Contains Nonbinding Recommendations

Draft – Not for Implementation

Technical Considerations for Non-Clinical Assessment of Medical Devices containing Nitinol

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE

This draft guidance document is being distributed for comment purposes only.

Document issued on April 19, 2019.

You should submit comments and suggestions regarding this draft document within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions about this document, contact the Division of Applied Mechanics at (301) 796-2501, or Matthew Di Prima, Ph.D. at (301) 796-2507 or by email matthew.diprima@fda.hhs.gov.

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

Preface

Additional Copies

Additional copies are available from the Internet. You may also send an e-mail request to CDRH-Guidance@fda.hhs.gov to receive a copy of the guidance. Please use the document number 17013 to identify the guidance you are requesting.

Table of Contents

I. INTRODUCTION AND SCOPE 1

II. BACKGROUND 2

III. DEFINITIONS 3

IV. TECHNICAL RECOMMENDATIONS 4

A. GENERAL INFORMATION 5
B. MECHANICAL TESTING 6
C. CORROSION TESTING 8
D. BIOCOMPATIBILITY 12
E. LABELING 13

Technical Considerations for Non-Clinical Assessment of Medical Devices containing Nitinol

Draft Guidance for Industry and Food and Drug Administration Staff

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 or Office responsible for this guidance as listed on the title page.

I. Introduction and Scope

Nitinol is a commonly used material in the medical device industry. Device manufacturers have used nitinol's unique properties (i.e., pseudoelasticity and shape memory behavior) to design innovative medical devices that would not be possible with conventional materials. Nitinol has been extensively used in cardiovascular devices such as stents, heart valves, guidewires, and vena cava filters. The use of nitinol in other device areas is growing, particularly for products intended for use in minimally invasive procedures.[1] The thermomechanical behavior and processing sensitivity of nitinol raise special considerations when compared to conventional metals such as stainless steel, titanium, or cobalt-chrome alloys. Due to the unique properties of nitinol, the Agency has developed this draft guidance to provide FDA's current thinking on technical considerations specific to devices using nitinol. These recommendations are intended to be general and not product-specific and should be evaluated in conjunction with the intended use and technological characteristics of your device and any relevant device-specific guidances. The purpose of this draft guidance is to outline technical considerations associated with medical devices that have at least one patient contacting component comprised of nitinol.

For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[2] For additional information on the appropriate use of consensus standards in the preparation and evaluation of premarket submissions for

[1] Duerig T, Pelton A, Stöckel D. An overview of nitinol medical applications. Materials Science and Engineering: A. 1999;273:149-60.

[2] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

medical devices, refer to the "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices Guidance."[3]

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. Background

Nitinol is a nearly equiatomic metal alloy of nickel and titanium. Nitinol's unique mechanical properties have made it a commonly used material in medical devices. The use of nitinol in medical devices began over three decades ago in product areas such as orthodontic archwires, cardiovascular guidewires, and surgical instruments. Its use has increased over the past two decades into different device areas such as orthopedic fracture fixation, cardiovascular stents, and transcatheter heart valves. With an increasing trend to treat patients using minimally invasive procedures, nitinol has become a popular choice of material due to its ability to return to its original shape after being deformed or after heat is applied. These properties are due to reversible transformations between the austenite and martensite phases, which may be temperature-induced (shape-memory) or stress-induced (pseudoelasticity). As a result, nitinol can withstand greater reversible deformations without plastic deformation than conventional metals such as stainless steel, titanium, or cobalt-chrome alloys.[4]

Given the complex properties of nitinol, characterizing the thermomechanical behavior of nitinol devices presents unique considerations when assessing safety and effectiveness. Previous literature has elucidated the impact of manufacturing on transformation temperatures and mechanical performance of nitinol devices.[5] In addition, standards developing organizations such as American Society for Testing and Materials (ASTM) have produced standards to aid the medical device industry in characterizing nitinol. These standards define terminology associated with nitinol materials, including specifications for chemical, physical, mechanical, and metallurgical properties, and test methods to characterize the transformation temperatures and mechanical properties of nitinol.

