis

DESs are combination products subject to section 503(g) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 353(g)), because they are a combination of two different types of regulated components (a device and a drug) that are physically and/or chemically combined and produced as a single entity (21 CFR 3.2(e)(1)). A combination product is assigned to an Agency component, such as the Center for Devices and Radiological Health (CDRH) or the Center for Drug Evaluation and Research (CDER), for premarket review and regulation based on a determination of the product's *primary mode of action*.

In response to several *requests for designation* under 21 CFR 3.7, the Agency determined that for current DESs where the device component maintains coronary artery patency and the drug component augments the safety and/or effectiveness of the uncoated (bare) stent by preventing

restenosis, the device mode of action is the primary mode of action.[3] Therefore, the premarket review and regulatory responsibility for these coronary DESs has been assigned to CDRH with significant consultation from CDER.

B. Application Requirements

1. Product Classification

Coronary DESs, where the device component provides the primary mode of action, are regulated as Class III devices that require the submission and approval of a premarket approval (PMA) application prior to commercial marketing in the United States. To meet the standard for approval, the PMA application must contain (or include by reference) valid scientific evidence to provide a reasonable assurance of safety and effectiveness of the DES when used in accordance with its labeled indication (21 U.S.C. 360c(a)(1)(C), 360c(a)(2)-(3)). Such evidence will usually consist of nonclinical, animal, and human clinical testing.

2. IDE Application Requirements

FDA has determined that DESs pose a significant risk as defined in 21 CFR 812.3(m), and as such, are not exempt from the requirement to submit an investigational device exemption (IDE) application (21 CFR 812.2(b), 812.20(a)(1). When an IDE application is required, a sponsor must not begin a clinical trial in humans in the United States until FDA has approved the application (21 CFR 812.20(a)(2), 812.42). Sponsors of such studies must comply with the following:

- IDE regulations (21 CFR 812)
- Regulations governing institutional review boards (IRB) (21 CFR 56)
- Informed consent (21 CFR 50) [4]

The companion document contains a listing of the elements FDA recommends be included in an original IDE application.

FDA strongly encourages sponsors to use pre-submission interactions to obtain informal guidance regarding product development prior to submission of an original IDE application.[5] FDA comments provided to sponsors during the pre-submission process are informal input, intended to facilitate open communication between the sponsor and the Agency. Pre-submission interactions for a DES can be broad-based, or can focus on particular areas, such as engineering testing, CMC testing, or

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[3] See "Jurisdictional Update: Drug-Eluting Cardiovascular Stents," http://www.fda.gov/oc/combination/stents.html. This Jurisdictional Update discusses DESs for which the primary mode of action is the action of the device component in maintaining vessel patency. However, a DES for which the primary mode of action is attributable to the drug component would be assigned to CDER.

[4] You should review the statutory definition of applicable clinical trial to determine if your trial must be registered to comply with the law. *See* PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)). http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf Information can be submitted to ClinicalTrials.gov using the Protocol Registration System (PRS). For more information visit the PRS Information Page (http://prsinfo.clinicaltrials.gov).

[5] FDA intends to develop guidance on pre-submissions.

clinical protocols. Sponsors should clearly identify questions or particular items they would like to have addressed as part of the pre-submission interaction. It may be appropriate to meet or hold pre-submission discussions with Agency staff more than once, at different stages of the development process.

3. IND Application Requirements

Preclinical and clinical evaluation of the drug substance alone (e.g., not delivered via a stent) may be appropriate to fully characterize potential toxicities (see Section IV. below). Human studies of an investigational drug in the United States must be conducted under an IND application (21 CFR Part 312). The IND application should specify that the eventual intended use of the drug is to be in combination with a stent.[6]

4. PMA Application Requirements

To meet the standard for approval, a PMA application must provide reasonable assurance of the safety and effectiveness of the finished DES (21 USC 360c(a)(1)(C)). See the companion document for a list of the elements FDA recommends be included within an original PMA application.

Because of the extensive amount of nonclinical information that is typically needed (especially when the drug component is a new molecular entity, or NME, that has never been the subject of a new drug application) coupled with the relatively long primary endpoint timeline for a DES (e.g., 12 months or longer), applicants may wish to consider using the Modular PMA application program.[7] A modular PMA application is a compilation of discrete sections, or modules, submitted at different times, as each is completed. Together the modules make up a complete application. The potential advantage associated with the modular approach is that if any deficiencies in a particular section are noted by FDA, the applicant may be able to resolve them earlier in the review process than would occur with a traditional PMA application, where a complete application is submitted in a single submission.[8]

5. Master Files

Drug Master Files (DMFs) and Device Master Files (MAFs) permit the submission of proprietary information to FDA so that parties other than the owners of that information may rely on it. With the permission of the holder of that master file, a third party applicant may rely on the information in that master file to support the third party's application to FDA (e.g., IDE or PMA), even though the contents of the master file remain proprietary to the holder of the master file (See 21 CFR 314.420, 814.3(d), 814.9(a)). The Agency will not review a DMF or MAF in support of a third party's application unless the third party applicant submits in its application a letter of authorization (LOA)

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[6] See the CDER guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drug*.

[7] See guidance for industry and FDA staff, *Premarket Approval Application Modular Review.*

[8] Ibid.

from the holder of the DMF or MAF, which authorizes FDA to refer to the master file in support of that application.[9]

As outlined in Section IV.C of the *Guideline for Drug Master Files*, each DMF should contain only one type of information and all supporting data. If the DMF is administratively incomplete or inadequate, it will be returned to the submitter with a letter of explanation from the Drug Master File Staff, and it will ***not*** be assigned a DMF number. If you intend to submit a DMF that does not conform to the *Guideline for Drug Master Files*, we recommend that you contact the appropriate review division or Drug Master File Staff before making the submission.

We recommend that a sponsor intending to reference (or file) a DMF allow for sufficient time for the Drug Master File Staff to administratively determine the adequacy of the DMF and assign a DMF number before an IDE is submitted, given the 30-day review timeframe for IDE applications. Additionally, sponsors who reference a DMF or MAF as a source of supportive data for an IDE or PMA should clearly identify the specific volume and page number of the referenced information for ease of review.

We have not issued guidance on the content of Device Master Files. In general, we will not accept a submission as a MAF if it is not substantive in nature and does not contain information that may reasonably be regarded as trade secret or confidential commercial information.

6. Letters of Authorization (LOA)

An LOA authorizes FDA, in its review of an application such as an IDE or PMA, to refer to information contained in another regulatory submission such as an NDA, IND, ANDA, DMF, MAF, IDE, or PMA. As part of its review of an IDE or PMA for a DES, FDA will review information from a referenced file only when the IDE or PMA applicant submits an LOA from the holder of that file, authorizing FDA to refer to the file in support of the IDE or PMA application. The extent of access granted to the IDE or PMA applicant is typically a business arrangement between the respective parties. An LOA may give the applicant the authority to rely on all of the information in a regulatory file, or, if the right to reference is not totally inclusive, on only specific portions of the file. A copy of the LOA should be included as part of the original IDE and subsequent PMA applications, with the original LOA submitted to the DMF. (Please refer to Section V.A of the *Guideline for Drug Master Files* for specific information to be included within an LOA.)

An LOA may grant FDA either the *right to reference* or the *right to reference **and** discuss* the information included within one regulatory submission (e.g., NDA, IND, ANDA, DMF, MAF, IDE, PMA) in support of another regulatory submission (e.g., IDE, PMA).

With a *right to reference* authorization letter, FDA will not discuss the contents of the referenced submission with the third party applicant. In the event there are outstanding or unresolved issues related to FDA's review of the referenced submission, the Agency will inform the third party applicant of the general nature of the outstanding issues that must be adequately addressed by the

[9] See FDA guidance on *Drug Master Files* and the *Introduction to Master Files for Devices* for more information on the submission of DMFs and MAFs

referenced application holder, but will not identify the specific issues. Alternately, if the holder of the referenced submission chooses not to address outstanding issues, the third party applicant could potentially generate the requested data independently.

A *right to reference and discuss* authorization letter allows FDA to review the reference submission as part of the third party's application, and permits FDA to discuss information within the referenced submission with the third party applicant. In the event that there are outstanding issues arising from FDA's review of the referenced submission that directly apply to the third party's IDE or PMA, this permission to discuss permits the Agency to discuss these issues directly with the IDE or PMA applicant instead of requiring FDA to discuss specific issues solely with the holder of the referenced submission.

C. Least Burdensome Principles

The issues identified in this guidance document are issues we believe should be addressed before a coronary DES can be marketed. In developing this guidance, we carefully considered the relevant statutory criteria for Agency decision making. We believe that we have identified the least burdensome approach to resolving the issues presented in the guidance. If, however, you believe that there is a less burdensome way to address an issue, we recommend you follow the procedures outlined in the guidance for industry *A Suggested Approach to Resolving Least Burdensome Issues.*

III. PRODUCT DEVELOPMENT PATHWAYS FOR DRUG ELUTING STENTS

The development of a new DES calls for a thorough exploration of the safety of all of the relevant components of the product intended for clinical use (e.g., stent, polymer/carrier, and drug), the composite finished DES, and the delivery system. DES development can present numerous challenges in that the action of the finished product (such as drug release profile) will affect the evaluations to be conducted on the individual components, especially the drug substance. However, testing of the finished product should be limited to in vitro and animal testing until sufficient safety information is generated to support the introduction of the DES into humans under IDE.

An overview of a potential development pathway is described directly below. The following sections discuss the factors that can affect the development pathway for a DES as well as how the amount of new information to be generated will be affected by both the extent of prior information on each of the components and the need to understand local and potentially systemic effects of the drug. Sponsors and applicants should carefully consider all of the information in this section in determining the appropriate development pathway for a particular DES.

A. The DES Development Pathway — Overview

The developmental process typically begins with selection of the drug, polymer or other carrier (if applicable), and stent platform. The stent platform may be chosen for its previously demonstrated performance, or it may be a new design developed specifically for use as a DES. In selection of the polymer or other carrier, considerations will include the following:

- The ability to control drug elution
- The compatibility of the polymer with the arterial tissue
- The ability of the polymer to conform to the stent platform without significant delamination upon stent delivery and deployment

Whether previously studied or newly developed, the drug substance is intended to limit the growth of excess neointimal hyperplasia after the injury caused by the stenting procedure without preventing ultimate re-endothelialization of the stented artery. Selection of the drug dose, both total dose and dose density, is critical. The amount of drug to be delivered should be carefully evaluated to ensure that the lowest effective dose is chosen to minimize potential toxicities. Sponsors are encouraged to consider dose-ranging studies of the DES in animals and possibly in humans to aid in identification of an optimal dose.

1. Drug Substance

The drug substance should be carefully characterized through evaluation of its chemistry, mechanism of action, and safety profile. In vitro and animal testing will reveal the types of toxicities that may result from the drug and the exposure levels at which those toxicities occur. Animal toxicology testing should establish the No Observed Adverse Effect Level (NOAEL), the highest exposure at which no adverse effects occur.

Developmental animal studies of the DES are encouraged to provide an understanding of the local and systemic exposure to the drug substance. Even if the amount of drug available systemically is below the limit of detection of the assay used, the potential for toxicity may still exist. Therefore, animal toxicology studies of the drug substance may be important to fully understand the potential for adverse effects following stent implantation. If implantation of the DES results in significant systemic exposure, data from human safety studies, specifically, single and multiple IV dose escalation studies, should be provided (previously conducted or new). If implantation of the DES in animals does not result in significant systemic exposure, data from human safety studies should not generally be needed (see Section IV.B. on how to determine when systemic exposure is considered to be significant).

When needed, these single and multiple IV dose escalation studies, conducted in healthy volunteers, will provide critical safety information about the drug and its potential toxicities in humans. The NOAEL determined in the animal studies described above should be used to select the starting dose. These studies, in addition to metabolic studies, which are intended to describe the distribution, metabolism, and excretion characteristics of the drug, should be performed ***prior*** to initiation of human clinical studies of the DES under an IDE.

Information regarding the drug substance may be available to the IDE or PMA applicant through the right to reference a third party's IND or NDA. However, if the referenced submission does not relate to intravenous or intra-arterial administration of the drug, as would be delivered by a coronary DES, FDA may require that additional information related to intravascular safety be included in the IDE and PMA applications. In some situations, particularly when the right of reference is not available and a sponsor is relying on information in the public domain, additional studies (e.g., drug interaction) may help the sponsor adequately support the safety of the drug, polymer, or stent

component of a DES. FDA should be consulted on the need for additional studies in this situation (See also Section IV. below).

2. Finished DES

The finished DES and its delivery system should be fully characterized. Characterization will include engineering studies, biocompatibility evaluation, animal studies, and development of complete chemistry, manufacturing and controls (CMC) information, including sterilization, packaging, and shelf life/stability testing.

Evaluation of the finished DES in humans should include meaningful clinical information related to stenting outcomes, as well as a systemic pharmacokinetic (PK) study. If significant systemic drug exposure occurs as a result of DES implantation (see Section IV.B. below), a careful evaluation of factors that may affect exposure, such as concomitant drugs and comorbidities (such as renal or hepatic failure), should be carried out.

The clinical study program should include the pivotal trial(s) to support marketing approval, extended follow-up of the patients in the pivotal trials following the primary endpoint evaluation, and appropriate postapproval studies.

More specific recommendations regarding each of these development steps can be found in the following sections of this document.

B. Factors Influencing Development: Prior Information on Components

1. Stent Platform

Stent platforms used in a DES may be chosen based on previously used bare metal stents or may be developed expressly for use in the DES. If nonclinical testing has been performed on the platform as a bare metal stent, much of this information may be incorporated by reference. Certain additional testing on the finished DES, such as coating integrity and particulate matter evaluation, should also be carried out. Additionally, the sponsor/applicant should consider whether the coating process or other manufacturing steps will affect the stent integrity or corrosion resistance and repeat appropriate bench testing (see Section VI.B.) as necessary.

2. Delivery System

Delivery system testing should be carried out as described in section VI.B. below. Evaluation of aspects such as delivery and handling characteristics, when previously studied in conjunction with a bare metal or other previously approved stent, can be incorporated by reference; however, delivery system testing that incorporates the drug-eluting stent (e.g., deployment, balloon burst) should be conducted using the intended DES and delivery system combination.

3. Polymer/Carrier

As described in section V below, a full physicochemical description of any polymers used as drug carriers should be provided either in the original application or by reference to DMFs, MAFs, or other sources. Any change in the properties of the polymer due to the incorporation of the drug substance within the polymer or the application of the polymer to the stent should be evaluated.

4. Drug Substance

An understanding of the systemic pharmacology and toxicology of the drug substance[10] and its metabolism in the body is essential to guide the design of the clinical studies of the DES with respect to monitoring for adverse events. Given this aim, testing should be performed ***prior*** to initiation of an IDE for the DES.

The amount of ***new*** evidence needed to support the safety and effectiveness of a DES will be determined by the amount of existing information about each of the components and, particularly, the drug substance. For a DES using a *studied* drug, that is, a molecular entity that has been previously approved or studied under IND (i.e., has an approved NDA or ANDA, or has undergone human clinical studies under an active IND), the information on systemic use described below may be available for the DES manufacturer to incorporate by reference. An *unstudied* drug that is a molecular entity that has not been approved for use in humans or that does not have study information available should undergo testing as described in Section IV below to develop this information before human testing of the DES.

C. Factors Influencing Development: Local and Systemic Exposure

For any DES, the primary exposure to the drug substance will occur at the coronary artery wall directly apposed to the stent and *downstream* in the stented vessel and myocardium. Exposure in the rest of the body will be much lower. At first glance, this could suggest that evaluation of the systemic toxicity of the drug substance alone should not be necessary and that the animal and clinical testing of the finished DES should be sufficient to demonstrate preliminary safety of the DES. However, several factors challenge this conclusion.

First, although the total dose of drug on a DES is almost always much lower than that given in a systemic administration (e.g., orally or by injection), the exposure at the artery wall may be many times higher than the blood levels achieved after an oral or injected dose. Therefore, the potential toxicity at the coronary wall at the DES implantation site and within the coronary vascular bed and myocardium distal to the DES implantation site should be studied. Animal studies of the finished DES will be critical to this understanding, but as is typical of animal toxicology studies, it is also important to assess the potential toxicity of exposure to higher doses than in the finished DES. Animal studies of local doses well above those expected from a DES to examine the safety margin over the doses that will be used in human DES implants should be completed.

Second, it has been our experience that in certain situations (i.e., multiple stents, major active metabolites), systemic drug exposure from a stent, or stents, can cause systemic toxicities.

[10] For the purpose of this guidance, *drug substance* is considered the active pharmacological agent.

Therefore, it is crucial to have information gathered under acute and chronic conditions on the systemic safety and toxicity profiles of the drug to be used in a DES system ***prior*** to initiating clinical studies.

Furthermore, there is a greater need for information about the safety of the drug component prior to beginning clinical studies of a DES because of the permanence of the DES. In addition, the planned DES clinical trials may not explore the full range of clinical use likely to occur after marketing approval, and there is a need to consider whether this more extensive use of permanent implants may place patients at risk. As a result, an appropriate understanding should be gained of the safety of the drug component prior to clinical studies with a DES.

In summary, a manufacturer of a new DES should establish preliminary evidence of the safety of the DES prior to beginning human clinical trials (under an IDE, or under an IND if intravenous clinical study of the drug substance alone is needed). A complete assessment of safety and effectiveness of the DES should be submitted in the PMA application. Recommended testing to address issues related to systemic pharmacology, toxicology, and safety of the drug substance follows. FDA remains open to alternative methods to obtain this information as well to other considerations, such as when the drug incorporated in the DES has known toxicities that may require modifications to the recommendations below.

IV. SYSTEMIC PHARMACOLOGY, TOXICOLOGY, AND SAFETY DATA FOR THE DRUG SUBSTANCE ALONE

FDA believes that systemic pharmacology, toxicology, and safety data on a drug substance to be incorporated in a stent are needed to fully understand the safety profile of the finished DES. Nonclinical, and often clinical, studies should be performed as part of the effort to demonstrate the safety of a DES.

A. General Considerations

A first step in characterizing a drug involves performing systemic nonclinical pharmacology and toxicology studies of the drug substance using in vitro (cell culture) or in vivo (animal) models. These nonclinical studies help provide an understanding of the metabolism of the drug, its distribution and accumulation (e.g., in the regional myocardium or other important organs), and whether the effects of the drug might be significantly affected by the presence of certain enzymes. Animal testing will also help assess potential toxicities that cannot be identified during clinical trials and will define the No Observed Adverse Event Level (NOAEL), which is used to determine the starting dose for human safety studies (see Section IV.B.). In some cases, animal testing may establish that an adequate factor of safety exists between the levels of drug exposure likely to be reached in humans and the levels of exposure at which toxicities are seen in animal studies. In some situations, when a sufficient safety margin exists, this testing may support the conclusion that human intravenous safety studies would not be necessary to ensure safety of clinical systemic exposure. In addition to determining the severity of the observed toxicities in animals and a careful definition of the local, regional, and systemic adverse effects in animals, it is important to define the *slope* of the

relationship between toxicity and exposure over a broad range of doses, extending to levels in excess of the dose anticipated for use in humans.

- Determining when human safety studies are needed – PK parameters and the NOAEL

When deciding whether human intravenous safety studies also will be needed, one should first consider what pharmacokinetic parameter—Cmax (maximum concentration) or AUC (area under the curve describing concentration versus time) over some specific time—should be the basis of the safety factor. If the parameter that best predicts toxicity is AUC (which is most likely the case), it is important to base any comparisons on AUCs integrated over the same or nearly the same time courses.

A second important consideration is identifying the preclinical toxicity that establishes the NOAEL. Usually, this is based on testing in the *most sensitive species* and on the adverse effect seen at the lowest dose.

When considering the relevance of a preclinical model for intravenous administration, the exposure should, ideally, resemble the exposure from a DES. Release of drug from a DES can generally be expected to follow two-phase kinetics—a first-order (or relatively fast) process with a time constant on the order of hours and a zero-order (or very long time constant) process. the preclinical intravenous exposure intended to match this would include infusion over several hours (first-order phase) followed by a lower prolonged or repeated infusion (if the half-life in plasma is much less than the release rate from a DES).[11] We recognize, however, that mimicking the time course of release from the stent can greatly complicate the animal study. Furthermore, matching the DES release should not be necessary when toxicity is likely to be mostly related to Cmax and the AUC over the first several hours, and the safety margin related to this period is of greatest concern. In such cases, preclinical assessment following a single bolus administration should be acceptable.
In such cases, preclinical assessment following a single bolus administration should be acceptable.

Another consideration for the relevance of a preclinical model is the possibility of species-specific metabolism. If a metabolite is prominent in humans, but not in the animal, the resulting NOAEL may not be pertinent to human exposure. If a sufficiently sensitive assay is available, it may be appropriate to do a microdose study in humans[12] to confirm similar metabolism.

