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UNDERSTANDING INVESTMENTS IN THE MEDICAL DEVICE SECTOR

Part 1: FDA Classifications & Regulations

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TABLE OF CONTENTS

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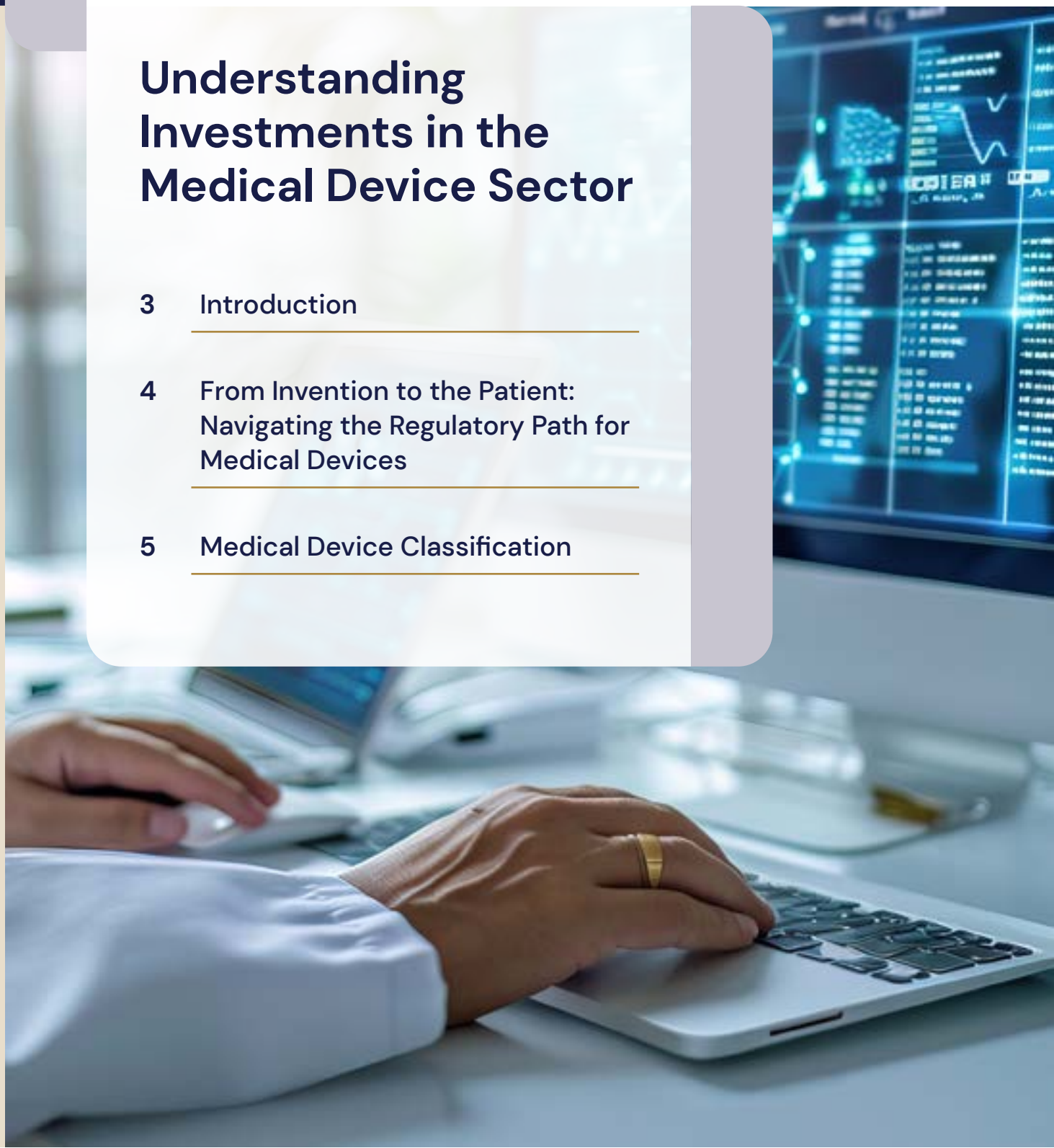

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The medical device industry is poised for explosive growth after the downturn in investment following the COVID pandemic. Technologic advances in molecular medicine and neurobiology, robotics, and artificial intelligence (AI) combined with a supportive regulatory environment at the U.S. Food and Drug Administration (FDA) provide fertile ground for new MedTech product development. This age of technology acceleration and globalization is driving invention and discovery at an unprecedented pace. For example, the number of AI-based patent applications filed by the MedTech sector almost quadrupled from 2018 to 2022 with 2771 MedTech patents published in 2022[1] And this explosive growth continues as the United States granted 3,600 medical technology patents in 2023[2]

Market trends are also positive for the MedTech sector as consumers focus on healthy lifestyles and healthcare providers & payers migrate to personalized medicine and at-home care, fostering the growth of wearable devices, remote patient monitoring, and at-home diagnostic testing that enable patient-centric medicine. In the coming wave of medical innovation, there will be a plethora of investment opportunities in MedTech, from wearables to structural and electronic implants to AI-driven diagnostic algorithms.

