Tampereen yliopisto

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REGULATORY CONTROLS FOR THE UNITED STATES MARKET ENTRY OF MEDICAL DEVICE

Case flow cytometry

Faculty of Medicine and Health Technology (MET)
Bachelor's thesis
April 2023

TIIVISTELMÄ

Eerika Suokas: Lääkinnällisten laitteiden sääntely - tavoitteena Yhdysvaltojen markkinat
Kandidaatin tutkielma
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Tässä tutkimuksessa tarkastellaan mitä säännöksiä lääkinnällisen laitteen valmistajan tulee ottaa huomioon, kun tavoitteena on viedä laite Yhdysvaltojen markkinoille.

Esimerkkinä lääkinnällisestä laitteesta käytetään virtaussytometria, joka on tehokas työkalu solupopulaatioiden erilaisten ominaisuuksien analysointiin. Tuloksia voidaan käyttää diagnostisiin sekä terapeuttisiin tarkoituksiin. Teknologian kehittyessä myös uusia innovaatioita syntyy, joten jotta markkinoille saadaan turvallisia ja tehokkaita tuotteita, vaadittavien säännösten ymmärtäminen on tärkeää.

Koska tutkimuksessa keskitytään Yhdysvaltoihin, käsitellään maan tärkeimpiä lainsäädäntöjä ja säädöksiä, jotka liittyvät lääkinnällisiin laitteisiin. Näitä ovat muun muassa Yhdysvaltojen elintarvike- ja lääkeviraston ohjeistus, Yhdysvaltojen laki, liittovaltion lainsäädäntö sekä lääkinnällisten laitteiden luokittelu. Tutkimuksessa selviää, että virtaussytometri luokitellaan Yhdysvalloissa luokan II lääkinnälliseksi laitteeksi, joka vaatii 510(k) -hakemuksen kun tavoitellaan lupaa myydä sekä markkinoida tuotetta laillisesti Yhdysvalloissa.

Luokan II laitteisiin sovelletaan yleisiä sekä erityisiä säännöksiä. Yleisiä säännöksiä sovelletaan jokaisen kategorian lääkinnällisiin laitteisiin. Niiden tarkoitus on osoittaa todisteita laitteen turvallisuudesta sekä tehokkuudesta. Nämä säännökset ovat kaikille lääkinnällisille laiteluokille samat. Yksi tärkeä osa yleisiä säännöksiä on laadunvalvontajärjestelmä, jolla varmistetaan tuotannon tasalaatuisuus sekä sen dokumentointi. Erityiset säännökset vaaditaan, kun yleiset säännökset yksinään eivät riitä turvallisuuden ja tehokkuuden takaamisen todistamiseen. Nämä ovat laitekohtaisia ja niistä löytyy tietoa Yhdysvaltojen elintarvike- ja lääkeviraston sivuilta. Koska markkinoilta löytyy jo hyväksytty virtaussytometri, voidaan sitä käyttää hakemuksessa vertailukohteena, kunhan riittävä todiste samankaltaisuudesta on liitteenä.

Kaikista näistä säännöksistä tulee dokumentoida tarpeenmukaisen todistusaineiston kanssa 510(k) -hakemuksessa. Mikäli Yhdysvaltojen elintarvike- ja lääkevirasto hyväksyy hakemuksen, voidaan lääkinnällistä laitetta myydä sekä markkinoida laillisesti Yhdysvaltojen markkinoilla.

Avainsanat: flow cytometry, FDA regulation, regulatory controls, medical devices

ABSTRACT

Eerika Suokas: Regulatory controls for United States market entry of medical device - Case flow cytometry
Bachelor's thesis
Tampere University
Degree Programme of Biotechnology
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In this thesis the regulatory controls for the United States market entry of medical devices are being investigated, using flow cytometer as an example of a medical device. The aim of this thesis is to find out what are the applied regulatory controls of flow cytometers required to be applied and undertaken in order to legally market the device in the United States.

Flow cytometry is an effective tool for analyzing different characteristics of cell populations. The results can be used for diagnostic and therapeutic purposes and therefore the devices must be proven to be safe and effective.

The legislation and regulation in the United States will be covered thoroughly, including the role of the Food and Drug Administration, United States Code and Code of Federal Legislation as well as the classification of medical devices. It will be found that a flow cytometer is a class II device that requires 510(k) submission to be marketed in the United States.

Class II devices are subject to general and special regulatory controls. General controls are the minimum requirements for the assurance of safety and effectiveness. One of the subparts under general control includes the Current Good Manufacturing Practices (CGMPs), which have a big effect on the quality system the medical device manufacturer should implement and follow. When general controls alone are not enough, device-specific special controls are required.

Investigating the regulatory controls of flow cytometers is important so the manufacturers can implement the regulations for the assurance of safety and effectiveness and provide innovations to the market, therefore being able to contribute to the growth and success of the whole industry. This would then benefit patients, clinicians, and researchers around the world.

Keywords: flow cytometry, FDA regulation, regulatory controls, medical devices

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Tampere, 26.4.2023

Eerika Suokas

CONTENTS

1. INTRODUCTION

Flow cytometry has become an attractive method with its popularity growing in the past twenty years since the technology required for it has improved a lot and it has been able to be utilized in different applications. (Macey, 2007) Flow cytometry can be used to provide diagnostic and therapeutic support for the treatment of different severity level diseases, therefore being a medical device. The flow cytometry technique can be utilized in various fields of applications, such as cancer and molecular biology, immunology, virology, and infectious disease monitoring. (McKinnon, 2018) One of the key challenges is the need to balance innovation and safety as technology advances and new applications are being developed.

Medical devices are regulated all around the world. The regulatory actions vary, depending on the geographical location where the device is being marketed as well as the classification of the device. In every area, the devices are classified according to the rules in that specific location. This thesis is investigating the regulation of class II medical devices in the United States, using flow cytometers as a case example. In the United States, Food and Drug Administration is the responsible authority for the regulation and control of medical devices. (Commissioner, 2021b) As the regulation is such a wide topic, it was narrowed down to investigate the applicable regulatory controls of class II medical devices, in order to enter the United States market. The purpose of the regulatory controls is to ensure the safety and effectiveness of the medical devices, in order legally market and sell the medical device. The aim of this thesis is to find out what are the applied regulatory controls for the United States market entry of flow cytometers.