If the parameter that best predicts toxicity is AUC, it is important to base any comparisons on AUCs integrated over the same or nearly the same time courses. Empirically, we recommend a comparison based on $AUC_{0\text{-}24h}$.

- Determining when human safety studies are needed – calculating the safety factor

Because multiple stents are commonly used in humans, the exposure parameter (generally,

[11] The DES should initially be studied in an animal model to inform the design of the animal IV toxicology study.

[12] See the CDER guidance for industry *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drug*.

$AUC_{0\text{-}24h}$) measured from implantation of the DES in the animal model should be adjusted to reflect the use of 120 mm of stented length as a likely maximum length to be encountered in common clinical use. In a vast majority of cases, if the safety factor (ratio of the NOAEL $AUC_{0\text{-}24h}$ level in the animal to the corresponding exposure $AUC_{0\text{-}24h}$ in humans) is a factor of 100 or more, DES clinical studies can be initiated without a prior intravenous administration human safety study. This conclusion is based on the observation that >100 fold increase in sensitivity to toxic effects in humans versus animals is extremely unusual for drugs. See the following example.

The NOAEL for the most sensitive relevant toxicity (in the monkey) occurs at a dose that produces $AUC_{0\text{-}24h}$ = 4500 ng-h/mL. If a single 40 mm DES in the mini-pig produces $AUC_{0\text{-}24h}$ = 3 ng-h/mL; 120 mm of stent would be expected to yield an $AUC_{0\text{-}24h}$ of 9 ng-h/ml, still just 1/500 of the NOAEL. Absent other factors, it may be reasonable to conclude that no intravenous study in humans would be necessary before the first DES implantation in humans.

- Previously studied drugs

For a previously studied drug, much of the information discussed below may be available for incorporation in an IDE or PMA application through a right to reference or other means. However, in some cases, gaps in the preexisting safety data may be identified. For example, for a drug that has been developed for oral administration, additional nonclinical testing pertaining to the intravenous route (e.g., hypersensitivity, hemocompatibility) may not have been performed and should be conducted.

Where reference rights are unavailable, a sponsor may be able to use information in the public domain (e.g., published literature) in support of an application. When a DES relies for approval on data in a previously approved application for the drug substance to which the sponsor has an LOA, or on literature in the public domain, the sponsor or applicant should demonstrate that the active ingredient of the DES is the same as the active ingredient in the reference drug.

B. Nonclinical Pharmacology and Toxicology

For an unstudied drug that has never been studied in humans, preclinical safety testing and pharmacology studies should be conducted to fully characterize the drug-related effects, metabolites, and toxicities of the drug administered intravenously (IV). Studies should be designed to describe desired as well as off-target pharmacology and also potential drug toxicities; data from these studies should be used to select safe starting doses for clinical trials.[13]

The timing and types of studies that should be performed are described in International Conference on Harmonisation **(**ICH) M3, *Timing of Pre-clinical Studies in Relation to Clinical Trials*. Toxicology studies in two species, including one non-rodent species, should be designed to describe

[13] See also Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers at http://www.fda.gov/cder/guidance/5541fnl.htm.

a maximum tolerated dose (MTD) and determine the NOAEL. The duration of these studies should, at a minimum, span the length of time the DES is estimated to release drug in vivo. The minimum duration should be two weeks for a DES without a polymer or other drug carrier, which could be considered as a single IV dose drug study. The NOAEL from the IV studies should provide significant safety multiples over the clinical systemic exposure from multiple DES implants.

Other recommended toxicology studies are designed to assess potential toxicities that may not be monitorable in clinical studies. For example, tests for potential genetic toxicity (ICH S2A and S2B), tests for reproductive toxicity (ICH S5), and safety pharmacology studies (ICH S7A and S7B). Tests for the assessment of potential carcinogenicity are also described in the ICH guidances (S1A and S1B). However, if drug exposure to the local tissue is shown to last less than six months, carcinogenicity studies will generally not be required. Note that finished product biocompatibility testing does not obviate the need for safety and pharmacology testing of the drug substance alone.

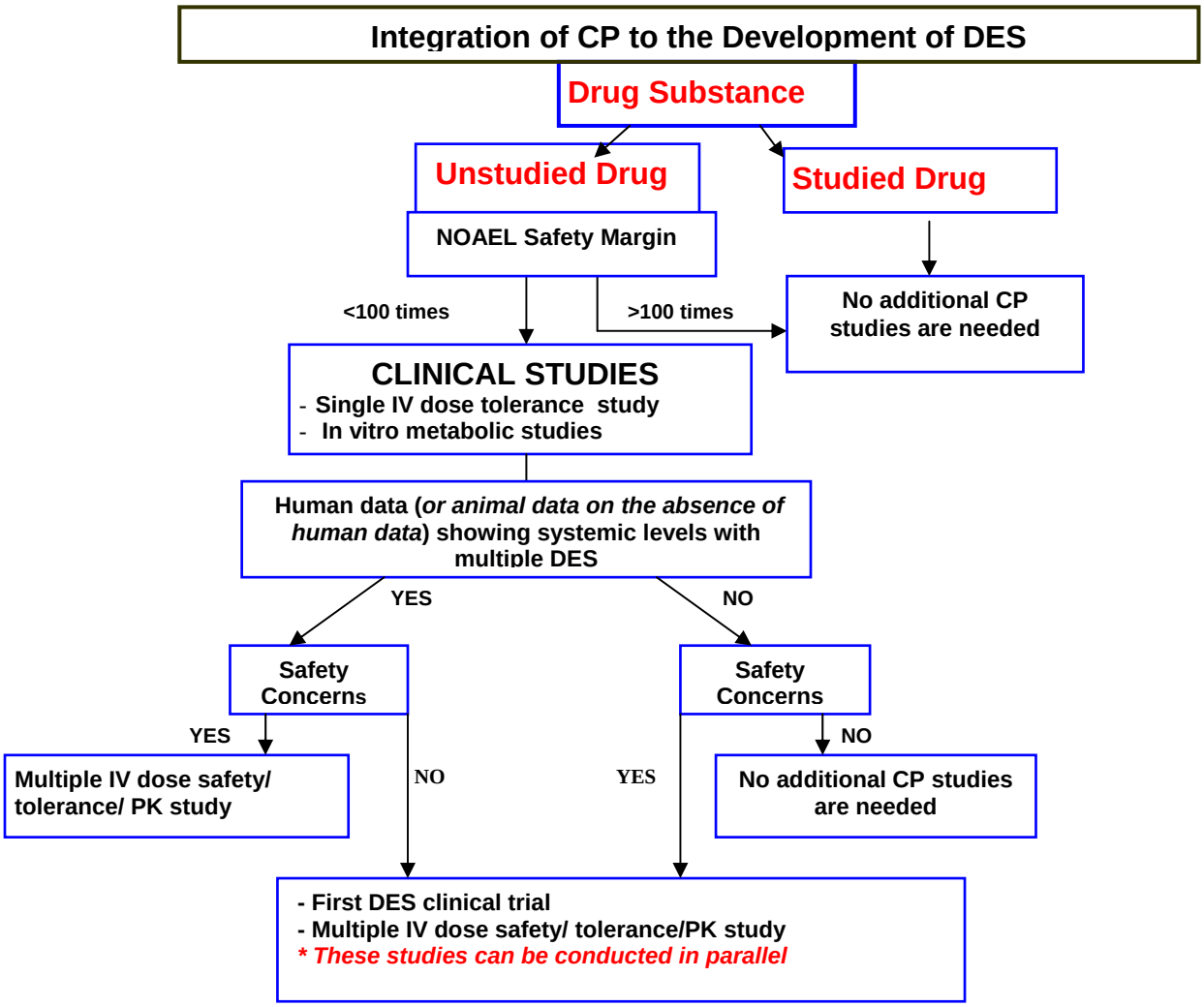
C. Clinical Pharmacology and Clinical Tolerance and Safety Information

The decision tree provided in this section describes the clinical pharmacology (CP) studies that should be considered for the assessment of the drug substance during the development of a DES. The key focus of the tree is the initial determination about whether the drug is an unstudied drug, about which little is known, or a previously studied drug, about which there already is a thorough understanding and adequate information with an appropriate safety profile is referenced in the application.

Human safety studies of the drug alone in healthy volunteers can provide critical information regarding the tolerability, safety, and pharmacokinetics of a drug substance. Whether such studies are needed will depend on the systemic exposure that will arise from the stent and how this compares with the exposure seen in animal studies, specifically the NOAEL, of the most sensitive species.

In general, for drugs that are well understood no additional clinical pharmacology studies are warranted since all the factors that affect a drug's safety and efficacy from a systemic point of view will already have been well characterized. If a drug has been previously studied and the resulting information is available, these studies need not be repeated. However, if the DES will incorporate a total amount of drug higher than that used in previous studies of the drug alone or result in higher sustained levels, additional information would be necessary to address the safety of the higher dose.

For an unstudied drug, the need for studies to elucidate the distribution, metabolism, and excretion of the drug, and any intrinsic or extrinsic factors that could affect exposure should be carefully assessed. Some of the metabolic information can be based on in vitro methods, notably the role of CYP450 enzymes in metabolism; some can be obtained from studies on the DES. As already mentioned, in some cases, human studies involving micro-doses may facilitate the assessment of the drug's pharmacokinetics.



Significant systemic exposure may not have been observed in animal studies of the DES, in part because the number of stents that can be implanted in an animal is limited. The potential for multiple stent use in routine clinical practice should be considered when determining whether a single IV dose escalation human study is needed to understand the systemic levels at which toxicities are first observed. Absent other factors that increase concern, a separation between the NOAEL established in the most sensitive animal species and the systemic exposure that could be reached of two orders of magnitude could mitigate the need for human studies of systemic drug safety.

If human PK data (using the DES) are available from previously conducted studies outside the United States, these data may provide a direct measure of systemic exposure (instead of the indirect measure based on animal data on the DES) and further determine whether such a substantial separation from toxicity causing concentrations exists. On the other hand, for DES where appreciable systemic drug concentrations can reasonably be expected and for drugs with animal or human toxicities that occur at only slightly above the anticipated human exposures, the full range of studies to evaluate the consequences of systemic exposure to the drug would be warranted. Animal

toxicology studies will then also serve to determine what is considered to constitute an initial safe dose for human systemic drug safety studies.

The usual next steps in developing a DES that incorporates an unstudied drug would involve single and multiple ascending dose studies. If the systemic exposure to the drug from a DES (or from multiple DESs) is sufficiently low (i.e., a reasonable safety factor exists between the NOAEL and the expected systemic exposure in man based on animal studies of the DES), such studies would probably not be informative.[14] However, it should be noted that an adequate assessment of systemic exposure from the DES in an animal model can only be made if the release characteristics of the drug are well-characterized and have been shown to have minimal variation from stent to stent.

For unstudied drugs, testing to elucidate the distribution, metabolism and excretion characteristics of the drug are essential in understanding the safety and efficacy profile of this new entity.

1. Single IV Dose-Escalation Study

If a single IV dose-escalation study is indicated, the selected initial dose should be based on the NOAEL information from the animal nonclinical studies. The drug should be given via intravenous administration (if feasible). This study should be designed to collect information on the drug substance's tolerance, safety, and pharmacokinetics following administration of single doses and escalating up to the maximum tolerated dose. The exposure should be engineered to resemble that produced by the DES.

2. Multiple IV Dose-Escalation Study

If the time course for release from a DES is long, data from a multiple IV dose- or from a continuous infusion dose-escalation study to mimic the stent exposure should be provided.

3. Mass Balance Study

We suggest that a mass-balance study be performed to define and assess the systemic exposure, the disposition and pathways of elimination (including metabolism and excretion), and pharmacokinetic measures or parameters of the drug substance administered intravenously.

The mass balance study should be based on the drug substance tagged with a radioactive label (i.e., ^{14}C, ^{3}H) to allow for sensitive monitoring of the distribution patterns of the tested drug after its intravenous administration. Blood (plasma or serum as appropriate), urine, and fecal samples should be collected and assayed for radioactive label. Other routes of elimination should be monitored as appropriate. Both the parent drug substance and any metabolites present should be identified.

4. In Vitro and In Vivo Metabolic Studies

[14] We note that single and multiple ascending dose studies are small and quite well monitored, and the insight into human toxicity can be quite valuable.

Since an integral part in understanding the safety of an unstudied drug is determining its metabolic pathway and whether there is formation of any active/toxic metabolites, the Agency recommends that a drug's metabolism and metabolic pathway, as well as the activity of major metabolites, be assessed relatively early in development of the DES.

In vitro metabolic studies designed to assess the P450 metabolizing enzymes of the drug as well as to characterize the P450 isoenzymes that are inhibited or induced by the drug should be conducted so that the clinical implications of interactions can be assessed later in the DES clinical studies.

In vitro metabolic studies can frequently serve as an adequate screening mechanism to assess the contribution of cytochrome P450 on the metabolism of the drug, so that subsequent in vivo testing will be unnecessary. In contrast, when positive findings of active or toxic metabolites arise in in vitro metabolic studies, we recommend that drug interaction information be obtained from the clinical trials using a drug interaction-population PK approach.

Information on the design and data analysis of the metabolic studies can be found in guidances *In Vivo Drug Metabolism/Drug Interaction Studies* and *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro.*

5. Bioanalytical Methods

Validated bioanalytical methods should be used when evaluating the concentrations of the drug and its metabolites in the clinical pharmacology and metabolic studies. Information on the validation of assays can be found in the guidance *Bioanalytical Method Validation.*

V. CMC INFORMATION

This section provides guidance on the information to be submitted regarding the chemistry, manufacturing, and controls (CMC) aspects of (1) the drug substance and (2) the finished product, followed by the information needed for (3) the engineering evaluation. The information can be provided in the submission, or incorporated by reference to another regulatory submission (e.g., DMF, NDA, ANDA, PMA, MAF) with copies of the LOA provided in the relevant section of the IDE or PMA application. All of the topics described for the drug substance and finished product should be included for both IDE and PMA submissions.

Because the product described in an initial IDE application will be permanently implanted into patients with potentially life-threatening coronary artery disease, the CMC section should address all of the items that would be provided in a PMA application. However, the level of detail and the degree of documentation will differ in that the information for the IDE will focus more on patient safety and product development and less on product and process controls.

In general, the information for the drug substance component is expected to be similar for both IDE and PMA submissions. However, it is recognized that the finished product is still under development at the time of the initial IDE submission. Consequently, clinical trials may be allowed to proceed even though manufacturing processes are not fully optimized, analytical methods

validation is incomplete, and the acceptance criteria for the finished product tests are still tentative, provided all parameters that relate to safety are well characterized. The sponsor/applicant is strongly encouraged to meet with the Agency before the initial IDE submission, during development and before submitting a PMA application to discuss critical drug-related issues and the information needed at various stages of development.

A. CMC for the Drug Substance Component[15]

The following items should be included for the drug substance in both the IDE and PMA submissions. When submitting an IND (e.g., when the drug substance is an unstudied drug and human safety studies will be conducted in the United States), guidance on Phase 1 (CMC section) should be carefully consulted.[16]

1. Physical and Chemical Characterization

The chemical structure of the drug substance (including stereochemistry), molecular formula, and molecular weight should be provided. All appropriate names or designations for the drug substance should be listed (e.g., USAN, Chemical Abstracts, IUPAC, code number). The physicochemical properties of the drug substance should be described and should include, but not be limited to, information on the following, as appropriate:

- General description (e.g., appearance, color, physical state)
- Melting or boiling points
- Optical rotation
- Solubility profile (aqueous and nonaqueous, as applicable)
- Solution pH
- Partition coefficients
- Dissociation constants
- Identification of the physical form (e.g., solid-state form, solvates, and hydrates) that will be used in the manufacture of the finished product

2. Elucidation of Structure

The chemical structure of the drug substance should be confirmed using physical and chemical techniques, such as elemental analysis, mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, ultraviolet (UV) spectroscopy, infrared (IR) spectroscopy, X-ray crystallography, and other tests (e.g., functional group analysis, derivatization, complex formation).

3. Manufacturer

[15] See the CDER guidance *Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*. Another drug substance guidance is forthcoming that, once finalized, will supersede this guidance.

[16] See the CDER guidance *Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drug*.

The name, address, and manufacturing responsibility should be provided for each facility (including contract manufacturers and testing laboratories) that will be involved in the manufacturing or testing of the drug substance. The addresses should be those of the locations where the relevant manufacturing or testing operation will be performed. Registration numbers (i.e., CFN, FEI numbers) should be provided to facilitate CGMP inspections.

4. Manufacture and Control

The description of the manufacturing process should include a flow diagram and a narrative of the processes and process controls that will be used to manufacture the drug substance. The flow diagram should include each manufacturing step with chemical structure, solvents, reagents, auxiliary materials, critical operating parameters, and expected yield. A narrative description of the sequence of manufacturing steps and the scale of production should be provided in more detail than that given in the flow diagram.

Process controls used to monitor and adjust the manufacturing process should be provided and include in-process tests and acceptance criteria. These controls should ensure that intermediates and drug substance will conform to their established specifications.

Specifications, certificates of analysis, and quality or grade of the starting materials, reagents, solvents, and auxiliary materials that will be used to manufacture the drug substance (including deriving it from a biological source) should be provided. When appropriate, specific tests and acceptance criteria to control microbial contamination in materials derived from biological sources should be included in the specifications.

5. Specifications

Specifications are established to control the quality of the drug substance and should focus on those characteristics necessary to ensure the safety and efficacy of the finished product**.** The specifications should include all tests, analytical procedures, and associated acceptance criteria to which each batch of a drug substance will conform over its retest period/shelf-life.[17] Acceptance criteria are numerical limits, ranges, or other measures for the tests described. We recommend that the information be presented in tabular form.

Analytical procedures, including validation information, for each of the tests proposed in the specification should be described in detail. If the analytical procedure is in the current version of the United States Pharmacopeia (USP) or other FDA-recognized standard reference (e.g., AOAC International Book of Methods), details need not be provided. Analytical procedures should be validated to demonstrate that the methods are suitable for their intended use. Validation should include experimental data (e.g., representative chromatograms with peak identification).[18]

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[17] See ICH Guidance *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and Drug Products: Chemical Substances*.

[18] See ICH Guidances *Q2A Text on Validation of Analytical Procedures* and *Q2B Validation of Analytical Procedures: Methodology*.

Acceptance criteria should be primarily based on consideration of safety, efficacy, manufacturability, and stability. The justification for the acceptance criteria can be demonstrated by batch analysis data for all relevant batches, e.g., nonclinical, clinical, and primary stability batches. The batch analysis reports should include:

- Batch identity (i.e., batch number) and size
- Date of manufacture
- Site of manufacture
- Manufacturing process (e.g., synthetic route A)
- Intended use (e.g., clinical, nonclinical, stability)
- Results for each parameter tested; tabular format is recommended

6. Reference Standards

Information on the reference standards or reference materials used for testing the drug substance should be provided. A reference standard obtained from an official source should be identified. A reference standard not from an official source should be appropriately characterized. A list of any available reference standards for impurities should be included.

7. Container/Closure System

A description of the container closure system for the drug substance should be provided, including the identity of materials of construction for each primary packaging component and specifications.

8. Stability

Stability data should be generated in accordance with ICH guidances.[19] The studies conducted, protocols used, and the results of the studies should be summarized. The discussion should include (1) a summary of stability batches tested, storage conditions used, attributes tested, acceptance criteria, test schedule, and analysis of all available data (including a summary of the statistical analysis if performed) and (2) conclusions regarding the storage conditions and retest or expiration dating period, as appropriate. Data regarding stability under stressed (e.g., pH extremes, oxidation, heat, light) conditions should also be provided. We recommend that the results of stability studies be presented in tabular form.

B. CMC for the Finished Product

For the purpose of this section, the phrase *finished product* refers to a packaged and sterilized DES that contains all the materials (e.g., drug and polymer coating materials) applied to or incorporated within a bare metallic stent substrate and the stent delivery system. The following sections discuss the information on the finished product that should be submitted in support of an IDE or PMA

[19] See ICH guidance *Q1A(R2) Stability Testing of New Drug Substances and Products.*

application.[20] Section V.B. provides recommendations on the chemistry, manufacturing, and controls information on the finished product from a drug perspective. Section VI.B. (Engineering Evaluation) provides recommendations regarding assessment of coating integrity and Section VII.A. (Manufacturing -- Quality System (QS) Regulation and Current Good Manufacturing Practice (CGMP) Regulations) provides recommendations for additional manufacturing and quality control information needed for the finished product from a QS regulation/CGMP regulation perspective. You may wish to provide all of this information relating to the drug and device constituent parts of the combination product in one section of the PMA or separately with cross-reference to the other sections as appropriate.

1. Description of the DES

A detailed description of the finished DES should be provided and should include the proprietary name, model numbers, stent sizes, product code, and intended use. Detailed engineering drawings should also be provided. In addition to a detailed written description, a cross-sectional schematic of the stent platform, coating layers (e.g., primer layer, polymer/drug layer, drug-free polymer topcoat) and stent delivery system should also be included that pictorially depicts the coating and drug distribution across the stent geometry (e.g., length, circumference, strut sides, adluminal, abluminal). The schematic should also include a description of the drug release mechanism. The total drug content (µg/stent) and drug dose density (µg/mm^2) should also be provided for each stent size.