[3] https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM077295

[4] Stockel D. Nitinol medical devices and implants. Minimally Invasive Therapy & Allied Technologies. 2000;9(2):81-88

[5] Pelton AR, Dicello J, Miyazaki S. Optimisation of processing and properties of medical grade Nitinol wire. Minimally Invasive Therapy & Allied Technologies. 2000;9(2):107-118.

Previous literature has shown the corrosion resistance of nitinol to be highly dependent on surface processing.[6,7] *In vivo* corrosion of nitinol may decrease the safety profile or performance of the device by adversely impacting mechanical properties and/or biocompatibility. To obtain stakeholder input regarding best practices for corrosion testing and the impact of corrosion on the performance and safety profile of metals (including nitinol), FDA held a public workshop titled "Cardiovascular Metallic Implants: Corrosion, Surface Characterization, and Nickel Leaching" (March 8–9, 2012).[8] The information gathered from this workshop was published[9] and used to update the FDA's guidance document for "Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems."[10] However, the recommendations in that guidance were specific to intravascular stents and delivery systems. With the expansion of nitinol to other product areas, the Agency is issuing this general guidance document outlining the technical considerations when using nitinol in medical devices.

III. Definitions

Austenite start temperature (As) - "the temperature at which the martensite to austenite transformation begins on heating in a single-stage transformation or the temperature at which the R-phase to austenite transformation begins on heating in a two-stage transformation."[11]

Austenite finish temperature (Af) - "the temperature at which the martensite to austenite transformation is completed on heating in a single-stage transformation or the temperature at which the R-phase to austenite transformation is completed on heating in a two-stage transformation."[12]

Final finished form - term used for a device or device component that includes all manufacturing processes for the "to be marketed" device including packaging and sterilization, if applicable.

Martensite start temperature (Ms) - "the temperature at which the transformation from austenite to martensite begins on cooling in a single-stage transformation or the temperature at

---

[6] Zhu L, Trepanier C, Pelton A, Fino JM. Oxidation of Nitinol and its Effect on Corrosion Resistance. ASM Materials and Processes for Medical Devices 2003.

[7] Sullivan SJ, Dreher ML, Zheng J, Chen L, Madamba D, Miyashiro K, et al. Effects of Oxide Layer Composition and Radial Compression on Nickel Release in Nitinol Stents. Shape Memory and Superelasticity. 2015;1(3):319-27.

[8] http://web.archive.org/web/20130203225843/http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm287535.htm

[9] Nagaraja S, Di Prima M, Saylor D, Takai E. Current practices in corrosion, surface characterization, and nickel leach testing of cardiovascular metallic implants. Journal of Biomedical Materials Research Part B: Applied Biomaterials. 2016;105(6):1330-1341.

[10] Available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071986.pdf

[11] ASTM F2005-05 (Reapproved 2015): Standard Terminology for Nickel-Titanium Shape Memory Alloys

[12] ibid

which the transformation from R-phase to martensite begins on cooling in a two-stage transformation."[13]

Martensite finish temperature (Mf) - "the temperature at which the transformation from austenite to martensite is completed on cooling in a single-stage transformation or the temperature at which the transformation from R-phase to martensite is completed on cooling in a two-stage transformation."[14]

Shape memory alloy - "a metal which, after an apparent plastic deformation in the martensitic phase, undergoes a thermoelastic change in crystal structure when heated through its transformation temperature range resulting in a recovery of the deformation."[15]

Preconditioning (simulated use) - loading, tracking and/or deployment of test devices, as they would occur in clinical use.

