An overview of recent FDA activity on materials in medical devices

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In this article, the authors provide an overview of recent US Food and Drug Administration (FDA) interest and activity relating to the materials in implants regulated as medical devices. Since 2019, the increase in public and regulatory scrutiny of medical implants has resulted in an FDA advisory committee meeting, revised corrosion testing guidance, and proposed new labeling disclosures.

Introduction
Medical devices offer innovative ways of treating various conditions and can provide life-saving technology that enhances patients’ quality of life. However, medical implants involve placing materials in the human body that are not viewed as natural to that environment. To illustrate, the normal and expected reaction to a medical implant, including a pacemaker or a simple suture, is known as the “foreign body reaction,” which can be confusing and even frightening to a layperson. But the scientific community and regulatory officials have decades of experience evaluating and observing the impact of medical implants on the human body, which includes observing the impact of certain materials that are often used in implants. In addition, the FDA has mandated...
certain standard testing for medical implants to make sure the materials used in
the devices are biocompatible with or tolerable to patients.

In 2019, the FDA announced it would review safety concerns relating to
implantable or insertable medical devices. This announcement followed the
June 2018 release of the Bleeding Edge documentary on Netflix, which drew
attention to the medical device industry. The documentary followed the lives of
patients and activists who reported adverse outcomes allegedly related to a
contraceptive device, vaginal mesh, a robotic surgical system, and chrome-
cobalt hip replacements. The documentary was said to have “rattled the
medical device industry.”

For the past 5 years, the FDA’s attention has been on the medical device
industry, and particularly on materials used in medical implants that have long
been thought of and established as safe and effective. For example, the FDA has
held advisory committees on certain types of medical implants and reported
adverse events associated with the implants and/or materials in the implants, as
well as potential immunological responses to metal-containing implants. The
agency has also issued recent guidance on the type of testing needed to support
the approval of medical devices containing nitinol. In May 2021, the FDA’s
Center for Devices and Radiological Health (CDRH) published a discussion paper
seeking comments on a proposed framework to include specific information on
materials used in medical device labeling.

This article provides an overview of the FDA’s past treatment of and recent
focus on the materials in medical implants and whether the materials could be
causing adverse outcomes in certain patient population. Although a recent
advisory committee made clear that the science has some way to go in
providing definitive guidance on how to test patients and predict adverse
outcomes, that uncertainty has not stopped the FDA from acting in the
meantime.

FDA regulation of medical devices
The FDA’s regulation of medical devices has evolved. The term “device” is
defined in the Federal Food Drug and Cosmetic Act of 1938 (FFDCA) to mean
instruments, implements, machines and other things intended to diagnose
diseases or other conditions and treat disease in humans. Further, any items
intended to affect the structure or function of the body of humans or other
animals are considered devices.

Any person who manufactures, holds, or distributes medical devices is subject
to regulation under the FFDCA. However, from 1938 to 1976, there were no
mandates that devices should be reviewed or approved before they were put in
commerce. Devices were subject to federal regulation and enforcement after
the fact because the FDA lacked authority to keep unsafe products from
entering commerce.
In 1976, Congress enacted the Medical Device Amendments of 1976, finally giving the FDA power to require premarket review for medical devices. The 1976 amendments created a classification scheme that categorized devices into one of three classes – Class I, Class II, or Class III – according to their perceived threat to health and safety and the regulatory burden they must satisfy before approval:

- **Class I devices** are viewed as posing little to no threat to health and safety and are subject only to general controls over manufacturing processes.  
- **Class II devices** require special controls to assure their safety and effectiveness, which may prompt the FDA to promulgate performance standards, postmarket surveillance, and patient registries, and/or develop and disseminate guidelines and recommendations.
- **Class III devices** require even more controls to ensure their safety and effectiveness and are generally used to support or sustain human life, are important in preventing the impairment of human health, or prevent an unreasonable risk of illness or injury.

The medical implants subject to recent FDA scrutiny are typically categorized as Class III devices. In general, manufacturers of Class III devices must gain premarket approval (PMA) from the FDA by submitting an application disclosing the available scientific knowledge about the device. PMA is a complex process, requiring full reports of all information on safety and effectiveness investigations of the device, including details about the device’s components, ingredients, properties, and operating principles. The FDA’s PMA regulation for new devices requires that a complete description of the device be included in the application detailing the aspects of the device that could affect safety or effectiveness. This description must include each functional component or ingredient of the device.

