Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing"

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

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When final, this document will supersede Blue Book Memorandum #G95-1 Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing," dated May 1, 1995.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation

Preface

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Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing"

Draft Guidance for Industry and FDA Staff

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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. You can use an alternative approach if the 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.

1. Introduction

FDA has developed this guidance document to assist industry in preparing Premarket Applications (PMAs), Humanitarian Device Exemptions (HDEs), Investigational Device Applications (IDEs), Premarket Notifications (510(k)s), and *de novo* requests for medical devices that come into direct or indirect contact with the human body in order to determine the potential toxicity resulting from contact of the component materials of the device with the body. The purpose of this guidance is to provide further clarification and updated information on the use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." . When final, this guidance will therefore replace ODE General Program Memorandum #G95-1 (1995), entitled Use of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." This guidance document also incorporates several new considerations, including assessment of known or potentially toxic chemicals (e.g., color additives), and sample preparation for submicron or nanotechnology components, in situ polymerizing and bioabsorbable materials, which were not previously discussed in #G95-1.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

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

2. Scope

The scope of this document is limited to the biological evaluation of sterile and non-sterile medical devices that come into direct or indirect contact with the human body. This document specifically covers ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" but also is relevant to other biocompatibility standards (e.g., ASTM).

This document discusses the following issues:

- test selection;
- general testing considerations, including sample preparation;
- specific considerations for the following testing: cytotoxicity, sensitization, hemocompatibility, pyrogenicity, implantation, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and biodegradation;
- use of animal safety studies to justify omission of specific biocompatibility tests;
- assessment of known or potentially toxic chemical entities; and
- content of a biocompatibility test report.

In addition, the guidance outlines example documentation language that may be helpful when comparing the composition of a test article to the composition of the final device or in comparing the composition of a previously tested product to the composition of a current product.

Sponsors[1] are advised to initiate discussions with the appropriate review division in the Office of Device Evaluation, CDRH, prior to the initiation of long-term testing of any new device materials to ensure that the proper testing will be conducted. In addition, if your product is a combination product, we note the general principles of this guidance would apply, but additional or modified testing may be needed. As such, we encourage you to discuss these products with the appropriate review divisions. We also recognize that an ISO standard is a document that undergoes periodic review and is subject to revision. Through the FDA standards recognition process, ODE provides information regarding the extent of recognition of the ISO 10993 series of standards through supplementary information sheets published on our website.[2] FDA recommends that full test reports be provided for all tests performed because ISO 10993 includes general methods with multiple options, and in some cases does not include acceptance criteria or

[1] For purposes of this guidance document, use of the term "sponsor" may also mean manufacturer, submitter or applicant.

[2] See FDA's Database on Recognized Consensus Standards at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm and input "10993-1" for the Reference Number.

address assessment of results. It is therefore not appropriate to submit a declaration of simple conformity with respect to ISO 10993.[3] FDA will make updates to this guidance document as appropriate should future revisions to ISO 10993 result in significant changes to the recommendations in this document.

3. Test Selection: ISO 10993 Part 1 and the FDA-Modified Matrix

This guidance considers assessment of biocompatibility to be an evaluation of the final finished device. It is therefore important to clarify the use of the term "material" or "materials" throughout this document. The Agency makes a clearance or approval decision for a medical device as it is supplied in its final finished form. The Agency does not clear or approve individual materials that are used in the fabrication of medical devices. The biocompatibility of a final device depends not only on the materials but also on the processing of the materials, manufacturing methods (including the sterilization process), and the manufacturing residuals that may be present on the final device. The use of the term "material" in this document refers to the final finished medical device and not the individual material constituents. This approach is consistent with recommendations found in ISO 10993-1[4] and ISO 10993-12.[5]

A. Evaluation of local and systemic risks

Biological evaluation of medical devices is performed to determine the potential toxicity resulting from contact of the component materials of the device with the body. The device materials should not, either directly or through the release of their material constituents: (i) produce adverse local or systemic effects; (ii) be carcinogenic; or (iii) produce adverse reproductive and developmental effects. Therefore, evaluation of any new device intended for human use requires data from systematic testing to ensure that the benefits provided by the final product will exceed any potential risks produced by device materials.

When selecting the appropriate tests for biological evaluation of a medical device, one should consider the chemical characteristics of device materials and the nature, degree, frequency and duration of exposure to the body. In general, the tests include: *in vitro* cytotoxicity; acute, sub-

[3] Refer to FDA's "Guidance for Industry and FDA Staff – Recognition and Use of Consensus Standards," available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077274.htm, for information regarding the recognition and use of national and international consensus standards, including declarations of conformity to these standards, during the evaluation of premarket submissions for medical devices.
[4] ISO 10993-1:2009 "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"
[5] ISO 10993-1:2007 "Biological evaluation of medical devices – Part 12: Sample preparation and reference materials"

chronic and chronic toxicity; irritation; sensitization; hemocompatibility; implantation; genotoxicity; carcinogenicity; and effects on reproduction, including developmental effects. However, depending on certain device or material characteristics, the intended use of the device, target population, and/or the nature of contact with the body, these general tests may not be sufficient to demonstrate the safety of certain devices. Additional tests for specific target organ toxicity, such as neurotoxicity and immunotoxicity, may be necessary for some devices. For example, a neurological device with direct contact with brain parenchyma and cerebrospinal fluid (CSF) may require an animal implant test to evaluate its effects on the brain parenchyma, susceptibility to seizure, and effects on the functional mechanism of choroid plexus and arachnoid villi to secrete and absorb CSF. The specific clinical application and the materials used in the manufacture of the new device will guide selection of the appropriate tests.

Some devices are made of materials that have been well characterized chemically and physically in the published literature and have a long history of safe use. For the purposes of demonstrating the substantial equivalence of such devices to other marketed products, it may not be necessary to conduct all of the tests suggested in the FDA matrix of this guidance. FDA reviewers are advised to use their scientific judgment in determining which tests are needed for the demonstration of substantial equivalence in a 510(k) submission. In such situations, the sponsor should be able to document the use of a particular material in a legally marketed predicate device or a legally marketed device with comparable patient exposure in order to justify omission of recommended biocompatibility tests. For the purpose of demonstrating a reasonable assurance of safety and effectiveness in a PMA application, an independent assessment of the biocompatibility of the device is necessary; however, sponsors may leverage information from existing approvals or clearances. Refer to Section 10, Component and Device Documentation Examples for additional information on comparisons to a legally marketed device.

If literature is used to support omission of certain biocompatibility tests, the submission should include information on the applicability of the dose, route, and frequency of exposure from the literature report(s) as compared to the proposed device use. In addition, while literature may be appropriate to support the omission of certain toxicity tests, it may not be appropriate to justify omission of all biocompatibility studies. For example, No Observed Adverse Event Level (NOAEL) and Low Observed Adverse Event Level (LOAEL) data could be used to justify omission of acute, subchronic, or chronic system toxicity assessments, but would not be relevant for genotoxicity, local and systemic carcinogenicity, sensitization, or reproductive toxicity assessments.

B. History and Use of Tripartite and ISO 10993 Standards

In 1986, FDA, Health and Welfare Canada, and Health and Social Services UK issued the Tripartite Biocompatibility Guidance for Medical Devices. This Guidance was used by FDA reviewers, as well as by manufacturers of medical devices until 1995, to select appropriate tests to evaluate the adverse biological responses to medical devices. To harmonize biological

response testing with the requirements of other countries, in 1995 FDA agreed to apply the ISO standard, Part 1, described below, in the review process in lieu of the Tripartite Biocompatibility Guidance.

The International Standards Organization (ISO), in an effort to harmonize biocompatibility testing, developed a standard for biological evaluation of medical devices (ISO 10993). The scope of this multi-part standard is to evaluate the effects of medical device materials on the body. The first part of this standard "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process," provides a framework in which to plan biological evaluation of medical devices, and if needed, guidance for selecting tests to evaluate the biological response to medical devices. Most of the other parts of the ISO standard deal with appropriate methods to conduct biological tests that may be identified when following Part 1 of the standard.