Pseudoelasticity (superelasticity) - "nonlinear recoverable deformation behavior of Ni-Ti shape memory alloys at temperatures above the austenite finish temperature (Af)."[16]

IV. Technical Recommendations

The following section contains a description of the type of information that we recommend you include in a premarket submission of a device made from nitinol. The type of premarket submission that is appropriate for your nitinol device is determined by the regulatory classification of your device. The type and amount of data necessary to support your regulatory submission will vary depending on the intended use, risk profile, and classification for the device type. For devices manufactured with multiple types of nitinol (e.g., components with different surface finishes), we recommend that you provide the suggested information for each type of nitinol. Where available, device-specific guidance documents may include additional technical recommendations that should be considered.

Nitinol is used in a diverse range of medical devices, with varying durations of contact. The recommendations in this guidance document vary depending on the anticipated duration of contact. The anticipated duration of contact in this guidance document follows ISO 10993-1 2009 "*Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process*"[17] Section 5.3, with definitions listed below.

a) Limited exposure – devices whose cumulative single, multiple or repeated use or contact is up to 24 hours.

[13] ASTM F2005-05 (Reapproved 2015): Standard Terminology for Nickel-Titanium Shape Memory Alloys
[14] ibid
[15] ibid
[16] ibid
[17] Refer to the 2016 Guidance "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" (https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM348890) for clarifaction and updated information on the use of this standard.

b) Prolonged exposure – devices whose cumulative single, multiple or repeated long-term use or contact is likely to exceed 24 hours but not 30 days.
c) Permanent contact – devices whose cumulative single, multiple or repeated long-term use or contact exceeds 30 days.

A. General Information

The performance and behavior of nitinol depends on a number of factors including alloy composition, thermal history, and surface processing. Based on the intended use of the device containing nitinol, different material behavior or performance may be desirable. We recommend that you provide the following general information on your nitinol-containing devices for prolonged exposure and permanent contacting devices. For limited exposure devices, some of this information may not be necessary. For example, functional testing performed for passive cardiac guidewires may be sufficient in lieu of providing the information listed below. Where device-specific guidances are available, these may be useful to determine what type of information is needed. Alternatively, Sponsors may wish to discuss the use of functional testing with FDA early in their device development process. FDA recommends that sponsors use the Q-Submission process to facilitate these discussions.[18]

1. Material Composition

The composition of nitinol can be tuned to optimize performance for a particular intended use. If your nitinol conforms to a recognized consensus standard, this information should be included in your submission (e.g., ASTM F2063 (*Standard Specification for Wrought Nickel-Titanium Shape Memory Alloys for Medical Devices and Surgical Implants*)). If your nitinol does not conform to a recognized consensus standard, we recommend you provide the nitinol composition and a description of its specific properties.

2. Manufacturing

Manufacturing parameters including heat treatments and surface processing can alter the behavior and performance of the nitinol device. Therefore, we recommend that you provide a flow chart to identify the manufacturing processes leading from your raw material to the final device sterilization (if relevant). Of specific interest are thermal processes (e.g., laser cutting, annealing, thermal shape setting). Additionally, surface processing has a significant effect on the corrosion/nickel leach performance of nitinol. Therefore, we recommend that you provide a detailed description of any surface

[18] For more information see "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176

processing steps (e.g., honing, microblasting, pickling, polishing, passivation) so the risk of corrosion and nickel release can be evaluated. In addition, you should describe any final post-processing cleaning steps, and discuss how these steps are designed to remove any surface residuals that could impact biocompatibility.

3. Pseudoelasticity/Shape Memory Behavior

Nitinol can be "tuned" via composition and thermal treatments to either have pseudoelastic (superelastic) or shape memory behavior at the desired operating temperature. As these two behaviors are different, it should be stated in the submission which one is being used. If neither behavior is being employed, that also should be clarified.

