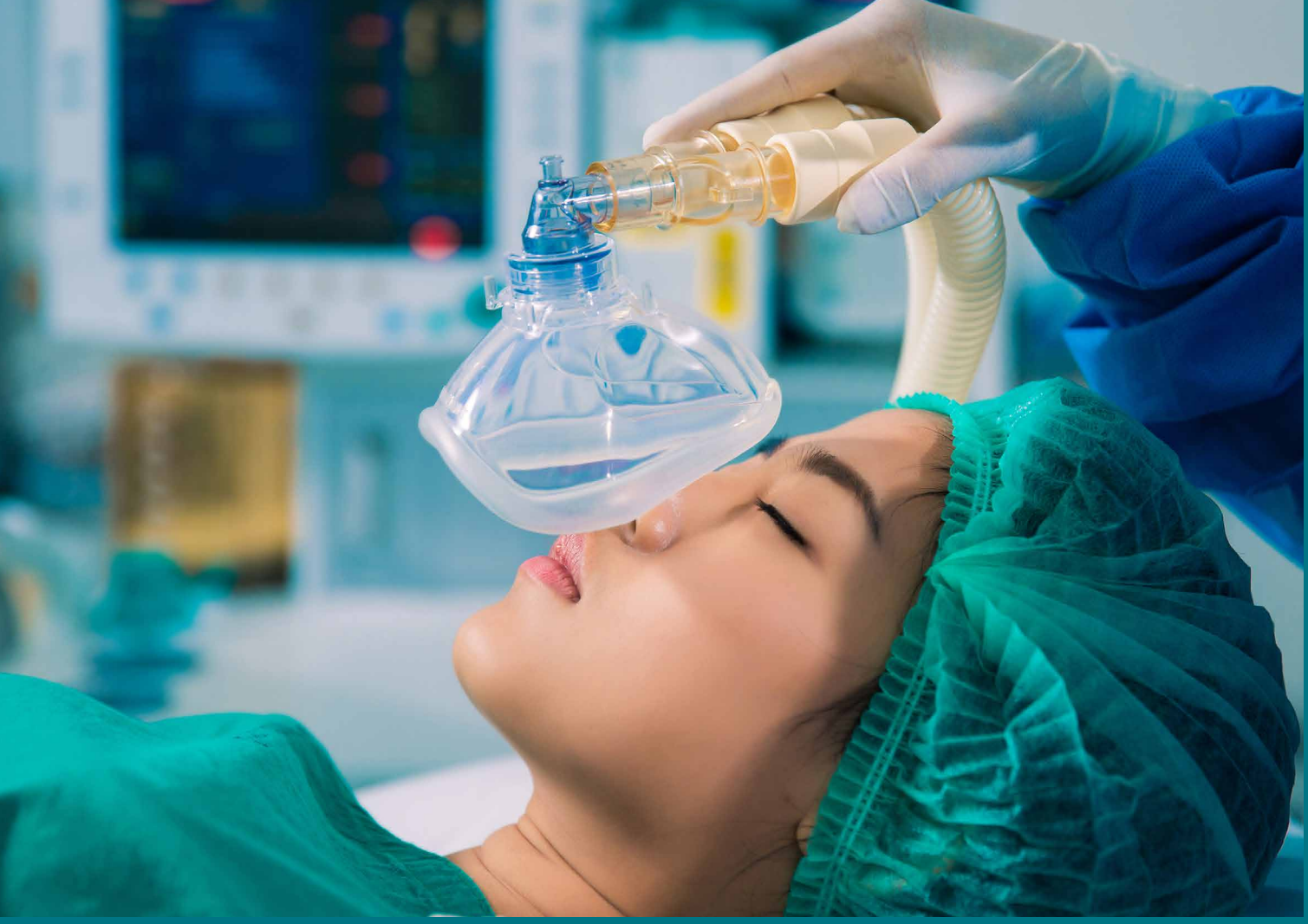


BIOCOMPATIBILITY TESTING OF GAS PATHWAYS IN MEDICAL DEVICES

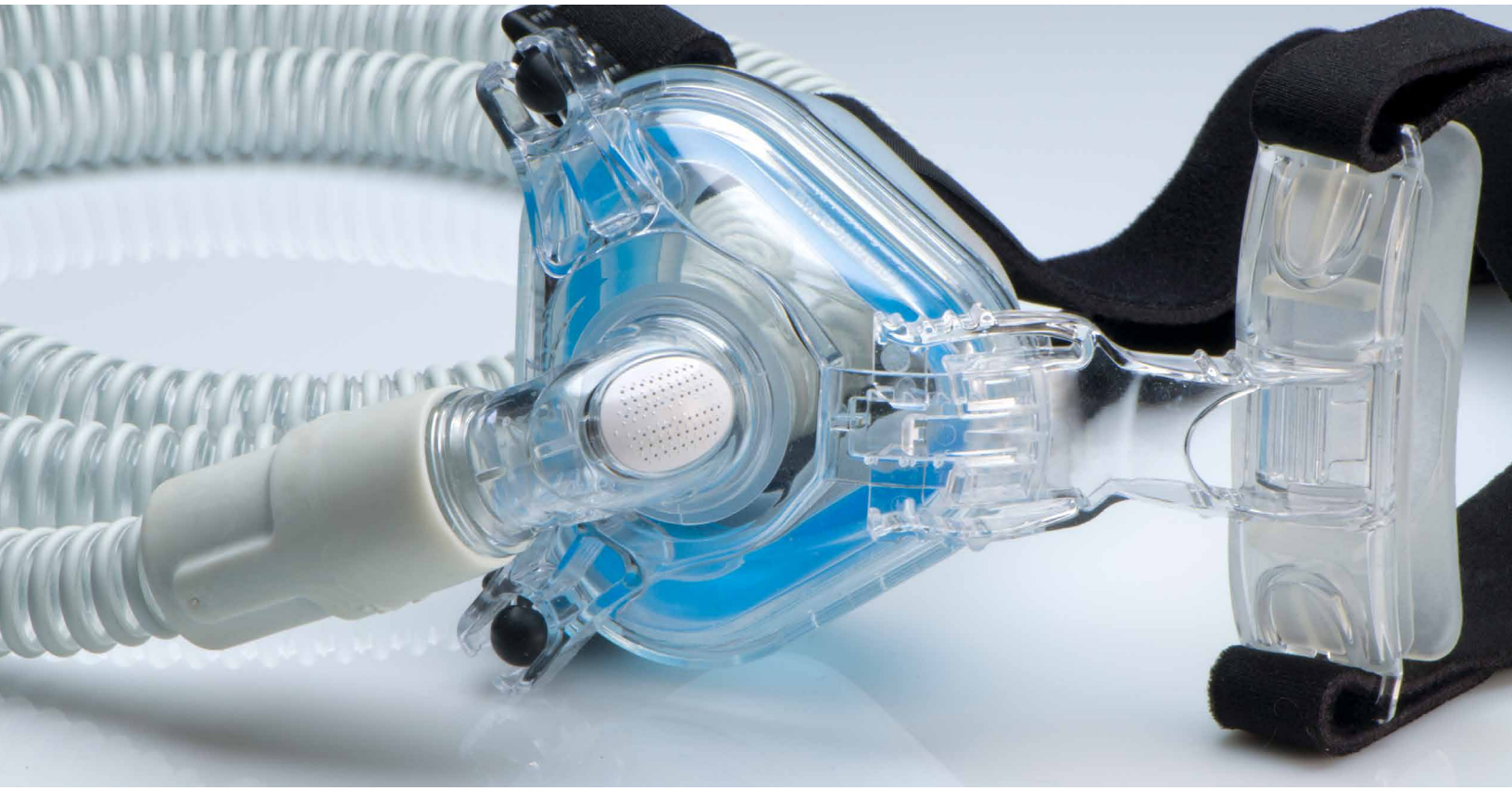
EXECUTIVE SUMMARY

Many medical devices used to assist in the diagnosis, monitoring or treatment of respiratory issues or to deliver anesthesia or gas-borne medications can pose a unique set of risks to patients. Air from these devices and their associated parts and accessories often infiltrate human passageways essential for breathing, putting them in direct contact with internal tissues that can be highly sensitive to the chemical emissions and condensates they produce. This exposure can result in health and safety consequences for patients who are receiving therapy, anesthesia, or who are subject to respiratory intubation.