2. Product Development

This section should contain information on the development studies conducted to establish that the components of the finished DES, the formulation, manufacturing process and controls, and packaging system are appropriate for the purpose specified in the application. The studies included in this section can be distinguished from controls used for routine batch release. Additionally, this section should identify and describe the formulation and process attributes, including critical parameters that can influence batch reproducibility, product performance, and quality. Development reports allow the Agency to understand critical variables and focus attention on high-risk aspects of a product and process.

a. Components of the Finished DES Product

- Drug Substance

Key physicochemical characteristics (e.g., solubility, hydrophobicity, stability) of the drug substance should be discussed and those characteristics that can influence the performance and manufacturability of the finished product should be assessed. The compatibility of the drug substance with the excipients in the finished product should also be addressed, and if there is any evidence of physical or chemical incompatibility, justification for using the component should be provided.

[20] See the CDER guidance for industry *Submitting Documentation for the Manufacturing of and Controls for Drug Products* (1987). Another drug product guidance is forthcoming that will supersede the 1987 guidance.

- Excipients

The choice of excipients (e.g. polymer carriers), their concentrations, and the characteristics that can influence the finished product performance or manufacturability should be discussed. The applicant should demonstrate an understanding of the effects of excipient variability on the critical quality attributes of the finished product. Since organic solvents are usually employed to dissolve both the drug substance and polymer carrier to form a coating solution, the rationale for choice of solvent should be provided. The ability of functional excipients (e.g. antioxidants) to perform throughout the intended shelf life of the DES should also be discussed.

- Stent Substrate and Delivery System

The design of and the rationale for the selection of the key elements of the stent substrate[21] (e.g., materials, surface characteristics and area, cell structure, engineering performance), which can influence the performance and manufacturability of the finished DES, should be discussed. The applicant should also describe the components and design elements of the stent delivery systems used for stent deployment in the coronary vasculature.

b. Formulation Development

Since a DES is formulated to provide *extended release* of the drug substance, a description of the drug release mechanism (e.g. erodible polymer matrix, diffusion) should be provided. The development of target release rates of the drug from the polymer matrix should be discussed. The applicant should provide a scientific rationale for the selection of the final formulation by evaluating appropriate models for drug release. The applicant should show how the formulation and product construction were chosen, incorporating the principles of modern pharmaceutical development practices, Quality System regulations, and/or Design Control requirements as appropriate.[22,23,24]

c. Manufacturing Process Development

The selection of the manufacturing process with emphasis on understanding its critical aspects should be described. Manufacturing process development generally starts with the identification of critical quality attributes of the finished product, which are necessary for its desired performance. Manufacturing process options in conjunction with appropriate control

[21] See Guidance for Industry and FDA staff on *Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.*

[22] See also the CDER guidance for industry *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*.

[23] See ICH Guidance *Q8 Pharmaceutical Development.*

[24] See 21 CFR 820.30 for more detailed Design Control requirements.

strategies that can reliably result in finished product with critical quality attributes within acceptable ranges should be considered. Critical process parameters that should be controlled or monitored to ensure batch-to-batch reproducibility and to minimize intra-batch variability should also be discussed. This approach demonstrates knowledge and understanding of the product and associated processes, which in turn provides greater assurance of product quality. The benefits of having an efficient and reliable process, with reduced reliance on end-product testing, include enhanced manufacturing efficiency and a reduced risk of producing a poor quality product. These concepts, when implemented, would be a significant advantage to stent manufacturers who typically produce small batch sizes. Operations using process analytical technologies (PAT)[25] that measure an endpoint indicating the manufacturing process (e.g., coating) is under control are preferable to a measurement of a quality attribute on representative samples. Generally, this allows for adjustments to process parameters to mitigate anticipated variation in raw materials, equipment, environment, or other conditions.

d. Packaging System Development

The applicant should describe how the packaging system was selected and designed to provide protection and maintain sterility throughout the shelf life of the finished product. The suitability of the packaging system should be demonstrated with respect to protection from moisture, oxidation, and light, and compatibility of materials with all components of the finished product.

3. Physical and Chemical Characterization

The morphology of the solid drug-polymer carrier system in the finished product should be described (i.e., dispersed drug phase, continuous separate drug phase, reservoirs). Micrographs of the surface and full thickness cross-section of the coating should be provided. The micrographs will aid in gaining an understanding of the drug release process, which may have implications for coating durability and particulate matter formation.

A detailed description of the physical and chemical tests performed to characterize the finished product should be provided. The physical, chemical, and mechanical characteristics of a DES are critical to ensure finished product quality and performance. Physical and chemical characterization of a DES should include tests for surface coat composition, coating/carrier thickness and uniformity, and coating/carrier erodability as applicable. These tests are useful for characterization and may be provided as one-time tests—not to be confused with routine control and release testing.

Note: These tests are a subset of testing recommendations provided in Section VI.C of this guidance for the mechanical/engineering performance tests for the finished DES.

4. Components and Composition

[25] See 21 CFR 820.30 for more detailed Design Control requirements.

A qualitative and quantitative list of drug substance(s) and excipients making up the finished product should be provided. We recommend including a detailed components and composition table per unit and per batch for each stent configuration to be marketed. Ingredients used in the manufacture of the finished product, regardless of whether or not they appear in the finished product, such as solvents, should be identified. Ingredients of human or animal origin should also be identified and their use supported with appropriate safety information.

a. Component Function

The function (i.e., role) of each ingredient in the formulation should be described. Ingredients that are used in the manufacture but are not intended to be part of the finished product (e.g. solvents) should be identified as processing agents.

b. Component Controls

The applicant should identify all component tests that the finished product manufacturer will routinely perform as well as test results that will be accepted from the excipient and drug substance manufacturer (Certificate of Analysis, COA). At a minimum, the finished product manufacturer must perform an appropriate component identification test (21 CFR 211.84(d)(2)).

(i) Drug Substance

See Section V.A.

(ii) Excipients

Compendial excipients should comply at a minimum with the monograph standard in the official compendium and be identified as such. The monograph tests may not be sufficient or appropriate for use in a DES and additional testing may be needed, especially for the polymer/carrier (see below). When analytical procedures from an official compendium or other FDA recognized standard references (e.g., AOAC International Book of Methods, analytical procedures from EP or JP that are interchangeable with a USP *General Chapter*) are used, they should be verified as suitable under actual conditions of use. The following information should be provided for each compendial excipient:

- Name and address of the supplier
- COA from the supplier
- Results from any additional testing

For each noncompendial excipient, detailed information should be provided in the submission or in an MAF/DMF and should include the following:

- Name and address of the supplier

- Method of manufacture (e.g. flow chart, all components used in the manufacturing)
- Specifications and validation of analytical procedures
- COA from the supplier
- Additional information as appropriate (e.g. safety data for novel excipients)

Since most DESs use a polymer matrix as a carrier or barrier for the drug release, special attention should be paid to this component. In addition to the items listed above, the following information should also be included for the polymer:

- Description and function of polymer (including a rationale for each component, if a co-polymer)
- Polymer characterization and properties
- Chemical structure (monomer fractions, if co-polymer)
- Identity test (matches infrared or NMR reference spectrum) and any other acceptance tests with associated analytical methods
- Average MW, MW range, and MW distribution (including MW methodology validation)
- Glass transition temperature (Tg) (and melting temperature, Tm, if applicable)
- Density
- Residual levels of catalysts, solvents, impurities, and monomers
- Composition by weight percentage (if polymer carrier is a blend)
- Sampling and storage conditions
- Stability (e.g., measurement of polymer molecular weight, resistance to oxidation, light, heat, ionizing radiation)

Many of these items should be tested on a routine basis as part of the polymer specifications and adequate justification should be provided for any exclusions.

It is important to note that although an MAF/DMF may be referenced for the polymer, the MAF/DMF might not contain sufficient and/or appropriate information to support omission of testing on the finished product. For example, the MAF/DMF may only provide certificate of analysis (COA) information about the chemical properties of the unprocessed polymer, but additional data on the polymer following the intended processing/manufacturing (including sterilization) should be provided.

(iii) Stent Substrate and Delivery System

The following detailed information for each component used in the fabrication of the stent substrate and its delivery catheter system should be provided:

- Name and address of the supplier
- Method of manufacture (e.g., laser cutting for stent)
- Specifications and validation of analytical procedures
- COA from the supplier or incoming receiving specifications if no COA provided

5. Manufacturer

The name, address, and manufacturing responsibility should be provided for each facility (including contract manufacturers and testing laboratories) that will be involved in the manufacturing or testing of the finished product.[26] Addresses should be provided for the locations where the relevant manufacturing or testing operation will be performed. Registration numbers (i.e., CFN, FEI numbers) should be provided to facilitate GMP inspections. This information may be submitted in the Manufacturing -- Quality System (QS) Regulation and Current Good Manufacturing Practice (CGMP) Regulations section (see Section VII.A. below) and incorporated by reference or reproduced here for ease of review.

6. Manufacturing Process and Controls

A complete description of the manufacturing process and controls (or a reference to this information) should be provided within this section of an application to provide a thorough understanding of the critical attributes that should be assessed at final product release and to assess the potential impact of changes made in the manufacturing procedures used during the course of product development. A discussion of any differences between the manufacturing process to be used for the marketed product and any used to produce batches for clinical efficacy and/or primary stability studies should be addressed in the PMA application. This should include an evaluation of how the differences will not adversely affect the performance of the product. (See also Section VII.A below.)

a. Flow Diagram

A flow diagram (or series of flow diagrams) should be provided that includes all the steps in the manufacturing process for the finished DES. The diagram should include the following:

- Steps where materials enter the process (e.g., catheters, stents, polymers)
- Critical processing steps that may have an influence on the chemical or physical properties of the stent, polymer, or drug (e.g., application of coating, including any primers or coupling agents, use of oxygen scavengers or antioxidants, crimping of stent onto catheter, heat sets, use of sheath protectors)
- In-process testing (identify method) and the manufacturing step where it is performed
- Sterilization (identify method) and packaging steps
- Any end-process (reliability) testing conducted prior to product release
- Differentiation of manual versus automated processes
- Depiction of differences in manufacturing processes for the catheters (e.g., Over-The-Wire versus Rapid eXchange)

[26] A statement should be provided that ruminant-derived materials from bovine spongiform encephalopathy (BSE) countries as defined by the U.S. Department of Agriculture (9 CFR 94.11) are not used or manipulated in the same facility.

We recommend that the diagram be color-coded (and/or shape-coded) to differentiate materials, processes, and inspection steps.

b. Description of the Manufacturing Process

A description should be provided of the ***entire*** manufacturing process, including packaging, which should illustrate the sequence of steps undertaken and the scale of production. The description should include equipment identified by type (e.g., coating process chambers) and capacity. Any novel processes or technologies (e.g., coating methodology) should be described in detail.

c. Process Controls

Controls used to monitor the manufacturing process should be described, including operating parameters, environmental controls, and process/in-process tests. A description of critical process controls (as justified in section V.B.2.c. *Manufacturing Process Development*) should include tests, analytical procedures, limits (ranges), or other acceptance criteria.

In some cases, results from in-process controls can be used in lieu of finished product testing. This approach, however, should be supported with data that demonstrate a clear relationship between in-process testing and the critical quality attributes of the finished product.

d. Sterilization Process

The sponsor should clearly identify the method of sterilization (e.g., ethylene oxide, E-beam radiation, gamma) along with the specific parameters (e.g., concentrations, humidity, time, and temperatures) and an assessment of its effect on the finished product. The assessment should address the effects on such elements as coating integrity, drug substance, and polymer carrier stability.

See Section VI.C for engineering test methods to evaluate the effect of sterilization on the coating characteristics.

7. Packaging System

A description and the following information on each component of the primary packaging system for the finished product should be provided:

- Supplier/manufacturer
- Composition
- Quality/grade of materials
- Schematic drawing including dimensions, tolerances, etc.
- Specifications

The same type of information should be provided for functional secondary packaging components as well. For nonfunctional secondary packaging components (e.g., those that do not provide additional protection), only a brief description is necessary.

8. Finished Product Specifications

Regulatory specifications should be provided for the finished product; these specifications apply to every batch at release and throughout shelf-life. A specification consists of a list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the tests described. An example of a regulatory specification table is provided in Appendix A. Finished product specifications should focus on those characteristics found to be useful in ensuring product quality as it relates to safety and efficacy. Testing should be performed on every batch of the finished product after packaging and sterilization. All testing should be performed on expanded stents, unless otherwise justified. To ensure that the regulatory specifications are met throughout the shelf life, tighter acceptance criteria may be established for product release.

When product knowledge and process understanding have been demonstrated in the application, and relevant in-process control strategies are being implemented routinely, it may be possible to use in-process tests in lieu of traditional off-line end-product testing. In addition, PAT, if applied, can serve as a basis for real-time release of the finished product to demonstrate that each batch conforms to established regulatory attributes. It should be emphasized that any alternate proposals to end-product testing should be discussed with the Agency during development and regulatory approval obtained before implementation.

The analytical procedures and their validation[27] should be described in detail for each test listed in the specifications. Acceptance criteria should be primarily based on consideration of safety, efficacy, manufacturability, and stability. The justification for the acceptance criteria can be based upon batch analysis data for all relevant batches (e.g., nonclinical, clinical, and primary stability batches). Ideally, the data should be representative of batches of finished product manufactured using different lots of drug substance, polymer, and coating solution. The sampling plan should be described. The batch analysis reports should include:

- Batch identity (i.e., batch number) and size
- Date of manufacture
- Site of manufacture
- Manufacturing process
- Intended use (e.g., clinical, stability)
- Results for each parameter tested, in tabular format

A *batch* is defined as a quantity of DES produced according to a single manufacturing order during the same cycle of manufacture. A batch should be made with only one lot of coating solution. Combining stents having different expanded diameters into one batch would only be appropriate

[27] See ICH guidances *Q2A Text on Validation of Analytical Procedures* and *Q2B Validation of Analytical Procedures: Methodology*.

when the stents originated from the same diameter tubing, have the same design/platform, and only differ in the balloon diameter to be used. Combining stents of different lengths into one batch is discouraged.

Because DES batch sizes are typically small and end-product testing consumes a large quantity of test samples, the applicant may consider any of the following alternative approaches:

- Using in-process testing as a substitute for some release tests (e.g. residual solvents). In these cases, the tests should still be listed in the finished product specifications with appropriate notation.
- Using the same test samples for several release tests (e.g. identification, assay, and content uniformity).
- Using a smaller number of samples than recommended by USP for certain tests (e.g. content uniformity) with tighter acceptance criteria.
- Using *quality by design* principles, which rely less on end-product testing and more on building quality into the product and process design.

General tests that are expected to be included in the specifications for a finished DES are listed below. A tabular format similar to the example shown in the Appendix A is recommended for presentation of the specifications.

a. Appearance

A qualitative description of the finished DES should be provided. Any visualization or imaging methods adequate to ensure that the DES meets its specifications should be included.

b. Identification

Identification testing to establish the identity of the drug substance in the finished product should be specific (e.g., infrared spectroscopy or a chromatographic method in combination with an additional test such as UV diode array or MS) and able to discriminate between compounds of closely related structure that are likely to be present. Identification solely by a single chromatographic retention time, for example, is not regarded as being specific. However, the use of two chromatographic procedures, where the separation is based on different principles, or a combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS, is generally appropriate.

c. Assay

A specific, stability-indicating assay to determine content should be included for all drug substances in the finished product. In many cases, it is possible to employ the same procedure (e.g., HPLC) for assay of the drug substance and quantitation of impurities.

When use of a nonspecific assay can be justified, other supporting analytical procedures should be used to achieve overall specificity. When the assay is not stability indicating, a separate impurity assay can be employed. A specific procedure should be used when there is evidence of inactive ingredient interference with the nonspecific assay.

d. Impurities and Degradation Products

Any impurities, degradation products, and/or residual solvents are included in this category. We recommend sponsors refer to the ICH Q3B guidance covering finished product impurities. Appropriate stability-indicating analytical methodology should be used to monitor degradation products and acceptance limits should be defined for individual specified degradation products, both identified and unidentified, unspecified degradation products, as well as total degradation products.

e. Content Uniformity

This test assesses drug content variation from stent to stent within a batch and is to be distinguished from uniformity along an individual stent length. The latter is typically a one-time test to establish coating uniformity. The method and limits established in USP <905> Uniformity of Dosage Units are considered appropriate for determining content uniformity within DES batches.

f. Drug Release

The specification should include a test for in vitro drug release. The test should be performed over a sufficient period of time and include a sufficient number of time points to correlate to in vivo release. The test is generally used as a quality control tool and should be discriminatory. The results should ideally be reported as percent of label claim released per unit time. See section VI. E. for additional details regarding in vitro elution testing.

g. Package Integrity and Sterility

A test procedure and acceptance criterion for evaluation of sterility testing and package integrity should be included. When test methods differ significantly from compendial test methods, a demonstration of the equivalency to the compendial method should be provided. Parametric release can be proposed when appropriate data are generated during development and validation.

The tests and methods demonstrating the integrity of the microbiological barrier of the packaging system should be well defined and scientifically justified. Sufficiently sensitive packaging integrity testing may reduce the need for end product sterility testing.

h. Endotoxins

A test procedure and acceptance criteria for endotoxins, using a procedure such as the Limulus Amoebocyte Lysate (LAL) test, should be included in the specification.

Note: All blood-contacting cardiovascular devices and combination products should be non-pyrogenic regardless of whether any claims regarding their *non-pyrogenic* status are made in the labeling. Pyrogenicity testing is used to help define limits to protect patients from the risk of febrile reaction. Pyrogenic responses to gram-negative bacterial endotoxins can be tested using standard methods such as the USP Bacterial Endotoxins Test (<85>) using LAL. Pyrogenic responses to leachables over the implant life can be tested using a material-mediated pyrogenicity test. See the companion document (Section titled "General Biocompatibility Considerations") for additional specifics on materials-mediated pyrogenicity testing.

i. Particulate Matter—Batch Release

This test evaluates the presence of sub-visible particulate matter. Particulate matter may include particles shed from the formulation components as well as extraneous particles from the stent platform, stent delivery system, packaging, and environmental factors. Appropriate testing and acceptance criteria should be established for particulate matter. See section VI.B for analytical procedures for characterizing particulate matter.

j. Additional Testing

Additional testing of the finished DES may be necessary to address unique characteristics of an individual DES. Examples include tests for polymer molecular weight, residual monomers, catalysts, or other additives.

9. Stability

Stability testing is performed to support the establishment of a shelf life or expiration dating period for a DES (See also Section VII.C below). Stability studies should also be conducted during investigational phases to support product stability for the duration of clinical trials.

A stability protocol should be provided that includes storage conditions, time points, test parameters, analytical methods, and acceptance criteria. The formal stability protocol can include an appropriate matrixing and bracketing design. At a minimum, the protocol design should include the extremes (in terms of both stent dimensions and total drug load) as well as an intermediate size to provide assurance of consistent behavior across the entire proposed matrix of DES sizes to be commercialized.[28] If there are design differences (e.g., multiple stent platforms) within the proposed DES matrix, the sponsor should bracket each design or provide a scientific rationale to support the applicability of the sizes that are tested for the entire product matrix. We recommend that stability testing include samples from a minimum of three finished product batches for each size tested.

[28] See ICH guidance *Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products.*

Stability testing should be conducted under ICH recommended conditions at room temperature (25°C/60% RH or 30°C/65% RH) and accelerated conditions (40°C/75% RH).[29] If long-term testing is conducted at 25°C/60% RH and a significant change as described in ICH Q1A(R2) is observed in the results obtained for a DES tested under accelerated conditions, additional testing using intermediate conditions (30°C/65% RH) should be conducted and evaluated against significant change criteria.

For each set of stability data provided, the sponsor should identify the packaging system, the batch number and scale, manufacturing date and site, the manufacturing process and formulation. For ease of review, the Agency recommends that all stability information be provided in tabular format. See Appendix A for an example of a stability table.

In general, the following tests should be performed at each of the preselected stability time points on a minimum of three finished product batches to generate the primary stability data used to support an expiration date:

- Appearance
- Assay/drug content
- Impurities/degradation products
- In vitro drug release
- Particulate matter[30]

In addition, some tests, such as sterility, and package integrity, should be performed at release, annually, and at expiry.

If different finished product manufacturing sites will be used, appropriate release/stability data to ensure the consistency and equivalency of the finished product should be generated. Generally real-time, room temperature data should be used to establish a DES shelf life. However, based on the quality of the data (e.g., accelerated, long-term testing) provided by the applicant, a reasonable extrapolation of data may be considered to assign the shelf life. It is recommended that simulated transportation/shipping studies also be conducted as a one-time test to support excursions that may occur during distribution of a DES.