Technology driven MedTech companies need significant capital to navigate the complexities of engineering, manufacturing, regulatory approvals, and market access, but the path to financing is challenging. Thousands of private companies with promising and proven technologies are competing for funding from a relatively limited number of investment banks, venture funds, and wealthy family offices that specialize in healthcare and life science investing. In order to realize the promise of the amazing advances in medicine propelled by MedTech, new funding paths are needed.

Physicians, researchers, and healthcare professionals have unique, experiential knowledge to evaluate new technologies and to assess their utility in medical practice. Healthcare professionals understand not only the medical technology, but also the challenges and pathways to market acceptance. However, the limits on communication, participation and high minimum investments have limited their involvement in this funding endeavor. In the last decade a new regulatory regime has come into being that democratizes the private markets, allows for mass communications on potential deals, and facilitates lower minimum investment amounts. This enables more individual investors, physicians and healthcare professionals in particular, to participate in private offerings. The confluence of regulatory changes at the SEC and the FDA has created a positive market environment for MedTech investment, and physicians and healthcare professionals are positioned to benefit, both professionally and financially, provided that they participate in private market opportunities.

LeagueMed has been founded to provide a platform for the healthcare community to participate in private MedTech deals. The LeagueMed.com platform delivers valuable industry insights about finance and the business of medicine, professional education, and presentation of investment opportunities in private MedTech and healthcare companies. The editorial focus of LeagueMed is to educate our community of healthcare professionals about how to invest in the private capital markets, how to evaluate technology and regulatory risk, and how members can leverage their education, training, and experience to enhance their professional and financial well-being.

[1] https://www.marks-clerk.com/insights/news/medtech-sector-sees-surge-in-ai-patent-applications-marks-clerk-ai-report-2023-reveals/
[2] https://www.epo.org/en/about-us/statistics/patent-index-2023/statistics-and-indicators/european-patent-applications/top-10-technical-fields/medical-technology

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From Invention to the Patient: Navigating the Regulatory Path for Medical Devices

What Are Medical Devices?

According to the FDA website, Medical devices range from simple tongue depressors and bedpans to complex programmable pacemakers, and closed loop artificial pancreas systems. Additionally, medical devices include in vitro diagnostic (IVD) products*, such as reagents, test kits, and blood glucose meters. Certain radiation-emitting electronic products** that have a medical use or make medical claims are also considered medical devices. Examples of these include diagnostic ultrasound products, x-ray machines and medical lasers[3]

Medical devices are subject to regulation according to the Food, Drug, and Cosmetic (FD&C) Act based on 1) their intended use; and 2) indication for use (i.e. the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended).

Per Section 201(h)(1) of the Food, Drug, and Cosmetic Act, a device is:

An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

(A) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
(B) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, *or*
(C) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o).

In Vitro Diagnostics*

In vitro diagnostics (IVD) are tests done on samples such as blood or tissue that have been taken from the human body. In vitro diagnostics can detect diseases or other conditions and can be used to monitor a person's overall health to help cure, treat, or prevent diseases.

In vitro diagnostics may also be used in precision medicine to identify patients who are likely to benefit from specific treatments or therapies. These in vitro diagnostics can include next generation sequencing tests, which scan a person's DNA to detect genomic variations.

Some tests are used in laboratory or other health professional settings and other tests are for consumers to use at home.

Radiation Emitting Electronic Products**

Radiation emitting electronic products are regulated by the FDA Center for Devices and Radiological Health (CDRH). The purpose is to prevent unnecessary exposure to radiation due to the use of these products.

1. The term "electronic product radiation" means
   A. any ionizing or non-ionizing electromagnetic or particulate radiation, *or*
   B. any sonic, infrasonic, or ultrasonic wave, which is emitted from an electronic product as the result of the operation of an electronic circuit in such product;
2. The term "electronic product" means
   A. any manufactured or assembled product which, when in operation,
      i. contains or acts as part of an electronic circuit and
      ii. emits (or in the absence of effective shielding or other controls would emit) electronic product radiation, or
   B. any manufactured or assembled article which is intended for use as a component, part, or accessory of a product described in clause (A) and which when in operation emits (or in the absence of effective shielding or other controls would emit) such radiation;
3. The term "manufacturer" means any person engaged in the business of manufacturing, assembling, or importing of electronic products.

Most radiation-emitting products are not considered to be medical devices. However, if you make any medical claims, your product is a medical device also subject to the provisions of the FD&C Act for medical devices in addition to the provisions for radiation emitting products[4].

[3] https://www.fda.gov/medical-devices/classify-your-medical-device/how-determine-if-your-product-medical-device
[4] https://www.fda.gov/medical-devices/classify-your-medical-device/does-product-emit-radiation

Medical Device Classification

The FDA assigns medical devices to one of three regulatory classes: Class I, Class II or Class III, based on the level of control necessary to provide reasonable assurance of its safety and effectiveness. All medical devices are subject to standard regulatory controls for manufacturing, packaging, and labeling. Class I devices pose little or no risk to the patient or provider (bandages, stethoscopes, wheelchairs); Class II devices pose low to moderate risk (at-home diagnostic tests, syringes, catheters); Class III devices (implantable prosthetics, Software as a Medical Device or SaMD, pacemakers). Each of these classifications has defined regulatory requirements and pathways to clearance.

