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Abstract: In an effort to better understand current test practices and improve nonclinical testing of cardiovascular metallic implants, the Food and Drug Administration (FDA) held a public workshop on Cardiovascular Metallic Implants: corrosion, surface characterization, and nickel leaching. The following topics were discussed: (1) methods used for corrosion assessments, surface characterization techniques, and nickel leach testing of metallic cardiovascular implant devices, (2) the limitations of each of these *in vitro* tests in predicting *in vivo* performance, (3) the need, utility, and circumstances when each test should be considered, and (4) the potential testing paradigms, including acceptance criteria for each test. In addition to the above topics, best practices for these various tests were discussed, and knowledge gaps were identified. Prior to the workshop, discussants had the option to provide feedback and information on issues relating to each of the topics via a voluntary preworkshop assignment. During the workshop, the pooled responses were presented and a panel of experts discussed the results. This article summarizes the proceedings of this workshop and background information provided by workshop participants. J Biomed Mater Res Part B: Appl Biomater, 105B: 1330–1341, 2017.

Key Words: corrosion, cardiovascular, metal ions, metal (alloys)

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INTRODUCTION

Corrosion resistance is an important property of metallic implants. For cardiovascular devices specifically, corrosion has been observed in explanted devices months after implantation.[1–5] Pitting corrosion has been documented as early as 5 mo postimplantation in explanted nitinol abdominal aortic aneurysm stent grafts with more severe types of corrosion detected in devices implanted for up to 8 years. In addition, recent analyses of human explanted stents suggest localized corrosion and metal ion release to vascular tissue may occur in these devices.[2–4]

In addition to mechanical device failures that may occur due to significant corrosion, adverse biological responses to metal ions released are a concern. Although various modes of toxicities ranging from allergic reaction to nephrotoxicity and carcinogenicity have been reported for nickel compounds at varying doses,[6–9] the overall biological impact of metal ion release from implanted devices is unclear. Corrosion byproducts from metal implants have been shown to modulate inflammatory cell processes and in the case of cardiovascular stents, this may be a contributing factor to neointimal thickening and in-stent restenosis.[10,11] In addition, release of metal ions due to corrosion may affect patients with metal allergies. In particular it has been shown that nickel can be immunotoxic, especially in those with nickel allergies, which has been estimated at 10% of the adult population with a higher prevalence in women (17%) than men (3%).[6,12–15]

While the true incidence of hypersensitivity-related adverse events in cardiovascular implants cannot be determined based on currently available information, the general incidence appears to be low. Nevertheless, there is a substantial body of literature consisting of data from case studies and small to midsized clinical evaluations, which attribute varying hypersensitivity responses to implants, both systemic and local, ranging from pruritus to inflammatory reactions leading to in-stent restenosis and periprosthetic incompetence in a valve.[16–26] Some reported reactions were transient in nature and could be addressed with medical management, while other symptoms were persistent and led to rare cases of device explantation. While these varied and numerous reports of adverse events are attributed to nickel sensitivity, a clear connection between a specific clinical failure mode for a device type and nickel allergy has not yet been established. For example, there have been a small number of studies examining the incidence of restenosis in coronary stent patients with nickel allergy.[23,27–30] Half of these studies suggest no correlation between nickel allergy status of the patient and

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restenosis, while the others suggest a positive correlation with restenosis.

Corrosion of metallic devices may occur through several pathways and cardiovascular device manufacturers use a variety of *in vitro* tests to assess corrosion resistance of their implants. Some dissolution of metal ions is expected when metallic devices are implanted in the body, and the nature and quantity of ions released from devices affect their biocompatibility. To assess the potential for general corrosion in real-time, immersion testing may be performed. Although there is currently no FDA-recognized standard test method for medical implant metal ion release, this relatively simple test method involves immersing the device in fluid such as phosphate buffered saline (PBS) and aliquots of this fluid are analyzed at prespecified time intervals to determine the amount of metal ions released from the device. However, because there is no accepted standard method for immersion testing, test conditions and data reporting can vary significantly, making it problematic to compare results between studies.

The American Standard of Testing and Materials (ASTM) standard test method F2129 (Standard Test Method for Conducting Cyclic Potentiodynamic Polarization Measurements to Determine the Corrosion Susceptibility of Small Implant Devices) is a commonly used method to evaluate localized corrosion susceptibility by cardiovascular device manufacturers. If localized corrosion occurs, this test method provides the voltage (breakdown potential) required to initiate corrosion on the device surface. Although not representative of *in vivo* conditions, this accelerated test provides a detailed method to determine corrosion behavior of devices relatively quickly and consistently. In 2004, Corbett proposed acceptance criteria for this test based primarily on expected electrical potentials *in vivo*.[31] He proposed that implants with a breakdown potential exceeding 600 mV would be considered as having acceptable corrosion resistance, while potentials below 300 mV are unacceptable. However, there is considerable debate within the medical device community on the use of these acceptance criteria and their clinical relevance.[32,33] The inability to generate universal acceptance criteria for preclinical corrosion testing is due to difficulties in directly observing corrosion clinically and correlating this with *in vitro* corrosion tests.

In addition to pitting corrosion, there are other corrosion mechanisms such as galvanic and fretting corrosion that should be considered. There are also many factors that affect corrosion resistance in metallic devices. The passive oxide layer is extremely important in corrosion resistance and biocompatibility of metals exhibiting such an oxide layer. In particular, the final chemical composition and thickness of the passive oxide layer are factors that affect corrosion resistance and metal ion release.[34–36] These variables can be influenced by final processing steps during manufacturing such as polishing, passivation, and heat treatment. For example, Trepanier *et al*. have shown that surface processing methods such as electropolishing, passivation, and certain heat treatments of metal stents can improve *in vitro* corrosion behavior compared with untreated stents.[37,38] Electropolishing of nitinol has also been shown to reduce the amount of surface nickel and result in high breakdown potentials.[39] Zhu *et al*. demonstrated that the time and temperature at which these metals are heat-treated affect the composition and thickness of the oxide layer. Specifically, the breakdown potential based on ASTM F2129 testing decreased from 1000 mV to less than 0 mV when the oxide thickness increased from 0.01 to 10 μm.[40] In addition, they showed that thick oxide layers can crack under mechanical stress/strain and may expose the metal subsurface to accelerate corrosion. Another important factor in corrosion is the electrochemical environment of the device *in vivo*. There are many different anatomical locations where cardiovascular devices may be implanted and each location has a unique local biochemical environment that may include serum, platelets, proteins, and cells. There have been limited studies to quantify these *in vivo* driving forces for corrosion. The earliest work by Hoar and Mears measured rest potentials of stainless steel and titanium in goat femurs and human fingers for up to 90 days. They found rest potentials varied from 100 to 600 mV and that scratching the surface of these devices caused a transient drop in potential for up to 30 min.[41] More recent studies measured rest potentials of approximately −300 to 400 mV for nitinol and stainless steel wires implanted into femoral, iliac, and abdominal arteries of human subjects.[42,43] Although these papers provide information on electrical potentials *in vivo*, there is large variability among these studies creating difficulties in determining the driving forces for corrosion when implanted, as well as how those potentials can vary over time.