All this is done by starting in the second chapter by looking at the basis of the flow cytometers to understand what kind of medical device is referred to as a case example in this study. The third chapter will investigate the United States Public Health regulation system to find out the correct organizations to whom the medical device manufacturer must report and from where to find information. In the fourth chapter, the classification of medical devices in the United States will be investigated as it is an essential step of the regulatory process, determining the following actions. In the fifth chapter, the regulatory controls, including general controls together with Current Good Manufacturing Practices (CGMPs) and the special controls are discussed. A few examples are given of what the regulatory controls mean in the case of the flow cytometers. The last chapter concludes the main findings of this study.

2. FLOW CYTOMETRY

2.1 Basis of flow cytometry

Flow cytometry is an effective technique used in biotechnology. It can be used to determine the phenotypes of the analyzed cells. From a heterogenous mixture, the cell types, sizes, and other external and internal characteristics can be determined. (Adan et al., 2017) Flow cytometry is the technique utilized and the device itself used for doing that is called a flow cytometer. Typically, three functional units make up the system. First and most importantly, the functionality of the system requires one or more laser light sources combined with a sensing system, often called a detector. Secondly, a hydraulic system for the controlled passage of the analyzed liquid is needed. The third main functional unit includes a computer for the collection and analysis of the gathered data based on the signals coming from the detector. (Macey, 2007)

The basic principles of the functionality of the flow cytometer depend on the laws of physics, most importantly electronics, fluidics, and optics. The fundamental operation of the device is based on the light-scattering properties of the analyzed cells. An essential feature of flow cytometry is to be able to focus a stable particle stream where the analyzed particles such as cells will be illuminated one at a time. The particle stream is focused by using hydrodynamic fluid pressure, which can be referred to by the term “flow sheath” as well. Flow cytometry is also highly dependent on the fluorescence emissions affected by fluorescent particles. That will be discussed in one of the following chapters in more detail since it is such a big part of flow cytometry. (Sklar, 2005) A schematic representation of a flow cytometer can be seen in figure 1 below.

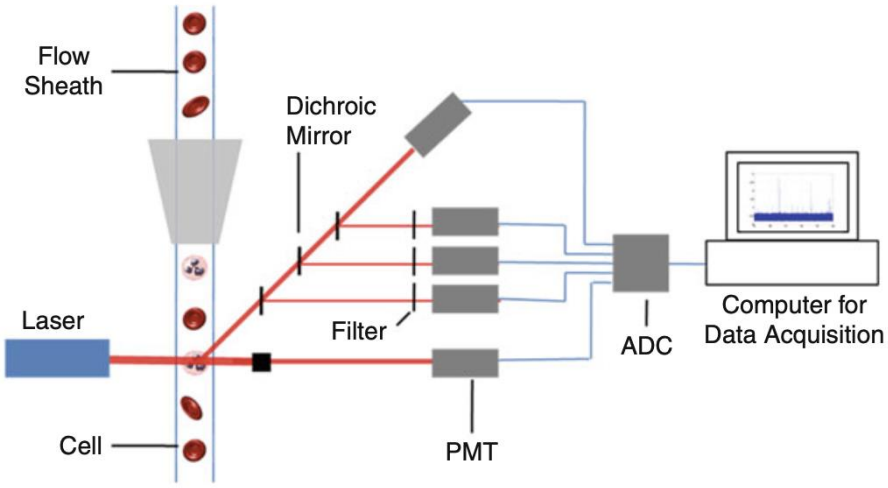


Figure 1. *A schematic representation of a flow cytometer (Wei et al., 2017)*

The most common structure of a flow cytometer includes the sensing system combined with the laser consisting of dichroic mirrors, filters, and a photomultiplier tube (PMT) as well as an analog-to-digital converter (ADC) which can be seen in figure 1. The PMT is responsible for the detection of the forward scattered (FSC) and sideways scattered (SSC) light which is a result of the individual cell passing through the focused laser beam, resulting in the excited fluorescence. The fluorescence emission resulting from the excited fluorescent markers when illuminated by laser light is also detected by PMT which then converts all of the signals into analog signals. The ADC then converts the analog signal into a digital signal which can be further analyzed by a computer. (Wei et al., 2017) As there are many manufacturers of flow cytometers, there is also a wide range of devices. One example of a flow cytometer is in below figure 2, from which the main unit of the flow cytometer and reagents connected to the autosampler can be seen.

Figure 2. *ThermoFisher Scientific Attune flow cytometer ("Attune Flow Cytometers - FI," n.d.)*

2.2 History & development

It could be claimed that the basis of the flow cytometer was first developed in 1954 when an instrument with the possibility of cell counting and sizing was made. The device was called a "flow analyzer" and it was developed by Wallace Coulter. The first clinical flow cytometers were introduced almost 30 years later in 1983. As the technology developed, it enabled the improvement of efficiency and data analysis year after year. By 1999 it was possible to detect 11 different fluorochromes with the help of lasers and in 2003 high-speed digital technology enabled fast data sorting. Since that, the technology has only improved and it has allowed the development of flow cytometers for several purposes like diagnosis and treatment of a wide variety of conditions. (Macey, 2007)

As already mentioned, the basic use case for flow cytometers is to provide data for diagnostic and therapeutic support for the treatment of diseases besides research purposes. The most regular use

case of flow cytometry is simply counting subsets of cells in a heterogenous population or counting the number of cells. (Moloney and Shreffler, 2008) Nowadays flow cytometry is a fundamental method, especially in the diagnosis of hematolymphoid malignancies which are cancers related to blood, bone marrow, and lymphoid organs. The tumor cells often circulate in the blood circulation and can be detected using specific signal markers. Besides diagnosis, also the prognosis can be determined, and the response to the therapy monitored. This way the treatment can also be personalized according to individual needs. (Ortolani, 2011)

To mention a more specific example, a flow cytometer could be used to identify the differentiation state of $CD8^+$ T cells by looking at the expression of the specific cell surface, or intracellular proteins. $CD8^+$ T cells, also called cytotoxic T-lymphocytes, have a major impact on clinical relevance on several different occasions. They are crucial for the immunity of the cells, including the defense against viruses, pathogens, and bacteria, and can be found in excessive amounts from cells within tumors. A detailed overview of the $CD8^+$ T-cell heterogeneity can be obtained by flow cytometry by adapting the flow cytometry panels depending on the hypothesis. Being able to detect and target specific $CD8^+$ T cell populations is a game changer in T-cell-based immunotherapies. As an example, it has been found that some $CD8^+$ T-cells have similarities to stem cells and therefore have the capability for superior tumor regression. With the help of flow cytometry, the different subsets of $CD8^+$ T cells can be separated and the immunotherapy can be personalized according to the individual's needs and response. (Cossarizza et al., 2021)