4. Transformation Temperatures

As stated previously, variations in transformation temperatures of nitinol have been shown to affect mechanical properties. Therefore, we recommend you provide phase transformation temperatures of your final finished form (ie., with all manufacturing including sterilization, if relevant). When possible, samples from a minimum of three production lots should be used because nitinol transformation temperatures are sensitive to small variations in manufacturing processes, such as temperature or heating duration. If the pseudoelastic properties are being utilized, we recommend providing austenite finish (Af) temperature. If shape memory properties are utilized, you should also provide austenite start (As), martensite start (Ms), and martensite finish (Mf) temperatures as these temperatures govern the shape memory behavior. We recommend using the methods described in ASTM F2004 (*Standard Test Method for Transformation Temperature of Nickel-Titanium Alloys by Thermal Analysis*), ASTM F2082 (*Standard Test Method for Determination of Transformation Temperature of Nickel-Titanium Shape Memory Alloys by Bend and Free Recovery*), or an equivalent method. For devices that are expected to be load bearing, we recommend ASTM F2082 as it incorporates deformation. We recommend you provide specifications for acceptable transformation temperature ranges for your device to ensure your device will perform properly as a psuedoelastic or shape memory material.

B. Mechanical Testing

Nitinol has unique thermomechanical properties. When available, device-specific guidance or standards should be used to assess the mechanical performance of your device. If mechanical testing will be performed as part of your non-clinical testing plan, the following specific considerations may apply depending on device design and/or intended use.

1. Experimental Testing Considerations

a. The pseudoelastic behavior of nitinol leads to a region of near constant stress over a range of strains. Therefore, we recommend you conduct mechanical testing under strain or displacement control unless otherwise justified.

b. Some devices are designed such that they may be exposed to strains prior to and/or during implantation. For example, cardiovascular stents are compressed to a smaller diameter onto a delivery system and tracked through vasculature prior to deployment. In addition, orthopedic staples are extended prior to implantation. Therefore, we recommend you account for any deformation as a preconditioning step prior to mechanical testing.

c. Due to the thermomechanical response of nitinol, mechanical testing including fatigue testing should be performed at a clinically relevant temperature unless otherwise justified.

d. Some devices are exposed to cyclic loading conditions during use (i.e., fatigue loading). If you conduct accelerated fatigue tests, we recommend that you use phosphate buffered saline (PBS) as a test solution and do not conduct your tests in air because fatigue testing of nitinol in air has been shown to be sensitive to test frequency due to heating effects.[19] If you choose to conduct fatigue testing in air, we recommend you provide a scientific rationale.

e. For devices intended to utilize the shape memory properties of nitinol, we recommend a cyclic shape memory test at a clinically relevant temperature range and number of cycles. This testing should assess functional performance and device integrity.

2. Computational Stress/Strain Analyses

If you plan to conduct computational analyses, we recommend the following to ensure the unique thermo-mechanical properties of nitinol are properly captured:

a. The constitutive laws applicable to nitinol can differ substantially from traditional metals.[20] Therefore, you should simulate nitinol material with an appropriate material model. You should document and justify the parameters used in the material model.

[19] Wagner et al (2004). "Structural fatigue of psuedoelastic NiTi shape memory wires." Materials Science and Engineering A. Vol 378 pp 105-109.

[20] Ford DS, and White SR. Thermomechanical behavior of 55Ni45Ti nitinol. Acta Materialia 1996;44(6):2295-2307.

b. Material model parameters may be obtained from ASTM F2516 (*Standard Test Method for Tension Testing of Nickel-Titanium Superelastic Materials*) at the relevant clinical conditions (e.g., temperature, preconditioning).

c. If your manufacturing process includes shape setting, this may relieve stresses and strains, which your computational analysis should reflect.

d. Unlike traditional metals, nitinol fatigue life is strain dependent. Therefore, for a fatigue analysis, the traditional stress-based fatigue life estimates (e.g., Goodman, Soderberg diagrams) are not applicable. You should calculate fatigue safety factors using a constant life curve defined in terms of mean and alternating strains for a relevant number of cycles. We recommend that you evaluate the constant life curve applicable to your device by experimental testing of nitinol samples subject to identical processing and preconditioning step(s) to your finished device.

e. You should validate your nitinol computational analyses. Validation test conditions should address the range of stress/strain states that you are modeling. For example, if your device is expected to be loaded and unloaded, include loading that validates the accuracy of your model for both upper and lower plateau stresses.