In an effort to better understand current test practices and improve nonclinical testing of cardiovascular metallic implants, the Food and Drug Administration (FDA) held a public workshop. This article summarizes the proceedings of the 2012 FDA Workshop on Cardiovascular Metallic Implants: Corrosion, Surface Characterization, and Nickel Leaching.

FDA WORKSHOP

The FDA held a workshop March 8–9, 2012 attended by members of the cardiovascular medical device community including device manufacturers, contract test laboratories, and academics. Approximately 60 representatives from the medical device community discussed the following topics: (1) Current corrosion test methods, surface characterization techniques, and nickel leaching methods used to evaluate metallic cardiovascular implant devices; (2) limitations of each of these tests to predict actual *in vivo* performance; (3) need, utility, and circumstances when each test should be considered; and (4) potential testing paradigms, including possible acceptance criteria for each test. The workshop was divided into four sessions: corrosion; surface characterization of nickel-containing alloys; nickel leach and toxicity; and summary and potential testing paradigms. Each session included one to three presentations followed by a brief summary of the responses compiled from a voluntary preworkshop assignment, and then discussion among participants.

TABLE I. Current Testing Practices (Prefatigue Testing) Aggregated Across All Device Types and Alloys

Scan Rate (mV/s)	***n* = 83**
1 mV/s	36%
0.2 mV/s	64%
Solution	***n* = 72**
PBS	73%
Other (e.g., 0.9% saline, HBSS)	13%
Do you use a control?	***n* = 47**
Yes	49%
No	30%
if appropriate/sometimes/depends	21%
If yes what do you use?	***n* = 33**
another marketed device	94%
Other (self-couple)	6%
For covered or coated devices, do you induce damage to the covering such as coating, for stent grafts and drug-eluting stents?*	***n* = 36**
Yes	64%
No	17%
if appropriate/sometimes	19%

PBS, Phosphate-Buffered Saline; HBSS, Hanks-Buffered Saline Solution

DATA COLLECTION

Workshop participants were asked to complete a voluntary preworkshop assignment to obtain a better understanding of current bench testing strategies and practices, and to facilitate discussion during the meeting. There were a total of 23 individual respondents; 18 medical device manufacturers, 3 contract test laboratories, and 2 other (material supplier and consultant). Raw data were aggregated and analyzed by FDA. Some respondents provided data for multiple devices, and in these cases, data from each device were analyzed as a unique entry. In some cases, respondents did not provide responses to all questions, and as a result, the total sample size varied for each question. The device types for which preworkshop assignment responses were received include coronary stents, peripheral vascular stents including renal and neurovascular stents, cardiac implants (e.g., valves, occluders, other coronary implants), and other noncoronary vascular implants (e.g., various stent grafts, various endovascular stents, inferior vena cava filters).

RESULTS

Corrosion

To better understand the current corrosion testing landscape, participants were requested to provide information on corrosion test practices, outcomes, and proposed modifications to existing test methods in the preworkshop assignment. Basic information regarding the respondents' devices and types of corrosion testing performed for cardiovascular implants ($n = 94$) was collected. Respondents indicated that their devices were composed of nitinol (53%), 316L stainless steel (18%), cobalt chrome alloys (27%; MP35N, L605, Elgiloy), or other alloys (2%). Fifty-three percent ($n = 50/94$) of devices were electropolished with and without other treatments such as passivation or coating, 7% ($n = 7/94$) were only subjected to passivation, 17% ($n = 16/94$) used other surface finishing methods, 4% ($n = 4/94$) had no finishing treatment (2 nitinol, 2 cobalt chrome alloy) and the surface finishing method was unknown or unreported for 18% of devices.

Ninety percent ($n = 85/94$) of devices were assessed using pitting corrosion testing (per ASTM F2129), and 52% ($n = 48/93$) of devices were assessed using galvanic corrosion testing. Fretting corrosion was assessed as part of fatigue testing for 40% ($n = 37/92$) of the devices. Fretting corrosion was assessed separately from fatigue testing for 16% ($n = 15/93$) of the devices. When asked if other corrosion tests were performed on these devices, 57% ($n = 39/68$) of responses indicated "yes" or "maybe," and the tests included open circuit potential, explant analysis, and/or immersion tests.

In addition to the types of testing performed, respondents were asked whether corrosion was observed in *in vitro* ($n = 17$) or *in vivo* ($n = 17$) testing. For *in vitro testing*, 12% indicated that corrosion was observed (nickel release and corrosion) and for *in vivo* testing, 11% indicated corrosion was observed (handling-induced corrosion was suspected for one of the two cases).

Pitting corrosion. Respondents were asked to provide information on test practices for pitting corrosion assessments performed per ASTM F2129 (Table I). Of the 90 individual device responses, 21% of responses were of cobalt chrome alloy devices, 23% stainless steel, and 50% nitinol. For covered or coated devices, 64% ($n = 23/36$) indicated that they induce damage to the covering such as coating, for stent grafts and drug-eluting stents. Only 1 respondent (3%) indicated that they intentionally scratch the surface, 2 (6%) did not specify how damage was induced, and all others indicate that they subject devices to simulated use and/or delivery and deployment to induce damage. Sixty-eight percent ($n = 13/19$) of individual respondents provided results from ASTM F2129 testing performed on devices both before (prefatigue) and after (postfatigue) cyclic mechanical testing. Five percent ($n = 1/19$) indicated that they only performed ASTM F2129 testing on samples post-fatigue, while 26% ($n = 5/19$) indicated that they only performed testing on nonfatigued samples. There were no notable differences in test practices for devices made of different alloys.

