

1 **Use of International Standard ISO-**  
2 **10993, "Biological Evaluation of**  
3 **Medical Devices Part 1: Evaluation**  
4 **and Testing"**  
5  
6

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7 **Draft Guidance for Industry and**  
8 **Food and Drug Administration**  
9 **Staff**

10  
11 *DRAFT GUIDANCE*

12  
13 **This guidance document is being distributed for comment purposes only.**  
14 **Document issued on: April 23, 2013**

15  
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20 comments to <http://www.regulations.gov>. Identify all comments with the docket number listed in  
21 the notice of availability that publishes in the *Federal Register*.

22  
23 For questions regarding this document, contact Doyle Gantt, 301-796-6372, [a.gantt@fda.hhs.gov](mailto:a.gantt@fda.hhs.gov)  
24 or Jennifer Goode, 301-796-6374, [jennifer.goode@fda.hhs.gov](mailto:jennifer.goode@fda.hhs.gov).

25  
26 **When final, this document will supersede Blue Book Memorandum #G95-1**  
27 **Use of International Standard ISO-10993, "Biological Evaluation of Medical**  
28 **Devices Part 1: Evaluation and Testing," dated May 1, 1995.**  
29



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

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## **Preface**

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91 **Use of International Standard ISO-10993,**  
92 **"Biological Evaluation of Medical Devices**  
93 **Part 1: Evaluation and Testing"**  
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95  
96 **Draft Guidance for Industry and FDA Staff**  
97

98 *This draft guidance, when finalized, will represent the Food and Drug Administration's*  
99 *(FDA's) current thinking on this topic. It does not create or confer any rights for or on any*  
100 *person and does not operate to bind FDA or the public. You can use an alternative approach*  
101 *if the approach satisfies the requirements of the applicable statutes and regulations. If you*  
102 *want to discuss an alternative approach, contact the FDA staff responsible for implementing*  
103 *this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number*  
104 *listed on the title page of this guidance.*

105  
106 **1. Introduction**

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

121  
122 FDA's guidance documents, including this guidance, do not establish legally enforceable  
123 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should  
124 be viewed only as recommendations, unless specific regulatory or statutory requirements are

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

127

## 128 **2. Scope**

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

133

134 This document discusses the following issues:

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

143

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

148

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

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<sup>1</sup> For purposes of this guidance document, use of the term “sponsor” may also mean manufacturer, submitter or applicant.

<sup>2</sup> 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.

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160 address assessment of results. It is therefore not appropriate to submit a declaration of simple  
161 conformity with respect to ISO 10993.<sup>3</sup> FDA will make updates to this guidance document as  
162 appropriate should future revisions to ISO 10993 result in significant changes to the  
163 recommendations in this document.

164  
165

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

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

178  
179

**A. Evaluation of local and systemic risks**

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

187

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

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<sup>3</sup> 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.

<sup>4</sup> ISO 10993-1:2009 “Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process”

<sup>5</sup> ISO 10993-1:2007 “Biological evaluation of medical devices – Part 12: Sample preparation and reference materials”

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191 chronic and chronic toxicity; irritation; sensitization; hemocompatibility; implantation;  
192 genotoxicity; carcinogenicity; and effects on reproduction, including developmental effects.  
193 However, depending on certain device or material characteristics, the intended use of the device,  
194 target population, and/or the nature of contact with the body, these general tests may not be  
195 sufficient to demonstrate the safety of certain devices. Additional tests for specific target organ  
196 toxicity, such as neurotoxicity and immunotoxicity, may be necessary for some devices. For  
197 example, a neurological device with direct contact with brain parenchyma and cerebrospinal  
198 fluid (CSF) may require an animal implant test to evaluate its effects on the brain parenchyma,  
199 susceptibility to seizure, and effects on the functional mechanism of choroid plexus and  
200 arachnoid villi to secrete and absorb CSF. The specific clinical application and the materials  
201 used in the manufacture of the new device will guide selection of the appropriate tests.  
202

203 Some devices are made of materials that have been well characterized chemically and physically  
204 in the published literature and have a long history of safe use. For the purposes of demonstrating  
205 the substantial equivalence of such devices to other marketed products, it may not be necessary  
206 to conduct all of the tests suggested in the FDA matrix of this guidance. FDA reviewers are  
207 advised to use their scientific judgment in determining which tests are needed for the  
208 demonstration of substantial equivalence in a 510(k) submission. In such situations, the sponsor  
209 should be able to document the use of a particular material in a legally marketed predicate device  
210 or a legally marketed device with comparable patient exposure in order to justify omission of  
211 recommended biocompatibility tests. For the purposes of demonstrating a reasonable assurance  
212 of safety and effectiveness in a PMA application, an independent assessment of the  
213 biocompatibility of the device is necessary; however, sponsors may leverage information from  
214 existing approvals or clearances. Refer to Section 10, Component and Device Documentation  
215 Examples for additional information on comparisons to a legally marketed device.  
216

217 If literature is used to support omission of certain biocompatibility tests, the submission should  
218 include information on the applicability of the dose, route, and frequency of exposure from the  
219 literature report(s) as compared to the proposed device use. In addition, while literature may be  
220 appropriate to support the omission of certain toxicity tests, it may not be appropriate to justify  
221 omission of all biocompatibility studies. For example, No Observed Adverse Event Level  
222 (NOAEL) and Low Observed Adverse Event Level (LOAEL) data could be used to justify  
223 omission of acute, subchronic, or chronic system toxicity assessments, but would not be relevant  
224 for genotoxicity, local and systemic carcinogenicity, sensitization, or reproductive toxicity  
225 assessments.  
226

### **B. History and Use of Tripartite and ISO 10993 Standards**

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

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

235  
236 The International Standards Organization (ISO), in an effort to harmonize biocompatibility  
237 testing, developed a standard for biological evaluation of medical devices (ISO 10993). The  
238 scope of this multi-part standard is to evaluate the effects of medical device materials on the  
239 body. The first part of this standard "Biological evaluation of medical devices - Part 1:  
240 Evaluation and testing within a risk management process," provides a framework in which to  
241 plan biological evaluation of medical devices, and if needed, guidance for selecting tests to  
242 evaluate the biological response to medical devices. Most of the other parts of the ISO standard  
243 deal with appropriate methods to conduct biological tests that may be identified when following  
244 Part 1 of the standard.