With the 2009 revision of the ISO Standard, Part 1, the focus of the document changed from how to determine which biocompatibility tests to conduct, to an approach that considers existing information prior to determining if biocompatibility testing is needed. With the advancement of scientific knowled[illegible]rding t[illegible]mechani[illegible]ns of tis[illegible]p[illegible], the 2009 revision to this standard attem[illegible]ted to [illegible]inimi[illegible]ize the [illegible]umbe[illegible]r and expo[illegible]re of test ani[illegible]als by giving preference to chem[illegible]cal cons[illegible]tue[illegible]ting and *in vitro* mod[illegible]situation[illegible] where these methods yield equally relev[illegible]nt infor[illegible]ati[illegible] to th[illegible] obta[illegible]ed fr[illegible] *in vivo* models."[6] For FDA submissions, final [illegible]rodu[illegible]biocompatibil[illegible]y t[illegible]ting (us[illegible]g b[illegible]th *in vitro* an[illegible] *in vivo* models), and/or adequate chemical characterization in conjunction with supplementary biocompatibility testing may be acceptable.

The ISO 10993 Standard Part 1 uses an approach to test selection that is very similar to the original Tripartite Guidance (G87-1), including the same seven principles.

1. The selection of material(s) to be used in device manufacture and its toxicological evaluation should initially take into account full characterization of all materials of manufacture, for example, formulation for each component material, including adhesives, known and suspected impurities, and constituents associated with processing. In situations where materials of manufacture may be proprietary from a supplier, device master files[7] (MAF) for a material component(s) submitted to CDRH may assist in determining the formulation of some components of the final device. However, this may not be sufficient or represent the full characterization of the final

[6] ISO 10993-1:2009 "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"

[7] Additional Information regarding master files for devices is available online at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm142714.htm

device and additional analysis may be needed. There currently is no standard established for the content or completeness of a master file submitted to CDRH. Because the information in a master file may be specific to the material and does not address device fabrication, frequently the information contained in material master files submitted to CDRH is insufficient to address all the characterization or biocompatibility questions that pertain to the final finished medical device.

2. The material(s) of manufacture, the final product and possible leachable chemicals or degradation products should be considered for their relevance to the overall toxicological evaluation of the device.

3. Tests to be utilized in the toxicological evaluation should take into account the bioavailability of the material (i.e., nature, degree, frequency, duration and conditions of exposure of the device to the body). This principle may lead to the categorization of devices which would facilitate the selection of appropriate tests.

4. Any *in vitro* or *in vivo* experiments or tests should be conducted in accordance with recognized Good Laboratory Practice (GLP) including, but not limited to, the assignment of competent trained staff in the conduct of biocompatibility testing. If information on nonclinical laboratory studies is provided, a statement that all such studies have been conducted in compliance with applicable requirements in the Good Laboratory Practice regulation in 21 CFR Part 58 should be provided. Alternatively, if any such study was not conducted in compliance with such regulation, a brief statement of the reason for the noncompliance should be provided, and a scientific justification is needed to support the validity of the testing performed.

5. Full experimental data, complete to the extent that an independent conclusion could be made, should be submitted to the reviewing authority unless testing is conducted according to a recognized standard that does not require data submission.

6. Any change in chemical composition, manufacturing process, physical configuration or intended use of the device should be evaluated with respect to possible changes in toxicological effects and the need for additional toxicity testing.

7. The toxicological evaluation performed in accordance with this guidance should be considered in conjunction with other information from other non-clinical tests, clinical studies and post-market experiences for an overall safety assessment.

C. The FDA Modified Matrix

Like ISO Part 1, and Tripartite, this guidance also uses a tabular format (matrix) to outline the recommendations based on the various factors discussed above for testing to be submitted in support of an IDE or marketing application.

The matrix in this guidance consists of two tables. Attachment A, Table 1 - Initial Evaluation Tests for Consideration, includes tests for consideration recommended by ISO 10993-1:2009, and additional tests FDA recommends for consideration as previously identified in G95-1. Attachment B, Table 2 - Supplementary Evaluation Tests for Consideration, are not included in the 2009 version of ISO 10993-1, but were included in previous revisions of ISO 10993, as well as G95-1. In addition, Attachment C is a biocompatibility flow chart for the selection of toxicity tests, and is slightly revised from #G95-1. Additional testing may be requested to fully characterize the toxicology profile, if novel materials or manufacturing processes are used (i.e., materials or processes that have not previously been used in a marketed medical device with the same type and duration of contact).

If your device has multiple types of exposure, you should consider testing from both categories for your device. For example, devices that contact the patient gas pathway (i.e., masks, tubing) are externally communicating due to the potential for chemical leachants from the device to enter the patient airway. Some gas pathway contacting devices may also fall into an additional category such as skin or mucosal membrane contact. Endotracheal tubes are classified by ISO 10993-1 as being mucosal contact. However, these devices are an extension of the gas pathway acting as a conduit to the patient airway and lungs. Therefore, we have considered these devices to be classified as both mucosal contact and externally communicating for evaluation of biocompatibility.

While in general, FDA agrees with the framework established in ISO 10993-1, FDA has made several modifications to the testing identified in that standard for the reasons outlined below.

Attachment A, Table 1 – Initial Evaluation Tests for Consideration

FDA has suggested that acute systemic toxicity, subchronic toxicity and implantation tests be considered for a broader set of devices/patient exposures than outlined in ISO 10993-1:2009. For example, for devices in contact with mucosal membranes for longer than 24 hours (e.g., neonatal feeding tubes), certain toxicities that would not be detected with short term assessments could exist and lead to adverse events, and should be considered for additional testing.

FDA has also suggested that irritation tests be considered for a broader set of devices/patient exposures than outlined in ISO 10993-1:2009. For example, devices with indirect contact with the blood could introduce chemical leachants from the device infusion channel that could be irritants, and therefore should be investigated with additional tests.

FDA has also suggested that genotoxicity tests be considered for a broader set of devices/patient exposures than outlined in ISO 10993-1:2009. For example, for all devices used in extracorporeal circuits, even if the contact is less than 24 hours, genotoxicity testing is recommended because of the high surface area, increased potential for chemical leaching, and introduction of any leachables into the systemic circulation.

In addition, sponsors are advised to consider conducting a separate test to detect chemical components of device materials which may be pyrogenic. This type of material-mediated pyrogenicity is identified as a subset of acute systemic toxicity in Part 1 of ISO 10993. See also Section 5 for more information about assessment of pyrogenicity.

If it is unclear in which category a device falls, we recommend consulting device-specific guidance or contacting the appropriate review division for more information. For example, FDA has historically considered devices used to drain fluids (such as Foley catheters) as externally communicating devices rather than as surface devices contacting mucosal membranes.

Attachment B - Table 2 - Supplementary Evaluation Tests for Consideration

Previous revisions of ISO 10993 included tabular indications for when toxicity and carcinogenicity testing should be considered. With ISO 10993-1:2009, these columns, along with the columns for biodegradation and reproductive and developmental toxicity were removed from the tables and instead annex A now states: "In addition to the framework set out in Table A.1, the following should be considered based on a risk assessment, which considers the specific nature and duration of exposure: chronic toxicity, carcinogenicity, biodegradation, toxicokinetics, immunotoxicity, reproductive/developmental toxicity or other organ-specific toxicities." For permanent devices in contact with the mucosal membrane, breached or compromised surfaces, the blood path, or tissue/bone/dentin, FDA recommends that chronic toxicity be considered, since there could be toxicities associated with long-term contact that might not be detected with short-term assessments. In addition, FDA recommends that carcinogenicity testing be considered for all permanent externally-communicating and implanted devices, unless chemical characterization testing and data from the literature are provided to justify omission of this type of testing.

Attachment C – Biocompatibility Flow Chart

Attachment C includes a flow chart which outlines how FDA reviewers historically have assessed whether any biocompatibility testing is needed, and how information provided by the sponsor may support the biocompatibility of the final, sterilized device.

D. Test Selection

As described in Attachments A, B, and C, sponsors should evaluate the need for each of the recommended tests to assess biocompatibility. All tests included in the matrix may not be relevant for all devices. Thus, the modified matrix is only a framework for the selection of tests

and not a checklist of required tests. A scientifically-based rationale for omission of any recommended test should be included with the submission. Material formulation and processing information may not always be needed for medical device submissions; however, this information may assist the sponsor when providing justifications for omission of any recommended tests. Reviewers who are uncertain about the applicability of a specific type of test for a specific device should consult a senior toxicologist.

