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Bringing a Medical Device to the U.S. Market via the 510(k) Pathway

Metropolia University of Applied Sciences

Bachelor of Engineering

Chemical Engineering

Bachelor's Thesis

24 May 2022

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Title:	Bringing a Medical Device to the U.S. Market via the 510(k) Pathway
Number of Pages:	80 pages
Date:	24 May 2022
Degree:	Bachelor of Engineering
Degree Programme:	Biotechnology and Chemical Engineering
Professional Major:	Chemical Engineering
Supervisors:	Jukka Niiranen, Principal Lecturer Päivi Turta, Head of Operations (Medical Device)

Before entering the United States market, medical devices must meet related regulatory and quality requirements. There are several premarket submission procedures, and one of them is a 510(k) submission.

This thesis focuses on requirements related to the 510(k) process and interpreted them from the manufacturer's point of view. In addition, it also addresses Food and Drug Administration´s (FDA) Quality System Regulation (QSR) requirements that concern the device manufacturing stage (Production and Process Controls & Acceptance Activities). Consequently, this thesis aims to provide information on the 510(k) pathway and relevant QSR requirements to a manufacturer wishing to market its medical device in the U.S. medical device market.

The subject of this thesis was very extensive. Subsequently, the manufacturer cannot obtain all the regulatory information from this thesis. For instance, the manufacturer's actions and device must meet all the regulatory requirements of the FDA's own quality management system known as "QSR". There is a total of 15 subparts included in the QSR, and this thesis describes two of them (Production and Process Controls & Acceptance Activities). However, the 510(k) pathway is described extensively, and the manufacturer can learn its main points by reading this thesis. Consequently, the goal of this thesis was accomplished, as it provides a large amount of information and recommendations to a manufacturer wishing to market their medical device via the 510(k) pathway, but it also offers some basic knowledge of the U.S. regulatory requirements concerning medical devices.

Keywords: Medical Device, IVD, FDA, 510(k), Substantial Equivalence, QMS, QSR

Tekijä:	Veli-Matti Katajamäki
Otsikko:	Lääkinnällisen laitteen tuonti USA:n markkinoille 510(k):n kautta
Sivumäärä:	80 sivua
Aika:	24.5.2022
Tutkinto:	Insinööri (AMK)
Tutkinto-ohjelma:	Bio- ja kemiantekniikka
Ammatillinen pääaine:	Kemian prosessitekniikka
Ohjaajat:	yliopettaja Jukka Niiranen rekisteröintipäällikkö Päivi Turta

Ennen kuin lääkinnälliset laitteet pääsevät Yhdysvaltojen markkinoille, niiden on täytettävä niihin liittyvät regulaatio- ja laatuvaatimukset. On olemassa erilaisia myyntilupahakemusprosesseja, joiden avulla Yhdysvaltojen markkinoille on mahdollista päästä. Näistä yksi on 510(k)-hakemusprosessi.

Tämä opinnäytetyö keskittyi 510(k)-prosessiin liittyviin vaatimuksiin, joita on tulkittu valmistajan näkökulmasta. Tämän lisäksi työ käsitteli myös Yhdysvaltojen elintarvike- ja lääkeviraston (FDA) laadunhallintajärjestelmän vaatimuksia, jotka koskevat etenkin lääkinnällisen laitteen valmistusvaihetta (Tuotanto- ja prosessiohjaus & hyväksymistoiminta). Näin ollen opinnäytetyön tarkoituksena oli antaa tietoa 510(k)-hakemusreitistä markkinoille ja asiaankuuluvista laadunhallintajärjestelmän vaatimuksista valmistajalle, joka haluaisi markkinoida lääkinnällistä laitettaan Yhdysvaltojen lääkinnällisten laitteiden markkinoilla.

Opinnäytetyön aihe oli erittäin laaja, minkä vuoksi valmistaja ei voi saada kaikkea tarvitsemaansa FDA:n säätelytietoa tästä opinnäytetyöstä. Esimerkiksi valmistajan toiminnan ja laitteen on täytettävä kaikki FDA:n QSR-laadunhallintajärjestelmän vaatimukset, jossa on yhteensä 15 alaosaa, joista kaksi kuvattiin tässä opinnäytetyössä (tuotanto- ja prosessiohjaus & hyväksymistoiminta). 510(k)-hakemusreitti on kuvattu laajasti, ja valmistaja voi oppia siitä olennaisimmat kohdat lukemalla opinnäytetyön. Näin ollen opinnäytetyön tavoite saavutettiin opinnäytetyön tarjotessa runsaasti tietoa ja suosituksia valmistajalle, joka haluaisi markkinoida lääkinnällistä laitettaan 510(k)-hakemusreitin kautta, samalla oppien myös perustietoa Yhdysvaltojen lääkinnällisiä laitteita koskevista regulaatioista.

Avainsanat: Lääkinnällinen laite, IVD, FDA, 510(k), olennainen vastaavuus, laadunhallintajärjestelmä, QSR

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List of Abbreviations

AI: Additional Information

CAPA: Corrective and Preventive Actions

CDRH: Center for Devices & Radiological Health

CE: Conformité Européenne

CER: Clinical Evaluation Report

CFR: Code of Federal Regulations (U.S.)

cGMP: current Good Manufacturing Practices

COVID-19: Coronavirus Disease 2019

DCC: Document Control Center

DHF: Design History File

DHR: Design History Record

DMR: Device Master Record

DoC: Declaration of Conformity

EU: The European Union

EU IVDR: The European Union’s In Vitro Diagnostic Regulation 2017/746

EU MDR: The European Union’s Medical Device Regulation 2017/745

FDA: The Food and Drug Administration (U.S.)

FY: Fiscal Year

GMP: Good Manufacturing Practices

HDE: Humanitarian Device Exemption

HHS: Department of Health and Human Services (U.S.)

HUD: Humanitarian Use Device

IDE: Investigational Device Exemption

IMDRF: International Medical Device Regulators Forum

ISO: International Organization for Standardization

IVD: *In vitro* -Diagnostic.

MD: Medical Device

MDR: Medical Device Report (U.S.)

NSE: Not Substantially Equivalent

OOPD: Office of Orphan Products Development

PMA: Premarket Approval

QMS: Quality Management System

QMSR: Quality Management System Regulation

QSIT: Quality System Inspection Technique

QSR: Quality System Regulation

RTA:	Refuse to Accept
SE:	Substantially Equivalent
U.S.:	The United States
USD:	United States Dollar

1 Introduction

The healthcare industry is thriving worldwide, especially in the United States (U.S.), where healthcare in 2020 accounts for approximately 20% of the U.S. gross domestic product [1]. It has been estimated that in 2020-2030 the global medical device market will grow by around 5% annually as the importance of the healthcare system has been noticed over the years due to the ongoing coronavirus disease 2019 (COVID-19) pandemic, ageing population, and the growth of infectious- and chronic diseases [2].

As the world population has grown and will grow, more and more new medical- and technological innovations are needed, boosting economic growth by increasing efficacy and productiveness and optimising patient outcomes [3]. COVID-19 pandemic has shown that the economy is dependent on a functional and prepared healthcare system and that the need for innovations in healthcare is constant. The pandemic has caused layoffs, killed millions, overthrown companies, and affected people's moods, thus negatively impacting economic growth and paramountly affecting people's lives.

In 2017, 40% of the global medical device market focused on the U.S. medical device market, and the share has grown even more significant since then [4]. For example, in 2016 medical device market in the U.S. was valued to be 147$ billion [5], and by 2023 the value is estimated to grow to as much as 208$ billion [6; 7].

As the medical device industry includes all-around devices and tools for diagnosing, therapy and monitoring, it is dependent on other industries. The U.S. market has superiority over other markets in this case, as the U.S. medical device industry has collaborated effectively with other highly developed U.S. industries such as microelectronics, instrumentation, and biotechnology. Collaborations have led to numerous innovations and advances in the U.S., such as the discovery of new biomarkers, robotic assistance and neuro-stimulators. [7]

Figure 1 shows U.S. medical device revenues during 2001-2009, and the data is gathered by the Food and Drug Administration (FDA) and published in 2011 in their report. Unfortunately, there is no newer data about U.S. medical device revenues gathered by the FDA.

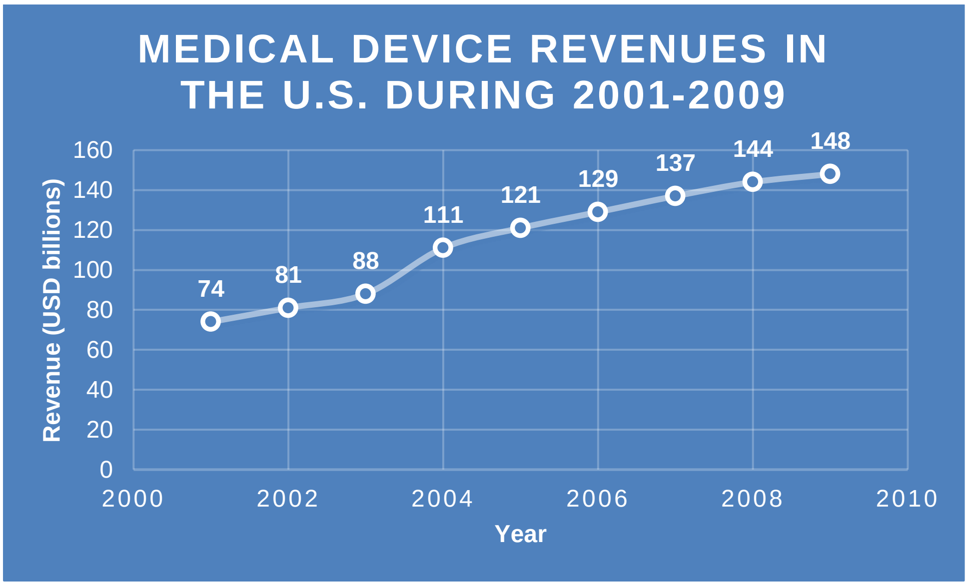


Figure 1. Medical device revenue growth in the U.S. during 2001-2009 [Edited from 8, p. 9].

As seen in Figure 1, the growth of the medical device industry in the U.S. had doubled in ten years and has continued its increase to this day. As stated earlier that by 2023 the U.S. medical device is estimated to be 203$ billion. Additionally, in 2021 the U.S. medical device market size was claimed to be approximately 186$ billion [9].

Developed medical industry and medicines will always be needed. Innovations and advances in the industry are targeted to pursue a forever quest to diagnose and treat different medical conditions more efficiently. The U.S. has an advantage in that quest, as said, as an owner of a vast medical device industry, which continues to grow at an increasing rate year by year, offering 2 million jobs in the U.S. [10]. Figure 2 provides a perspective of how large the medical device industry in the U.S. is and how the U.S. dominates it. It shows the top 10 medical device companies and their total revenue in 2021. Of the companies seen in Figure 2, only three are non-American (Philips, Siemens and Fresenius).

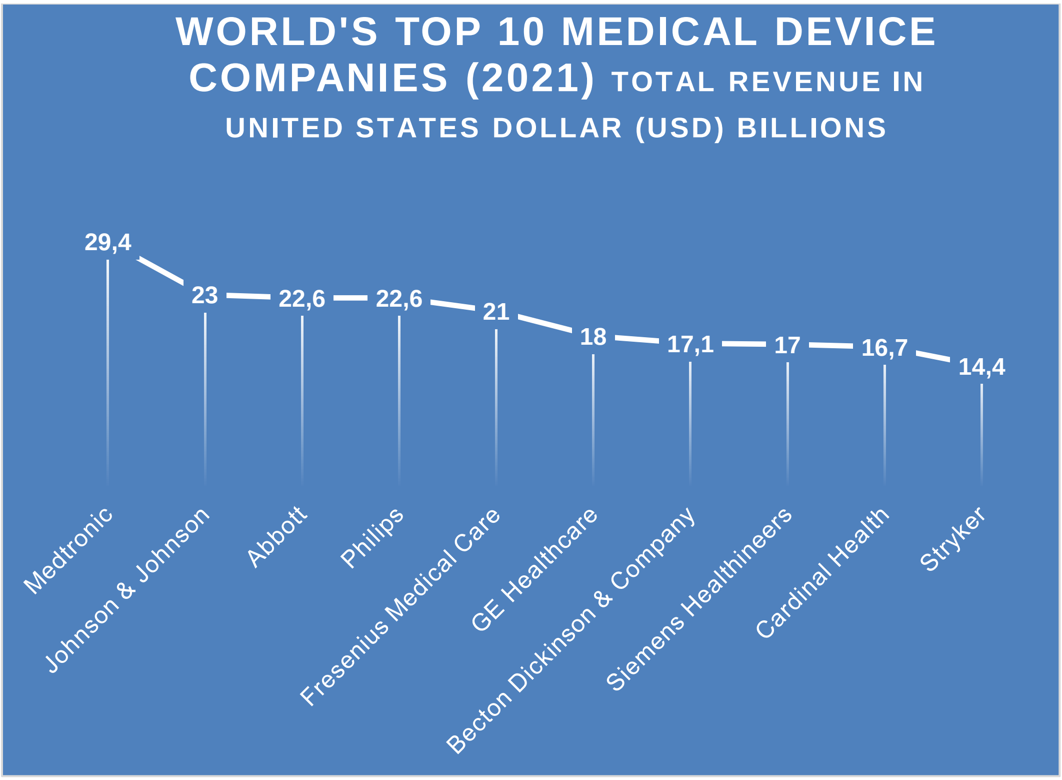


Figure 2. Top 10 medical device companies in 2021 [Edited from 11].

1.1 Medical device market in Finland

In Finland, the medical device industry has also grown significantly. In 2019, exports of medical devices such as patient monitoring and X-Rays increased by 5.1% to 1.7€ billion, which was 70% of total health technology exports [12]. However, due to the COVID-19 pandemic, the exports of medical devices in 2020 and 2021 in Finland were 1.52$ billion, which is approximately a 10% decrease from 2019 [13; 14].

Exports of *In Vitro* Diagnostics (IVDs) had also grown by 10% in 2019, and the total export of IVDs was 656€ million. The significance of the U.S. market can be seen in Finland as well. Exports to the U.S., in general, had grown by 8.7% in 2019, and total exports of health technology products to the U.S. were 934€

million (38.5% of all exports). The European Union (EU) and China, which is the most significant IVD market for Finland, were other important markets where Finland marketed health technology products in 2019. [12] The substantial rise in IVDs can be noticed when comparing their exports in 2019 and 2021. In 2021 exports of IVDs were 920€ million [14]. One reason for its rise can be the COVID-19 pandemic and the selling of COVID-19 tests, which is noticeably an IVD test.

1.2 Aim of this thesis

Before entering the U.S. market, products must meet related regulatory and quality requirements. There are several premarket submission procedures, but this thesis focuses on requirements related to the 510k process to demonstrate the effectiveness and safety of medical devices by indicating that the new device is substantially equivalent to a predicate device already cleared in the U.S.

Medical devices in the U.S. are heavily regulated and have all kinds of roadblocks, and because of this, some manufacturers might avoid placing the device in the U.S. market. Thus, this thesis aims to clarify these requirements related to devices and their production.

1.3 U.S. Food and Drug Administration

When talking about the Food and Drug Administration in this thesis, it is meant precisely the U.S. FDA. Many countries have their own Food and Drug Administrations, such as India and China (China’s FDA is nowadays called as National Medical Products Administration), as sizeable medical device markets. However, generally everywhere, for example, all over the internet and literature, FDA explicitly means the U.S. FDA. This is because the U.S. medical device market, as said, is an enormous and significant market globally. Furthermore, the U.S. FDA is very well known for its strict and distinctive regulatory requirements.

The FDA is an agency under the American government's Department of Health and Human Services (HHS) [15]. The FDA controls the public health by ensuring the efficacy and safety of medical devices, biological products, and many other products related to human health. Moreover, the FDA is responsible for advancing the public health by helping speed up different innovations that make medical devices safer, effective, and more cost-effective. This also applies to other medical products. [16]

The FDA plays a vital role in the U.S. anti-terrorism actions by securing the food supply and assuring its safety. Additionally, the FDA prevents naturally and deliberately impending public health threats by advancing the development of medical products to respond to public health threats. [16]

The specific responsible organization unit for medical devices within the FDA is the Center for Devices & Radiological Health (CDRH). CDRH's primary mission is to assure that medical devices are top-quality, safe, and effective for patients and providers and that there is constant access to them. Legible and accessible science-based information about the products handled by the CDRH is gathered and then provided to consumers, patients and providers. [17] Figure 3 shows the organisation chart of the FDA.

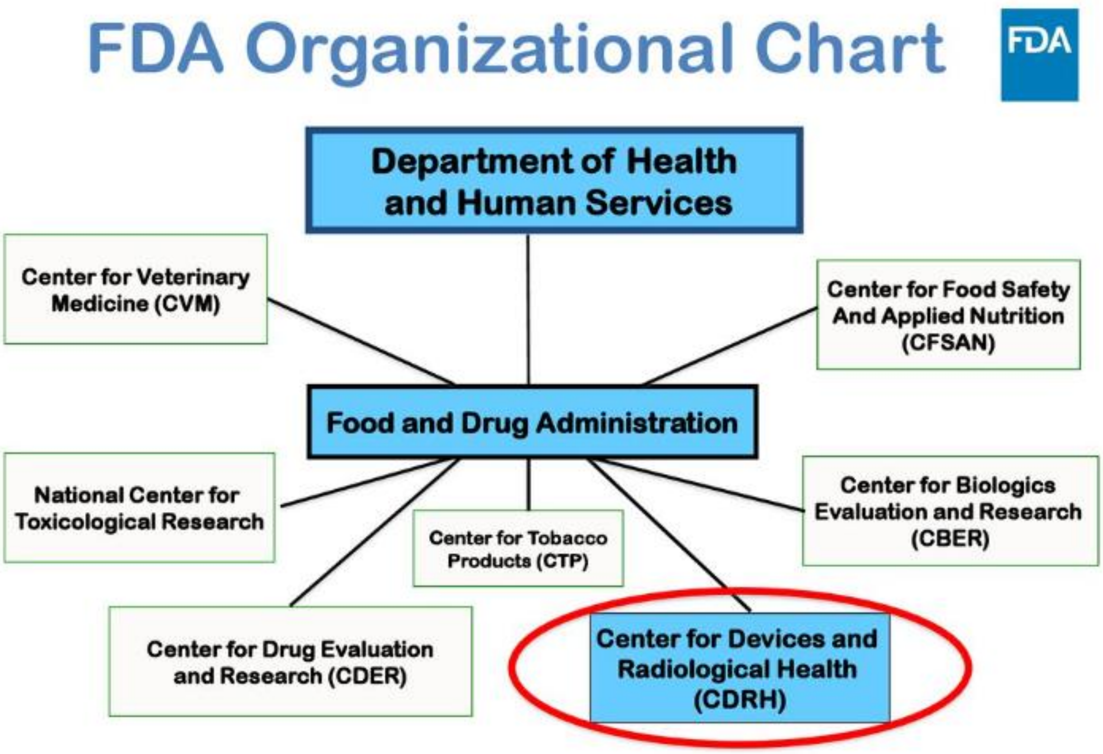


Figure 3. The FDA organization chart [18].

2 Medical devices and IVD tests

Different markets classify products as medical devices (or IVDs) differently; thus, there is no exact definition. A product might be a medical device in some markets but not in other markets. Consequently, the device classification depends on the market and its regulations.