The U.S. Food and Drug Administration (FDA) requires that manufacturers of medical devices seeking pre-market approval under its 510(k) program to submit testing data validating the biocompatibility of any patient-contacting material. Yet, despite these requirements, the FDA reports that nearly one-third of 510(k) submissions provide inadequate information regarding device biocompatibility, or fail to provide any biocompatibility data at all.[1] The failure to conduct adequate biocompatibility testing or to submit sufficient documentation validating biocompatibility typically results in the rejection of a 510(k) submission or an extend delay in its review by the FDA.

Published in March 2017, ISO 18562, *Biocompatibility evaluation of breathing gas pathways in healthcare applications,* is a series of international standards that outlines the general principles for the evaluation of the biological characteristics of medical devices used in respiratory care or to supply anesthesia or other substances through the respiratory tract. The series consists of four parts that address acceptable practices for assessing and managing biocompatibility risks. It also details specific testing protocols for emissions of particulate matter and volatile organic compounds (VOCs), as well as for leachable substances found in condensate produced by the device.

This UL white paper discusses the importance of biocompatibility testing of breathing gas pathways in medical devices, and how testing in accordance with the technical requirements of the ISO 18562 series of standards can strengthen claims of biocompatibility in support of FDA 510(k) submissions. Beginning with a brief review of the FDA's clearance process for medical devices and the current timelines for the agency's review of 510(k) submissions, the paper then discusses the specific biocompatibility challenges associated with medical devices that include breathing gas pathways. The white paper provides an overview of the structure and requirements of the ISO 18562 series of standards and concludes with information on UL's approach to assessing and validating the biocompatibility of gas pathways in medical devices.



THE FDA'S CLEARANCE PROCESS FOR MEDICAL DEVICES

Virtually, all medical devices sold or marketed in the U.S. must meet mandatory regulations administered by the FDA in order to protect the health and safety of patients and healthcare providers alike. Approximately, 80 percent of all medical devices are covered under the FDA's 510(k) premarket notification program.

The 510(k) review program requires device manufacturers to submit extensive documentation supporting the "substantial equivalence" of their devices to other legally marketed medical devices previously cleared by the FDA (referred to as "predicate devices"). "Substantial equivalence" refers to factors such as a device's design, construction, use indications, safety performance, effectiveness and any other applicable characteristics. Accordingly, the scope and depth of information provided with a 510(k) submission must be sufficient to allow FDA reviewers to determine whether the subject medical device is substantially equivalent to an identified predicate device.

In the latest round of Medical Device User Fee negotiations, FDA reiterated its commitment to a 90-day review for 510(k) submissions received directly from medical device manufacturers.[2] Yet, compared with an average clearance time of just 40 days in the late 1970s and early 1980s, only about 19 percent of 510(k) submissions made in 2016 were actually cleared by the agency within 90 days. Instead, manufacturers experienced an average wait of more than 175 calendar days from the date they filed their 510(k) submission with the FDA until they received final clearance. And the clearance time was even longer for manufacturers of anesthesiology devices (those likely to have gas pathways), averaging 245 days from submission to clearance.[3]

This extended clearance time can be partially attributed to a number of factors, including the increased complexity of today's medical devices, as well as the growing number of submissions from non-U.S. companies.[4] However, incomplete or insufficient information in 510(k) submissions may well be the leading cause in the extended clearance times experienced by manufacturers. FDA data indicates that the agency requests additional data in connection with as many as three out of every four 510(k) submissions it receives.[5] Missing or incomplete information typically involves data related to performance testing, clinical evaluations and device biocompatibility.

BIOCOMPATIBILITY CHALLENGES IN MEDICAL DEVICES WITH GAS PATHWAYS

Modern medical devices are comprised of a diverse range of materials and components, each with their own physical and chemical characteristics. Although many of these materials may pose minimal risk when incorporated into products intended for general use, their inclusion in medical devices expands the scope of potential safety considerations. These considerations can include breakdown or decomposition of device materials attributable to heat or wear during normal device operation or the migration of chemicals from internal device components into the patient breathing air path.