The FDA uses the terms "cleared" and "approved" to describe different levels of review for products. FDA approval is generally considered a higher standard than FDA clearance.

FDA Clearance

A product is considered "cleared" if the manufacturer can show that it's "substantially equivalent" to another legally marketed device that's already been approved or cleared. For example, the Apple Watch has FDA clearance as a Class II medical device. To get clearance, manufacturers can submit a Premarket Notification (510(k)) to the FDA, which doesn't require clinical trial data. The FDA evaluates the device's safety and effectiveness by comparing it to other devices, and most products receive 510(k) clearance within three months.

FDA approval

A product is considered "approved" if the FDA determines that its benefits outweigh its known risks for its intended use. This is often required for products that could pose a significant risk of injury or illness but could also have health benefits. To get approval, manufacturers must submit a Premarket Approval (PMA) application that includes scientific and legal documents and results from clinical investigations.

Class I and II Medical Devices

Most Class I and II medical devices require pre-market notification through the 510(K) pathway, which is described in detail on the FDA website[5]. A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is as safe and effective, that is, substantially equivalent, to a legally marketed device (section 513(i)(1)(A) FD&C Act)[6]. Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalence claims. The pre-market submission must be made 90 days prior to market introduction of a new medical device. A device may not be marketed in the U.S. until the submitter receives a letter from the FDA finding the device is substantially equivalent.

What is Substantial Equivalence?

A 510(k) requires demonstration of substantial equivalence to another legally U.S. marketed device. Substantial equivalence means that the new device is as safe and effective as the predicate.

A device is substantially equivalent if, in comparison to a predicate it:

- has the same intended use as the predicate; and
- has the same technological characteristics as the predicate; *or*
- has the same intended use as the predicate; and
- has different technological characteristics and does not raise different questions of safety and effectiveness; and
- the information submitted to FDA demonstrates that the device is as safe and effective as the legally marketed device.

A claim of substantial equivalence does not mean the new and predicate devices need to be identical. FDA first establishes that the new and predicate devices have the same intended use and any differences in technological characteristics do not raise different questions of safety and effectiveness. FDA then determines whether the device is as safe and effective as the predicate device by reviewing the scientific methods used to evaluate differences in technological characteristics and performance data. This performance data can include clinical data and non-clinical bench performance data, including engineering performance testing, sterility, electromagnetic compatibility, software validation, biocompatibility evaluation, among other data[7].

[5] https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-notification-510k
[6] https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-notification-510k
[7] https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-notification-510k#se

Class III Devices and the Pre-Market Approval (PMA) Process[8]

Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. Examples of Class III devices include implantable prosthetics, pumps, and neurostimulators, diagnostic tests for infectious disease or cancer, and defibrillators.

Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices. A PMA application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the Class III device. The PMA typically requires substantial pre-clinical research and comprehensive human clinical trials in intended treatment populations, similar to the New Drug Application (NDA) requirements for novel drug products.

The De Novo Designation[9]

For devices that provide reasonable assurance of safety and effectiveness for the intended use, but for which there is no legally marketed predicate device, the De Novo request provides a marketing pathway to classify novel medical devices as Class I or Class II rather than Class III, which requires a full PMA application. Novel medical devices that have no predicates are automatically classified as Class III. The De Novo request was originally established in 1997, but its use as a novel regulatory pathway has expanded only since 2017 when the final FDA guidance was first published.

There are two options to submit a De Novo request for the FDA to make a risk-based evaluation for classification of the device into class I or II:[10]

- Option 1: After receiving a high-level not substantially equivalent (NSE) determination (that is, no predicate, new intended use, or different technological characteristics that raise different questions of safety and effectiveness) in response to a 510(k) submission.
- Option 2: Upon the requester's determination that there is no legally marketed device upon which to base a determination of substantial equivalence (therefore without first submitting a 510(k) and receiving a high-level NSE determination).

The FDA has established a pre-submission process for all device and drug submissions, enabling manufacturers to communicate and collaborate with the agency on testing methodology and clinical protocols that can demonstrate the regulatory controls necessary to provide a reasonable assurance of safety and effectiveness. The pre-sub is especially important for medical device manufacturers seeking a De Novo classification to obtain FDA feedback on the evidence, including non-clinical and/or clinical data, that will likely be necessary to support the De Novo request. Although De Novo applications typically require non-clinical and clinical trial data to demonstrate safety and effectiveness, the regulatory requirements and associated costs are much reduced as compared with a PMA application.

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[8] https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-approval-pma
[9] De Novo Classification Process (Evaluation of Automatic Class III Designation) Guidance for Industry and Food and Drug Administration Staff
[10] https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/de-novo-classification-request