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

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Guidance for Industry and Food and Drug Administration Staff

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This document updates and augments (but does not replace) *Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems* guidance, issued April 18, 2010.

For questions regarding this document, contact the Interventional Cardiology Devices Branch at or the Peripheral Interventional Devices Branch at (301) 796-7000.

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

Office of Science and Engineering Laboratories

Preface

Public Comment

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Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) current thinking on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

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 (http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm071863.htm), we are issuing this 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. 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 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. This guidance or parts of this guidance may not be applicable to stents with components intended to degrade.

Intravascular stents, including balloon expandable and self-expanding stents, are class III devices whose product codes are given in the table below.

Table 1: Product Codes for Stents Addressed in this Guidance

Product Code	Device
MAF	Stent, Coronary
NIM	Stent, Carotid
NIN	Stent, Renal
NIO	Stent, Iliac
NIP	Stent, Superficial Femoral Artery

These devices require a premarket approval (PMA) application before marketing. See sections 513(a) and 515 of the Federal Food, Drug, and Cosmetic Act (the FD&C 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 (see http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm287535.htm). 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, or having components made of, nickel-rich alloys (e.g., nitinol, 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-rich 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 additional tests that would add little valid scientific evidence regarding the safety and effectiveness of the device. For example, corrosion testing post-accelerated durability testing has generally not provided value over evaluating corrosion on as-manufactured stents. 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 the results do not meet the pre-specified acceptance criteria or an established surface finishing process is not used, we recommend that you perform further testing outlined in the specific test sections below and the flow chart in Appendix 1. If available, data obtained from other assessments, such as animal or clinical studies, may supplement the analysis of the corrosion and ion leach potential of the device, and should be considered as part of the risk analysis 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 (i.e., non-fatigued) stent according to the method described in the currently recognized version of ASTM F2129[1] or equivalent method. The test setup should meet the criteria

[1] ASTM F2129 Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices. Please see FDA's Recognized Consensus Standards database (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm) for the most current information on which editions are recognized by FDA.

outlined in ASTM G5-14[2] (figure 2, Table x2.1). Testing should be performed after subjecting the device to simulated use testing, which includes crimping, tracking, and deployment of the device through an *in vitro* fixture that mimics *in vivo* anatomic conditions (See section C2. Delivery, Deployment, and Retraction in the *Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems* guidance). Alternatively, the stent may be subjected to strains expected during simulated use (e.g. bending) without passing through a tracking fixture, with justification. 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 (e.g. by taking samples from multiple lots). In addition, the number of samples tested and sampling scheme should be justified with consideration of variability in results. If your worst case stent size cannot be accommodated in the test fixture, alternate device sizes or shortened samples may be used with justification. We recommend that you discuss the variability of your results.

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. When practical, we recommend that you plot all polarization curves in one graph. You should report whether your test setup met the criteria outlined in ASTM G5-14. Results should be assessed against your acceptance criteria. The acceptance criteria for the pitting corrosion testing should be determined by comparison to a legally marketed device with good clinical history of use (i.e. no history of corrosion-related fractures or adverse events associated with nickel release). Alternatively, while there is a lack of data directly linking *in vitro* corrosion testing to *in vivo* corrosion outcomes, conservative guidelines have been published by Rosenbloom and Corbett, which may also be used to establish the acceptance criteria[3]. If breakdown occurred in any samples tested, you should include results of the visual inspection of your device before and after testing to assess evidence of pitting. Images of sufficient magnification should be included to support these observations and identify pit locations.

Literature or previous performance data may support the pitting susceptibility assessment of your stent. However, the materials, design, and fabrication processes specific to your stent may reduce or eliminate the applicability of literature or previous experience with your device. For example, the pitting corrosion resistance of nitinol is sensitive to processing variables such as heat treatment and surface finish, and therefore, literature would not be

[2] ASTM G5-14 Standard Reference Test Method for Making Potentiostatic and Potentiodynamic Anodic Polarization Measurements

[3] Rosenbloom, S. N. and R. A. Corbett (2006). An Assessment of ASTM F 2129 Test Results Comparing Nitinol to Other Implant Alloys. Proceedings of the International Conference on Shape Memory and Superelastic Technologies (ASM International), Pacific Grove, CA.

applicable. In cases where manufacturing changes that could impact surface finish are implemented, ASTM F2129 testing or surface characterization should be performed to demonstrate that the surface is not adversely altered.