245  
246 With the 2009 revision of the ISO Standard, Part 1, the focus of the document changed from how  
247 to determine which biocompatibility tests to conduct, to an approach that considers existing  
248 information prior to determining if biocompatibility testing is needed. With the advancement of  
249 scientific knowledge regarding the basic mechanisms of tissue responses, the 2009 revision to  
250 this standard attempted to "minimize the number and exposure of test animals by giving  
251 preference to chemical constituent testing and *in vitro* models, in situations where these methods  
252 yield equally relevant information to that obtained from *in vivo* models."<sup>6</sup> For FDA  
253 submissions, final product biocompatibility testing (using both *in vitro* and *in vivo* models),  
254 and/or adequate chemical characterization in conjunction with supplementary biocompatibility  
255 testing may be acceptable.

256  
257 The ISO 10993 Standard Part 1 uses an approach to test selection that is very similar to the  
258 original Tripartite Guidance (G87-1), including the same seven principles.

259  
260 1. The selection of material(s) to be used in device manufacture and its toxicological  
261 evaluation should initially take into account full characterization of all materials of  
262 manufacture, for example, formulation for each component material, including  
263 adhesives, known and suspected impurities, and constituents associated with  
264 processing. In situations where materials of manufacture may be proprietary from a  
265 supplier, device master files<sup>7</sup> (MAF) for a material component(s) submitted to CDRH  
266 may assist in determining the formulation of some components of the final device.  
267 However, this may not be sufficient or represent the full characterization of the final

---

<sup>6</sup> ISO 10993-1:2009 "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"

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



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- 268 device and additional analysis may be needed. There currently is no standard  
269 established for the content or completeness of a master file submitted to CDRH.  
270 Because the information in a master file may be specific to the material and does not  
271 address device fabrication, frequently the information contained in material master files  
272 submitted to CDRH is insufficient to address all the characterization or  
273 biocompatibility questions that pertain to the final finished medical device.  
274
- 275 2. The material(s) of manufacture, the final product and possible leachable chemicals or  
276 degradation products should be considered for their relevance to the overall  
277 toxicological evaluation of the device.  
278
  - 279 3. Tests to be utilized in the toxicological evaluation should take into account the  
280 bioavailability of the material (i.e., nature, degree, frequency, duration and conditions  
281 of exposure of the device to the body). This principle may lead to the categorization of  
282 devices which would facilitate the selection of appropriate tests.  
283
  - 284 4. Any *in vitro* or *in vivo* experiments or tests should be conducted in accordance with  
285 recognized Good Laboratory Practice (GLP) including, but not limited to, the  
286 assignment of competent trained staff in the conduct of biocompatibility testing. If  
287 information on nonclinical laboratory studies is provided, a statement that all such  
288 studies have been conducted in compliance with applicable requirements in the Good  
289 Laboratory Practice regulation in 21 CFR Part 58 should be provided. Alternatively, if  
290 any such study was not conducted in compliance with such regulation, a brief statement  
291 of the reason for the noncompliance should be provided, and a scientific justification is  
292 needed to support the validity of the testing performed.  
293
  - 294 5. Full experimental data, complete to the extent that an independent conclusion could be  
295 made, should be submitted to the reviewing authority unless testing is conducted  
296 according to a recognized standard that does not require data submission.  
297
  - 298 6. Any change in chemical composition, manufacturing process, physical configuration or  
299 intended use of the device should be evaluated with respect to possible changes in  
300 toxicological effects and the need for additional toxicity testing.  
301
  - 302 7. The toxicological evaluation performed in accordance with this guidance should be  
303 considered in conjunction with other information from other non-clinical tests, clinical  
304 studies and post-market experiences for an overall safety assessment.  
305

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### 306 **C. The FDA Modified Matrix**

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

310  
311 The matrix in this guidance consists of two tables. Attachment A, Table 1 - Initial Evaluation  
312 Tests for Consideration, includes tests for consideration recommended by ISO 10993-1:2009,  
313 and additional tests FDA recommends for consideration as previously identified in G95-1.  
314 Attachment B, Table 2 - Supplementary Evaluation Tests for Consideration, are not included in  
315 the 2009 version of ISO 10993-1, but were included in previous revisions of ISO 10993, as well  
316 as G95-1. In addition, Attachment C is a biocompatibility flow chart for the selection of toxicity  
317 tests, and is slightly revised from #G95-1. Additional testing may be requested to fully  
318 characterize the toxicology profile, if novel materials or manufacturing processes are used (i.e.,  
319 materials or processes that have not previously been used in a marketed medical device with the  
320 same type and duration of contact).

321  
322 If your device has multiple types of exposure, you should consider testing from both categories  
323 for your device. For example, devices that contact the patient gas pathway (i.e., masks, tubing)  
324 are externally communicating due to the potential for chemical leachants from the device to enter  
325 the patient airway. Some gas pathway contacting devices may also fall into an additional  
326 category such as skin or mucosal membrane contact. Endotracheal tubes are classified by ISO  
327 10993-1 as being mucosal contact. However, these devices are an extension of the gas pathway  
328 acting as a conduit to the patient airway and lungs. Therefore, we have considered these devices  
329 to be classified as both mucosal contact and externally communicating for evaluation of  
330 biocompatibility.

331  
332 While in general, FDA agrees with the framework established in ISO 10993-1, FDA has made  
333 several modifications to the testing identified in that standard for the reasons outlined below.

#### 334 **Attachment A, Table 1 – Initial Evaluation Tests for Consideration**

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

340  
341  
342 FDA has also suggested that irritation tests be considered for a broader set of devices/patient  
343 exposures than outlined in ISO 10993-1:2009. For example, devices with indirect contact with  
344 the blood could introduce chemical leachants from the device infusion channel that could be  
345 irritants, and therefore should be investigated with additional tests.

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

352  
353 In addition, sponsors are advised to consider conducting a separate test to detect chemical  
354 components of device materials which may be pyrogenic. This type of material-mediated  
355 pyrogenicity is identified as a subset of acute systemic toxicity in Part 1 of ISO 10993. See also  
356 Section 5 for more information about assessment of pyrogenicity.

357  
358 If it is unclear in which category a device falls, we recommend consulting device-specific  
359 guidance or contacting the appropriate review division for more information. For example, FDA  
360 has historically considered devices used to drain fluids (such as Foley catheters) as externally  
361 communicating devices rather than as surface devices contacting mucosal membranes.