Besides obtaining an overview of the cell populations, the proteins associated with the cells in a sample, could be determined with the help of flow cytometry together with specific fluorescent molecules that attach proteins either intra- or extracellularly. Some specific proteins such as mutated growth factor receptors are involved in the malignant transformation mechanisms. If an excessive amount of growth factor receptors such as EGFR, Her^2/Neu, PDGF-r, IGFR, c-Met, and several others are being detected in the cells it could be a sign of mutation leading to cancer. Often hematological malignancies such as leukemia, lymphoma, and multiple myeloma could be identified with this type of flow cytometric diagnosis. (Cossarizza et al., 2021)

To conclude, with the help of flow cytometry, several properties of cells can be determined, often enabling the diagnosis of different diseases, such as hematological malignancies, and treatment planning. It could be also used for research purposes. Flow cytometry can be utilized to find out properties such as the cell phenotype, sizing, the existence of different kinds of membrane receptors and antigens, and DNA plus RNA content. After the conducted flow cytometry, a lot of data exists from which an analysis can be made and some specific conditions such as cancer could be determined together with the support of other diagnostic methods. Overall, the flow cytometer has developed to be a very multi-functioning In Vitro Diagnostic (IVD) device. (Gormley et al., 2016)

2.3 Fluorescent reagents

Flow cytometry as a technique is highly dependent on the use of fluorescent molecules as briefly discussed above already. Since the entire flow cytometry analysis is based on the light scattering properties of the analyzed molecules, various fluorescent dyes are essential tools to find out the targeted components from the analyzed population. The basic principle to be used to stain the components of the cells is quite simple. For example, different monoclonal antibodies (mAbs) can be labeled with fluorochromes. The mAbs then target either the surface of the cell or specific intracellular components, such as receptors. (Macey, 2007) The absorption of one wavelength by a fluorochrome occurs, and the following emission of usually a little bit longer wavelength is called fluorescence emission. On an atomic level, a molecule called the fluorescent probe absorbs a photon of light with certain energy and wavelength and emits it with lower energy and higher wavelength. There are very few naturally fluorescent cellular components and therefore the analyzed cells need to be stained by fluorescent probes to be able to reveal the wanted structures and components when an analysis by flow cytometer is conducted. (Sklar, 2005) Below in figure 3, the fluorescently labeled antibody is attached to a cell surface antigen and when being excited with a certain wavelength of laser light it results in fluorescence emission and scattering.

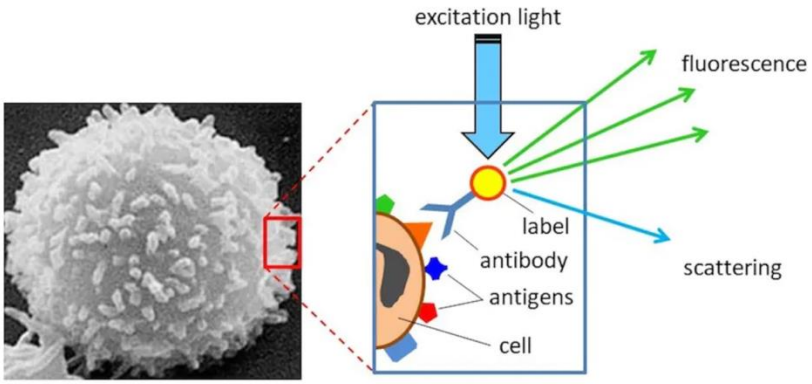


Figure 3. *Fluorescently labeled antibody on a cell surface antigen, excited by a specific wavelength resulting in fluorescence emission and light scattering (Murphy, 2022)*

The significant development of fluorescent particles has been one of the factors affecting the widening development of flow cytometry in general as well. Previously, a problem existed with spectral overlap when a fluorescence emission associated with one fluorochrome was detected by multiple detectors, and the spectral overlap required compensation. Nowadays the number of fluorochromes to be used has increased and the techniques for compensating for the spectral overlap have improved as well. The first fluorochromes used were often quite low in molecular weight but

during these years, there have been developed other dyes as well with higher molecular weight, different spectral properties, greater stabilities, and higher quantum yields. (Macey, 2007)

To conclude, one must consider the correct fluorescent dyes which are appropriate for the purpose. There are a wide variety of options available and depending on the goals, the most reasonable fluorochrome for that occasion should be selected. The flow cytometer would not be as effective without the fluorescent dye and it is important to understand that an analysis of the cells is highly dependent on the flow cytometer itself and the used fluorescent dyes together, not only the device.

3. UNITED STATES PUBLIC HEALTH REGULATION

3.1 United States Food and Drug Administration

Since this study is focusing on the regulatory controls in the United States (U.S.), it is important to have a look at the structure of the legislation there. The Department of Human and Health Services (HHS) of the United States was created to protect essential human services and U.S. people's health. HHS is a cabinet-level executive branch department of the United States Federal Government. Under HHS there is a collection of different level organizations, agencies, and offices that are categorized under Public Health Service (PHS). One of the subordinate operating federal agencies under the PHS was established in 1906 and is The United States Food and Drug Administration (FDA). (Affairs (ASPA), 2015)

Since the early 20th century, FDA has been the main responsible organization for ensuring both, the safety and efficiency as well as security of human and veterinary drugs, biological products, and medical devices. Besides that, FDA is enforced to secure the safety of the U.S. food supply, cosmetics, and products that emit radiation. By doing all that, the mission of the FDA is to help companies to speed up their innovations which would make medical products more effective, safer, and affordable. This would then benefit the whole of society. Another way FDA is encouraging individuals to maintain and improve their health is by sharing easily available accurate and science-based information. (Commissioner, 2021b)

Therefore, all medical devices, that are being marketed in the United States are regulated by the FDA. To be more exact, FDA is still further divided into several smaller level organizations, one of them being the Center for Devices and Radiological Health (CDRH) which is the organization responsible for the regulation of medical devices. All laws of the United States are organized by subject into the United States Code (U.S.C.). Under Title 21, starting from Chapter 9, The Federal

