

Spring 2022

The Submission of a Section 513(g) Request For Information

Morgan Ashley Lano

Follow this and additional works at: <https://scholarcommons.sc.edu/etd>



Part of the [Biomedical Engineering and Bioengineering Commons](#)

Recommended Citation

Lano, M. A. (2022). *The Submission of a Section 513(g) Request For Information*. (Master's thesis). Retrieved from <https://scholarcommons.sc.edu/etd/6743>

This Open Access Thesis is brought to you by Scholar Commons. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of Scholar Commons. For more information, please contact digres@mailbox.sc.edu.

THE SUBMISSION OF A SECTION 513(G) REQUEST FOR
INFORMATION

by

Morgan Ashley Lano

Bachelor of Science
University of South Carolina, 2019

Submitted in Partial Fulfillment of the Requirements

For the Degree of Master of Science in

Biomedical Science

School of Medicine

University of South Carolina

2022

Accepted by:

Francis G. Spinale, Director of Thesis

Robert Price, Reader

Jay Potts, Reader

Tracey L. Weldon, Interim Vice Provost and Dean of the Graduate School

© Copyright by Morgan Ashley Lano, 2022
All Rights Reserved.

ACKNOWLEDGEMENTS

I would like to acknowledge and express my gratitude to my advisor Dr. Francis Spinale for providing me with the opportunity to work on this project and for his continuous guidance. I would also like to acknowledge my readers, Dr. Robert Price and Dr. Jay Potts for their instruction inside and outside of the classroom. They have assisted me the entirety of my graduate school experience. I acknowledge the assistance I have received from Joann Nagy for her role as of Student Services Program Coordinator and Edie Goldsmith, the director of the Biomedical Sciences Graduate program. assistance she has provided me with. I also give my thanks to the Instrument Resource Facility and the staff that has given me outstanding advice. I would like to acknowledge Angela Hitch and Lisa Freeburg for their endless support and encouragement during the progression of this project.

ABSTRACT

The U.S. Food and Drug Administration holds authority over the regulation of medical devices. To assure the safety of the public, medical devices are designated into classes according to their risk of danger and intended use. The device must meet the criteria of the assigned premarket submission to be legally marketed in the United States. Section 513(g) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360c(g)) is a request for information concerning the classification and regulation of a device. There is an empty spot in the market for continuous monitoring of coagulation status. The Coagulation Companion by MicroVide is a device designed to fluorescently quantify a key enzyme involved in the coagulation cascade, plasmin, as a means of monitoring clot formation and degradation in pediatric patients undergoing congenital heart surgery. Through the submission of a 513(g) Request for Information, non-binding information on the device's generic device type, Class, pre-market submission, and product code would apply to the Coagulation Companion.

TABLE OF CONTENTS

Acknowledgements.....	iii
Abstract.....	iv
List of Figures.....	vii
List of Abbreviations	viii
Chapter 1: Introduction.....	1
1.1 FDA and Devices.....	1
1.2 Formation of a Blood Clot.....	2
1.3 The MicroVide Coagulation Companion.....	2
Chapter 2: The U.S. Food and Drug Administration.....	4
2.1 The Pure Food and Drug Act.....	4
2.2 The Federal Food, Drug and Cosmetic Act	4
Chapter 3: Medical Devices Under the FDA.....	6
3.1 Classes of Devices	6
3.2 Regulatory Controls.....	7
3.3 Medical Device Safety.....	11
Chapter 4: Section 513(g) Request for Information	13
4.1 The 513(g) Submission.....	13
4.2 The Agency’s Response.....	15
Chapter 5: The Coagulation Companion	17
5.1 The Coagulation Cascade and Plasmin.....	17

5.2 The Unmet Need	19
5.3 Section 513(g) Request Submission	20
Chapter 6: Conclusion.....	35
References.....	36

LIST OF FIGURES

Figure 3.1 The Pathways for a Medical Device to Enter the Market	10
Figure 5.1 The Coagulation Cascade	18
Figure 5.2 The Coagulation Companion as Assembled.....	23
Figure 5.4 A Kit of Disposable Items	24
Figure 5.5 The Syringe Pump with a 2.5 mL Syringe	25
Figure 5.6 An Internal View of the Coagulation Companion.....	27
Figure 5.7 A Labelled Microdialysis Catheter.....	28
Figure 5.8 The PMT Detection System	29

LIST OF ABBREVIATIONS

CDRH	Center for Devices and Radiological Health
C.F.R.....	Code of Federal Regulations
FD&C.....	Food, Drug and Cosmetic Act
FDA.....	Food and Drug Administration
ID	Inner Diameter
LED.....	Light-Emitting Diode
MDR	Medical Device Reporting
OD.....	Outer Diameter
PEEK.....	Polyetheretherketone
PMA.....	Premarket Approval
PMN.....	Premarket Notification
PMT	Photomultiplier Tube
SE.....	Substantially Equivalent
U.S.C.....	United States Code

CHAPTER 1

INTRODUCTION

1.1 FDA and Devices

In 1938, the United States Congress passed the FD&C Act to provide the government with authority over the safety and efficacy of food, drugs, and cosmetic items. Enforcing product standards and regulatory requirements deterred mislabeled, dangerous, and ineffective products from entering the market in 1976. The FDA's control was expanded to include the regulation of medical devices. The Center for Devices and Radiological Health (CDRH) is responsible for assessing the safety and effectiveness of a medical device prior to it entering the market and for continuing to monitor the device as it is marketed. Devices are sorted into one of three classes determined by their potential risk to the user and the depth of regulation required to determine that the product is both safe and effective.

Section 513(g) of the FD&C Act governs requests “for information respecting the Class in which a device has been classified or the requirements applicable to a device under [the] Act.” (Food, Drug and Cosmetic Act, 1938). For a product to be considered a “device”, it must meet the requirements as described in section 201(h) of the FD&C Act (21 U.S.C. 321(h)). Based solely upon the information the requestor provides, the FDA will respond with their non-binding advisement on the device's possible classification,

the type of premarket submission required to market the device, and other requirements which may be applicable.

Often times, medical device manufacturers submit a 513(g) request to establish the regulations that will precede the device's approval for marketing. Low risk device classes are subject to fewer controls which allows for a quick approval process. The 513(g) request serves as a tool to predict the regulations relevant to the device so that the manufacturer has the option of altering the device before proceeding to a premarket submission.

1.2 Formation of a Blood Clot

The coagulation cascade is the process by which a blood clot is formed once a blood vessel is damaged. There are two pathways with both leading to the production of fibrin which, forms the blood clot. Plasmin is an enzyme involved in the degradation of fibrin. Once the need for clotting ceases, plasminogen is cleaved into its active form, plasmin, to destroy fibrin (Medcaf & Keragala, 2021). Fibrinolysis is tightly regulated, so high levels of plasmin reflect the need to restore normal blood flow (Napolitano & Montuori, 2021). Monitoring the presence of active plasmin indicates the need to form or degrade fibrin, indicating coagulation status.

1.3 The MicroVide Coagulation Companion

The Coagulation Companion is a device by MicroVide. The device functions continuously by injecting the device's plasmin substrate into the subcutaneous space of the patient's shoulder through a microdialysis catheter. The substrate is cleaved by active plasmin which causes the substrate to fluoresce. The substrate flows back through the

microdialysis needle and to the detector where the fluorescence is quantified. The device provides continuous monitoring for the best estimates of the blood's ability to form clots.

This 513(g) is being submitted for the Coagulation Companion in order to get the FDA's current views on the classification of the device and the regulatory requirements in place for such a device. With the FDA's regulatory guidance, the correct premarket requirements can be met, and the submission can be filed to earn the Coagulation Companion the ability to enter the market as a medical device legally marketed in the United States.

CHAPTER 2

THE U.S. FOOD AND DRUG ADMINISTRATION

2.1 The Pure Food and Drug Act

Though the federal government has been involved in the safety of agricultural products since 1848, it was not until the 1906 Pure Food and Drugs Act that they engaged in regulation of food and drugs (History, Art & Archives). The Act was constructed following a wave of journalists revealing the shocking conditions in which foods were being prepared for human consumption (FDA, 2019). The public outrage in response to Upton Sinclair's 1906 novel, *The Jungle*, an exposé of the foul conditions of the meat-packing industry, drove the U.S. Congress to propose legislation to counteract the unsanitary food processing conditions (Fortin, 2016). The U.S. House of Representatives passed the Act on June 29th of 1906, with 240 representatives voting in favor and 17 voting against (FDA, 2019). President Theodore Roosevelt signed the Act into law the following day. "For preventing the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein, and for other purposes," (Federal Food and Drugs Act, 1906). The central focus of this law concerned the regulation of consumer-obtainable products rather than the regulation of those which were upcoming and yet to reach the market (Fortin, 2016). The Act eliminated many dangerous products from the market but was not without a loophole (The Food and Drug Administration: The Continued History of Drug Advertising, n.d.). In the 1911 *United States v. Johnson* Supreme Court case, it was ruled

that the term “misbranded” only referred to false statements of identity and did not cover statements as to curative effect (Holmes, 1911). Legal proceedings could only take place if it was evident that the manufacturer’s intent was to defraud the customers, which made it difficult to stop the sales of dangerous products.