362  
363 **Attachment B - Table 2 - Supplementary Evaluation Tests for Consideration**  
364 Previous revisions of ISO 10993 included tabular indications for when chronic toxicity and  
365 carcinogenicity testing should be considered. With ISO 10993-1:2009, these columns, along  
366 with the columns for biodegradation and reproductive and developmental toxicity were removed  
367 from the tables and instead Annex A now states: “In addition to the framework set out in Table  
368 A.1, the following should be considered based on a risk assessment, which considers the specific  
369 nature and duration of exposure: chronic toxicity, carcinogenicity, biodegradation,  
370 toxicokinetics, immunotoxicity, reproductive/developmental toxicity or other organ-specific  
371 toxicities.” For permanent devices in contact with the mucosal membrane, breached or  
372 compromised surfaces, the blood path, or tissue/bone/dentin, FDA recommends that chronic  
373 toxicity be considered, since there could be toxicities associated with long-term contact that  
374 might not be detected with short-term assessments. In addition, FDA recommends that  
375 carcinogenicity testing be considered for all permanent externally-communicating and implanted  
376 devices, unless chemical characterization testing and data from the literature are provided to  
377 justify omission of this type of testing.

378  
379 **Attachment C – Biocompatibility Flow Chart**  
380 Attachment C includes a flow chart which outlines how FDA reviewers historically have  
381 assessed whether any biocompatibility testing is needed, and how information provided by the  
382 sponsor may support the biocompatibility of the final, sterilized device.

383  
384 **D. Test Selection**

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

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

394  
395 ISO 10993, Part 1, Section 4.1 states that “Evaluation may include both a study of relevant  
396 preclinical and clinical experience and actual testing. Such an evaluation might result in the  
397 conclusion that no testing is needed if the material has a demonstrable safe history of use in a  
398 specified role and physical form that is equivalent to that of the device under design.”<sup>8</sup> In order  
399 to conclude that no additional testing is needed, the sponsor should provide evidence that for  
400 each material, the intended use, physical form, formulation, processing, component interactions,  
401 and storage conditions are the same as for the comparator product(s). In cases where there are  
402 differences, these need to be explained and justified. Clinical data may be of limited utility if  
403 specific toxicology endpoints are not included in the monitoring plan.

404

## 405 **4. General Biocompatibility Testing Considerations**

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

410

### 411 **A. Use of Final Product or Representative Sample**

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

419

### 420 **B. In Situ Polymerizing and Bioabsorbable Materials**

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

---

<sup>8</sup> *Ibid.*

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

431

### **C. Biological Response Resulting from Device Mechanical Failure**

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

447

### **D. Submicron or Nanotechnology Components**

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

458

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<sup>9</sup> 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.

<sup>10</sup> Gil, P.R.; Oberdorster, G.; Elder, A.; Puentes, V.; Parak, W.J. “Correlating physico-chemical with toxicological properties of nanoparticles: the present and the future” *ACS Nano*, 2010, 4, 5527-5531.

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

- 461
- 462 • Careful characterization of the test sample.
- 463 • Selection of extract conditions (e.g., solvent type) that avoid testing artifacts that are not  
464 clinically relevant.
- 465 • Assurance that the test article used is representative of what will be used clinically.
- 466

467 For test selection, the following items are also important:

- 468
- 469 • Consideration of standard biocompatibility tests in the context of contemporary literature  
470 on the validity of individual tests for assessment of submicron components.
- 471 • Assurance that the sub-micron components will not interfere with the conduct of a chosen  
472 test.
- 473 • Consideration of any additional toxicity issues that might be relevant to submicron  
474 particles, such as absorption, distribution and accumulation into organs, potential  
475 metabolism, and elimination, since there are greater concerns associated with submicron  
476 particles that cannot be readily detoxified and/or eliminated from the body.
- 477

## 478 **E. Sample Preparation for Extract Testing**

479 For biocompatibility testing conducted using extracts of samples,<sup>11</sup> we recommend that you:

- 480
- 481 • Determine the appropriate amount of test material as outlined in ISO 10993-12<sup>12</sup> or an  
482 equivalent method, using surface area to extractant volume ratios. Mass to extractant  
483 volume ratios should only be used if surface area cannot be calculated, or if use of mass  
484 will result in a larger sample. If there is a need for an alternate extraction ratio,  
485 appropriate justification should be provided. For some test systems, there may be  
486 standardized alternatives for test-specific extraction conditions that may provide a  
487 different level of extraction (e.g., guinea pig maximization testing per ISO 10993-10,  
488 Annex E).<sup>13</sup>
- 489
- 490 • Use both polar and nonpolar extractants. In some cases, other solvents may be used,  
491 where appropriate. For example, mixed polarity solvents (e.g., ethanol/water 20:80) may  
492 be useful to optimize extraction of certain amphiphilic molecules that pose toxicity  
493 concerns. Also, where devices do not have direct body contact but only have indirect

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<sup>11</sup> For biocompatibility testing, extracts could include residuals at the surface of testing samples or leachables migrating from the bulk of test samples.

<sup>12</sup> ISO 10993-12: 2007 “Biological evaluation of medical devices – Part 12: Sample preparation and reference materials.”

<sup>13</sup> ISO 10993-10: 2010 “Biological evaluation of medical devices – Part 10: Tests for irritation and skin sensitization.”

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494 contact via a polar solution (e.g., qualification of the inner channel material of a  
495 cardiovascular catheter where the inner channel is only used for the infusion of saline),  
496 justification for omission of testing with a non-polar solution may be acceptable.  
497

- 498 • Use extraction conditions that are adequate for testing of leachables from the device  
499 given its expected use. Traditional biocompatibility extraction methods, such as those in  
500 ISO 10993-12 (e.g., 37°C for 72 hours; 50°C for 72 hours; 70°C for 24 hours; or 121°C  
501 for 1 hour) are acceptable for many biocompatibility tests. For prolonged contact devices  
502 and permanent implants, testing at 37°C may not be sufficient to obtain an extract that  
503 represents the chemicals that may leach out over the use life of the device. However, in  
504 some cases, temperatures above 37°C result in degradants that may not occur in clinical  
505 use and may result in toxicities not representative of the final product. Therefore, a  
506 justification for the selected extraction conditions should be provided.  
507
- 508 • Describe the condition of the test extract (e.g., color, presence of any particles), and  
509 explain any changes in the test extract (pre- and post-extraction) and the source of these  
510 changes (e.g., test article degradation).
- 511
- 512 • Use the extracts without additional processing (e.g., no filtration, centrifugation or other  
513 methods to remove particulates; no pH adjustment), unless otherwise justified.
- 514
- 515 • If extraction samples are not used immediately, we recommend that you use them within  
516 the time frame outlined in ISO 10993-12 or an equivalent method. We recommend that  
517 you describe the details of storage conditions for the test extract, and explain why storage  
518 will not affect your test results (i.e., as stated in ISO 10993-12, “stability and  
519 homogeneity of extract under storage conditions shall be verified”).  
520