Food, Drug, and Cosmetic Act (FD&C Act) can be found. FD&C Act is a federal law enacted by the Congress of the United States. Therefore, since the FDA is responsible for the regulation of medical devices, they generate the regulations based on the laws outlined in the FD&C Act or any other laws in the United States Code that apply to the activities undertaken by FDA. To issue the FDA regulations, FDA also follows the procedures required by the Administrative Procedure Act which is another U.S federal law covering the processes by which federal agencies develop and issue regulations, often meaning public input on a proposed regulation before FDA issues final regulation, which is also federal laws but not included in the FD&C Act. (Commissioner, 2021a)

The regulations based on the FD&C Act can be found in a separate Code of Federal Regulations (CFR), which is a collection of general and permanent rules, but not laws, published by the executive departments and agencies of the U.S. Federal Government. The content under Title 21 of the CFR is primarily reserved for the rules of the FDA and they are being updated once a year, often around April, and the changes will be published several months later. (Health, 2018a)

To summarize, FDA is the responsible organization for the regulation of medical devices in the U.S. With the help of the FD&C Act laws, determined in Chapter 21 of the United States Code, FDA determines the regulations and guidelines that have been written down under the Title 21 of Code of Regulations.

3.2 FDA's impact on and actions in corporations

When a manufacturer is developing a new medical device, the target is often to successfully bring the product into the market. The initial and most critical step of the process is to have a throughout understanding of the product in question. The company must be able to classify the device according to the FDA instructions which will determine the actions required to be able to market the device in the United States. If the product is a combinatory product with several FDA-regulated parts, the primary mode of action (PMAO) of the device should be determined. This is the case with flow cytometry as well, the device and the reagents are separate FDA-regulated parts, and this thesis is focusing on the device, the flow cytometer. In case of uncertainty, the Office of Combinatory Products (OCP) can be contacted and they will guide how to proceed forward. (Health, 2022c)

Medical devices might require marketing approval or clearance in order to enter the product into the U.S. market, and even if not, they must still follow the applicable regulatory controls. Therefore, it is important to know the product, to understand what actions need to be undertaken. The kind of devices that require marketing clearance or approval can apply and possibly gain it from FDA. The classification is one of the most essential steps and it will also determine the required actions that follow. Therefore, it will be covered in more detail in the following chapter, and the classification of flow cytometry devices will be determined. (Health, 2022c)

If the device requires clearance or approval to be marketed, the next step of the process will be preparing the correct type of premarket submission. There are several types of premarket submissions, but four of them are the most common ones and they have been listed in table 1 together with reasoning when to select and which type of submission. (Van Norman, 2016)

Table 1. *Different types of premarket submissions and the reasoning for choosing them (Van Norman, 2016)*

Type of premarket submission	**When to choose?**
510(k) – Premarket notification (PMN)	The device is proven to be similar in all essentials like a predicate device in terms of intended use. For class I & II devices.
PMA – Premarket Approval	Strong, valid, and scientific evidence is required for indicating the safety and effectiveness of the device for the intended use. For class III devices.
De Novo Classification Request	General controls are believed to indicate adequate assurance of the safety and effectiveness of the device for the intended use. No legally marketed predicate device exists.
HDE – Humanitarian Device Exemption	Devices that are meant to treat and benefit patients with rare diseases or conditions. For class III devices.

As can be seen from table 1, depending on the class of the device and its intended use, a different kind of premarket submission is required. The class of the device and type of submission will also have some effect on the stringency of the process. (Van Norman, 2016) Besides the class of the device, one important factor affecting the required type of submission is the fact whether a predicate device exists or not. A predicate device means a device that is similar in all essentials in terms of intended use exists and can already be marketed legally in the U.S. markets. Therefore, it can be used as a reference and point of comparison for the new medical device premarket submissions. (Health, 2019b) Numerous aspects must be taken into account when preparing the premarket submission. Depending on the type of submission, a variety of factors will be valued. Some of the most important things the manufacturer should consider and provide evidence of have been listed in table 2 below with the reasoning. (Health, 2022c)

Table 2. *Information to be included in the premarket submission (Health, 2022c)*

The manufacturer should consider:	**Why?**
Design controls	Class II and class III devices must be designed in accordance with Design Controls under the Quality System Regulation 21 CFR 820.30
Nonclinical Testing	The testing should comply with the Good Laboratory Practices (GLP) 21 CFR 58
Consensus standards	FDA encourages the use of international consensus standards
Clinical Evidence	For the submissions that need clinical evidence, approval of an Investigational Device Exemption (IDE) might have to be applied from FDA
Labeling	Device Labeling regulations must be followed, found under the Labeling 21 CFR 801

As already said, the information required varies depending on the type of the device and submission and a detailed look at the requirements must be taken with every different device separately and individually. After sending the premarket submission with the essential information to the FDA, the communication process between the FDA and the manufacturer will begin. For example, you can propose FDA how you will undertake some actions of regulation according to your interpretation of the CFR and the FDA could comment on that and possibly make you change something according to their point of view. (Health, 2022c)

To conclude, it is the manufacturer's responsibility to be aware of what actions are required to be taken depending of the type of medical device. Plenty of information can be found online and FDA offers several kinds of different ways and channels where the manufacturer may ask for advice if facing some challenges. (Commissioner, 2021c) The manufacturer should be able to interpret the regulations and apply them to their medical device. For the help of that, FDA offers guidance documents where the interpretation of the policy on certain regulatory issues is described. (Health, 2022b)

4. CLASSIFICATION OF MEDICAL DEVICES IN THE UNITED STATES

4.1 Categorization into three classes

The legal definition of a medical device can be found in the U.S.C. According to Chapter 21 in the U.S.C., section 321(h), a medical device can be considered to mean “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or another similar or related article, including any component, part, or accessory”, which meets the following three conditions A) it should be recognized in the official National Formulary, or other United States Pharmacopeia, or any supplement to them, B) it is meant for the diagnosis or disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in a human or other animals C) it is going to affect the structure or any function of the body of a human or other animals. Besides the three conditions the device should not utilize chemical action, nor it is dependent upon being metabolized to achieve the primary intended purposes. (21 U.S.C. 321(h))

Now that the definition of the term medical device has been covered, it is time to have a look into the three categories of medical devices that exist, class I, II, and III. As already discussed, when planning to prepare a device for the market in the U.S., the most important first step will be to classify the device according to the FDA classifications and instructions.