For medical device components that must be evaluated for direct contact with external or internal human tissues, such as cannulas, breathing masks or intubation mechanisms, additional exposures to volatile organic compounds (VOCs) and condensates must be considered. For devices with complex breathing gas pathways, including electromechanical components, the potential risks associated with their use can be challenging to identify.

Biocompatibility risks can also be introduced through manufacturing and post-production processes that can have an adverse effect on components and materials. For example, contact with lubricants or other chemicals during production or maintenance can compromise the chemical integrity of a device. Similarly, extended use can degrade some components, and certain sterilization and disinfection techniques may adversely affect device emissions.

These examples help to illustrate the complexity of the overall risk profile associated with biocompatibility of medical devices with gas pathways. They also serve to highlight the challenges in identifying and conducting the testing and evaluation necessary to provide regulatory authorities with assurances regarding the safety of such devices.

THE IMPORTANCE OF TEST METHODS IN VALIDATING BIOCOMPATIBILITY

A comprehensive biocompatibility evaluation looks at all the potential adverse effects on a human body that may result from components and materials used in a medical device. In determining the specific tests to conduct, special consideration is given to how a medical device will actually be used, the intended patient population, e.g., adult, pediatric, etc., and the degree and duration of contact between the device and the patient.

Until recently, evaluating biocompatibility of medical devices with gas pathways has been conducted in accordance with the requirements of ISO 10993-1:2009, *Biological evaluation of medical systems – Part 1: Evaluation and testing within a risk management system.* ISO 10993-1 provides a detailed framework for an assessment program to thoroughly evaluate the biocompatibility of a device under evaluation. It also requires a detailed risk analysis to identify the actual testing to be performed, as well as any additional tests that might be necessary to evaluate other biological aspects.

However, scientists, researchers and regulators have raised concerns regarding the effectiveness of the assessment framework presented in ISO 10993-1 in addressing specific risks associated with the use of medical devices with breathing gas pathways. Despite its usefulness in addressing the biological evaluation of medical devices, the standard lacks the necessary specificity to address the totality of risks associated with these devices, including risks associated with the presence of airborne and particle VOCs.

Additional concerns have also been raised about how the biocompatibility requirements of ISO 10993-1 have been applied by regulators and testing laboratories in their assessment of medical devices with gas pathways. Specifically, some parties have interpreted the requirements applicable to "direct contact" materials equally applicable to materials with "indirect contact." In some cases, this divergence in interpretation of the standard's requirements has resulted in additional testing of questionable benefit.

Finally, in many circles, questions have been raised regarding the scientific validity and the ethics of ISO 10993's reliance on animal-based cytotoxicity testing to assess biocompatibility. Although ISO 10993-2, *Biological evaluation of medical devices – Part 2: Animal welfare requirements*, offers guidance on the reduction in the number of animals used for testing and encourages the replacement of animal testing with other scientifically-valid forms of assessment, any use of animal testing can be problematic, especially when more advanced, non-animal-based methods are now widely available.

ABOUT ISO 18562

To address the specific aspects of the evaluation of gas pathways not covered in ISO 10993-1, the International Organization for Standardization (ISO) published the ISO 18562 series of standards in March 2017. The standards series, which was developed by ISO/TC 121, *Anaesthetic and respiratory equipment*, Subcommittee SC 3, *Lung ventilators and related equipment*, is comprised of four separate standards that describe a risk-based approach specific to the evaluation of breathing gas pathways in medical devices and other healthcare applications for relevant biocompatibility issues, and detail specific testing methods to detect the risk of particulate matter, VOCs and leachables in condensate.