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

522 For products that include components with different lengths of contact (e.g., limited, prolonged  
523 or permanent), we recommend that you conduct extraction tests on the components separately. If  
524 the components are combined into a single test sample, this will dilute the amount of component  
525 materials being presented to the test system and may not identify potentially toxic agents that  
526 would have been found if the components were tested separately. For example, this would  
527 include implants with delivery systems and certain kits.  
528

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

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

535

## 536 **5. Test-Specific Considerations**

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

541

### 542 **A. Cytotoxicity**

543 For tests where the sample is extracted in growth media, we recommend that extractions be  
544 conducted at 37°C for 24 hours using a vehicle that will allow for extraction of both polar and  
545 nonpolar constituents from the test sample, such as mammalian cell culture media (MEM) and  
546 5% serum.

547

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

551

### 552 **B. Sensitization**

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

555

#### 556 **Guinea Pig Maximization Test (GPMT)**

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

560

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



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571  
572 If a primary irritation study is not included in the sensitization protocol, adverse findings at the  
573 end of the study may be due to irritation or sensitization, and additional studies to determine the  
574 causality may be needed.

575

#### 576 **Local Lymph Node Assay (LLNA)**

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

580

- 581 • The LLNA can be used for testing metal compounds (with the exception of nickel and  
582 nickel-containing metals) unless there are unique physicochemical properties associated  
583 with these materials that may interfere with the ability of the LLNA to detect sensitizing  
584 substances.
- 585
- 586 • The LLNA can be used for testing substances in aqueous solutions unless there are  
587 unique physicochemical properties associated with these materials that may interfere with  
588 the ability of the LLNA to detect sensitizing substances. When testing substances in  
589 aqueous solutions, it is essential to use an appropriate vehicle, to maintain the test  
590 substance in contact with the skin (e.g., 1% Pluronic L92<sup>14</sup>) so that adequate exposure  
591 can be achieved, as demonstrated by positive control results.

592

593 LLNA may not be appropriate in the following circumstance:

594

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

598

599 If LLNA testing is performed, CDRH recommends that a fully validated standardized method be  
600 used. Currently, the only CDRH-recognized validated method is a radioactive LLNA test  
601 performed using ASTM F2148.<sup>15</sup>

602

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

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<sup>14</sup> 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.

<sup>15</sup> ASTM F2148-07e1 "Standard Practice for Evaluation of Delayed Contact Hypersensitivity Using the Murine Local Lymph Node Assay (LLNA)."

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- 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)  $\geq 1.6$  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)  $\geq 1.8$  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).
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### C. Hemocompatibility

625

626 For blood-contacting devices (regardless of contact duration), we recommend that you consider hemolysis, immunology (complement activation), and thrombogenicity testing. If testing is not

627 conducted, we recommend that you provide a scientific justification for omission of a test. For

628 example, complement activation and *in vivo* thrombogenicity testing is not generally needed for

629 indirect blood-contacting devices.

630

631

632 For hemolysis testing, we recommend that both direct and indirect (extract) methods be

633 conducted per ASTM F756,<sup>16</sup> or an equivalent method (e.g., NIH Autian method).<sup>17,18</sup>

634

635 Immunology testing should appropriately address the various complement activation pathways.

636 We recommend that you assess direct contact *in vitro* C3a and SC5b-9 fragment activation using

637 established testing methods such as an ELISA test. In addition, equivalent complement testing

638 methods such as ASTM F2065<sup>19</sup> and ASTM F1984<sup>20</sup> can be used. Alternatively, you may

---

<sup>16</sup> ASTM F756-08 “Standard Practice for Assessment of Hemolytic Properties of Materials.”

<sup>17</sup> Autian J, “Toxicological Evaluation of Biomaterials: Primary Acute Toxicity Screening Program,” *Artif Organs*. 1977 Aug;1(1):53-60.

<sup>18</sup> 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.

<sup>19</sup> ASTM F2065-00(2010) “Standard Practice for Testing for Alternative Pathway Complement Activation in Serum by Solid Materials.”

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

642  
643 We recommend thrombogenicity be assessed as part of a safety study conducted in a relevant  
644 animal model, where such a study is planned for other reasons. Alternatively, for many types of  
645 devices where animal safety studies are not conducted, a 4-hour canine venous unheparinized  
646 model can be used to assess thrombogenicity. In some cases (e.g., if your device includes novel  
647 materials, or there are questionable findings from the animal safety study), a 4 hour canine *in*  
648 *vivo* thrombogenicity test may be necessary in addition to the animal safety study. If only a  
649 portion of the device is being utilized for thrombogenicity testing, the sponsor should confirm  
650 that the sample is representative of all materials that would be in direct contact with blood. In  
651 addition, we recommend that for all *in vivo* thrombogenicity assessments, regardless of whether  
652 evaluation was from the safety study or canine model, color photographs of the device/vessel  
653 explants should be provided.

654  
655 While the 4 hour canine *in vivo* thrombogenicity study has limitations, it has historically  
656 provided useful information on how synergistic mechanisms (e.g., material and geometry of the  
657 device) cause thrombosis. The vessel to device ratio should be considered, such that larger  
658 vessels are used for larger diameter devices to maintain a diameter relationship similar to what  
659 will be seen in patients. In the 4 hour canine *in vivo* thrombogenicity study, we do not  
660 recommend the use of anticoagulation because the presence of anticoagulant will likely confound  
661 the assessment of the thrombogenic potential of a device in this model, making the study non-  
662 informative, which would be contrary to the Agency's position on minimizing animal use. Also,  
663 the data from the unheparinized model could be used to assess the risk of thrombus formation in  
664 the patient population where anticoagulants cannot be used for clinical reasons even if the device  
665 is indicated for use with anticoagulation. For devices with elevated thrombus scores (i.e., not  
666 thromboresistant), it may be necessary to screen for device related characteristics, such as  
667 surface defects, that may contribute to greater thrombogenicity. Additionally, we may  
668 recommend that you repeat the study with heparinization to confirm that heparinization will  
669 counter the thrombogenic response seen in the unheparinized study. In these cases, labeling  
670 should be considered that contraindicates use of the subject device in unheparinized patients.  
671 For some devices for which a 4 hour canine venous thrombogenicity model is not appropriate,  
672 such as oxygenators, a series of *in vitro* blood damage assessments (both static and dynamic) can  
673 be used to support regulatory submissions, if adequate rationales are provided.