As also mentioned in the first chapter regarding the basis of flow cytometry, there are two FDA-regulated parts in the flow cytometer, the device with the illumination source and the fluorescent reagents. When developing a flow cytometer, the regulation and classification of the device must be taken care of. Most likely the reagents will be bought from another organization, and the manufacturer of the reagents has taken care of the required FDA regulation from their side. This study examines a flow cytometer as a medical device.

According to FDA, medical devices can be classified into three major categories: I, II, or III or according to the risk factor of the device. The device class increases at the same pace as the degree of risk factor, and so does the regulatory control as well. Therefore, the devices classified into category I have the least regulatory controls as class III has the most stringent one. (Health, 2020) The general controls are the most basic level provisions that provide assurance of the safety and effectiveness of the device and they apply to all medical device classes. (Health, 2019a) On the other hand, special controls are device-specific and required when the general controls alone are not sufficient enough to assure safety and effectiveness. (Health, 2019c) Premarket approval is a

whole own process of regulatory and scientific review where the class III medical device's safety and effectiveness are being evaluated and might lead to premarket approval. (Health, 2023a) In table 3 the different applied regulatory controls and submission types for each of the classes are summarized. The medical devices are being categorized into three categories by the following matter, defined in CFR, under Title 21, Chapter I, Subchapter H, part 860.3 Definitions.

Class I – For the assurance of the safety and effectiveness of the device, the general controls are sufficient to provide a reasonable guarantee. If an insufficient guarantee exists, it is accepted since the device is not life-supporting or life-sustaining, which does not present a potential unreasonable risk of illness or injury. The general controls mentioned are determined in FD&C Act and will be going through in a more detailed way in the next chapter. (21 CFR 860.3 “Class I”)

Class II – For the assurance of the safety and effectiveness of the device, the general controls alone might not be sufficient enough to provide a reasonable guarantee. Therefore, special controls are required if the possibility of establishing information utilizing special controls exists. The information to be included in the special controls can be further found in the CFR. If the device is represented to be used for supporting or sustaining human life, the Commissioner will examine, determine, and describe the special controls required for the assurance of the safety and effectiveness of the device. (21 CFR 860.3 “Class II”)

Class III – For the assurance of the safety and effectiveness of the device, insufficient information exists on whether general controls are sufficient enough to provide a reasonable guarantee or whether the special controls in addition to general controls would provide the assurance. In addition to that, the device is life-supporting, life-sustaining, or significantly important since it is supposed to be used in preventing impairment of human health, or the device prevents a potentially unreasonable risk of illness or injury. (21 CFR 860.3 “Class III”)

Table 3. *Classes with their regulatory controls and submission types (Health, 2020)*

Classification	**Applied regulatory controls**	**Submission type**
Class I	general controls	510(k)
Class II	general controls & special controls	510(k)
Class III	general controls & premarket approval	PMA, HDE

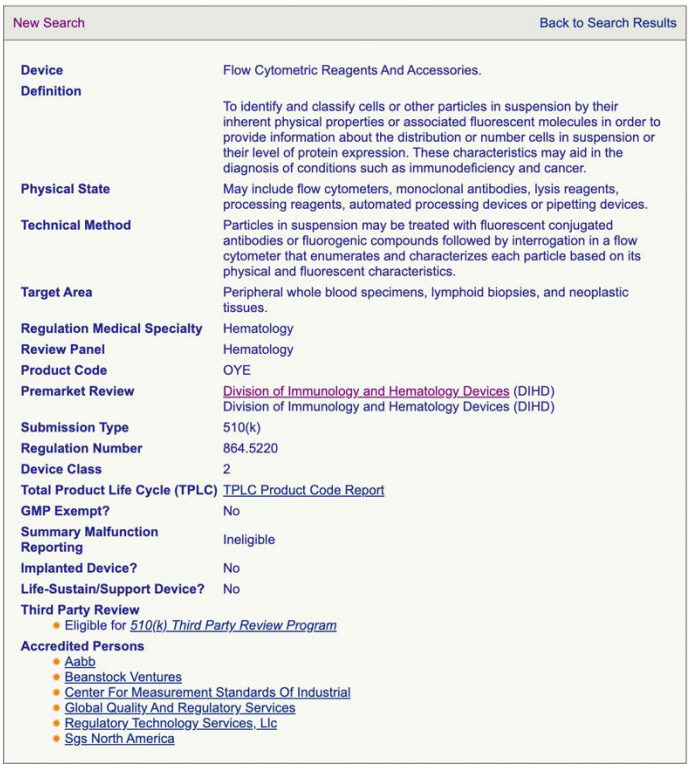
FDA has classified approximately 1700 different generic types of devices and they have been grouped into 16 medical specialties referred to as panels. After that, each of the 16 generic medical specialties has been assigned to one of the three regulatory classes defined above. This is done based on the level of control necessary to assure the safety and effectiveness of the device which is the basis of the classification. Those 16 medical specialties groups can be referred to as predicate devices. If no such predicate device exists, the De Novo Classification request must be done as described in the second chapter. The device classification depends on the intended use of the device and also upon indications for use. (Health, 2018b)

There are two methods to be used to find out the predicate device and classification regulation for the device. A classification database and a device panel exist and can be used as help during the classification processes. From the classification database, a manufacturer can search for a part of the device name. From the device panel, the classification could be identified by using the help of a medical specialty if it is already known. Once the predicate device is found, there is a lot of information about the applied regulatory controls for the specific application and citations of CFR which apply to the device regulation. (Health, 2019b)

To conclude, the medical devices applicable to FDA regulation can be categorized into three different classes depending on their degree of risk factor. Based on the class to which the medical device belongs, the applied regulatory controls will be determined. The classification also determines the required type of submission to apply for marketing clearance or approval.

4.2 Classification of flow cytometers & choice of submission type

To find out the classification of the flow cytometer the most reasonable way to start would be to use the classification database to find out if it already has a predicate device or not. Quite quickly from the database, a “Flow Cytometric Reagents And Accessories” predicate device category can be found. Another way of finding the predicate device could have been to use the device panel and make a conclusion that the flow cytometer belongs to the group of “hematology medical specialty” and find out the matching device from that category. (Health, 2020) In figure 4 there is a screenshot from the FDA’s product classification page of the device “Flow Cytometric Reagents And Accessories”. From the figure, many important things such as the device class and submission type can be found. This predicate device can be then used as a reference when applying for clearance for a new flow cytometer device that is not legally on the market yet.