2.2 The Federal Food, Drug and Cosmetic Act

In 1933, the Chief Education Officer, Ruth Lamb, and Chief Inspector, George Larrick, of the FDA called attention to the insufficient regulation with an exhibit demonstrating 100 harmful or dishonest products which did not fall within jurisdiction of the FDA (FDA, 2018). The public found the exhibit so disturbing that it was labelled the “American Chamber of Horrors” (FDA, 2018). President Franklin Roosevelt signed the Federal Food, Drug, and Cosmetic Act (FD&C Act) in 1938, solving many shortcomings of the 1906 Act (FDA, 2018). The 1938 Federal Food, Drug, and Cosmetic Act served to fortify the FDA’s authority over product regulation. The FDA’s authority over foods and drugs was expanded to include cosmetics and medical devices. (Office of the Commissioner, 2018) For the first time, product regulations were placed prior to production decreasing the likelihood of mislabeled or dangerous products reaching the market. The manufacturers faced the threat of criminal charges should they fail to comply to the new standards. (Part II: 1938, Food, Drug, Cosmetic Act, 2018) In 1976, the FD&C Act was amended to introduce regulatory measures for medical devices to assure safety and effectiveness of the products.

CHAPTER 3

MEDICAL DEVICES UNDER THE FDA

3.1 Classes of Devices

Once a product is confirmed to meet the definition of device as described in Section 201(h), the CDRH categorizes it into one of the three device classes. The device classes are based on the extent of risk the device poses to the device user and the regulation requirements to determine the product safe for marketing. In December of 2021, the CDRH reported that Class I contained 35% of medical devices, Class II contained 53%, and Class III contained 9%. The remaining 3% were considered Unclassified.

3.1.1 Class I

Class I consists of devices which pose minimal risk of harm. In this category, there are devices such as manual stethoscopes and adhesive bandages. Generally, these devices are simple in design. They are for external use and do not directly impact the health of the user. Only general regulatory controls are relevant to these devices.

3.1.2 Class II

Devices with moderate risk are sorted into Class II. The devices present greater potential danger than Class I, but less than that of Class III. A large focus of this Class is

on monitoring systems such as apnea monitors and insulin. General regulatory controls and, if available, special regulatory controls apply to Class II devices.

3.1.3 Class III

The highest risk devices are grouped into Class III. These are devices that are purposed to support life, implanted into the body, or have severe risk of injury. Devices such as heart valves and cardiac pacemakers are considered in Class III. Devices within Class III must comply with general regulatory controls and have premarket approval, though occasionally a premarket notification will be accepted in its place.

3.2 Regulatory Controls

3.2.1 Premarket Notification Exempt

Devices within Classes I or II may be exempt from the premarket notification process. Section 510(k) of the FD&C Act states that the 510(k) exemption of a device is limited to “the extent that the device has existing or reasonably foreseeable characteristics of commercially distributed devices within that generic type”. A device must have the same intended use and the same technological features of the generic device type to be considered exempt. The devices themselves have very low risk of harm “to the extent that misdiagnosis as a result of using the device would not be associated with high morbidity or mortality,”. The FDA reported that 93% of Class I devices were with exemptions in 2021. General controls such as good manufacturing practices, establishment registration, and device listing, apply to all devices, including those considered exempt from the premarket notification process.

Postamendment device are those which entered the market after the 1976 Amendments to the FD&C Act. Due to the rapid advancement of technology, most developing devices claim substantial equivalence to the ones approved after the amendment. Preamendment devices are those that entered commercial distribution prior to May 28th of 1976 and have the same intended use. The Code of Federal Regulations requires the device to not have been “significantly changed or modified” since that date and to not have a PMA application published by the FDA. These devices are exempt from the premarket notification process.

3.2.2 Premarket Notification

A premarket notification, more frequently referred to as a 510(k), seeks FDA clearance of a medical device. It is the most common type of submission to demonstrate product safety and effectiveness. 510(k) submissions frequently do not require clinical data to support the device’s clearance. The majority of Class II devices and an occasional Class I or Class III device are required to complete this type of submission.

The product must be compared to at least one device legally marketed in the United States to claim substantial equivalence as described in Section 513(i)(1)(A) of the FD&C Act. The FDA identifies a legally marketed medical device as eligible to claim substantial equivalence as “a device that was legally marketed prior to May 28, 1976 (preamendments device), or a device which has been reclassified from Class III to Class II or I, a device which has been found SE through the 510(k) process, or a device that was granted marketing authorization via the De Novo classification process under section

513(f)(2) of the FD&C Act that is not exempt from premarket notification requirements”. These devices are termed “predicates”.

The definition of a valid substantially equivalent medical device, which may be considered a predicate, is outlined in The Medical Device Amendments of 1976, 21 U.S.C. § 360c(i)(1) which states that if “the device has the same intended use as the predicate device and ... has the same technological characteristics as the predicate device” or “has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed necessary”. The supplementary proof of equivalency is essential in establishing lack of deviation from the safety and effectiveness already shown by the legally marketed device.

3.2.3 Premarket Approval

Premarket Approval, or PMA, is for devices where general controls and premarket notifications were proven insufficient in proving safety and effectiveness. All Class III devices require a PMA to gain FDA approval. As Class III is comprised of the devices with the highest potential danger, the device’s review is significantly more intense than the 510(k). Clinical data is required for this submission, usually involving human clinical trials. Figure 3.1 presents the basic routes for device entry to the market.

3.2.4 De Novo

The De Novo classification is an alternative pathway for novel devices. The Code of Federal Regulations identifies this route as a way to “establish an efficient, transparent, and thorough process to facilitate De Novo classification into Class I or Class II devices

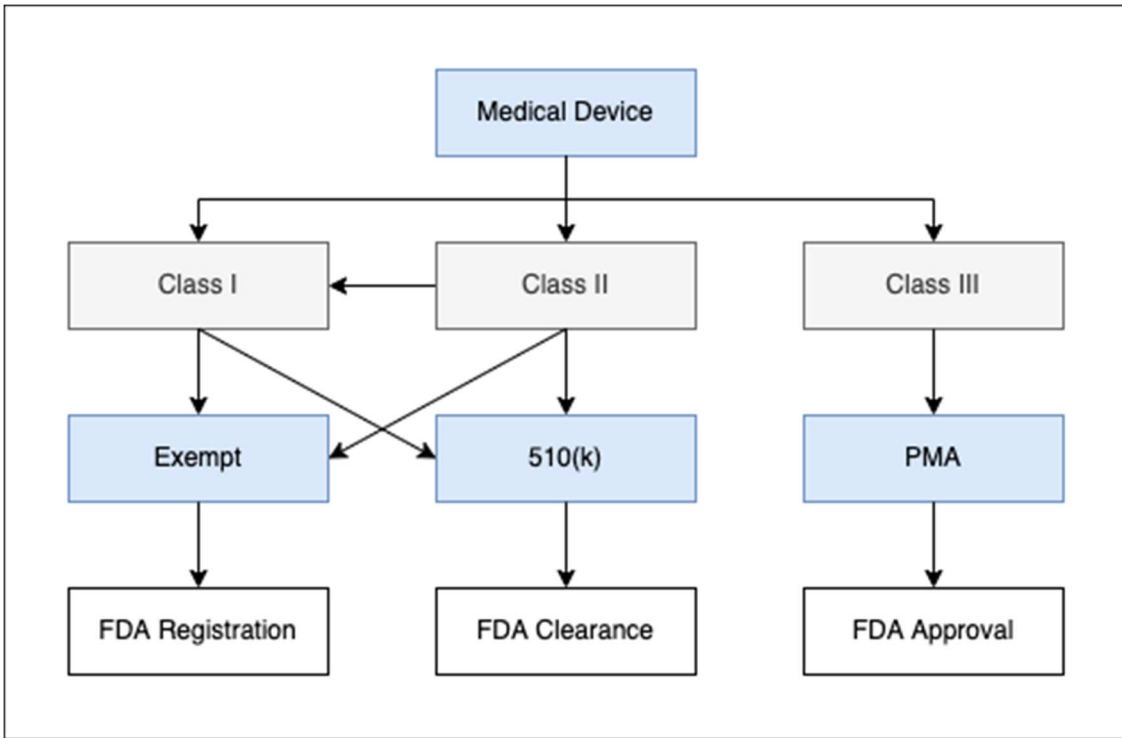


Figure 3.1 The Pathways for a Medical Device to Enter the Market.

for which there is no legally marketed device on which to base a review of substantial equivalence, and which meet the definition of Class I or Class II”. Though De Novo devices are of low to moderate risk, Class III is the only classification allowed as the FDA has not regulated anything similar enough to be considered substantially equivalent, no matter the level of safety.