10. Labeling

Detailed guidance on labeling and examples of text that can be used are included in the stand-alone companion document. CMC information should appear in the **Description** sections of the label.

11. Environmental Assessment

An Environmental Assessment or request for a waiver (with justification) should be submitted (21 CFR 814.20(b)(11)).

[29] See ICH guidance *Q1A(R2) Stability Testing of New Drug Substances and Products*.

[30] See section VI. B for test method considerations for particulate matter testing as part of the stability protocol.

VI. NONCLINICAL STUDIES OF THE FINISHED DES

A. Summary Tables

FDA recommends that a master table be compiled to summarize all mechanical performance, animal, and clinical testing that has been conducted in support of the DES to either be tested clinically (under the IDE) or commercialized (for the PMA application) in the United States. An example of the parameters to be captured in tabular format as part of the master table has been included in the Companion Document to this guidance. The master table should be provided and updated, as necessary, for both IDE and PMA applications. To enable the integration of the master table into the regulatory submission, the sponsor/applicant may decide to divide the table into more discrete units (e.g., separate tables for engineering, PK, pharmacology/toxicity studies for the drug substance, and animal studies in support of the DES). This table, or set of tables, will greatly aid in the sponsor's and the Agency's assessment of whether sufficient supportive acute and chronic safety and/or effectiveness data have been provided for the proposed DES as part of both the IDE and PMA reviews.

Also for ease of review, FDA recommends that a one-page summary of significant trial design parameters for each clinical study conducted in support of either the IDE and/or PMA applications be provided. The companion document includes more details regarding this recommendation.

In the event that the DES evaluated in nonclinical or clinical studies differs from the DES that is intended for commercialization, the sponsor/applicant should provide an appropriate justification for the applicability of testing provided. This justification, which can include additional limited testing, can be referred to as a *bridging* document. FDA will assess the significance of any such differences when determining whether sufficient information has been provided to support initiation of a clinical study (IDE) or whether valid scientific evidence has been submitted to provide reasonable assurance of safety and effectiveness for a PMA application.

B. Engineering Evaluation

The battery of tests and content and format of test data outlined in FDA's guidance document on bare metal intravascular stents and their associated delivery systems[31] are relevant for this guidance and for DES development. FDA recommends that sponsors complete ***all*** tests outlined in that guidance on the finished DES intended for commercialization. Additionally, for those tests that evaluate characteristics that could be affected by the addition of the drug and/or drug coating, sponsors should compare those results with the performance characteristics of the bare metal stent system in a side-by-side fashion. If a test article other than the finished, sterilized DES (e.g., bare metal stent, prototype, coupon) is used for a specific test, a scientific rationale should be provided for the applicability of the test article.

[31] See guidance for industry and FDA staff on *Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems.*

FDA recommends that the final, finished DES be evaluated to determine the initial performance characteristics of the DES. However, if there are ***any*** differences between DES tested for initial characterization, clinical builds (DES used in the human studies) and the DES sought to be commercialized (due to scale up of the manufacturing process), the changes should be clearly documented and, as a part of the PMA submission, appropriate additional testing should be conducted or a scientific rationale provided to demonstrate that these modifications will not affect the safety and effectiveness of the DES.

A thorough description of the entire manufacturing process should be provided for review. This description should clearly indicate whether any modifications have been made to the native stent platform (e.g., texturizing of the stent surface, use of coupling agents, polishing) to facilitate coating deposition/adhesion onto the stent substrate. The potential effect of additional processing steps on the durability of the stent substrate as well as the coating should be evaluated.

Since unintended delamination or premature dissolution of a DES coating may influence its clinical performance and/or mechanical integrity, ***additional*** evaluations and suggested modifications to the battery of traditional engineering testing as outlined in the guidance document referenced above should be taken into consideration for a DES.

- Test protocols

In addition to the test data (summaries are not typically sufficient), detailed test protocols, which include the loading parameters, test conditions, samples tested, acceptance criteria, and conclusions drawn for each of the tests performed on finished, sterilized product, should be provided for FDA review. A brief description of the derivation or development of the test method, or identification of other applications in which the method has been previously used should be included.

Test protocols should assess the worst-case conditions that the DES is likely to experience in clinical practice. Both device configuration and physiologic conditions can affect the performance of a DES.

Extreme device dimensions, tolerances, sizes, and any other important device parameters should be evaluated. We also recommend that the outer limits of physiologic variables, such as blood pressure, vascular compliance, and anatomic types, be examined. All test conditions should be clearly stated in the test protocol and supported with references to applicable literature, standards, or both. Occasionally, the worst performing combination of device configuration and physiologic conditions occurs in the mid-range of the relevant variables. This should be considered when developing protocols to ensure that the worst performing combination has been evaluated.

The term *coating* may refer to the drug carrier (usually polymeric, but not limited to such), the drug itself if it is solely coated onto the stent platform, any other coating, or the drug carrier even if it is incorporated onto the stent in a geometry other than a coating.

1. Coating Characterization

As part of the overall coating characterization of a finished DES, the sponsor should conduct additional studies on a one-time basis as part of the product assessment to establish an understanding of their DES system as well as appropriate baseline data. FDA believes that adequate baseline characterization of a DES may help the sponsor identify potential coating integrity concerns earlier rather than later in the development process. It should be noted that the tests recommended to characterize the coating and to assess acute and chronic coating integrity are not typically considered quality control (QC) tests; however, tests for particulate matter recommended in Section VI.B.3.iii are suggested as part of the QC assessment as described.

Specifically, testing should be provided to address each of the following issues as part of characterization studies:

- Coating thickness and uniformity along the stent length (both abluminal and adluminal surfaces, if relevant), circumferentially, and along the sides of the struts.
- Adhesion of the coating to the stent substrate. We recommend a quantitative characterization of the adhesion strength. If the coating consists of multiple layers (e.g., primers), we recommend that a quantitative test be performed to determine the cohesive strength between the layers.
- Chemical identification of particles recovered as part of particulate matter testing (see Section VI.D.3 below)

2. Coating Integrity

The acute and chronic integrity of coating on the stent substrate should be assessed to provide reasonable assurance that the coating is able to sustain its integrity according to its design specifications. The Agency requests that the sponsor qualitatively and quantitatively determine whether subjecting a DES system to expansion, deployment, and repetitive cycling modalities as experienced in the clinical setting will influence the ability of the coating to interact appropriately with the stent substrate. Part of this evaluation will entail determining whether there are areas where the coating has not been adequately deposited onto the substrate (e.g., defects such as bare spots or webbing due to manufacturing) versus areas in which the coating may have physically dislodged (e.g., delaminated) from the substrate due to being subjected to mechanical forces.

As part of this testing, it is recommended that a sampling plan be implemented to examine multiple lots of DES as well as comparing regions of high stress/strain versus low stress/strain areas to assess both inter- and intra-lot variability. A sufficient number of images should be provided so that FDA can make an assessment of consistency.

Furthermore, FDA recommends that coating integrity be evaluated by testing under certain conditions ***before*** and ***after*** aging (at a minimum, the product should be aged to the requested shelf life). These samples do not need to be real-time aged, but can be subjected to accelerated aging conditions.

For this section of the guidance, *acute* refers to any time up through expansion and deployment of the DES, whereas *chronic* refers to any time after assessment of the initial stent deployment in a simulated vessel throughout the lifetime of the implant.

- Acute coating integrity

Acute coating integrity of a DES should be assessed via some visualization method (e.g., scanning electron microscope). The stents used for this characterization should be representative of the finished product, subjected to all manufacturing processes, including sterilization. A visual assessment of the coating integrity on all appropriate surfaces of the DES after expansion in air to nominal diameter with characteristics appropriately quantified (e.g., continuity, voids) is strongly recommended to establish a baseline for comparison to coating characteristics after testing performed under other conditions.

Further visual characterization of the coating should be performed after deployment of the DES to the maximum diameter as described in the Instructions for Use. If overexpansion of the DES (post-dilatation) is to be allowed, this should be taken into consideration as part of this testing. It is recommended that deployment be simulated in an in vitro model intended to mimic in vivo physiologic and anatomic conditions (e.g., tortuous path, aqueous environment). The stent should be in direct contact with the simulated vessel without the use of other coatings, lubricants, sheaths, or protective wraps between the stent and simulated vessel. The rationale for the final model selected should be provided.

Ideally, the coating should not significantly change in configuration or prematurely delaminate from the stent substrate upon expansion or deployment.

- Chronic coating integrity

Chronic coating integrity or, for a degradable polymer system, the loss of coating integrity over time, can be assessed by performing accelerated durability testing in a simulated in vivo environment. It is highly recommended that the visual integrity of a DES after 30 and 400 million cycles of fatigue testing (representing approximately 1 and 10 years of equivalent implant time) be compared to baseline data in a side-by-side fashion. For degradable polymer systems, timepoints for evaluation may be specific to the expected degradation profile. A detailed fatigue test protocol, clearly describing the test equipment, aqueous environment, frequency, loading parameters, and mounting of samples should be provided with the results from these tests.

The sponsor should consider the following when designing tests to appropriately demonstrate the chronic coating integrity of a DES:

1. The sponsor should clearly indicate whether the sample consists of single or multiple stents along with a justification supporting test methods testing multiple samples. Since there is a reasonable expectation that stents will be overlapped during some clinical procedures, accelerated durability testing should be performed on multiple stents in an overlapped configuration.
2. We recommend that testing be conducted with stents in a bent configuration, with a clinically relevant radius of curvature.

3. If a product's drug elution is completed in a short time relative to the intended lifetime of the product, coating integrity test samples should be pre-eluted for a worst-case evaluation. This is a particularly important consideration for those coatings that become porous over time because of drug elution.

4. At a minimum, we recommend that these additional tests be performed on the finished DES for the worst-case product sizes for each stent design to demonstrate that the acute and chronic integrity of the coating has not adversely affected the characteristics of the DES system.

5. This testing can be combined with fatigue testing intended to evaluate integrity of the stent platform, if the apparatus can accommodate both tests.

Refer to the section immediately below for additional issues related to characterization of the coating integrity of a DES.

3. Particulate Matter Characterization

FDA recommends measurement of particulate matter generated by breakdown of the coating or from the stent platform, stent delivery system, and product packaging both at release and after aging. Particulate matter testing serves multiple purposes: (1) it provides an indirect evaluation of the coating integrity of the finished product and (2) it establishes the number of particles that can potentially be introduced systemically using the stent system. FDA believes that the main purpose in particulate matter testing for DESs is to provide a level of assurance of patient safety in terms of total particulate matter introduced into the bloodstream. Therefore, since the concern applies to the total number of particles released into the bloodstream, the test should apply to the entire stent delivery system, not just the stent.

a. Testing Considerations

The sponsor should consider the following when designing tests to appropriately determine the number, size and/or type of particles for a DES system when subjected to the conditions described in b-d below.

1. Particle counting and sizing methods should be described and validated. It is recommended that as part of the method validation, a known amount of various particle sizes be introduced into the test setup and the amount of particles recovered quantified. The number of particles recovered should closely approximate the number artificially introduced into the system.

2. Appropriate precautions should be implemented to ensure that the particles are suspended during sampling for particle counting and sizing to minimize artifacts from the test system. In our experience, particles > 50 μm have the tendency to settle and/or stick to the reservoir between particle counting. We recommend running a *blank* in which no stent is present and any particles present in the system are captured and counted. These counts represent test artifact and should be subtracted from the results when a stent (or stents) is introduced into the system

3. The number of samples (a stent, not a strut or portion of a stent) used, the stent size, and the stent lot should be specified for each test. The selection of the samples should be scientifically justified.

4. We recommend that for baseline, overexpansion, and simulated use conditions described in sections b, c, and d immediately below, testing be performed on the extremes (*four corners* size matrix — see example table, below) and an appropriate intermediate stent size for the entire stent matrix proposed.

Example of *Four Corners* Size Matrix

LENGTH (MM)								
		8	11	15	18	21	24	27
Diameter (mm)	2.5	X						X
	3.0				X			
	3.5							
	4.0	X						X

5. For evaluation of particulate matter generated on fatigue testing, the worst-case size(s) for each stent design should be tested. A justification for the sizes selected for testing should be provided; the rationale may include information gained from the finite element analysis.

6. For each test performed, a robust number of stents from multiple stent lots (minimum of 3 batches) should be evaluated.

7. Appropriate acceptance criteria should be proposed for particles ≥ 10 μm and ≥ 25 μm. The sponsor should provide valid scientific evidence, including chemical identification of the particles recovered to support the proposed specifications.

8. We recommend that particulate matter results be provided in a side-by-side fashion (e.g., comparing baseline and post-tracking deployment).

Note: In the event that an accessory device (e.g., embolic protection, atherectomy) is intended to be used in conjunction with a DES, the sponsor should provide appropriate supportive engineering performance test data to ensure that the integrity of the coating is maintained. We recommend that sponsors contact appropriate FDA staff to discuss engineering testing recommendations.

b. Characterization

For the purposes of *characterization* of the finished, sterilized DES, particulate matter testing should be performed and particles collected and appropriately measured for several different test cases:

- Baseline (expansion to nominal diameter)

Such testing should involve expansion of the stent to its nominal diameter in a beaker of solution. If the stent is not a balloon-deployed stent and is self-expanding, this condition and the over-expansion condition described below may be equivalent and combined into one test condition.

- Over-expansion (maximum deployed diameter, including post-dilatation limits, as specified in the IFU)

This testing should involve expansion of the stent to the maximum diameter allowed, as described in the post-dilatation limits in the IFU in a beaker of solution.

- Simulated use (e.g., during tracking and deployment)

This testing should be performed with use of an in vitro model as described in section B.2 (acute coating integrity) above. Note that physiologically relevant worst-case conditions should be applied. To ensure measurement of the total number of particles that could be potentially introduced into the bloodstream, the stent delivery system should be inserted into the text fixture to the point at which it would be inserted in clinical use.

- Fatigue/durability testing

This testing should be performed with use of a test fixture as described in section B.2 (chronic coating integrity) above. Note that physiologically relevant worst-case conditions should be applied. This should include multiple stents placed in an overlapped and bent configuration. It is recommended that particulate matter generation be measured at multiple time points, rather than at t=0 and 400 million cycles. One advantage of this approach is that a pattern/trend of particulate matter generation can be described (e.g., plateaus, monotonic increases). Depending on this trend, the sponsor may be able to determine the appropriate number of fatigue cycles (which may be significantly less than 400 million) necessary to demonstrate that the coating will not unintentionally break apart or, for a degradable polymer system, to quantify the particulate matter generation associated with the degradation of the polymer.

c. Quality Control

If the amount of particulate matter recovered from over-expansion testing and simulated use testing is substantially similar, either test may be used for quality control testing. However, if these two test conditions resulted in different amounts of particulate matter, the more challenging test, the simulated use condition, should be performed for quality control purposes. In either case, the test should be performed on every batch of product manufactured as part of batch release (see Section V.B.8 above for other parameters to be measured for batch release).

d. Stability

For stability testing, we recommend that aged samples be evaluated using the simulated use test condition. If the over-expansion condition is used for quality control purposes, additional testing using the simulated use condition should be performed on stability batches at t=0. It is highly recommended that particulate matter generation over time be evaluated at each time point in the stability protocol (instead of only at t=0 and t=proposed expiration date). In the event that the particle counts continually increase with aging or fail to meet the

acceptance criteria at the proposed expiration date, additional data will be available to support a shorter expiration date for the DES.

4. Corrosion Potential of a DES

If the underlying stent substrate of the DES is metallic, FDA recommends that the sponsor evaluate the effects of cracked or delaminated coatings on corrosion resistance. We recommend that corrosion testing be performed after intentionally creating a defect in the coating, which exposes the base stent substrate. We recommend testing according to the methods described in ASTM F746 [32] or an equivalent method. The sponsor can modify the method by incorporating the experimental setup described in ASTM F2129.[33]

Additionally, since there is a reasonable expectation of stent overlap during clinical procedures, the potential for fretting corrosion between two DESs should also be addressed. The sponsor should ensure that micromotion between strut elements is actually occurring. We recommend that the sponsor incorporate examination of samples for fretting corrosion as part of fatigue/durability testing. A scientific rationale for the number of samples evaluated for fretting corrosion should be provided.

If a stent contains more than one type of metal, such as a laminate, we recommend that the resistance of the stent to galvanic corrosion be demonstrated. If stents of different materials will be overlapped during clinical procedures and the contacting or overlapping stents may be made of different materials, we recommend that the potential for galvanic corrosion between stents be addressed. We recommend testing according to the methods described in ASTM G71,[34] or an equivalent method. Sponsors can modify the method by incorporating the experimental setup described in ASTM F2129.

5. Degradable coatings

If a DES has a degradable polymer carrier, the environments for the experimental tests described above should be carefully taken into consideration since they may affect the interpretation of the results. Therefore, we recommend that a full characterization be performed of the degradation profile (both in vitro and in vivo) of the biodegradable polymer carriers. The resulting information should be used to design the test environment for the evaluations described above, as well as to assess the appropriate timelines for additional nonclinical studies (e.g., supportive animal studies, elution characteristics).

The durability of the degradable coating becomes important near the end of the coating lifetime when degradation has weakened the coating. We therefore recommend that particulate matter testing be conducted in fatigue testing for the life of the coating. The trend or pattern of particulate matter generation as the coating degrades should be described. It may also be instructive to observe

[32] ASTM F746 Standard Test Method for Pitting or Crevice Corrosion of Metallic Surgical Implant Materials.

[33] ASTM F2129 Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices.

[34] ASTM G71 Standard Guide for Conducting and Evaluating Galvanic Corrosion Tests in Electrolytes.

the coating via visual/microscopic methods near the end of the coating lifetime to characterize the pattern of degradation to understand the potential for increased particulate matter generation (e.g., Does the degradation occur preferentially at the surface or stent interface once some interface has been exposed? Is the degradation patchy?).

Shelf life/stability characterization becomes very important for degradable/resorbable polymers. For example, exposure to humidity may begin the degradation process and therefore not only reduce the shelf life, but increase the elution at early stages of the product and decrease the effective lifetime of the coating.

It is also very important to characterize the effects of the sterilization processes on the coating, because many processes (e.g., irradiation) reduce the molecular weight of the polymers, which may allow an increase of elution at early stages of the product and reduce the effective lifetime of the coating.

C. Biocompatibility

Biocompatibility testing should be conducted in accordance with ISO 10993.[35] For certain tests, evaluation of the stent should be carried out separately from the delivery system. For additional considerations related to biocompatibility testing, refer to the companion document.

D. Animal Safety Studies

Prior to undertaking GLP animal safety studies, pilot DES animal studies should be conducted to evaluate the degree of systemic exposure, local vascular and regional myocardial levels of the drug component of the stent. This information can be discussed with FDA and will inform the need for, and extent of, separate studies or data on systemic clinical pharmacology.

DES nonclinical in vivo safety studies conducted in appropriate validated healthy animal models are intended to assess handling characteristics (delivery and deployment), the biological response to the DES, drug effects, and stent-related pathology. In addition, these studies are used to identify potential clinically relevant major adverse events that should be considered prior to beginning human clinical trials or that may influence clinical study design. The design of these studies should also evaluate stents that incorporate a safety margin over the highest drug dosage and greatest polymer concentration intended to be evaluated in the IDE clinical study as well as for all reasonably anticipated intended clinical uses of the DES.

Animal studies should compare combinations of the stent components (i.e., bare stent, and stent + polymer + drug) in both nonoverlapping and overlapping configurations. The sponsor should clearly identify any differences (e.g., stent design differences, polymer thickness, drug amounts) between the DES used for nonclinical studies and the proposed IDE study.

Studies of stent + polymer (without drug) should be performed if safety concerns are observed with the finished DES product so as to help identify whether pathologic changes are more likely due to

[35] ISO 10993-1 Biological evaluation of medical devices—Part 1: Evaluation and testing.

the drug or the coating. The *stent + polymer* sample should include both biodegradable and non-biodegradable polymer carriers as well as the primer layer.

If observed pathologic changes are believed to be secondary to species-specific arterial responses, an approved DES can be considered as an additional control treatment arm. Additionally, sponsors can consider using an approved DES as a control treatment arm to demonstrate superiority of the test DES with respect to sustained neointimal growth supression, more rapid stent endothelialization, reduced fibrin deposition, improved vasomobility, reduced inflammation, and reduced positive remodeling/stent strut mal-apposition.

Demonstration of probable product safety is currently considered to be the primary purpose of the nonclinical animal studies. Demonstrating potential product efficacy (i.e., inhibition of neointimal hyperplasia) is an important secondary endpoint. However, for any given drug-device combination, the potential efficacy observed during animal studies should be appropriate to ***balance*** any potential safety concerns that were observed during the same studies. Also, it is reasonable to presume that the demonstration of the potential efficacy of a new DES in an animal model may assume increasing importance over time if multiple DESs are approved for clinical use.

Refer to the companion document for general recommendations regarding good animal husbandry.