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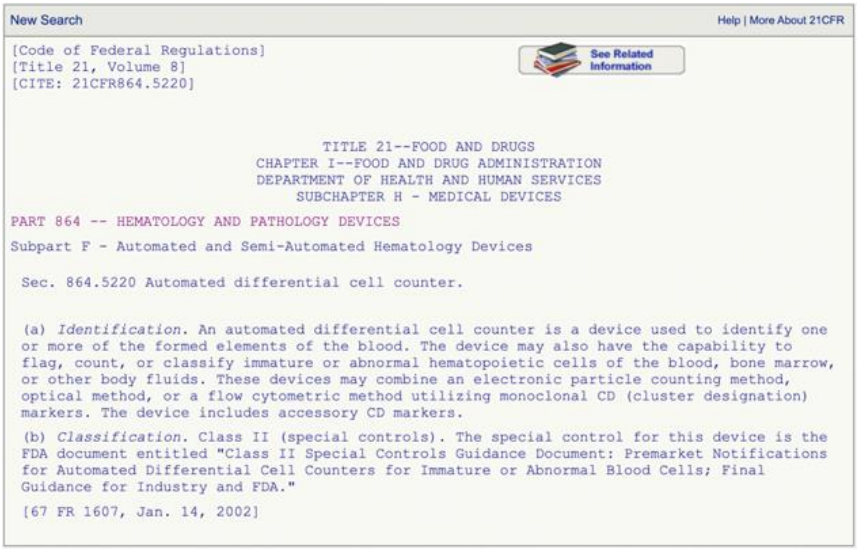
Device	Flow Cytometric Reagents And Accessories.
Definition	To identify and classify cells or other particles in suspension by their inherent physical properties or associated fluorescent molecules in order to provide information about the distribution or number cells in suspension or their level of protein expression. These characteristics may aid in the diagnosis of conditions such as immunodeficiency and cancer.
Physical State	May include flow cytometers, monoclonal antibodies, lysis reagents, processing reagents, automated processing devices or pipetting devices.
Technical Method	Particles in suspension may be treated with fluorescent conjugated antibodies or fluorogenic compounds followed by interrogation in a flow cytometer that enumerates and characterizes each particle based on its physical and fluorescent characteristics.
Target Area	Peripheral whole blood specimens, lymphoid biopsies, and neoplastic tissues.
Regulation Medical Specialty	Hematology
Review Panel	Hematology
Product Code	OYE
Premarket Review	Division of Immunology and Hematology Devices (DIHD) Division of Immunology and Hematology Devices (DIHD)
Submission Type	510(k)
Regulation Number	864.5220
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

Third Party Review
- Eligible for *510(k) Third Party Review Program*

Accredited Persons
- Aabb
- Beanstock Ventures
- Center For Measurement Standards Of Industrial
- Global Quality And Regulatory Services
- Regulatory Technology Services, Llc
- Sgs North America

Figure 4. *Screenshot from the FDA's database showing the predicate device for flow cytometers ("Product Classification," screenshot taken 25.2.23)*

In figure 4, the regulation number is also able to be seen meaning that from CFR, part 864.5220 below title 21 is subject to this kind of device. This specific part of the CFR can be seen in figure 5 and it includes a more detailed identification and classification of the specified flow cytometric device. As the class II devices are subject to both general and special controls, in part b of the 21 CFR 864.5220 the document for the guidance of special controls is also stated. General and special controls subjected to flow cytometers will be discussed in the next chapter in more detail.



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[CITE: 21CFR864.5220]

See Related Information

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

PART 864 -- HEMATOLOGY AND PATHOLOGY DEVICES

Subpart F - Automated and Semi-Automated Hematology Devices

Sec. 864.5220 Automated differential cell counter.

(a) *Identification.* An automated differential cell counter is a device used to identify one or more of the formed elements of the blood. The device may also have the capability to flag, count, or classify immature or abnormal hematopoietic cells of the blood, bone marrow, or other body fluids. These devices may combine an electronic particle counting method, optical method, or a flow cytometric method utilizing monoclonal CD (cluster designation) markers. The device includes accessory CD markers.

(b) *Classification.* Class II (special controls). The special control for this device is the FDA document entitled "Class II Special Controls Guidance Document: Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells; Final Guidance for Industry and FDA."

[67 FR 1607, Jan. 14, 2002]

Figure 5. *Screenshot from part 864.5220 of the 21CFR for the identification and classification of hematology and pathology devices ("CFR - Code of Federal Regulations Title 21,", screenshot taken 25.2.23)*

Now it is very clear that flow cytometers have a predicate device, and they belong to medical devices class II which requires the 510(k) submission, meaning the device is applied to general and special regulatory controls. The manufacturer is required to provide adequate and satisfactory evidence in the 510(k) submission to demonstrate the safety and effectiveness of the device, along with the supporting evidence that serves as the basis for determining substantial equivalence with the predicate device. The equivalence information should include clear comparison systematically, for example doing side-by-side comparisons between the devices. This is often meaning data and information supporting a finding of substantial equivalence, including also all possibly harmful adverse information. In the case of differences, it should be shown that they do not adversely affect safety and effectiveness. (Health, 2023b)

To summarize, flow cytometers belong to class II medical devices, require 510(k) which is also called a pre-market notification, and are subject to general and special controls. The 510(k) submission has to include substantial evidence of the safety and effectiveness of the device, which is an essential part of the Current Good Manufacturing Practices (CMGPs) the manufacturer has to follow. The general controls and CGMPs, as well as the special controls applicable to flow cytometers, will be investigated in the following chapter.

5. ASSURANCE OF SAFETY AND EFFECTIVENESS

5.1 General controls subjected to flow cytometers

Flow cytometers are subject to general and special regulatory controls. General controls are the minimum requirements for the assurance of the safety and effectiveness of a medical device. (Health, 2019a) They are being applied to all medical devices except the ones that have been exempted by the regulations, often being class I devices. As stated in the Code of Federal Regulations, the general controls have been written down in the United States Code and more detailed definitions, laws, and rules are included in the following sections of the FD&C Act, listed in table 4 below. As can be seen from table 4, there are seven chapters in the U.S.C. where the general controls for medical devices are being determined.