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. As an alternative to using marketed stents for galvanic corrosion testing, coupons representing an expected worst-case galvanic coupling, that are subjected to identical manufacturing processes may be used. In addition, 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.

Intravascular metallic stents should have a polished, passive and clean surface unless a justification for an alternative surface is provided. 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) do not meet pre-specified acceptance criteria, we recommend that you characterize the material surface of your finished product in terms of passivation layer chemical composition vs. depth and/or perform *in vitro* nickel leach testing (see Appendix 1). However, if you do not have a final passivation step, or use the same surface finishing process as for a marketed stent with good clinical history, or if you do not use a commonly used surface finishing process, we recommend that you perform surface characterization of your device. Commonly used surface finishing processes may include a process with any final passivation step such as electropolishing, chemical etch. 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. This characterization should include multiple assessments at various representative areas on the device surface including the locations that may be most difficult to polish. Acceptance criteria for surface characterization should be pre-specified based on oxide thickness and composition. While there is limited information on the correlation between oxide thickness to nickel release, work by Fasching *et al*

indicates that nickel release increases substantially as the oxide thickness increases from 20 to 200nm for nitinol[4]. In addition, information gathered from prior submissions of nitinol devices indicate that an oxide layer of less than 50nm typically do not result in significant levels of nickel release. If information on oxide thickness of other legally marketed nitinol implants with good clinical history of use is available, this information may also be used to set your acceptance criteria. The oxide layer should consist primarily of TiO_2 (for nitinol) and should not contain nickel-rich regions.

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-rich alloys, we recommend that you consider the potential for nickel ion release from your device. Specifically, if the corrosion resistance and passivation layer characterization results do not meet pre-specified acceptance criteria 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, we recommend using a buffered solution, such as phosphate buffered saline (PBS). We recommend testing be conducted for at least 60 days. Alternatively if the testing demonstrates that the surface is stable (i.e. the release rate falls below a predetermined level based on toxicological risk assessment), testing may be concluded earlier, with a minimum test duration of 30 days. A justification should be provided for reducing the test duration. Solution sampling should be conducted at adequate intervals and over a sufficient duration to sufficiently characterize the nickel release profile of the device *in vitro*. You should use a sampling regimen that will adequately capture any initial bolus release of nickel. For example, sampling intervals for nitinol implants might include at least days 1, 2, 4, 7, 14, 21, and 28 days for the first month of cumulative exposure time, and at least bi-weekly thereafter. Alternative sampling frequencies may be used with justification.

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 C2. Delivery, Deployment, and Retraction in the *Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems* guidance), or as outlined in section A1. Pitting Corrosion Potential in the current guidance update. Test

[4] Fasching, A., E. Kuş, et al. (2009). The effects of heat treatment, surface condition and strain on nickel-leaching rates and corrosion performance in nitinol wires. Materials and Processes for Medical Devices, ASM International, Minneapolis MN.

devices should be representative of final sterilized devices and selected such that potential variations due to manufacturing can be assessed (e.g., by taking samples from multiple lots), with a justification for the number of samples tested and sampling scheme. 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). A justification of sample selection should be provided (e.g. if largest sample does not fit testing apparatus).