ISO 10993, Part 1, Section 4.1 states that "Evaluation may include both a study of relevant preclinical and clinical experience and actual testing. Such an evaluation might result in the conclusion that no testing is needed if the material has a demonstrable safe history of use in a specified role and physical form that is equivalent to that of the device under design."[8] In order to conclude that no additional testing is needed, the sponsor should provide evidence that for each material, the intended use, physical form, formulation, processing, component interactions, and storage conditions are the same as for the comparator product(s). In cases where there are differences, these need to be explained and justified. Clinical data may be of limited utility if specific toxicology endpoints are not included in the monitoring plan.

4. General Biocompatibility Testing Considerations

Sample preparation is a critical variable in the conduct of the biocompatibility assays. Therefore, it is important to understand how the test samples compare to the final sterilized product. The example test article documentation language included in Section 10 below can be used to detail how any differences may or may not affect biocompatibility of the final product.

A. Use of Final Product or Representative Sample

If the final product cannot be used as the test sample, you may need to fabricate a test sample (e.g., coupons) that is representative of the final product. If there are differences between the final product and the test sample, additional testing may be necessary to justify use of the test sample instead of the final product. This testing may include data to demonstrate that the test sample materials elute chemical leachants of the same type and relative quantity compared to the final product. In addition, exhaustive extraction and surface characterization techniques may be requested to support use of the representative test samples.

B. In Situ Polymerizing and Bioabsorbable Materials

For *in situ* polymerizing and bioabsorbable materials, we recommend that test sample preparation be representative of the finished product. In addition, we recommend that toxicity be assessed for the finished product as well as at various time points over the course of polymerization and/or degradation to ensure that starting, intermediate and final degradation

[8] *Ibid.*

products are assessed. For *in vivo* tests, the follow-up time points would depend on the polymerization and degradation kinetics. We recommend that assessments continue until the polymer is no longer present in the tissue, or until the biological tissue response is demonstrated to be stable. For *in vitro* extraction tests, chemical analytical testing of the extract may be useful to determine whether single or multiple tests are needed. The method for simulated degradation will depend on the material.

C. Biological Response Resulting from Device Mechanical Failure

Although the scope of ISO 10993-1 specifically excludes biological hazards arising from any mechanical failure, FDA believes this potential risk is important to consider when designing biocompatibility studies. For certain devices, such as those incorporating a coating or multiple material components, it is possible that mechanical failure could alter the biological response to the device. For example, if coating particles are released from a coated device, those particles could lead to a biological response because of their material properties, such as geometric and/or physicochemical properties. In addition, coating delamination could expose the biological system to leaching of different chemicals or to an increased level of chemicals from the substrate material. Another consideration is whether the surface topography could change with mechanical loading in such a way that the biological response changes. We recommend that your sample selection for biocompatibility testing incorporate these considerations. If your assessment does not include testing to evaluate potential biological hazards due to mechanical failure, your rationale for why such testing is not needed may include the results of other nonclinical tests such as bench testing or animal safety studies.

D. Submicron or Nanotechnology Components

It is now generally accepted[9,10] that there can be unique properties associated with submicron or nanotechnology components such as, aggregation, agglomeration, immunogenicity or toxicity. Medical devices with sub-micron components may require specialized techniques for characterization and biocompatibility tests. Limitations may apply when using chemical leachates-based ISO 10993 test methods in the analysis of submicron component biocompatibility assessments. You should consult relevant literature and standards during the development of test protocols for device specific submicron or nanotechnology component biocompatibility assessments, and contact the respective review division prior to initiation of the test.

[9] Kunzmann, A.; Andersson, B.; Thurnherr, T.; Krug, H.; Scheynius, A.; Fadeel, B. "Toxicology of engineered nanomaterials: Focus on biocompatibility, biodistribution and biodegradation" Biochimica et Biophysica Acta, 2011, 1810, 361-373.

[10] Gil, P.R.; Oberdorster, G.; Elder, A.; Puntes, V.; Parak, W.J. "Correlating physico-chemical with toxicological properties of nanoparticles: the present and the future" ACS Nano, 2010, 4, 5527-5531.

For biocompatibility assessment of devices with sub-micron components, you should consider the following:

- Careful characterization of the test sample.
- Selection of extract conditions (e.g., solvent type) that avoid testing artifacts that are not clinically relevant.
- Assurance that the test article used is representative of what will be used clinically.

For test selection, the following items are also important:

- Consideration of standard biocompatibility tests in the context of contemporary literature on the validity of individual tests for assessment of submicron components.
- Assurance that the sub-micron components will not interfere with the conduct of a chosen test.
- Consideration of any additional toxicity issues that might be relevant to submicron particles, such as absorption, distribution and accumulation into organs, potential metabolism, and elimination, since there are greater concerns associated with submicron particles th[illegible] be r[illegible]oxified [illegible]d/or eli[illegible] from [illegible] body.

E. Sample Pre[illegible]aratio[illegible] fo[illegible] [illegible]act Te[illegible]ting

For biocompatibili[illegible] testing con[illegible]ucted u[illegible]ng [illegible]xtracts o[illegible] sa[illegible]ples,[11] we rec[illegible]mmend that you:

- Determine the appropriate amount of test material as outlined in ISO 10993-12[12] or an equivalent method, using surface area to extractant volume ratios. Mass to extractant volume ratios should only be used if surface area cannot be calculated, or if use of mass will result in a larger sample. If there is a need for an alternate extraction ratio, appropriate justification should be provided. For some test systems, there may be standardized alternatives for test-specific extraction conditions that may provide a different level of extraction (e.g., guinea pig maximization testing per ISO 10993-10, Annex E).[13]

- Use both polar and nonpolar extractants. In some cases, other solvents may be used, where appropriate. For example, mixed polarity solvents (e.g., ethanol/water 20:80) may be useful to optimize extraction of certain amphiphilic molecules that pose toxicity concerns. Also, where devices do not have direct body contact but only have indirect

[11] For biocompatibility testing, extracts could include residuals at the surface of testing samples or leachables migrating from the bulk of test samples.

[12] ISO 10993-12: 2007 "Biological evaluation of medical devices – Part 12: Sample preparation and reference materials."

[13] ISO 10993-10: 2010 "Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization."

contact via a polar solution (e.g., qualification of the inner channel material of a cardiovascular catheter where the inner channel is only used for the infusion of saline), justification for omission of testing with a non-polar solution may be acceptable.

- Use extraction conditions that are adequate for testing of leachables from the device given its expected use. Traditional biocompatibility extraction methods, such as those in ISO 10993-12 (e.g., 37°C for 72 hours; 50°C for 72 hours; 70°C for 24 hours; or 121°C for 1 hour) are acceptable for many biocompatibility tests. For prolonged contact devices and permanent implants, testing at 37°C may not be sufficient to obtain an extract that represents the chemicals that may leach out over the use life of the device. However, in some cases, temperatures above 37°C result in degradants that may not occur in clinical use and may result in toxicities not representative of the final product. Therefore, a justification for the selected extraction conditions should be provided.

- Describe the condition of the test extract (e.g., color, presence of any particles), and explain any changes in the test extract (pre- and post-extraction) and the source of these changes (e.g., test article degradation).

- Use the extracts without additional processing (e.g., no filtration, centrifugation or other methods to remove particulates, no pH adjustment) unless otherwise justified.

- If extraction samples are not used immediately, we recommend that you use them within the time frame outlined in ISO 10993-12 or an equivalent method. We recommend that you describe the details of storage conditions for the test extract, and explain why storage will not affect your test results (i.e., as stated in ISO 10993-12, "stability and homogeneity of extract under storage conditions shall be verified").

F. Inclusion of multiple components or materials in a single sample

For products that include components with different lengths of contact (e.g., limited, prolonged or permanent), we recommend that you conduct extraction tests on the components separately. If the components are combined into a single test sample, this will dilute the amount of component materials being presented to the test system and may not identify potentially toxic agents that would have been found if the components were tested separately. For example, this would include implants with delivery systems and certain kits.

