September 30, 2013

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2013-D-0920; Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems; Draft Guidance for Industry and Food and Drug Administration Staff

Dear Sir/Madam:

The Advanced Medical Technology Association (AdvaMed) provides these comments in response to a request for comments regarding the Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) “Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems; Draft Guidance for Industry and Food and Drug Administration Staff.” Notice of this draft guidance and request for comments were published in Fed. Reg. Vol.78, No. 169 (August 30, 2013).

AdvaMed is the world’s largest association representing manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures and more effective treatments. Our members range from the largest to the smallest medical technology innovators and companies. More than 70 percent of our members have less than $30 million in domestic sales annually. We welcome the opportunity to comment on this guidance and look forward to working with FDA to ensure the revised guidance meets the needs and expectations of both FDA and industry.

AdvaMed is pleased to provide these comments and appreciates the efforts of FDA to inform the coronary and peripheral stent industry about selected updates to FDA’s thinking regarding certain non-clinical testing for these devices. Knowing current thinking on testing requirements allows industry to accurately plan product development activities, including the prediction of realistic timelines and product development costs. It also allows industry to prepare high quality submissions and ensures all submissions for a product type address the same requirements.
This guidance clarifies FDA’s expectations for corrosion testing. However, as presentations at the FDA workshop (“Cardiovascular Metallic Implants: Corrosion, Surface Characterization, and Nickel Leaching”, March 8-9, 2012) made clear, there is no evidence that patients with intravascular metallic implants have been or are today being harmed by corrosion or leaching. Continued diligence, however, is required to minimize this potential harm.

Overall, we are in agreement with FDA’s suggestion to a stepwise approach to testing. We do, however, have suggestions for several provisions of the draft guidance. Please see Attachment A and the accompanying line-numbered draft guidance (Attachment B).

Sincerely,

/s/

Ruey C. Dempsey RAC
Associate Vice President
Technology and Regulatory Affairs
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<th>Change/comment</th>
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<tr>
<td>55</td>
<td>Change from:</td>
<td>Biodegradable stents composed of polymers are under development. Although these devices are non-metallic, they may contain radiopaque markers that could contain nickel.</td>
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<tr>
<td></td>
<td>…made of nitinol and other nickel-containing alloys…</td>
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<td>To:</td>
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<td></td>
<td>…made of or having components made of nitinol and other nickel-containing alloys…</td>
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<tr>
<td>78-80, 155-156</td>
<td>Provide clarification of “…established surface finishing process…”</td>
<td>Electroplating is listed as an example of an established surface finishing process, but other processes are equally acceptable including those that do not conform to ASTM standards. We suggest that the guidance elaborate on what criteria define an established surface finishing process.</td>
</tr>
<tr>
<td>78, 80, 153, 169</td>
<td>FDA should provide guidance that aligns with 21 CFR 820.30 Design Control, where the user needs are determined, the tests and specifications for the product are established and the product is tested to determine whether or not they meet the specification. The use of a priori specifications is, therefore, essential to scientific decision-making. As such, characterization testing should be done during product development or to establish appropriate acceptance criteria. It would be unfitting to conduct such testing after verification testing is complete, as suggested in this guidance document.</td>
<td>Specifically, it is not necessary for FDA to suggest additional testing “if results are inconclusive” when acceptance criteria should be established. Unfortunately, there are no widely established acceptance criteria defined for local surface atomic or chemical characterization. As a result, performing surface characterization testing when results from the initial characterization testing (e.g., pitting corrosion) “are inconclusive” will not conclude that a device is acceptable. In addition surface characterization has limited use in characterizing the safety and effectiveness of the full device as its sampling area is small. If, however, science supports such, FDA should add guidance on acceptable alternative surface characterization acceptance criteria (e.g., passivation layering chemical composition vs. depth, new material versus predicate comparable material) to set acceptance criteria for functional whole device tests such as the potentiodynamic pitting corrosion test.</td>
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## ADVAMED COMMENTS

