Patient Advocates' Comments to the FDA on Metals in Implants
Immunology Devices Panel of the Medical Devices Advisory Committee;
Notice of Meeting; Establishment of a Public Docket; Request for Comments
Docket No. FDA-2019-N-3767

Patient Safety Action Network's Medical Device Roundtable
Advocating Safety in Healthcare E-Sisters (ASHES)
Washington Advocates for Patient Safety
Breast Implant Victim Advocacy
Breast Implant Safety Alliance
Medical Device Problems
USA Patient Network
Just Call Me Ray

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Patient advocate organizations submit these comments in response to Federal Register Public Docket and Request for Comments to the Immunology Devices Panel of the Medical Devices Advisory Committee (Docket No. FDA-2019-N-3767). Some from these groups attended and spoke at the November 13-14, 2019, FDA meeting of the Immunology Devices Panel of the Medical Devices Advisory Committee.

We have serious concerns about the direction the agency is taking with regard to adverse immunological reactions to metals in medical device implants. Our concerns are discussed below, as well as our recommendations that: (1) FDA require the materials with which such implants are made to be disclosed prior to moving them to market; (2) post market surveillance be given the highest priority including User Fee funding; (3) FDA collaborate with other agencies to educate physicians about potential harm from metals in implants that may not obviously present as implant related; (4) FDA develop a body of evidence regarding biocompatibility of implant materials in the human body and immediately look to other specialties that do have evidence on these issues; and (5) FDA require changes in the material composition of existing devices to go through a thorough review regarding biocompatibility. We also support the creation of a multi-stakeholder workgroup that includes patient representatives to develop educational materials for patients and physicians regarding the potential adverse immunological reactions to implantable devices.

INTRODUCTION

In November 2018, Former FDA Commissioner Scott Gottlieb issued a promise to strengthen and improve the 510(k) pathway to bring medical devices to market. The public and patients advocated for more stringent proof of implanted medical device materials' biocompatibility. The same month, FDA held two days of hearings on the topic of immunological responses to metals in medical devices. These hearings came *after* the FDA published standards of biocompatibility testing in draft guidance for a new lab accreditation Program.[1] The timing of this draft guidance prior to the announcement of the public hearings on metals in implants demonstrates that the FDA has already charted a course that *assumes* the biocompatibility of device materials. Although the FDA White Paper presented for the November hearings mentions toxicity, during

the hearings the focus was directed toward profiling patients whose immune systems might predispose them to adverse reactions.

Dr. Laura Santambrogio stated in her invited testimony that it is indeed rare to find an innate level of hypersensitivity in the general population, because few individuals have the required set of specific biomarkers to trigger such a response. However, 2014 research that Dr. Santambrogio co-authored explained that toxic metals trigger biologic responses, causing negative immune system reactions. The research emphasized the urgency in determining the association between the metals and toxic responses because of the large population worldwide carrying these devices.[2]

Still, the mantra of rarity was driven home at every turn during the hearing, citing registry and MAUDE reporting data, which is grossly incomplete. To close the circle on this argument of rarity, the FDA panel asserted that it was difficult to find evidence to explain the negative interactions, because such incidences are extremely rare. The FDA has erroneously concluded that cause and effect has not been established between the toxicity of materials and the adverse events creating an epidemic of human harm and suffering.

HOW MANY PATIENTS ARE AT RISK?

No entity routinely documents how many devices are implanted into patients, so it is mathematically impossible to determine rarity without such a denominator.

Jeanne Lenzer has estimated, *"About 32 million Americans — or about one in 10 — have at least one medical device implanted, from artificial joints to cardiac stents, surgical mesh, pacemakers, defibrillators, nerve stimulators, replacement lenses in eyes, heart valves and birth control devices."*[3] The sheer numbers of people estimated to have medical implants warrants a very close watch over the reactions these devices may have when placed inside human bodies. Confounding the search for identifying the total number of patients with adverse immunological reactions is the fact that over 50 million Americans are diagnosed with some form of arthritis.[4] Many of them have joint replacements and are taking medications that suppress the immune system symptoms of their disease and thus may not be easily identified as having an adverse immunological reaction.