3.3 Device Safety

3.3.1 Postmarket Surveillance

Postmarket surveillance may be required to determine the long-term side effects of a marketed medical device under Section 552 of the FD&C Act. A postmarket surveillance plan outlines the methods a manufacturer intends to use for the ongoing observation of marketed devices as described in 21 C.F.R. § 882.10. According to 21 U.S.C. § 360(l), Class II or III devices may be ordered to provide postmarket surveillance if: the device’s failure would significantly impact the user’s health, is significantly used by pediatric patients, is intended to be implanted in the human body for over a year, or is intended to be a life-sustaining or life-supporting device used outside a device user facility. The type of surveillance design is chosen to fit the device’s area of concern and must be agreed upon by the manufacturer and the FDA. Under the FD&C Act, the FDA may keep a device under postmarket surveillance for no longer than 36 months unless agreed upon by the manufacturer.

3.3.2 Medical Device Reporting Program

To ensure that a legally marketed device continues to meet the FDA’s standards of safety and effectiveness, the Medical Device Report (MDR) Program was formed. The

submission of reports by manufacturers, device user facilities, and importers is mandatory when a device suspected to have contributed to user injury is identified as stated in The Medical Device Reporting regulation. Though not mandatory, it is encouraged that healthcare professionals and consumers submit voluntary reports if they notice signs of a device potentially causing harm. These reports serve as records for the number of adverse events surrounding a particular device. A device with a large number of reports is more likely to be directly related to injury compared to a device with few reports.

3.3.3 Recalls

Recalls are used to remove or correct consumer products that do not meet the standards set by the FDA. A recall, as defined by 21 C.F.R. § 7, is “a voluntary action that takes place because manufacturers and distributors carry out their responsibility to protect the public health and well-being from products that present a risk of injury or gross deception or are otherwise defective”. The FDA offers guidance on policies and procedures concerning recalls to assist manufacturers. If a manufacturer fails to voluntarily conduct a recall, the FDA may exercise their right to issue a recall under 21 C.F.R. § 810 Medical Device Recall Authority. For manufacturers to proceed with the removal or correction of a medical device, the FDA must determine the product to not meet their standards. A report on medical device recalls is prepared weekly by the FDA and is available to the public.

CHAPTER 4

SECTION 513(G) REQUEST FOR INFORMATION

4.1 The 513(g) Submission

4.1.1 Scope of Information

The 513(g) is submitted when a manufacturer is interested in determining the device status and the regulations that would be placed upon a product. The information provided in the response allows the manufacturer to determine if they should move forward with the premarket submission, modify the device to achieve the preferred designation, or to discard the product if it is not a device. If there is no obvious classification code to fit the product, predicting the device Class is difficult. The 513(g) submission would be the most successful way to predict the device Class without knowing the code.

Section 513(g) only manages information concerning the classification and regulation of medical devices. The agency does review information concerning substantial equivalence to existing devices or any proof of safety and effectiveness. Substantial equivalence, safety, and effectiveness of a product are not considered within the request. Appropriate testing, whether it be clinical, nonclinical, or animal, will not be discussed.

All information provided is non-binding and to be used as suggestions. Information regarding performance data and requests for medical device reclassification

are not handled in this submission. The FDA reader is restricted in product information and must base their assessment on only the information provided in the submission.

4.1.3 Content within the Submission

The 513(g) Request is the formal approach for obtaining information about the classification and regulation of a medical device. The FDA's reader relies solely on the information provided within the submission to form their opinion on the product. A descriptive mechanism of action and a highly detailed device description clarifies the agent's overall understanding of the device.

The information required to meet the 513(g) Request requirements are separated into four sections: a cover letter, the device description, the device's intended use, and any proposed labeling materials. The FDA offers a guidance document for industry and staff titled "FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug and Cosmetic Act" containing the procedures surrounding the Submission of a 513(g) Request for Information. The required contents are described as follows:

Your cover letter should include: the date of the request, the name of the device, any specific question(s) concerning the Class in which a device has been classified and/or the regulatory requirements applicable to a device, the requestor's name, address, telephone number, fax number, and email address, and the 513(g) requestor's signature.

As applicable, the description of the device should include: a list of materials and components used in/with the device, photographs, engineering drawings, and/or samples of the device, a summary of the device's operational principles, a description of the type

and amount of energy to be used or delivered by the device, and a description of similar devices in commercial distribution in the United States, if available.

Device Uses include the following information: the disease or condition with respect to how the device is to be used, prescription versus over-the-counter use, part of the body or type of tissue applied to or interacted with, frequency of use, physiological purpose, patient population; and any other labeling information related to the patient use of the device.

Ifeanyi Uwemedimo, a device determination policy analyst within the Office of Regulatory Programs, recommends that the device description is kept clear and brief. The information should be focused on providing an explanation as to how the device accomplishes its intended use. The addition of pictures and schematics may assist in conveying the device's mechanisms to the FDA reader. Labelling claims are those made beyond the intended function of the device and can help in determining the medical device's risk and if performance data must be included to support the claim.

One electronic copy of the submission or one paper copy is sent to the Centers for Devices and Radiological Health. There is a user fee of \$5,061 required before the agency begins to review the 513(g) submission. The price is reduced to \$2,530 for "Small Businesses" whose gross annual sales are under \$100 million for the most recent tax year.

4.2 The Agency's Response

513(g) submissions are confidential and will not be reported by the FDA. None of the information provided in the request is an official decision and is only to be considered advice. To determine a new device's Class, the FDA reviewer will consult the relevant databases containing product codes, 510(k)s, and De Novo submissions to seek similar

devices which have been regulated by the FDA. The technology and intended use described within the submission will be referred to when considering regulations and seeking precedents set by approved medical devices. In some cases, the lead reviewer may consult an internal subject matter expert to better comprehend the product. A product involved in many disciplines may require an extended period of time as more research must be completed to form an adequate response. Typically, responses to the 513(g) submission are typically provided within 60 days of receipt. The Agency's response will take the form of a formal letter and will only be sent once an agreement is reached between reviewers concerning the contents of the response.

If the product is considered to be a device as defined in section 210(h) of the FD&C Act, it will be noted in the response. The device being either a preamendment or postamendment device type will be address. The response will identify a classification code and classify the device in either: Class I or II subject to the 510(k) requirement; Class I or II exempt from the 510(k) requirement; or Class III subject to the 510(k) or PMA requirements. Directions towards the appropriate premarket guidance document will be provided. Additional information on extra requirements, such as the regulation of radiation-emitting devices, will be discussed.

Alternatively, the product may be determined to not be a device or that it is a combination product. If the product is not a device, it will be noted in the response. If it is seen as a product regulated by the FDA, the response will direct the submitter to the correct department. A combination device is one which could fall under the jurisdiction of multiple Centers. For this determination, directions will be given for contacting the Office of Combination Products.

CHAPTER 5

THE COAGULATION COMPANION

5.1 The Coagulation Cascade and Plasmin

The National Institutes of Health defines a blood clot as “A mass of blood that forms when blood platelets, proteins, and cells stick together.” Coagulation is the process by which a blood clot is formed. As the pathway features downstream activation, the term “cascade” has been applied. The factors involved in coagulation are proteins which exhibit enzymatic activity once activated. Thirteen factors are involved in the cascade: factor I (fibrinogen), factor II (prothrombin), factor III (tissue factor), factor IV (ionized calcium), factor V (proaccelerin), factor VI (unassigned), factor VII (proconvertin), factor VIII (antihemophilic factor), factor IX (plasma thromboplastin component), factor X (Stuart-Prower factor), factor XI (plasma thromboplastin antecedent), factor XII (Hageman factor), and factor XIII (fibrin-stabilizing factor) (Chaudhry et al., 2021). The pathways flow with a domino effect with each factor activating the next. The intrinsic and extrinsic pathways merge into the common pathway with factor X, the only factor shared by the pathways as seen in figure 5.1.

The intrinsic pathway utilizes factors I, II, IX, X, XI, and XII. Exposure to negatively charged artificial surfaces, such as glass, fibers, and some plastics, activate factor XII to trigger the intrinsic pathway. The pathway begins with the activated factor XII activating factor XI. The active form of factor XI, along with calcium ions, activates factor IX. Active factor IX congregates with factor VII on membrane surfaces, stabilized