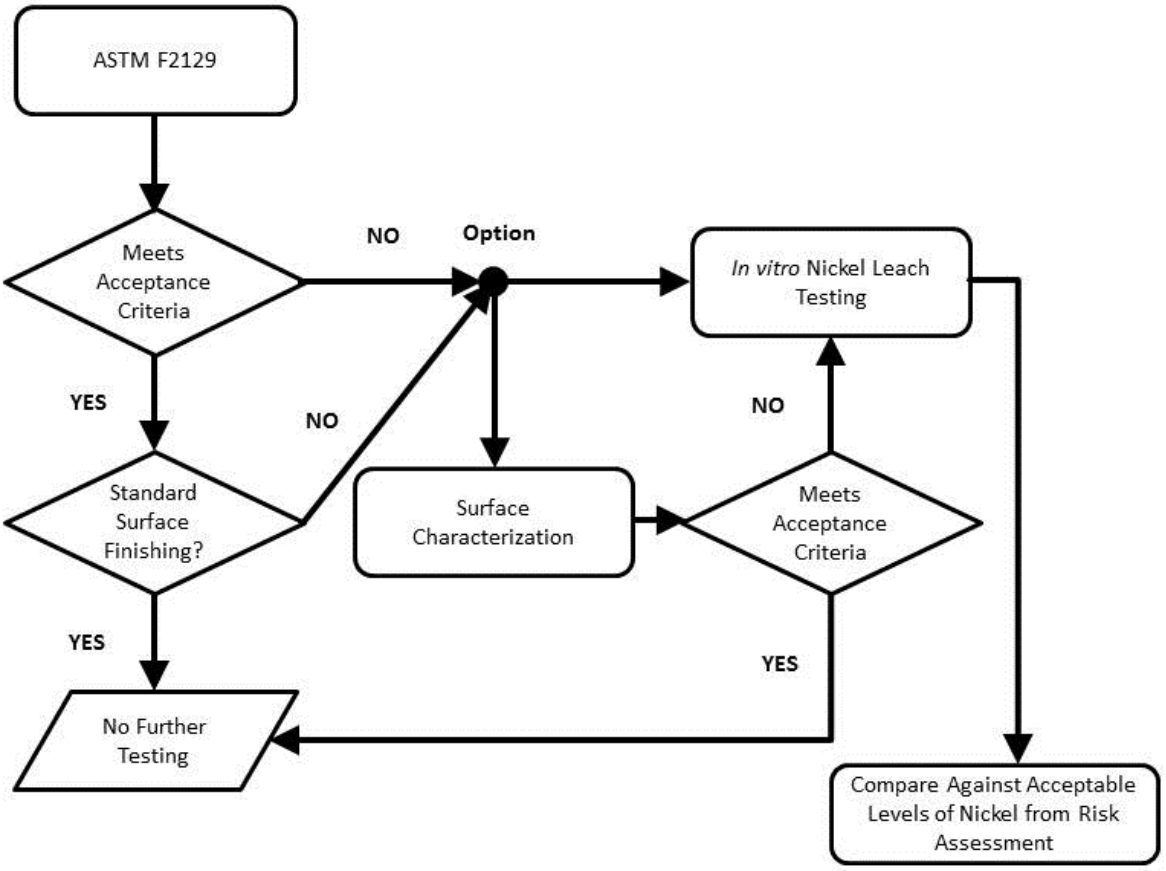
Validation testing should be performed and summarized in the test report. This validation testing should include validation of the analytical instrumentation as well as an extended (>14 days) spike and recovery test to demonstrate that nickel is not lost out of solution, (e.g., due to adsorption onto the extraction container) during testing. 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 nickel solubility in the test solution should be considered in your rationale. For example, a surface to volume ratio of 0.1 to 1cm^2/mL may be appropriate if the nickel released does not approach the nickel solubility limit in the test solution and is sufficiently above the detection limit.
We recommend that you replace the entire test solution at each time point sampled, or an alternative method may be used with justification.

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 will be performed, a risk assessment should be performed prior to testing. The risk assessment should establish acceptable limits for nickel released from the device based on potential toxicological risks. The results of *in vitro* nickel leach testing should then 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 (≥30 days) 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.

Appendix 1 – Testing Paradigm Flowchart



Fasching, A., E. Kuş, et al. (2009). The effects of heat treatment, surface condition and strain on nickel-leaching rates and corrosion performance in nitinol wires. Materials and Processes for Medical Devices, ASM International, Minneapolis MN.

Rosenbloom, S. N. and R. A. Corbett (2006). An Assessment of ASTM F 2129 Test Results Comparing Nitinol to Other Implant Alloys. Proceedings of the International Conference on Shape Memory and Superelastic Technologies (ASM International), Pacific Grove, CA.