For devices or device components that contain multiple materials with differing surface areas or differing exposure to the body, if one or more materials is new (i.e., not used before in this type and duration of contact), it may also be necessary to test the new material component(s) separately as well. For example, for a catheter-based delivery system that contains a new balloon

material, tests of both the delivery system and the balloon alone may be necessary to ensure adequate assessment of both materials.

5. Test-Specific Considerations

We recommend that you consider the following issues when conducting any of the tests identified below. While there are other biocompatibility tests outlined in Attachments A and B, only certain tests are discussed below. The test-specific issues discussed in this section have been included because they are often inadequately addressed in many submissions.

A. Cytotoxicity

For tests where the sample is extracted in growth media, we recommend that extractions be conducted at 37°C for 24 hours using a vehicle that will allow for extraction of both polar and nonpolar constituents from the test sample, such as mammalian cell culture media (MEM) and 5% serum.

For novel materials (i.e., materials that have not previously been used in a marketed medical device with the same type and duration of contact), we recommend that both direct contact and elution methods be considered.

B. Sensitization

There are two types of sensitization tests that are generally submitted in support of IDE and marketing applications to CDRH.

Guinea Pig Maximization Test (GPMT)

When this test is used, we recommend that test reports confirm that all female animals used in the testing are not pregnant, as pregnancy can reduce the ability of a female animal to detect a sensitization response.

Assays with positive controls using the same source and strain of animals should be performed regularly (at least once every 6 months) in order to ensure the reproducibility and sensitivity of the test procedure. We recommend that test reports include positive control data from concurrent testing or from positive control testing within 3 months (before or after) of the device testing using the same methods and source and strain of animal. We also recommend that your positive control testing include a minimum of 5 animals to demonstrate a reproducible and appropriately positive response in the test system. If a periodic positive control fails, all GPMT data generated after the last positive GPMT response is considered invalid because there is no assurance that the test system is working. Therefore, repeating positive control testing to justify a failed positive control test is not acceptable.

If a primary irritation study is not included in the sensitization protocol, adverse findings at the end of the study may be due to irritation or sensitization, and additional studies to determine the causality may be needed.

Local Lymph Node Assay (LLNA)

CDRH will evaluate use of LLNA tests for medical devices on a case-by-case basis for medical device extract/residuals that are comprised of chemical mixtures. LLNA tests may be appropriate in the following circumstances:

- The LLNA can be used for testing metal compounds (with the exception of nickel and nickel-containing metals) unless there are unique physicochemical properties associated with these materials that may interfere with the ability of the LLNA to detect sensitizing substances.

- The LLNA can be used for testing substances in aqueous solutions unless there are unique physicochemical properties associated with these materials that may interfere with the ability of the LLNA to detect sensitizing substances. When testing substances in aqueous solutions, it is essential to use an appropriate vehicle, to maintain the test substance in contact with the skin (e.g., 1% Pluronic L92[14]) so that adequate exposure can be achieved as demonstrated by positive control results.

LLNA may not be appropriate in the following circumstance:

- Instead of the LLNA test, we recommend the use of the GPMT test for devices made from novel materials, or when testing substances that do not penetrate the skin but are used in devices that contact deep tissues or breached surfaces.

If LLNA testing is performed, CDRH recommends that a fully validated standardized method be used. Currently, the only CDRH-recognized validated method is a radioactive LLNA test performed using ASTM F2148.[15]

The following test methods may be used as alternatives. If a nonradioactive LLNA method, such as the LLNA: 2-Bromodeoxyuridine-Enzyme Linked Immunosorbent Assay (BrdU-ELISA) test or the LLNA: Daicel Adenosine Triphosphate (DA) test, is used, we recommend you also consider the following:

[14] Boverhof DR, et. al. "Interlaboratory validation of 1% pluronic L92 surfactant as a suitable, aqueous vehicle for testing pesticide formulations using the murine local lymph node assay." Toxicol Sci, 2008, 105(1): 79-85.
[15] ASTM F2148-07e1 "Standard Practice for Evaluation of Delayed Contact Hypersensitivity Using the Murine Local Lymph Node Assay (LLNA)."

- For the LLNA: BrdU-ELISA test, the accuracy and reliability supports the use of the test method to identify substances as potential skin sensitizers and nonsensitizers using a stimulation index (SI) ≥ 1.6 as the decision criterion to identify substances as potential sensitizers. For borderline positive responses between an SI of 1.6 and 1.9 there is a potential for false positive results that could limit the usefulness of this type of LLNA test.

- For the LLNA: DA test, the accuracy and reliability support use of the test method to identify substances as potential skin sensitizers and nonsensitizers using a stimulation index (SI) ≥ 1.8 as the decision criterion to identify substances as potential sensitizers. For borderline positive responses between an SI of 1.8 and 2.5 there is a potential for false positive results that could limit the usefulness of this type of LLNA test. In addition, the LLNA: DA might not be appropriate for testing substances that affect ATP levels (e.g., substances that function as ATP inhibitors) or those that affect the accurate measurement of intracellular ATP (e.g., presence of ATP degrading enzymes, presence of extracellular ATP in the lymph node).

C. Hemocompatibility

For blood-contacting devices (regardless of contact duration), we recommend that you consider hemolysis, immunology (complement activation), and thrombogenicity testing. If testing is not conducted, we recommend that you provide a scientific justification for omission of a test. For example, complement activation and *in vivo* thrombogenicity testing is not generally needed for indirect blood-contacting devices.

For hemolysis testing, we recommend that both direct and indirect (extract) methods be conducted per ASTM F756,[16] or an equivalent method (e.g., NIH Autian method).[17,18]

Immunology testing should appropriately address the various complement activation pathways. We recommend that you assess direct contact *in vitro* C3a and SC5b-9 fragment activation using established testing methods such as an ELISA test. In addition, equivalent complement testing methods such as ASTM F2065[19] and ASTM F1984[20] can be used. Alternatively, you may

[16] ASTM F756-08 "Standard Practice for Assessment of Hemolytic Properties of Materials."

[17] Autian J, "Toxicological Evaluation of Biomaterials: Primary Acute Toxicity Screening Program," Artif Organs. 1977 Aug;1(1):53-60.

[18] National Institute of Arthritis, Metabolism, and Digestive Diseases. (1977). *Report of a Study Group for the Artificial Kidney – Chronic Uremia Program: Evaluation of Hemodialyzers and Dialysis Membranes* (NIH Publication No. 77-1294). Washington, DC: U.S. Government Printing Office.

[19] ASTM F2065-00(2010) "Standard Practice for Testing for Alternative Pathway Complement Activation in Serum by Solid Materials."

provide a rationale for omitting this testing, if all the materials used in the formulation and processing of the device have a history of previous use in blood-contacting devices with similar contact duration.

We recommend thrombogenicity be assessed as part of a safety study conducted in a relevant animal model, where such a study is planned for other reasons. Alternatively, for many types of devices where animal safety studies are not conducted, a 4-hour canine venous unheparinized model can be used to assess thrombogenicity. In some cases (e.g., if your device includes novel materials, or there are questionable findings from the animal safety study), a 4 hour canine *in vivo* thrombogenicity test may be necessary in addition to the animal safety study. If only a portion of the device is being utilized for thrombogenicity testing, the sponsor should confirm that the sample is representative of all materials that would be in direct contact with blood. In addition, we recommend that for all *in vivo* thrombogenicity assessments, regardless of whether evaluation was from the safety study or canine model, color photographs of the device/vessel explants should be provided.

While the 4 hour canine *in vivo* thrombogenicity study has limitations, it has historically provided useful information on how synergistic mechanisms (e.g., material and geometry of the device) cause thrombosis. The vessel to device ratio should be considered such that larger vessels are used for larger diameter devices to maintain a diameter relationship similar to what will be seen in patients. In the 4 hour canine *in vivo* thrombogenicity study, we do not recommend the use of anticoagulation because the presence of anticoagulant will likely confound the assessment of the thrombogenic potential of a device in this model, making the study non-informative, which would be contrary to the Agency's position on minimizing animal use. Also, the data from the unheparinized model could be used to assess the risk of thrombus formation in the patient population where anticoagulants cannot be used for clinical reasons even if the device is indicated for use with anticoagulation. For devices with elevated thrombus scores (i.e., not thromboresistant), it may be necessary to screen for device related characteristics, such as surface defects, that may contribute to greater thrombogenicity. Additionally, we may recommend that you repeat the study with heparinization to confirm that heparinization will counter the thrombogenic response seen in the unheparinized study. In these cases, labeling should be considered that contraindicates use of the subject device in unheparinized patients. For some devices for which a 4 hour canine venous thrombogenicity model is not appropriate, such as oxygenators, a series of *in vitro* blood damage assessments (both static and dynamic) can be used to support regulatory submissions, if adequate rationales are provided.