1. Appropriate Validated Models

Because of the similarities in the size, anatomic distribution, and time-dependent progression neointimal growth within stents in human coronary arteries, the swine model has historically been relied on for testing of intracoronary devices. However, because of inherent differences between animal and human vascular responses to stent implantation, animal testing is primarily focused on the evaluation of safety, rather than sustained long-term efficacy. Small animal models (e.g., rabbit iliac artery) can provide complimentary data on optimal dose finding and DES mechanism of action.

Currently, there is no animal model that can both (1) replicate the heterogeneity of human atherosclerotic coronary disease and (2) accommodate the sizes of catheters and stents used in humans. Due to potential experimental complexity and in the absence of studies demonstrating predictive capabilities, atherosclerotic animal models to test the safety and performance of these products have not been routinely requested. However, although advanced stenotic atherosclerotic lesions in animals may not be available, sponsors may consider DES implantation in modifications of normal vessels (e.g., intimal lipid/inflammatory cell-rich or fibrotic lesions) to test device performance in vascular environments that may be relevant to human use.

2. Standards for Evaluation

Unless there is a specific reason to do otherwise, the stent should be implanted in an artery that has no prior injury. Antiplatelet therapy should be administered based on the current clinical standard of care and that to be used during the clinical study.

The Agency recommends the use of, at minimum, general animal study guidelines, necropsy, and arterial histopathology methods, including those described below. The study findings from each stent

type (i.e., bare stent, stent + polymer + drug, and if indicated, stent + polymer) should be compared. We recommend the following.

- A complete general necropsy (gross and detailed histopathology) should be performed, as well as gross and radiographic evaluation of stented vessels and the heart, including an evaluation of vessel wall and stent structural integrity (e.g., strut fractures, polymer fragments), assessment of stent malapposition, and multiple anatomical regional sections from organs perfused by the stented artery.
- We recommend pressure perfusion fixation and plastic embedding for stented arteries.
- For stents ≤ 30 mm in length, we recommend evaluation of a minimum of three sections per stent (proximal, mid and distal), plus one section 5 mm beyond each end of the stent.
- For stents > 30 mm in length, see section VI.F.7 of this guidance.
- For arterial histopathologic sections, a descriptive histopathology report (including micrographs illustrating the findings) and histomorphometric analysis as well as interpretation of data are recommended. We also recommend a thorough evaluation of the arterial biological response to the DES describing the following points.
  - The morphologic features of the neointima and the extent of stent strut coverage by neointima
  - The extent of endothelialization (scanning electron microscopy should be considered)
  - Alterations of the media (e.g., necrosis, thinning of media or loss of cellularity) and adventitia
  - Locations and amounts of fibrin
  - Location and severity of dystrophic calcification
  - Evidence of the loss of vessel wall structural integrity
  - Characterization of the inflammatory response and fibrosis within the neointima, media, and adventitia
- We recommend that you specifically evaluate and report the presence of mural thrombus formation and evaluate the potential for thromboembolism and the significance of stent-related embolic material in selected regions of organs perfused by the stented vessel. Stent strut mal-apposition to the arterial wall should be reported. For the porcine coronary model, in particular, the presence of granulomas should be noted.
- We recommend that all pathology and histopathology reports be written by the examining pathologists or clinicians and attached as an appendix to the final GLP study report.
- We recommend inclusion of a broad selection of representative, thoroughly described gross photographs, radiographs (evaluating stent integrity, configuration, and extent of stent overlapping), and photomicrographs of arterial cross sections from stented arteries in the final pathology. We encourage the submission of representative photomicrographs describing the histopathology scoring system used to describe the severity of histopathology endpoints. In addition, thumbnail, low, and higher magnification photomicrographs of all

arterial sections should be included as an appendix in the final pathology report. To ease review, we recommend providing all gross photographs, radiographs, and photomicrographs in electronic format.

- Histomorphometric evaluation of sections is essential for the assessment of DES biological response and safety. These measurements should minimally include the following: neointimal area, neointima thickness at each strut site, medial area, internal and external lamina area, lumen area and percent area stenosis. Measurements should be performed on each stent section (proximal, middle, and distal), and a mean measurement for each parameter for the entire stent should be reported. From these data, the percentage of the stent narrowed by neointimal tissue (percent stent stenosis) can be calculated. A mean injury score for each stent should be determined.

The non-stented adjacent arterial sections (5 mm proximally and distally) should undergo comprehensive histologic evaluation including an assessment of arterial injury, neointimal thickening, inflammation, and thrombus deposition.

Quantitative coronary angiography (QCA) is recommended for appropriate stent diameter implantation (stent to artery ratio) to avoid excessive vascular injury secondary to oversizing. The use of intravascular ultrasound (IVUS) evaluation is recommended in a subset of animal studies to demonstrate strut apposition to the arterial wall both post-procedure and at follow-up in a subset of animals.

Following DES implantation, any sudden or unscheduled animal deaths should be vigorously investigated for cause. In such cases, a thorough necropsy should be conducted, including evaluating all stented arteries and specifying the cause of death. Any clinical problems (e.g., fever, allergy, evidence of renal or hepatic dysfunction) should also be recorded. We recommend that complete data on thrombus, myocardial infarction, aneurysm, and perforation be collected and included with the pathology report within the IDE submission.

3. Study Duration

Animal studies designed to assess biological response and safety of the final clinical version of the DES should be conducted prior to first in human use. At a minimum, 1- and 6-month studies are suggested; 3-month animal data are optional, and depending on the results, may be sufficient to begin a clinical feasibility trial.

In view of the mechanism of action of most DESs, longer term follow-up studies (e.g., beyond 6 months) are likely to be necessary to assess (1) chronic inflammatory reactions, (2) delayed or incomplete endothelialization, (3) late stent thrombosis and restenosis, and (4) chronic biological responses to the surface polymer after complete drug elution and, in the case where a biodegradable polymer is used that takes longer than 6 months to fully degrade.

In nonclinical studies at all time points, histology should be carefully evaluated for polymer delamination from the stent.

Note: Given the differences in injury and healing responses between the animal models and humans, in addition to inherent variability between the designs of different DES systems, a definitive long-term follow-up time point for animal model studies to assess late effects cannot be explicitly recommended.

4. Biological Response

We recommend that a three-way comparison of the histopathological findings for the bare metal stent, polymer-only stent (if indicated), and the polymer-drug stent combination be conducted at appropriate time points, minimally to include 1 and 6 months. We recommend that at least six to eight samples of each of the stent types be evaluated with a minimum of three to four animals per time point. We recommend enrollment of extra animals in anticipation of possible early animal deaths.

a. Histopathology Endpoints Assessing Drug Effects

Study endpoints should focus on the characterization of localized drug effects within the vessel wall of the stented vessel as well as immediately proximal and distal to the stented vessel segment (i.e., to observe any potential edge effects). Evidence of DES-related drug effects and pathology includes factors such as mural thrombus formation, fibrin deposition, inflammation (strut associated; neointima, media, adventitia), granulomas, neointimal smooth muscle density, medial necrosis and thinning, dystrophic calcification, endothelialization, vessel wall hemorrhage, and neoangiogenesis. We recommend that a scoring system be used to record the incidence and severity reported by stent segment region (i.e., proximal, mid, distal).

b. Downstream and Edge Drug Effects

It is important to evaluate whether a drug produces pathology in the tissue ***downstream*** from the stent. Using the highest total drug dosage proposed for clinical use, a thorough gross and histopathology evaluation of multiple anatomic regional sections of myocardium perfused by the stented artery should be conducted to identify stent-related cardiac pathology (e.g., infarcts, thromboembolic material, myocardial necrosis and fibrosis).

In addition, the drug effects immediately proximal and distal to the stented segment of the vessel (referred to as an *edge effect*) should be assessed. Using similar histopathology and histomorphometric endpoints as described above (VI.C.2 and 4a), the findings should be compared to the stent segment of the vessel.

If long stents are evaluated separately (refer to section VI.F.7), this evaluation should be completed both for standard length stents and for long stents.

5. Drug Dosage Safety Margin

The objective of studies of stents with higher drug and polymer dosages than will be applied to the clinical or to-be-commercialized version of the stent is to establish a safety margin over and above the dose intended for clinical use. These studies can reveal whether adverse effects are observed at higher dosages, and at what dosage the effects are observed. The following drug formulation characteristics

should be used to describe a DES.

- Dose density
- Total dose loaded
- Coating thickness
- Amount of drug delivered to the tissues
- Residual amount of drug on the stent
- Release rate

In animal studies intended to establish a safety margin, the dose density, amount of drug or polymer loaded, and number of stents should be designed to justify a margin of safety over the proposed clinical trial dose. In addition, drug release characteristics should be analyzed in relation to local tissue drug concentration, vascular biological responses and local toxicity. The release rate is important because it directly correlates with the local vascular toxicity. Additional animal studies should be carried out to evaluate the safety of stents containing higher dosages of drug and polymer (i.e., a three- to ten-fold margin over the intended drug dosage density of the final product) to evaluate whether the DES has an appropriate local, regional, and (possibly) systemic safety margin with regard to drug dosage density. If loading high drug concentrations onto the stent is technically difficult or significantly alters the degradation profile for a degradable carrier, the Agency recommends evaluating regions of overlapped stents to theoretically support safety margins. Evaluation of over-dosage stents should include the longest, largest diameter stent, and if multiple stents are routinely used, the combined drug density of the highest number of, and the longest, stents allowed in the planned human study.

6. Overlapping Stents

Since overlapping stents are commonly implanted in current clinical practice, animal studies should be undertaken to evaluate the safety of overlapping DESs and provided as part of the IDE submission. Stents overlapping by a minimum of 4 mm should be evaluated at 1 and 6 months (optionally at 3 months), in a minimum of six stents per stent type. Histopathology sections should be obtained from both overlapped and non-overlapped regions. Histopathology and histomorphometric endpoints should be reported and compared by stent segment (i.e., proximal, overlapped, distal stent).

Due to the likely possibility that multiple overlapping stents will be used, FDA recommends that animal testing on overlapping stents be provided as part of the PMA submission whether or not testing is included within the clinical study to provide a preliminary assurance of safety.

7. Long Stents

A separate evaluation should be completed for the longest stent model if a long DES (i.e., >30 mm) is to be marketed. Evaluation of angiography and histopathology is particularly important to characterize the biological and drug response along the full length of the stent. Histopathology sections should cut at approximately 10 mm intervals, plus one section 5 mm proximally and distally beyond each end of the stent. The Agency will not routinely request comparisons to *long* stent

controls. Results of the long DES may be compared to those observed for standard-length control stents and DES.

E. Clinical Pharmacology and Drug Release Kinetics

This section provides suggestions on elements to consider in the assessment of the clinical pharmacokinetics of a DES and on the evaluation of both in vivo and in vitro release characteristics of the drug from a DES.

1. Clinical Pharmacology Information

a. Evaluation of the Systemic Pharmacokinetics of a DES

The evaluation of the pharmacokinetics (PK) of a DES can be accomplished in one of the trials of patients implanted with the DES. The sponsor should provide a detailed protocol describing the design of the PK study. The in vivo drug release kinetic information generated during the animal studies could be useful in designing the human PK study (i.e., appropriate PK sampling times, length of PK study).

To obtain PK information at the highest possible drug exposure, it is recommended that the PK evaluation occur in a trial including patients receiving multiple and overlapping stents. The measures or parameters for the drug should include area under the plasma concentration versus time curve (AUC), peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), elimination half-life ($T_{1/2}$), and total clearance (Cl_t). If there are major metabolites associated with the therapeutic or toxic effects of the drug, they should also be determined.

b. Population-PK

A population PK-sparse sampling approach can also be used for the collection of clinical PK data for the DES from patients enrolled in the clinical trials. See CDER's guidance for industry *Population Pharmacokinetics.*

c. Bio-Analytical Methods

The evaluation of the samples collected during the PK study should be evaluated for drug content using properly validated analytical methods. Additional information on validation of methods can be found in CDER's guidance for industry *Bioanalytical Method Validation.*

2. Drug Release Kinetic Information

a. Evaluation of In Vivo Drug Release

The in vivo drug release information generated in the animal studies can be very useful (1) in the design of the in vivo human PK assessment conducted as part of the clinical program (i.e.,

appropriate PK sampling times, length of PK study), (2) in the development of in vitro release methodology that mimics the in vivo drug release, and (3) in the development of an in vivo-in vitro correlation (IVIVC).

The in vivo release of a drug can be divided into two types. First, the release can be directly measured using the amount of drug remaining in explanted stents with respect to time until complete drug elution profile is obtained. The release can also be measured using the blood and/or tissue concentration data. The in vivo release profile generated using the first method represents drug release from the stent to the surrounding tissues and systemic circulation while that generated using the second method represents drug released from the stent and the surrounding tissue into the systemic circulation.

- Drug Tissue Levels and Systemic Distribution

The in vivo local and systemic drug kinetics of the DES to be used in the IDE clinical studies and submitted in the PMA application for marketing approval (if there are modifications) should be thoroughly characterized in an appropriate animal model. The release of drug from the stent should be evaluated at specified time intervals covering the complete drug elution profile (immediately after implantation until the drug is completely eluted from the stent). Drug concentrations should be assessed in the blood, in arterial tissue, and in myocardial tissue proximal and distal to the stent, as well as in remote tissue, such as the liver, lung, and kidney. In the tissue surrounding the stent, the drug should be evaluated until there are no longer detectable levels.

Assessments should include whether the drug's concentration is uniform along the stent length or preferentially distributed at either end. Evaluations should compare the terminal elimination $t_{1/2}$ of drug from stent to the true elimination $t_{1/2}$ obtained after IV administration. If drug release from the stent is slower than the elimination process (flip-flop phenomenon), the rate limiting step is the release of drug from the stent.

b. Evaluation of In Vitro Drug Release Kinetics

In vitro release testing is a powerful and useful tool for obtaining data related to a product's quality and, potentially, its clinical performance. The Agency considers the development of acceptable, discriminating in vitro elution methodology and specifications as critical for the adequate characterization of a DES product tested clinically as well as to validate consistency in the commercially manufactured product. Because this testing serves multiple important purposes, including use in DES characterization, batch release, and stability testing, the in vitro elution method for the testing of the release of drug from the DES should be developed and validated as early in the development process as possible and definitely prior to submission of the PMA application.

The in vitro drug release/elution kinetics should be evaluated under appropriate conditions based on the mechanism of drug release and to emulate hydrodynamic considerations of stent deployment. In vitro drug release kinetics characterization should provide valuable insight on the time course of drug release and on the drug remaining on the stent. The relative

solubility of the drug also determines the relative kinetics such that a more lipophilic drug exhibits a longer time of elution. We recommend that the in vitro release profile generated with the chosen method mimic the in vivo elution behavior of the drug from the DES. If this is not possible (e.g., the in vivo release is limited), the in vitro method should be optimized for its ability to detect manufacturing lots outside the boundaries established in the clinical trials.

A detailed description of the optimal in vitro elution methodology and the developmental parameters (i.e., equipment/apparatus, in vitro release media, agitation/speed, temperature, pH, assay) that were used to identify this method as most appropriate should be submitted to the Agency in the IDE. Also, the method validation information showing that the chosen method is able to detect manufacturing changes (under meaningful testing) that may have an effect on the release of the drug should be submitted. Validation studies are important for identifying critical formulation and manufacturing variables during development, establishing relevant controls for manufacturing, and developing a relevant stability indicating test method for final product testing. An in vitro test method based on mechanism of drug release can also be a valuable tool for ensuring unchanged performance of manufactured lots.

The elution profile should be complete and cover at least 80 percent of drug release of the label amount or whenever a plateau is reached. We recommend use of at least six samples per testing variable. The elution data (individual, mean, profiles) should be reported as the cumulative percentage of drug eluted with time (the percentage is based on the product's label claim).

In vitro drug release kinetics should be reproducible between stents within a lot and between manufacturing lots and should be stability-indicating. The chosen method should be discriminatory and sensitive enough to reject lots that would have less than acceptable clinical performance.

For the setting of the drug release/elution acceptance criteria, the following points should be considered:

- The in vitro elution specifications should encompass the timeframe over which at least 80 percent of the drug is eluted or where the plateau of drug elution is reached if incomplete elution is occurring.
- Data from lots used in the clinical trials and stability studies, and also on to-be-marketed batches, should be used.
- The establishment of at least three sampling times covering the initial, middle, and terminal phases of the complete elution profile data should be selected. The acceptance criteria ranges should be based on the overall elution data generated at these times.
- Acceptance criteria should be set in a way to ensure consistent performance from lot to lot.

- The chosen acceptance criteria should not allow the release of any lots with elution profiles outside those that were tested clinically.

The applicant should note that an agreed upon in vitro elution test (i.e., specifications and acceptance criteria) is critical as a quality control (QC) tool during the stability program and establishment of the DES shelf life and is part of the QC tests performed for the release of DES batches.

c. In Vitro-In Vivo Correlation

The ultimate goal of an in vitro-in vivo correlation (IVIVC) is to establish a meaningful relationship between in vitro behavior of a DES product and in vivo performance of the same product, which would allow in vitro release data to be used as a surrogate for in vivo behavior. Thus, the main objective of developing and evaluating IVIVC is to empower the in vitro release test to serve as a surrogate marker for in vivo bioavailability. One additional primary purpose of establishing an IVIVC is to minimize the number of human studies needed for the approval of scale-up and postapproval changes in manufacturing processes (e.g., those that do not change the mechanism of release). We recommend that the following factors be considered when establishing the IVIVC:

- Mechanism of drug release from the stent
- Formulation and manufacturing process factors that influence the release kinetics
- In vitro method conditions (e.g., hydrodynamics, media composition)
- In vivo stent deployment factors

To obtain an in vitro-in vivo relationship, two sets of data should be collected. The first set contains the in vitro data, usually drug release data from an elution test, and most often takes the form of percentage of drug released as a function of time. The second data set contains the in vivo data. For a DES, the in vivo release of a drug can be assessed by determining the blood-drug concentration data and also by measuring the amount of drug remaining to be released from the recovered stents. Although data from either or both methods can be used in the development of an IVIVC, for a DES, the systemic drug levels might be very low or below quantitation limit. Thus it becomes more feasible in constructing the IVIVC model to use the in vivo release data from the explanted stents. A model that integrates both (i.e., mechanism of drug release and systemic drug concentration) may provide a means for developing a physiologically based PK model for predicting drug disposition and for establishing relevant mechanism based IVIVC.

Once the in vitro and in vivo data sets are available, a mathematical model describing the relationship between the in vitro and in vivo data sets should be developed. One mechanism for determining whether a correlation exists between the in vitro release kinetics and the in vivo tissue uptake is to plot the amount of drug released in vitro versus the amount released in vivo at the same time points to see whether a point-to-point relationship exists (level A correlation). When trying to develop such a relationship, the in vivo data set is fixed. Once this information is generated, it establishes the relevant performance of the DES product. On

the other hand, the in vitro release profile may be modified through changes in the release test conditions to obtain a consistent relationship between the percentage of drug released in vitro and the fraction of drug released in vivo.

Additional information on the development and validation of an IVIVC can be found in CDER's guidance for industry *In vivo/In vitro Correlations.*

VII. FINISHED PRODUCT MANUFACTURING, STERILIZATION, PACKAGE INTEGRITY, AND SHELF LIFE

A. Manufacturing — Quality System (QS) Regulation and Current Good Manufacturing Practice (CGMP) Regulations

A PMA must include a complete description of the methods, facilities, and controls in sufficient detail that FDA can make a knowledgeable assessment of the quality control used in producing the finished DES (see 21 CFR 814.50). Although particular aspects of the manufacturing of the finished DES are addressed in Section V.B., Chemistry, Manufacturing, and Controls, a full description of the manufacturing methods, facilities, and controls must be provided at the time of the PMA submission (see 21 U.S.C. 515(c)(1)(C)).

A drug-device combination product must meet current good manufacturing practice requirements for both the drug and device constituent parts of the combination product (e.g., 21 CFR 210/211 for drugs, 21 CFR 820 for devices). For a discussion of the Agency's current thinking on how to apply these manufacturing requirements for a combination product, you may wish to refer to the draft guidance for industry *Current Good Manufacturing Practice for Combination Products*, issued by the agency in September 2004.[36] The draft guidance describes a quality management framework for combination products that, if properly implemented, would give manufacturers the flexibility to select either the CGMP regulations (21 CFR 210/211) or the Quality System regulation (21 CFR 820) as their umbrella manufacturing operating system, provided their current good manufacturing practice operating system incorporates key specific provisions pertaining to the other part of their combination product.[37] Under such an approach, if the Quality System (QS) regulation (21 CFR 820) is chosen as the umbrella set of regulations for the manufacturing operative system for a DES product, complete manufacturing and quality control information for the DES product would be provided pursuant to the QS regulation (see 21 CFR 814.20(4)),[38] incorporating key, specific provisions from the drug CGMP regulations (21 CFR 211). Likewise, if the CGMP regulation is chosen as the umbrella manufacturing operating system, complete manufacturing and quality control information should be provided for the DES product pursuant to the CGMP regulations (21 CFR

[36] See http://www.fda.gov/oc/combination/OCLove1dft.html.

