

Magazine

REGULATORY PERSPECTIVES

Navigating Nitinol's Biocompatibility, Potential Toxicity, and the Evolving Regulatory Landscape

The material and market attributes make a clear case for nitinol's broad applications in medical device manufacturing.

September 12, 2023



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Nitinol is an alloy derived from nickel (Ni) and titanium (Ti) that has become increasingly popular in medical devices due to its superelasticity and shape memory. Superelasticity is the ability of an alloy to accommodate a relatively large shape change

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(deformation) when a mechanical load is applied, and spontaneously regain its original shape when the mechanical load is removed. Shape memory is the alloy's ability to be mechanically deformed into a new shape at a lower temperature, and then regain its original shape when heated to a higher temperature. These properties provide a significant advantage in medical applications, facilitating elastic deployment in devices such as wires.¹

Favorable biocompatibility—i.e., the ability of a medical device or material to perform with an appropriate host response, as defined by ISO 10993-1—is another critical feature of **nitinol**, making it suitable for implants. Its fatigue and kink resistance, especially in tight areas, along with its extreme corrosion resistance—which minimizes nickel ion release—are further advantages. Moreover, being non-ferromagnetic, nitinol offers better MRI compatibility than stainless steel, while providing 10-20 times greater flexibility.¹

The United States represents almost 41% of global nitinol use. The \$36.5 million market (2021) is projected to grow to around \$72.5 million by 2028, according to Medgadget data. The material and market attributes make a clear case for nitinol's broad applications in medical device manufacturing. However, the nickel in nitinol can be problematic if it is not carefully considered and exposure is not controlled.

How Prevalent is Nitinol Use?

Nitinol is a part of various devices and applications. The material is used in numerous orthopedic devices such as fracture fixators, bone anchors, intramedullary nails, and spinal intervertebral spacers.² In dentistry, it is used in orthodontic arch wires, dental implants, and endodontic files for root canals.

Nitinol has also been incorporated into implantable cardiac

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devices, catheter tubes, catheter reinforcement coils, breast cancer tumor markers, endoscopic stone retrieval baskets, suture threaders, filters, needles and also in medical tubing.

Due to its excellent thermal connectivity and efficient conductivity, nitinol is also used in electrodes. This has led to its incorporation into ablation catheter tips, surgical instruments, brain-control-interface implants, and cryoablation devices. Nitinol's varied and continually expanding use in medical devices underscores its important role in advancing patient care and treatment efficacy.³

The Nickel Challenge

The primary toxicological concern with nitinol—which comprises 40%-50% nickel and 50%-60% titanium—is the potential release of nickel ions.

The most commonly reported adverse health effect associated with nickel exposure is contact dermatitis.⁴ A comprehensive 20-year retrospective cross-sectional study of approximately 44,000 patients patch tested for contact allergies further substantiated nickel's potential health impact. The study found that 17.5% of patients reported nickel sensitivity, defined as a positive patch test for nickel. More than half (55%) of these reactions were clinically relevant, with a predominance among female patients.⁵ A multinational patch test group reported hypersensitivity reactions to implanted metallic devices, suggesting an increased risk of systemic reactions.⁶

Research has also indicated a significantly higher incidence of nickel hypersensitivity among ulcerative colitis patients, emphasizing the complex systemic response to nickel exposure.⁷ The systemic consequences of nickel exposure extends to the central nervous system, as nickel can cross the blood-brain barrier. These data underscore the need for

continued diligence in monitoring and controlling potential nickel release from nitinol containing medical devices.

Biocompatibility Challenges

Examining nitinol's cytotoxic potential further illuminates the challenges associated with its use in medical devices. Rongo et al. investigated the cytotoxicity of coated and uncoated nickel-titanium archwires in human gingival fibroblasts for up to 30 days. Their results indicated that uncoated nitinol wires displayed slight cytotoxicity (cell viability between 60%–90%) on days one, seven, and 14, and moderate cytotoxicity (cell viability between 30%-59%) on day 30.⁸

Nickel ion release should be considered one potential cause of any cytotoxicity test failure with a nitinol-containing device. Cytotoxicity and sensitization tests can help evaluate risk for contact dermatitis and other hypersensitivity reactions.