[20] ASTM F1984-99(2008) "Standard Practice for Testing for Whole Complement Activation in Serum by Solid Materials."

D. Pyrogenicity

Implants, as well as sterile devices in contact directly or indirectly with the cardiovascular system, the lymphatic system, or cerebrospinal fluid (CSF) (regardless of duration of contact), and devices labeled as "non-pyrogenic" should meet pyrogen limit specifications. Pyrogenicity testing is used to help protect patients from the risk of febrile reaction. There are two sources of pyrogens that should be considered when addressing pyrogenicity. The first, material-mediated pyrogens, are chemicals that can leach from a medical device. Pyrogens from bacterial endotoxins can also produce a febrile reaction similar to that mediated by some materials.

We recommend that you assess material-mediated pyrogenicity using traditional biocompatibility extraction methods (e.g., 50°C for 72 hours; 70°C for 24 hours; or 121°C for 1 hour per ISO 10993-12), using a pyrogenicity test such as the one outlined in the USP 34 <151> Rabbit Pyrogen Test or an equivalent validated method. For devices that contain heat labile or heat sensitive materials, (e.g., drugs, biomolecules, tissue derived components) which may have the potential to undergo deformation or material configuration/structural change at high temperature, sample extraction at 37°C per ISO 10993-12 is recommended.

Bacterial pyrogens are traditionally addressed as part of the sterility assessment. We recommend that you refer to the most recent sterility guidance document for recommendations related to testing to determine endotoxin levels for sterile devices.[21]

We recommend that both the bacterial endotoxin and rabbit material mediated pyrogen testing be conducted for devices that do not need to meet pyrogen limit specifications because of the nature of body contact but intend to be labeled as 'non-pyrogenic.'

E. Implantation

For many types of materials, intramuscular implantation is often more sensitive than subcutaneous implantation due to the increased vascularity of the muscle versus the subcutaneous space.[22] If there are characteristics of the device geometry that may confound interpretation of this test, it may be acceptable to use coupons instead of finished product for muscle implantation testing, with appropriate justification. In some cases, subcutaneous implantation testing may be appropriate, provided that justification is given.

[21] Although the sterility guidance has been written to address sterility information for 510(k) submissions, the information about bacterial endotoxin testing is also relevant to devices submitted in IDE or PMA applications.

[22] Shelley Y. Buchen, Cunanan CM, Gwon A., et al. Assessing intraocular lens calcification in an animal model. J Cataract Refract Surg. 2001; 27:1473-1484.

In addition to implantation studies in subcutaneous, muscle, and bone tissues, as described in ISO 10993-6, clinically relevant implantation testing for toxicity endpoints is often needed for certain implant devices with relatively high safety risks. Clinically relevant implantation studies are critical to determine the systemic and local tissue responses to the implant in a relevant anatomical environment under simulated clinical conditions. In some cases, the toxicity outcomes that would be obtained from a clinically relevant implantation study can be assessed as part of animal safety studies that are performed to assess overall device safety (e.g., the protocol for an animal study to evaluate delivery and deployment of a device may also include assessment of relevant toxicity endpoints).

Clinically relevant implantation and muscle implantation tests may be informative to the overall toxicity assessment of both the material components of the product and the final product when used in its intended anatomical location. Muscle implantation tests may be omitted when clinically relevant implantation studies are conducted. However, the muscle implantation study may be helpful as a screening test to look at local toxicities. For example, because the muscle implants tend to form a fibrous capsule around the implant, any materials eluted over time from the test article will be contained within the capsule, and therefore might result in an exaggerated response that might not necessarily be observed in the site-specific implant study. In addition, a well-defined muscle implantation study is often helpful to interpret the data from clinically relevant implantation studies that may include other confounding factors (e.g., concomitant treatments may interfere with tissue response). Therefore, muscle implantation studies should be considered as a supplemental test even when clinically relevant implantation studies are performed, especially when new materials/chemicals are used in a medical device or the results of the clinically relevant implantation study raise toxicity concerns.

For implantation testing of products with materials that intentionally degrade, we recommend that tests include interim assessments to determine the tissue response during degradation (i.e., when there is minimal or no degradation, if applicable; during degradation; and once a steady state has been reached with respect to material degradation and tissue response). Selection of interim assessment time points may be based on *in vitro* degradation testing.

F. Genotoxicity

Genotoxicity testing is requested when the genotoxicity profile has not been adequately established. FDA traditionally requests genotoxicity testing, even if the device will not have a permanent duration of use.

Because no single test can detect all genotoxins, we recommend the following 3 tests be conducted: [23]

- Bacterial gene mutation assay. This test is conducted with engineered strains of *Salmonella typhimurium* and *Escherichia coli* designed to detect all possible single base pair changes as well as frameshift mutations (OECD 471[24]).

- An *in vitro* mammalian genotoxicity assay. A choice of one of the following is recommended:
  a) the Mouse Lymphoma gene mutation assay (OECD 476[25]), which is preferred since it detects the broadest set of genotoxic mechanisms associated with carcinogenic activity;
  b) an *in vitro* chromosomal aberration (CA) assay (OECD 473[26]); or
  c) an *in vitro* micronucleus assay (OECD 487[27]).

- An *in vivo* cytogenetics assay. A choice of one of the following is recommended:
  a) a bone marrow micronucleus (MN) Assay (OECD 474[28]);
  b) a bone marrow chromosomal aberration (CA) assay (OECD 475[29]); or
  c) a peripheral blood MN assay.

G. Carcinogenicity

CDRH recommends that carcinogenicity potential be assessed to determine the necessity of carcinogenicity testing for an implant device or a device with a novel material (regardless of the duration of contact). Because there are carcinogens that are not genotoxins, FDA believes that the assessment of carcinogenicity cannot rely solely on the outcomes of genotoxicity testing and therefore the following elements should be considered in conjunction with genotoxicity testing on the final product.

- Include the complete chemical formulations and manufacturing residuals for all components of the device. The sponsor should identify how much of each chemical would theoretically be present in an individual device (assume worst-case, e.g., the

[23] All of the OECD guidelines referenced in this section are incorporated by reference in ISO 10993-3, which is recognized by FDA.
[24] OECD 471 (1997) "Guidelines for Testing of Chemicals – Bacterial Reverse Mutation Test"
[25] OECD 476 (1997) "Guidelines for the Testing of Chemicals – *In Vitro* Mammalian Cell Gene Mutation Test"
[26] OECD 473 (1997) "Guidelines for the Testing of Chemicals – *In Vitro* Mammalian Chromosome Aberration Test"
[27] OECD 487 (2010) "Guidelines for the Testing of Chemicals – *In Vitro* Mammalian Cell Micronucleus Test"
[28] OECD 474 (1997) "Guidelines for the Testing of Chemicals – Mammalian Erythrocyte Micronucleus Test"
[29] OECD 475 (1997) "Guidelines for the Testing of Chemicals – Mammalian Bone Marrow Chromosome Aberration Test"

largest device) as well as in the worst-case patient exposure situation (e.g., assume a worst-case situation where a patient might receive multiple devices, if this scenario could reasonably occur in clinical use). For components that are provided by third-party suppliers where the chemical formula is proprietary, device manufacturers should encourage suppliers to use device master files to provide chemical formulation information to the FDA.

- Identify potential leachants and breakdown products (which may not be included as original materials or processing agents). Consideration should be given to the effects of all processing agents (e.g., adhesives, mold cleaning agents, mold releasing agents, sterilization chemicals) that come into contact with the device.