THE FDA IS USING INCOMPLETE, LIMITED DATA

MAUDE data are both limited by gross under-reporting, the use of summary reports, exclusion of patient outcome information, redaction of implant specific identifiers, and an assumption of acceptable collateral damage. The rate of reporting is estimated to be as low as 0.5%-2% of all occurrences.[5] The continued use of summary reports allows manufacturers to lump together thousands of negative outcomes as one report, masking the true size of the problems. Patient Problem codes are redacted by the FDA, making it impossible to establish cause and effect by connecting devices to their health consequences. Even more problematic, adverse health outcomes are seldom properly categorized or understood to be related to the implant. If diligence is not given at point of care to establish the etiology of symptoms, then outcomes such as cardiomyopathy or kidney failure will never be associated with the metals in implanted

medical devices. FDA MAUDE data is also fraught with inaccurate, or at the least unclear, information. One analysis found that the most severe outcome, death, was shown to be mis-categorized as malfunction or injury 17.5% – 24.7% in the sampled device reports.[6]

According to Dr. Steve Tower, Cobalt is fundamentally toxic and should never be implanted in the human body. Extrapolated from the research he has been doing with his own patients, there are probably one million Americans at risk of cobalt poisoning due to the cobalt in hip, knee, or shoulder devices.[7]

Still, the only data the public has are the adverse event reports made to the FDA MAUDE system by device companies, health care providers, health care facilities and patients. Although these reports reflect a very small tip of the iceberg, the numbers from MAUDE regarding problems with these devices are far from small. Based on MAUDE data from Device Problems, more than 3.3 million adverse event reports (including those from alternate summary reports) are documented regarding knee and hip implants, Essure implants, breast implants and expanders, and dental implants. Unfortunately MAUDE doesn't allow for identifying adverse immunological reaction to the devices, but the overwhelming majority of them report injuries as opposed to device malfunctions. Alternative Summary Reporting data revealed 2.1 million dental implant adverse events, with 95% of the reports indicating serious injury or rejection. Further analysis of 30,000 physician reports using 17 search terms often used with toxic responses, found the use of those terms 32,000 times in relationship to knees, hips, and some cardiac devices.[8]

Current U.S. registries contain information on a limited number of patients and details submitted to the registry are not available to the general public or most health care providers, including non-participating surgeons.

The need for more research on biocompatibility is compelling. Even experts have provided conflicting information. At the November 2019 hearing, Immunology Panel Member, Dr. Joshua Jacobs, repeatedly emphasized that the adverse outcomes were a result of patient characteristics triggering an immune response, even though in 2003 he wrote, *"Concern about the release and distribution of metallic degradation products is attributable to the known, potential toxicities of the elements used in implant alloys, particularly Co and Cr."*[9]

Decisions regarding evidence of biocompatibility should be based upon biologic science that captures information over an extended period. The current practice of reliance upon substantial equivalence to previously untested devices and in vitro lab bench testing does not prove biocompatibility. First, such "non-clinical bench tests are generally part of design verification, not validation, and therefore, testing can be performed on prototype units, which may differ slightly from the final product. Second, at the time engineering is testing a device, they may not know whether it is identical to the finished product for which a company will submit to FDA. It may be the tentative final design or a prototype."[10] These practices brought us metal on metal hips with outlandish claims of 20-year implant survival rates. Reality was nowhere near that mark! According to the research of Zhidao Xia et al (2017), the necessary oversimplification of in vitro mechanical testing cannot capture the complex interaction of several metals, nor is it predictive of biologic response. The use of more complex in vivo studies demonstrated that the "immunogenicity and toxicity of particles is a leading factor in the onset and severity of reactions."[11]