[37] The Agency has since announced its intent to issue a Proposed Rule on Current Good Manufacturing Practice for Combination Products (72 Fed. Reg. No, 236 (2007), available at www.RegInfo.gov/public/do/eAgendaViewRule?ruleID=279375.

[38] See, e.g., guidance for industry *Quality System Information for Certain Premarket Application Reviews,* www.fda.gov/cdrh/comp/guidance/1140.pdf, for more information.

Parts 210 and 211), incorporating key, specific provisions from the device QS regulation (21 CFR 820).

B. Sterilization

The PMA application should identify the sterilization method and include the validation for the sterilization method and the sterility assurance level (SAL) achieved. In general, sterile devices would meet an SAL of 10^{-6}, unless there is a substantial scientific justification provided for not being able to achieve this level and for why patients would not be at increased risk. Sterilization validation should be carried out in accordance with a recognized standard or equivalent method.[39]

C. Package Integrity

Package integrity testing should be performed to demonstrate the ability of the package to maintain the sterility of the product contained within it. Package integrity testing generally consists of a whole package physical integrity test in conjunction with a seal integrity test. Some methods for package integrity testing may be found in ISO 11607.

Additionally, appropriate testing should be conducted to evaluate the ability of the packaging to withstand forces generated during shipping and distribution from the manufacturer to the end user. Test methods such as those described in ISO 2248 and ISO 8318[40] may be appropriate.

D. Shelf life testing

In addition to the tests recommended to demonstrate stability of the DES discussed above (see Section V.B.9), testing should also be performed to demonstrate that the functionality of the stent and delivery system (i.e., mechanical performance), the coating integrity, and the package integrity have not degraded over the requested shelf life. Testing should be performed on a finished, sterilized DES product that has been manufactured and packaged in the same manner as intended to be commercialized. Due to the presence of the polymer and drug components accelerated aging is not appropriate for stability testing as described in Section V.B.9 above; however, testing to establish the continued functionality of the stent and delivery system may be conducted using samples subjected to accelerated aging. For certain tests, such as coating integrity, accelerated aging conditions can have a significant detrimental impact on the DES such that real-time aging should be considered.

[39] FDA recognizes the following standards for steam, ethylene oxide, and radiation sterilization, respectively: ISO 11134, ISO 11135, and ISO 11137 (see guidance for industry *Recognition and Use of Consensus Standards,* http://www.fda.gov/cdrh/ost/guidance/321.html.

[40] ISO 2248 Packaging – Complete, filled transport packages – Vertical impact test by dropping; ISO 8318 Packaging — Complete, filled transport packages and unit loads — Sinusoidal vibration tests using a variable frequency

VIII. CLINICAL ASSESSMENT OF DRUG-STENT COMBINATIONS

A. General Considerations

Clinical trials of a new DES should not begin until the sponsor demonstrates that there is reason to believe that risks to subjects are outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained. Depending on the amount of available information, a feasibility study may be recommended to allow the collection of initial data in human subjects. If feasibility (sometimes referred to as "first in human") data are available from studies undertaken outside the United States (OUS), additional data collection in a feasibility study in the United States may not be necessary. However, the quality, applicability, and duration of such OUS feasibility studies will be critical to assess whether these data can be considered directly or indirectly applicable to the DES intended for clinical use in the United States. Such information should be reported in the Report of Prior Investigation section of an IDE. The companion document includes an example of a one-page summary that may be used for ease of review.

FDA encourages study sponsors to use the pre-submission process[41] to gain informal feedback on proposed clinical protocols for DES, including feasibility or pivotal studies. Additionally, although FDA generally does not regulate device clinical studies performed outside of the United States, we are willing to provide informal feedback on clinical protocols for OUS studies that are planned to support either an IDE or PMA application.

FDA believes that a clinical protocol for a coronary DES should include the following elements:

- Clear statement of the intended use
- Clinical development plan designed to develop the data needed to support the intended use
- Study hypothesis(es)
    - Primary and secondary study endpoints for both safety and effectiveness
    - Criterion for study success, (i.e., which hypotheses must be met for the study to be declared a success or *win*)
    - Allocation of Type I error (alpha) for primary and secondary hypotheses, as appropriate
- Plan for assessing safety in which all adverse events are identified and analyzed
- Plan for assessing safety and effectiveness on the basis of an intent-to-treat population as well as an evaluable population
- Study design with inclusion/exclusion criteria
- Case report forms
- Statistical analysis plan
- Risk/benefit analysis
- Informed consent[42]

[41] See guidance on *IDE Policies and Procedures,* http://www.fda.gov/cdrh/ode/idepolcy.pdf.

[42] You should review the statutory definition of applicable clinical trial to determine if your trial must be registered to comply with the law. *See* PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)). http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf

- Data and Safety Monitoring Board (DSMB) charter
- Balance of premarket and postapproval data development
- Labeling that accurately presents any previously collected study data

A number of the above elements are discussed in greater detail below.

B. Intended Use

The sponsor should identify, as clearly and precisely as possible, the intended use of the DES. The specific indications should include the following:

- Lesion types (e.g., de novo, in-stent restenosis)
- Target population (e.g., stable angina, acute coronary syndrome (ST elevation myocardial infarction, non-ST-segment elevation myocardial infarction, unstable angina)
- Conditions for use
- Anatomical sites of application of the DES (native coronary artery, saphenous vein or arterial grafts, left main coronary artery, ostial, chronic total occlusion, bifurcation) and range of lesion lengths and vessel diameters
- Expected outcomes

The intended use determines the objectives of the clinical trial, which are generally to demonstrate the safety (i.e., associated morbidity and mortality) and effectiveness (i.e., associated patient benefit) of the product for a defined clinical benefit in a target population under specific conditions of use.[43]

C. Objectives for DES Trials

Following the approval of the first two coronary DES, data were collected that suggested a small but significant increase in the rate of stent thrombosis associated with DES as compared to bare metal stents, occurring after the first year of implantation. FDA convened an Advisory Panel meeting on December 7 and 8, 2006, in an effort to fully characterize the risks, timing, and incidence of DES thrombosis. Three topics were discussed by the experts on the panel, DES manufacturers, and clinical investigators: (1) the rates of stent thrombosis and associated clinical sequelae (death and MI) when DES are used in accordance with their labeled indications; (2) the rates of stent thrombosis and associated clinical sequelae (death and MI) when DES are used in a broader, more complex population of patients and lesions; and (3) the optimal duration of dual antiplatelet therapy in patients who receive DES. More specific information about the meeting and the conclusions reached are available on FDA's Web site.[44]

Information can be submitted to ClinicalTrials.gov using the Protocol Registration System (PRS). For more information visit the PRS Information Page (http://prsinfo.clinicaltrials.gov).

[43] Although indications are commonly refined over time as clinical data from feasibility studies are analyzed, at the pivotal trial stage of product development, the intended use and indications should be in reasonably sharp focus.

[44] FDA statements available at http://www.fda.gov/cdrh/news/091406.html and http://www.fda.gov/cdrh/news/010407.html. Panel summary and transcript available at http://www.fda.gov/ohrms/dockets/ac/cdrh06.html#circulatory.

As an outcome of that panel meeting, FDA recommends that all DES clinical programs address the following questions as part of the information provided to demonstrate a reasonable assurance of safety and effectiveness:

1. The rates of critical clinical endpoints related to safety and effectiveness, such as death, myocardial infarction, and need for revascularization should be determined.

2. The rate of death and myocardial infarction (MI) should be determined. Not only are these critical safety endpoints, but adequate precision around the rates of death and MI is needed to understand the impact of stent thrombosis on the overall safety and effectiveness profile of a DES.

3. The rate of stent thrombosis over time should be addressed. For example, the rate of stent thrombosis up to and after 1 year should be determined, including whether the rate increases, decreases, or plateaus over time. Analyses should be presented for both patients receiving the DES within the labeled indication and patients representing broader use of the product.

4. The following aspects of adjunctive antiplatelet therapy (APT) should be addressed.
   - Describe the profile of patient compliance with recommended antiplatelet therapy
   - Determine how often dual APT is being extended beyond the recommended duration
   - Describe the frequency and duration of APT interruption
   - Identify what, if any, bridging strategies during interruption were used
   - Capture any and all invasive or surgical procedures that were deferred because of the need for continued APT
   - Define the rate of significant bleeding complications associated with APT

Clinical resistance to antiplatelet therapy (resistance to aspirin, clopidogrel, or both) may emerge as an important risk factor for stent thrombosis. Evaluation of responsiveness resistance to antiplatelet therapy may be a future recommended test. FDA is open to different approaches and trial designs to address these critical questions. Suggested approaches are discussed in the sections to follow.

D. Study Designs

Randomized controlled trials (RCTs) are the most appropriate trial design for a new DES, although for certain additional indications beyond initial approval (e.g., additional stent diameters, lengths or certain lesion types), other trial designs may be appropriate. Both superiority and noninferiority RCTs can be used to support the safety and effectiveness of a DES.

1. Superiority Study

For a DES, an RCT study design could compare a DES, as the investigational device, to a bare metal stent, as the control arm. However, the choice of control in a superiority design is not limited to a bare metal stent. A sponsor may choose to evaluate the superiority of an investigational DES to an *active* DES control (i.e., an FDA approved DES). The investigational DES should be shown to be superior to the preselected control by a margin agreed to be clinically significant by the clinical

community and FDA. In a bare metal control trial, it may also be useful to include a third arm, another DES; this enables assurance of comparability to other DESs.

2. Noninferiority Study

The noninferiority, or *equivalence*, approach to study design has been used increasingly in clinical trial settings where a placebo or previous standard of care as control is either unavailable or unacceptable for logistical or ethical reasons. In this design, patients are randomized to investigational DES or active DES control, as above, but the study hypothesis is noninferiority, not superiority.

A *noninferiority clinical trial* usually refers to a study designed to show that an investigational device is as effective, or almost as effective, as an approved device or a standard of care (active control), from which it is then inferred that the investigational device is effective. In fact, the study actually demonstrates that the investigational device is not inferior to the control by more than a prespecified noninferiority margin delta. The margin delta used would be the largest acceptable reduction in therapeutic response with the investigational device (i.e., the maximum tolerable treatment difference such that the new device would still be considered sufficiently effective). Before a noninferiority margin can be chosen, the treatment effect size for the active control device, compared to the previous standard of care (BSM, in the case of DES), should be established based on historical evidence of safety and effectiveness from controlled clinical trials. Subsequently, the noninferiority margin for a new trial can be chosen based on clinical judgment regarding the proportion of the initial effect size that should be maintained in the new comparison. It is also critical to consider whether there is reason to believe that past examples of safety and effectiveness would still be applicable to the current study (the *constancy assumption*). We recommend that sponsors discuss selection of an appropriate noninferiority margin with FDA as the clinical study is being designed.

To investigate whether the investigational device is noninferior to the control, the appropriate null hypothesis is that the control is better than the investigational device by at least the noninferiority margin. The alternative hypothesis is that the investigational device is not worse than the control by the noninferiority margin. These two hypotheses are the essence of how FDA views *noninferiority* trials.

Although the noninferiority trial design is a strategy that could be used when a placebo-controlled study cannot be conducted, there are some limitations to the noninferiority study design that should be considered prior to adopting this approach. When a noninferiority study includes as a control a DES that has not been directly compared to a BMS, the potential exists for a downward drift in the true difference in safety and effectiveness between the investigational DES and a BMS. After serial noninferiority studies, this so-called outcome drift could lead to a situation in which the investigational DES could be found noninferior to the latest *noninferior* DES, but no longer superior to a BMS, if such a direct comparison were made.

The quantification of delta should be clinically relevant and statistically feasible and should be established through cogent discussion and agreement between the sponsor and the Agency. The quantity needs to be sufficiently small so that, from a clinical point of view, the investigational

device can still be considered to be noninferior to the control as long as the advantage of the control over the investigational device is smaller than delta. Additionally, the delta should not be so large, that in a direct comparison with the previous standard of care (in this case, bare metal stents), the new treatment could be noninferior to the active control, but no longer superior to a bare metal stent (so-called *outcome drift*[45]). To investigate whether the investigational device is noninferior to the control, the appropriate null hypothesis is that the control is better than the investigational device by at least delta, against the alternative hypothesis that the investigational device is not worse than the control by delta. These two hypotheses are the essence of how FDA views *noninferiority* trials.

Although the non-inferiority trial design is a strategy that could be used when a placebo-controlled study cannot be conducted, there are some limitations to the noninferiority study design that should be considered prior to adopting this approach. For example, selection of an appropriate delta value, while ideally based on prior data and expectations of performance, should be determined by what is a clinically meaningful definition of a *delta*, agreed to by the clinical community and FDA. In addition, the trial design and analysis plan should take into consideration the potential for outcome drift.

3. Endpoints for DES Trials

Based on the definition of effectiveness (21 CFR 860.7), the most direct method of providing valid scientific evidence of effectiveness is to select an appropriate clinical outcome and design a study to evaluate a statistically significant and clinically meaningful treatment effect.

FDA recommends that definitions for outcomes of interest (death, MI, Target Lesion Revascularization (TLR), Target Vessel Revascularization (TVR), stent thrombosis) be standardized in the protocol. One potential set of definitions can be found in Cutlip et al.,[46] although alternate definitions may be proposed with a clinical justification.

a. Primary Endpoint – Clinical Endpoints

Historically, the conventional intracoronary device study endpoint has typically been a composite endpoint (e.g., target vessel failure (TVF), which is a composite of death, nonfatal myocardial infarction (MI), and target vessel revascularization (TVR) after an index stenting procedure). The paper by Cutlip et al. referenced above recommends the use of a patient-oriented composite including all death, MI, and TVR and a device-oriented composite including cardiac death, target vessel MI, and TLR. We recommend the use of the device-oriented composite as a primary clinical endpoint. Other endpoints may be appropriate for specific studies; a clinical justification should be provided for the endpoint selected.

Although a composite may not be the ideal primary endpoint, because the components have different weights, the use of such a composite allows for trials of reasonable sample size to be conducted. For example, a trial seeking to evaluate mortality would need tens of

[45] Outcome drift can occur when successive generations of inferior devices are found to be non-inferior to the previous generation as an active control, but might be inferior if tested against the original placebo treatment.

[46] Cutlip et al., on behalf of the Academic Research Consortium. Circulation 2007:115;2344-2351. Clinical endpoints in coronary stent trials: a case for standardized definitions.

thousands of patients to be enrolled to allow sufficiently powered hypothesis testing. Although trials will not be powered to enable assessment of the individual components, FDA will carefully consider the outcomes for each component of the composite when making our assessment of the risk-benefit profile for the new DES.

The initial DES approvals were based on a primary endpoint assessment at 9 months post-implant. FDA currently believes that a 12-month primary endpoint, with a substantial proportion of patients having 2-year data at the time of marketing application submission, is critical to assess the potential for important adverse events such as stent thrombosis (and related deaths and MIs) that may occur after 9 months. Patients in all trials to be used to support approval of a PMA application should be consented at the time of enrollment for follow-up to 5 years.

b. Primary Endpoint – Nonclinical Imaging Endpoints

Imaging-derived measures of restenosis, such as percent diameter stenosis and late lumen loss, are potentially powerful effectiveness endpoints. Such outcome measures have the advantage of providing quantitative data for the comparison of specific parameters of stent performance, such as suppression of neointimal hyperplasia. Furthermore, they can provide additional effectiveness data, even in patients who have not developed a major clinical adverse event, and consequently have the potential to increase the *sensitivity* of outcome measures between treatments. Imaging endpoints are commonly measured as continuous variables and this powerful discriminatory advantage can be apparent with sample sizes considerably smaller than typically needed for clinical endpoints. However, the use of these potential imaging measures as primary endpoints does not preclude the need for evidence of safety through evaluation of a clinical endpoint, such as death, MI, and/or TLR, either individually or as a composite.

FDA believes that use of an imaging endpoint as the sole primary effectiveness endpoint in pivotal DES trials is currently acceptable only for certain ***second-generation*** DESs, such as iterative modifications from currently approved DESs and/or indication expansion, in specific patient populations or in specific vessel or lesion types. For a novel DES, clinical studies performed to support regulatory approval should include at least one study of sufficient size that has as its primary endpoint a clinical endpoint and is appropriately powered for statistical demonstration of superiority or non-inferiority against an appropriate control. See Section VIII.D for more discussion of next-generation DESs.

It should be noted that there is a well-described impact of protocol-mandated angiography on clinical revascularization rates. For this reason, we recommend that angiography and IVUS be captured in a study separate from the pivotal trial or, if included in the pivotal trial, protocol-mandated angiography should be scheduled after the 12-month clinical visit.

c. Primary Endpoint – Use of Multiple Endpoints

An alternative strategy is the use of appropriate composite or co-primary clinical and imaging endpoints as outcome measures. For example, developing co-primary endpoints is

one potential method. If co-primary endpoints are proposed for the trial, the selection of the noninferiority margin for the clinical endpoint may be less conservative than when used as a stand-alone endpoint, reflecting the fact that additional information from another parameter (such as angiograph) is being evaluated. When using co-primary endpoints, FDA recommends that adequate adjustments for correlation between the endpoints and preservation of type I error be carefully considered. Study success using co-primary endpoints is typically defined as meeting both endpoints. Appropriate definitions for superiority and for selection of noinferiority margins should be discussed with the Agency when the use of multiple endpoints is contemplated.

d. Secondary Endpoints

Separate from the primary endpoint chosen for effectiveness, we recommend collecting additional vessel imaging information to evaluate healing and remodeling of the arterial wall, including parameters such as stent apposition, aneurysm formation, edge effects, and quantification of intimal proliferation, especially at the proximal and distal borders of an implanted DES. Quantitative coronary angiographic (QCA) analyses should report stent, lesion, and analysis segment parameters to assess the importance of any edge effects caused by the drug. The angiographic analysis should also include review and analysis for stent fracture; use of a grading system such as that described by Rocha-Singh et al.,[47] may be helpful for reporting the incidence and type of fracture, if observed. Side branch occlusion, when observed, should also be reported.

The secondary endpoints will, in most cases, not be descriptive and exploratory, not leading to additional claims. If a formal comparison of treatment arms for a secondary endpoint is desired, formal null and alternative hypotheses should be developed and pre-specified in the protocol. If no pre-specified hypotheses are included in the protocol, p-values for such comparisons will not be appropriate and should not be presented in labeling. If analyses beyond descriptive statistics are planned for secondary endpoints, appropriate steps should be taken to adjust for multiple comparisons and to preserve Type I error. Sponsors with studies ongoing prior to the issuance of this guidance should discuss with FDA an appropriate approach for presentation of such analyses in the labeling.

4. Considerations for DES incorporating an unstudied drug

When a DES incorporates an unstudied drug, the data from a sufficient number of patients exposed to the new DES should be collected for submission in the PMA. The number of patients should be large enough to enable the detection with adequate precision of low frequency adverse events (i.e., those occurring at a rate of 1 percent or less) that may be associated with the unstudied drug. A single study or multiple studies (both randomized trials and single-arm registry studies) can be used to complete this population.

[47] Rocha-Singh, et al, Performance goals and endpoint assessments for clinical trials of femoropopliteal bare nitinol stents in patients with symptomatic peripheral arterial disease. Catheter Cardiovasc Interv 2007;69(6):910-919

Also, certain additional safety data beyond what are typically collected in a stent trial should be obtained and provided in the PMA to allow for analysis of potential drug-related adverse events. The specific safety data to be collected will generally be specific to the drug incorporated on the stent; however, the following are examples of typically requested information:

- Liver enzyme values pre- and post-procedure and at appropriate follow-up intervals
- Hypersensitivity reactions (definition should be pre-specified) including symptoms, signs, and relevant laboratory values, treatment, and clinical course
- White blood cell counts to document the incidence of leukopenia
- EKG parameters
- EKG changes, particularly QT intervals
- Concomitant medications

Sponsors with such DES are encouraged to meet with FDA prior to beginning clinical trials to ensure that case report forms capture appropriate cardiac and non-cardiac safety information.

5. Blinding Concerns in DES Clinical Studies

In a randomized controlled trial, the use of study blinding, or masking, further reinforces the integrity of the random allocation of patient assignment and assessment of treatment effect. In a superiority RCT study design using a DES and its corresponding bare metal stent, a triple-blinded (i.e., patient, physician and monitoring committee are all blinded) study design is logistically possible because of the physically similar appearance of the DES and bare metal stents. However, for some medical devices, designing a double-blinded (i.e., patient and physician are blinded to treatment assignment) or triple-blinded RCT can be impractical and logistically impossible because of the physical characteristics and/or the mode of action of the product (e.g., a DES versus coronary artery bypass grafting (CABG)). For noninferiority study designs that are evaluating a DES with different platforms, the DES might have different physical characteristics (e.g., radiologically and/or visually different in appearance), making such study blinding logistically difficult to implement. Because certain individuals involved in stent handling/implantation at the time of the index procedure will have knowledge of treatment assignment.