- Provide a thorough literature review, identify the search terms, and conduct an analysis of the toxicity of the chemicals. If potential carcinogens are found in the device, the sponsor should identify and quantify these chemicals and determine how much of the potential carcinogen and/or carcinogenic byproducts would be available in a single product in a worst-case scenario (e.g., assuming 100% formation of the potential carcinogen and 100% bioavailability). A cancer risk assessment should also be provided with literature evidence to demonstrate that the amount of the potential carcinogen(s) available in the device does not pose an unacceptable carcinogenic risk. This analysis should also be provided assuming a maximum number of devices likely to be placed in a single patient in clinical use.

If carcinogenicity testing is warranted (e.g., when data is not available to provide an adequate assessment or assessment indicates there is a potential risk), consideration of available test models should include:

- Standard rodent long term carcinogenicity bioassays (OECD 451[30] or OECD 453[31]) to evaluate the potential for systemic carcinogenic effects. FDA recognizes that solid-state carcinogenicity occurs frequently in rodents. In the event that local tumors are present, FDA recommends that the sponsor provide a discussion of the potential for chemically-induced as well as solid state carcinogenicity.

- RasH2 transgenic mouse model, with confirmation of stability of transgene status. FDA recommends that prior to conducting carcinogenicity testing, the sponsor discuss proposed testing with CDRH to ensure that the study design is appropriate to assess the potential risk.

[30] OECD 451 (2009) "Guidelines for the Testing of Chemicals – Carcinogenicity Studies"
[31] OECD 453 (2009) "Guidelines for the Testing of Chemicals – Combined Chronic Toxicity/ Carcinogenicity Studies"

H. Reproductive and Developmental Toxicity

FDA recommends that reproductive and developmental toxicity be assessed to evaluate the potential effects of medical devices, materials and/or their extracts on reproductive function, embryonic development (teratogenicity), and prenatal and early postnatal development as described in ISO 10993-1. We recommend that you consider this testing for novel implant materials, regardless of the type of contact, and materials or devices in contact with reproductive organs. In addition, it may be useful to consider this testing in patients of reproductive age if device materials may be systemically distributed (e.g., bioresorbable devices). For materials with known reproductive toxicity risks, testing and/or labeling to mitigate these risks may be necessary. FDA recommends that prior to conducting reproductive and developmental toxicity testing, the sponsor discuss proposed testing with CDRH to ensure that the study design is appropriate to assess the potential risk.

I. Biodegradation Testing

FDA recommends that *in vivo* biodegradation testing be conducted in an appropriate animal model if the device is designed to be biodegradable. As described in ISO 10993-1, parameters that affect the rate of degradation should be described and documented. Sponsors should report the rate of degradation and the biological response to the degrading device. If a toxic response is seen, additional *in vitro* testing is recommended to identify the source of the toxicity, such as potential chemicals of concern. FDA recommends that prior to conducting biodegradation testing, the sponsor discuss proposed testing with CDRH to ensure that the study design is appropriate to assess the potential risk. Protocols and test reports (see Section 9 for recommended elements to include in a test report) from characterization of degradation products should be provided in the submission.

6. Use of animal studies to justify omission of specific biocompatibility tests

A safety study of the final finished device performed in a relevant animal model can be designed to include assessments that may be used to justify omission of some biocompatibility tests. When choosing this approach, the animal study should be designed to evaluate the biological response to the test article implanted in a clinically relevant implantation site. If biocompatibility assessments such as implantation, *in vivo* thrombogenicity, and chronic toxicity are included in the animal safety study design, the scientific principles and recommendations in the appropriate ISO10993 test method should be considered.

7. Assessment of Known or Potentially Toxic Chemical Entities

For chemicals used in a device for the first time, or for chemicals with known or potential toxicities (e.g., color additives, or drugs used in combination products), additional information should be provided to determine whether toxicology information beyond standard biocompatibility testing is needed.

CDRH evaluates the safety of medical devices based on duration of exposure and nature of contact. Inherent in the review of medical devices is an understanding of the body's entire exposure to the product, including all chemical entities contained within the product. For devices containing these unknown or potentially toxic chemicals, such as color additives, the evaluation of safety should be based on both the risk of the chemical (i.e., the level of toxicological concern) and the duration of exposure (i.e., bioavailability).

Based on these principles, the following information will guide CDRH's assessment of these chemicals.

For all devices containing such chemical(s), the following descriptive information should be provided:

1. The identity of the chemical by common name, chemical name, and Chemical Abstract Services (CAS) number.

2. If known,[32] the composition (i.e., if a color additive, whether the colorant is comprised of a pigment or encapsulated in polymer), formula and formula weight, structural information, and manufacturing and purity information on the chemical, such as a detailed description of the manufacturing process (including the substances used and the amounts used in the synthesis, reaction conditions), specifications for the chemical, analysis of multiple batches of the chemical, and identification of major impurities;[33]

3. The specific amount of each chemical in the formulation by weight percent of the applicable component and total amount (e.g., µg) in the device;

[32] The amount of information available, within the submission or by reference to a device or drug master file, may impact how much additional testing of the chemical constituents is needed to fully assess the level of toxicological concern.

[33] For more information, see "Guidance for Industry: Color Additive Petitions - FDA Recommendations for Submission of Chemical and Technological Data on Color Additives for Food, Drugs, Cosmetics, or Medical Devices" http://www.fda.gov/ForIndustry/ColorAdditives/GuidanceComplianceRegulatoryInformation/ucm171631.htm.

4. The identity of any other devices marketed in the U.S. (by device name, manufacturer, and submission number) where the chemical entity has been previously used, if known, and provide comparative information on the composition and amount(s) used.

In addition, to evaluate the bioavailability of the chemical to the patient, the following exposure information should be provided:

5. An exposure assessment for each chemical (i.e., whether the chemical and, for color additives, any relevant associated impurities, is bioavailable). Note that for certain chemicals, elution from the device may not be necessary for the chemical to induce toxicity. If testing is conducted to demonstrate that the chemical is not bioavailable, provide the test report, including details of the test conditions, to confirm that the chemical is stable under the intended conditions of use.

If the information above demonstrates that the chemical is not bioavailable, either because the chemical is physically sequestered in a device component with no direct or indirect patient contact, or based on the results of testing conducted as described in 5 above, **no further information is ne**[illegible]

If the information [illegible]ove sug[illegible]est[illegible]le chem[illegible]cal i[illegible]bioav[illegible], the fol[illegible]wing toxicological information should[illegible]e prov[illegible]ed:

6. A safety assessment for each chemical entity using toxicity information from the literature and available, unpublished studies for all known toxic effects. Where the full toxicology profile for the chemical entity is not available, either from the supplier or from a previous medical device submission, the full battery of toxicity tests on the chemical entity (i.e., tests in addition to those outlined in Attachments A and B, including but not limited to genotoxicity; reproductive and developmental toxicity; and carcinogenicity) may also be needed or a scientific rationale provided for their omission.

The bioavailability of the chemical entity and the available toxicological data should be used to assess the level of toxicological concern. One approach to this assessment is to consider whether, if all of the chemical were to become bioavailable, how this amount compares to the amount at which toxicities are known or thought to exist. If available toxicity information suggests that even if all of the chemical were to become bioavailable, no toxicity concern would exist (i.e., the amount is well below the amount at which toxicity concerns are present), **no further information is needed**.

However, if the bioavailability of the total amount of the chemical would lead to potential toxicity concerns, further information will be needed to determine how much of the chemical is

bioavailable as well as the fate of the chemical within the body. Specifically, the following information should be provided:

7. Data to demonstrate the amount of color additive bioavailable (e.g., eluted) from the device over 30 days (or worst-case exposure that might be reasonably encountered in clinical use plus a safety margin). If elution testing is conducted to address this concern, include:

    a. Justification for the extraction solvents (which will be dependent on the chemical nature of the color and the polymer matrix);

    b. Justification for the allowable levels eluted to include calculation of patient exposure. If repeat dosing is possible or probable, this should be considered in the patient exposure calculation.

8. If the chemical is confirmed to be bioavailable, assessment(s) of the fate of the chemical in a clinically relevant animal model should be provided to assess the timing of elimination and pharmacokinetic analyses (e.g., absorption, distribution, metabolism, and excretion (ADME)). We recommend that a sponsor consider relevant device specific guidances if available or contact the review division to discuss the appropriate animal model.