**Draft Guidance for Industry and FDA Staff**

**Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems**

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<tr>
<td>94</td>
<td>Include instructions for providing a justification for not conducting pitting corrosion potential testing when the as-manufactured stent comprises non-metallic material.</td>
<td>Coronary stents comprising polymeric or ceramic materials will not undergo traditional pitting corrosion. This is due to the materials being electrical insulators as well as not possessing the reduction/oxidation chemistry of metallic materials.</td>
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<td>95</td>
<td>Delete &quot;The test set-up should meet the criteria outlined in ASTM G5 (figure 2, Table x2.1).&quot;</td>
<td>Including criteria from ASTM G5 is burdensome and unnecessary. ASTM F2129 is specified and contains adequate and appropriate guidance for corrosion testing.</td>
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<tr>
<td>104-106, 158-159, 182-184</td>
<td>Delete: “multiple lots (≥ 3).” Revise to include: &quot;lots sampled such that potential variations due to manufacturing can be assessed, with a justification for the number of samples tested.&quot;</td>
<td>It is unclear what additional value is added by performing characterization testing on a pre-determined, arbitrary number of lots as there are various methods to ensure that inter-lot and intra-lot variability is acceptable. For example, when the manufacturing process (cutting, electro-polishing, cleaning, passivation, etc.) for the respective metal/alloy has been well characterized, and the inter-lot and intra-lot variability has been established with acceptable results; the requirement to perform multiple lot assessment for other characterization tests provides little additional or no scientific value. Additionally, &quot;lots&quot; are defined differently in different companies and, therefore, will not represent the same sampling plan.</td>
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<tr>
<td>107</td>
<td>Delete: “Additional samples may be needed if there is wide variability in the test results.”</td>
<td>Too subjective to provide any guidance. Language implies that testing output is not at the appropriate design verification stage but at a development stage.</td>
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<td>116-118</td>
<td>Add: &quot;When it is not practical to separate the two stents, each test may be conducted by testing two paired, fatigued overlapping stents or other appropriate configurations.&quot;</td>
<td>It may not be practical to separate the stents without changing the corrosion potential or fretting damage. The durability tests may be setup specifically for testing the mechanical durability of the device and not setup to be a precursor to corrosion. Because these tests are for mechanical durability, the solution may not be controlled properly for a corrosion test, or specifically representative of the in-vivo environment, and could allow differential aeration cells to be developed; therefore, it would not provide realistic results on a subsequent pitting corrosion test.</td>
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**Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems**

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| 121-122     | **Delete:** “We recommend that you plot all polarization curves in one graph when practical”  
**Add:** “When practical and appropriate, a selection of polarization curves may be plotted together for a given sample group or sub-group to illustrate or graphically summarize results.” | At the sample sizes required for statistical support or addressing manufacturing variability, this is rarely practical. |
| 123-126     | To be consistent with ASTM F2129-08 section 11.6, replace 123-126 with “The pitting corrosion report contains a generic description of the appearance of any corrosion observed on the tested specimen.” | Generic description on post corrosion test sample is sufficient, because the corrosion test procedure described in the ASTM F2129-08 standard recognizes that the corrosion test is designed to intentionally reach conditions that are sufficiently severe to cause breakdown and deterioration of medical devices and may not necessarily be encountered in vivo. Consequently, there is no clinical relevancy established to the pitting corrosion test. Therefore, the additional details being proposed are not relevant. |
| 123-127     | **Revise:** “You should include images from visual inspection of your device before …… spatial distribution”  
**Change To:** “You should include results of the visual inspection of your device before and after testing to assess evidence of pitting. Images may be included to support these observations.” | The result of a visual inspection for pitting is the observation of pitting and not the generation of images. Images may be used to characterize the observations. |
**ADVAMED COMMENTS**