Alternatively, devices need not undergo the full PMA application process if the device is found to be “substantially equivalent” to a device that was on the market before the enactment of the 1976 amendments. This is known as the premarket notification process, or 510(k) notification, and it does not constitute FDA approval but does allow for the device to be marketed to the public. The standard for substantial equivalence in a 510(k) review requires the FDA to assess the technological characteristics of the predicate device and the new device, which involves evaluating the materials of the new device compared with the predicate device. This evaluation typically requires manufacturers to provide descriptive information comparing the materials of the devices. Ultimately, the FDA evaluates the differences to determine their effect on safety and effectiveness.

The FDA generally considers a device safe when the scientific evidence demonstrates that the probable health benefits outweigh the probable risks. In March 2012, the FDA released what it described as “first-of-a-kind” guidance for device manufacturers on the benefit-risk determinations during premarket review for PMA and new devices. The guidance explained how FDA staff...
consider risks and benefits during premarket review, by relying on principal factors such as:

- Type, magnitude, and duration of risk or benefit;
- Probability that a patient will experience the risk;
- Patient tolerance for risk;
- Availability of alternative treatments; and
- Value the patient places on treatment.

This guidance was again recently updated and re-issued in August 2019 to supersede guidance that had already been updated and re-issued 3 years earlier.  

Recent FDA action relating to the materials used in medical devices

Advisory committee meetings

FDA advisory committees provide independent advice from outside experts on issues related to medical devices. They are generally comprised of a chair; several members; and a consumer, industry, and sometimes patient representative. The committees advise the FDA but do not have the authority to make final decisions. They are subject to federal laws and regulations that dictate how the committee should be convened and deal with potential conflicts of interest. The FDA’s CDRH has established advisory committees to provide professional expertise and assistance on the development, safety, effectiveness, and regulation of medical devices. CDRH has five advisory committees, including a Medical Devices Advisory Committee with 18 different panels covering medical specialty areas. In 2010, CDRH made changes to how it operated these expert panels due to a significant increase in the number of meetings during the preceding years.

These advisory committee meetings have been convened recently to focus on the materials comprising specific devices. For example, in November 2019, the FDA organized a meeting to address immunological responses to metal-containing medical implants. In March of that year, before the announcement of the meeting, FDA commissioner Scott Gottlieb, MD, and CDRH director, Jeff Shuren, MD, issued a joint press release on the agency’s recent efforts to evaluate the materials used in medical devices. In the statement, they said the agency recognized that the majority of devices work as expected and with no adverse reactions. However, they also acknowledged that a “growing body of evidence” suggested that a small subset of patients may be at risk of adverse responses to certain materials in medical implants, such as an inflammatory response and tissue changes, that cause pain and other symptoms. They announced a broad effort to engage the scientific community and other stakeholders to assess the current state of the science, identify gaps, and develop approaches to improve the safety of devices. As part of that effort, Gottlieb and Shuren announced the plan to hold the advisory committee meeting in the fall of 2019 to discuss metal-containing implants and the potential risk for certain patients to have exaggerated immune and inflammatory responses to metals.
In advance of the November advisory committee meeting, the FDA released a comprehensive white paper on the biological responses to metal implants, focusing on metals and alloys commonly used in the medical device industry for implants. The white paper provided the agency’s review of the then-available scientific information related to metals and their use in medical implants. The FDA explained in the paper that it had undertaken extensive postmarket reviews of data associated with specific metal-containing implants over several years previously after safety concerns were raised relating to metal-on-metal hip implants and a permanent birth control device. According to the FDA, the concerns associated with those devices raised questions about how the immune systems of recipients of these devices might respond to the presence of metal in the device and to what degree, if any, those responses might produce clinically significant symptoms or adverse outcomes.

At the meeting, the FDA and invited presenters summarized known science on biological responses to metal implants. The topics covered metal corrosion, immunological and toxicological mechanisms associated with adverse events, clinical manifestation, the FDA’s approach to biocompatibility, biomarkers, and screening tests for patients. The panel discussed factors that might affect a patient’s risk of adverse response, such as the extent of wear, alloy composition, microstructure, and the surface coating of an implant. The panel deferred many areas of inquiry to future study because there was neither scientific evidence that potential adverse effects were related to the implants or a method for identifying those who might have a systemic immune response to a medical implant.