Despite the availability of literature confirming the relationship of toxic metals to adverse outcomes, the FDA has chosen to ignore information that does not support their conclusions. Conclusions without evidence are conjecture. In this area, cause and effect have not been the focus of scientific studies. Literature reviews have been largely confined to orthopedic studies, primarily of MoM hip joints even though the issue of metals in implants spans a wide range of devices, such as sterilization coils, IUDs, cardiac devices, hips, knees, shoulders, staples, screws, plates, breast implants, filshie clips, dental implants and hardware, and more. Also, the FDA has disregarded the literature in other areas of science related to metals such as Nickel, Cobalt, Chromium, and Titanium in the alloys used in the human body environment. Significantly, environmental, occupational, and toxicological studies, which could have provided useful information, were not given priority in the FDA's literature review. At the November hearing, panel members were dismissive of relevant data from occupational hazard studies demonstrating toxicity occurring at low blood serum cobalt levels (>1ppb).

ADVERSE IMMUNOLOGICAL REACTION TO THE METALS IN IMPLANTS ARE NOT RARE

This narrative that adverse immunological reactions to metals in implanted medical devices are rare partially ties back into the FDA's use of limited data from adverse event reports and registries as discussed above. However, there is also a statistical merry-go-round being engaged. If the premise of a search for cause presumes that the cause does not exist, it is likely no evidence will be found. However, if the researchers would look to agencies whose duty it is to track population health, the FDA would find that statistically, immune responses to metal are not rare at all.

One definition of rare is found in the federal Orphan Drug Act, which the FDA oversees. There, "rare diseases or conditions" are defined as those affecting less than 200,000.[12] So, by definition, a condition affecting more than 200,000 people is not rare. This federal law sought to define "rare" in order to elicit a response to such conditions. We think that a condition, such as adverse immunological reaction from metal implants, which affects more than 200,000 people, warrants a response and action by the FDA.

"It is estimated that up to 17% of women and 3% of men are allergic to nickel and that 1% to 3% of people are allergic to cobalt and chromium. These types of reactions can be localized reactions that are limited to one area, but they can also be more generalized and affect other more distant parts of the body."[13]

One analysis cited the combined results of approximately 50 studies showing the incidence of metal sensitivity:

- Among the general population is about 10-15%, with Nickel sensitivity being the highest at approximately 14%.
- Among patients with implants, regardless of whether their implants are well-functioning or poorly functioning, is about 25%, almost twice as high as that of the general population.
- Among patients with a failed implant is 50-60% (compiled from five investigations), five times that of the general population and two to three times higher than all patients with metal implants.[14]

How rare is something that effects 10-15% of the general population? With a U.S. population of 328 million,[15] metal hypersensitivity easily exceeds the "rare" definition of 200,000 people. If over one million hip and knee replacements are done every year,[16] and if 25% of those people have adverse immunological reactions to the metals, within 4 years a million people would experience these adverse events due to implants that are intended to be used for a much longer period of time. And, that is not rare.

Clearly, just saying that something is rare, does not make it true. And, clearly, it is irresponsible and dismissive of the FDA to put forth the premise that negative reactions to implant metals are rare. The inflexibility of this premise has led the FDA to conclude that cause and effect has not been established between device materials and the adverse outcomes. It is time for the FDA to listen to the real experts: patients who live with the constant barrage of symptoms brought on by immune responses to toxic levels of heavy metals corroding and wearing in their bodies. Epidemiology reminds us all that the absence of evidence is NOT the evidence of absence. Simple logic reminds us that if we cannot find what we are looking for, we are either looking in the wrong place, or we must change the object of our search. To believe that adverse events caused by toxicity/hypersensitivity to metals in implants are rare is to remain willfully blind.