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<sup>20</sup> ASTM F1984-99(2008) "Standard Practice for Testing for Whole Complement Activation in Serum by Solid Materials."

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### 675 **D. Pyrogenicity**

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

683  
684 We recommend that you assess material-mediated pyrogenicity using traditional  
685 biocompatibility extraction methods (e.g., 50°C for 72 hours; 70°C for 24 hours; or 121°C for 1  
686 hour per ISO 10993-12), using a pyrogenicity test such as the one outlined in the USP 34 <151>  
687 Rabbit Pyrogen Test or an equivalent validated method. For devices that contain heat labile or  
688 heat sensitive materials, (e.g., drugs, biomolecules, tissue derived components) which may have  
689 the potential to undergo deformation or material configuration/structural change at high  
690 temperature, sample extraction at 37°C per ISO 10993-12 is recommended.

691  
692 Bacterial pyrogens are traditionally addressed as part of the sterility assessment. We recommend  
693 that you refer to the most recent sterility guidance document for recommendations related to  
694 testing to determine endotoxin levels for sterile devices.<sup>21</sup>

695  
696 We recommend that both the bacterial endotoxin and rabbit material mediated pyrogen testing be  
697 conducted for devices that do not need to meet pyrogen limit specifications because of the nature  
698 of body contact but intend to be labeled as ‘non-pyrogenic.’

### 700 **E. Implantation**

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

707

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<sup>21</sup> 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.

<sup>22</sup> 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.

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

717  
718 Clinically relevant implantation and muscle implantation tests may be informative to the overall  
719 toxicity assessment of both the material components of the product and the final product when  
720 used in its intended anatomical location. Muscle implantation tests may be omitted when  
721 clinically relevant implantation studies are conducted. However, the muscle implantation study  
722 may be helpful as a screening test to look at local toxicities. For example, because the muscle  
723 implants tend to form a fibrous capsule around the implant, any materials eluted over time from  
724 the test article will be contained within the capsule, and therefore might result in an exaggerated  
725 response that might not necessarily be observed in the site-specific implant study. In addition, a  
726 well-defined muscle implantation study is often helpful to interpret the data from clinically  
727 relevant implantation studies that may include other confounding factors (e.g., concomitant  
728 treatments may interfere with tissue response). Therefore, muscle implantation studies should be  
729 considered as a supplemental test even when clinically relevant implantation studies are  
730 performed, especially when new materials/chemicals are used in a medical device or the results  
731 of the clinically relevant implantation study raise toxicity concerns.

732  
733 For implantation testing of products with materials that intentionally degrade, we recommend  
734 that tests include interim assessments to determine the tissue response during degradation (i.e.,  
735 when there is minimal or no degradation, if applicable; during degradation; and once a steady  
736 state has been reached with respect to material degradation and tissue response). Selection of  
737 interim assessment time points may be based on *in vitro* degradation testing.

738

## **F. Genotoxicity**

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

743

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744 Because no single test can detect all genotoxins, we recommend the following 3 tests be  
745 conducted:<sup>23</sup>

746

- 747 • Bacterial gene mutation assay. This test is conducted with engineered strains of  
748 *Salmonella typhimurium* and *Escherichia coli* designed to detect all possible single base  
749 pair changes as well as frameshift mutations (OECD 471<sup>24</sup>).
- 750 • An *in vitro* mammalian genotoxicity assay. A choice of one of the following is  
751 recommended:
  - 752 a) the Mouse Lymphoma gene mutation assay (OECD 476<sup>25</sup>), which is preferred since it  
753 detects the broadest set of genotoxic mechanisms associated with carcinogenic  
754 activity;
  - 755 b) an *in vitro* chromosomal aberration (CA) assay (OECD 473<sup>26</sup>); or
  - 756 c) an *in vitro* micronucleus assay (OECD 487<sup>27</sup>).
- 757 • An *in vivo* cytogenetics assay. A choice of one of the following is recommended:
  - 758 a) a bone marrow micronucleus (MN) Assay (OECD 474<sup>28</sup>);
  - 759 b) a bone marrow chromosomal aberration (CA) assay (OECD 475<sup>29</sup>); or
  - 760 c) a peripheral blood MN assay.

761

762

## 763 G. Carcinogenicity

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

770

- 771 • Include the complete chemical formulations and manufacturing residuals for all  
772 components of the device. The sponsor should identify how much of each chemical  
773 would theoretically be present in an individual device (assume worst-case, e.g., the  
774

---

<sup>23</sup> All of the OECD guidelines referenced in this section are incorporated by reference in ISO 10993-3, which is recognized by FDA.

<sup>24</sup> OECD 471 (1997) “Guidelines for Testing of Chemicals – Bacterial Reverse Mutation Test”

<sup>25</sup> OECD 476 (1997) “Guidelines for the Testing of Chemicals – *In Vitro* Mammalian Cell Gene Mutation Test”

<sup>26</sup> OECD 473 (1997) “Guidelines for the Testing of Chemicals – *In Vitro* Mammalian Chromosome Aberration Test”

<sup>27</sup> OECD 487 (2010) “Guidelines for the Testing of Chemicals – *In Vitro* Mammalian Cell Micronucleus Test”

<sup>28</sup> OECD 474 (1997) “Guidelines for the Testing of Chemicals – Mammalian Erythrocyte Micronucleus Test”

<sup>29</sup> OECD 475 (1997) “Guidelines for the Testing of Chemicals – Mammalian Bone Marrow Chromosome Aberration Test”

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

- 781
- 782 • Identify potential leachants and breakdown products (which may not be included as  
783 original materials or processing agents). Consideration should be given to the effects of  
784 all processing agents (e.g., adhesives, mold cleaning agents, mold releasing agents,  
785 sterilization chemicals) that come into contact with the device.  
786
  - 787 • Provide a thorough literature review, identify the search terms, and conduct an analysis of  
788 the toxicity of the chemicals. If potential carcinogens are found in the device, the  
789 sponsor should identify and quantify these chemicals and determine how much of the  
790 potential carcinogen and/or carcinogenic byproducts would be available in a single  
791 product in a worst-case scenario (e.g., assuming 100% formation of the potential  
792 carcinogens, and 100% bioavailability). A cancer risk assessment should also be  
793 provided with literature evidence to demonstrate that the amount of the potential  
794 carcinogen(s) available in a device does not pose an unacceptable carcinogenic risk. This  
795 analysis should also be provided assuming a maximum number of devices likely to be  
796 placed in a single patient in clinical use.