The FDA has defined medical devices as, for example, instruments, machines, *in vitro* reagents, or other similar articles. Medical devices are intended to diagnose, cure, treat or prevent different diseases and conditions, primarily in humans. It does it by changing the structure or functions of a human body and does not claim its purpose by chemical metabolism or as a drug. [19] Medical devices vary from simple to complex, as a bandage is a medical device like a pacemaker because both are intended to treat or prevent different conditions.

Tests analysing samples that are collected from the human body; for instance, blood (serum, plasma, or whole blood), urine, cerebrospinal fluid or tissue, are called IVD tests. IVD tests are mainly used to detect diseases such as COVID-19 or other conditions, such as pregnancy with a home pregnancy test. Furthermore, overall health or physiological state can be monitored using an IVD test; a person with diabetes can monitor blood sugar levels with a blood glucose test. Thereby a person knows to take appropriate actions that prevent blood sugar levels from rising too high or falling too low. Some IVD tests can only be done by professionals and some at home as a self-test.

The difference between a medical device and an IVD is that an IVD does not come in direct contact with the patient and, therefore, does not cure, treat or prevent diseases or conditions. It can only detect diseases or conditions. Instead, a medical device will often come in contact with the patient and can cure, detect, treat, or prevent diseases or conditions [19]. An illustrative example of the difference would be, for instance, the difference between a single-use blood glucose test and a continuous blood glucose monitor. A continuous blood glucose monitor is a medical device that is in contact with the patient all the time, and in addition to detecting alarming glucose levels, it can prevent them from rising or falling because the patient can take measures early as the device shares data continuously. A single-use blood glucose test is an IVD because it only detects glucose levels at a certain moment and does not come in direct contact with the patient. Additionally, "*in vitro*" means that the experimentation is done outside the living organism. Figure 4 shows a continuous blood glucose monitor and a single-use blood glucose test.

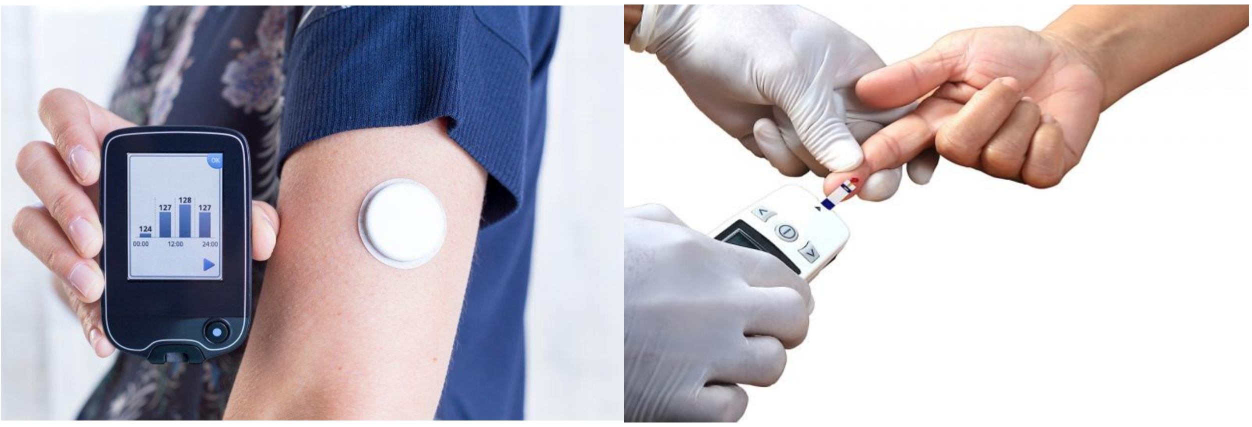


Figure 4. A continuous blood glucose monitor (MD) [20] and a single-use blood glucose test (IVD medical device) [21].

2.1 Safety and effectiveness of medical devices

The FDA emphasises the effectiveness and safety of devices; therefore, it is necessary for the manufacturer to understand what exactly that means, and when a device can be classified as safe and effective.

The clinical effectiveness of a medical device is achieved when it exhibits the effect for the medical condition intended according to the manufacturer. For example, a magnesium blood test is indicated to be used in conjunction with clinical evaluation to aid in diagnosing and monitoring hypomagnesemia, which is often linked to metabolic, cardiac, or neurological disorders. The manufacturer needs reasonable assurance that the magnesium blood test medical device is scientifically valid, which can be achieved from available clinical tests, bench-top tests and literature, inferring that hypomagnesemia is diagnosed via low magnesium levels in the blood. If the manufacturer has scientific validity and clear objectives, the medical devices can be assumed to be safe and effective.

In reality, there are other phases for proving that the medical device is safe and effective, and many other aspects are needed to be considered in addition to the phase mentioned above. The overall process for proving that the device is safe and effective can be read from IMDRF's (International Medical Device Regulators Forum) Final Document chapter 5, "Essential Principles Applicable to all Medical Devices and IVD Medical Devices". The answer to the question of device's safety and effectiveness is complex, and in principle, all actions mentioned in IMDRF's document are required to be taken by the manufacturer during the whole lifetime of the medical device to achieve this very same outcome.

2.2 Medical device classification

Most medical device markets categorise the devices based on a risk-based device classification system. This means that the classification depends on the intended use and indications for the use of the device. The intended use tells what the purpose of the device is. [22, p. 3, 5; 23] For example, the purpose of a stethoscope is to listen to sounds produced from the heart or lungs, which allows the doctor to draw necessary conclusions. The indications for use determine the disease or condition that the medical device in question will, for example, diagnose and prevent [22, p. 5]. For instance, the doctor can notice the fast heart rate with the stethoscope. Generally, the higher the risk for any patient harm or illness the intended use and indications for use has, the more challenging time the manufacturer will face in bringing the device to the market. A stethoscope is an example of a low-risk device. For medical device manufacturers, it is essential to know why the classifications matter for several reasons:

- For the manufacturer to enter the market, the classification of the medical device affects the regulatory path to market and, in many cases, the coverage of clinical evidence that the device must fulfil to reach the market. The golden rule is that the higher the classification is, the stricter requirements it will have. Therefore, more measures are needed to be conducted for high-risk medical devices.

- An important aspect to notice for manufacturers is that the stricter the device regulatory requirements are, the more time it will take to get a medical device to the market and the more costly it will become.

- During the product development phase, the classifications help the manufacturer establish different requirements, such as design controls to ensure the safety and effectiveness of the device. [22, p. 3]

2.3 Classification system in the U.S.

In the U.S., medical devices are classified into three different classes: Class I, II and Class III. The classifications are risk-based, which means that the Class I devices hold the lowest risk for harm between the patient and the device. Class II has a moderate risk, and Class III contains the highest risk for patient harm. Generally, as mentioned, the device's risk can be concluded from the device's intended use and indications for use. [22, p. 5; 23; 24] One illustrating example of how indications for use statement can affect the device classification is that a contact lens that is used all the time is classified as a Class III device. Still, a contact lens used only part-time is classified as a Class II device because it has different indications for use, and the extended wear the former lens has, carries a more significant risk for harm.

In the U.S., the FDA and its section (as previously mentioned) CDRH regulates medical devices. Generally, in the U.S. medical device classification system, three regulatory controls are defined by the FDA, which are as follows [23; 24]:

- general controls, which apply to Class I devices;

- general and special controls, which apply to Class II devices; and

- general and special controls and premarket approval, which apply to Class III devices [23; 24].

Figure 5 illustrates the types of medical devices in each class. The colours indicate the safety of these devices; green (Class I) is the safest classification, and red (Class III) is the most unsafe classification. In addition, Figure 6 demonstrates that most medical devices are classified as Class II devices, and Class III devices are the most uncommon.

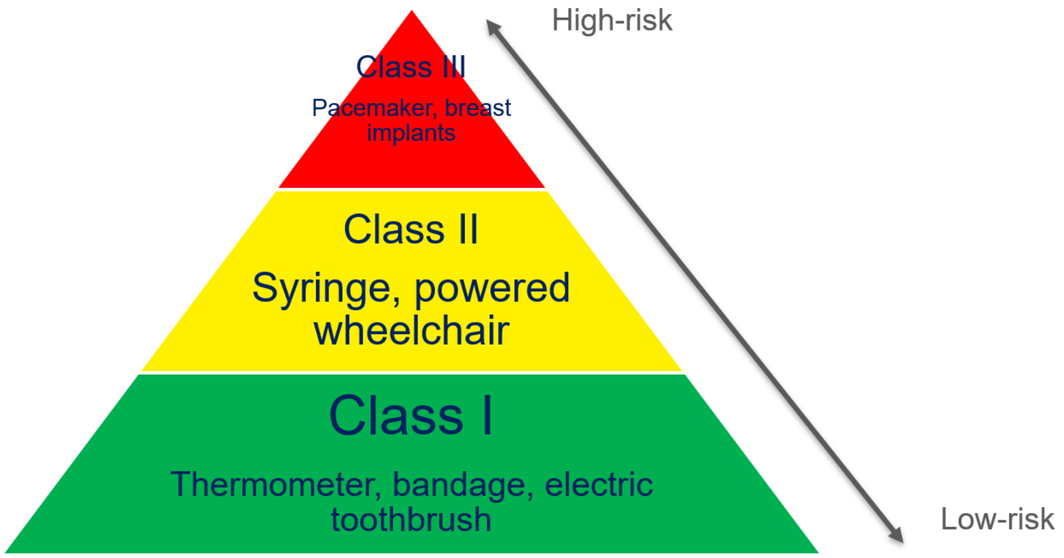


Figure 5. Example of a medical device in each classification and its risk for patient harm.

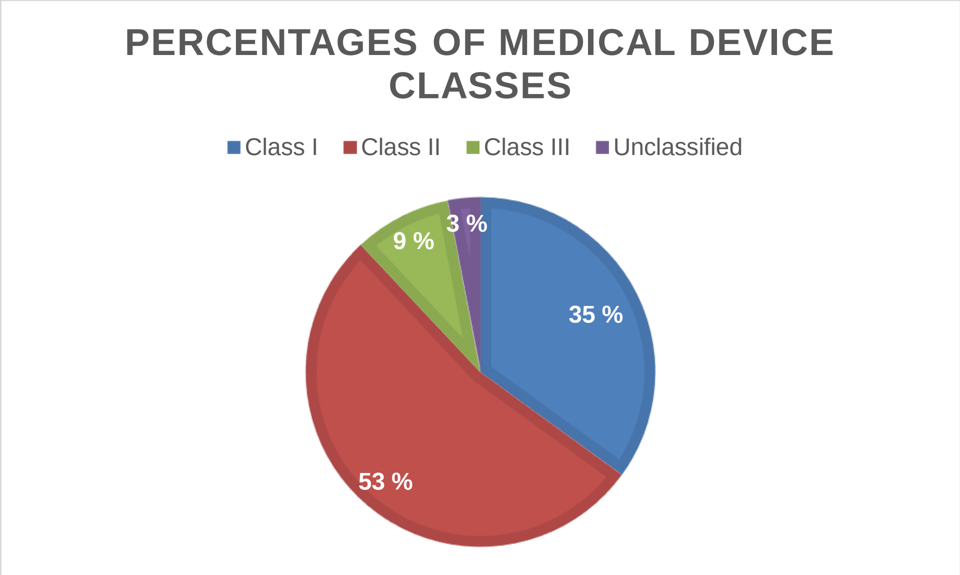


Figure 6. The proportions of medical device classes in the U.S. market [Edited from 25].

2.3.1 Class I

Class I devices do not have an essential role in supporting or sustaining life. Furthermore, these devices have minimal contact with patients and have a marginal impact on patients' health. Compared to, for example, Class III devices, these devices are not in contact with the patient's central nervous system or internal organs. Hence, devices belonging to this category are called "low risk medical devices". Due to having a low risk for patient harm and not being vital in sustaining life, bringing these devices to the market is notably less time-consuming. [24; 26]

2.3.2 Class II

Medical devices belonging to this class differ from Class I devices in that they hold a higher risk for patient harm. Therefore, Class II devices are called "moderate risk devices". The FDA has determined that general controls for Class II devices are deficient in yielding rational guarantees of the device's safety and effectiveness. Thus, the devices require FDA special controls in addition to general controls. For example, syringes and contact lenses (depending on if it is a part-time lens or a full time) belong to this classification. Class II devices are usually marketed through the 510(k)-submission process. [24; 26]

2.3.3 Class III

Because Class III medical devices are generally used as devices that sustain or support life but may cause a high risk for patient harm, these devices are called “high risk medical devices”. Considering that the Class III devices carry an increased risk for patient harm than Class II devices, the general and special controls are not enough to clarify device safety and effectiveness of this classification. Therefore, the FDA has determined that Class III devices must almost always go through the Premarket Approval (PMA) process to assure the safety and effectiveness of the device. For example, defibrillators and pacemakers are Class III medical devices. [24; 26]

2.3.4 Unclassified

An unclassified device is a device that was on the market before the enactment of the Medical Device Amendments to the FD&C in 1976 and does not yet have a classification regulation. These devices are also known as “pre-amendment devices”. [27, p. 4]

Unclassified devices require a 510(k) submission until they are classified, and then they can be marketed via PMA, 510(k), or they can be exempt from premarket submission. It depends on the classification they are given [27, p. 4].

2.4 Determining device classification for the U.S. market

The first step the manufacturers have to do to know what classification their device belongs to is to define the intended use and indications for use for the device. After the intended use and indications for use for the device in question are known, the correct regulation needs to be found. [22, p. 6] Medical devices have different specialities. For instance, a medical device can be cardiovascular or dental. The FDA has different regulation citations for different medical specialities, and for medical specialities, the regulation citations are under 21 CFR 862-892. Figure 7 shows regulation citations 862-892 and the medical speciality under certain regulations.

CFR Title 21 - Food and Drugs: Parts 862 to 892

862	Clinical chemistry and clinical toxicology devices
864	Hematology and pathology devices
866	Immunology and microbiology devices
868	Anesthesiology devices
870	Cardiovascular devices
872	Dental devices
874	Ear, nose, and throat devices
876	Gastroenterology-urology devices
878	General and plastic surgery devices
880	General hospital and personal use devices
882	Neurological devices
884	Obstetrical and gynecological devices
886	Ophthalmic devices
888	Orthopedic devices
890	Physical medicine devices
892	Radiology devices

Figure 7. Medical specialities and their regulation citations [28].

For instance, if the manufacturer’s medical device is a powered toothbrush, the manufacturer goes to check device options that belong to Part 872 Dental devices. If the device is found from the options, its regulation number is discovered as well. In the case of a powered toothbrush, the regulation number is found, as seen in Figure 8.

Subpart G - Miscellaneous Devices

§ 872.6010 - Abrasive device and accessories.
§ 872.6030 - Oral cavity abrasive polishing agent.
§ 872.6050 - Saliva absorber.
§ 872.6070 - Ultraviolet activator for polymerization.
§ 872.6080 - Airbrush.
§ 872.6100 - Anesthetic warmer.
§ 872.6140 - Articulation paper.
§ 872.6200 - Base plate shellac.
§ 872.6250 - Dental chair and accessories.
§ 872.6290 - Prophylaxis cup.
§ 872.6300 - Rubber dam and accessories.
§ 872.6350 - Ultraviolet detector.
§ 872.6390 - Dental floss.
§ 872.6475 - Heat source for bleaching teeth.
§ 872.6510 - Oral irrigation unit.
§ 872.6570 - Impression tube.
§ 872.6640 - Dental operative unit and accessories.
§ 872.6650 - Massaging pick or tip for oral hygiene.
§ 872.6660 - Porcelain powder for clinical use.
§ 872.6670 - Silicate protector.
§ 872.6710 - Boiling water sterilizer.
§ 872.6730 - Endodontic dry heat sterilizer.
§ 872.6770 - Cartridge syringe.
§ 872.6855 - Manual toothbrush.
§ 872.6865 - Powered toothbrush.
§ 872.6870 - Disposable fluoride tray.
§ 872.6880 - Preformed impression tray.
§ 872.6890 - Intraoral dental wax.

Figure 8. Example of a powered toothbrush and its regulation number.

The view shown in Figure 9 can be obtained by clicking the regulation number seen in Figure 8. The manufacturer compares its intended use and indications for use if they align with the specific regulation number. Furthermore, the device classification is seen, which in this case is Class I.

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H - MEDICAL DEVICES

PART 872 -- DENTAL DEVICES

Subpart G - Miscellaneous Devices

Sec. 872.6865 Powered toothbrush.

(a) *Identification.* A powered toothbrush is an AC-powered or battery-powered device that consists of a handle containing a motor that provides mechanical movement to a brush intended to be applied to the teeth. The device is intended to remove adherent plaque and food debris from the teeth to reduce tooth decay.

(b) *Classification.* Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to the limitations in § 872.9.

[55 FR 48440, Nov. 20, 1990, as amended at 59 FR 63009, Dec. 7, 1994; 66 FR 38800, July 25, 2001]

Figure 9. Example of a powered toothbrush and its classification details.

2.5 Classification system in the EU

The classification system in the EU resembles the U.S. system, as it is similarly based on device risk and thus patient harm. However, in the EU, there are four classes: Class I, Class IIa, Class IIb and Class III. In addition, IVDs are classified under the IVD regulation as Class A, B, C and D. Whereas in the U.S., they are classified similarly as medical devices (Class I, II and III) [29]. The device risk grows from Class I (or A) to Class III (or D).

To begin with, manufacturers cannot market their device in the EU market if they have not obtained a CE (Conformité Européenne) marking for the device. The CE mark in the device proves that the devices are recognised to meet expressive safety, health, and environmental protection requirements that the European Union's Medical Device Regulation 2017/745 (EU MDR) has defined. The requirements for obtaining a CE marking differ between device categories and classifications. [30] Therefore, it can be said that the EU classification system is a "rule-based system".

For IVDs to get CE marking, the European Union's In Vitro Diagnostic Device Regulation 2017/746 (EU IVDR) requirements must be met [31], which is one of the differences between the EU and the FDA, as the FDA does not have its own specified regulation for IVDs as the EU does.

The CE marked medical devices fall into three categories, which are as follows:

1. non-invasive,

2. invasive, and

3. active.

The difference between the categories is presented in Figure 10. The category to which the device belongs is needed to be determined first before defining the classification. In addition to invasiveness, the duration time for use (transient, short- or long-term use) affects for determining the classification, and EU MDR has set different rules for different categories. [22, p. 12]

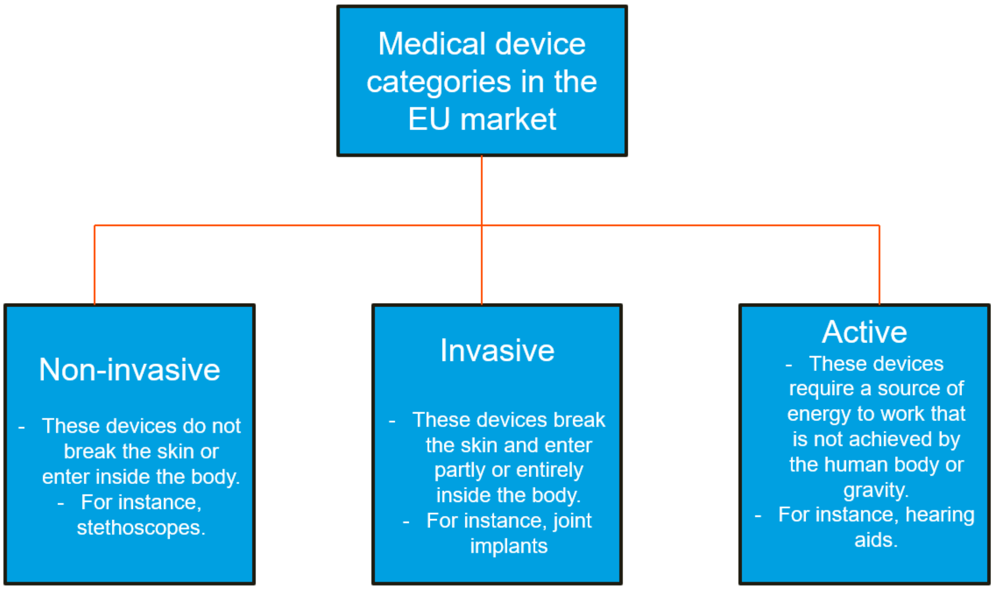


Figure 10. Differences between medical device categories in the EU Market [Edited from 22, p. 12].