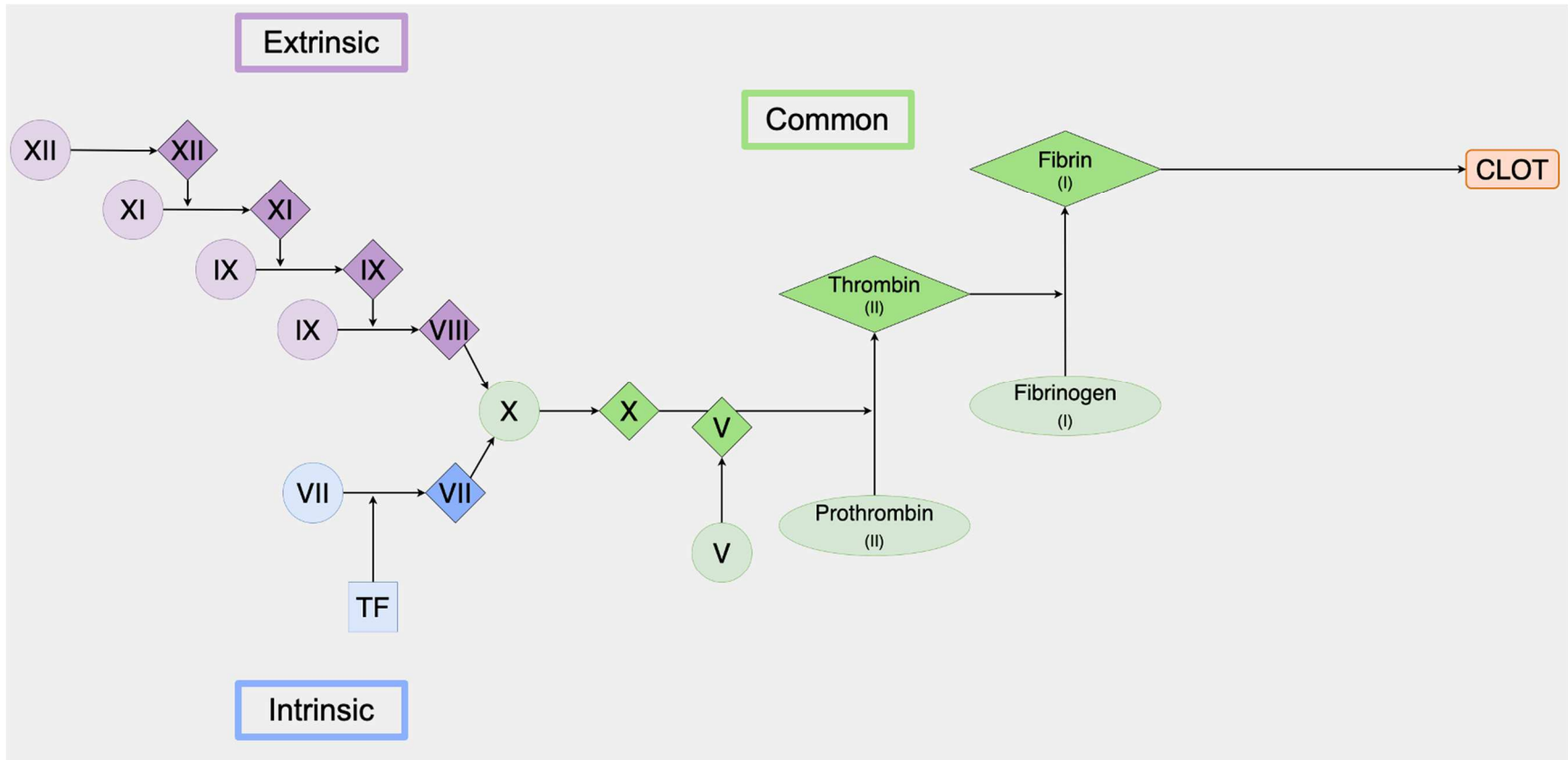


Figure 5.1 The Coagulation Cascade. The processes of forming a blood clot through the extrinsic and intrinsic pathways.

by calcium ions. The complex binds to and activates factor X and enters the common pathway. The extrinsic pathway utilizes factors I, II, IV, and X. It is triggered by the contact of factor VII with a membrane protein called tissue factor that is released by when the cells that line the blood vessels undergo damage. Active factor VII activates factor X and the common pathway is entered.

The common pathway utilizes Factors I, II, V, VII, and X. The pathway begins with the activation of factor X either intrinsically with factor VII and active factor IX or extrinsically with factor VII, tissue factor, and calcium. Active factor X along with factor V cleave prothrombin into thrombin. The thrombin activates factors XI, V, VIII, and XIII as well as cleaving fibrinogen into fibrin. The fibrin congregates into fibers and is stabilized by factor XII to form netting. The buildup of this structure eventually forms a thrombus (clot).

The major negative regulation fibrinolytic mechanism of the coagulation cascade is through the enzyme plasmin (McGilvray, 2001). Plasminogen is cleaved to its active form, plasmin, by tissue-type plasminogen activator or urokinase plasminogen activator (Baker, 2020). Once there is no longer a need for clotting, Plasmin is active in fibrin degradation. Plasmin levels increase as a response to excessive blood clotting which may be used to indicate coagulation status.

5.2 The Unmet Need

Anticoagulants are medications used to restrict the blood's ability to form clots. They are commonly prescribed to prevent post-operative blood clots from forming. If an inappropriate quantity of anticoagulant is introduced, potentially fatal bleeding may occur

preoperatively, hemoglobin or complete blood counts, screening tests for bleeding disorders, and testing for patients receiving anticoagulants may be used to predict the risk of bleeding but are not infallible. In a 2019 study, 215 patients undergoing elective cardiac surgery were studied and found that post-operative bleeding complications were observed in 26.5% of the cases (Klinge et al., 2019). Hemostasis management is specifically difficult in pediatric patients as procoagulation factors and anticoagulation factors differ in levels, characteristics, and interactions from those in adults (Achey et al., 2020). The lower quantity of blood in babies and young children due to small size contributes to the severe nature of any blood loss.

The medical device market lacks a device which is capable of continuous monitoring of blood coagulation. Current options for coagulation monitoring are static and slow. Successful monitoring of factors indicating coagulation status can lead to a lower volume of blood lost post-operatively and a lower mortality rate.

5.3 The Section 513(g) Request Submission

5.3.1 Cover Letter

Along with the submitter's contact information on the cover letter of the 513(g), specific questions were listed as follows:

1. Would this device be considered a combination device due to the plasmin substrate?
2. What classification regulation applies to this device?
3. What Class of device within the generic device type applies to this device?

4. Is there a required pre-market submission required prior to marketing for this device?
5. Are there other FDA requirements which apply to this device type?
6. What product code is assigned to the Coagulation Companion?

5.3.2 Device Description

The Coagulation Companion (figure 5.1) is a continuous flow and detection system that monitors the enzymatic activity of plasmin, a key indicator of coagulation state. It is intended to help prevent post-operative blood loss in pediatric patients undergoing cardiac surgery for congenital heart repairs. The Coagulation Companion is a composite device containing:

- Syringe Pump
- Flow Through Optical Cell
- PMT Detection System
- Integrated Touchscreen

Additional components are sterile and disposable items that include:

- Syringe (2.5 mL)
- Plasmin substrate (6 μ M)
- Polyetheretherketone (PEEK) tubing (0.65 mm OD x 0.12 mm ID, 1 meter)
- Microdialysis catheter (4 mm membrane length, 0.5 mm membrane diameter)

Figure 5.3 demonstrates the path in which the components are assembled. The dotted box indicates the components contained within the device while the other components are disposable. Figure 5.4 shows a kit representing the disposable items.



Figure 5.2 External View. The front of the Coagulation Companion has the openings “IN” for substrates entering the detection system and “OUT” for the waste.

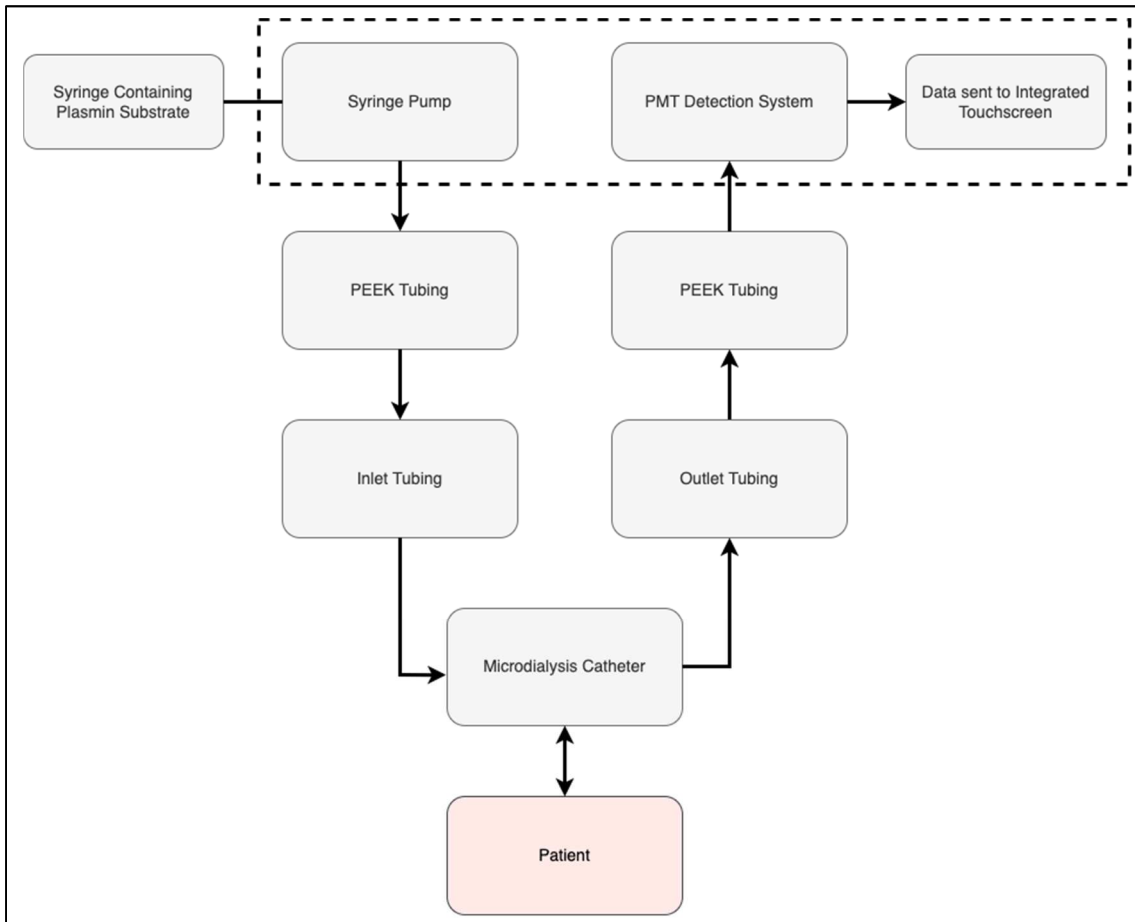


Figure 5.3 The Coagulation Companion as Assembled. The device components are indicated by the box.