Table 4. *General controls and the sections of the FD&C Act where they can be found. (21 CFR 860.3 "General controls")*

Title	**Section of FD&C Act**
Adulteration	501
Misbranding	502
Registration, listing, and premarket notification	510
Banned devices	516
Notification and other remedies	518
Records, reports, and unique device identification	519
General Provisions	520

The flow cytometer manufacturer should be able to demonstrate compliance with the general controls in the 510(k) submission. For example, a flow cytometer manufacturer could provide evidence of accuracy, precision, linearity, and sensitivity measured by performance testing. Several tests could include for instance measuring the detection limit of the flow cytometer by using known fluorescent markers at different concentrations. Also, numerous repetitions of measurements should be made to find out about the reproducibility of the measurements, and naturally, everything should be recorded and reported. As another example, the manufacturer could provide instructions for the maintenance and repair of the device including information on proper cleaning and disinfection of the device, as well as guidance on how to perform routine maintenance and repair procedures. All this could be done for example by providing quality system documentation where compliance with the relevant regulations can be seen. In practice, this would mean for example providing certain types of user manuals for the end users, in line with the regulation. As a last example, the flow cytometer manufacturer must follow the Unique Device Identification (UDI) System meaning a unique device identifier must be in place on all device labels and packages. The purpose of doing that is to adequately identify the flow cytometers starting from the manufacturing, through distribution until patient use. This must also be appropriately reported and submitted to the Global Unique Identification Database (GUDID). (Health, 2022e) To conclude, there are numerous amounts of actions the general controls determine for the flow cytometer manufacturer, just a few examples were mentioned above to give an idea about the general controls in action.

5.2 Good Manufacturing Practices

Good Manufacturing Practices (GMP) is a set of guidelines set for the assurance of medical devices to be manufactured and controlled consistently and meet the appropriate quality standards for their intended use. The intended use is determined by the product specification. ("Good Manufacturing Practices," n.d.) As mentioned above, manufacturers must establish and follow quality systems

(QS) to demonstrate compliance with the general controls in the 510(k) submission. The following of quality systems must continue after the notification as well so that they are continuously able to prove that the products meet the applicable requirements, controls, and specifications. The QS every manufacturer has in place is called Current Good Manufacturing Practice (CGMP). CGMP requirements are a part of the general controls, more specifically part of “general provisions” which have been prescribed under section 520(f) of the FD&C Act, which is codified in 21 U.S.C § 360j(f). The requirements are also implemented in part 820 of the CFR. (Health, 2022d)

The Quality System (QS) is a specific set of regulations that implement the CGMP requirements for medical devices, such as flow cytometers. The medical device manufacturer must establish and maintain the specific requirements of the QS. For the manufacturer to conform to the CGMPs, requires explaining the methods, facilities, and controls used for the manufacturing, packing, storage, and installation of the device according to the quality policy. (21 CFR 820.20(a))

Compliance with the QS/CGMP requirements is a critical part of ensuring the safety and effectiveness of flow cytometers and it is part of the general controls regulatory requirements, which must be in place for the manufacturer to obtain and maintain FDA approval for their products. In CFR, chapter I, subchapter H “medical devices”, part 820 “Quality system regulation”, subpart from A to O can be found. A screenshot of this part from CFR is in figure 5 and the titles from A to O can be seen. These are the parts of the quality system that should be in place and reported accordingly so the manufacturer can prove to follow the CGMPs required to be able to demonstrate compliance with the general controls in the 510(k) submission.

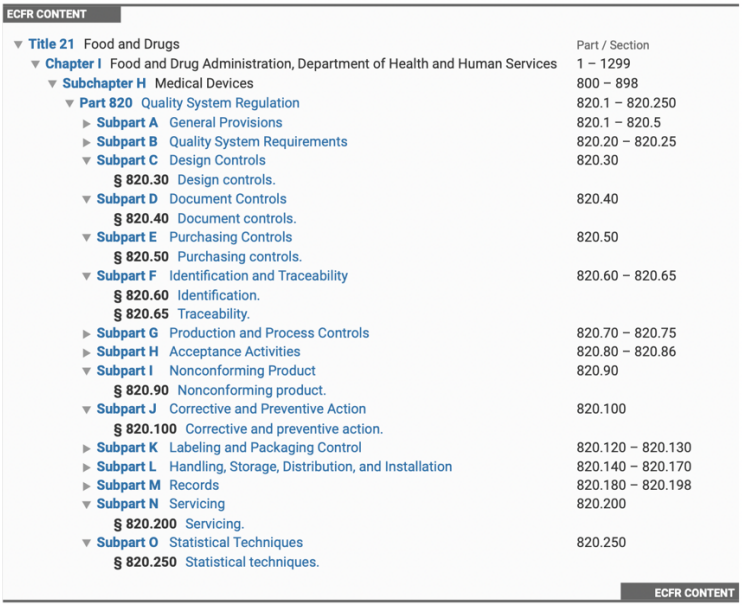

Figure 5. *21 CFR Part 820 with subparts (“21 CFR Part 820 -- Quality System Regulation,”, screenshot taken 22.3.2023)*

At the beginning of part 820 under Title 21 the scope of the CGMP is written down, which defines the applicability of the regulation, meaning the quality of the regulation being relevant or appropriate. Each medical device manufacturer should evaluate the applicability of the CGMP guidelines written in the 820 to their manufacturing, products, and services.

To summarize the main points of scope 21 CFR 820.1(a)(1), CGMP has been created to ensure that the finished medical devices intended for human use would be safe, effective, and in compliance with the FD&C Act. In case a manufacturer deals only in some operations subject to the regulations, they need to comply only with the requirements applicable to the operations in which they are engaged. For example, manufacturers of certain parts and components of the finished medical device should put to account the applicable requirements as well. (21 CFR 820.1(a)(1))

There is an enormous number of actions the CGMP requires the manufacturer to take into account. The main actions of CGMP ensuring the safety and effectiveness of the flow cytometer will be summed up next. The manufacturer must establish and follow written procedures for the design, manufacture, packaging, labeling, storage, installation, and servicing of the flow cytometer. For manufacturing, testing, and inspection, the manufacturer must maintain appropriate facilities, equipment, and controls. All this should be monitored throughout the manufacturing and designing process by conducting quality control testing and monitoring to ensure that the flow cytometer meets specified requirements for sure. In case any deviations or failures occur, they should be investigated and addressed immediately during the manufacturing process. Also, corrective, and preventive action (CAPA) procedures should be implemented to address any identified quality problems and for preventing their reoccurrence in the future. The manufacturer must also establish and maintain records and procedures for device manufacturing testing, inspection, and complaint handling. (21 CFR 820.1(a)(1))

The manufacturer of the flow cytometer must establish and maintain a quality system to demonstrate compliance with general controls in the 510(k) submission and follow the CGMP requirements outlined in title 21 CFR Part 820. In conclusion, to conform to CGMPs, a flow cytometer manufacturer must explain the methods, facilities, and controls used in the manufacturing, packaging, storage, and installation of the device. Compliance with CGMP is critical to ensuring the safety and effectiveness of flow cytometers, which are used to analyze and sort cells. The CGMP regulations require the manufacturers to establish and follow written procedures including appropriate facilities, equipment, and controls for the design, manufacturing, packaging, labeling, storage, installation, and servicing of the device. CAPA procedures should be implemented to address any identified quality problems and prevent their recurrence in the future. The CGMP requirements

ensure that the finished flow cytometers are safe, effective, and in compliance with the FD&C Act. This helps to minimize risk and improve patient outcomes.