In addition to general test practices for ASTM F2129, respondents provided the number of samples tested prefatigue and post-fatigue, and what they believed current/best practices are in regards to sample size (Figure 1). For nitinol devices, the median number of samples tested was about 9, while for devices composed of other alloys, the median was about 5. Note that when a respondent submitted a range of sample size in their response, such as 7–10, the mean value of the response was used in the analysis.

Histograms of minimum and mean rest potentials (E_r) for nitinol, stainless steel, and cobalt chrome alloys are shown in Figure 2. The minimum rest potentials reported by respondents for nitinol devices ($n = 23$) ranged from -500 to -62 mV. The minimum and mean rest potentials for nitinol devices

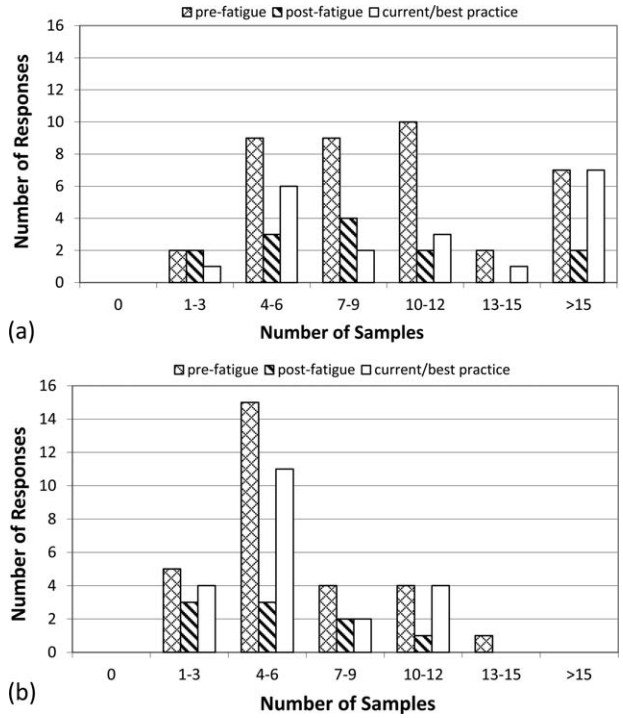

FIGURE 1. (a) Number of samples reported for prefatigue, postfatigue, and current/best practices for ASTM F2129 testing for nitinol devices, (b) Number of samples reported for prefatigue, postfatigue, and current/best practices for ASTM F2129 testing for devices made of all other alloys. The median values for nitinol devices were as follows: prefatigue = 10, postfatigue =8, and current/best practices = 10. The median values for devices made of all other metal alloys were as follows: prefatigue = 5, postfatigue =6, and current/best practices = 5.

had median values of −324 and −198 mV, respectively. The minimum rest potentials for stainless steel based devices ($n = 10$) ranged from −300 to 0 mV. For cobalt chrome based devices ($n = 10$), the minimum rest potentials ranged from approximately −400 to >0 mV. The minimum and mean rest potentials for stainless steel devices had median values of −75 and −1 mV, respectively. The minimum and mean rest potentials for cobalt chrome-based devices had median values of −171 and −35 mV, respectively.

Histograms of minimum and mean breakdown potentials (E_b) for nitinol, stainless steel, and cobalt chrome alloys are shown in Figure 3. The minimum breakdown potentials reported by respondents for nitinol devices ($n = 24$) ranged from −100 to 800 mV. The mean breakdown for nitinol devices was more variable among respondents ($n = 22$) with similar frequency of breakdown occurring from 0 to 800 mV. The minimum and mean breakdown potentials for nitinol devices had median values of 174 and 388 mV, respectively. For respondents that used electropolishing as a final surface treatment, the range of breakdown potentials was −14 mV to no breakdown; whereas if no surface processing was performed, the breakdown range was −100 to 250 mV (data not shown). For stainless steel ($n = 9$) and cobalt chrome alloy ($n = 7$) devices, minimum breakdown potentials reported for devices using these materials ranged from 26 to >800 mV. Respondents for stainless steel and cobalt chrome alloys generally had minimum breakdown potentials that were higher compared with nitinol, with mean breakdown potentials typically in the 300–800 mV range. The minimum and mean breakdown potentials for stainless steel devices had median values of 390 and 658 mV, respectively. The minimum and mean breakdown potentials for cobalt chrome-based devices had median values of 564 and 654 mV, respectively.

Histograms of minimum and mean breakdown potential minus the rest potential ($E_b - E_r$) for nitinol, stainless steel, and cobalt chrome alloys are shown in Figure 4. The minimum $E_b - E_r$ potentials reported for nitinol devices ($n = 18$) ranged from 63 to >800 mV. The minimum and mean $E_b - E_r$ potentials for nitinol devices had median values of 345 and 613 mV, respectively. For stainless steel and cobalt chrome alloy devices, there were fewer responses than nitinol devices ($n = 4$–6), but minimum $E_b - E_r$ potentials reported for devices using these materials ranged from 65 to >800 mV. Stainless steel and cobalt chrome devices had minimum $E_b - E_r$ potentials typically greater than 600 mV. The mean $E_b - E_r$ potentials for stainless steel devices ($n = 6$) varied from 280 mV to no breakdown and the mean $E_b - E_r$ potential for cobalt chrome ($n = 6$) alloys were all greater than 600 mV. The minimum and mean $E_b - E_r$ potentials for stainless steel devices had median values of 445 and 642 mV, respectively. The minimum and mean