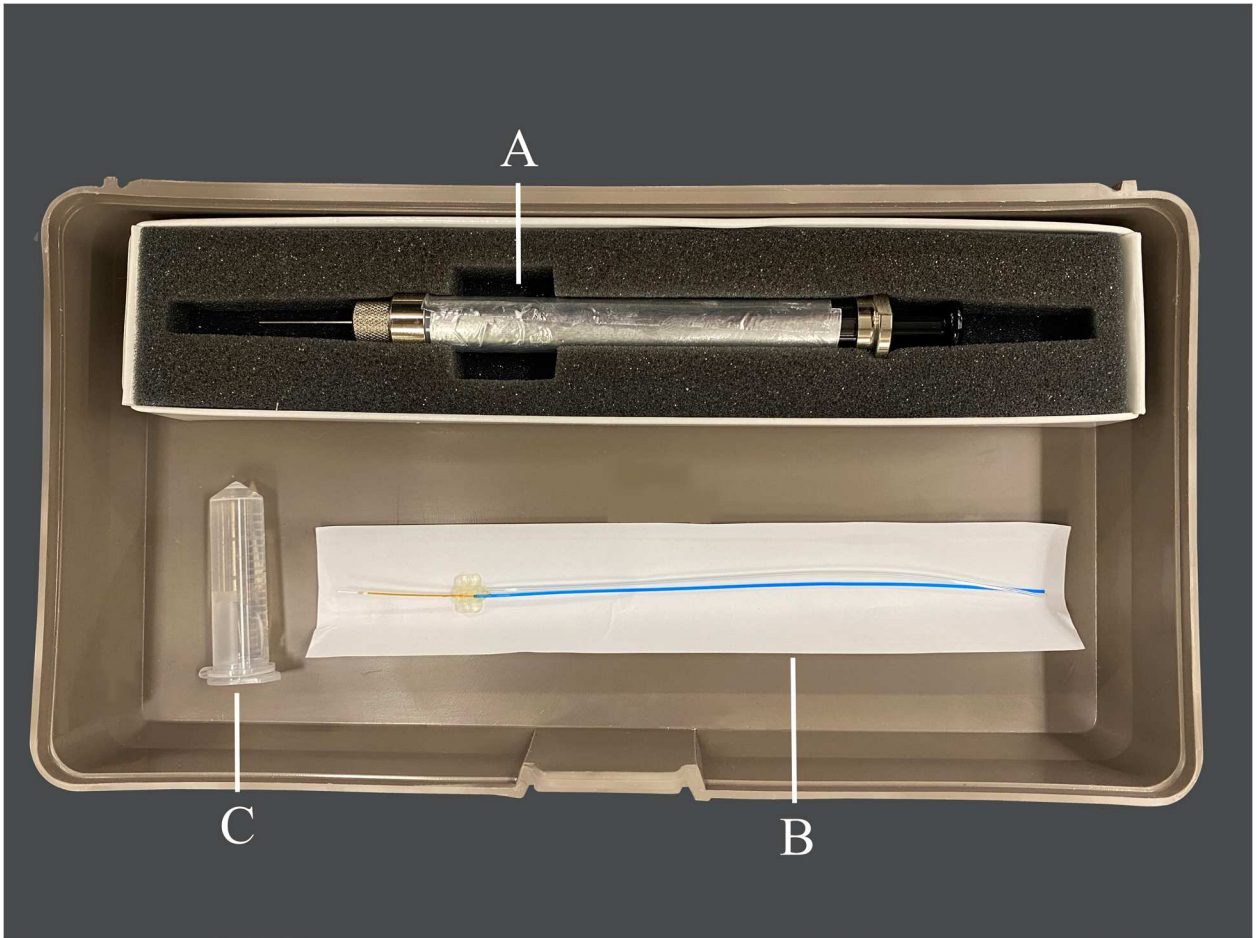


Figure 5.4 A Kit of Disposable Items. Included are (A) a 2.5 mL sterile syringe, (B) a microdialysis catheter with PEEK tubing, and (C) plasmin substrate.

The Coagulation Companion is a consolidated device with the syringe pump (Figure 5.5) and detection system defined by a single unit (Figure 5.6). A 2.5 mL sterile syringe containing the plasmin substrate is located within the syringe pump.

The plasmin substrate is GMP-grade D-Ala-Leu-Lys-7-amido-4-methylcoumarin, CAS No.: 104881-72-3, from BOC Sciences. Each 100 mL vial holds approximately 23.9 mg of the plasmin substrate. It is reconstituted in the hospital's pharmacy prior to use with 100 mL normal saline followed by two 1:10 dilutions. Ultimately, the concentration is 6 μ M. The plasmin substrate uses a LED light source and has an excitation wavelength of 360 nm and an emission wavelength of 460 nm. The If the Coagulation Companion is used for its maximum amount of time, three hours, a total of 3.16 μ g of the plasmin substrate will be administered.

The syringe pump infuses the substrate at a pre-calibrated flow rate, 6 μ L/minute, into the interstitial space. The substrate flows through the PEEK tubing, through the inlet tubing of the microdialysis catheter (Figure 5.7) which is placed subdermally in the shoulder region. The plasmin substrate is infused and quickly equilibrates with the interstitial fluid. The substrate moves from high to low concentrations forming a concentration gradient. The syringe pump continuously forces substrate into the interstitial fluid. This high concentration drives the flow of the processed substrate through the outlet tubing of the microdialysis catheter. The plasmin substrate flows through the PEEK tubing and into the 10 μ L cuvette housed within the PMT Detection System (Figure 5.8). The substrate within the cuvette is subjected to a 380-nm LED and produces a fluorescent signal that is amplified in the PMT. The fluorescence is digitally