2.6 Medical device regulation differences between the EU and the U.S.

Both EU and FDA regulations for medical devices are strict, as it is essential for medical devices to be safe and effective to use, and the quality of the products is crucial for both the EU and the FDA. There are many similarities between them, and the implementation of the EU MDR and IVDR brought the EU and the U.S. much closer to each other regarding the requirements. Key areas of scrutiny under both regulations include clinical data, product information, performance testing, labelling, benefit-risk assessments, residual risks, and post-market surveillance.

Additionally, ISO 13485 (an internationally recognised standard for a quality management system for medical devices) standard is harmonised with EU MDR, and FDA quality system requirements comply with ISO 13485. However, there are three essential differences, in addition to the classification system between the EU and FDA regulations:

- testing and audit/inspection requirements,
- details, and
- terminology and documentation.

2.6.1 Testing requirements differences

In the U.S., testing requirements differ between classifications. Class I devices do not require FDA inspection and can self-declare by showing appropriate documents. Class II devices have a testing protocol because of the 510(k) pathway. For Class III devices, more comprehensive technical sections with data, including non-clinical and clinical investigations, are required to prove to the FDA that the device can be approved or cleared for market. [32]

EU MDR requires some Class I (sterile devices, devices with measuring function and reusable surgical instruments) devices conformity assessment involving a third-party (notified body authorised by the competent authority), whereas all other Class I products can be self-declared by the manufacturer. For Class IIb and Class III, more comprehensive testing and technical documentation are required, but risk evaluation is also more extensive for higher risk devices by the EU MDR. [32]

2.6.2 Detail differences

The FDA has split sections in the 21 CFR Quality System Regulations, where regulations for each device classification are described. However, the FDA does not detail its regulatory requirements as much as EU MDR, where details are more extensively told. For instance, the responsibilities of notified bodies, the process of getting a CE mark, the importance of a clinical evaluation report and many more requirements under EU MDR are described as detailed as possible. And because the FDA has not detailed its requirements so comprehensively, it can set a roadblock for manufacturers who wish to market in the U.S. but still avoid it because of a limited understanding of its requirements. [32]

2.6.3 Terminology and documentation differences

The terminology used by the FDA and within the EU differs. For example, the FDA has specific terms for design and manufacturing documentation, where the FDA likes to use the terms Design History File (DHF) and Device Master Record (DMR). Generally, the DHF contains all the records that describe the design history of a finished device, and the DMR contains all the documents for the needed procedures and specifications for a finished device [33, p. 7; 34, p. 41-42]. In addition, therefore, the DMR can be called the recipe of a medical device. EU MDR/IVDR does not use these terms. However, it requires technical documentation that includes the same data elements

The FDA and EU MDR both require documentation of, for example, planning, risk management, design and device manufacturing and verification and validation activities. In the EU, a design manufacturing report, which includes all validations of manufacturing activities, must be complied with and is required by notified bodies to obtain a CE mark. [32]

However, the key difference in documentation between the FDA and EU MDR is the Clinical Evaluation Report (CER) required by EU MDR. CER contains data that manufacturers gather, including a literature review of the device or similar devices. In addition, search results for identifying known hazards or/and risks of device use are listed from vigilance databases to the CER. All devices within whatever class with a CE mark must have CER, differing from the FDA requirements that do not require CER. [32]

3 Regulatory requirements and legislation in the United States

Because the U.S. legislation follows a risk-based system for device regulation, clinical data is required, and the FDA review standards increase with device classification. Due to this device classification, the tiered regulation system makes room for the FDA to dedicate not only more time but also resources when climbing the classification system, which makes the review of higher-class devices more time-consuming and, of course, more costly. [35, p. 427; 36]

Regulatory requirements are noteworthy for medical device manufacturers wishing to market internationally, as the requirements differ substantially between markets. For example, the EU, the U.S. and China all have their own rules and regulations for medical devices, but they also share some similarities.

In the U.S., medical device manufacturers must obey different kinds of regulatory requirements. Premarket notification 510(k) and Quality System Regulation (QSR) are two of the key regulatory requirements in the U.S., and the other critical regulatory requirements are as follows:

- medical device reporting,
- establishment registration and device listing, and
- labelling requirements [36].

3.1 Establishment registration and device listing

A place of business at a single general physical location, where the medical device is, for instance, manufactured, assembled, or processed some other way, is called an establishment [34, p. 123]. By establishment registration, it is intended that owners or operators of these businesses mentioned above that want to produce and distribute medical devices for use in the U.S. must register annually to the FDA. In most cases, a user fee is included in the establishment registration for most medical device establishments (Tables 1 and 2 show which establishments must pay the user fee), and it may change every Fiscal Year (FY). In FY 2022, the user fee to be paid is 5672$. [37]

In addition to user fees and registration, medical device establishments must list the devices they market to the FDA. Possible actions or changes made to the devices must also be listed to the FDA, and it is required by law that the registrations and device listing are submitted electronically. Nevertheless, electronic submission is not required if the FDA grants an exemption (waiver) from it, but the manufacturer must have a valid reason why the electronic submission is not possible. [38] The registration and device listing describe where the medical devices are manufactured. This is important for the FDA as one of its primary missions was to effectively prepare and respond to a public health emergency.

However, not all establishments are required to register, list, or pay the user fee. One affecting factor is whether the establishment is foreign or domestic. The FDA has made tables for domestic and foreign establishments that instruct what kind of establishments must register, list, or/and pay the fee. Tables 1 and 2 are the abovementioned tables that the FDA has prepared.

Table 1. Domestic establishments [39].

Domestic establishments

Activity	Register	List	Pay Fee
Contract manufacturer (including contract packagers)	**YES** 807.20(a)(2)	**YES** 807.20(a)(2)	**YES**
Contract sterilizer	**YES** 807.20(a)(2)	**YES** 807.20(a)(2)	**YES**
Device being investigated under IDE	**NO**	**NO** 807.40(c)	**NO**
Domestic Distributor that does not import devices	**NO** 807.20(c)(3)	**NO**	**NO**
Any establishment located in a foreign trade zone involved with the manufacture, preparation, propagation, compounding, assembly, or processing of a device intended for commercial distribution in the United States	**YES**	**YES**	**YES**
Import agent, broker, and other parties who do not take first possession of a device imported into the United States	**NO**	**NO**	**NO**
Initial Importer	**YES** 807.40(a)	**NO** Identify manufacturers per 807.20(a)(5)	**YES**
Maintains complaint files as required under 21 CFR 820.198	**YES**	**YES**	**YES**
Manufacturer of accessories or components that are packaged or labeled for commercial distribution for health-related purposes to an end user	**YES** 807.20(a)(6)	**YES** 807.20(a)(6)	**YES**
Manufacturer of components, that are not otherwise classified as a finished device, that are distributed only to a finished device manufacturer	**NO** 807.65(a)	**NO**	**NO**
Manufacturer (including Kit Assemblers)	**YES** 807.20(a)	**YES** 807.20(a)	**YES**
Manufactures a custom device	**YES** 807.20(a)(2)	**YES** 807.20(a)(2)	**YES**
Refurbishers or remarketers of used devices already in commercial distribution in the United States.	**NO**	**NO**	**NO**
Relabeler or Repackager	**YES** 807.20(a)(3)	**YES** 807.20(a)(3)	**YES**
Remanufacturer	**YES**	**YES**	**YES**
Reprocessor of single use devices	**YES** 807.20	**YES** 807.20	**YES**
Specification Consultant Only	**NO**	**NO**	**NO**
Specification Developer	**YES** 807.20(a)(1)	**YES** 807.20(a)(1)	**YES**
U.S. Manufacturer of export only devices	**YES** 807.20(a)(2)	**YES** 807.20(a)(2)	**YES**
Wholesale distributor that is not a manufacturer or importer	**NO**	**NO**	**NO**

Table 2. Foreign establishments [39].

Foreign Establishments

Activity	Register	List	Pay Fee
Contract Manufacturer (including contract packagers)	YES 807.40(a)	YES 807.40(a)	YES
Contract Sterilizer	YES 807.40(a)	YES 807.40(a)	YES
Custom Device Manufacturers	YES 807.20(a)(2)	YES 807.20(a)(2)	YES
Device Being Investigated under IDE	NO 812.1 (a)	NO 812.1(a), 807.40(c)	NO
Foreign Exporter of devices located in a foreign country	YES 807.40 (a)	YES 807.40 (a)	YES
Foreign Manufacturers (including Kit Assemblers)	YES 807.40(a)	YES 807.40(a)	YES
Maintains complaint files as required under 21 CFR 820.198	YES	YES	YES
Manufacturer of accessories or components that are packaged or labeled for commercial distribution for health-related purposes to an end user	YES 807.20(a)(5)	YES 807.20(a)(5)	YES
Manufacturer of components that are distributed only to a finished device manufacturer	NO 807.65(a)	NO	NO
Relabeler or Repackager	YES 807.20(a)(3)	YES 807.20(a)(3)	YES
Remanufacturer	YES	YES	YES
Reprocessor of Single-use Device	YES 807.20(a)	YES 807.20(a)	YES
Specification Developer	YES	YES	YES

U.S. Agent

Foreign establishments that manufacture, distribute, or work in some other way to import a medical device in the U.S. are required to have a U.S. agent (only one agent is allowed). The U.S. agent must be a resident of the U.S. or have a place of business located in the U.S. [40; 41] Generally, the agent works as a liaison between the FDA and the company. There are three primary responsibilities that the agent works for:

1. helps with the communication between the FDA and the company;
2. helps and answers questions related to the imported devices; and
3. helps the FDA to schedule an inspection of the company's facilities [40; 41].

As the agent works as a communication gate between the FDA and the company, the FDA could provide information or/and documents straight to the agent. For this reason, it is necessary and noteworthy for the companies to hire an experienced and reliable agent so that the documents are handled appropriately and do not fall into the wrong hands. [41]

The FDA must be informed about who is the agent working for the foreign establishment, and their address, telephone, and e-mail must be notified. In turn, the U.S. agent must confirm to the FDA that they are working as a representative/liaison for the foreign establishment in question. [40]

3.2 Medical device reporting

Suppose the manufacturer's device causes or contributes to an adverse event, which is an unwanted experience between the device and its user. For instance, an adverse event can be an event that causes one or more of the following:

- death,
- life-threatening situation,
- hospitalisation,
- congenital disability, and/or
- permanent damage, for instance, a disability [42].

If the device has caused or contributed to an adverse event, then, in that case, the manufacturer must report to the FDA that their device has caused death or seriously harmed the user, and it may happen again because of device malfunction [43, p. 4].

The FDA’s goal with medical device reporting (MDR) regulation is to identify and correct device malfunctions, and the three basic requirements of the MDR regulations are as follows:

1. Reports of adverse events that the medical device has caused or contributed must be submitted to the FDA.

2. Documentation of all complaints that concern the medical device in question must be established and maintained. All complaints must be reviewed to determine if they are adverse events.

3. Written procedures for maintaining, developing, and implementing to determine and estimate all medical device events must be done to know if the event is an adverse event. [43, p. 2]

3.3 Labelling requirements

First off, a label displays written, printed, or graphic matters upon the container of the medical device. Labelling, therefore, includes all labels upon the container of the medical device. [34, p. 42]

Labelling should at least inform the name of the medical device and its packer or distributor and the primary location of the business. If the business mentioned in the labelling is not the manufacturer, the labelling then should inform the manufacturer’s name. In addition to these, the labelling must inform the device’s intended use and adequate directions for use. With the adequate directions for use, the instructions on how to use the device safely and as purposed must be described. [44]

The above-mentioned labelling requirements are minimum requirements for labelling. In 21 CFR Part 801, all medical device labelling requirements defined by the FDA are included, and 21 CFR Part 809 consists of all IVD labelling requirements.

4 Regulatory pathways to markets in the U.S.

There are several pathways to market a medical device in the U.S., and the paths mainly differ based on the device's classification. Consequently, it is essential to understand the FDA classification system for a manufacturer to choose the correct pathway. Figure 11 explains the basic process of selecting the right pathway to the U.S. medical device market. The colours indicate the difficulty of the pathway. Green is the easiest, yellow is more arduous, and orange is the hardest.

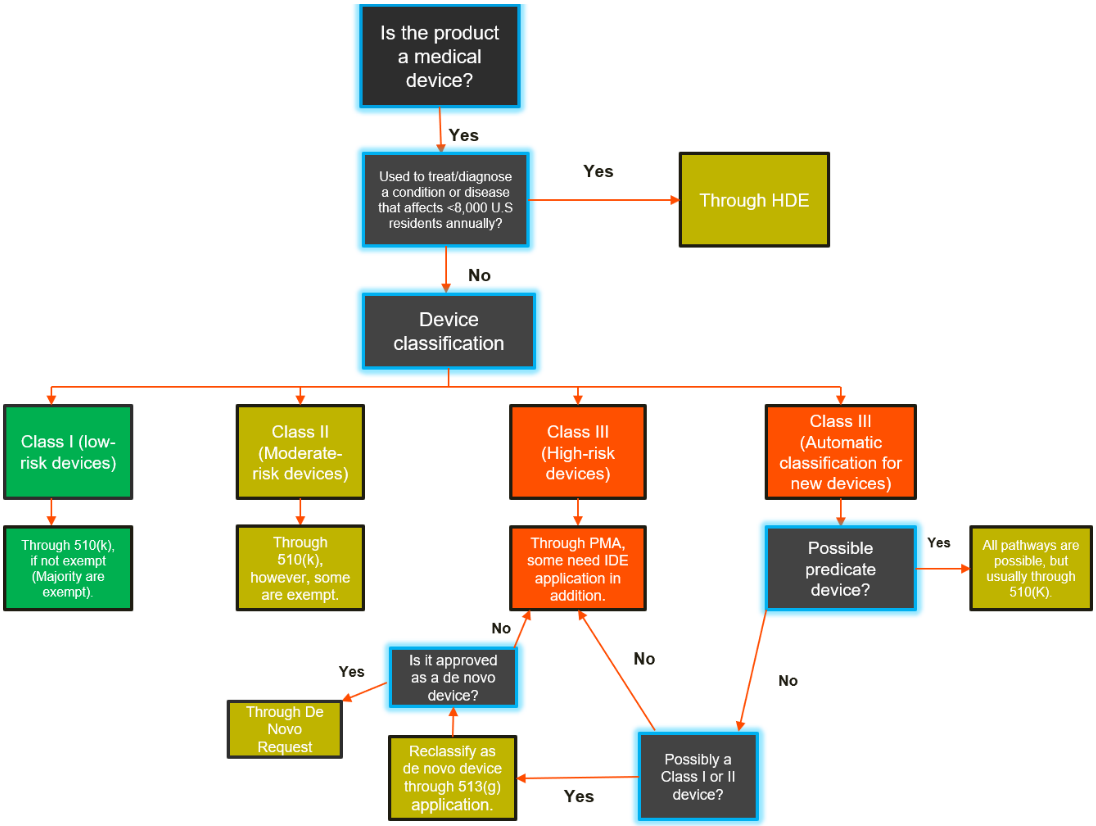


Figure 11. Basic process of selecting a pathway to the U.S. medical device market [Edited from 45, p. 283].

Additionally, Figure 12 shows the four most common pathways to market a medical device in the United States. Premarket notification 510(k) is covered later in section 5.

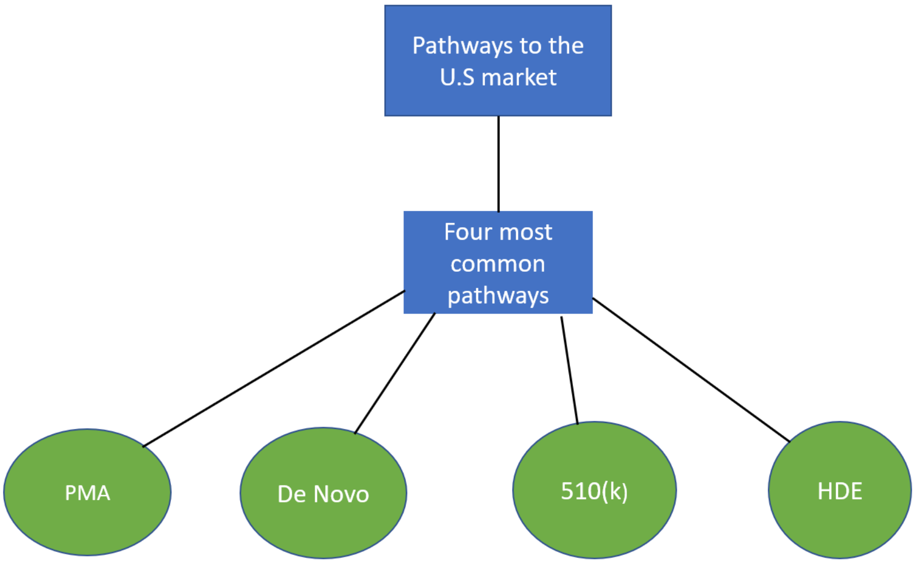


Figure 12. Different pathways to the U.S. market

Each pathway or also known as premarket submission, has its own sets off, where they also differ:

- processes,
- scientific validity and its need,
- submission review duration, and
- applicable laws and regulations.

Table 3 concludes the differences between the 510(k), PMA and De Novo pathways concerning their review time, fees, and the number of yearly clearances.

Table 3. Key differences between 510(k), PMA and De Novo pathways.

	510(k)	PMA	De Novo

FDA review time (goal)	90 days	180 days	150 days
Standard User fee (FY 2022)	12 745$	374 858$	112 457$
Small business user fee (FY 2022)	3186$	93 714$	28 114$
Number of yearly clearances or approvals (2021)	2996. Got by adding together all 510(k) devices cleared in 2021.	1352. Got by adding together all PMA approved devices in 2021.	According to the De Novo FDA database search during 01/01/2021-01/01/2022, there were 30 devices granted through De Novo submission.

4.1 510(k)

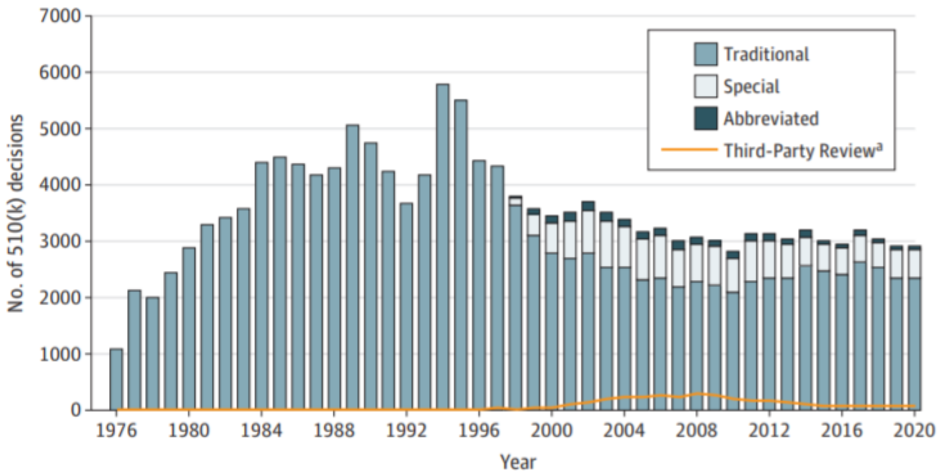
510(k) premarket submission is used to demonstrate the efficiency and safety of the device to the FDA and that the device is substantially equivalent to a different legally marketed device [46; 47, p. 2; 48, p. 6]. However, the FDA has exempted some devices from 510(k) by regulation (21 CFR 862-892). For example, most low-risk (Class I) and some moderate-risk (Class II) medical devices are exempt from 510(k) requirements. High-risk medical devices (Class III) do not require a 510(k) submission; instead, they require a PMA, which is a more demanding level of inspection. [24; 26] Therefore, the 510(k) submission is usually only required for medical devices with a moderate patient harm risk.