For color additives, the following additional information should be provided:

9. Regulation within Part 21 of the CFR to which the color additive complies, if applicable (with clarification on how the color additive used in the device is listed in the CFR in terms of identity, limitations on amounts permitted in the products, color additive specifications, etc.). The sponsor should identify all regulations for the particular color additive, even if the listing(s) is for a different application (e.g., different device application, use in food packaging).

10. Determination of the need for batch certification in accordance with regulations issued under 721(c) for that use (i.e., color additives not requiring certification are listed under 21 CFR 73 (Subpart D)). Color additives that require batch certification are listed under 21 CFR 74 (Subpart D), and detailed manufacturing information may be needed.

11. If the chemical is a color additive, and the information requested in #7 and #8 above demonstrates that the color additive will be bioavailable for more than 30 days, a Center for Food Safety and Applied Nutrition (CFSAN) review of a color additive petition (CAP) will also be necessary. In addition, if there is no CFR listing and no toxicity data

in the literature, regardless of the length of bioavailability, then a CFSAN review of a CAP would also be necessary.

8. Labeling Devices as "-Free"

FDA notes that to communicate with users regarding potential allergenic or toxic materials, some sponsors have requested to include statements in the device labeling such as "latex-free," "DEHP-free," "BPA-free," or "pyrogen-free." FDA is concerned that these statements are not accurate because it is not possible to reliably assure that there is an absence of the allergen or toxin in the medical product. Use of such terms may give users a false sense of security when using a medical product. If a sponsor elects to include a statement in medical product labeling indicating that a specific material was not used in the manufacture of their medical product or medical product container, FDA recommends the use of a statement such as "Not made with natural rubber latex" or "Not made with BPA" based on material certification to indicate that natural rubber latex or BPA is not used in the device or device component. If this statement is made without any qualification, it should apply to the entire product and all of its packaging. A sponsor can also elect to make a statement that certain components of the medical product or product container are not made with the material of concern. For example, "The <vial stopper> is not made with natural rubber latex."[34]

Sponsors who currently include statements such as "latex-free" or "DEHP-free" in medical product labeling should update their medical product labeling to show the recommended labeling statement as described above. Alternatively, sponsors should consider removing "latex-free" type statements from medical products and medical product packaging.

9. Contents of a Test Report

In order to assess biocompatibility testing or chemical characterization performed to support an IDE or marketing application, FDA recommends that full test reports be provided for all tests performed. In general, the test reports should include the sections described below.

Sample Preparation

As described in Section 4 above, the test report should identify the test specimen; if the test article is not the final finished device, also provide a justification for the test article used. If the

[34] See the FDA Draft Guidance "Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex" available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm340972.htm?source=govdelivery.

test uses extracts, the report should explain how those extracts were obtained, and indicate the appearance the extract (color, cloudy vs. clear, and presence of particulates).

Test Method

The test report should provide a summary of the method used. If the method used is not in a published standard or guidance document, a full description of the method should be provided. If the test method is a modified version of a method in a published standard or guidance document, the test report should include an explanation of the differences and their potential impact on interpretation of the results.

The test report should identify any protocol deviations and their impact on the conclusions drawn from the test.

Test Parameters and Acceptance Criteria

The test report should identify the test parameters and acceptance criteria applied. If the test method is not in accordance with a published standard or guidance document that includes defined acceptance criteria, a rationale for the acceptance criteria should be provided.

Analysis of Resul

The test report sho ld provi e a ummar of th test r sults and include t bles with each data point, and statistic nal s, w ere appr ri te. For xam le, the test re ort for hemolysis should include a description of the test, blank, positive, and negative supernatant conditions, in addition to the absorbance and percent hemolysis data.

For any test in which the results indicate a potential toxicity, the report should include a discussion of any test-specific issues that might have affected results, and any other available information (such as the results of animal safety studies) that might provide additional context for interpretation. For example, if a device made from polypropylene results in a grade 2 cytotoxicity in an L929 assay, which might be acceptable per ISO 10993-5, the sponsor should provide additional information regarding the potential source of the toxicity, since polypropylene is not generally expected to be cytotoxic. Conversely, skin-contacting electrodes with adhesives containing detergents might be expected to have higher than grade 2 cytotoxicity in an L929 assay, which could be acceptable if the sponsor is able to confirm that there are no other chemical constituents causing the adverse cytotoxic response. In general, potential toxicities identified through biocompatibility testing should be evaluated considering the intended use of the device and as part of the overall benefit/risk assessment.

Conclusions

The test report should describe the conclusions drawn from the test results, and the clinical significance of the conclusions.

10. Component and Device Documentation Examples

In certain instances, it may not be clear how the test article compares to the final device. In other cases, a sponsor may choose not to perform certain tests, based on the fact that the current product is the same as a previously tested product. The following examples may be helpful to document a rationale for these approaches.

A. Component Documentation

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

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

> **Comparison to previously marketed device:** "The **[polymer/metal/ceramic/composite name] [component name]** of the final sterilized device is identical to the **[component name]** of the **[name]** (previously marketed device[35]) in formulation, processing, sterilization, and geometry, and no other chemicals have been added (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents)."

B. Device Documentation

If the above statement is true for all of the fabrication material formulations, processes, and sterilization methods (if applicable), either of the following general statements can be provided:

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

> **Comparison to previously marketed device:** "The final sterilized device is identical to **[name]** (previously marketed device) in formulation, processing, sterilization, and geometry and no other chemicals have been added (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents)."

[35] We recommend that you include the submission number and date of submission where the reference device was approved or cleared.

C. New Processing/Sterilization Changes

If there are any processing or sterilization changes that the sponsor believes will ***not*** alter the biocompatibility of the final, sterilized device, the sponsor should use the component documentation language, and include either of the following qualifiers:

Comparison to test article: "…with the exception of **[identify change]**. FDA submission exhibit **[#]**, page **[#]**, submitted on **[date]**, provides scientific information to demonstrate that the **[processing/sterilization]** change does not alter the chemical or physical properties of the final sterilized product, and therefore, results from the test article can be applied to the final sterilized product."

Comparison to previously marketed device: "…with the exception of **[identify change]**. FDA submission exhibit **[#]**, page **[#]**, submitted on **[date]**, provides scientific information to demonstrate that the **[processing/sterilization]** change does not alter the chemical or physical properties of the final sterilized product, and therefore, results from the **[name]** (previously marketed device) can be applied to the final sterilized product."

NOTE: The information provided to support a claim that processing and sterilization changes will not affect chemical or physical properties of the final sterilized device should be provided in sufficient detail for FDA to make an independent assessment, and arrive at the same conclusion.

NOTE: Changes in raw material suppliers or raw material specifications could introduce different types or quantities of residual chemicals, and could result in a toxic response (even if the base material has a long history of safe use in similar applications).

NOTE: Surface alterations due to processing, even at the micron or submicron level, could result in geometrical or chemical changes at the surface that could result in a toxic response (even if the base material has a long history of safe use in similar applications).

D. New Formulation Changes

If there are any formulation changes the sponsor believes will ***not*** alter the biocompatibility of the final, sterilized device, the sponsor should use the component documentation language, and include the following qualifier:

Comparison to test article: "…with the exception of **[identify change]**. FDA submission exhibit **[#]**, page **[#]**, submitted on **[date]**, provides scientific information to demonstrate that the formulation change does not alter the chemical or physical properties of the final

sterilized device, and therefore, results from the test article can be applied to the final sterilized device."

Comparison to previously marketed device: "…with the exception of **[identify change]**. FDA submission exhibit **[#]**, page **[#]**, submitted on **[date]**, provides scientific information to demonstrate that the formulation change does not alter the chemical or physical properties of the final sterilized device, and therefore, results from the **[name]** (previously marketed device) can be applied to the final sterilized device."

For example, if your predicate device contains a Pebax resin, and your subject device contains a new grade of Pebax, your documentation should include a qualifier that states that the untested Pebax grade varies only in the concentration of specific formulation components. Formulation changes that introduce novel components, or a higher concentration of an existing component, may require new testing if the upper and lower bounds of each component have not been previously evaluated.