5.3 Special controls subjected to flow cytometers

Special controls are regulatory controls required when the general controls alone are not sufficient enough to provide a reasonable guarantee of the assurance of safety and effectiveness of the medical device. They are required to be taken into action when a possibility of establishing information utilizing special controls exists. (21 CFR 860.3 “Class II”) This concerns class II devices as discussed in chapter 3.1. In more detail, the manufacturer of class II devices must first conform to the general controls. Besides that, the manufacturer must moderate the specific health risks identified by either complying with the guidelines or applying alternative measures that provide equivalent assurance of safety and effectiveness. One of the actions of special controls also requires the manufacturer to obtain a verification of similarity with the predicate device from the FDA before marketing the device. (Health, 2022a)

The special controls are device-specific, meaning they are unique to a particular device. (Health, 2019c) From figure 5, it can be seen, that the special controls for flow cytometers can be found in the FDA document entitled “Class II Special Controls Guidance Document: Premarket Notifications for Automated Differential Cell Counters for Immature or Abnormal Blood Cells; Final Guidance for Industry and FDA.” The document gives guidance on what kind of aspects must be taken into consideration in the special controls of flow cytometers. It includes abbreviated 510(k) content, software validation activities, accuracy, precision, performance, linearity, carryover, specimens, reference values, and labeling. It can be seen the list includes several same aspects that are required in general controls. However, the special controls document provides more detailed information on how to address the specific aspects associated with the flow cytometer in order to avoid possible risks and this way assure the safety and effectiveness, which would not be assured with only general controls. (Health, 2021)

To give a couple of more specific examples, the document includes detailed information on how to validate the software of the flow cytometer. FDA even offers a supplemental data sheet that indicates further documentation of what the manufacturer should include in the submission when submitting the declaration of conformity. The special controls guidance document also states the flow cytometer manufacturer should follow certain National Committee for Clinical Laboratory Standards (NCCLS) documents in order to measure and provide evidence of the accuracy, precision, and performance of the device. In summary, the special controls of medical devices include a more specific set of guidelines that must be followed to provide reasonable assurance of the safety and

effectiveness of the device. They are device specific and therefore determined for each predicate device individually. The special controls of flow cytometers can be found in a document assigned to that product class, at the FDA's official page. (Health, 2021)

6. CONCLUSIONS

The aim of this thesis was to investigate what are the applied regulatory controls for a medical device to enter the United States markets. A flow cytometer was used as a case example. Flow cytometry is a powerful analytical technique that is used in various fields such as medicine, biology, and research. (Sklar, 2005) Together with other medical devices, it plays a crucial role in the diagnosis, treatment, and monitoring of various diseases. The safety and effectiveness of these devices are critical in ensuring patient safety and achieving successful outcomes.

In the United States, Food and Drug Administration (FDA) is responsible for regulating medical devices and therefore ensuring the safety and effectiveness of the products. The regulations are based on the federal laws outlined in the FD&C Act in the United States Code (U.S.C). (Commissioner, 2021a) Based on the FD&C Act, a more specified set of regulations can be found in a separate Code of Federal Regulations (CFR).

The classification of medical devices was covered as it will determine the following actions and applicable regulatory controls. It was found out the flow cytometer is a class II medical device and therefore subject to general and special controls. A predicate device for flow cytometer exists as well. Therefore, for the manufacturer to be allowed to market the product legally, a 510(k) clearance must be made. In the clearance, the manufacturer must provide evidence for the substantial equivalence to the predicate device. Also, compliance with general and special controls must be presented as it is a class II device.

The general controls are the most basic level provisions that provide assurance of the safety and effectiveness of the device, and they apply to all medical device classes. (Health, 2019b) One important part of general controls is the Current Good Manufacturing Practices (CGMPs), referring to a quality system (QS) that manufacturers should implement and follow. The CGMPs together with the QS ensure that the medical devices are manufactured controlled and in a consistent manner, to meet the required quality standards for their intended use and this way demonstrate com-

pliance with the general controls. (Health, 2022d) Special controls are required when general controls alone are not providing enough guarantee of assurance of the safety and effectiveness of the medical device. (21 CFR 860.3 “Class II”) They are device-specific controls, found within the information of predicate devices and need to be reported in the 510(k) clearance together with the general controls. (Health, 2019c)

The regulation of medical devices is a quite challenging process and difficulties were noticed as well. One of the issues is, that FDA is encouraging the use of international consensus standards. However, FDA regulations are not fully harmonized with International Organization for Standardization (ISO) standards. Could be speculated, that it would be easier for manufacturers if all standards were fully harmonized across different countries and regulatory bodies. Even though this study was focusing on the regulation in the United States, it should be taken into account that some manufacturer might market their product in several different countries, and it would benefit everyone if the regulations would be made simpler in this aspect. Luckily, the FDA seeks to harmonize the Quality Management System (QMS) requirements in the close future with the internationally recognized ISO13485 quality management system which is used by several different regulatory authorities. This will then make an impact on the CGMPs of flow cytometers as well since QMS is an essential part of the CGMPs. (Health, 2022d)

In conclusion, the regulatory controls for the United States market entry were investigated using a flow cytometer as a case example. Since flow cytometers are class II medical devices, they are subject to general and special controls which must be reported in the 510(k) clearance in order to enter the U.S. markets. By embracing these controls highlighted in this thesis, manufacturers can ensure that their flow cytometers are of the highest quality and that they meet the needs of patients, clinicians, and researchers around the world.

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