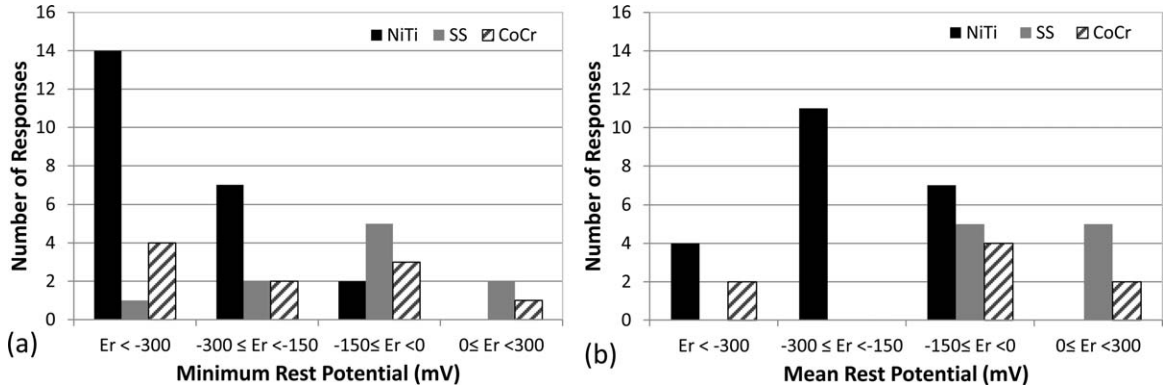

FIGURE 2. Histograms of minimum (a) and mean (b) rest potentials (E_r) for nitinol (NiTi), stainless steel (SS), and cobalt–chromium (CoCr) alloys.

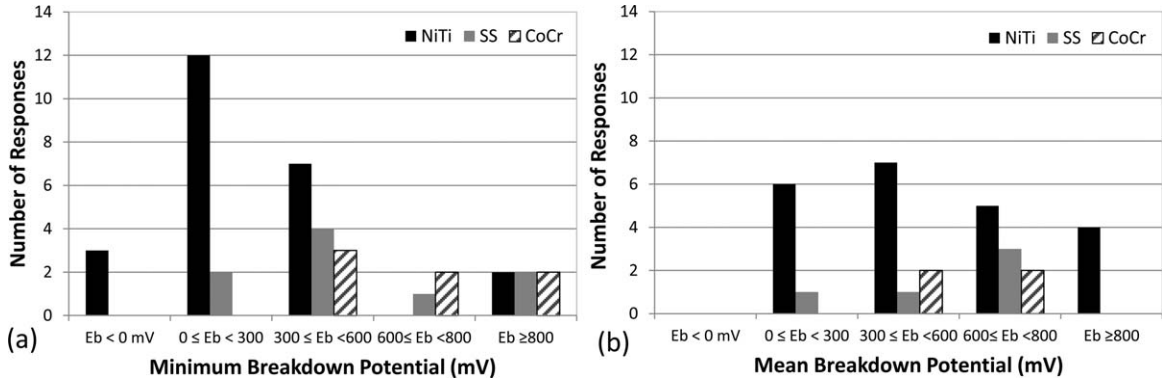

FIGURE 3. Histograms of minimum (a) and mean (b) breakdown potentials (E_b) for nitinol (NiTi), stainless steel (SS), and cobalt–chromium (CoCr) alloys.

$E_b - E_r$ potentials for cobalt chrome-based devices had median values of 918 and 949 mV, respectively.

Respondents were also asked to provide the protection potential (E_p) of their devices. For stainless steel, 73% of respondents ($n = 8/11$) indicated repassivation did not occur during ASTM F2129 testing. Of those that observed repassivation, *Ep* values ranged from −300 to −30 mV with a median of −48 mV. Approximately 36% of respondents ($n = 5/14$) for nitinol devices indicated that repassivation did not occur. Of those that observed repassivation, *Ep* values ranged from −300 to −65 mV with median of −100 mV. For cobalt chrome-based devices, 43% of respondents ($n = 3/7$) stated that repassivation did not occur. The *Ep* values when repassivation occurred were highly variable with ranges from −23 to 913 mV and a median value of 458 mV.

A histogram of acceptance criteria for ASTM F2129 minimum E_b and $E_b - E_r$ potentials used by respondents is shown in Figure 5. Approximately 67% of respondents ($n = 16/24$) set their minimum acceptance criterion for breakdown potential to be greater than or equal to 300 mV, while 25% set a breakdown potential of greater than or equal to 600 mV as their minimum acceptable level. It is interesting to note that 17% of respondents did not have an acceptance criterion for breakdown potential (E_b) for ASTM F2129 testing. In contrast, 67% of respondents ($n = 16/24$) did not use $E_b - E_r$ potential as their acceptance criterion. Of those that did, most respondents stated that an $E_b - E_r$ potential greater than 600 mV was acceptable.

Galvanic corrosion. To better understand when galvanic corrosion testing is considered, respondents were asked under what conditions they believed galvanic corrosion testing is needed. Specifically, when asked if galvanic corrosion testing is needed even if ASTM F2129 test results are "good" for a single device containing dissimilar metals, the majority of respondents ($n = 16$) indicated yes or maybe, with only 2 respondents indicating that they believed testing was not needed. The most common reason cited for the need for galvanic corrosion testing in addition to ASTM F2129 was the difference in driving forces for corrosion in the two tests; externally applied voltage for the potentiodynamic polarization test, and difference in equilibrium potentials and surface areas for galvanic corrosion testing. Many "no" and "maybe" responses also stated galvanic corrosion testing may not be necessary if the different metal components on the galvanic series are close, and/or there is a low cathodic to anodic component surface area ratio. Some indicated that galvanic corrosion testing may be viewed as a confirmatory test for corrosion susceptibility, in addition to ASTM F2129 testing.

The majority of respondents ($n = 12$) indicated that there is value in testing overlapped devices of dissimilar metals; 4 respondents indicated "no" and 2 responded "maybe." In addition to reasons cited above for performing galvanic

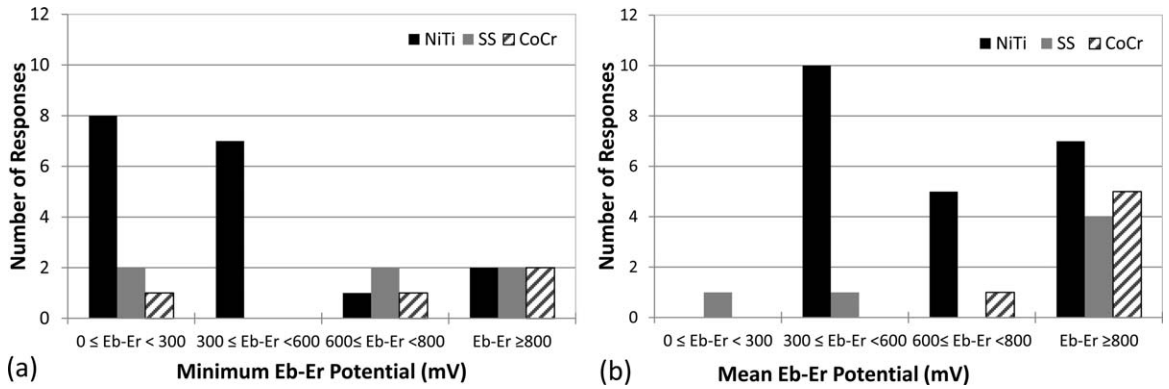

FIGURE 4. Histograms of minimum (a) and mean (b) breakdown minus rest ($E_b - E_r$) potentials for nitinol (NiTi), stainless steel (SS), and cobalt–chromium (CoCr) alloys.