Different types of 510(k) submissions

There are three different 510(k) submissions:

1. traditional 510(k) (described more extensively in section 5),
2. special 510(k), and
3. abbreviated 510(k).

It is essential to know which category the medical device falls in. The traditional 510(k) is the most used 510(k) submission, and it can be used in all circumstances when seeking device marketing authorisation through the 510(k) pathway. The special and abbreviated 510(k) submissions are less common, and these submissions are only allowed to be used when certain factors are met. Figure 13 indicates the distribution of different 510(k) submissions,



510(k) program	Median (IQR) annual clearances by 10-y time periods 1976-1985	1986-1995	1996-2005	2006-2015	2016-2020
Clearances	3073 (2194-3526)	4323 (4184-4953)	3532 (3004-3122)	3043 (3004-3122)	2929 (2898-3013)

Figure 13. A number of 510(k) decisions between 1976-2020 [35, p. 425].

As seen in Figure 13, the traditional 510(k) is the most common 510(k) submission; however, special- and abbreviated 510(k)s have gained popularity in recent years. Additionally, as the figure and the median indicate, 510(k) submissions peaked in the 1980s and 1990s but have been in a declining ratio since then.

The special 510(k) submission is for medical devices already cleared by the FDA by the traditional 510(k) submission. Nevertheless, significant changes have been made to the devices after that; thus, they must get cleared again, but this time by the special 510(k) pathway. [47, p. 6; 49; 50]

The abbreviated 510(k) can be submitted to the FDA when clarifying substantial equivalence to an FDA guidance or standard. It is a “Document comparison” rather than a “Device comparison”. [47, p. 5; 49; 50] This pathway is comparatively unpopular, as seen earlier in Figure 13. Additionally, Figure 14 summarises the main differences between the 510(k)s.

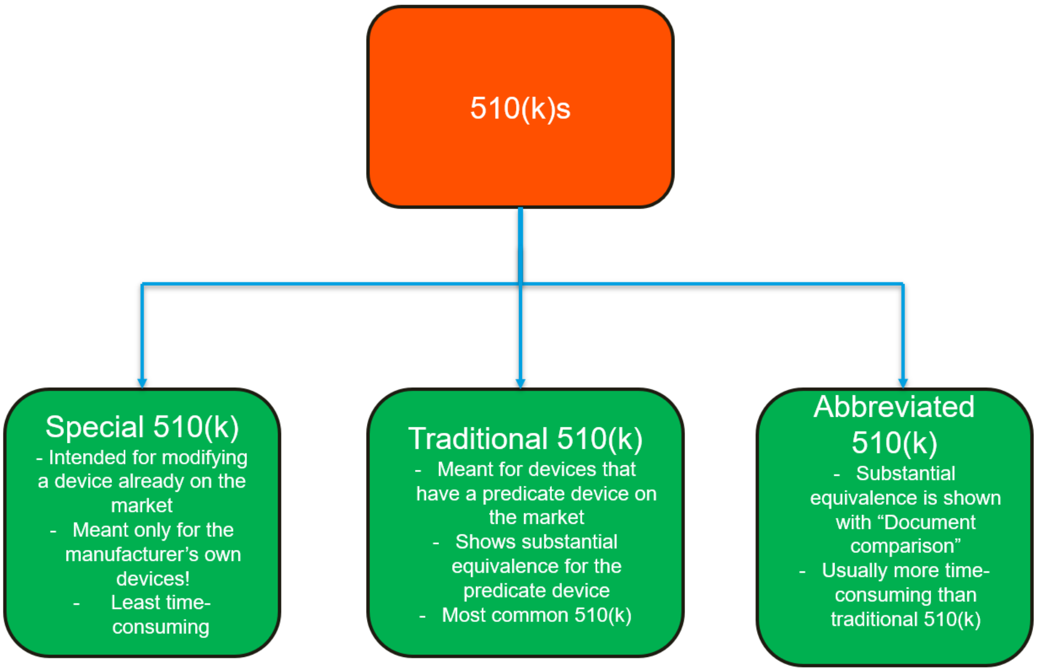


Figure 14. Main differences between the different 510(k)s.

4.2 510(k) exempt

Devices that are exempt from 510(k) requirements (most Class I and some Class II devices) do not need the formal and usual 510(k) submission to be legally marketed, meaning they do not need the FDA clearance to get to the U.S. medical device market [36].

There are two possible 510(k) exempt cases. One is exempt from both 510(k) and QSR requirements, and the other is exempt from only 510(k) requirements. The differences between these cases are listed below:

1. Manufacturers whose device is exempt only from 510(k) submission need the implementation and use of a quality system compliant with a QSR. In addition, establishment registration and product listing with the FDA is required. Generally, the FDA expects the QSR to be followed for these devices.

2. Manufacturers whose device is exempt from both QSR and 510(k) requirements do not need to follow all the QSR requirements; only requirements concerning maintaining records (21 CRF 820.180) and complaint files (21 CFR 820.198) must be followed. Additionally, establishment registration and product listing to the FDA must be done. [51]

Even though the QSR requirements are not required for devices exempt from them, they are still recommended to be followed for the manufacturer’s and customer’s sake. By following these regulations, which represent the FDA’s idea of a safe and effective device, and good engineering and quality practices, the manufacturers can get the best of their device. Therefore, customer satisfaction for the device can be ensured as the lack of adherence could lead to a device that might cause harm or work ineffectively. [51]

4.3 Premarket approval

Premarket approval is a pathway for high risk (Class III) medical devices. Because these devices usually are life-supporting or have a high risk for patient harm or illness, they hold the strictest regulatory controls. General and special controls are used in Class I and II devices, but they are insufficient in Class III devices. Therefore, a premarket approval application is required for these particular devices to achieve permission to the U.S. market, and to accomplish that permission by the FDA, the FDA has to determine that the scientific evidence contained in the PMA is enough for the device to be assured safe and effective for its intended use(s). [52]

Investigational device exemption

Clinical studies show, for example, how well a new medical device works in a targeted human population and tests (e.g., new ways of diagnosing or preventing diseases). An investigational device is allowed to be used in a clinical study via an investigational device exemption (IDE) submission to collect data on the safety and effectiveness of the device [53]. IDE submissions are usually used to support, for instance, a PMA, which requires a lot of proof of the safety and efficacy of the medical device. Therefore, an IDE is mainly used for high risk devices. Before the upcoming study is initiated, all clinical evaluations of the investigational device(s) used in the study are required to have an FDA approved IDE, if not exempt. [53]

The submitter must demonstrate the reasoning to believe that the benefits gained from the device outweigh the possible risks and that the device is effective for the intended use [54, p. 6].

4.4 De Novo Classification Request

De Novo differs from the usual 510(k) in that device falling into this submission type, general controls alone (like Class I devices), or general- and special controls (like Class II devices) can assure the safety and effectiveness of the intended use, however, they do not have a predicate device. And because a predicate device was not available, in the future, a device that was marketed through the De Novo pathway can be used as a predicate device (if applicable) for future 510(k) submissions of a new device. [55]

A medical device that does not have a predicate device and falls into whatever classification is classified as Class III devices automatically and must go through the strict PMA application process. The manufacturer, in this case, can ask for the FDA to reclassify a low to moderate risk device as a “De Novo” device and then go through the De-Novo pathway. If the FDA does not approve the reclassification, the device must go through the PMA pathway as a Class III device. [56, p. 6-7]

4.5 Humanitarian Device Exemption

A humanitarian device exemption (HDE) is a submission made to the FDA for Class III medical devices that diagnose or treat diseases or conditions that affect not more than 8,000 U.S. residents per year, and three criteria affect for submitting an HDE, which are listed below:

1. Because HDE is for Class III devices, the submission must contain a large scale of scientific validity and information that the device does not cause a significant risk for patient harm. Furthermore, the benefits of use must outweigh the risks of patient harm.

2. The device is for diagnosing or treating a disease or condition that does not affect more than 8,000 U.S. residents yearly.

3. Without HDE, there is no device that a person can use to diagnose or treat the disease or condition, which means that no comparable device is on the market (excluding another HDE device). [57, p. 2]

A manufacturer's device designed to go the market via this route must first be identified as a humanitarian use device (HUD), which is achieved with an application to the Office of Orphan Products Development (OOPD) under the FDA [57, p. 2]. Eventually, devices that go through the HDE review type are classified as "HDE" devices.

5 Traditional 510(k)

Traditional 510(k) is the most popular 510(k) submission, and generally, it contains information about the manufacturer's medical device in an organised manner. In addition to the basic information about the device, the traditional 510(k) includes data about the device's performance and safety, which is eminently meaningful for the FDA, as they emphasise the importance of effectiveness and safety.

In the traditional 510(k) process, the medical device must be "substantially equivalent" to another previously legally marketed medical device in the U.S. If the new medical device that is wishing to get to the U.S. market does not have a substantially equivalent device (also known as predicate device), the marketing pathway process through traditional 510(k) is not possible. Therefore, the process is dependent on substantial equivalence to other similar products. For the manufacturer's sake, it is essential to understand the importance of substantial equivalence mainly for two following reasons:

1. saves time; and

2. saves a substantial amount of money.

If the device in question does not have a predicate device, the device will be classified as a Class III device. It, therefore, will go through the demanding PMA process (unless De Novo classification is possible), as seen earlier in Figure 11. PMA applications are very costly and more time consuming when compared to 510(k) submissions.

5.1 Substantial Equivalence

In traditional 510(k), the FDA wants the new medical device to be substantially equivalent to another similar medical device, legally marketed in the U.S. The new device must be as safe and effective as its predicate, making the devices substantially equal. A similar device legally marketed in the U.S. is known as a predicate device.

Substantial equivalence can be achieved when the new device and its predicate have the same intended use and technological characteristics. However, a device can also be substantially equivalent if it has the same intended use as the predicate device, but its technological characteristics are different. Nevertheless, the difference between technological characteristics must not raise questions of safety and effectiveness. Technological characteristics include, for instance, device design, material, effectiveness, safety, biocompatibility and standards. The FDA must also be informed about differences in technological characteristics, demonstrating that the device is as safe and effective as the predicate device. [46; 58, p. 2; 59] In a nutshell, the new medical device has substantial equivalence if the following two things match:

1. predicate and the new medical device have the same intended use, and

2. possible differences must not stand out too much from each other and raise questions about the safety and performance of the new device.

It is almost inevitable that the devices have some differences between them, the intended use is usually the same, but their technological characteristics differ [48, p. 8]. Table 4 shows an example of a new device with the same intended use, but the technological features vary slightly from the predicate device. However, it does not raise questions about safety and effectiveness and, therefore, has substantial equivalence.

Table 4. Comparison of a predicate rest and a new pregnancy test [60, p. 3]. The middle column describes the properties of the new test, and the rightmost column describes the properties of the predicate test.

Device & Predicate Device(s):	K193318	K123436
Device Trade Name	Distinct® Early Detection Pregnancy Test	First Response Early Result Pregnancy Test
General Device Characteristic Similarities		
Intended Use/Indications For Use	Qualitative detection of human chorionic gonadotropin in urine to aid in the early detection of pregnancy	Same
Specimen	Urine	Same
Indications/Intended Users	Over the Counter (OTC)	Same
Test Principle	Lateral Flow Immunoassay	Same
Format	Dip and Midstream	Same
Detection Time	Early detection of pregnancy; 5 days before the expected period (6 days before the day of the missed period)	Same
General Device Characteristic Differences		
Traceability	WHO 5th International Standard for hCG	WHO 4th International Standard for hCG
Read Time	3 to 10 minutes	3 minutes

Table 4 shows that the pregnancy test kits' traceability and read time vary, but that does not make the new pregnancy test less safe or effective for use. Another observing example of acceptable technological feature difference would be, for instance, that a contact lens has a different colour than its predicate [48, p. 9].

The FDA uses scientific methods to estimate possible differences in technological characteristics and performance data to determine whether the device provides the same level of safety and effectiveness as the predicate device. Performance data includes, for example, clinical data and non-clinical bench performance data, which give data on sterility and engineering performance testing, among other data. [46]

Figure 15 demonstrates the process when proving substantial equivalence to a predicate device.

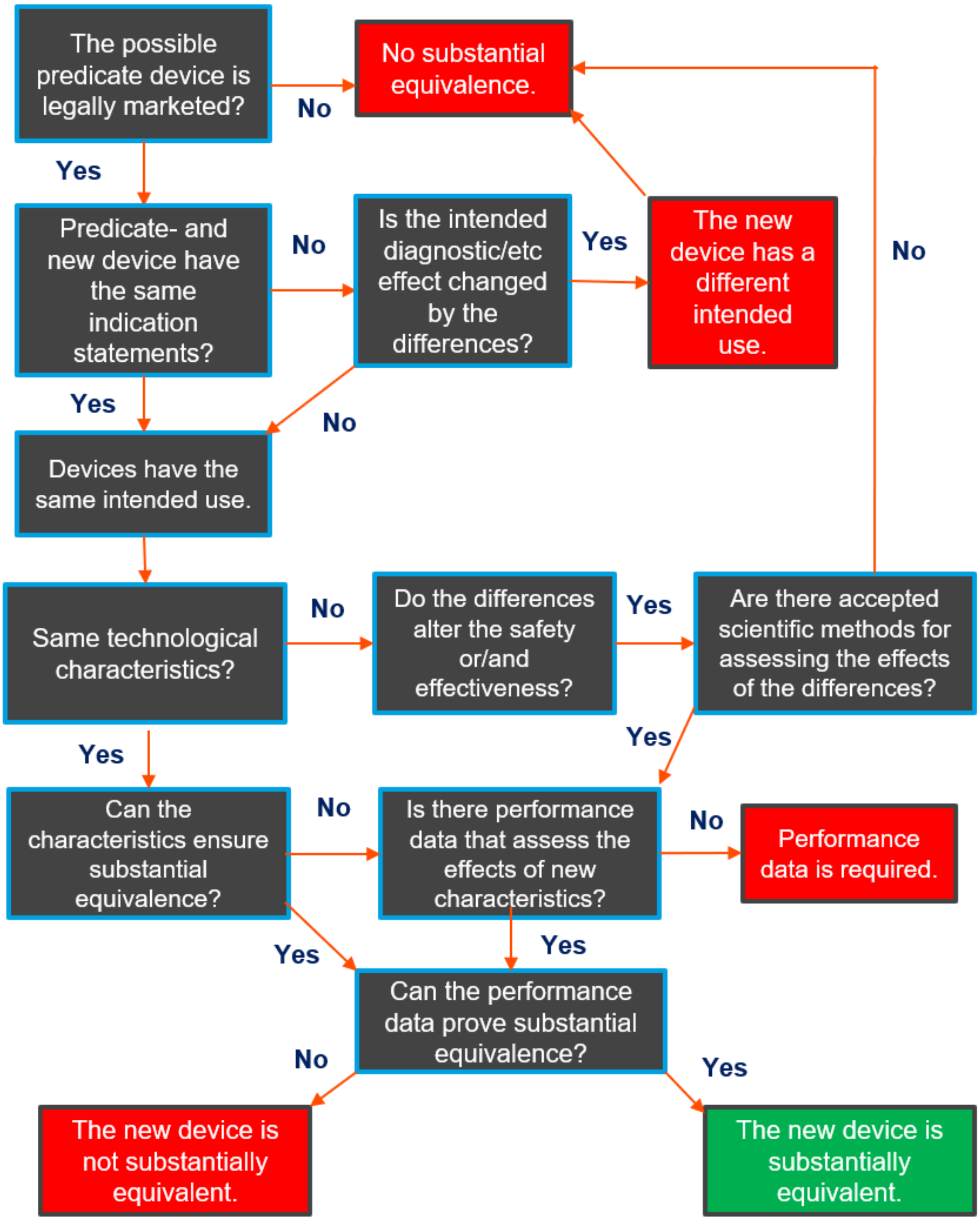


Figure 15. Overview of proving substantial equivalence [Edited from 48, p. 7; 61, p. 27].

Manufacturers are not allowed to market the medical device in the U.S. until the FDA has sent a clearance letter to the submitter, informing if the device is substantially equivalent [62, p. 3]. In case of the device is not substantially equivalent, the submitter is usually asked to resubmit another 510(k) with new data. However, if new data to support a new 510(k) is not available to support substantial equivalence, the submitter can use the De Novo Classification process to request a Class I or II designation, ask for reclassification of the device or submit a PMA. [46]

No substantial equivalence

In summary, it can be seen in Figure 15 that there are four main scenarios when substantial equivalence cannot be achieved:

1. a legally marketed predicate device is not found,
2. different intended use than the predicate device has,
3. different technology, and
4. performance data was lacking or missing.

The most common reason for not finding substantial equivalence is that the performance data lacks, as Figure 16 indicates. The data in Figure 16 is from 2010 gathered by the FDA. It may have changed over the years, but generally thinking, the performance data affects the most because a “SE” (Substantially Equivalent) decision is not possible without it.

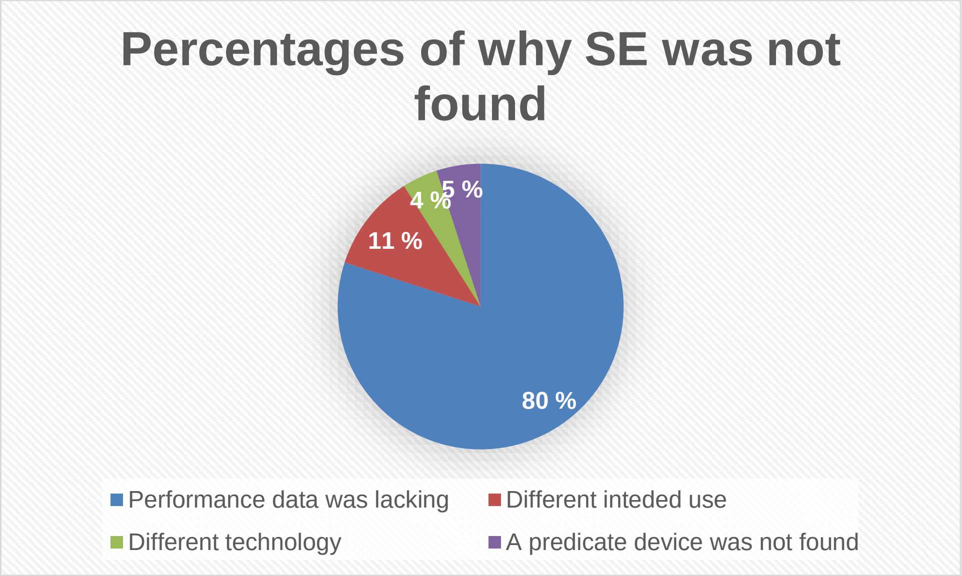


Figure 16. Reasons why substantial equivalence was not found and their proportions in 2010 [Edited from 62, p. 3-4].