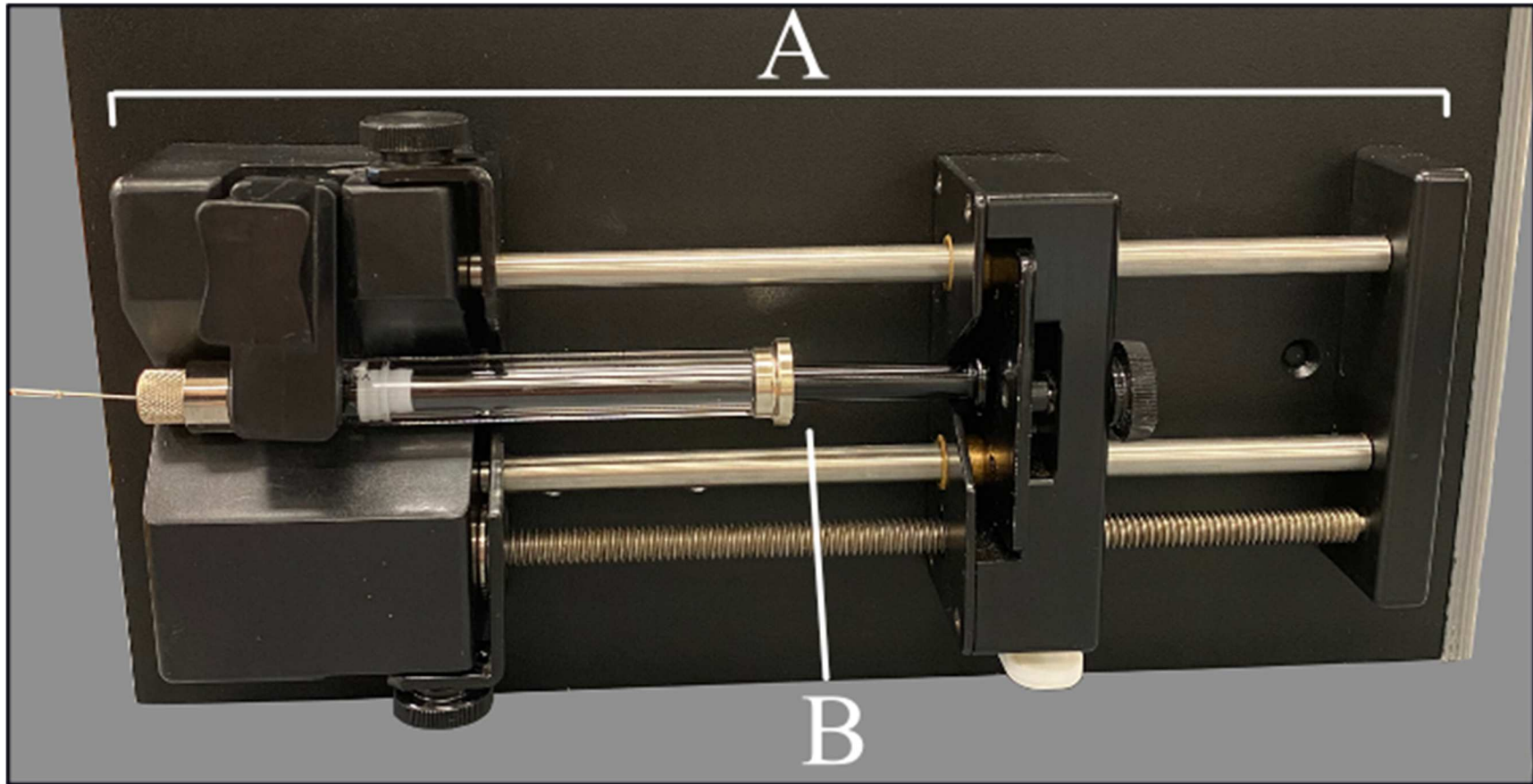


Figure 5.5 The (A) Syringe Pump with a (B) 2.5 mL Syringe.

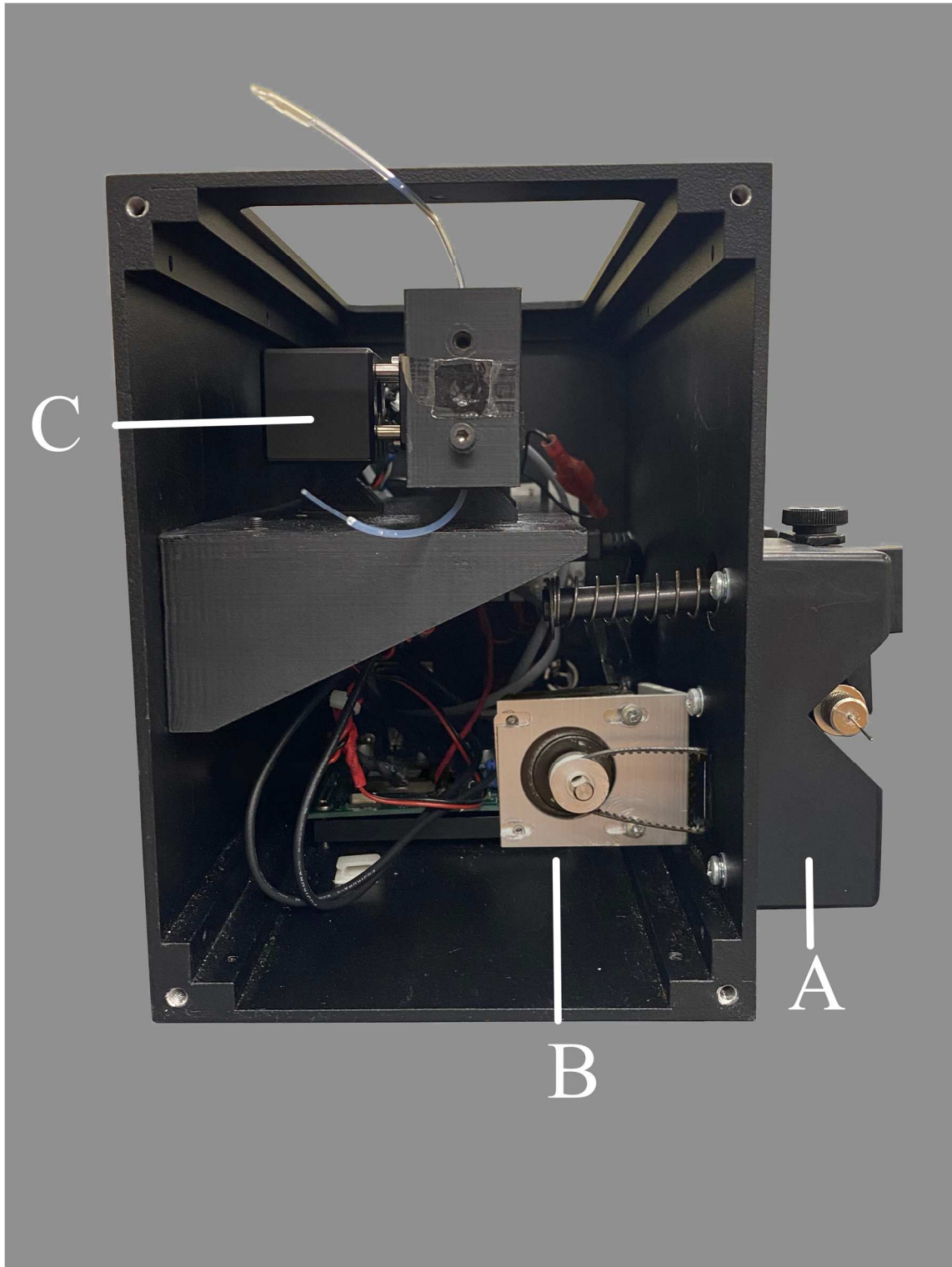


Figure 5.6 An Internal View of the Coagulation Companion. (A) Syringe Pump, (B) Syringe Pump Motor, and (C) PMT Detection System.

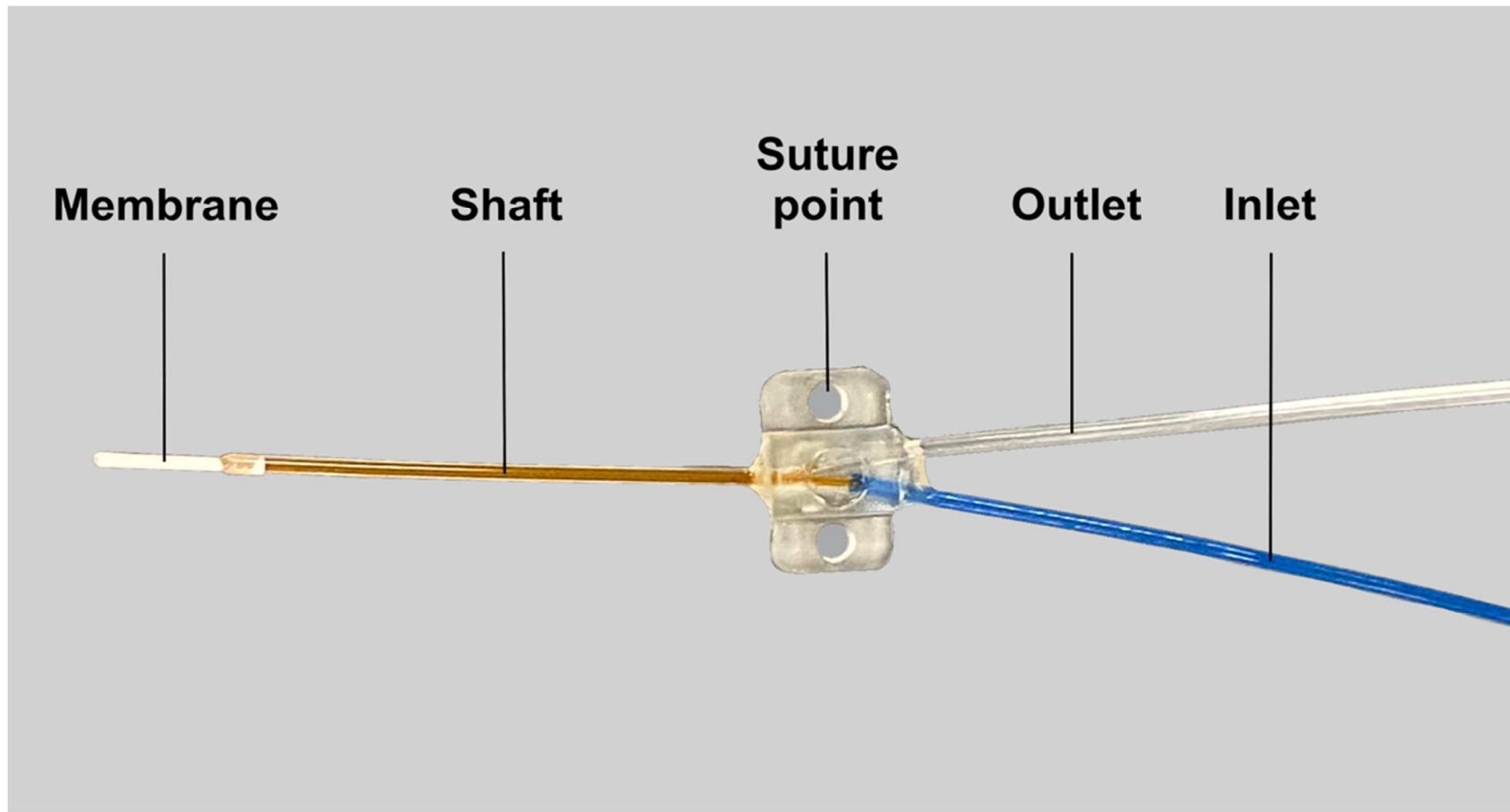


Figure 5.7 A Labeled Microdialysis Catheter.