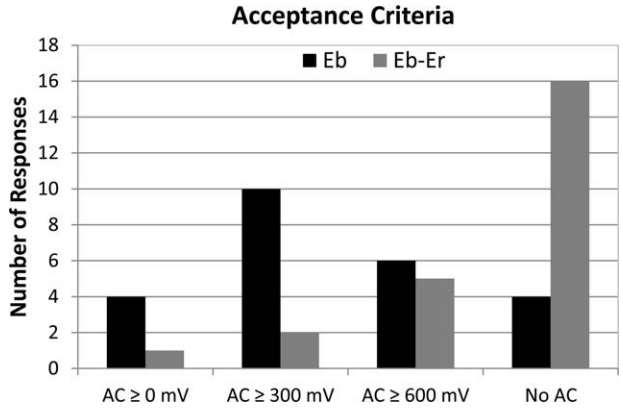

FIGURE 5. A histogram of ASTM F2129 acceptance criteria (AC) derived from the minimum breakdown (E_b) or breakdown minus rest ($E_b - E_r$) potentials used by respondents.

corrosion testing for a single device made of dissimilar metals, the most common reasons cited for performing testing using overlapped devices was to assess performance when overlap with another device is likely to occur during clinical use, and to assess effects of localized transient corrosion behavior due to the overlap. The most common responses against testing overlapped devices were difficulty in determining with the galvanic couple to test and obtaining other devices (e.g., a competitor's device) to use in the testing, and that most alloys used in cardiovascular implants are close in the galvanic series. Respondents were also asked to provide information on test practices for galvanic corrosion testing, and these are summarized in Table II.

Surface characterization

The surface characterization session of the workshop and accompanying preworkshop assignment focused on various surface characterization techniques, how they are used, and what information can be gained from these assessments for devices made from stainless steel, nitinol, and cobalt chrome alloys. There were three general categories of surface characterization of interest: surface morphology, surface chemistry, and depth profiling. The technique most commonly used to assess surface morphology was scanning electron microscopy (SEM), X-ray photoelectron spectroscopy (XPS) and Auger electron spectroscopy for surface chemistry, and XPS paired with sputtering to etch down the surface and using a focused ion beam to create a cross-section of the surface paired with a surface chemistry technique for depth profiling.

Responses regarding surface characterization usage for each alloy are presented in Table III. The percentage shown for each assessment technique is based on the total number of responses for each material type, which is displayed next to each material-type label. The responses to the questions regarding the general usage of surface characterization techniques are shown in Table IV. A common theme among the responses was that once the manufacturing and material processing has been established, the surface is not expected to change, and other functional verification methods would identify surface defects. The cost of equipment, operating costs and maintenance, lack of expertise, and insufficient work load for dedicated facilities were common reasons for contracting out surface characterization. The small scan region and inability to characterize the entire surface area of a device using these techniques were the primary reasons respondents identified for why an acceptance criteria based on surface characterization techniques would be inappropriate.

Nickel leach

Unlike other functional testing used to evaluate the surface-mediated properties of nickel-containing alloys, such as ASTM F2129 for pitting and crevice corrosion, there is no standardized method for conducting these *in vitro* nickel leach assessments. In general, devices are immersed in solution and the solution is sampled and analyzed to assess the nickel concentration at prescribed time points. However, because the methods are not standardized, one of the goals of the preworkshop assignment was to assess the extent of variation in the test methodologies that are currently used. The responses indicated that there were consistencies among some of the test parameters. For example, all testing was conducted on final, sterilized devices at 37°C, primarily using PBS as the immersion medium, with 85% ($n = 13$) of respondents reporting using PBS. Testing was also generally conducted in the absence of external mechanical loads, and the solution pH and open circuit potential were not monitored. Also, 66% ($n = 12$) of respondents indicated that testing was only done under static conditions, that is, there was no stirring or agitation of the solution during the testing. Seventy-seven percent ($n = 13$) of respondents used

TABLE II. Current and Reported "Best Practices" for Galvanic Corrosion Testing of a Single Device Containing Dissimilar Metals

Do You Measure the Uncoupled Potential Before and After?	***n* = 20**
Yes	50%
No	25%
Only before	25%
Do you monitor the coupled potential?	***n* = 20**
Yes	80%
No	20%
What is the endpoint of your test?	***n* = 19**
Time[a]	79%
Steady state current	21%
What acceptance criteria do you use for steady state current?	***n* = 15**
None	47%
Rate of mass loss or corrosion rate	27%
$\leq$4 nA/cm^{2b}	27%
How many samples do you use per test?	***n* = 18**
Number of Samples[†]	Number of Responses
1 to 3	7
4 to 6	9
>6	2

[a] 12–24 h was the most common time endpoint used; 11% ($n = 2$) of up to 72 h; 5% ($n = 1$) of up to 6 days

[b] $\leq$3 nA/cm^2 ($n = 3$); 2–4 nA/cm^2 ($n = 1$) [†]Median = 5

TABLE III. Surface Characterization Technique Usage in Terms of Overall Response and Per Material Type

	Surface Morphology	Surface Chemistry		Depth Profiling	
	SEM (%)	AES (%)	XPS (%)	XPS ± Sputter (%)	FIB (%)
Nitinol ($n = 17$)	100	59	71	35	29
SS ($n = 12$)	92	42	42	17	17
CoCr ($n = 7$)	100	29	43	14	29

The percentage of usage is based on the total number of response for each material type and is displayed next to each material type label.
SS, stainless steel; SEM, scanning electron microscopy; AES, Auger electron spectroscopy; XPS, X-ray photoelectron spectroscopy; FIB, focused ion beam

inductively coupled plasma mass spectrometry (ICP-MS) as the analytical method, although some respondents reported using analytical methods with lower specificity and higher limits of detection and quantitation, such as atomic emission spectroscopy (ICP-AES) and optical emission spectroscopy (ICP-OES).