We recommend that submission of computational stress/strain analysis reports follow the "Reporting of Computational Modeling Studies in Medical Device Submissions Guidance."[21]

C. Corrosion Testing

Nitinol's corrosion susceptibility is dependent on the manufacturing and surface finishing processes[22] used to make the final finished form as well as potentially the geometry of the final finished form. As corrosion can lead to nickel ion release or even a compromise of the mechanical integrity of the device, we recommend that pitting corrosion testing of the nitinol device be performed for prolonged exposure and permanent contacting devices. If pitting corrosion testing results meet pre-specified acceptance criteria (for details on acceptance criteria see Section C.1.: Corrosion Testing - Pitting Corrosion) and your device is manufactured using established surface finishing[23] such as electropolishing, chemical etch, or

[21] Available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM381813

[22] Sullivan et al (2017). The effect of surface processing on in-vivo corrosion of Nitinol stents in a porcine model. Acta Biomaterialia. Vol. 16 pp 385 -396

[23] When considering the effect of manufacturing processes on surface finish, surface characterization (e.g., chemical composition vs. depth) compared to an established surface finish may provide insight into the quality of your protective oxide layer.

mechanical polishing, then further testing may not be necessary. If the results of the testing do not meet pre-specified acceptance criteria or your device is not manufactured using established surface finishing processes, we recommend characterizing the extent of nickel ion release. A flowchart (Figure 1) is provided to illustrate the recommended testing paradigm for corrosion and nickel ion release susceptibility.

Corrosion testing is generally unnecessary for limited contact devices; however, such testing may be requested in situations such as devices with an electrically active component, a dissimilar metal couple, or a degradable metal/polymer component where these features could accelerate nitinol corrosion. In these cases, we recommend you seek more detailed feedback via the Q-submission process per the guidance "Requests for Feedback on Medical Device Submission: The Pre-Submission Program and Meetings with FDA Staff."[24]

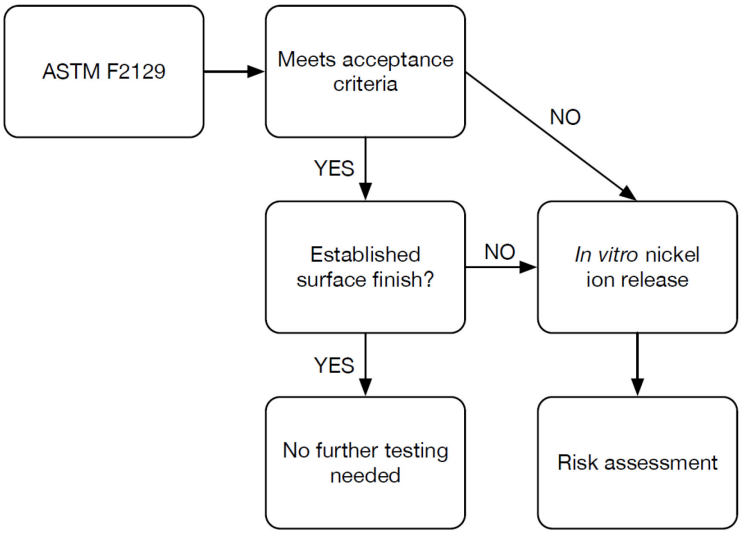

Figure 1. Corrosion testing paradigm flowchart

1. Pitting Corrosion

We recommend conducting pitting corrosion testing per ASTM F2129 (*Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices*).