**Draft Guidance for Industry and FDA Staff**

**Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems**

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<td>127-132</td>
<td>Delete: “The materials, design, and fabrication processes specific to your stent may reduce or eliminate the applicability of generic literature or previous experience with stents that may be used to address pitting susceptibility in lieu of testing.” Add: “Generic literature or previous measured performance with the same stent design, materials and manufacturing process may address pitting susceptibility in lieu of additional testing. However, use of novel materials, design elements, or fabrication processes specific to a stent may impact, reduce or eliminate the applicability of generic literature or previous experience.” Revise: For example, the pitting corrosion resistance of nitinol is sensitive to processing variables such as heat treatment and surface finish; therefore, for a nitinol stent, generic literature is <em>not applicable</em> should <em>not be used as a primary data source</em> and you should characterize of the corrosion potential of the finished stent <em>should be conducted.</em></td>
<td>Original sentence lacks clarification of when testing is required, and thus, inconsistent with Guidance for Industry and FDA Staff - Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems, April 18, 2010. FDA should accept the potential value of generic literature during product characterization. For novel materials, it may be appropriate to reference generic literature. FDA should consider revising this language to broaden the use of generic literature to incorporate its use as a secondary data source. Because it is common for medical device manufacturer to use the same materials (same supplier, same material, same manufacturing, etc.) that have already been characterized and/or proven clinical safety record, this clarification is necessary.</td>
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<td>155</td>
<td>Remove recommendation to perform surface characterization as a blanket statement on all devices. Add: “…surface characterization of your device or provide justification for not performing the characterization.”</td>
<td>Endovascular therapies use various forms of finishing for stents from raw laser cut tube, raw wire, EP laser cut &amp; EP wire, and wire chemical etching without any known issues of corrosion from these devices. Looking at the oxide layer will not provide us with any additional information into the corrosion resistance of the material in application.</td>
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<td>161</td>
<td>Add: “For stents or polymeric scaffolds whose only metallic components are radiopaque markers, a justification pertaining to the marker purity or properties of a noble metal surface may replace surface characterization.”</td>
<td>Biodegradable, polymeric scaffolds or stents for coronary use are in development whose only metallic components are radiopaque markers. These markers may be relatively nickel free or composed of high purity noble metals. Many noble metals, and their alloys, do not have a surface oxide layer to characterize and the composition of the bulk material is indicative of the surface chemistry.</td>
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<td>Line(s) No.</td>
<td>Change/comment</td>
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<td>167-171</td>
<td>Revise: For devices containing nickel, we recommend that you consider the potential for nickel ion release from your device. Specifically, if when the corrosion resistance and passivation layer characterization results are inconclusive unexpected for your device. We recommend that you quantify nickel ion release from your device over time by measuring concentrations of nickel leached from the device into a fluid at physiologic temperature and pH.</td>
<td>FDA should consider revising the criteria for when Nickel ion release testing should be conducted. There are no criteria for what is a conclusively good passive layer. Therefore, by definition passive layer chemical characterization testing may always be inconclusive. Strict adherence to this guidance would then require Nickel ion release testing for all devices in this category.</td>
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<td>188-193</td>
<td>Remove recommendation for performing ‘Validation testing’ of analytical instruments used to conduct Nickel Ion release testing (biocompatibility).</td>
<td>As a requirement of the Quality System Regulation, “test system validation” is carried out for test systems used for validation and for associated test equipment. This recommendation is not necessary and necessitates adding similar language in other sections throughout this guidance document for consistency.</td>
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<tr>
<td>202</td>
<td>Revise: “If in vitro nickel leach testing is performed on a novel material or design/manufacturing change that increases nickel exposure, a risk assessment…”</td>
<td>Once an acceptable level of nickel exposure is established taking into consideration all nickel adverse effects applicable to the intended clinical use, repeating material risk assessment is only necessary when exposure is unknown (i.e., novel material) or increased based on the available evidence.</td>
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<td>Other</td>
<td>Suggest adding a decision flowchart in the guidance document</td>
<td>This guidance document could be further strengthened by adding a flowchart to help clarify and visualize for industry when additional testing would be expected from FDA.</td>
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Select Updates for Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems - Draft Guidance for Industry and Food and Drug Administration 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.

I. Introduction and Scope

FDA has developed this guidance to inform the coronary and peripheral stent industry about selected updates to FDA's thinking regarding certain non-clinical testing for these devices. While FDA is in the process of making more substantial updates to the Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems guidance, we are issuing this "short guidance update" on select sections in order to notify the industry in a timely manner of our revised recommendations.