In general, the ISO 18562 standards series addresses gas pathways of medical devices, parts or accessories that provide patients with respiratory care, or that supply gasses, medicines or other substances via the respiratory tract. Specific devices included under the scope of the standards include, but are not limited to:

- Ventilators
- Anesthesia workstations
- Breathing systems
- Oxygen conserving equipment
- Oxygen concentrators
- Nebulizers
- Low-pressure hose assemblies
- Humidifiers
- Heat and moisture exchangers
- Respiratory gas monitors
- Respiration monitors
- Masks
- Mouth pieces
- Breathing tubes
- Breathing system filters
- Y-pieces
- Incubator chambers
- Any breathing accessory

THE SPECIFIC FOCUS OF EACH PART OF THE STANDARD SERIES IS AS FOLLOWS:

• ISO 18562-1, *Biocompatibility of breathing gas pathways in healthcare applications – Part 1: Evaluation and testing within a risk management process*—Part 1 of the series outlines the general principles intended to govern the biological evaluation of gas pathways within a risk management process. Among other risks, it specifically addresses those arising from the potential contamination of the gas stream from gas pathways from within a medical device. However, it does not address contamination that may already be present in gas supplied from other sources.

• ISO 18562-2, *Biocompatibility of breathing gas pathways in healthcare applications – Part 2: Tests for emissions of particulate matter*—Part 2 of the ISO 18562 series addresses the presence of particulate matter, that is, particles suspended in the breathing gas. It prescribes a testing method for measuring emissions of any particulates ranging from 0.2-10µm in size. The standard allows use of gravimetric filter measurement or use of a more sophisticated laser particle counter. Particulate concentration for particles less than 2.5 micrometers (PM2.5) and less than 10 micrometers (PM10) are then compared against acceptance criteria as presented in ISO 18562-1.

• ISO 18562-3, *Biocompatibility of breathing gas pathways in healthcare applications – Part 3: Tests for emissions of volatile organic compounds (VOCs)*—Part 3 of the standards series covers testing methods that can be used to quantify VOCs emitted from components and materials in the gas pathway that are present in the breathing gas stream. Prescribed methods of sampling VOC emissions under ISO 18562-3 include the use of sorbent media consistent with the requirements of ISO 16000-6, *Indoor air – Part 6: Determination of volatile organic compounds in indoor and test chamber air.* Alternatively, VOC emissions samples can be collected using canisters in accordance with the requirements of ASTM D 5466, *Standard test method for determination of volatile organic compounds in atmospheres (canister sampling methodology).*

• ISO 18562-4, *Biocompatibility of breathing gas pathways in healthcare applications – Part 4: Tests for leachables in condensate*—The final Part of the standards series,

ISO 18562-4 covers testing to quantify hazardous, water-soluble substances that are leached from the components or materials of medical devices with gas pathways. Under the standard, condensate is first extracted from the interior surfaces in accordance with the procedures detailed in ISO 10993-12, and then assessed for metal ion content and the presence of organic impurities. Condensate samples are also subject to cytotoxicity and sensitization testing.

It is important to note that none of the testing methods described or referenced in Parts 2, 3 or 4 of the ISO 18562 standards series involve the use of animals or other forms of in-vivo assessment.

UL'S APPROACH TO THE TESTING OF MEDICAL DEVICES WITH GAS PATHWAYS

UL's testing and exposure assessment services offer manufacturers a comprehensive approach to assessing the compliance of medical devices with gas pathways with the requirements of the ISO 18562 series of standards. A comprehensive biocompatibility assessment includes testing for particles, VOCs and leachable condensates within the context of a comprehensive risk assessment process, as prescribed by the ISO 18562 series.