Nonetheless, because there is a potential for considerable investigator and/or patient bias introduced by knowledge of treatment assignment, possibly confounding study outcomes and diminishing the scientific validity of the study, the study design should incorporate blinding to the maximum extent possible, maintaining the blind for patients (single-blind), follow-up study investigators, and study staff to minimize the potential for bias and confounding. In addition, increasing the objectivity of study parameters as much as possible and including special analytical methods to evaluate for the potential influence of bias in study outcome are potential ways to maximize the scientific validity of study design.

6. Independent Oversight of Drug-Eluting Stent Trials

Many of the novel technologies employed in a DES have never been used previously in the same combinations or anatomic locations in human beings. This fact raises new questions of safety for participants in investigational DES trials. Given that most DESs under development are intended to be permanent implants and that safe and reliable retrieval of deployed stents is generally not possible, a heightened and constant vigilance during the conduct of a DES trial is necessary. With this in mind, FDA strongly recommends the use of data monitoring committees (DMC, also called data safety monitoring boards, or DSMBs) for DES studies to keep track of and evaluate significant adverse events, including stent thrombosis, in real time (i.e., as the study enrollment progresses).[48] Sponsors are responsible for ensuring proper monitoring of the investigations (21 CFR 812.40), and must select monitors qualified by training and experience to monitor the investigational study (21 CFR 812.43(d)). Before the study begins, the DMC/DSMB charter should have an adequate monitoring plan (e.g., number of predetermined meetings, timing of reports, appropriate stopping rules, correspondence to FDA as appropriate) in place to adequately ensure that patients are not subjected to undue risk. For sponsors conducting multiple trials with the same investigational DES, FDA recommends that sponsors as part of their obligation to monitor the studies, use the same DMC/DSMB for both studies or have a *super-DMC/DSMB* that communicates with the DMC for each trial be considered. If this is not possible, the sponsor should ensure that the DMCs/DSMBs for each of the studies communicate frequently and regularly exchange safety information and ensure that all members of the committee are apprised of the global safety data for the investigational DES.

FDA strongly recommends that interpretation of data from tests such as angiograms, IVUS, and ECGs be performed by independent core labs and that blinded adjudication of clinical events be conducted by a clinical events committee (CEC Clinical adjudication committees should be independent of core lab analysis centers to avoid potential bias. .

E. Statistical Analysis Plan

The proposed protocol should include a comprehensive statistical analysis plan with prospectively defined methods to address the following:

- Study hypotheses
- Sample size calculation
- Blinding
- Number of proposed study centers
- Study success criteria
- Effectiveness patient populations (e.g., intent-to-treat, evaluable)
- Pooling of data
- Covariate adjustments

[48] Guidance for clinical trial sponsors on *Establishment and Operation of Clinical Trial Data Monitoring Committees*, March 2006.

- Stratification
- Protocol deviations
- Handling drop-outs and methods to address missing data
- Analysis plan and statistical methods
- Data auditing

1. Analysis Cohorts

The *intention-to-treat* population, which is defined as the cohort of all patients randomly assigned to treatment in an RCT design, is usually the preferred population for superiority studies. Intention-to-treat analysis allows for the evaluation of all patients who enroll in the study, even though some may not complete the study (e.g., patients who are, for any reason, lost to follow-up, drop-outs, or terminated by investigator). In an RCT design, the intention-to-treat principle means that any comparison of the treatments is based on comparison of the outcome results of all patients in the treatment groups to which they were randomly assigned. Within the protocol, the sponsor should prospectively specify the analysis plans that will account for patients who do not complete the study. The sponsor should also present analysis of the per protocol patient cohort (i.e., patients who enter and complete the study according to protocol) and the as-treated patient cohort (recognizing such analyses are subject to bias).

Comparison of outcomes on the basis of intention-to-treat, per protocol, and as-treated patients allows assessment of outcome robustness. Analysis details should be prospectively agreed to by the sponsor and FDA.

2. Poolability Considerations for DES Studies

Pivotal studies of DES should be conducted at multiple investigational sites. Additionally, there can be advantages to conducting multiple clinical studies of the same DES. Potential advantages to combining data from different studies include having the ability to evaluate DES performance across a broader population than can be achieved by one study and could increase generalizability of study results because of wider demographic and geographic inclusion. Furthermore, demonstration of comparable DES performance across different investigational sites and studies can permit more robust conclusion of product safety and efficacy. However, when planning to conduct clinical studies at multiple investigational centers, or in centers OUS (outside the United States), an analysis of poolability of data should be included in the prospective analysis plan.

When FDA considers foreign data as supportive evidence for U.S. product approval, a key consideration in assessing the applicability of OUS studies in support of product safety and effectiveness is to evaluate the generalizability of the OUS studies to the patient population and to medical practice in the United States. Factors that FDA considers include, for example,

- Patient demographic and clinical characteristics
- Geographic differences in medical practice
- Differences in study protocol

These factors have the potential to affect DES performance in terms of both safety and effectiveness. Some examples of key factors that should be addressed when considering the poolability of results and extrapolating study results to those expected in the United States can be found in the stand alone companion document.[49]

Whether studies have been conducted solely in the United States or both in or out of the United States, statistical analysis should examine the homogeneity of demographic and procedural covariates across centers and geographical regions. Evaluation of interactions between treatment and region is recommended. Furthermore, outcome comparability should be examined after adjustment for covariate differences, using multivariate regression modeling and propensity scoring methodology. In addition, sensitivity analysis should be performed to verify the robustness of any statistical modeling using pooled data.

FDA is willing to comment informally on OUS study protocols through the pre-submission process. Such comments may increase the likelihood that these data can be used to support a PMA application.

F. Adjunctive Pharmaceutical Regimens

Optimal duration of antiplatelet therapy and use of glycoprotein IIb/IIIa inhibitors and direct thrombin inhibitor treatments in DES patients are currently unclear and may significantly affect clinical outcomes. Consequently, to minimize confounding variables in the interpretation of the study results, a uniform regimen of intra- and postprocedure concomitant medications should be used. Careful consideration should be given to the optimal dosage and duration of antiplatelet therapy for DES postimplantation, given the delay in endothelialization within DES compared to that of bare metal stents and subsequent concerns regarding stent thrombosis due to premature discontinuation of antiplatelet therapy.

At the December 2006 Circulatory System Devices Advisory Panel meeting on DES thrombosis , the Panel recommended that the labeling for the two approved DES include reference to the AHA/ACC/SCAI practice guidelines. FDA agreed with this recommendation and both approved DES Instructions for Use include this information. For this reason, for trials that use the CYPHER stent or TAXUS stent as the control DES, we currently recommend that the prescribed antiplatelet therapy follow the AHA/ACC/SCAI guidelines[50]; that is, patients should receive aspirin and a minimum of 3 (CYPHER) or 6 months (TAXUS) of clopidogrel with therapy extended to 12 months in patients at a low risk of bleeding. Despite the desire to have administration and use of dual antiplatelet therapy, circumstances will cause some patients to have different regimens, and FDA is particularly interested in how differences in duration affect patient outcome. Therefore, patients should be carefully monitored and case report forms should be designed to capture compliance with prescribed antiplatelet therapy and significant bleeding complications over the course of the trial.

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[49] See draft guidance for industry and FDA staff on *Coronary Drug-eluting Stents – Nonclinical and Clinical Studies: Companion Document*," published together with this document.

[50] Available at http://www.acc.org/qualityandscience/clinical/guidelines/percutaneous/update/index.pdf

Eventual product labeling should include both the prescribed antiplatelet therapy and patient compliance with that therapy as experienced in the clinical trials and should clearly specify the risks of premature antiplatelet medication discontinuation.

G. Follow-Up from Clinical Studies

Although nonclinical and clinical testing of DESs provide invaluable information on the short-term safety and effectiveness of these products in a select patient population, such as that typically found in the clinical trial setting, much information on the performance and safety profile of a DES can be obtained only when the product moves into the larger, more diverse patient population after marketing.

For purposes of regulatory approval, the current primary endpoint data for DES studies should be collected over a period of approximately 12 months after implantation of the DES. However, DES study length should be viewed in terms of the entire follow-up, which should extend through a 5-year clinical follow-up period. Although the 12-month postimplantation endpoint might be acceptable for a PMA submission, the study is not considered complete until study patients have completed their long-term clinical follow-up as described in the protocol. At a minimum, this would include annual follow-up telephone evaluations and, preferably, annual study visits, for five years in a significant cohort of patients enrolled in the pivotal, feasibility, and/or any additional clinical studies conducted to support product approval. During the long-term follow-up phase, the occurrence and sequelae of late phenomena, such as incomplete stent apposition, late stent thrombosis, and polymer compatibility issues, are important parameters that should be evaluated. The actual duration of dual antiplatelet therapy and any interruptions should be captured as well (see Section C above for objectives related to antiplatelet therapy).

At the time of PMA submission, all available long-term follow-up from the pivotal and supplementary clinical studies should be provided to demonstrate the ***chronic*** performance of the DES. Additionally, as part of the PMA review, the applicant is also required to submit a bibliography of all published reports and other information relevant to an evaluation of the safety and effectiveness of the device (see 21 CFR 814.20(b)(8)).

During the PMA review, a three-month update of any additional clinical data must be submitted (21 CFR 814.20(e)). The applicant must submit new information learned about the device from ongoing or completed studies that may reasonably impact an evaluation of the safety and effectiveness of the product or that may reasonably affect the draft labeling. Note that when reasonably limited in scope, this update would be considered a minor amendment to the PMA. Additional (i.e., later) endpoint evaluations, a significant increase in the number of evaluable patients, or new analyses may be considered a major amendment requiring significant review. In addition, as a condition of approval for a PMA application, applicants are required to submit updated clinical reports to the Agency (§ 814.82 and 814.84)

To minimize patient losses-to-follow-up, sponsors should request patient consent to five-year follow-up at the time of enrollment in clinical studies. Additionally, the case report forms should include the specific questions the sponsor or representative will ask the patient during telephone

follow-up to ensure that appropriate information is being collected and to minimize bias since treatment assignment may be known upon disclosure of the primary endpoint results.

VIII. POSTAPPROVAL CONSIDERATIONS

A. Postapproval Studies

Postapproval surveillance provides a framework for assessing unanticipated risks secondary to human factors, product manufacturing changes, or rare occurrences in real-world patient populations.

Therefore, in addition to postapproval follow-up of clinical outcomes from the patients enrolled in the preapproval clinical trials, the Agency will generally require the collection of additional postapproval data for a DES (§ 814.82(a)(2)). Serious but rare DES-related adverse events that might only be identified in a postapproval period include late stent thrombosis, drug interactions, unforeseen complications of multivessel or overlapping stent placement, and experience with a DES in different patient demographic subsets not adequately represented in preapproval studies (i.e., *real world* use). A proposed postapproval study protocol should be included in the PMA application.

The postapproval study should have two primary goals: assessment of the rate of stent thrombosis and assessment of the rate of cardiac death plus MI. As discussed above, the postapproval data collected on currently approved DESs have signaled a potential increase in late stent thrombosis after one year compared to bare metal stents. However, it is not known if this rate plateaus or continues to increase over time, nor is the impact of stent thrombosis on rates of cardiac death and MI completely understood. Therefore, one primary endpoint of the postapproval study should be the rate of stent thrombosis after one year. As stent thrombosis is closely associated with cardiac death and MI, a second primary endpoint of the postapproval study should be a comparison of the rate of cardiac death and MI between the new DES and the control stent used in the pivotal study. To gain a better understanding of these risks in the setting of actual clinical use of the product, FDA recommends that postapproval data be collected on a series of patients who are consecutively enrolled to avoid the introduction of selection bias.

A sufficient number of patients should be enrolled to confirm that the upper bound of the one-sided 95 percent confidence interval around the observed rate of stent thrombosis between 12 and 24 months, 24 and 36 months, 36 and 48 months, etc. is ≤ 1 percent with at least 80% probability for patients treated in accordance with the labeled indication. The total study sample size should be sufficient to ensure a sufficient number of patients treated in accordance with the labeled indication are available for analysis.

To evaluate the rate of cardiac death and MI, we suggest that the cohort of patients treated in accordance with the labeled indications be pooled with the preapproval pivotal trial to reach a sample size sufficiently large to provide adequate power to compare the rates of cardiac death and target vessel MI for the new DES and the control stent used in the pivotal study and to rule out an increased risk. This cohort of postapproval patients may be in a single-arm or randomized study, and data pooling may be approached from either a frequentist or Bayesian perspective.

Additionally, postapproval studies to date have demonstrated that routine clinical use of DESs typically includes the treatment of patients outside of the labeling indications, including higher risk patient and lesion subsets. Based on this previous experience, FDA recognizes that a postapproval study of consecutively enrolled patients is likely to include patients representing a broader use of the product and recommends that data from such patients be analyzed separately to better understand whether significant safety issues exist in the treatment of these patients.

All patients should be consented for five years of follow-up. If stent thrombosis rates are demonstrated to plateau or decrease in prior years, shorter follow-up may be sufficient. Alternatively, if stent thrombosis rates continue to increase, longer term follow-up or specific labeling changes may be appropriate.

A postapproval study protocol should include the following elements:

- Study hypothesis(es) - Primary and secondary endpoints
- Study design with inclusion and exclusion criteria
- Definitions for outcomes of interest
- Sample size calculation
- Statistical analysis plan
- Informed consent document
- DMC/DSMB information
- Case report forms
- Types of participating centers (e.g., teaching vs. non-teaching, location, size, primary vs. referral center and so on)
- Data monitoring procedures, including whether a CEC will be used
- Detailed study timeline, including enrollment goals (for sites, physicians and study subjects) and a plan in case enrollment goals are not met.
- Interim and final report schedule

The statistical plan should include planned descriptive statistics on certain subgroups of interest including:

Demographics

- Age (age < 65 years; age ≥ 65 years)
- Sex (male, female)
- Race and ethnicity

Patient characteristics

- Patients with diabetes, further characterized as insulin-requiring or noninsulin-requiring
- Patients with renal insufficiency, further characterized as creatinine clearance (rCl) using the Cockcroft-Gault equation (CrCl > 60 mL/min, CrCl ≥ 30 and ≤ 60 mL/min, CrCl < 30 mL/min)
- Degrees of left ventricular (LV) dysfunction (ejection fraction < 30%, 30-40%, > 40%)
- Patients with 3 vessel disease

- Patients with 2 vessel disease including proximal left anterior descending coronary artery disease

Lesion characteristics

- Lesions in the setting of acute ST elevation myocardial infarction (STEMI)
- Percutaneous coronary interventions within 36 hours of non-STEMI ACS
- Lesion length (≤ 20 mm, 21-30 mm, 31-40 mm, > 40 mm)
- Vessel diameter (2.0 - ≤ 2.5 mm; 2.6 – 2.9 mm; 3.0 - ≤ 3.5 mm, and > 3.5 mm)
- Ostial lesions
- Bifurcation lesions
- Trifurcation lesions (i.e., left main coronary artery, left circumflex coronary artery, left anterior descending artery, and ramus intermedius)
- Thrombus-containing lesions
- Lesions with residual dissection post stenting
- Left main coronary artery (LMCA) lesions
  - Include whether disease was ostial, mid, or terminal and whether or not it involved the ostial LAD +/- LCFX
- Chronic total occlusions (CTO)
- Saphenous vein grafts (SVGs)
- Arterial grafts (internal mammary artery, radial artery, gastroepiploic artery)
- Post-brachytherapy
- Instent restenosis (ISR) (BMS)
- Instent restenosis (ISR) (DES)
- Overlapping BMS
- Overlapping DES
- Overlapping BMS and DES
- Non-overlapped multiple stents (in the same vessel or in different vessels)
- Intravascular ultrasound guidance for initial stent deployment

Case report forms should capture patient compliance with prescribed antiplatelet therapy and significant bleeding complications.

For patients who experience stent thrombosis, in addition to the above characteristics, the following additional information should be reported:

- BMS or DES (name of stent, length, and diameter)
- Postdilatation (balloon diameter and lengths used as well as the postdilatation atmospheres achieved)
- Clarification of antithrombotic regimen received prior to initial stenting, including doses (aspirin, Plavix), including clarification of whether or not patient received a loading dose of Plavix and what the actual dose was.
- Antithrombotic regimen the patient was on at discharge (ASA, Plavix)
- Patient compliance with antiplatelet therapy and significant bleeding complications

- Any discontinuation of Plavix and/or aspirin and whether or not there was premature discontinuation of these medications

Effective postapproval identification of product risks relies on active collaboration of manufacturers, regulatory bodies, and healthcare facilities to detect and report product-related injuries and other adverse events. Although data collected as part of postapproval studies can and should be submitted to the FDA in postapproval reports to the PMA, sponsors should note that, to support an expansion in indications, they should conduct the study under an approved IDE. FDA is willing to consider the implementation of nested studies, with protocols approved under an IDE, within postapproval studies to support certain additional indications, such as long lesions and patients with two-vessel coronary artery disease. A prospective, hypothesis-driven analysis plan should be provided for FDA review in an IDE application or IDE supplement prior to initiation of the overall postapproval study. Alternatively, sponsors may choose to pursue additional indications in separate studies under an IDE to evaluate these uses in the intended patient population.

Sponsors should contact the CDRH review division for more information on the use of these studies to support additional indications. For more information on postapproval studies, see the CDRH guidance for industry and FDA staff on *Procedures for Handling Post-Approval Studies Imposed by PMA Order*.

B. Adverse Event Reporting

Because a DES is regulated under the device provisions of the Act, the adverse event and device defect reporting requirements for devices are applicable.[51] The medical device reporting (MDR) requirements mandate that manufacturers report to the Agency (1) all device-related deaths and serious injuries and (2) all malfunctions of the device or similar device that would be likely to cause or contribute to a death or serious injury if the malfunction were to recur (21 CFR 803.3).

Serious injury/(*Serious illness*) (§803.3(aa)(1)) is an injury or illness that:

- Is life threatening, even if temporary in nature
- Results in permanent impairment of a body function or permanent damage to a body structure

or

[51] Each constituent part of a combination product is governed by a different set of postmarket reporting requirements (for drugs, 21 CFR Parts 310 and 314, and for devices 21 CFR Part 803). This is the case for a DES product. The Agency has announced its intention to issue a Proposed Rule, Postmarket Safety Reporting for Combination Products that would clarify the postmarketing safety reporting requirements for combination products (72 Fed. Reg. No. 82, 22515 (2007). The proposed rule would provide a framework for the reporting of adverse events for combination products and specify the circumstances in which following one set of postmarket safety reporting regulations (e.g., 21 CFR 803) generally would meet the requirements of another set and the circumstances in which these requirements would be supplemented with specific reporting provisions applicable to the constituent part of the combination product.

- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

A *malfunction* (§803.3(m)) means the failure of the device to meet its performance specifications or otherwise perform as intended.

Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed, as defined in 21 CFR 801.4.

An *MDR reportable event* (§ 803.3) means:

(1) An event that user facilities become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury

or

(2) An event that manufacturers or importers become aware of that reasonably suggests that one of their marketed devices:

(i) May have caused or contributed to a death or serious injury

or

(ii) Has malfunctioned and that the device or a similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Furthermore, as explained in the Preamble to the FR Notice of December 11, 1995, Vol. 60, No. 237, relating to 21 CFR Part 803 – in Comment 12:

A malfunction is reportable if any one of the following is true:

- The chance of a death or serious injury occurring as a result of a recurrence of the malfunction is **not** remote.
- The consequences of the malfunction affect the device in a catastrophic manner that may lead to a death or serious injury.
- A malfunction results in the failure of a device to perform its essential function and compromises the device's therapeutic, monitoring, or diagnostic effectiveness, which could cause or contribute to a death or serious injury, or other significant adverse device experiences required by regulation (the essential function of a device refers, not only to the device's labeled use, but for any use widely prescribed within the practice of medicine).
- The malfunction involves a long-term implant or a device that is considered to be life-supporting or life-sustaining and thus is essential to maintaining human life.

or

- The manufacturer takes or would be required to take action under section 518 or 519(f) of the Act as a result of the malfunction of the device or other similar devices.

For more information see the Medical Device Reporting (MDR) Web site at: http://www.fda.gov/cdrh/mdr/, and you may direct questions regarding MDRs to the Reporting Systems Monitoring Branch at 240-276-3464.

Instructions for completing MedWatch Form 3500A are available at http://www.fda.gov/medwatch/report/instruc_10-13-06.htm. MedWatch Form 3500A is available at http://www.fda.gov/medwatch/safety/3500a.pdf.

Adverse events reported through MDR are shared with CDER so that drug-related aspects of postapproval adverse events reported to CDRH can be evaluated.