Section III of this guidance provides cross-reference and updates to the related sections of the existing Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems guidance. Following the close of the comment period on this guidance, FDA intends to consider the comments received, revise this guidance as appropriate and publish it in final. Simultaneously, FDA will issue an update to the existing guidance to cross-reference where this selected updates guidance supersedes the existing recommendations. Subsequently, FDA will incorporate the elements of this final guidance into an anticipated revision of the entire Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems guidance.

This guidance provides updates only for the following topics:

- Pitting corrosion potential;
- Galvanic corrosion;
- Surface characterization; and
- Nickel ion release.

This guidance document addresses self-expanding and balloon expandable extracranial intravascular stents and their associated delivery systems. The scope includes extracranial intravascular stents placed in coronary or peripheral arteries and saphenous vein grafts but is not limited to stents used in these locations; other vascular indications outside of the intracranial vasculature are also included.
Intravascular stents, including balloon expandable and self-expanding stents, are class III devices whose product codes are given in the table below.

<table>
<thead>
<tr>
<th>Product Code</th>
<th>Device</th>
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<tr>
<td>MAF</td>
<td>Stent, Coronary</td>
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<tr>
<td>NIM</td>
<td>Stent, Carotid</td>
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<tr>
<td>NIN</td>
<td>Stent, Renal</td>
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<tr>
<td>NIO</td>
<td>Stent, Iliac</td>
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<tr>
<td>NIP</td>
<td>Stent, Superficial Femoral Artery</td>
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<tr>
<td>NXP</td>
<td>Stent, Tibial</td>
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These devices require a premarket approval (PMA) application before marketing. See sections 513(a) and 515 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 814.

II. Background and Rationale

FDA held a public workshop entitled "Cardiovascular Metallic Implants: Corrosion, Surface Characterization, and Nickel Leaching" on March 8-9, 2012 that provided information on current practices for performing these tests. A pre-workshop assignment on test practices and outcomes completed by participants from industry, test houses, and academia served as a basis for moderated discussions at this workshop. Regarding corrosion testing, the general consensus was that no single corrosion assessment can be used to assess in vivo corrosion susceptibility. However, nearly all respondents indicated that they performed pitting corrosion testing, and more than half of the respondents indicated that they performed galvanic corrosion testing. Therefore, in the current guidance, we have updated a key aspect of sample conditioning for pitting corrosion testing that is less burdensome, and included additional information on when galvanic corrosion testing may be omitted with justification, based on information gained from the workshop.

Corrosion of implant devices made of nitinol and other nickel-containing metal alloys (e.g., stainless steel, MP35N) results in the release of nickel ions, which may lead to various modes of toxicities. However, there are no suitable standard test methods for measuring metal ion release from intravascular stents. Therefore, based on currently available scientific evidence and industry practices discussed at the workshop, we have included information on test methods for in vitro nickel ion release testing. Furthermore, both nickel ion release and corrosion characteristics are dependent on surface finishing for nitinol and for some other nickel-containing alloys. While there is insufficient information to quantitatively correlate surface oxide characteristics to device performance characteristics at this time, workshop participants indicated that surface characterization may be most useful as a tool to assess the root cause of poor device performance characteristics (e.g., corrosion susceptibility or nickel ion release). We have therefore modified the recommendations for when surface characterization should be performed to consider outcomes from other characterization testing and surface finishing techniques used.
Based on the information obtained from this workshop, FDA was able to refine existing
recommendations on when certain tests should be performed or considered, such that industry
can avoid performing tests that would add little valid scientific evidence regarding the safety and
effectiveness of the device. In addition, information on test methods for pitting and galvanic
corrosion, as well as nickel ion release, has been updated, which we believe will aid in test
protocol development. While pitting corrosion potential, surface characterization, and in vitro
nickel ion release testing are described in different sections of the Non-Clinical Engineering
Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems
guidance, taken together, the results of these tests are interrelated and provide a global
perspective on the corrosion and ion leach potential of the stent. We recommend that you
initially assess the pitting corrosion potential of your stent. If results are inconclusive or an
established surface finishing process is not used, we recommend that you perform surface
characterization. If the corrosion resistance and surface characterization results are inconclusive
for your device, we recommend that you also quantify nickel ion release from your device. Then,
a risk assessment should be performed, basing estimated exposure on in vitro nickel ion release
testing, to determine the potential safety risks associated with nickel released from the device. If
available, data obtained from other assessments, such as animal or clinical studies, may
supplement your analysis of the corrosion and ion leach potential of your device, and should be
considered as part of your risk assessment for these potential failure modes.