One consensus takeaway from the advisory committee was that it was important and beneficial for patients to have device packaging labels that include a list of the elemental composition of the implant. In May 2021, following up on the consensus recommendation from the advisory committee, the FDA formally solicited feedback from stakeholders in a discussion paper on how labeling should disclose the elemental composition of medical devices. The discussion paper suggests the agency is considering requiring manufacturers to specify the constituent elements of metal alloys, such as stainless steel, cobalt chrome, nitinol, and other materials, and possibly disclosing the presence of any residues or byproducts of the manufacturing process. This level of transparency would be unprecedented for medical devices and consistent with a general theme in the food and drug space toward transparency and providing more information for consumers and healthcare providers.

**Guidance on testing for corrosion of nitinol**

On 15 October 2020, the FDA issued guidance on technical considerations, including corrosion testing, for the use of nitinol in medical devices. Nitinol is an alloy comprised of almost equal parts nickel and titanium, and the combination of these metals produces a layer of titanium oxide that enhances the alloy’s corrosion resistance. Nitinol is a unique material with certain
properties, including superelasticity (the ability to recover from strains, such as compression) and shape memory, that make it suitable for use in medical devices, particularly devices delivered through minimally invasive techniques to areas such as the heart and brain. If corrosion occurs to nitinol used in medical devices in vivo, it could adversely affect the properties of nitinol and its biocompatibility.

The FDA’s 2020 nitinol guidance followed other guidance the agency had issued in 2015 on best practices for corrosion testing and technical considerations related to the use of nitinol in stents. The FDA had previously issued guidance regarding corrosion and leaching of metal ions in stents in 2005 and 2010. The FDA’s guidance for stents was consistent with prior guidance issued by the FDA in 1995 for medical device manufacturers for corrosion testing and biocompatibility of medical devices. When the agency issued the 2020 guidance on the biological evaluation of medical devices, it recognized the expansion of nitinol to other product areas and expanded the guidance to cover technical considerations with the use of nitinol in medical devices.

The primary concern with the use of metals in medical devices relates to the potential for corrosion of the metals, which can include the release of metal ions, which can compromise the mechanical integrity of the device and could, in rare circumstances, produce hypersensitivity reactions in patients who use the devices. As a result of these potential issues, the FDA has, over time, provided device manufacturers with recommended testing to perform during the development and approval process for the device. Thus, in the 2020 nitinol guidance, the FDA provides a corrosion-testing paradigm flowchart that recommends first testing devices with cyclic polarization testing in accordance with ASTM F2129-19a, the standard testing method recommended by the American Society for Testing Materials. The method involves measuring the device’s resistance to pitting and corrosion by using electrical voltage to determine the voltage at which the device starts to pit and corrode. This kind of test can be conducted in several hours. If the voltage is high enough and the acceptance criteria are met, no further testing is needed. If the results do not pass the ASTM F2129 the FDA recommends an in vitro test, such as a bench corrosion test, that measures the metal ion release rate and takes 60 days to perform. The FDA also recommends that the ISO 10993-1 standard be used for biocompatibility, including that a risk assessment be performed to compare the amount of nickel released from the device to a tolerable intake value for nickel, which is 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.” Separate, and apart from the question of whether corrosion could lead to someone who is allergic to the corroding material having a hypersensitivity reaction, these tolerable intake levels assess whether there should be concerns about potentially toxic levels of exposure to a substance.
Conclusion
The FDA is examining material science issues related to medical implants and using the regulatory tools at its disposal to be seen as proactive in response to media attention and patient concerns. Meanwhile, the agency and experts in this space continue studying the potential associations between certain small patient population and alleged adverse reactions from medical implants. The discussions at the FDA’s recent advisory committee meeting on metal implants suggest there is unlikely to be a single moment of clarity or a one-size-fits-all diagnosis of the problem. The panelists and the FDA itself have acknowledged that most patients who receive medical devices reap tremendous benefits, and the benefits of receiving these devices far outweigh the costs. There are likely many contributing factors to be teased out by scientists and the FDA in the coming years to identify which patients and devices are associated with adverse outcomes. The recent discussion paper and guidance published by the FDA demonstrates that the FDA will continue to create an active regulatory environment in response to patient advocacy groups and media attention. The FDA’s regulatory action details are difficult to predict, but there seems to be a greater focus on transparency. The advisory committee meeting also suggests the FDA will be closely monitoring new scientific developments relating to patient immune responses to medical implants.

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