As seen in Figure 17, approximately a quarter of 510k submissions in 2011 were not given a “SE” decision. However, this does not mean that three-quarters of approved substantial equivalence decisions are provided on the first try. The submission might get a “no substantial equivalence” decision several times, but the submitter can try again if the issues are resolved.

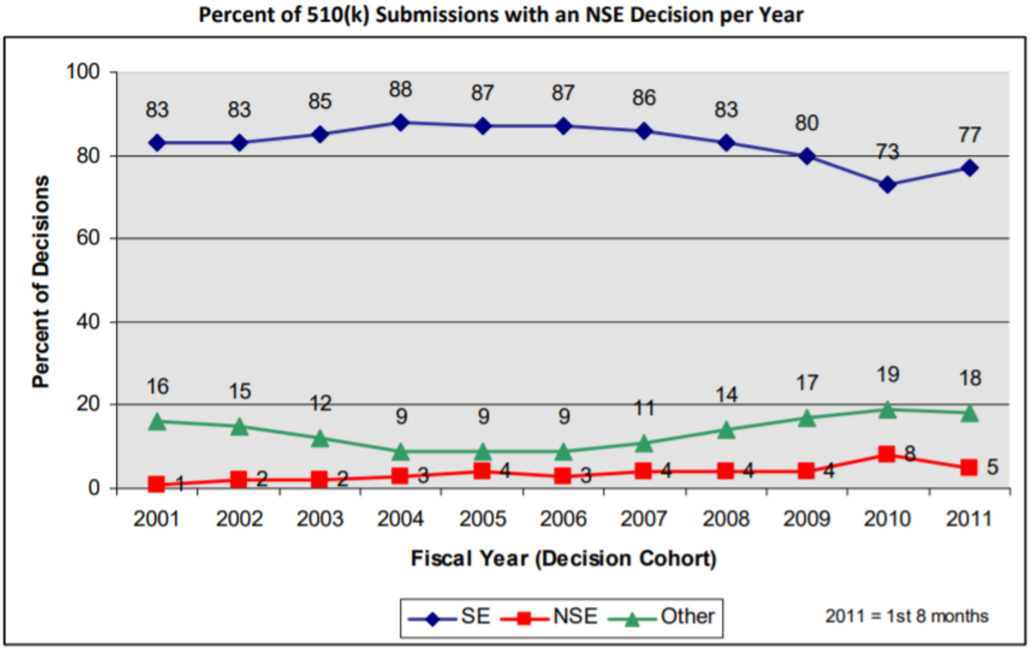


Figure 17. Percentage of how many 510(k) submissions got “no substantial equivalence” status during 2001-2011 [63, p. 2].

“Other” decisions seen in Figure 17 are when the submitter withdraws the submission before the FDA gives the conclusion or the submitter does not provide additional information when the FDA asks for it [58, p. 4]. And when putting “NSE” (Not Substantially Equivalent) and “Other” decisions together, it can be concluded that a quarter of the substantial equivalence submissions were not approved in 2011.

Companies must answer within the given timeframe for the requested information that the FDA asks in order to make the substantial equivalence decision. For instance, the FDA may request more testing on biocompatibility if animal deaths occurred in a study compared to the control group with no animal deaths. Another example of missing performance data is when reports of adverse events raise safety issues related to a failure in the device’s material. In this case, the FDA may ask for additional preclinical testing. Furthermore, the new device’s performance cannot be worse than the predicates. [62, p. 5]

The FDA allows new review cycles for companies to get a substantial equivalence determination for their device if given a “not substantially equivalent” decision. Table 5 shows how many review cycles it usually takes for the submitter to gain a substantial equivalence decision if they first got the NSE decision.

Table 5. No substantial equivalence decisions by review cycle [62, p. 6].

NSE decisions by Cycle

Final Decision	Cycles 1-3 % NSE	Cycles 4+ % NSE	Max Cycles
2005	93	7	6
2006	97	3	4
2007	93	7	4
2008	89	11	5
2009	85	15	7
2010	87	13	6

Table 5 shows that it is unusual to get an “SE” decision on the first try, as only 13% of the submission gained a “SE” status with 1-3 review cycles in 2010. In addition, there is a maximum amount of review cycles, which in 2010 was six cycles, and if the submission does not receive a “SE” status in less than the maximum review cycles, it will be given an “NSE” decision, and the submission will be withdrawn entirely.

5.2 Preparing a traditional 510(k) submission

In general, the preparing process for a traditional 510(k) submission has four stages, which are listed below:

1. define device classification,

2. find an applicable predicate device for showing substantial equivalence,

3. find suitable standards or guidance documents and prepare the 510(k) submission dossier, and

4. send the submission to the FDA [63, p. 2-5].

It may look like a short and simple route for the market, but as said initially, the path for the U.S. market has many roadblocks and mistakes to be made between different stages.

5.2.1 Defining device classification

Before defining the classification, the device must meet the FDA's definition of a medical device, and if it meets the definition, the classification for the device needs to be defined [63, p. 2].

Section 2.4 earlier described how the device classification should be performed. There are also other ways to define the classification, but the example in section 2.4 is the most common method for determining device classification. Another common method uses the FDA product classification database. For instance, if the manufacturer's device is a glucose meter, then the manufacturer writes "glucose meter" in the FDA database search, as Figure 18 demonstrates.

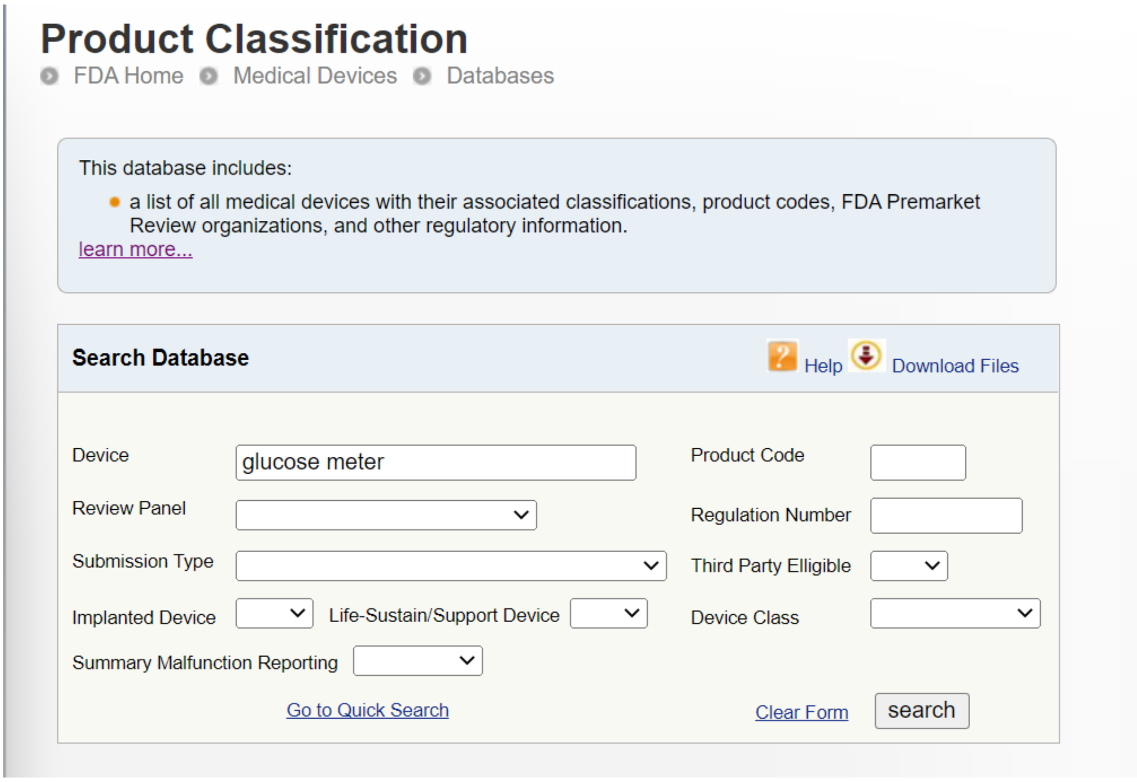
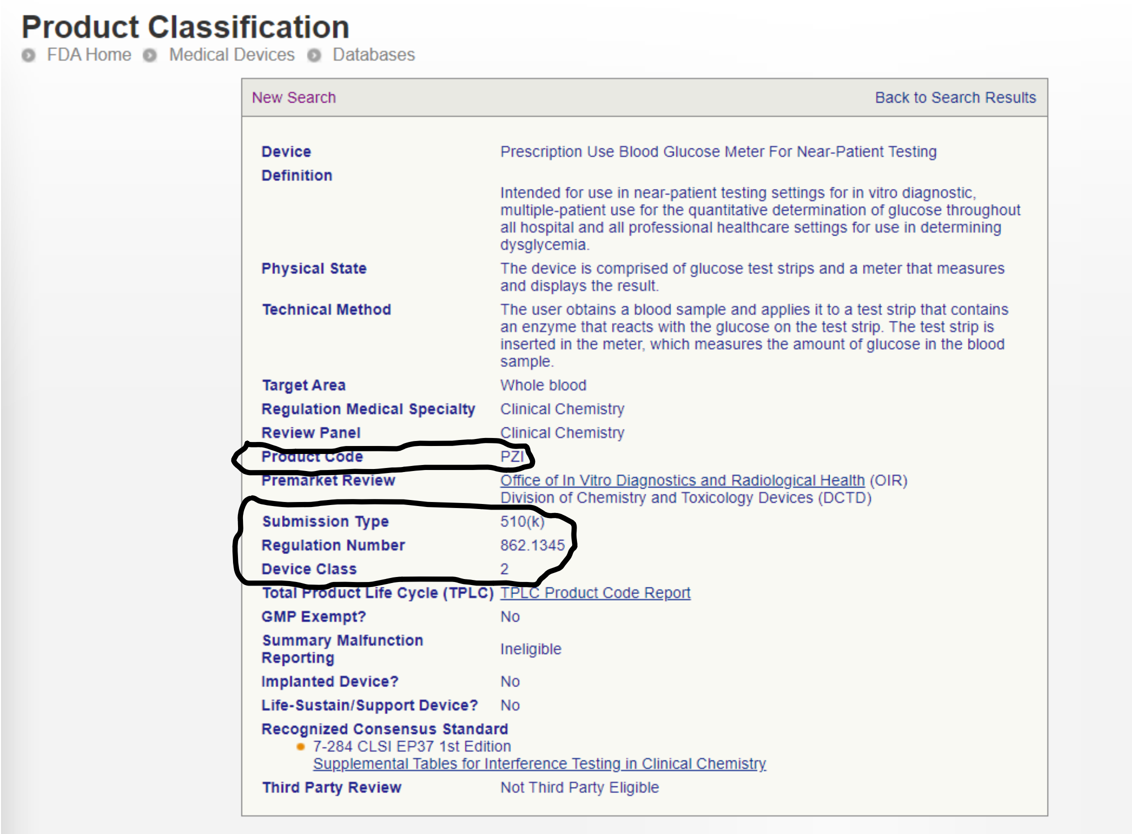


Figure 18. Product classification page in the FDA´s product classification database and a glucose meter as an example of a used keyword for a device search.

Clicking "search", the manufacturer sees the view shown in Figure 19, where classification, regulation number and product code are found, and also the submission type is found, which in this case is 510(k).



Product Classification

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Device	Prescription Use Blood Glucose Meter For Near-Patient Testing
Definition	Intended for use in near-patient testing settings for in vitro diagnostic, multiple-patient use for the quantitative determination of glucose throughout all hospital and all professional healthcare settings for use in determining dysglycemia.
Physical State	The device is comprised of glucose test strips and a meter that measures and displays the result.
Technical Method	The user obtains a blood sample and applies it to a test strip that contains an enzyme that reacts with the glucose on the test strip. The test strip is inserted in the meter, which measures the amount of glucose in the blood sample.
Target Area	Whole blood
Regulation Medical Specialty	Clinical Chemistry
Review Panel	Clinical Chemistry
Product Code	PZI
Premarket Review	Office of In Vitro Diagnostics and Radiological Health (OIR) Division of Chemistry and Toxicology Devices (DCTD)
Submission Type	510(k)
Regulation Number	862.1345
Device Class	2
Total Product Life Cycle (TPLC)	TPLC Product Code Report
GMP Exempt?	No
Summary Malfunction Reporting	Ineligible
Implanted Device?	No
Life-Sustain/Support Device?	No
Recognized Consensus Standard	• 7-284 CLSI EP37 1st Edition Supplemental Tables for Interference Testing in Clinical Chemistry
Third Party Review	Not Third Party Eligible

Figure 19. Information found on a glucose meter from the FDA product classification database as an example of a search result.

After defining the classification for the device, the manufacturer has to find a suitable predicate device. The product code is crucial, as similar devices are found with the product code.

5.2.2 Finding an applicable predicate device for showing substantial equivalence.

The manufacturer learns in Figure 19 that the glucose meter goes through the 510(k) pathway, and its product code is “PZI”. The manufacturer then goes to the FDA 510(k) database search and writes “PZI” as the product code, as Figure 20 demonstrates.

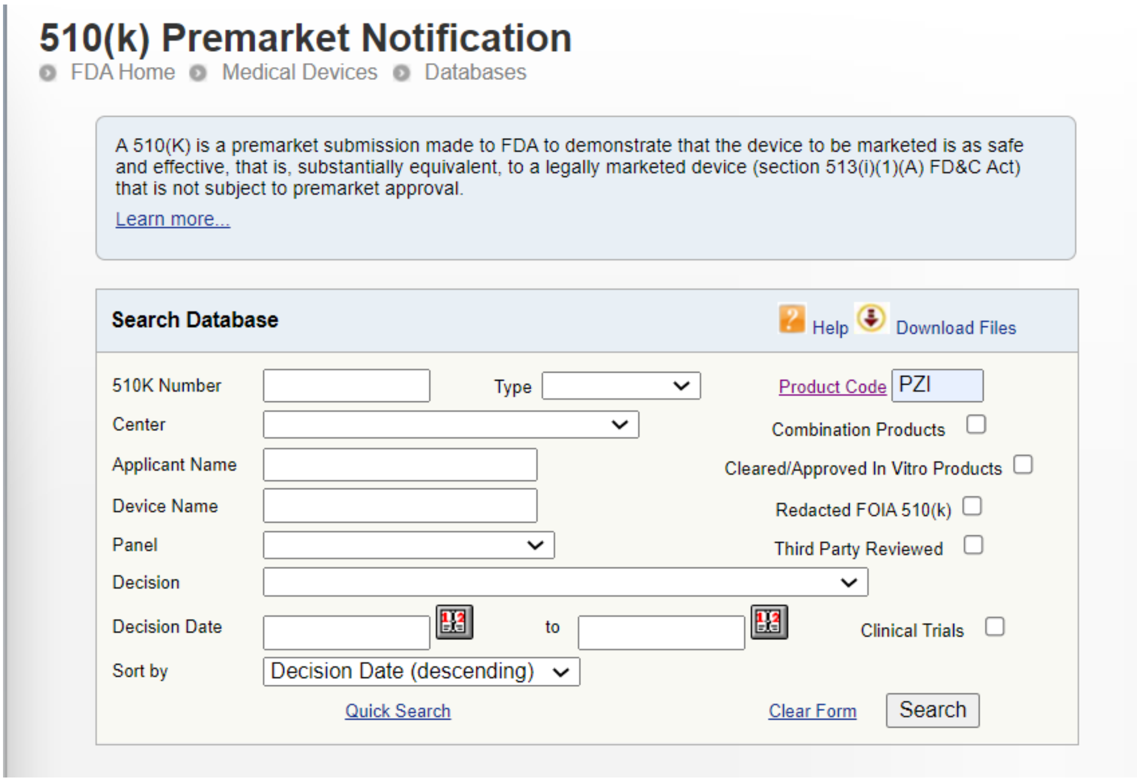

Figure 20. A 510(k) database search for the product code “PZI” as an example.

Clicking “search”, the manufacturer sees the view shown in Figure 21 and the devices under the “PZI” product code. The devices found are similar to the manufacturer’s device. The manufacturer then carefully reads the device descriptions and uses the most suitable device as a predicate device to prove substantial equivalence for the FDA.

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ProductCode: *PZI* **Decision Date To:** *05/01/2022*

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Device Name	Applicant	510(K) Number	Decision Date
Statstrip Xpress 2 Glucose Hospital Meter System	Nova Biomedical Corporation	K182549	12/13/2018
Statstrip Xpress Glucose Hospital Meter System	Nova Biomedical Corporation	K182552	12/13/2018
Statstrip Glucose Hospital Meter System	Nova Biomedical Corporation	K181043	07/12/2018
Statstrip Xpress 2 Glucose Hospital Meter System	Nova Biomedical Corporation	K163490	01/06/2017
Statstrip Xpress Glucose Hospital Meter System	Nova Biomedical Corporation	K161856	11/15/2016
Statstrip Xpress 2 Glucose Hospital Meter System	NOVA BIOMEDICAL CORPORATION	K152986	01/27/2016
Statstrip Xpress Glucose Hospital Meter System	NOVA BIOMEDICAL CORPORATION	K150461	05/20/2015
Statstrip Glucose Hospital Meter	NOVA BIOMEDICAL CORPORATION	K150281	05/06/2015
Statstrip Glucose Hospital Meter System	NOVA BIOMEDICAL CORPORATION	K132121	09/24/2014

Figure 21. Devices found from the 510(k) database under the “PZI” product code.

5.2.3 Suitable standards or guidance documents

The standards and guidance documents that apply to a medical device are device- or technology-specific. The manufacturer can get some help on what standards apply to their device from the predicate device’s clearance letter. If the predicate device meets a specific standard, the manufacturer’s device should meet the same standard.

The suitable standards and guidance documents can be found on the FDA website. For instance, there are plenty of guidance documents concerning device class. The FDA has a recognised consensus standards list available which should be reviewed to identify relevant standards applicable to the product.

5.3 Submission process

Finally, after the classification is defined, the predicate device and suitable standards or guidance documents are found, the 510(k) submission is ready to be gathered and sent to the FDA’s CDRH section.

The 510(k)-submission process consists of four different primary stages after the submission is sent, shown in order in Figure 22.

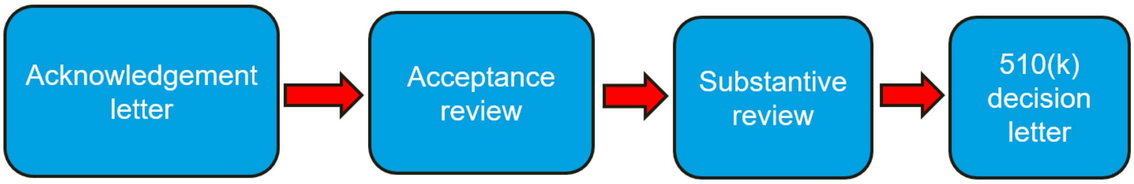

Figure 22. Process of the 510(k) submission.