C. Peri-Approval Studies

FDA has typically required postapproval studies for DESs. However, when the postapproval study protocol was approved only at the time of the PMA approval, FDA found that there were significant delays in beginning enrollment in the study due to delays in awaiting IRB review and approval. There was also confusion on the part of some IRBs regarding the rationale for an additional study of an approved product. The delays in enrollment and data collection in this scenario meant that an important source of postmarket data was unavailable to the manufacturer and to FDA for multiple months following PMA approval.

To minimize this delay, FDA has encouraged PMA applicants to submit the postapproval study protocol earlier in the PMA review process. If FDA has reached the conclusion that the PMA will be approved (e.g., only minor issues such as labeling are pending), the postapproval study protocol can be approved *in advance* of the PMA approval. A protocol for such a *peri-approval study* can be submitted as an IDE supplement. Upon IDE approval, the study can begin enrolling under the IDE with a prespecified patient limit, with the remainder of patients enrolled after PMA application approval. Consequently, the peri-approval study does not obviate the need for the collection of information after the initiation of marketing. The IDE approval does, however, enable a sponsor to ensure that IRB review/approvals are in place and selected sites are eligible for active enrollment of patients at the time of PMA application approval.

FDA strongly encourages sponsors to select a broad cross-sectional distribution of institutions (e.g., geographic location, private versus public versus academic hospitals, volume of procedures) to address generalizability of the study findings. The main impetus for the peri-approval approach has been to facilitate the enrollment of patients and streamline completion of the study so that both the FDA and the applicant can assess patient safety in a real-world scenario in a timely manner to support the total product life cycle of the DES.

D. Next Generation DES

DES candidates may employ a range of new and old technologies, making classification of a next-generation DES dependent on the specific components and/or modifications to the product. Unlike second-generation bare metal stents, in which modifications in a product line were limited to either the stent substrate (e.g., geometry, such as strut thickness, cell configuration, material), or delivery catheter, for DES, manufacturers should carefully consider that planned modifications to the stent substrate or polymer carrier may have unintended or unanticipated effects on other product performance parameters (e.g., changes in drug density, total drug load, elution kinetics) and on the overall safety and effectiveness of the finished product. Additionally, if a sponsor wants to make a manufacturing change in the coating process, depending on the change, it may be necessary to perform additional studies to ensure safety and/or effectiveness for the modified product if the rate and/or extent of drug elution is materially affected.

Some examples of questions for the sponsor or applicant to address regarding design modifications to a DES that may affect rate and/or extent of drug elution include, but are not limited to, the following:

- Is this a first generation DES, a combination of new and old technologies, or essentially a design iteration?

If the answer to "is this a first generation DES?" is no, some additional questions to address include:

- Which components of the DES system have stayed the same and/or which have been changed? Be sure to consider both intentional and unintentional changes that may have occurred.
- If the stent substrate has changed, what specifically has been altered (e.g., stent substrate material only (from 316L to CoCr); geometry elements, such as strut thickness, which can lead to differences in surface area; and/or a change in the drug density and/or drug content)?
- Has the delivery catheter been modified (e.g., distal tip or other elements)?
- Is the drug formulation the same or different (e.g., change in polymer/drug ratio, increased or decreased drug content)?
- Have any of these modifications resulted in alterations to the release kinetics (e.g., amount or significant modifications in profile)?
- Have there been any modifications in any critical manufacturing parameters (e.g., coating application, new sources of heat or humidity, sterilization method)?
- Does the new product still meet the original product specifications?
- How robust are the in vitro test methods and quality control specifications used to assess product variability to ensure product quality and consistency?

The significance of the changes in a DES system for a *second generation* DES will directly influence the amount of additional nonclinical and/or clinical testing needed to support the safety and efficacy

of a modified DES. FDA encourages sponsors and applicants to discuss with the Agency proposed changes to their DES and appropriate testing to validate those changes.

IX. COMPANION DOCUMENT

To facilitate the use of this guidance, a stand alone companion document is available to be used together with this guidance. It is posted with this guidance on the FDA Web site. The companion document contains the following:

- Suggested elements for an IDE application
- Suggested elements for a PMA application
- Example master table
- Example 1-pager describing DES clinical studies
- Example commitment table
- General biocompatibility considerations
- Example test article certification
- General guidelines regarding good animal husbandry
- Factors affecting poolability of US and OUS studies
- Guidance on labeling for a DES

APPENDIX A

Below is an example of a regulatory specification table for the finished DES product.

Tests	Acceptance Criteria[1]	Analytical Procedure
Appearance	Conforms to visual/microscopic description	Visual/Microscopic
Identification Tests	Retention time of the major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation obtained as specified in the assay in combination with UV	HPLC with diode array detection
Assay (Drug content)	90% - 110% of label claim	HPLC
Content Uniformity	USP <905>	HPLC
Degradation Products/Impurities Degradant A Impurity B Degradant at RRT[2] 0.8 Any individual unspecified impurity Total impurities	 NMT 0.5% NMT 0.6% NMT 0.3% NMT Q3B identification threshold NMT 1.2%	HPLC
Residual Solvent A	NMT 200 ppm	GC
Particulate Matter[3]	Release : NMT 2500 particles ≥ 10 µm NMT 200 particles ≥ 25 µm Shelf Life : NMT 3500 particles ≥ 10 µm NMT 300 particles ≥ 25 µm	Light obscuration as per USP <788>
Endotoxins	NMT 0.5 EU/mL	LAL (USP <85>)
Sterility or package integrity	Pass	USP <71>
Drug Release	10% - 20% 2 hours 20% - 50% 4 hours 40% - 70% 8 hours > 80% 24 hours	USP <724>

[1]In the table above, all numerical limits and the time points in the drug release test are for illustrative purposes only.
[2]Relative retention time
[3]Example of an attribute for which tighter release limits are assigned in order to maintain a safety margin so that the product remains within the approved shelf life acceptance criteria for that attribute.

Below are examples of stability testing protocols.

Long Term (25°C/60%RH) Stability Testing Protocol

		Time Points (months)				
Tests	Acceptance Criteria*	0	3	6	9	12
Appearance		X	X	X	X	X
Assay (drug content)		X	X	X	X	X
Impurities Individual Total		 X X	 X X	 X X	 X X	 X X
Drug Release		X	X	X	X	X
Particulate matter**		X	X	X	X	X
Endotoxins		X				X
Sterility		X				X

*Same as regulatory specifications

X indicates testing is performed at this time point.

** FDA recommends testing for particulate matter at every time point, but if testing is conducted less frequently, the expiration date will be limited by the latest time point at which particulate matter testing was conducted with passing results.

Accelerated (40°C/75%RH) Stability Testing Protocol

		Time Points (months)			
Tests	Acceptance Criteria*	0	1	3	6
Appearance		X	X	X	X
Identity		X	X	X	X
Assay (drug content)		X	X	X	X
Impurities Individual Total		 X X	 X X	 X X	 X X
Drug Release		X	X	X	X
Particulate matter		X	X	X	X

*Same as regulatory specifications

X indicates testing is performed at this time point.

GLOSSARY OF TERMS

Acceptance criteria: Numerical limits, ranges, or other suitable measures for acceptance of results of analytical procedures (see ICH guidance Q6A)

Acute: Refers to any time up through expansion and deployment of the DES

Chronic refers to any time after assessment of the initial stent deployment in a simulated vessel throughout the lifetime of the implant.

Adhesion: The degree of attachment between two different surfaces, such as a coating or film and the underlying material.

Area under curve (AUC): PK parameter, area under the blood concentration-time curve

(AOAC): Association of Official Analytical Chemists

Balloon expandable stent: A stent that is expanded by a balloon. The diameter of the stent increases as the balloon diameter increases. The stent remains expanded after deflation of the balloon.

Bare metal stent (BMS): An intravascular stent that is not coated with either a polymer or drug. Traditional materials for BMSs include 316L stainless steel and cobalt chromium alloy.

Batch: A specific quantity of a drug or other material that is intended to have uniform character and quality, within specified acceptance criteria, and is produced according to a single manufacturing order during the same cycle of manufacture (21 CFR 210.3(b)(2)). See also "lot."

Bias (statistical and operational): The systematic tendency of any factors associated with the design, conduct, analysis, and evaluation of the results of a clinical trial to make the estimate of a treatment effect deviate from its true value. Bias introduced through deviations in conduct is referred to as *operational bias*. The other sources of bias listed above are referred to as *statistical bias*.[52]

Clinical batch: Batch used to support the efficacy, safety, bioavailability, or bioequivalence of a product

Cmax: PK parameter, maximum observed blood concentration

Coating: The drug carrier (usually polymeric, but not limited to such), the drug itself if it is solely coated onto the stent platform, any other coating, or the drug carrier even if it is incorporated onto the stent in a geometry other than a coating.

Cohesion: The sticking of a surface to itself

Combination product: A product (defined in further detail in 21 CFR 3.2(e)) comprised of two or more different types of regulated entities (i.e., drug-device, drug-biologic, device-biologic, or drug-device-biologic products).

Component: For a drug: Any ingredient intended for use in the manufacture of a product, including those that may not appear in such product (21 CFR 210.3(b)(3)).

Component: For a device: any raw material, substance, piece, part, software, firmware, labeling, or assembly which is intended to be included as part of the finished, packaged, and labeled device (21 CFR 820.3(c)).

Chronic: See Acute.

Degradation product: A molecule resulting from a chemical change in a drug or polymer molecule brought about over time and/or by the action of light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure or packaging system. Also called decomposition product (see ICH guidance Q6A).

Device history record: (DHR) a compilation of records containing the production history of a finished device (21 CFR 820.3(i))

Double-blinded: A double-blind trial is one in which neither the subject nor any of the investigators or sponsor staff involved in the treatment or clinical evaluation of the subjects are aware of the treatment received. This includes anyone determining subject eligibility, evaluating endpoints, or assessing compliance with the protocol; blinding is maintained throughout the conduct of the trial.[53]

Blinding, or masking, is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence that the knowledge of treatment may have on the recruitment and allocation of subjects, their subsequent care, the attitudes of subjects to the treatments, the assessment of end-points, the handling of withdrawals, the exclusion of data from analysis, and so on.[54]

Drug-eluting stent (DES): A combination product consisting of both drug and device components. The device component consists of an intravascular stent platform that is used not only for radial support, but also as a vehicle for the delivery of an active pharmaceutical agent or drug. The drug component is commonly incorporated and released from a polymeric carrier, either a single polymer or a combination of polymers, which is physically or chemically adherent to the stent substrate. The purpose of the polymer carrier is to allow for adequate deposition of the drug onto the stent surface as well as to influence the release kinetics of the drug from the

[53] ICH Guidance E9 *Statistical Principles for Clinical Trials*
[54] ICH Guidance E9 *Statistical Principles for Clinical Trials*

stent surface. The DES is mounted onto a stent delivery system to deliver the stent to its final intended location in the vasculature.

Drug product: A finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients (21 CFR 314.3(b)).

Drug substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient (21 CFR 314.3(b)).

EP: European Pharmacopeia

Established name: The designated FDA official name, the compendial name, the USAN Council name, or the common or usual name (section 502(e)(3) of the Act and 21 CFR 299.4). Ordinarily, the established name of a drug will be the compendial name. However, FDA may designate an established name in cases where a monograph does not exist (see the CDER Data Standards Manual).

Excipient: Any component other than the drug substance(s) present in the finished product.

Extended release: Products that are formulated to make the drug available over an extended period after implantation.

Formulation: The qualitative and quantitative composition of the finished product. This is often called the composition statement.

Four corners: Refers to a 2 x 2 factorial of the largest and smallest diameters and lengths for *each* stent design.

Functional excipient: An excipient that performs a role in maintaining product quality or in achieving a desired in vivo performance.

Generalizability, generalization: The extent to which the findings of a clinical trial can be reliably extrapolated from the subjects who participated in the trial to a broader patient population and a broader range of clinical settings. [55]

Glass transition temperature (Tg): The temperature at which a polymer changes from glassy to elastomeric behavior.

Independent data monitoring committee (IDMC) (data and safety monitoring board, monitoring committee, data monitoring committee): An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical

[55] ICH Guidance E9 *Statistical Principles for Clinical Trials*

trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial. [56]

In-process material: Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of a finished product.

Intention-to-treat principle: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (i.e., the planned treatment regimen) rather than the actual treatment given (e.g., results from a patient who discontinues a treatment are counted in the treatment group). It has the consequence that subjects allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance with the planned course of treatment.[57]

Intravascular stent: For this guidance, an intravascular stent is a synthetic tubular structure intended for ***permanent*** implantation in the native coronary vasculature. The stent is designed to provide mechanical radial support after deployment; this support is meant to enhance vessel patency over the life of the stent. Once the stent reaches the intended location, it is expanded by a balloon or self-expanding mechanism.

JP: Japanese Pharmacopeia

Letter of authorization (LOA): A written statement by the holder or designated agent or representative (sponsor or applicant) permitting FDA the authority to access information included within one regulatory submission (e.g., IDE, PMA, MAF or DMF) to support a separate regulatory submission (e.g., IDE or PMA).

Lot: *Or batch* means one or more components or finished devices that consist of a single type, model, class, size, composition, or software version that are manufactured under essentially the same conditions and that are intended to have uniform characteristics and quality within specified limits (21 CFR 820.3(m)). (Note that a similar definition is provided within the CGMP regulations: A batch, or a specific identified portion of a batch, having uniform character and quality within specified acceptance criteria. In the case of a product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that ensures its having uniform character and quality within specified acceptance criteria (21 CFR 210.3(b)(10)).)

Master file: A reference source submitted to FDA, which may include drug master files (DMF), device master files (MAF), etc. A master file may contain detailed information on a specific manufacturing facility, process, methodology, or component used in the manufacture, processing, or packaging of a drug (21 CFR 314.420) or a medical device (21 CFR 814).

[56] ICH Guidance E9 *Statistical Principles for Clinical Trials*

[57] ICH Guidance E9 *Statistical Principles for Clinical Trials*

Master production record: A record containing the method of manufacture of the product, including, in part, the master formula of defined size, complete manufacturing and control instructions, in-process tests and acceptance criteria, equipment and operating parameters, yield and yield reconciliation calculations, and provisions for packaging and labeling (see 21 CFR 211.186(b)) See also "Device history record."

Molecular weight (MW) (of a polymer): Weight of an average polymer molecule. The two most popular expressions of molecular weight of polymers are *number-average molecular weight* (Mn) and *weight-average molecular weight* (Mw). Mn is the total weight of all the polymer molecules in a sample, divided by the total number of polymer molecules in a sample. This number represents the average weight of a chain, *Mi*, weighted according to number fraction of each component i. Mw is the average molecular weight of a chain, Mi, weighted according to weight fractions of each component i.

No Observed Adverse Effect Level (NOAEL*NOAEL* means the highest dose level that does not produce a significant increase in adverse effects. The NOAEL can serve as the starting point for determining a reasonably safe starting dose of a new drug in healthy human volunteers. Studies to determine the NOAEL by examining at least two different species are needed to identify the starting dose for intravenous human studies (see guidance for industry *Estimating the Maximum Starting Dose in Initial Clinical Trials for Therapeutics in Adult Health Volunteers*). The duration of an animal study is determined by the duration of drug elution from the stent. The minimum duration should be 2 weeks for a nonpolymerized drug, which is considered a single dose. See the guidance for industry *Single Dose Acute Toxicity Testing for Pharmaceuticals* and *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*, for more information.[58]

Noninferiority trial: A trial with the primary objective of showing that the response to the investigational product is inferior to a comparative agent by more than a defined amount (the noninferiority margin).

Novel excipient: An ingredient used for the first time in a human drug or combination product in the United States or in a new route of administration.

OUS: Outside the United States

Packaging system: The sum of packaging components that together contain and protect the product. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to a DES.

Partition coefficient: The ratio of the concentration of a chemical species in one environment to its concentration in another environment.

[58] In December 2002, the Agency issued a draft guidance for industry and reviewers *Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers*. Once finalized, it will represent the Agency's current thinking on this topic.

Per protocol set (valid cases, efficacy sample, evaluable subjects sample): The set of data generated by the subset of subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of major protocol violations.[59]

Pharmacodynamics: The study of the biochemical and physiological effects of drugs (and/or metabolites) on the body and the mechanisms of drug action, including the characterization of the relationship between the drug exposure and pharmacologic effects (efficacious and toxic), and the factors influencing such relationships. Often, the time course of these effects is also described.

Primary stability data: Data on the finished product stored in the proposed package for marketing under storage conditions that support the proposed shelf life

Quality: The suitability of a DES for its intended use. This term includes such attributes as the identity, content, purity, and potency.

Specification: The quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an application to confirm the quality of drug substances, products, intermediates, raw materials, reagents and other components including packaging system, and in-process materials. A specification sheet includes the list of tests, references to analytical procedures, and acceptance criteria.

Specified degradation product: An identified or unidentified degradation product that is selected for inclusion in the product specification and is individually listed and limited to ensure the safety and quality of the product

Statistical analysis plan: A statistical analysis plan is a document that contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data. [60]

Stent platform: The component of the DES that provides mechanical structural support when deployed in a vessel and is usually metallic and either balloon expandable or self-expanding.

Stent delivery system: A stent delivery system delivers a stent through the vasculature to its intended target site and then deploys the stent. A stent delivery system for a balloon expandable stent consists of a balloon catheter. Self-expanding stent delivery systems may or may not include a balloon.

[59] ICH Guidance E9 *Statistical Principles for Clinical Trials*

[60] ICH Guidance E9 *Statistical Principles for Clinical Trials*

Studied drug: a molecular entity that has been previously approved or studied under IND (i.e., has an approved NDA or ANDA, or has undergone human clinical studies under IND)

Superiority trial: A trial with the primary objective of showing that the response to the investigational product is superior to a comparative agent (active or placebo control). [61]

Tmax: PK parameter, time to maximum concentration

United States Pharmacopeia (USP): The United States Pharmacopeia (USP) is the official public standards-setting authority for all prescription and over-the-counter medicines, dietary supplements, and other healthcare products manufactured and sold in the United States.

Unspecified degradation product: A degradation product that is not included in the list of specified degradation products

Unstudied drug: a molecular entity that has not been approved for use in humans, or that does not have human clinical study information available

[61] ICH Guidance E9 *Statistical Principles for Clinical Trials*

BIBLIOGRAPHY

The following documents have either been referenced in this guidance or will be of interest to DES applicants and sponsors. They are grouped by document type and listed in alphabetical order.

Food and Drug Administration Guidance Documents

Application User Fees for Combination Products

Assessing User Fees: PMA Supplement Definitions, Modular PMA Fees, BLA and Efficacy Supplement Definitions, Bundling Multiple Devices in a Single Application, and Fees for Combination Products

Combination Products: Submission and Resolution of Formal Disputes Regarding the Timeliness of Premarket Review of a Combination Product (Dispute Resolution Guidance)

Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products

Current Good Manufacturing Practice for Combination Products

Dissolution Testing of Immediate Release Solid Oral Dosage Forms

Drug Master Files

Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro

Environmental Assessment of Human Drug and Biologics Applications

Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers

Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations

Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application

Format and Content of the Nonclinical Pharmacology/Toxicology Section of an Application

Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees

How to Write a Request for Designation

Immunotoxicology Evaluation of Investigational New Drugs

INDs for Phase 2 and Phase 3 Studies: Chemistry, Manufacturing, and Controls Information

Master Files: Part III – Guidance on Scientific and Technical Information

Nonclinical Studies for Development of Pharmaceutical Excipients

Non-Clinical Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems

PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Premarket Approval Application Modular Review

Single Dose Acute Toxicology Testing for Pharmaceuticals

Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances

Submitting Documentation for the Manufacturing of and Controls for Drug Products

International Conference on Harmonisation (ICH) Guidances

Q1A(R2) Stability Testing of New Drug Substances and Products

Q1B Photostability Testing of New Drug Substances and Products

Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products

Q2B Validation of Analytical Procedures: Methodology

Q3A(R) Impurities in New Drug Substances

Q3B(R) Impurities in New Drug Products

Q3C Impurities: Residual Solvents, December

Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals

S7A Safety Pharmacology Studies for Human Pharmaceuticals

S2A Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals

International Organization for Standardization (ISO)

2248 Packaging – Complete, filled transport packages – Vertical impact test by dropping

8318 Packaging — Complete, filled transport packages and unit loads — Sinusoidal vibration tests using a variable frequency

10993-1 Biological Evaluation of Medical Devices -- Part 1: Evaluation and Testing,

11607 Packaging for terminally sterilized medical devices —Part 1: Requirements for materials, sterile barrier systems and packaging systems

United States Pharmacopeia (USP)

<788> Particulate Matter in Injections (Small Volume)

<85> Bacterial Endotoxins

<71> Sterility

<724> Drug Release

<905> Content Uniformity

American Standards for Testing Materials (ASTM)

F746 Standard Test Method for Pitting or Crevice Corrosion of Metallic Surgical Implant Materials

F2129 Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion

G71 Standard Guide for Conducting and Evaluating Galvanic Corrosion Tests in Electrolytes

Susceptibility of Small Implant Devices