797

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

- 801
- 802 • Standard rodent long term carcinogenicity bioassays (OECD 451<sup>30</sup> or OECD 453<sup>31</sup>) to  
803 evaluate the potential for systemic carcinogenic effects. FDA recognizes that solid-state  
804 carcinogenicity occurs frequently in rodents. In the event that local tumors are present,  
805 FDA recommends that the sponsor provide a discussion of the potential for chemically-  
806 induced as well as solid state carcinogenicity.  
807
  - 808 • RasH2 transgenic mouse model, with confirmation of stability of transgene status. FDA  
809 recommends that prior to conducting carcinogenicity testing, the sponsor discuss  
810 proposed testing with CDRH to ensure that the study design is appropriate to assess the  
811 potential risk.

812

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<sup>30</sup> OECD 451 (2009) “Guidelines for the Testing of Chemicals – Carcinogenicity Studies”

<sup>31</sup> OECD 453 (2009) “Guidelines for the Testing of Chemicals – Combined Chronic Toxicity/ Carcinogenicity Studies”

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813 **H. Reproductive and Developmental Toxicity**

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

825

826 **I. Biodegradation Testing**

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

837

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

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

847



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848 **7. Assessment of Known or Potentially Toxic Chemical**  
849 **Entities**

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

854  
855 CDRH evaluates the safety of medical devices based on duration of exposure and nature of  
856 contact. Inherent in the review of medical devices is an understanding of the body's entire  
857 exposure to the product, including all chemical entities contained within the product. For  
858 devices containing these unknown or potentially toxic chemicals, such as color additives, the  
859 evaluation of safety should be based on both the risk of the chemical (i.e., the level of  
860 toxicological concern) and the duration of exposure (i.e., bioavailability).

861  
862 Based on these principles, the following information will guide CDRH's assessment of these  
863 chemicals.

864  
865 For all devices containing such chemical(s), the following descriptive information should be  
866 provided:

- 867  
868 1. The identity of the chemical by common name, chemical name, and Chemical Abstract  
869 Services (CAS) number.
- 870  
871 2. If known,<sup>32</sup> the composition (i.e., if a color additive, whether the colorant is comprised of  
872 a pigment or encapsulated in polymer), formula and formula weight, structural  
873 information, and manufacturing and purity information on the chemical, such as a  
874 detailed description of the manufacturing process (including the substances used and the  
875 amounts used in the synthesis, reaction conditions), specifications for the chemical,  
876 analysis of multiple batches of the chemical, and identification of major impurities;<sup>33</sup>
- 877  
878 3. The specific amount of each chemical in the formulation by weight percent of the  
879 applicable component and total amount (e.g., µg) in the device;
- 880

---

<sup>32</sup> 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.

<sup>33</sup> 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>.

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- 881 4. The identity of any other devices marketed in the U.S. (by device name, manufacturer,  
882 and submission number) where the chemical entity has been previously used, if known,  
883 and provide comparative information on the composition and amount(s) used.  
884

885 In addition, to evaluate the bioavailability of the chemical to the patient, the following exposure  
886 information should be provided:  
887

- 888 5. An exposure assessment for each chemical (i.e., whether the chemical and, for color  
889 additives, any relevant associated impurities, is bioavailable). Note that for certain  
890 chemicals, elution from the device may not be necessary for the chemical to induce  
891 toxicity. If testing is conducted to demonstrate that the chemical is not bioavailable,  
892 provide the test report, including details of the test conditions, to confirm that the  
893 chemical is stable under the intended conditions of use.  
894

895 If the information above demonstrates that the chemical is not bioavailable, either because the  
896 chemical is physically sequestered in a device component with no direct or indirect patient  
897 contact, or based on the results of testing conducted as described in 5 above, **no further  
898 information is necessary.**

899  
900 If the information above suggests that the chemical is bioavailable, the following toxicological  
901 information should be provided:  
902

- 903 6. A safety assessment for each chemical entity using toxicity information from the  
904 literature and available, unpublished studies for all known toxic effects. Where the full  
905 toxicology profile for the chemical entity is not available, either from the supplier or from  
906 a previous medical device submission, the full battery of toxicity tests on the chemical  
907 entity (i.e., tests in addition to those outlined in Attachments A and B, including but not  
908 limited to genotoxicity; reproductive and developmental toxicity; and carcinogenicity)  
909 may also be needed or a scientific rationale provided for their omission.  
910

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

918  
919 However, if the bioavailability of the total amount of the chemical would lead to potential  
920 toxicity concerns, further information will be needed to determine how much of the chemical is

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

923

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

928

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

931

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

935

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

942

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

944

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

951

952 10. Determination of the need for batch certification in accordance with regulations issued  
953 under 721(c) for that use (i.e., color additives not requiring certification are listed under  
954 21 CFR 73 (Subpart D)). Color additives that require batch certification are listed under  
955 21 CFR 74 (Subpart D), and detailed manufacturing information may be needed.

956

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

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961 in the literature, regardless of the length of bioavailability, then a CFSAN review of a  
962 CAP would also be necessary.  
963

## 964 **8. Labeling Devices as “-Free”**

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

979  
980 Sponsors who currently include statements such as “latex-free” or “DEHP-free” in medical  
981 product labeling should update their medical product labeling to show the recommended labeling  
982 statement as described above. Alternatively, sponsors should consider removing “latex-free”  
983 type statements from medical products and medical product packaging.  
984

## 985 **9. Contents of a Test Report**

986 In order to assess biocompatibility testing or chemical characterization performed to support an  
987 IDE or marketing application, FDA recommends that full test reports be provided for all tests  
988 performed. In general, the test reports should include the sections described below.  
989

### 990 **Sample Preparation**

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

---

<sup>34</sup> 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>.

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

995

#### **996 Test Method**

997 The test report should provide a summary of the method used. If the method used is not in a  
998 published standard or guidance document, a full description of the method should be provided.  
999 If the test method is a modified version of a method in a published standard or guidance  
1000 document, the test report should include an explanation of the differences and their potential  
1001 impact on interpretation of the results.

1002

1003 The test report should identify any protocol deviations and their impact on the conclusions drawn  
1004 from the test.