5.3.1 Acknowledgement/Hold letter

The acknowledgement letter shows the date of receipt and a number assigned to the 510(k) submission. The date of the receipt shows when the FDA received the 510(k) submission, and it also includes the valid user fee payment and a valid eCopy. After the acknowledgement letter, the submission continues into the acceptance review stage. [64]

In case the user fee payment and/or eCopy are not valid, the 510(k) submitter receives an email within seven days of receipt of the 510(k) from the Document Control Center (DCC), which includes a hold letter. The hold letter indicates to the 510(k) submitter that the user fee payment and/or eCopy were not valid, and the submitter has 180 calendar days to address the issue. The 510(k) will be withdrawn and excluded from the FDA review system if the issues are not resolved in time, and the 510(k) submitter must submit completely a new 510(k) to the FDA if still planning to market in the United States. [64]

5.3.2 Acceptance review

After the FDA has acknowledged the 510(k) submission, it is assigned to a proper lead reviewer determined by the FDA. The lead reviewer ensures that the 510(k) submission meets at least the minimum limits of acceptability. [64] The submitter can also check before submitting if the 510(k) submission meets the boundaries of acceptability by using the FDA's acceptance checklist guidance (this is only a recommendation, the lead reviewer always makes sure that the minimum limits are reached), which the lead reviewer also uses.

The FDA will send a notification to the submitter, which shows the result of the acceptance review and the contact information of the lead reviewer [64]. The possible outcomes of the acceptance review are shown in Figure 23, and an acceptable outcome (indicated as green in Figure 23) proceeds into a substantive review.

Figure 23. Alternative outcomes of the 510(k) acceptance review [Edited from 64].

In the Refuse to Accept (RTA) hold, the lead reviewer has found deficiencies in the acceptance review, and the submitter has 180 days to resolve the issues related to the acceptance review. Suppose the acceptability criteria were not met and the submitter does not fix the problems cited in the RTA hold in 180 days. In that case, the 510(k) submission will be deleted from the review system, and the submitter must start the 510(k) process from the beginning if still planning to market in the United States. [64]

5.3.3 Substantive review

After the acceptance review, the submission proceeds into a substantive review phase. A comprehensive review of the 510(k) submission is conducted, and the lead reviewer communicates with the 510(k) submitter, which happens through a substantive interaction. Usually, the substantive interaction is done in two ways: interactive review or additional information (AI), as seen in Figure 24, which shows the outcomes of the substantive review. [64]

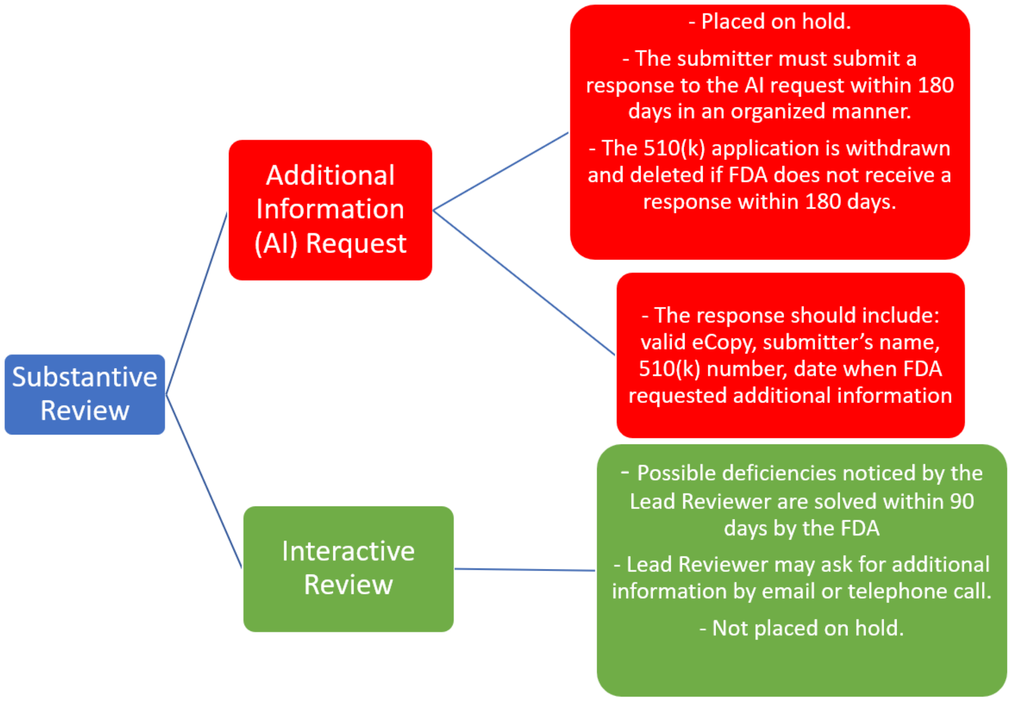

Figure 24. Alternative outcomes of the 510(k) substantive review [Edited from 64].

Additional information requested can be pretty much anything, varying from product name differing throughout the submission to the performance data missing or lacking. The typical mistakes that lead to the additional information request are described more extensively in section 5.4.

5.3.4 510(k) decision letter

The decision letter has two possible outcomes: the “Substantially equivalent” decision or the “Not substantially equivalent” decision. The FDA sends the decision letter to the submitter by email, and if substantial equivalence was found and no other issues occurred, the FDA then considers the submission as “cleared” [64]. Subsequently, the manufacturer can start marketing the device in the U.S.

5.4 510(k) duration – and what affects on it

The FDA aims to give a 510(k) decision in 90 days [63, p. 5; 64]. However, this is just the FDA’s goal. It is very uncommon to gain clearance for the U.S. market in 90 days by the 510(k) submission as the FDA and other regulatory authorities, such as in the EU, have become stricter on medical devices and their clinical data and testing requirements, which affects the market clearance duration. Figure 25 demonstrates how the 510(k) clearance process has become stricter since the 1970s when the clearance process was not as strict as it is nowadays, and due to that, the overall length to gain the FDA’s clearance has increased. Furthermore, medical devices nowadays have more technological features than in the 1970s, which means that more requirements are required to be fulfilled, which affects the market process’s length.

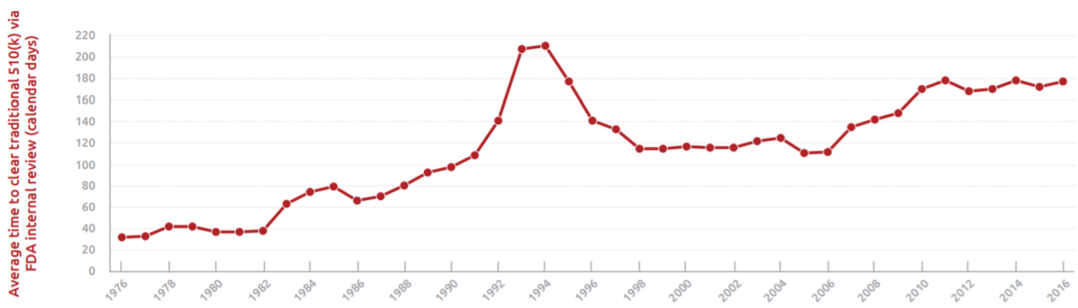

Figure 25. Average duration (days) to gain the FDA’s clearance with a traditional 510(k) and its growth between 1970-2016 [65, p. 4].

As seen from Figure 25, the average time to get the FDA's clearance with a traditional 510(k) more recently, for example, during 2010-2016, is approximately 170 days. Consequently, the estimated 90-day process length is just the FDA's goal, as stated earlier. However, it is possible but depends on the device and how the manufacturer has prepared for the clearance process. As expected, a manufacturer whose 510(k) submission has a lot to fix must wait longer than those that have prepared better. In fact, the most extended length to gain a 510(k) clearance is more than 3000 days [65, p. 10].

The time gone for the submission to gain a clearance is not only on the FDA's responsibility. If a manufacturer wants to gain a clearance as fast as possible, they should answer the additional information that the FDA asks for as quickly as possible. Figure 26 shows data on the review times from 2000-2010.

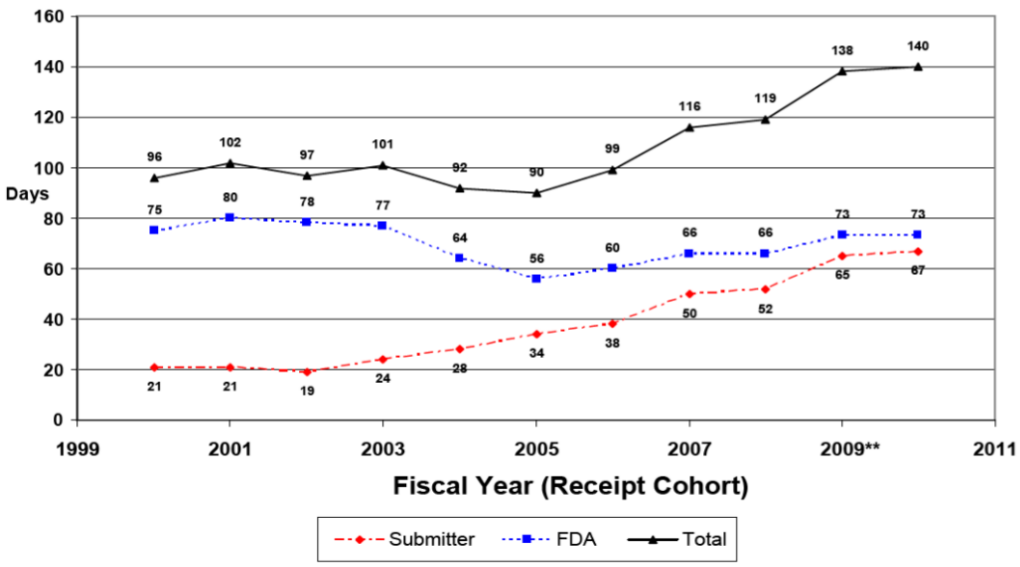

Figure 26. Average duration (days) for a 510(k) decision during 2000-2010 [66, p. 4].

The data from Figure 26 shows that the total average duration has grown from 96 days (2000) to 140 days (2010). Nowadays (in 2022), it is approximately 180 days [25]. The growth noticed in Figure 26 is due to submitters taking longer to answer the FDA's additional information request than before. In fact, the FDA's review times have decreased slightly from 2000 to 2010.

The device type also matters for a 510(k) clearance duration. For instance, the average time to get a 510(k) clearance for devices related to immunology was 250 days in 2016. In comparison, the average time for devices related to radiology was 112 days in 2016, as Figure 27 shows. In the same figure, it can be noticed that some device types have considerably (even half as fast) faster clearance processes than others.

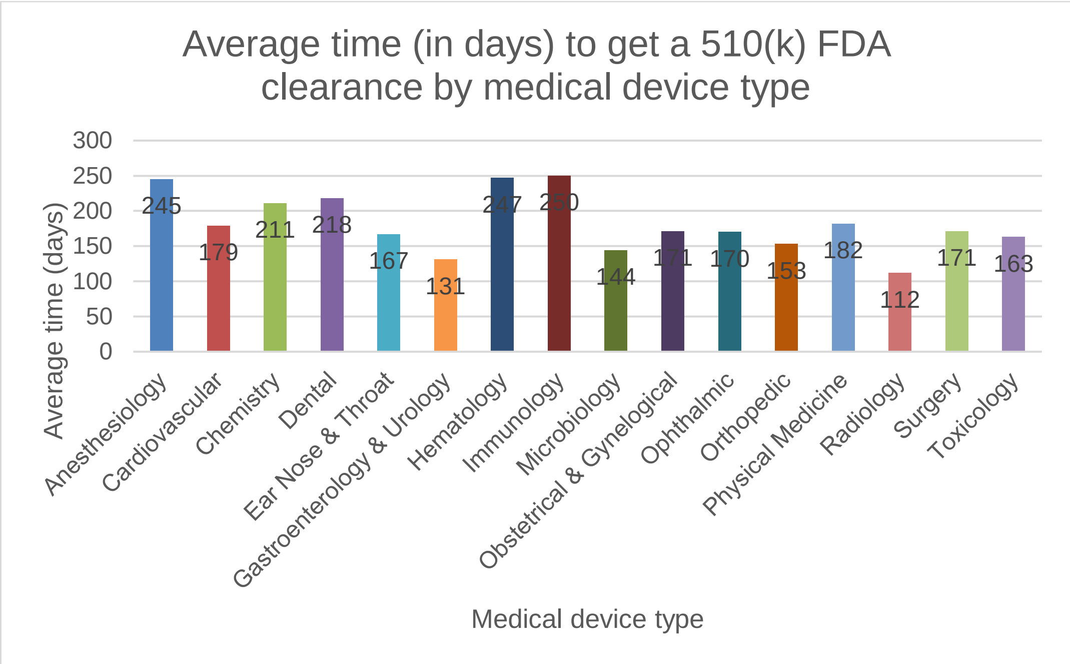

Figure 27. Medical device types and their average time in days to get a 510(k) clearance for the U.S. market [Edited from 65, p. 8].

The FDA has not stated why the clearance process takes longer for some device types. However, for example, when comparing devices for radiology and immunology and how many 510(k) clearances in 2021 were made for these types of devices, there is a vast difference. Figures 28 and 29 show an FDA 510(k) database search for immunological and radiological device types in 2021.

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Panel: *Immunology* **Decision Date From:** *01/01/2021* **Decision Date To:** *01/01/2022*

1 2 >

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Device Name	Applicant	510(K) Number	Decision Date
Hydrashift 2/4 Isatuximab	Sebia	K203184	11/12/2021
N Latex Flc Kappa, N Latex Flc Lambda	Siemens Healthcare Diagnostics Products GmbH	K201496	10/29/2021
Allergen-Specific Ige Assay 12 Allergen Bundle	Hitachi Chemical Diagnostics, Inc.	K193613	10/18/2021
Liaison Ferritin	DiaSorin Inc	K193650	09/14/2021
Elia Rib-P	Phadia AB	K202540	09/13/2021
Elia Rna Pol Iii	Phadia AB	K202541	09/13/2021
Aptiva Celiac Disease Igg Reagent	Inova Diagnostics, Inc.	K200230	08/26/2021
Diazyme Plac® Test For Lp-Pla2 Activity	Diazyme Laboratories Inc.	K203136	08/06/2021
Oncomate Msi Dx Analysis System	Promega Corporation	K200129	07/26/2021
Elia Smdp-S	Phadia AB	K202067	07/14/2021

Figure 28. A result of the 510(k) database search for immunological devices in 2021.

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New Search

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Device Name	Applicant	510(K) Number	Decision Date
Eco-X Series (Eco-X, Eco-X-S)	HDX WILL Corp.	K211159	12/30/2021
Convivo In Vivo Pathology Suite	Carl Zeiss Meditec AG	K211156	12/29/2021
Liversmart	Resonance Health Analysis Services Pty Ltd	K213776	12/29/2021
Sonosite Px Ultrasound System	FUJIFILM Sonosite, Inc.	K213763	12/27/2021
D²Rs And D²Rs 9090	Stephanix	K213479	12/23/2021
Ds Footankle 16ch Coils For 1.5t And 3.0t, Ds Hires Handwrist 16ch Coils For 1.5t And 3.0t, Ds Small Extremity 16ch Coils For 1.5t And 3.0t	Invivo Corporation	K213766	12/23/2021
Bonemri	MRIguidance B.V	K202404	12/22/2021
Claritas Ipet	Claritas HealthTech Pte Ltd	K213140	12/22/2021
Isr'obot Mona Lisa 2.0	Biobot Surgical Pte Ltd	K213411	12/22/2021
Solas Or	Cirdan Imaging Ltd	K213691	12/22/2021

Figure 29. A result of the 510(k) database search for radiological devices in 2021.

As Figure 28 showed, only 14 immunological devices were cleared in 2021 by the 510(k)-submission process, which is a massive difference from radiological devices, for which 417 devices were cleared in 2021 by the 510(k)-submission process, as Figure 29 showed. Therefore, it can be concluded that fewer 510(k) submissions related to the device type mean longer review time.

Moreover, another possible reason why radiological devices are much quicker to get an FDA clearance than immunological devices might be because radiology is well established nowadays, and no significant technological progress is not made anymore. On the contrary, immunology is progressing more and more nowadays, and the FDA might, thus, need more time to review the safety and effectiveness of immunological devices. In addition, the technological characteristics are more straightforward in some device types than in others, affecting the review length.

Typical mistakes that affect the 510(k) duration

What comes to the FDA strictness, it is evident that the FDA often asks for additional information, leading to a longer review time. There are many mistakes to be made in the 510(k) submission, but the most typical mistakes made by the submitters are presented in Figure 30.

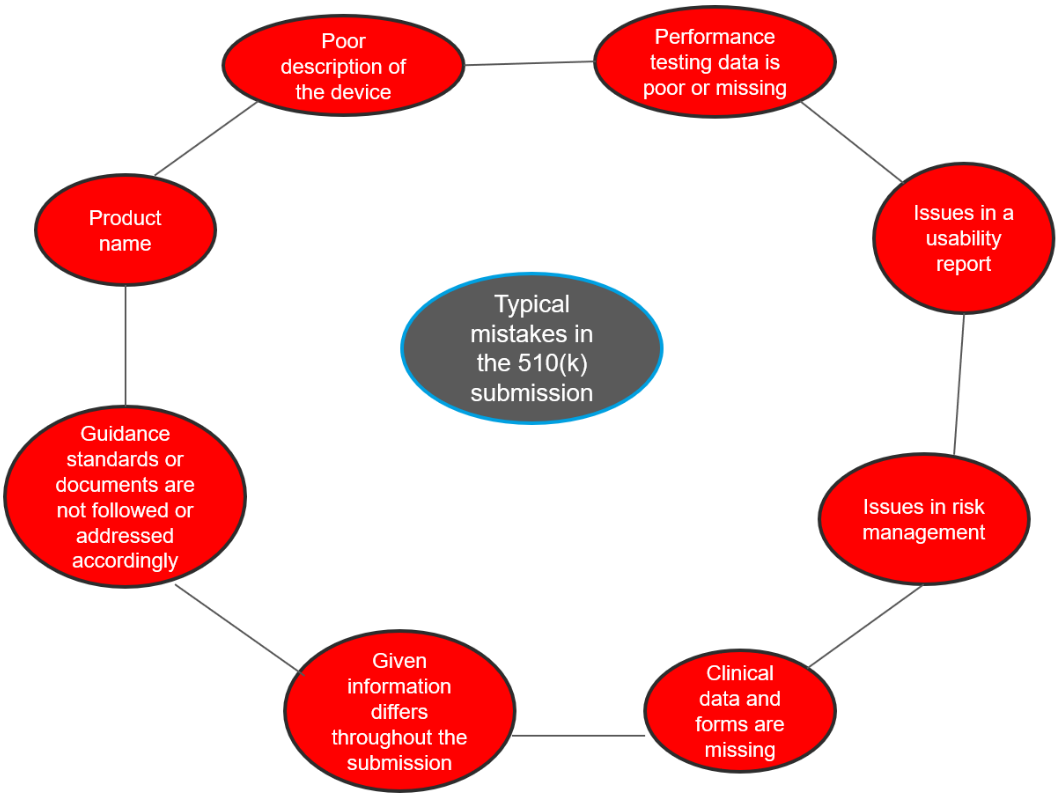

Figure 30. Eight most typical mistakes to be made in the 510(k) submission [Edited from 63, p. 6-7].

As Figure 30 shows above, there are several mistakes to be made, and these eight are just the most typical ones. Suppose the manufacturer is willing to avoid errors during the 510(k) submission. In that case, these eight common mistakes are what the company should primarily focus on; therefore, no usual unnecessary errors are made. Table 6 provides more details about the typical 510(k) submission errors.

Table 6. Detailed information about the typical mistakes made in the 510(k) submission [63, p. 6-7].