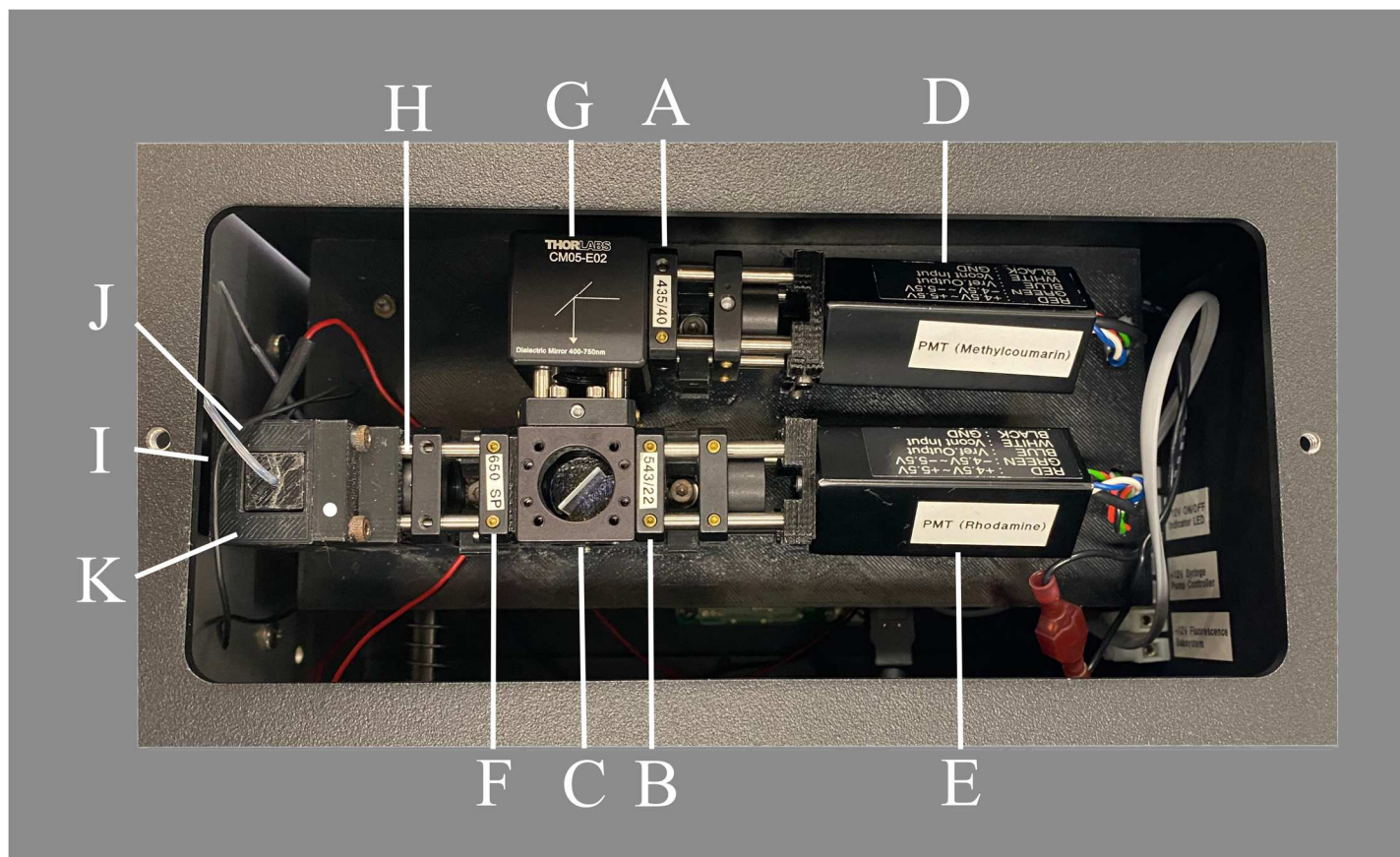


Figure 5.8 The PMT Detection System. (A) The methylcoumarin emission bandpass filter has an excitation of 435 nm and a bandwidth of 40 nm (B) The rhodamine emission bandpass filter has an excitation of 543 nm and bandwidth of 22 nm (C) The dichroic filter (D) The Methylcoumarin detector for plasmin (E) The Rhodamine detector for kallikrein (F) The short-pass filter only transmits wavelengths below 650 nm (G) Dielectric turning prism mirror (H) Achromatic lens (I) Flow Cell (J) Rhodamine excitation bandpass filter (K) Methylcoumarin excitation bandpass filter.

displayed on the 7-inch Raspberry Pi integrated touchscreen that can be used in the operating room.

The power supply of the Coagulation Companion uses a 12-volt adapter to regulate output voltage. This power supply provides an output range of 11-13 volts with output currents ranging from 1.36-1.15 A. The maximum output power is 15 watts.

5.3.3 Comparison with Similar Devices

TEG 6s Hemostasis System by Haemonetics (haemonetics.com) is a Class II device with the same intended use as the Coagulation Companion. The TEG 6s is intended to provide semi-quantitative indications of the hemostasis state of a venous blood sample for coagulation studies. It is comprised of the TEG Hemostasis analyzer and disposable TEG 6s Assay Cartridges. The system measures and records kinetic changes in a sample of 3.2% citrated whole blood as clotting occurs.

The TEG 6s Citrated Assay Cartridges contain three independent citrated assays. Clotting time, maximum clot strength, and fibrolysis after 30 minutes of reaching maximum clot strength are the variables of interest. The data is recorded using changes in physical clot elasticity.

The CMA Cerebral Tissue Monitoring System by CMA Microdialysis AB (mdialysis.com) is a Class II device with technology comparable to the Coagulation Companion. It is intended to monitor the perfusion status of cerebral tissue local to catheter placement. The components of the system include the CMA 70 Brain Microdialysis Catheters, CMA 106 Pump and Syringe, and CMA 600 Microdialysis Analyzer and software.

This system monitors biomarkers of ischemia in the brain. The parameters are glucose, lactate, and pyruvate levels. The principles of “microdialysis” are utilized by the system and resulting samples are collected in microvials and analyzed and displayed as trend curves. It is to be used by patients 18+ in cases where ischemia or hypoxia is a concern.

The microdialysis catheter utilized by the Coagulation Companion is from the brand CMA Microdialysis AB. The Coagulation Companion’s catheter placement is less invasive as it uses shoulder tissue rather than brain tissue. A comparison of the Coagulation Companion to the similar devices may be seen in table 5.1.

Indocyanine Green is a fluorescent medical dye that has been approved for commercial use since 1959. It is a cyanine dye used in determining cardiac output, hepatic function, liver blood flow, and ophthalmic angiography. A significantly higher quantity of Indocyanine Green is injected into the body compared to the Coagulation Companion’s plasmin substrate. The comparison between Indocyanine Green dye and plasmin substrate can be seen in table 5.2.

5.3.3 Intended Use

The Coagulation Companion is to be used to prevent post-operative blood loss. Use is by prescription only. The microdialysis catheter is placed under the skin in subcutaneous tissue and infuses a fluorescent substrate which quickly equilibrates with the interstitial space. There is no contact between the plasmin substrate and the blood stream. The returning fluid contains processed plasmin substrate. This is a single-use only product. The duration of use is the intraoperative and postoperative period with the

expectation of not to exceed 3 hours. The Coagulation Companion is intended to continuously monitor a key enzyme that indicates coagulation and clot degradation capabilities to prevent post-operative blood loss. The Coagulation Companion is to be used by pediatric patients, up to 21 years of age, undergoing congenital heart surgery. Approximately 40,000 children undergo congenital heart surgery in the United States each year.

5.3.4 Proposed Labeling

There is no proposed labeling for the Coagulation Companion.

Table 5.1 Device Comparison of Similar (green) and Unique (blue) Device Features.