Testing should be performed after subjecting the device to simulated assembly and implantation, which includes compression/loading and deployment of the device through an *in vitro* fixture that mimics *in vivo* anatomic conditions. Alternatively, the device can be subjected to stresses/strains expected during simulated use without the use of an *in vitro* fixture, with justification. This device conditioning is intended to simulate the clinical conditions of the device at the

[24] https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf

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 the final finished form 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 device size cannot be accommodated in the test fixture, alternative device sizes or shortened samples may be used with a scientific rationale.

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 discuss any deviations from the ASTM F2129 standard (e.g., test setup not meeting the criteria outlined in ASTM G5 (*Standard Reference Test Method for Making Potentiodynamic Anodic Polarization Measurements*)). Results should be assessed against your acceptance criteria. ASTM F2129 does not include an acceptance criterion. Therefore, the acceptance criterion for the pitting corrosion testing should be determined by comparison to a legally U.S. marketed comparator 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 paucity of data directly linking *in vitro* corrosion testing to *in vivo* corrosion outcomes, conservative guidelines have been published,[25] which may also be used to establish acceptance criteria. If breakdown occurred, you should include results of the visual inspection of your device before and after testing to assess evidence of pitting. Images of sufficient magnification (e.g., 200X or higher unless pitting can be identified at a lower magnification) should be included to support these observations and identify pit locations.

2. Nickel Ion Release

If your nitinol device does not exhibit acceptable corrosion resistance or does not employ an established surface finishing process, we recommend nickel ion release testing be performed. This testing should quantify nickel over time by measuring concentrations of nickel released from the device into a fluid at physiologic temperature and pH. To avoid excursions in pH, we recommend using a buffered solution, such as PBS. For prolonged exposures, immersion testing should be conducted for the entire anticipated duration of contact. For permanent implants, we recommend testing be conducted for at least 60 days. Solution sampling should be conducted at adequate intervals and over a sufficient duration to 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

[25] Corbett RA. Laboratory corrosion testing of medical implants. Proceedings of Materials and Processes for Medical Devices Conference; 2004: ASM International, Materials Park, OH.

ions. For example, sampling intervals for a permanent implant 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 to capture the initial bolus release of nickel followed by the chronic release behavior. Alternative sampling frequencies may be used with a scientific rationale.

Testing should be performed on devices in final finished form after subjecting the device to preconditioning that simulates device implantation (e.g., tracking and deployment for endovascular devices). Test devices should be 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 and size of devices tested. In cases where there are multiple sizes or different geometries, the devices should be selected and justified such that they represent the worst-case for nickel ion release (e.g., largest surface area, most challenging to surface finish, and/or highest local strains).

Validation testing should be performed and summarized in the test report. This validation testing should include validation of the analytical instrumentation as well as a spike and recovery test to demonstrate that nickel is not lost out of solution during testing (e.g., due to adsorption onto the extraction container). The duration should be at least equal to the longest interval during immersion 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 scientific 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 1 cm^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 with fresh solution.

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. These results should be used as part of your risk assessment as described in Section D: Biocompatibility.

3. Galvanic Corrosion

Similar to pitting corrosion, galvanic corrosion may lead to higher than anticipated rates of nickel ion release or compromised mechanical integrity. If nitinol is in contact with dissimilar metals, galvanic corrosion testing should be considered. We recommend the methods described in ASTM F3044 (*Standard Test Method for Evaluating the Potential for Galvanic Corrosion for Medical Implants*). As an alternative to using devices 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 scientific

justification may be provided, in lieu of testing, if the expected worst-case potential shift due to galvanic coupling is small and if the relative surface ratios of the cathodic to anodic materials are low (e.g., marker band to stent surface ratio).

D. Biocompatibility

To assess the biocompatibility of for your nitinol device, we recommend that you follow the guidance "Use of International Standard ISO10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process."[26] This guidance identifies the types of biocompatibility assessments that should be considered and recommendations regarding how to conduct related tests.