Typical mistake	Details about the mistake

Product name	The product name must stay the same throughout the submission. If the product name changes during the submission or is presented differently in different documents, it might confuse the FDA and therefore lead to a request for additional information.
Poor description of the medical device	The FDA cannot ensure the device's safety and effectiveness if the device description is inaccurate or incomplete. The description must support the intended use of the device. In general, the level of detail the FDA requires is higher compared to many other authorities.
Performance testing data is poor or missing	If there is no performance testing data, the FDA will ask for it because it is a requirement of a traditional 510(k). Figure 15 demonstrates that substantial equivalence could not be proven without performance testing data. Additional questions may also be received (e.g., if the scientific quality or clarity of the performance evidence is poor).
Issues in a usability report	If the testing was not done as informed in the guidance document, for instance, the sample size was too small; then the usability report is not valid.
Issues in risk management	In the U.S., risk management must follow the ISO 14791:2007 consensus standard. It is a heavy process and time-consuming and requires a lot of finalisation. Therefore, it is expected that the FDA will find some issues related to it. For instance, the FDA may encounter

	some problems in risk analysis that play a significant role in the development of medical device design.
Clinical data and forms are missing	Not all device types, but some require clinical performance data to prove substantial equivalence. If clinical data is needed, then applicable forms are also needed.
Guidance standards or documents are not followed or addressed accordingly	The FDA will ask for additional information if the device does not follow or address current guidance documents or standards for the device type and why the manufacturer is not following or addressing them.
Given information differs throughout the submission	The indications for use and intended use statements must stay the same throughout the submission and the submission dossier.

5.5 Overall cost of 510(k)

As listed in Table 3, the 510(k) standard fee is 12 745$, and for small businesses, the standard fee is 3186$ for FY 2022. In addition to these, the establishment registration fee must be paid, which costs 5672$ [37]. However, this is paid after the 510(k) submission is cleared by the FDA.

The device's substantial equivalence, safety, and effectiveness are shown with testing documented in unambiguous test plans and reports, which is the whole idea of the 510(k) submission. The testing of the device is the costliest part [67], and how much it costs depends entirely on the device. For instance, if the device needs clinical data to demonstrate safety and effectiveness, it will raise the overall cost. For a 510(k), clinical data may be required; it depends on the device; in particular Over-the-Counter devices require clinical data [68, p. 1], which are devices that the consumer can buy directly from the manufacturer or its distributor. The manufacturer can find information about if the device requires clinical data in the 510(k) submission from the FDA guidance documents and performance standards that apply to a specific device type, also known as “vertical” documents [69, p. 3].

Therefore, devices that need clinical data require more testing, meaning that the overall cost is higher for these devices than those that do not require clinical data. Additionally, devices with longer review time might indicate that they are more complex than devices with shorter review time, therefore requiring more testing and increasing the cost. This can also be seen in Class III devices that require a PMA application. All Class III devices require a wide range of clinical data [70]. Consequently, the FDA’s review time for PMAs is twice as long, and the cost might rise to over tens of millions, even to hundreds of millions, because they need more testing and regulatory requirements to be fulfilled than 510(k)s. For 510(k)s, the cost varies and depends, as said. Nevertheless, according to one source [71], which studied the 510(k) costs for 50 different devices, the median cost was approximately 3$ million, the lowest cost was 200 000$, and the highest cost raised to 41$ million. However, according to another source [72, p. 7, 29 & 38], claiming that average cost for 510(k) is approximately 31$ million. Therefore, the exact cost varies.

In summary, the cost consists of the testing part and submission part. Furthermore, some manufacturers might need some consulting help when, for instance, preparing the 510(k) submission for the FDA, which can cost the manufacturer tens of thousands, depending on how much the consultant(s) charge and how much time it takes. Additionally, because the standard fee cost is significantly lower for small businesses, it is recommended to apply for a small business qualification and certification.

Small business status and qualification

Companies are qualified for the FDA’s small business programs when gross receipts and sales do not exceed $100 million for the ongoing tax year. Sales and gross receipts of affiliates (if the company has any) must be included. [73, p. 5]

The benefit gained from the small business status is that the companies qualified as small businesses have reduced standard fees of application submissions (PMA, 510(k), etc.) [73, p. 8].

A small business status is valid for one Fiscal Year and its runs from October 1 through September 30. The small business status is not eternal, and companies must submit a new small business status request to the FDA if wished to grant the reduced standard fee. [73, p. 6] A new small business status request is needed because, for example, the sales and gross receipts may have changed [73, p. 16]. Due to this, the FDA wants to make sure it does not exceed the $100 million limit. A new small business status request for the next FY year must be submitted to the FDA before September 30, beginning from August 1 [73, p. 6].

6 Quality management system

Most major markets require the implementation and maintenance of a quality management system (QMS). ISO 13485 is an international quality management system standard for medical devices developed to meet the industry's specific needs. This standard is recognised by several countries and is used as the QMS requirement. Several markets, however, have their own specific requirements and legislation. For example, in the U.S., the FDA uses QSR as a quality management system.

A QMS contains different processes, responsibilities, procedures, and resources that focus on meeting customer requirements through quality policy and quality objectives in an organised manner [74, p. 2]. For instance, the FDA sees the seven subparts of the quality management system seen in Figure 31 as the main pillars for achieving the purpose of a QMS.

Figure 31. Seven main pillars of a quality management system instructed by the FDA [75, p. 14].

All of the subsystems seen in the figure have their own role in achieving the purpose of a QMS, and many are linked to each other. In total, there are 15 subsystems in the FDA's QMS, and they are shown in section 6.2.

6.1 Quality System Regulation

The FDA approved quality management system, QSR, also called FDA 21 CFR Part 820, is used to determine current Good Manufacturing Practice (cGMP) regulations [76, p. 2]. In a nutshell, minimum requirements for product manufacturing, processing, packaging, or holding are demonstrated with Current Good Manufacturing Practice regulations [77, p. 48]. Every manufacturer (that is required to follow QSR requirements) marketing their device in the U.S. must fulfil these minimum requirements.

Medical device manufacturers use the QSR to ensure that the products meet the requirements and specifications and thus gain access to the U.S. market in the first place and that they can continue their supply to the U.S. market. If the product meets the requirements and specifications, the safety and effectiveness of the product are ensured.

The QSR covers a lot of requirements in the chase of a safe and effective device. The requirements that the QSR covers directly determined and in words from the FDA, are: “the design, manufacture, packaging, labelling, storage, installation, and servicing of all finished devices intended for human use,” including the facilities and designs used for those processes [77, p. 3].

Foreign manufacturers from the EU who have marketed their devices already earlier in the EU medical device market and used the ISO 13485 quality management system must still meet the QSR requirements for their device to be able to market their device in the U.S. The FDA only approves the QSR quality management system and does not recognise other quality management systems, such as ISO 13485. [78, p. 1]

6.2 QSR subparts

Section 6 introduced the seven central pillars of the QMS in the U.S. In addition, there are additional subparts in the quality management system in the U.S. that manufacturers must establish all of these subparts to ensure that their device and QMS meet the FDA’s requirements. The subparts are seen in Figure 32.

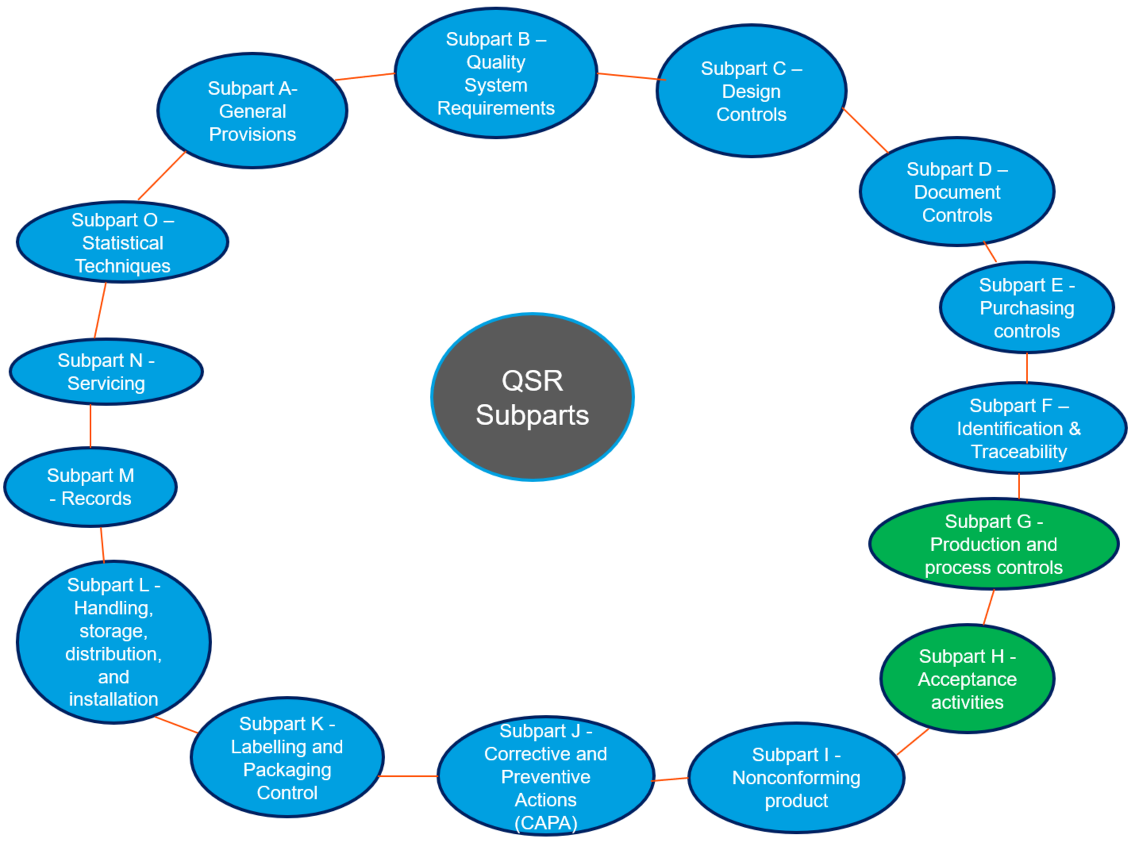

Figure 32. QSR subparts instructed by the FDA [Edited from 77, p. 6-26; 78, p. 2-4].

This thesis will focus on the subparts indicated in green (Acceptance Activities, Production and Process Controls) in order to give an overview of what is required from the manufacturer to maintain the product quality that was achieved during the design and development of the product, under the design controls subpart.

The FDA expects that the product supplied to the U.S. markets after FDA clearance/approval has each and every time the exact same safety, effectiveness and performance characteristics that were shown and proven during the product registration to the FDA. Production and process controls are among the four major subsystems identified by the FDA and thus are seen as very important [79]. Acceptance activities are very closely linked to production and process controls and are therefore reviewed in this thesis. These two subparts are key to making sure that the product safety and effectiveness are maintained throughout the product lifetime, and thus the manufacturer has the legal right to continue shipping the product to the U.S.

6.3 Subpart G – Production and Process Controls

From the product quality point of view, it is crucial that all factors affecting the product safety, efficacy and performance are identified, and all necessary control actions are planned and implemented not only to control but also to monitor and react to changes whenever needed. In other words, the production phase should be done in a controlled manner with predefined plans/ instructions and acceptance criteria for a successful production.

There is always a thought of what if the process does not perform as designed or intended. This way of thinking can be avoided with production and process controls, which are procedures, techniques, and methods purposed to manufacture devices that continually meet the manufacturer's predetermined device specifications [34, p. 59; 78, p. 3]. Therefore, the main idea of production and process controls is that the manufacturer, customer, inspector, or whoever will be working with the device can be sure that the process can reproduce and repeat itself safely and effectively and that the result meets all the specified requirements. If the manufacturer cannot be absolutely certain of the process outcome (100% verification/ inspection), process validation is needed. In validation, the process is objectively shown with a high degree of assurance to be capable of repeatedly meeting predefined acceptance criteria(s) and then approved according to established procedures [34, p. 62].

Production and process controls are linked with the DMR, which can be said to be the recipe of the medical device. This is because DMR contains procedures and specifications records for a device that is finished and fulfils all the predetermined specifications [33, p. 7; 34, p. 42]. In addition, production and process controls are one of the major subsystems of the QSR, as said, and are also included in the QSIT-Inspection; thus, FDA inspectors take great interest in it [79].

Therefore, it is imperative that its requirements have been implemented in the QMS and DMR and are maintained appropriately.

To make sure the device is in accordance with its specifications, manufacturers should make and be responsible for actions that develop, conduct, control and monitor production processes [34, p. 59]. The FDA has determined that process controls should include the following key aspects:

1. Document instructions, standard operating procedures, and methods describing the production and controls.

2. Process components, parameters and device characteristics should be controlled and monitored during production, and for all production processes, there should be a control in place. Therefore, a description of how the production is controlled and monitored is needed.

3. Inclusion of specified reference standards or codes against which the processes can be compared.

4. Approval that each piece of process equipment and the process is safe for its purpose. This is shown with qualifications and validations. First, the processing equipment must be proven that it works as intended and within specifications. After that, the process (consisting of different individual pieces of equipment) must be demonstrated to work repeatability as intended and to create the desired outcome within specifications.

5. Workmanship criteria. For instance, photos of an unacceptable device versus an acceptable device. [34, p. 59]

Production and process control aspects

Many aspects need to be considered in production and process controls, and they can vary between manufacturers because, for example, production facilities and environments differ. For instance, if environmental conditions could adversely affect device quality, the manufacturer must establish and maintain procedures that sufficiently control these environmental controls so that no adverse effect can impact device quality. Even though the environments may differ between manufacturers, all manufacturers must make sure that the manufacturing device's safety and quality do not take a negative impact because of environmental control and that the device specifications and requirements are fulfilled. In addition, there are several other factors that can introduce variation in the production and thus affect the product quality and therefore need to be taken care of. The production and process control aspects are shown in Figure 33.

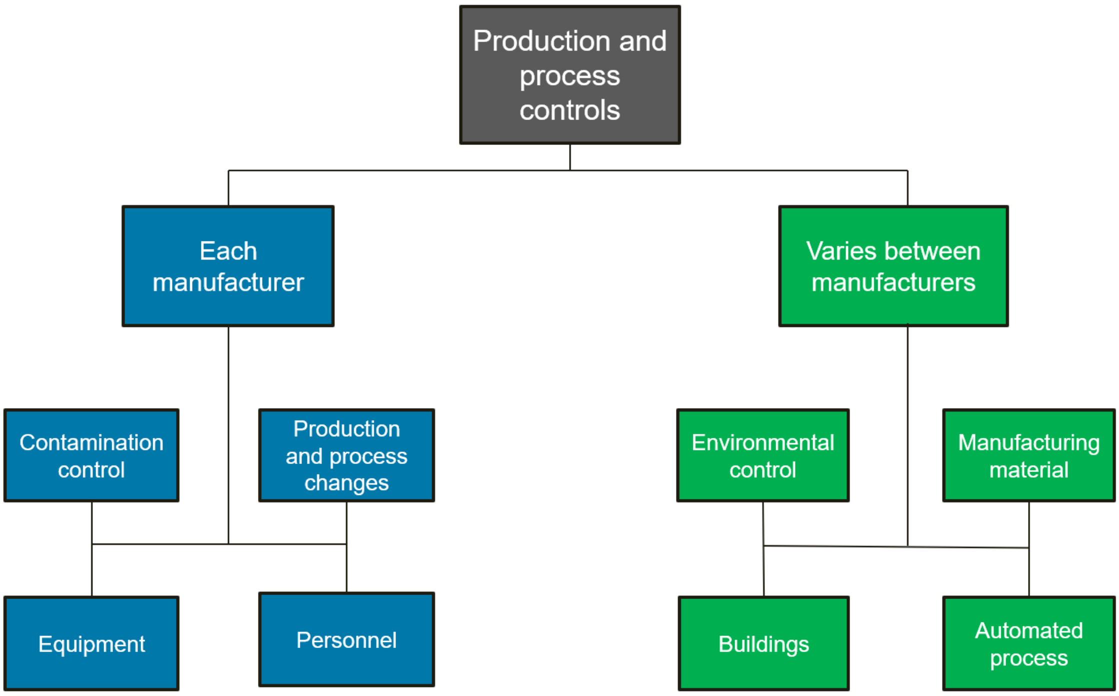

Figure 33. Aspects of production and process controls of the QSR subpart instructed by the FDA [Edited from 34, p. 59-60].

All these controls must be established and maintained. It is required by the U.S. law that all procedures are reviewed and approved.

6.4 Subpart H – Acceptance Activities

Acceptance activities ensure that the manufacturer's device is valid and fulfils requirements, and the ensuring is done by, e.g., inspections, tests or other control actions [76, p. 17; 78, p. 3; 80, p. 6]. Furthermore, based on these, the manufacturer can state that device is "valid," i.e., that it conforms to its specifications. Manufacturer's procedures should be established and maintained for these activities, and they are parted into three different sections:

1. receiving acceptance activities,
2. in-process acceptance activities, and
3. final acceptance activities.

Figure 34 describes what each acceptance activity part includes.

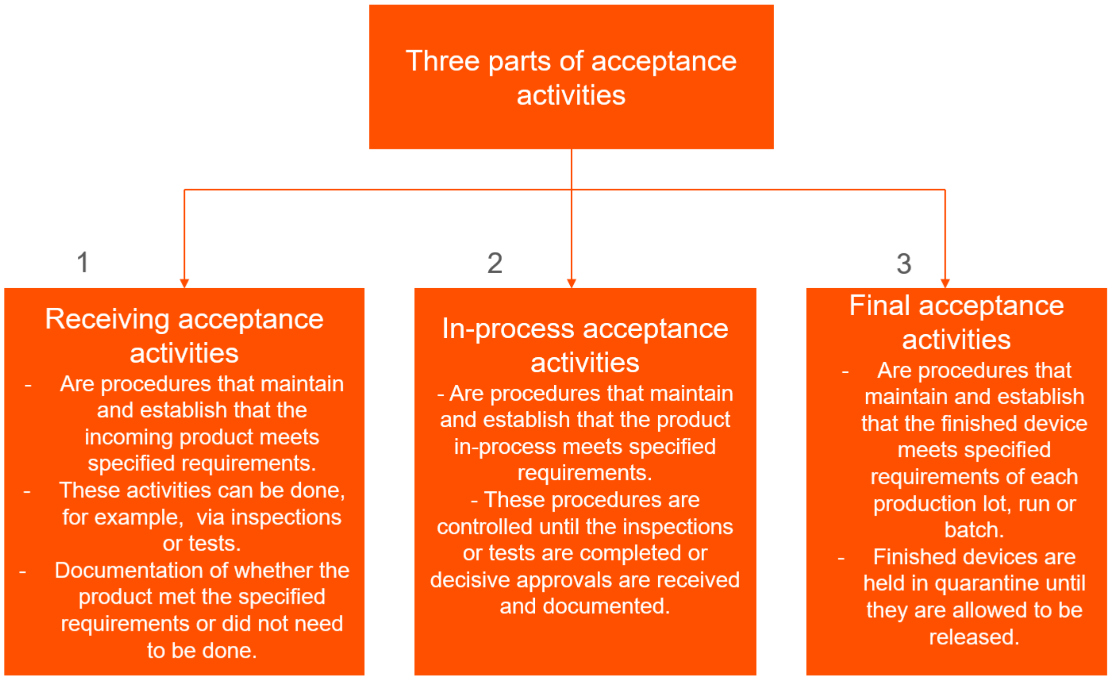

Figure 34. Acceptance activities of the QSR subpart instructed by the FDA [Edited from 80, p. 7-9].