KEEPING THESE ISSUES IN MIND, THE FDA SHOULD TAKE THE FOLLOWING ACTIONS TO ASSURE THAT MEDICAL DEVICES BEING IMPLANTED INTO PATIENTS ARE SAFE AND EFFECTIVE:

(1) Require device makers to disclose all implant materials: Materials in implants, including materials coating these implants, approved or cleared by FDA should be public information and labeled in the UDI database. This information should include a black box warning (if it exists). The material safety data sheet should be attached to the UDI record in addition to providing the instructions for use (IFUs) for the device. This would encourage physicians and health care providers' use of UDIs and allow them to use the data to protect their patients and their practices. This information should also be included on device labeling and in informed consent materials to patients for all implants. No trade secrets should be allowed for devices that are put inside people's bodies and cannot be removed without invasive procedures. Current practices prevent patients from declining implants to which they have a known allergy as well as learning about their allergies when they have an adverse immunological reaction to an implant.

(2) Post Market surveillance must be a priority. More resources need to be put toward these activities. User fees paid by the industry should be used to create a publicly transparent and accountable oversight system, including enforcement. Traditionally, the user fees have focused on the pre market side, however the 2017 amendments to MDUFA clearly state a broader purpose: *"The Congress finds that the fees authorized under the amendments made by this title will be dedicated toward expediting the process for the review of device applications* ***and for assuring the safety and effectiveness of devices****"* (emphasis added) (Title II, Sec 201). All prior efforts have been towards speeding up the process for putting medical devices on the market. Most of these devices are untested regarding what happens when they are implanted into people's bodies. With this level of experimentation on unsuspecting patients, the post market surveillance is our first line of defense, but is virtually non-existent. We have no idea

how many implants have been removed due to problems caused by the device, there is no systematic collection of what patients are experiencing and physicians are witnessing and there is no accessible repository for this information so it can be useful in assuring safe and effective devices. The current NEST program being developed does not meet standards of transparency that will enable every patient and every physician to benefit from the information reported to such a program.

(3) Education of physicians: FDA should collaborate with other relevant federal agencies within HHS, such as the Center for Medicaid and Medicare Services, on a "Dear Doctor" letter to provide information about the potential harm from metals in implants that may not obviously present as implant related. These efforts should target both surgeons and primary care doctors who are likely to be the first ones a patient will see for such symptoms. HHS/CMS, a primary payer for most implants, should have a vested interest in identifying problems early. A 2007 analysis found that Medicare pays for more than 60% of all hip implants.[17] A 2017 study indicates that the impact of metal on metal hip implants "on public health and health care costs are already considerable and will grow substantially in the next decade, considering the large number of patients implanted and the follow-up needed for lifespan of the implant and also after implant revision to monitor for adverse long-term effects." [18]

(4) Biocompatibility Research: FDA should develop a body of evidence regarding biocompatibility of implant materials in the human body. Such research is essential for the review to ensure the safety of medical implants. Immediately, FDA should look to other areas where evidence does exist - such as toxicology, electro-chemical engineering, immunology, cardiology, nephrology and urology – and begin using this information in their pre-market device reviews. These are not new issues - the agency has been discussing them for years regarding devices such as metal on metal hips, Essure, and Breast implants. Biocompatibility should be dealt with in a more comprehensive manner rather than waiting for large numbers of harmed patients to bring continuing problems to the FDA's attention over and over. Further, studies need to look at the long-term biological effects of implanted devices. One unique long-term study, with more than 20 years of follow up, suggests that elevated serum and urine cobalt and chromium concentrations may persist throughout the lifetime of the implant.[19]

(5) Changes to a device's material should trigger biocompatibility testing. FDA should require biocompatibility testing when companies propose changes in the composition of materials in existing devices. If a company claims changes reflect an improvement in the device, FDA should require them to demonstrate this in terms of biocompatibility. The current rules, which allow companies to send all but "substantial" changes in devices through the 510(k) process, should be not be allowed when they relate to a change in materials. Creating another pathway within 510(k) will not ensure patient safety.

Thank you for the opportunity to submit these comments. Questions may be directed to Linda Radach (linda.radach@gmail.com) or Lisa McGiffert (lmcgpsan@gmail.com).

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