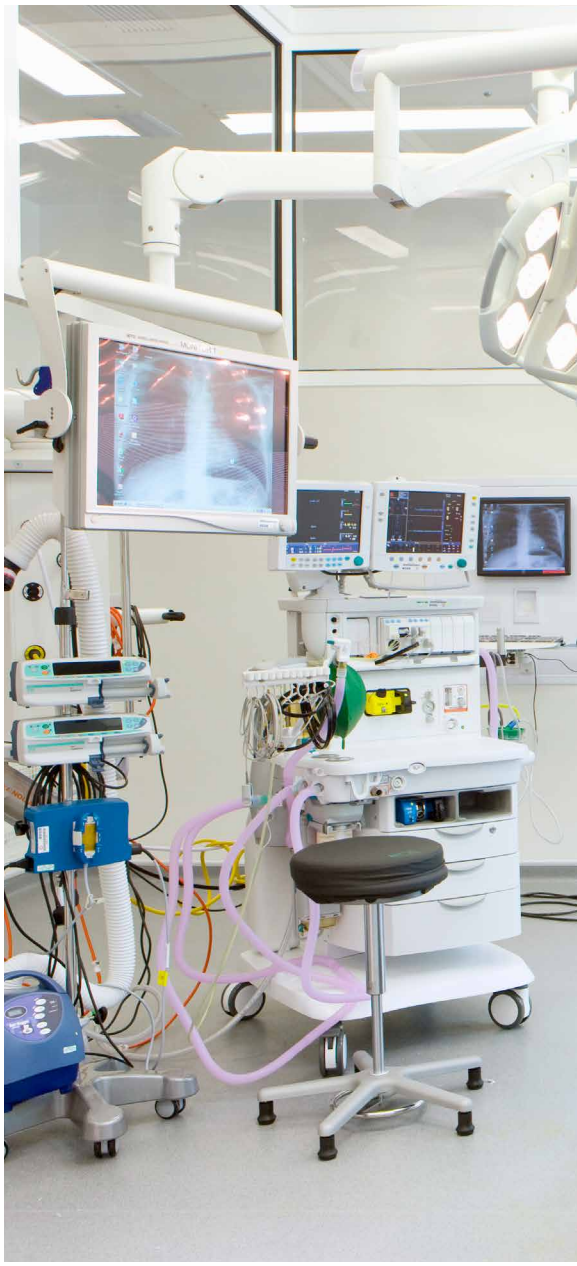
Developing a test program that adequately addresses worst-case conditions for each potential pollutant requires extensive knowledge of the device design, use indications, and operating modes. UL's experts work directly with product manufacturers to explain how key parameters, such as air flow rate and temperature, may affect the level of airborne particles and VOCs in the breathing gas stream.

UL also offers GREENGUARD Certification which provides a framework for managing compliance throughout the product lifecycle, including evaluation of material changes and process improvements. Medical devices with gas pathways that maintain GREEENGUARD Certification have been subject to an independent third-party evaluation and are better positioned to satisfy regulatory requirements regarding biocompatibility in the U.S., European Union and other major medical markets.

SUMMARY + CONCLUSION

Assessing the biocompatibility of medical devices with gas pathways is a complex process that must account for a number of potential health and safety risks to patients. The failure to provide a complete and thorough assessment consistent with applicable standards can result in requests from regulators for additional information on biocompatibility issues. And such requests typically result in delays in their decision regarding the approval of a given device, and lost revenue opportunities for device manufacturers.

The introduction of the ISO 18562 series of standards gives medical device manufacturers a detailed framework for the thorough assessment of the biocompatibility of medical devices with gas pathways. Based on the ISO 18562 standards, certification of medical devices in accordance with the requirements of UL's GREENGUARD program can help ensure a comprehensive assessment of biocompatibility risks, and smooth the path to regulatory approval.



For additional information on UL's services for medical devices with gas pathways, email **ENVIRONMENT@UL.COM** or call **+1.888.485.4733**

END NOTES

1. "Analysis of Pre-Market Review Times Under the 510(k) Program," U.S. Food and Drug Administration, Center for Devices and Radiological Health, November 9, 2011. Web. 4 October 2017. https://www.fda.gov/downloads/aboutfda/centersoffices/cdrh/cdrhreports/ucm263386.pdf.

2. "MDUFA Performance Goals and Procedures, Fiscal Years 2018 through 2022," U.S. Food and Drug Administration, December 2, 2016. Web. 4 October 2017. https://www.fda.gov/downloads/ForIndustry/UserFees/MedicalDeviceUserFee/UCM535548.pdf.

3. "How long it takes the US FDA to clear medical devices via the 510(k) process: An examination of 15,000 medical device applications cleared by the US Food and Drug Administration between 2012 and 2016," a report by The Emergo Group, March 2017. Web. 15 November 2017. https://www.emergogroup.com/sites/default/files/emergo-fda-510k-data-analysis-2017.pdf.

4. According to The Emergo Group report cited in Endnote #2, 510(k) submissions from non-U.S. companies accounted for more than 40 percent of all 510(k) submissions in calendar year 2016, up from just 22 percent in 2014.

5. See Endnote #1.

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