Finished devices held in quarantine are released when each of the following steps is completed:

- activities that the design master record requires are completed,
- a review of associated data and documentation is done, and
- the designated person(s) sign the authorised release, and the authorisation is dated. [80, p. 10]

Manufacturers should make a record of the acceptance activities that describe when the acceptance activity in question was completed, the results of it, the signature of the person(s) that performed the acceptance activities and the equipment used. The records must be included in the Design History Record (DHR). [80, p. 14]

In order to assure that the device which met the required acceptance activities is exclusively distributed, used or installed, the acceptance status should be maintained the whole time, starting from manufacturing to servicing of the device. This is done to indicate the conformance/nonconformance of the device with acceptance criteria. [80, p. 16] In fact, the typical mistake to be made in acceptance activities is that the manufacturer's inspection does not have a clear structure, and thus, the effectiveness is hard to ensure or prove [75, p. 17]. Consequently, it is essential to have predetermined acceptance criteria involved in the inspections, as the specifications and criteria must be met.

Nonconformance occurs when the device does not meet specific requirements, and thus, something might go wrong in the process. They can vary from minor nonconformances to major ones and are found during inspections, tests, audits, or negative customer feedback. Minor conformance is, for instance, a visual defect that does not affect the safety or performance of the device. Major conformance is, for example, an error during the production resulting in a situation where the validated manufacturing process was deviated due to the error. All nonconformities need to be handled in a controlled manner to make sure that a product that does not meet the acceptance criteria is not released.

6.5 FDA routine inspection

The FDA has a procedure for all manufacturers with an establishment license to check that the manufacturer's quality system is valid and follows the required quality regulations. It is defined by the U.S. law that the quality system has to be inspected once in two years for Class II and III devices, and the purpose is to keep manufacturers following the quality system regulations and therefore keep them honest in their actions [81; 82; 83, p. 2]. Even though it is defined by law, the quality systems are rarely inspected due to resource shortages [81]. Some manufacturers might still and will get inspected, and the following elements affect for the FDA to decide who to inspect:

- Complaints about the device from the industry and the public. Especially if the device has had severe violations or has caused or contributed to deaths or serious injuries.

- A follow-up inspection from the previous inspection to ensure that issues have been fixed.

- If the device is new and recently entered the market.

- If the device is either implantable, life-supporting or life-sustaining, or all of these (these are very high priority devices for the FDA to inspect). [84, p. 7-8]

The FDA uses the risk-based system in prioritising inspection firstly for Class III devices. Due to low resources, inspections for Class I devices do not really happen at all, only if some serious concerns appear around the device from the industry and the public, as mentioned.

It is evident that the manufacturers must follow the regulations, as resolving the possible warning letter may cost the manufacturer millions, and if things escalate, even more, the manufacturers' products may get a market ban in a worst-case scenario.

The FDA usually informs foreign manufacturers in good advance (approximately one month before) and domestic manufacturers approximately five days before the inspection takes place [81; 82]. Nevertheless, there is a possibility that the inspector will come for an unannounced inspection, especially if a follow-up inspection is needed. In that case, the FDA may favour coming for a surprise inspection to see that the needed changes have been conducted or if a concerning complaint from the public has been made, then the FDA might also come without notice. [85, p. 2] Therefore, it is recommended that the manufacturer is always ready for an FDA inspection.

The FDA inspector will primarily check that the company follows the FDA's quality system regulation subparts that are included in the QSIT-Inspection. Nevertheless, the inspection also includes a review of other regulatory requirements that are presented in Figure 35. [86, p. 1-2]

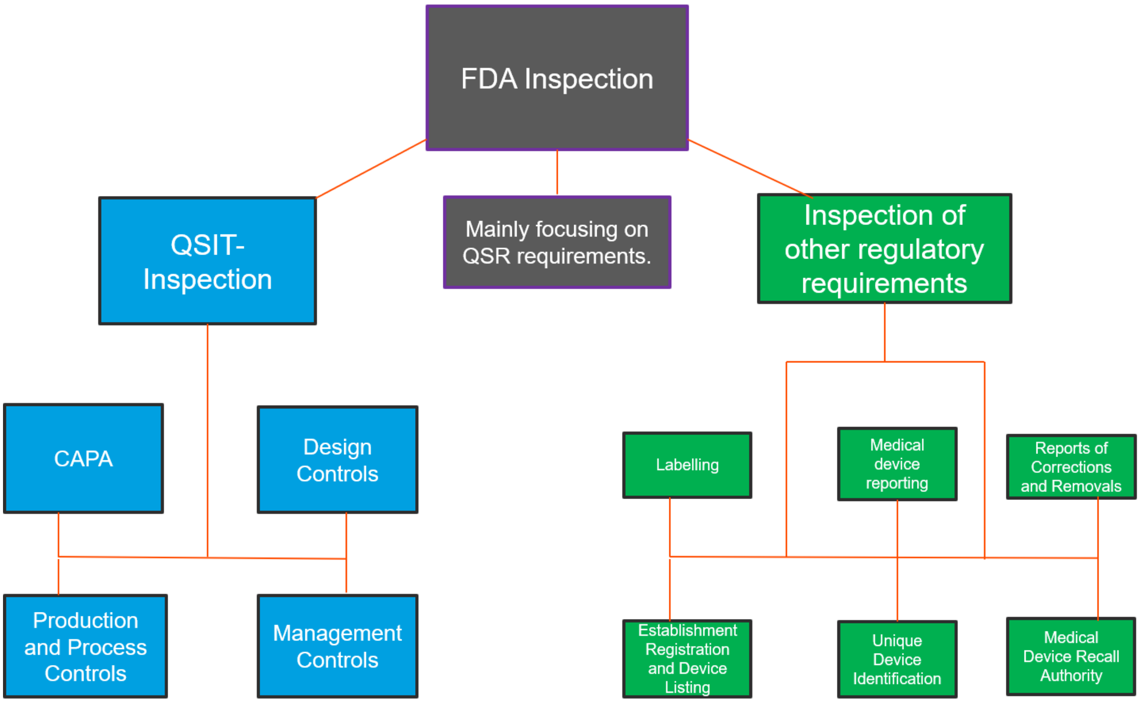

Figure 35. Overview of FDA inspection at manufacturer´s premises [Edited from 86, p. 1-2].

6.5.1 QSIT-Inspection

Quality System Inspection Technique (QSIT) – Inspection is the FDA's way of inspecting the quality management systems. It has been created to purposefully target the manufacturer's whole quality system in search of possible issues concerning quality. [86, p. 2]

This inspection technique focuses primarily on four major subsystems of the quality systems, as Figure 36 shows. The FDA believes that these four subsystems create the base for quality management systems. The CAPA (Corrective and Preventive actions) subsystem is the most important and central pillar of the quality management system. Generally, CAPA decides what is relevant and irrelevant, and all other subsystems send information to CAPA for further analysis. Then, the analysed data goes back to the subsystem where it came from, intending to inform and improve it. Figure 36 depicts this process. [79; 86, p. 2]

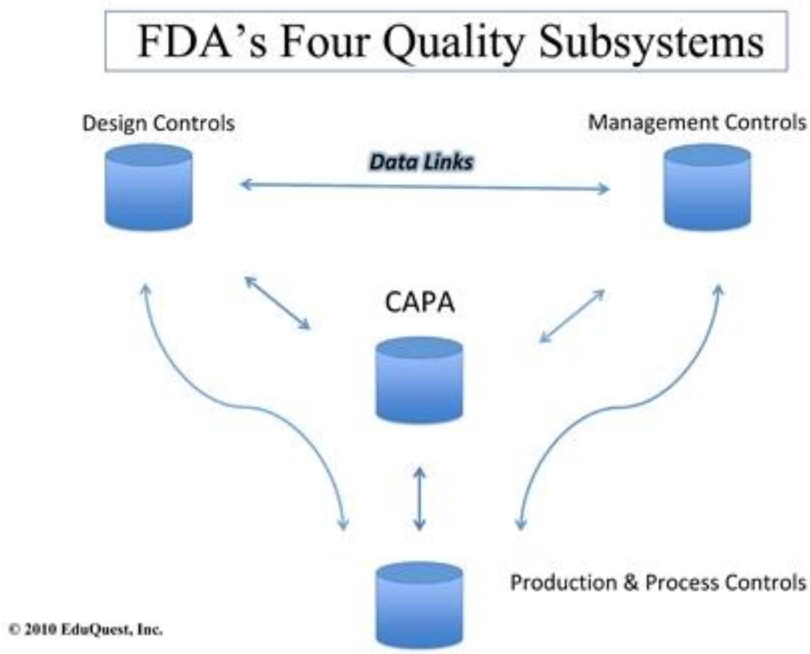

Figure 36. Illustration of how the four main subsystems work together [79].

CAPA identifies and searches for quality issues in the QMS and works as a feedback loop. FDA inspectors focus highly on the CAPA subsystem (most 483 observations are linked with CAPA), and the inspection usually starts from it. If there are issues found from it, the FDA may think that the manufacturer does not understand its own problems entirely, and because of this, the issues may impact customers due to not being resolved. [79]

6.5.2 Form 483

It is common for manufacturers to get Form 483 from the FDA inspector, as even minor deficiencies may cause this, and it is not necessarily a bad outcome yet. The bad outcome is to get a warning letter from the FDA if the issues presented in Form 483, given by the inspector, are not fixed accordingly, or the manufacturer does not respond to the FDA after being handed Form 483. [83, p. 2; 84, p. 6]

FDA Form 483 is a list of significant observations noticed by the inspector during the inspection. Significant observations are about conditions that the FDA classifies as severe and are found within the manufacturer's processes, devices, records, facility, equipment, or employment practices. Furthermore, an observation can be classified as a "possible problem", which is highly likely to happen due to conditions or/and events observed. The manufacturer must send an answer in 15 days to the FDA that demonstrates how the manufacturer will resolve or has resolved the observations presented in Form 483. If the manufacturer has corrected the observations, they must send a detailed document providing evidence of all the completed actions. If the manufacturer has not yet corrected the observations, they must send a plan and an estimated completion date of the incoming corrections. [83, p. 3-4; 84, p. 6]

A manufacturer can also be against the observations. In this case, the manufacturer's response to Form 483 must-have legitimate objective evidence and include descriptive information on why the noticed observation(s) are inaccurate. [83, p. 6]

6.5.3 Warning letter

In case of the manufacturer does not send an answer in 15 days to the Form 483 or the answer is unsatisfactory for the FDA because the response does not provide detailed and well-supported information about the corrections, the FDA thus may send a warning letter that describes that the manufacturer has violated the FDA's regulations. Typical violations of the FDA's regulations are:

1. violations of Good Manufacturing Practices (GMP),
2. classification laws and labelling violations, and
3. documentation and record violations [87].

The warning letter includes the manufacturer's violations and forces the manufacturer to take corrective actions. The manufacturer must respond to the letter in 15 days with a corrective action plan. The FDA then sends its personnel to conduct a follow-up inspection about a month later, and the target of this inspection is to determine the sufficiency and competence of the corrective actions made. If the FDA finds the corrective actions unsatisfactory or finds more violations, the FDA may take enforcement actions immediately. These actions include, for instance, product recalls, market bans, seizures, and many more unpleasant actions against the manufacturer. [87] These actions are the worst-case scenarios for the manufacturer to happen.

After all, a sure objective for medical device companies is that they must do everything to avoid getting a warning letter from the FDA because the letter will be available for everyone on the FDA website. Consequently, it damages the reputation of the manufacturer and may cause mentioned unpleasant actions against the manufacturer. The letter will not be removed from the website until the company has fixed the issues abovementioned in the warning letter. [86, p. 6]

6.6 ISO 13485 standard

ISO 13485 is globally recognised as the leading medical device QMS standard. And because the standard is worldwide known, it is also a harmonised model of QMS requirements for international markets. For instance, in the EU, EU MDR/IVDR regulation requirements for medical devices/IVDs must be fulfilled. The ISO 13485 standard is a harmonised standard that fulfils EU MDR/IVDR regulation requirements for the quality management system when followed.

The main goal of the ISO 13485 standard is to support the effectiveness of quality management systems but also customer requirements and to meet regulatory requirements. In addition, using this standard has great benefits. For instance, in a business sense, the variations are minimised, and manufacturers that comply their QMS with this standard can ensure that their device is safely designed, manufactured, and distributed. In addition, manufacturers can apply for an ISO 13485 certification if they have implemented an ISO 13485 QMS and meet all the requirements of ISO 13485. The certificate is not free but is great in a business sense because the certification grants reliability to customers. The Notified Body designated by the European Commission will value the certification when assessing the conformity of the medical device.

Generally, as said earlier, when manufacturers meet all the requirements in the ISO 13485 standard, then the manufacturers are often considered to meet the requirements of EU MDR/IVDR regulation, which must be followed to get a CE marking. Without a CE mark for the device, the manufacturer cannot market in the countries taking part in the European economic area. Figure 37 demonstrates the basic process for obtaining a CE mark for the medical device or IVD.

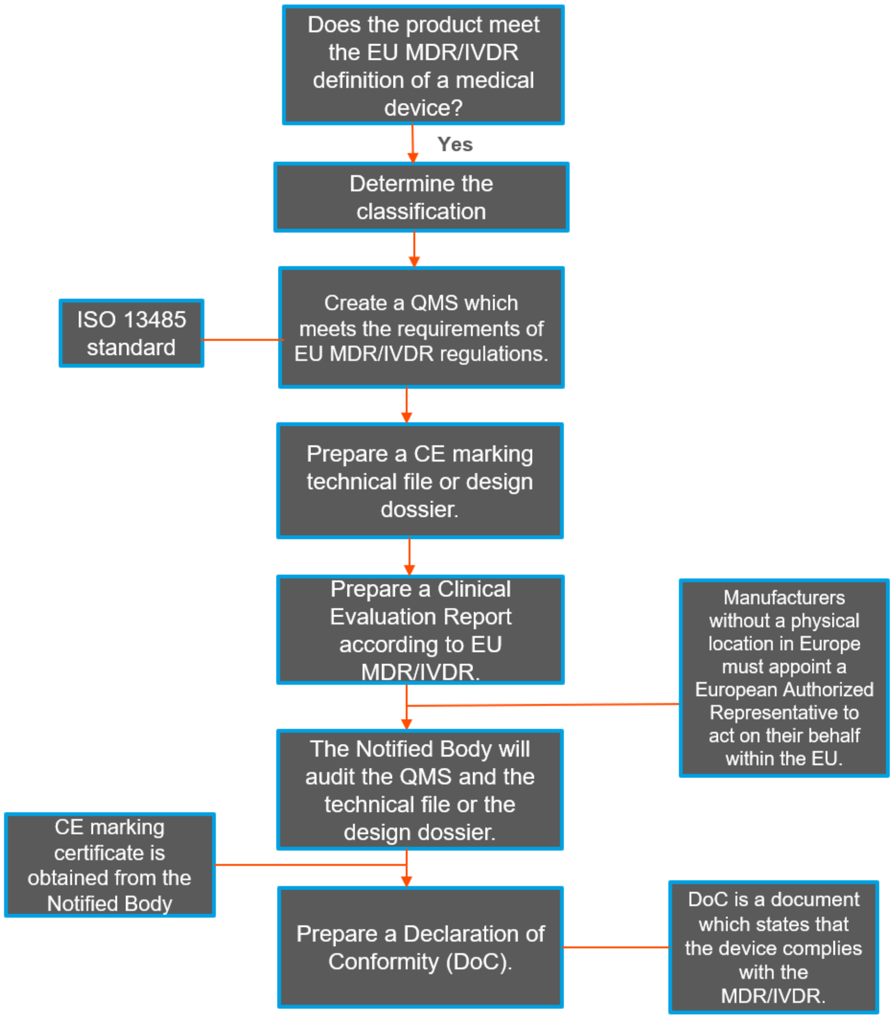

Figure 37. Route to obtain a CE marking for the medical device [Edited from 30].

6.6.1 Differences between ISO 13485 and FDA's QSR

FDA's QSR is also called 21 CFR 820, where the CFR stands for "Code of Federal Regulations"; therefore, it is a law, which ISO 13485 is not. ISO 13485 is a voluntary standard and is not required for a QMS; only recommended to be used. And because the QSR is a law in the U.S., it is more specific than the ISO 13485; for instance, complaint handling and reporting requirements are detailed more extensively [79].

ISO 13485 and QSR are primarily compared for their differences in the purpose of use, working scopes and histories. Consequently, there are no vast differences between them. Plus, as ISO 13485 is a very known standard and used quality management system, medical device manufacturers that implement ISO 13485 as their quality system are not expected to have a hard time changing their quality management system to fit QSR requirements if planning to market in the U.S. and *vice versa*. [88] Table 7 demonstrates the differences between them and gives a perspective of the differences.

Table 7. Differences between ISO 13485 and QSR [Edited from 88].

ISO 13485	QSR
Internationally recognised voluntary standard, which can be used as a QMS.	A law in the U.S. that must be used as a QMS.
The structure has been changed over the years, for example, the transition of ISO 13485:2003 to ISO 13485:2016.	The structure has stayed the same since 1996.
Is created collaboratively between ISO member countries.	Entirely created by the U.S.
Audits are done by third-party registrars.	Audits are done by FDA inspectors.

In addition to Table 7, ISO 13485 and QSR terminologies differ slightly. For instance, a requirement met with ISO 13485 is called “conformance”, but a requirement met with QSR is called “compliance”.

6.6.2 QSR changing to an ISO 13485 standard?

Because the QSR has structurally stayed the same since 1996 and regulatory expectations for quality management systems have changed over the years, the FDA proposes to harmonise QMS requirements for quality management systems under internationally recognised regulatory requirements, ISO 13485:2016. Most of the medical device markets use the ISO 13485:2016 standard, and thus, the changing process would harmonise QMS requirements for FDA-regulated devices with requirements used by the majority. [88; 89; 90]

Nonetheless, the FDA will not change the QSR completely to the ISO 13485 standard. The new QMS would be called a “QMSR” (Quality Management System Regulation), which practically is a harmonised version of ISO 13485 but contains some extra clarifications and requirements. [89; 90]

This is still a proposed rule that, if finalised, would ease the entering process to the U.S. market and the other way around, as the harmonisation makes the process simpler and reduces compliance burdens.

7 Conclusions

The FDA has its own strict country-specific procedures and legislations that manufacturers must follow to enter the U.S. market. The FDA has not really taken advantage of international harmonisation, which would most likely be beneficial not only for the U.S. but also for other countries. However, the FDA participates in the harmonisation (e.g., being a member of IMDRF). The strictness of EU regulatory requirements has grown over the years due to MDR/IVDR, and nowadays, FDA’s and EU MDR/IVDR strictness is comparatively similar. In addition, the FDA sees the harmonisation of the ISO 13485 QMS standard as a possible choice.

Many manufacturers see the FDA as unpredictable and somewhat ineffective compared to the EU, and the FDA has a quite rude and negative reputation, especially among foreign manufacturers, which might make manufacturers avoid the U.S. medical device market. For instance, Figure 38 concludes a survey made for over 200 medical technology companies and their opinions of EU and FDA regulatory performance. EU is indicated as green and the FDA as brown.

Figure 38. Regulatory performance of the FDA (brown) versus EU (green) [Edited from 72, p. 26-27].

As seen, the FDA‘s regulatory performance is pretty bad compared to that of the EU. Thus, this thesis aimed to clarify the FDA’s regulatory requirements, the most common pathway to the U.S. medical device market (traditional 510(k)), and the FDA’s quality management system requirements that affect the post-market phase. Additionally, this thesis included information and data on, for example, the FDA’s performance, market durations and costs, which might puzzle manufacturers who are preparing to market their devices in the U.S. Consequently, this thesis gives some preview for manufacturers of what lies ahead and what should be taken into account, especially when preparing a 510(k) for the FDA.

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