III. Select Updates

A. Material Characterization

1. Pitting Corrosion Potential

The following recommendations update Section IV.A.3 of the Non-Clinical Engineering
Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems
guidance regarding Pitting Corrosion Potential.

We recommend that you characterize the corrosion potential of your as-manufactured stent
according to the method described in ASTM F2129-14 or equivalent method. The test setup should
meet the criteria outlined in ASTM G59 (figure 2, Table D2.1). Testing should be performed after
subjecting the device to simulated use testing, which includes tracking and deployment of the
device through an in vitro fixture that mimics in vivo anatomic conditions (See section B2.
Delivery, Deployment, and Retraction in the Non-Clinical Engineering Tests and Recommended
Labeling for Intravascular Stents and Associated Delivery Systems guidance). This device
conditioning is intended to simulate the clinical conditions of the stent at the time of
implantation. You should test device sizes that are the worst-case in terms of corrosion
susceptibility based on surface area, size, and/or geometry. Considerations should be given to
factors such as geometry or size that may affect surface finishing such as adequate polishing of
regions of high curvature. Test devices should be representative of final sterilized devices and
selected such that potential variations due to manufacturing can be assessed (i.e. by taking
samples from multiple (≥3) lots), with a justification for the number of samples tested.
Additional samples may be needed if there is wide variability in the test results.
In addition to testing as-manufactured samples, if there is damage, such as but not limited to fractures or significant wear of your device during accelerated durability testing, additional testing of fatigued samples to evaluate the impact of resulting cracks or scratches on pitting and crevice corrosion potential should be considered. If corrosion testing is performed on post-fatigue samples (in addition to the as-manufactured testing described above), we recommend testing the same samples used in the fretting corrosion evaluation described in the Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems guidance according to the methods described in ASTM F2129 or equivalent method. Specifically, one stent from each overlapping pair subjected to fatigue cycling should be evaluated for pitting corrosion potential while the other stent from each pair is evaluated for fretting corrosion.

Test reports for pitting corrosion potential testing should be consistent with ASTM F2129. For example, test reports should include corrosion/rest potentials, breakdown potentials, as well as polarization curves. We recommend that you plot all polarization curves in one graph when practical. You should report whether your test setup met the criteria outlined in ASTM G5. Results should be assessed against your acceptance criteria. You should include images from visual inspection of your device before and after testing to assess evidence of pitting. Images of pitting should be of sufficient magnification to resolve the features of the pits. You should also include a discussion of your visual inspection, such as number and spatial distribution of pits.

The materials, design, and fabrication processes specific to your stent may reduce or eliminate the applicability of generic literature or previous experience with stents that may be used to address pitting susceptibility in lieu of testing. For example, the pitting corrosion resistance of nitinol is sensitive to processing variables such as heat treatment and surface finish; therefore, for a nitinol stent, generic literature is not applicable and you should characterize the corrosion potential of the finished stent.

2. Galvanic Corrosion

The following recommendations update Section IV.A.3 of the Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems guidance regarding Galvanic Corrosion.

We continue to recommend the Galvanic Corrosion testing recommendations as outlined in Section IV.A.3 of the Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems guidance. However, a justification may be provided, in lieu of testing, if the expected worst-case galvanic coupling potentials are small and if the relative surface ratios of the cathodic to anodic materials are low (e.g., marker band to stent surface ratio).
B. Material Composition

1. Surface Characterization

The following recommendations update Section IV.A.1 of the Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems guidance to clarify when Surface Characterization should be considered.