In contrast to consistencies identified across some parameters, there were wide variations in other key test parameters reported. Characteristics of the distributions of test parameters that could be quantified are presented in Table V. The sample size, duration of the testing, and sampling frequency varied substantially. For example, responses indicated that *in vitro* nickel release was evaluated for maximum time periods ranging from 1 week to 1 year. These are the extremes, however, with most responses indicating that testing was conducted for anywhere from 30 to 90 days depending on the observed behavior. The testing was carried out until the transient behavior suggested nickel release rates were below a prescribed limit indicating surface stability, and this could be demonstrated in as little as 30 days or may require 90 days or longer immersion time. There was also considerable variation in the number of time points sampled to characterize both acute ($\leq$7 days) and chronic ($>$7 days) nickel release. For release occurring within the first week of immersion, sampling ranged from daily to only once. We note that even though the median value for acute sampling was three, the time points selected were generally biased toward the first 3 days of immersion to accurately capture the initial leach rates, where the overall maximum release rate is expected. The same variability in the responses was also observed for chronic release sampling over the first 2 months of testing, which varied from weekly to monthly.

TABLE IV. Responses to Questions Regarding the Usage Surface Characterization

Should Surface Characterization Always be Performed?	***N* = 19**
Yes	7
No	12
Do you perform surface characterization in house?	***N* = 17**
Yes	8
No	9
Do you contract out any surface characterization work?	***N* = 17**
Yes	14
No	3
Should there be an acceptance criteria based on surface characterization?	***N* = 16**
Yes	2
No	14

In addition to the quantitative parameters summarized in Table V, other aspects of the testing were not consistent among the responses. For example, the method for retrieving the sample from the solution was divided nearly evenly between two distinct approaches. In the first approach, small aliquots were removed from the test container and replaced with an equivalent volume of fresh solution at each prescribed sampling time point. Alternatively, the entire solution was replaced at each time point by moving the device to a new test container with fresh solution. Eight percent ($n = 12$) of respondents reported the presence of precipitates in the solution during testing. To validate the test method and address this potential issue, a spike and recovery test can be conducted. However, the responses indicate that this is not currently a common practice, with only 33% ($n = 12$) of respondents indicating that they perform similar validation studies.

In addition to typical testing protocols, respondents were also asked to report nickel release rates from *in vitro* testing, as well as any acceptance criteria established. Because responses were primarily restricted to testing conducted on nitinol devices, only those results are presented. Figure 6 shows the distributions of responses related to the measured nickel release rates, which includes both the peak and chronic release rates. The reported values for the peak release rate range from 0.01 to 40 μg/day, with a median value of about 0.3 μg/day. Further, the range of proposed acceptance criteria for peak release, with both minimum and median values of 35 μg/day and a maximum of 670 μg/day, overlaps slightly with the range of measured values. Although peak release was observed primarily within 7

TABLE V. Distributions of Quantifiable *In Vitro* Nickel Leach Test Parameters

	Median	Minimum	Maximum	*n*
Number of devices	5	2	25	12
Extraction ratio (cm^2/mL)	1.0	0.1	6.0	7
Maximum test duration (days)	60	7	365	13
Number of sample points, time $\leq$ 7 days	3	1	7	11
Number of sample points, 7 days $<$ time $\leq$ 60 days	3	1	5	8

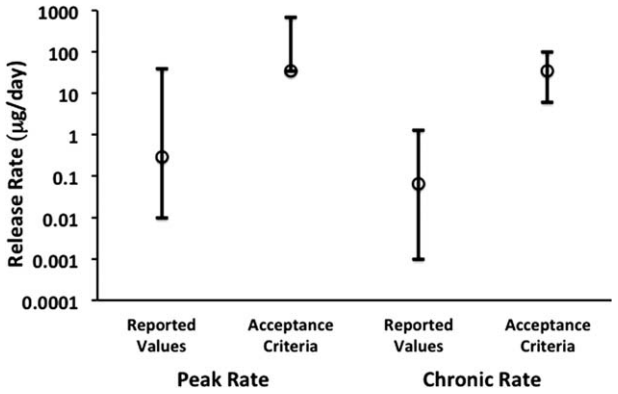

FIGURE 6. Distributions of reported values from *in vitro* nickel leach testing on nitinol devices and acceptance criteria. The plot indicates the ranges of responses for the reported values ($n = 12$) and proposed acceptance criteria ($n = 6$) for the peak nickel release rate as well as the values ($n = 9$) and acceptance criteria ($n = 7$) for chronic release rate. An open circle indicates the median value for each set of responses. Note that the chronic release statistics (that is, minimum value) only represent scenarios where finite (nonzero) numbers were reported.

days, 83% ($n = 12$) of responses indicated that maximum release rates occurred within the first 24 h after testing was initiated. Figure 6, also illustrates that the chronic release rates are an order of magnitude lower than the peak values, with median, minimum, and maximum values of 0.065, 0.001, and 1.3 μg/day, respectively. These values are all below the 6–100 μg/day range of proposed acceptance criteria for this testing. The proposed acceptance criteria for chronic release were comparable to those specified for peak release, that is, greater than 35 μg/day, with the exception of the 6 μg/day limit, which was specified only for infants.

It is unclear from these data if the large variability is due to material, device surface area or test protocol differences. In order to make a comparison on a material basis between devices, the leaching rates should be normalized by surface area. To facilitate such an analysis, FDA also asked respondents to report device surface area as part of the preworkshop assignment. The device surface areas reported ranged from 1 to 50 cm^2. Based on this information, the nickel release rates were normalized where possible. This resulted in a range of normalized peak release rates of 3–1200 ng cm^{-2} day^{-1} ($n = 9$), suggesting a similar, large variation in the material response. For chronic release, the variability was reduced by the surface area normalization with a range of 1–26 ng cm^{-2} day^{-1} ($n = 6$). We note that these ranges are consistent with previous literature reports on nitinol materials with different processing histories where the *in vitro* nickel release rates were assessed with a consistent set of test parameters.[44] This suggests that the observed variability is primarily due to differences in device manufacturing and not test protocols.