In addition, if *in vitro* nickel release testing will be conducted (see Figure 1), a risk assessment should be performed to compare the amount of nickel released from the device to a Tolerable Intake (TI) value for nickel. A TI value is defined in the ISO 10993-17:2002/(R)2012 standard (*Biological evaluation of medical devices -- Part 17: Establishment of allowable limits for leachable substances*) as an "estimate of the average daily intake of a substance over a specified time period, on the basis of body mass, that is considered to be without appreciable harm to health."

For adverse systemic effects that may occur following prolonged or permanent patient exposure to nickel released from a nickel-containing device, with the exception of hypersensitivity, CDRH recommends a TI value for parenteral (non-oral) exposure to nickel of 0.5 µg/kg/day (e.g., 35 µg/day for a 70 kg adult).[27] This value is based on systemic toxicity data from experimental animals following administration of nickel salts by parenteral routes of exposure (e.g., intravenous, intraperitoneal) and derived using the approach outlined in the ISO 10993-17 standard. The FDA has not established an oral TI for nickel; however, the US Environmental Protection Agency has established a Reference Dose (RfD) of 20 µg/kg/day (e.g., 1400 µg/day for a 70 kg adult) that is intended to be protective for lifetime oral exposure to nickel. It is important to note that the TI values are not intended to be protective for local effects (e.g., necrosis, inflammation, irritation) that may result from nickel release from an implant into tissues surrounding the implant. With regard to carcinogenicity, no increase in tumor incidence has been observed in rats or mice following long-term oral or inhalation exposure to soluble nickel compounds in well-conducted bioassays;[28] therefore, the TI for nickel ion released

[26] Available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM348890

[27] http://web.archive.org/web/20130203225843/http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm287535.htm

[28] Heim KE, Bates HK, Rush RE, Oller AR. (2007) Oral carcinogenicity study with nickel sulfate hexahydrate in Fischer 344 rats. Toxicology Applied Pharmacology. 224(2):126-37.

from nitinol is adequately protective for carcinogenicity. If any *in vivo* nickel exposure data exists for your device, these values should also be included in your risk assessment.

As the lower limit of nickel exposure that can elicit allergic reactions in some patients is not known, it is not possible to derive a hypersensitivity-based TI for nickel released from nitinol. Therefore, appropriate labeling is recommended (see Section E: Labeling).

If your nickel exposure estimate exceeds the recommended TI (i.e., 0.5 µg/kg/day), an alternative TI may be derived in certain cases, such as for significantly shorter exposure duration or other exposure routes (e.g., inhalation). To support the alternative TI, you should provide evidence (e.g., literature) that the potential toxicological risk(s) will be adequately mitigated or discuss how the probable benefit to health from the use of the device outweighs any probable risk of injury or illness from such use. Additional information on benefit-risk assessments can be found in the "Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions - Guidance for Investigational Device Exemption Sponsors, Sponsor-Investigators and Food and Drug Administration Staff"[29] and "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications - Guidance for Industry and FDA Staff."[30] If your nickel release exceeds the recommended or alternative TI and cannot be justified, device modifications (e.g., surface optimization) may be necessary to mitigate the risk.

E. Labeling - Warnings

Since there is no known lower limit on the amount of nickel that can elicit allergic reactions in some patients, we recommend that the risk of potential allergic reaction to nickel be mitigated through labeling for nitinol containing devices. Specifically, we recommend that the labeling include a warning for prolonged and permanent contacting devices. Note that a contraindication against use of nitinol-containing devices may be appropriate when the risk of use clearly outweigh any probable benefit.

We recommend the following warning (or similar) be included in your labeling:

> Warning: This device contains nitinol, an alloy of nickel and titanium. Persons with allergic reactions to these metals may suffer an allergic reaction to this implant. Prior to implantation, patients should be counseled on the materials

[29] Available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM451440

[30] Available at https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM517504

contained in the device, as well as potential for allergy/hypersensitivity to these materials.