1005

#### **1006 Test Parameters and Acceptance Criteria**

1007 The test report should identify the test parameters and acceptance criteria applied. If the test  
1008 method is not in accordance with a published standard or guidance document that includes  
1009 defined acceptance criteria, a rationale for the acceptance criteria should be provided.

1010

#### **1011 Analysis of Results**

1012 The test report should provide a summary of the test results, and include tables with each data  
1013 point, and statistical analyses, where appropriate. For example, the test report for hemolysis  
1014 should include a description of the test, blank, positive, and negative supernatant conditions, in  
1015 addition to the absorbance and percent hemolysis data.

1016

1017 For any test in which the results indicate a potential toxicity, the report should include a  
1018 discussion of any test-specific issues that might have affected results, and any other available  
1019 information (such as the results of animal safety studies) that might provide additional context  
1020 for interpretation. For example, if a device made from polypropylene results in a grade 2  
1021 cytotoxicity in an L929 assay, which might be acceptable per ISO 10993-5, the sponsor should  
1022 provide additional information regarding the potential source of the toxicity, since polypropylene  
1023 is not generally expected to be cytotoxic. Conversely, skin-contacting electrodes with adhesives  
1024 containing detergents might be expected to have higher than grade 2 cytotoxicity in an L929  
1025 assay, which could be acceptable if the sponsor is able to confirm that there are no other  
1026 chemical constituents causing the adverse cytotoxic response. In general, potential toxicities  
1027 identified through biocompatibility testing should be evaluated considering the intended use of  
1028 the device and as part of the overall benefit/risk assessment.

1029

#### **1030 Conclusions**

1031 The test report should describe the conclusions drawn from the test results, and the clinical  
1032 significance of the conclusions.

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1033

1034 **10. Component and Device Documentation Examples**

1035 In certain instances, it may not be clear how the test article compares to the final device. In other  
1036 cases, a sponsor may choose not to perform certain tests, based on the fact that the current  
1037 product is the same as a previously tested product. The following examples may be helpful to  
1038 document a rationale for these approaches.

1039

1040 **A. Component Documentation**

1041 For each component and any joining processes/materials (e.g., adhesives, sintering processes),  
1042 either of the following statements can be provided:

1043

1044 **Comparison to test article:** "The [polymer/metal/ceramic/composite name] [component  
1045 name] of the test article is identical to the [component name] of the final sterilized device in  
1046 formulation, processing, sterilization, and geometry, and no other chemicals have been added  
1047 (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents)."

1048

1049 **Comparison to previously marketed device:** "The [polymer/metal/ceramic/composite  
1050 name] [component name] of the final sterilized device is identical to the [component  
1051 name] of the [name] (previously marketed device<sup>35</sup>) in formulation, processing, sterilization,  
1052 and geometry, and no other chemicals have been added (e.g., plasticizers, fillers, color  
1053 additives, cleaning agents, mold release agents)."

1054

1055 **B. Device Documentation**

1056 If the above statement is true for all of the fabrication material formulations, processes, and  
1057 sterilization methods (if applicable), either of the following general statements can be provided:

1058

1059 **Comparison to test article:** "The test article is identical to the final sterilized device in  
1060 formulation, processing, sterilization, and geometry and no other chemicals have been added  
1061 (e.g., plasticizers, fillers, color additives, cleaning agents, mold release agents)."

1062

1063 **Comparison to previously marketed device:** "The final sterilized device is identical to  
1064 [name] (previously marketed device) in formulation, processing, sterilization, and geometry  
1065 and no other chemicals have been added (e.g., plasticizers, fillers, color additives, cleaning  
1066 agents, mold release agents)."

1067

---

<sup>35</sup> We recommend that you include the submission number and date of submission where the reference device was approved or cleared.

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1068 **C. New Processing/Sterilization Changes**

1069 If there are any processing or sterilization changes that the sponsor believes will *not* alter the  
1070 biocompatibility of the final, sterilized device, the sponsor should use the component  
1071 documentation language, and include either of the following qualifiers:  
1072

1073 **Comparison to test article:** "...with the exception of [identify change]. FDA submission  
1074 exhibit [#], page [#], submitted on [date], provides scientific information to demonstrate that  
1075 the [processing/sterilization] change does not alter the chemical or physical properties of the  
1076 final sterilized product, and therefore, results from the test article can be applied to the final  
1077 sterilized product."  
1078

1079 **Comparison to previously marketed device:** "...with the exception of [identify change].  
1080 FDA submission exhibit [#], page [#], submitted on [date], provides scientific information to  
1081 demonstrate that the [processing/sterilization] change does not alter the chemical or  
1082 physical properties of the final sterilized product, and therefore, results from the [name]  
1083 (previously marketed device) can be applied to the final sterilized product."  
1084

1085 NOTE: The information provided to support a claim that processing and sterilization  
1086 changes will not affect chemical or physical properties of the final sterilized device should be  
1087 provided in sufficient detail for FDA to make an independent assessment, and arrive at the  
1088 same conclusion.  
1089

1090 NOTE: Changes in raw material suppliers or raw material specifications could introduce  
1091 different types or quantities of residual chemicals, and could result in a toxic response (even  
1092 if the base material has a long history of safe use in similar applications).  
1093

1094 NOTE: Surface alterations due to processing, even at the micron or submicron level, could  
1095 result in geometrical or chemical changes at the surface that could result in a toxic response  
1096 (even if the base material has a long history of safe use in similar applications).  
1097

1098 **D. New Formulation Changes**

1099 If there are any formulation changes the sponsor believes will *not* alter the biocompatibility of  
1100 the final, sterilized device, the sponsor should use the component documentation language, and  
1101 include the following qualifier:  
1102

1103 **Comparison to test article:** "...with the exception of [identify change]. FDA submission  
1104 exhibit [#], page [#], submitted on [date], provides scientific information to demonstrate that  
1105 the formulation change does not alter the chemical or physical properties of the final

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1106 sterilized device, and therefore, results from the test article can be applied to the final  
1107 sterilized device.”

1108  
1109 **Comparison to previously marketed device:** "...with the exception of [identify change].  
1110 FDA submission exhibit [#], page [#], submitted on [date], provides scientific information to  
1111 demonstrate that the formulation change does not alter the chemical or physical properties of  
1112 the final sterilized device, and therefore, results from the [name] (previously marketed  
1113 device) can be applied to the final sterilized device.”