Nickel toxicity

In addition to *in vitro* nickel leach testing performed, respondents were asked to provide information on *in vivo* nickel release assessments performed. Only 10% ($n = 2$) of respondents indicated that they perform some type of *in vivo* assessment. Consequently, remaining questions on findings pertaining to *in vivo* assessments, as well as correlations with *in vitro* results were returned largely unanswered.

DISCUSSION

The purpose of the 2012 workshop was to provide a forum for the discussion of (1) various methods used for corrosion assessments, surface characterization techniques, and nickel leach testing of metallic cardiovascular implant devices, (2) the limitations of each of these tests to predict actual *in vivo* performance, (3) the need, utility, and circumstances when each test should be considered, and (4) the potential testing paradigms, including possible acceptance criteria for each test. The pre-workshop assignment served as the basis for discussions. In addition to the above topics, best practices for these various tests were discussed, as well as knowledge gaps.

The data provided by device manufacturers for this workshop gave insight into the nonclinical methods used to assess corrosion in medical devices. These data indicated that substantial variability existed in results from general (i.e., immersion testing) and localized (i.e., ASTM F2129) corrosion testing. In immersion testing, the peak nickel release rate for devices normalized by surface area had a 400-fold difference between a device with the largest nickel release when compared with a device with the lowest nickel leach rate. Breakdown potentials in ASTM F2129 testing for nitinol devices also had substantial variability, and to a lesser extent in stainless steel and cobalt-based alloys. Interestingly, some respondents did report breakdown values for cobalt chrome alloys although they are not expected to exhibit breakdown during ASTM F2129 testing.[45] Discussants noted that these alloys exhibit transpassive behavior that may be misinterpreted as breakdown. The variability in breakdown potentials may be attributed to differences in surface processing steps such as polishing, heat treatments, and passivation since respondents used many different final finishing steps to improve corrosion resistance. However, we also observed variability that was independent of final surface processing. For example, electropolished nitinol devices had breakdown potentials (E_b) ranging from 0 mV to no breakdown and $E_b - E_r$ potentials ranging from 200 mV to no breakdown. These results indicate that even when utilizing the same surface processing such as electropolishing, the process parameters used (e.g., solution composition, polarization conditions, electropolishing duration) may affect corrosion properties measured *in vitro*, and the interplay between these variables needs to be fully understood to optimize corrosion resistance. In addition, corrosion resistance of medical devices is sensitive to other factors such as design and processing differences. There is also a potential for additional variability due to differences in test method parameters, which may be minimized by the use of standards and common best practices.

Best practices for testing according to ASTM F2129 that are not specified in the standard were noted in the course

of the workshop discussions, as well as the preworkshop assignment. Based on the responses, there was no indication that the alloy of the medical device drove the decision to perform postfatigue corrosion testing. While discussants had disparate opinions on the value of performing postfatigue ASTM F2129 testing, the considerations surrounding this testing were identified. A potential value of performing post-fatigue ASTM F2129 is to assess corrosion susceptibility of devices after they are damaged due to fatigue/fretting. However, discussants also noted the challenges in performing ASTM F2129 testing on post-fatigue samples, such as the potential effects of drying the sample (required to form the electrical connections for the test setup), duration of time between fatigue testing and ASTM F2129 testing, storage condition of samples for this duration, limited number of samples, and general lack of a standardized test method for handling postfatigue samples. These challenges confound the test results and may render them uninterpretable. Several discussants noted that assessing corrosion visually postfatigue may be more informative than ASTM F2129 testing, and some indicated that both visual assessment and ASTM F2129 testing would be useful. Specifically, damage to the coating/covering of devices due to fatigue testing would not otherwise be assessed if only prefatigue samples are used. Conversely, other discussants noted that the potential applied via ASTM F2129 testing is greater than *in vivo* and would artificially bias areas of damage with a localized increase in current density. Some discussants noted that fundamentally, if the repassivation behavior of the damaged device is of interest, ASTM F2129 is not an appropriate test to assess this behavior.

Current practices for *in vitro* nickel leach testing were also the subject of extensive discussion during the workshop. While the sampling approach used was nearly divided in the pre-workshop assignment responses between taking an aliquot or replacing all of the media at each time point, discussants emphasized that the key consideration should be maximizing the driving force for leaching, that is, using a sufficiently large solution volume to device surface area ratio, while maintaining solution concentrations that can be detected with available analytical methods. This is in contrast to typical extractions prepared for biocompatibility testing (e.g., ISO10993 series of tests), where a relatively large surface area to volume ratio is used to obtain concentrated leachant solutions. It was also noted that a low solution concentration is not necessarily a limiting factor, because nickel is nonvolatile, and therefore, it is possible to concentrate the solutions after sampling. Also, due to the low nickel concentrations in typical test solutions, it was suggested that inductively coupled plasma mass spectrometry (ICP-MS) is the preferred analytical technique because it is the most sensitive. Using proper controls, specifically spike recovery and blank testing, were identified as essential to validate both the analytical methods and test configuration. This validation testing can obviate concerns with container contamination, evaporative loss, and the potential for nickel to precipitate out of solution. Further, acidifying the samples prior to characterization was suggested by discussants to ensure the total amount of nickel, not just soluble nickel, is captured and to circumvent concerns with container-material selection due to adsorption. Because it is not possible to acidify the solution for intermediate time points when sampling aliquots of the immersion solution, the measured nickel release may not be as accurate compared with whole solution replacement at each time point. The time frame of the test and sampling were also discussed. Discussants suggested that testing should be conducted until steady state behavior can be demonstrated and that a duration of 30 days is a common initial benchmark for assessment. If steady state is not obtained within this time, the test should be extended until steady state is achieved. Discussants also suggested that the ability to capture the steady state should be reflected in the sampling frequency, by sampling more frequently at early times where the transient is the largest. Finally, the utility of this testing postfatigue was questioned because of challenges such as contamination and potential inadvertent damage to the device due to handling, and because the samples are closer to an equilibrium state postfatigue, the release rates are almost always lower than testing performed prefatigue.