Risk Management and Mitigation

Preclinical testing is the first line of defense in risk management, and experienced partners can be crucial allies in mitigating the risks of nickel release from nitinol devices. For example, a trusted lab testing partner can help devise a comprehensive test strategy based on the nature and duration of device contact.

Chemical characterization, followed by a toxicological risk assessment, can identify if the device extracts contain nickel above the recommended regulatory levels for systemic toxicity, with the exception of hypersensitivity. Additionally, a targeted nickel ion release test can be performed to measure the quantity of nickel that leaches from the device under conditions chosen to simulate clinical use. For permanent implants, the U.S. Food and Drug Administration (FDA) **recommends** 60-day nickel release testing unless data indicates the nitinol component surface is stable (approaching equilibrium). In such cases, testing may be

concluded earlier, with a minimum 30-day test duration.

Several strategies can also be employed to limit undesirable nickel ion release. For example, coating the surface of nitinol implants with materials like silicon carbide has shown promising results, particularly in enhancing hemocompatibility for devices in direct contact with blood.⁹

Other surface treatments such as passivation, electropolishing, and laser surface modifications have been applied to nitinol devices. It has been shown that applying a titanium oxide layer effectively reduces corrosion and minimizes nickel ion release.¹⁰ Furthermore, ceramics or polymers like polyurethane, perylene, and PTFE have also been applied to improve corrosion resistance.

Such measures allow device manufacturers and lab testing partners to anticipate and address potential problems before nitinol-based devices enter the market. The range of specialized medical device applications that use nitinol—orthopedics, oncology, interventional cardiology, soft tissue surgery, orthodontics, neurology, etc. underscores the value of engaging a testing partner with equally broad experience and capabilities.

Risk communication, including informing patients and healthcare professionals about potential nickel sensitivity and providing clear instructions for use, is also integral. This requires accurate device labeling indicating the presence of nickel, per recommended regulatory guidelines. Furthermore, post-market surveillance that monitors device performance in real-world clinical settings can also identify unforeseen risks and ensure timely intervention. Put simply, risk management for nitinol devices requires a lifecycle approach that includes measured steps at each stage of device development.

Regulating Nitinol Use

The regulatory landscape for nitinol-containing medical devices has continually evolved as regulators and scientists have gained knowledge and experience with this alloy. This evolution has highlighted that certain applications of nitinol might require additional caution and may receive closer regulatory scrutiny.

These situations may include, but are not limited to:

- Contact types include surface/intact skin, surface/mucosal, or surface/breached-compromised, where the potential for local sensitization effects may be heightened.
- Specific patient groups whose underlying disease processes might amplify the chances of adverse immunological reactions. An example of this would be hypersensitivity in patients with ulcerative colitis⁷
- Scenarios where the release of nickel ions from the device is more likely, either due to the lack of a surface coating, an environment where the surface coating is more likely to wear or degrade, and/or instances of long-term contact duration.

Regardless of testing, a pre-submission and/or Q-submission meeting with the FDA and other relevant regulatory agencies is recommended for nitinol-containing devices to ensure sponsor and regulatory agency alignment. Testing partners that employ experienced chemists and toxicologists can provide expert assistance in navigating this process.

A Final Word

Nitinol's unique properties make it a compelling material choice for a myriad of medical device applications. However, its nickel content raises biocompatibility and toxicology concerns that must be addressed. Given the potential for adverse reactions, comprehensive preclinical testing and evaluation combined with effective post-market risk mitigation strategies are crucial.

Strategically chosen surface treatments and coatings can also

help mitigate potential risks in manufacturing.

FDA requires extensive testing for nitinol-containing devices, and international regulations often follow the agency's lead. As nitinol applications evolve, so does the regulatory landscape to ensure patient safety in these applications. A trusted lab testing partner can help manufacturers stay informed about these developments to ensure nitinol's safe use in medical devices.

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