1114  
1115 For example, if your predicate device contains a Pebax resin, and your subject device  
1116 contains a new grade of Pebax, your documentation should include a qualifier that states that  
1117 the untested Pebax grade varies only in the concentration of specific formulation  
1118 components. Formulation changes that introduce novel components, or a higher  
1119 concentration of an existing component, may require new testing if the upper and lower  
1120 bounds of each component have not been previously evaluated.

1121  
1122 NOTE: The information provided to support a claim that formulation changes will not affect  
1123 chemical or physical properties of the final sterilized device should be provided in sufficient  
1124 detail for FDA to make an independent assessment and arrive at the same conclusion. To  
1125 support this assessment, FDA requests that the following be included:

- 1126 a. formulation of the test article;  
1127 b. formulation of the final sterilized product; and  
1128 c. a discussion of why the differences would not require additional testing.  
1129

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**Attachment A:**

**Table 1 – Initial Evaluation Tests for Consideration**

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1132

1133

Device categorization by			Biologic effect								
nature of body contact (see 5.2)											
Category	Contact	Contact duration (see 5.3)	Cytotoxicity	Sensitization	Irritation or Intracutaneous reactivity	Systemic toxicity (acute)	Subchronic toxicity (subacute toxicity)	Genotoxicity	Implantation	Haemocompatibility	
		A – limited (≤ 24 h)									B- prolonged (>24 h to 30 d)
Surface device	Intact skin	A	X	X	X						
		B	X	X	X						
		C	X	X	X						
	Mucosal membrane	A	X	X	X						
		B	X	X	X	O	O		O		
		C	X	X	X	O	X	X	O		
	Breached or compromised surface	A	X	X	X	O	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 <sup>†</sup>	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 <sup>Δ</sup>		X
		B	X	X	X	X	X	X	X	X	X
		C	X	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	

1134

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.

† This issue includes tissue fluids and subcutaneous spaces

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Note 139 For all devices used in extracorporeal circuits

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**Attachment B:**

**Table 2 – Supplementary Evaluation Tests for Consideration**

Device categorization by			Biologic effect			
nature of body contact (see 5.2)		Contact duration (see 5.3) <b>A – limited</b> (≤ 24 h) <b>B- prolonged</b> (>24 h to 30 d) <b>C – permanent</b> (> 30 d)	Chronic toxicity	Carcinogenicity	Reproductive/Developmental	Biodegradable
Category	Contact					
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 <sup>+</sup>	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		

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1141

1142

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1145

1146

1147

1148

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.

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1149

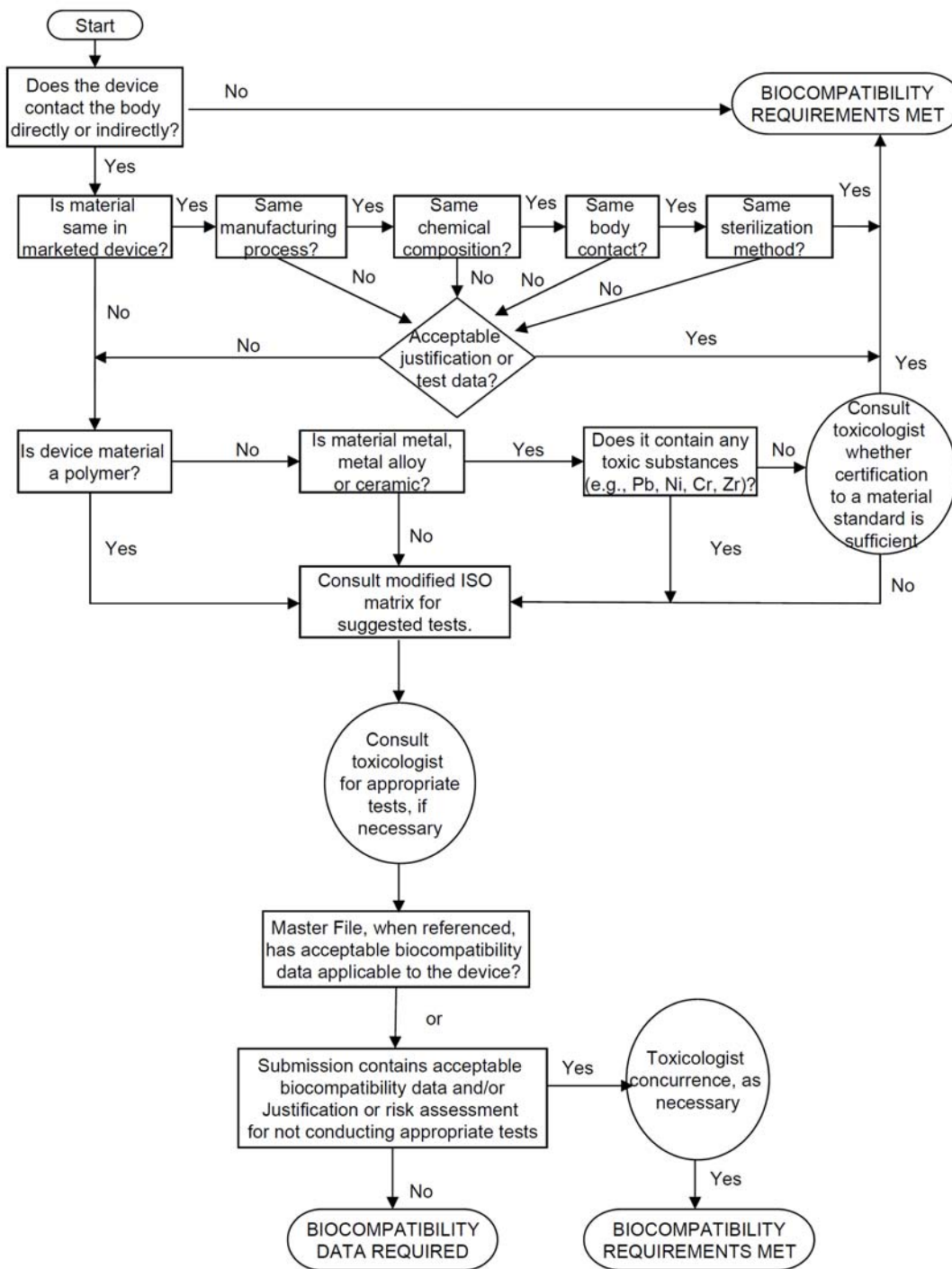
**Attachment C: Biocompatibility Flow Chart for the  
Selection of Toxicity Tests**

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