NOTE: The information provided to support a claim that formulation changes will not affect chemical or physical properties of the final sterilized device should be provided in sufficient detail for FDA to make an independent assessment and arrive at the same conclusion. To support this assessment, FDA suggests that the following be included:

a. formulation of the test article;
b. formulation of the final sterilized product; and
c. a discussion of why the differences would not require additional testing.

Attachment A:

Table 1 – Initial Evaluation Tests for Consideration

Device categorization by			Biologic effect							
nature of body contact (see 5.2) **Category**	**Contact**	**Contact duration** (see 5.3) **A – limited** (≤ 24 h) **B- prolonged** (>24 h to 30 d) **C – permanent** (> 30 d)	**Cytotoxicity**	**Sensitization**	**Irritation or Intracutaneous reactivity**	**Systemic toxicity** (acute)	**Subchronic toxicity** (subacute toxicity)	**Genotoxicity**	**Implantation**	**Haemocompatibility**
Surface device	Intact skin	A	X	X	X					
		B	X	X	X					
		C	X		X					
	Mucosal membrane	A	X		X					
		B	X		X	O	O		O	
		C	X		X	O	X	X	O	
	Breached or compromised surface	A	X		X	O				
		B	X	X	X	O	O		O	
		C	X	X	X	O	X	X	O	
External communicating device	Blood path, indirect	A	X	X	X	X				X
		B	X	X	X	X	O			X
		C	X	X	O	X	X	X	O	X
	Tissue/bone/dentin[+]	A	X	X	X	O				
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Circulating blood	A	X	X	X	X		O^		X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X
Implant device	Tissue/bone	A	X	X	X	O				
		B	X	X	X	X	X	X	X	
		C	X	X	X	X	X	X	X	
	Blood	A	X	X	X	X	X		X	X
		B	X	X	X	X	X	X	X	X
		C	X	X	X	X	X	X	X	X

X = Initial Evaluation Tests for Consideration

O = These additional evaluation tests should be addressed in the submission, either by inclusion of the testing or a rationale for its omission.

Note 1: Tissue includes tissue fluids and subcutaneous spaces

Note: For all devices used in extracorporeal circuits

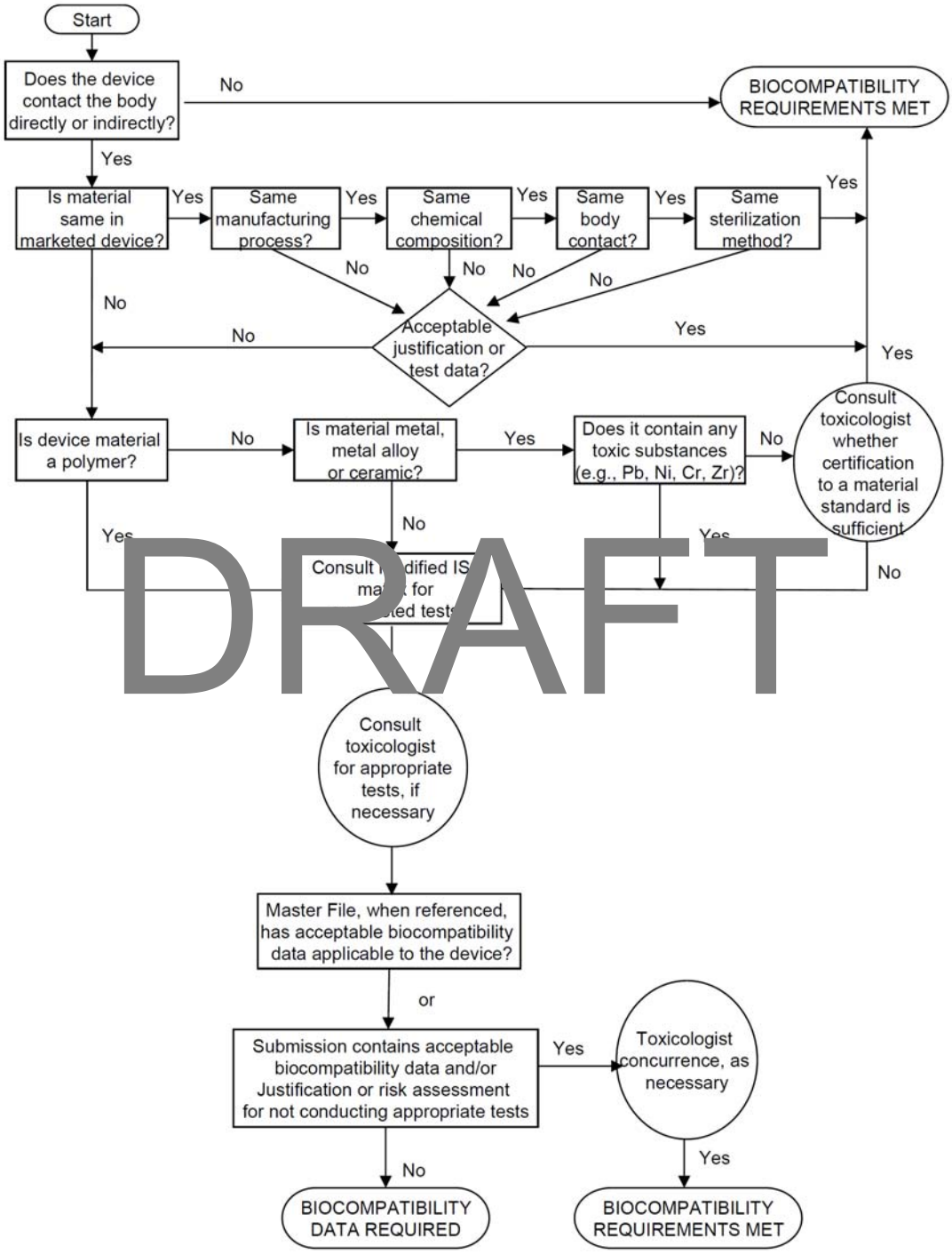
Attachment B:

Table 2 – Supplementary Evaluation Tests for Consideration

Device categorization by			Biologic effect			
nature of body contact (see 5.2)						
Category	**Contact**	**Contact duration** (see 5.3) **A – limited** (≤ 24 h) **B- prolonged** (>24 h to 30 d) **C – permanent** (> 30 d)	**Chronic toxicity**	**Carcinogenicity**	**Reproductive/Developmental**	**Biodegradable**
Surface device	Intact skin	A				
		B				
		C				
	Mucosal membrane	A				
		B				
		C	O			
	Breached or compromised surface	A				
		B				
		C	O			
External communicating device	Blood path, indirect	A				
		B				
		C	O	O		
	Tissue/bone/dentin[+]	A				
		B				
		C	O	O		
	Circulating blood	A				
		B				
		C	O	O		
Implant device	Tissue/bone	A				
		B				
		C	O	O		
	Blood	A				
		B				
		C	O	O		

X = ISO Evaluation Tests for Consideration
O = These additional evaluation tests should be addressed in the submission, either by inclusion of the testing or a rationale for its omission.

Attachment C: Biocompatibility Flow Chart for the Selection of Toxicity Tests


Start
Does the device contact the body directly or indirectly?
No
BIOCOMPATIBILITY REQUIREMENTS MET
Yes
Is material same in marketed device?
Yes
Same manufacturing process?
Yes
Same chemical composition?
Yes
Same body contact?
Yes
Same sterilization method?
Yes
No
No
No
No
No
Acceptable justification or test data?
No
Yes
Yes
Is device material a polymer?
No
Is material metal, metal alloy or ceramic?
Yes
Does it contain any toxic substances (e.g., Pb, Ni, Cr, Zr)?
No
Consult toxicologist whether certification to a material standard is sufficient
Yes
No
Yes
No
Consult toxicologist for appropriate tests, if necessary
Master File, when referenced, has acceptable biocompatibility data applicable to the device?
or
Submission contains acceptable biocompatibility data and/or Justification or risk assessment for not conducting appropriate tests
Yes
Toxicologist concurrence, as necessary
No
Yes
BIOCOMPATIBILITY DATA REQUIRED
BIOCOMPATIBILITY REQUIREMENTS MET

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