There was a clear concern expressed at the workshop that the majority of test methods discussed do not correlate well with *in vivo* performance. These concerns spanned test environment, acceptance criteria, as well as general applicability. With regards to corrosion testing per ASTM F2129; when asked if they had concerns with the limitation of the current corrosion test methods, 75% of respondents indicated that they did. The majority of these respondents cited the lack of *in vivo* performance correlation with the test results, specifically, how the breakdown potential determined by the testing relates to clinical/*in vivo* performance of a device. When asked if there should be acceptance criteria based on surface characterization, the majority indicated there should not be, citing that surface characterization is a local technique making it impractical to scan the entire device, and a lack of correlation between surface characterization results and *in vivo* performance. The discrepancy between *in vitro* and *in vivo* nickel release profiles was also discussed. Limited studies of serum nickel concentration after implantation of cardiac occluders and spinal fixation devices[46–48] showed peak levels at approximately 1 month or up to 2 years post-implantation and remained above baseline for several months to years postimplantation, respectively. In contrast, the majority of respondents indicated that *in vitro* release peaked by 24 h and dropped to near detection limit levels by about 7 days. Discussants noted challenges in assessing serum nickel levels in patients due to the low concentrations and confounding effects of environmental sources of nickel, and that animal studies with controlled exposure to nickel may be more suitable. Better correlation of nickel ion release kinetics from devices *in vitro* and *in vivo* would allow a more accurate assessment of potential patient exposure to nickel based on *in vitro* nickel leach testing results. Alternatively, discussants also suggested that it may be more practical to develop an *in vitro* test for nickel release with good precision and

benchmark the amount of nickel release from devices with good clinical performance, rather than to attempt to develop an *in vitro* test that more closely mimics *in vivo* release kinetics.

While there is a lack of *in vivo* correlation with the results from these *in vitro* tests, the tests do provide important insight into the behavior of the device. By combining the results of multiple tests, along with a better understanding of manufacturing and processing techniques, a more comprehensive picture of anticipated *in vivo* performance can be elucidated. It should be noted that no single standardized testing paradigm was identified. Some discussants suggested that the testing paradigm should be different for devices made of alloys with a good clinical history of use than those made from novel alloys, where additional characterization testing such as surface assessments may be warranted. While the majority of respondents perform ASTM F2129 corrosion testing, there was no dominant opinion on whether *in vitro* nickel leach testing should only be performed when corrosion test results are poor or marginal, or regardless of corrosion testing outcomes since the two tests assess different device performance characteristics. Several discussants noted that surface assessments are characterization tests rather than device performance tests, and are best suited to assess why a device may have poor corrosion resistance and/or high nickel release. Discussants indicated that the testing needed is ultimately dependent on the risk analysis for the device. As another use of ASTM F2129 corrosion testing, some discussants indicated that it may be a suitable initial screening tool when manufacturing changes are made that may impact the device's surface properties.

ASTM F2129 does not specify acceptance criteria and emphasizes comparison to other devices with a history of successful clinical use. Although workshop discussants generally indicated that this was a valid approach, difficulty in obtaining comparison devices was also noted. Establishment of fixed acceptance criteria would eliminate the need to obtain comparison devices. In 2004, Corbett published proposed acceptance criteria for ASTM F2129.[31] Since publication, industry has debated what the minimum breakdown potential should be to prevent corrosion *in vivo*. With $>40\%$ of respondents setting their minimum acceptable breakdown potential to be within the "marginally acceptable" range proposed by Corbett, it appears that a large percentage of respondents believe the proposed acceptance criteria are overly conservative. Since there is limited published information on the dynamic electrochemical environment that drives corrosion *in vivo*, it is unclear what an acceptable *in vitro* threshold to prevent corrosion *in vivo* should be. The lack of correlation between *in vitro* testing and *in vivo* corrosion is a significant knowledge gap in this field. To determine suitable acceptance criteria for ASTM F2129 testing, controlled studies are needed to establish the breakdown potentials that result in device pitting for its intended environment.

The relative lack of response to nickel toxicity-related questions in the preworkshop assignment may partly reflect the lack of clear data on the attribution and frequency of adverse events due to nickel released by metallic implants. Currently, no data in the literature could be found that suggests nephrotoxicity due to nickel ion release occurs in patients with cardiovascular metallic implants, and discussants indicated that the exposure to nickel ions needed to cause kidney damage is much higher than amounts released by implants, based on *in vitro* results reported in the workshop. Discussants also noted that nickel allergy-related events are rare in cardiovascular implants, and can often be resolved with medical management as also reported in a survey of interventional cardiologists ($n = 56$ respondents and $n = 1600$ cases).[49] The majority of clinical studies reporting nickel allergy to cardiovascular implants as the cause of clinical symptoms determined nickel allergy by using patch testing, which is currently the most widely used method. However, as discussants noted at the workshop, patch testing may not be an appropriate predictor of sensitization response to an implant since the mechanism of response is different between dermal exposure and exposure to an implant via other routes.[50] It was also noted that the reported incidence of nickel sensitivity to implants appears to be much lower than the incidence of general nickel sensitivity in the population. Development of assessment methods for the presence of local and/or systemic allergic reaction would aid in the determination of the true rate of metal ion allergy-induced adverse clinical events. Discussants also noted that a knowledge gap exists in understanding the form of nickel, that is, released by implants. These may include particulates, nickel ions, and soluble or insoluble nickel compounds, and the form might vary by device use and surface characteristics. Despite these knowledge gaps, a limit for nickel exposure would be useful to assess results from *in vitro* nickel leach testing.

Through the Cardiovascular Metallic Implants workshop, current test methods to assess corrosion susceptibility, nickel leach, and surface characteristics were identified, as well as the range of acceptance criteria used for some of these tests, and range of test outcomes.* Many knowledge gaps were identified, and these were primarily focused on correlation of *in vitro* test results with *in vivo* or clinical outcomes, and acceptance criteria for these *in vitro* tests. Nevertheless, workshop participants confirmed the utility of *in vitro* corrosion testing, as well as nickel leach testing and surface characterization in certain situations (e.g., use of a new alloy or when manufacturing of components is outsourced, and determination of the cause of poor corrosion resistance or high nickel release, respectively). Based on the information obtained through this workshop, select sections of the 2010 Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems guidance document were updated.†

*Additional information on the workshop including complete transcripts and select presentations can be found at http://onlinelibrary.wiley.com/doi/10.1002/jbm.b.33630/suppinfo

†http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM458490.pdf

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