Surface finish is known to affect other material properties such as corrosion and metal ion release for certain alloys (e.g., nitinol, MP35N, stainless steel). Therefore, if results from other characterization testing (e.g., pitting corrosion) are inconclusive, we recommend that you characterize the material surface of your finished product in terms of passivation layer chemical composition vs. depth. In addition, if you do not use a commonly used surface finishing process (e.g., electropolishing), we recommend that you perform surface characterization of your device. Special attention should be paid to surfaces and geometries that may be affected by heat or finishing processes. Surface characterization should be performed on multiple devices from multiple lots (≥3). This characterization should include multiple assessments at various representative areas on the device surface including the locations that may be most difficult to polish.

C. Biocompatibility

1. Nickel ion release

The following recommendations update Section IV.E of the Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems guidance regarding Nickel Ion Release.

For devices containing nickel, we recommend that you consider the potential for nickel ion release from your device. Specifically, if the corrosion resistance and passivation layer characterization results are inconclusive for your device, we recommend that you quantify nickel ion release from your device over time by measuring concentrations of nickel leached from the device into a fluid at physiologic temperature and pH. To avoid excursions in pH and the need for assessment of pH during sampling, we recommend using a buffered solution, such as phosphate buffered saline (PBS). We recommend testing be conducted for at least 60 days. Solution sampling should be conducted at adequate intervals and for sufficient duration to adequately characterize the nickel release profile of the device in vitro. You should use a sampling regimen that will adequately capture an initial bolus release of nickel. For example, sampling may be performed daily for the first seven days with weekly assessments thereafter.

Testing should be performed on as-manufactured devices after subjecting the device to simulated use testing, which includes tracking and deployment of the device through an in vitro fixture that mimics in vivo anatomic conditions (See section B2. Delivery, Deployment, and Retraction in the Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems guidance). Test devices should be representative of final sterilized devices and selected such that potential variations due to manufacturing can be assessed (i.e., by taking samples from multiple (≥3) lots), with a justification for the number of samples tested.
Additional samples may be needed if there is wide variability in the test results. The devices should be selected such that they represent the worst-case for nickel leaching (e.g., largest surface area).

Validation testing should be performed and included in the test report. This validation testing should include validation of the analytical instrumentation as well as an extended (>14 days) spike and recovery test to demonstrate that nickel is not lost out of solution, (e.g., due to adsorption onto the extraction container). The extraction ratio, or the ratio of the surface area of the tested device to the volume of test solution, should be provided along with a rationale for why the ratio was selected. Both the detection limit of the analytical instrumentation and driving force for nickel leaching should be considered in your rationale. Detection limit and driving force for leaching should also be considered when deciding to perform aliquot sampling versus replacing the entire test solution at each time point sampled as well as in your choice of using a different device for each time point or reusing the same device across multiple time points.

Test results should be reported as total cumulative release per device in micrograms, as well as a per day release (µg/day). In addition, if release rates are compared between devices or samples with different geometries, results should also be normalized by device surface area.

2. Risk Assessment

If in vitro nickel leach testing is performed, a risk assessment should also be performed to determine the potential safety risks associated with nickel released from the device. The results of in vitro nickel leach testing should be used as the basis for the exposure estimate. If any in vivo nickel exposure data exists for your device, these values should be included in your risk assessment as well. The risk assessment should consider route of exposure. While much of the literature on nickel toxicity is from studies with oral or inhalation as routes of exposure, and not intravascular exposure, it is known that chemicals that are toxic via one route of exposure may also be toxic via a different route of exposure. Standard route-to-route extrapolation methods should be used to address toxicity from different routes of exposure in the absence of data from the relevant route of exposure. The duration of exposure should be considered as well. In addition to acute and chronic non-cancer endpoints, if your device releases nickel in a chronic fashion (≥30 days) based on in vitro testing, carcinogenicity (including genotoxicity) and reproductive toxicity should be considered. In addition to systemic toxicity, local effects of nickel accumulation should also be discussed as part of your assessment of the device.

References used in the risk assessment, as well as a description of how the values used in the risk assessment calculations were derived, should be included in your risk assessment report.

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