Device	Coagulation Companion	TEG 6s Hemostasis System	CMA Cerebral Tissue Monitoring System
Manufacturer	MicroVide	Haemonetics Corporation	CMA/Microdialysis AB
Device Usage			
Clinical Application	To monitor coagulation state	To monitor coagulation state	To monitor trends in parameters indicating the perfusion status of cerebral tissue
Parameters Measured	Plasmin activity	Clotting time, clot lysis, clot strength, fibrogen contribution	Intracranial glucose, lactate, and pyruvate levels
Monitoring Style	Continuous	Stagnant	Stagnant
Patient Population Age	Pediatrics	Adults 18+	Adults 18+
Diagnostic Use	Monitoring only	Monitoring only	Monitoring only
Device Description			
Pathway Order: <ul style="list-style-type: none"> • Syringe pump • Microdialysis Catheter • Detector 	Same order	Different components	Same order
Microdialysis Catheter Placement	Subcutaneous tissue	No microdialysis catheter	Cerebral tissue
Detector	Optical (PMT)	Clot viscosity	Optical (Single Beam Filter Photometer)

Table 5.2 Comparison between Indocyanine Green to the Plasmin Substrate

Device	Indocyanine Green	Plasmin Substrate
Clinical Application	For determining cardiac output, hepatic function, and liver blood flow For ophthalmic angiography	For monitoring enzymatic activity related to coagulation status
Infusion Method	Intravenous	Subcutaneously
Quantity infused after 3 hours	5.4 mg	3.16 ug

CHAPTER 6

CONCLUSION

The U.S. Food and Drug Administration passed the Pure Food and Drug Act and the Federal Food, Drug and Cosmetic Act to regulate various products, including medical devices, to assure public safety. The FDA classifies medical devices into classes based on their potential user harm and the methods to use them. Each Class is subject to a different level of regulation, the highest risk products requiring the most proof of safety. Devices can continue to be monitored after marketing and can be subject to recalls if adverse events are reported. Section 513(g) of the U.S. FDC Act allows a manufacturer to submit a request for non-binding information regarding a device's classification and regulation. The submission of a 513(g) is useful in predicting the device Class the product would be placed in and what type of premarket submission would be required prior to entry into the U.S. market. The Coagulation Companion is a device which would fill the medical device market's need for a way to continuously monitor coagulation in pediatric patients to prevent post-operative bleeding. By including detailed information on the device's description and intended use in the 513(g) submission, the FDA's reader will be able to provide the most accurate response to the request.

REFERENCES

- Achey, M. A., Nag, U. P., Robinson, V. L., Reed, C. R., Arepally, G. M., Levy, J. H., & Tracy, E. T. (2020). The Developing Balance of Thrombosis and Hemorrhage in Pediatric Surgery: Clinical Implications of Age-Related Changes in Hemostasis. *Clinical and applied thrombosis/hemostasis : official journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis*, 26, 1076029620929092. <https://doi.org/10.1177/1076029620929092>
- Akorn. (2015). IC-GREEN: Label-Package Insert. Lake Forest, Illinois.
- Asamoah, A. K., & Sharfstein, J. M. (2010). Transparency at the Food and Drug Administration. *New England Journal of Medicine*, 362(25), 2341–2343. <https://doi.org/10.1056/nejmp1005202>
- Baker, S. K., & Strickland, S. (2020). A critical role for plasminogen in inflammation. *The Journal of experimental medicine*, 217(4), e20191865. <https://doi.org/10.1084/jem.20191865>
- Center for Devices and Radiological Health. (2018, September 26). Recalls, Corrections and Removals (Devices). U.S. Food and Drug Administration. Retrieved from <https://www.fda.gov/medical-devices/postmarket-requirements-devices/recalls-corrections-and-removals-devices#1>

Center for Devices and Radiological Health. (2020, February 7). Classify Your Medical Device. U.S. Food and Drug Administration. Retrieved from <https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device>

Chaudhry R, Usama SM, Babiker HM. Physiology, Coagulation Pathways. [Updated 2021 Sep 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK482253/>

De Novo Classification, 21 C.F.R. § 860 (2022) <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-860/subpart-D?toc=1>

Federal Food and Drugs Act of 1906, 21 U.S.C. § 1 (1906).
<https://catalog.archives.gov/id/5716297>

Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360(l) (2012)

Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 9 (1938)
<https://uscode.house.gov/view.xhtml?path=/prelim@title21/chapter9&edition=prelim>

Fortin, N. (2016). Introduction to Food Regulation in the United States. In *Food Regulation: Law, Science, Policy, and Practice* (2nd ed.). essay, Wiley.

Headlee, D. (n.d.). Humanitarian Device Exemption (Hde): Overview and Pre-approval Activities. U.S. Food and Drug Administration. Retrieved from <https://www.fda.gov/media/99947/download>.

Headlee, D. (n.d.). Introduction to the Premarket Approval Application (Pma) Program.

U.S. Food and Drug Administration. Retrieved from

<https://www.fda.gov/media/131254/download>.

History, Art & Archives, U.S. House of Representatives, “The Pure Food and Drug

Act,” [https://history.house.gov/Historical-Highlights/1901-1950/Pure-Food-and-](https://history.house.gov/Historical-Highlights/1901-1950/Pure-Food-and-Drug-Act/)

[Drug-Act/](https://history.house.gov/Historical-Highlights/1901-1950/Pure-Food-and-Drug-Act/) (March 31, 2022)

Holmes, O. W. & Supreme Court Of The United States. (1911) U.S. Reports: United

States v. Johnson, 221 U.S. 488. [Periodical] Retrieved from the Library of

Congress, <https://www.loc.gov/item/usrep221488/>.

How is My Medical Device Classified? (2021). U.S. Food and Drug Administration.

Retrieved from

<https://fda.yorkcast.com/webcast/Play/17792840509f49f0875806b6e9a1be471d>.

Jarow, J. P., & Baxley, J. H. (2015). Medical devices: US medical device regulation.

Urologic oncology, 33(3), 128–132. <https://doi.org/10.1016/j.urolonc.2014.10.004>

Klinge, M., Enkel, J., Speer, T., Bomberg, H., Baerens, L., & Schäfers, H.-J. (2020).

Bleeding complications after cardiac surgery, before anticoagulation start and

then with Argatroban or heparin in the early postoperative setting. *Journal of*

Cardiothoracic Surgery, 15(1). <https://doi.org/10.1186/s13019-020-1059-8>

Lu, C. H., & Hsiao, J. K. (2021). Indocyanine green: An old drug with novel applications. *Tzu chi medical journal*, 33(4), 317–322.

https://doi.org/10.4103/tcmj.tcmj_216_20

McGilvray ID, Rotstein OD. Assessment of coagulation in surgical critical care patients.

In: Holzheimer RG, Mannick JA, editors. *Surgical Treatment: Evidence-Based and Problem-Oriented*. Munich: Zuckschwerdt; 2001. Available from:

<https://www.ncbi.nlm.nih.gov/books/NBK6959/>

Medical Device Amendments of 1976, 21 U.S.C § 360c

[https://uscode.house.gov/view.xhtml?req=\(title:21%20section:360%20edition:prelim\)](https://uscode.house.gov/view.xhtml?req=(title:21%20section:360%20edition:prelim))

Medical Device Reporting, 21 C.F.R. § 803 (2014)

<https://www.federalregister.gov/d/2010-8863>

NCI Dictionary of Cancer terms. National Cancer Institute. (n.d.). Retrieved from

<https://www.cancer.gov/publications/dictionaries/cancer-terms/def/blood-clot>

Office of the Commissioner. (2018). *Milestones in U.S. Food and Drug Law*. U.S. Food

and Drug Administration. Retrieved from <https://www.fda.gov/about-fda/fda-history/milestones-us-food-and-drug-law>

Office of the Commissioner. (2018). Part III: Drugs and foods under the 1938 act and its amendments. U.S. Food and Drug Administration. Retrieved from <https://www.fda.gov/about-fda/changes-science-law-and-regulatory-authorities/part-iii-drugs-and-foods-under-1938-act-and-its-amendments>

Office of the Commissioner. (2022). FDA Overview Organization Chart. U.S. Food and Drug Administration. Retrieved from <https://www.fda.gov/about-fda/fda-organization-charts/fda-overview-organization-chart>

Office of the Commissioner. (2018). 80 years of the Federal Food, Drug, and Cosmetic Act. U.S. Food and Drug Administration. Retrieved from <https://www.fda.gov/about-fda/fda-history-exhibits/80-years-federal-food-drug-and-cosmetic-act>

Office of the Commissioner. of the. (2018). FDA History. U.S. Food and Drug Administration. Retrieved from <https://www.fda.gov/about-fda/fda-history>

Office of the Commissioner. of the. (2018). Part II: 1938, Food, Drug, Cosmetic Act. U.S. Food and Drug Administration. Retrieved from <https://www.fda.gov/about-fda/changes-science-law-and-regulatory-authorities/part-ii-1938-food-drug-cosmetic-act>

Office of the Commissioner. of the. (2019). Part I: The 1906 Food and Drug Act and Its Enforcement. U.S. Food and Drug Administration. Retrieved from <https://www.fda.gov/about-fda/changes-science-law-and-regulatory-authorities/part-i-1906-food-and-drugs-act-and-its-enforcement>

Palta, S., Saroa, R., & Palta, A. (2014). Overview of the coagulation system. *Indian journal of anaesthesia*, 58(5), 515–523. <https://doi.org/10.4103/0019-5049.144643>

Piermatteo, K. (n.d.). Is My Product a Medical Device? U.S. Food and Drug Administration. Retrieved from <https://fda.yorkcast.com/webcast/Play/e0eec5f6ee3d4947a70fcedef32993f71d>.

Piermatteo, K. (n.d.). The 510(k) Program. U.S. Food and Drug Administration. Retrieved from <https://www.fda.gov/media/89869/download>.

Premarket Approval of Medical Devices, 21 C.F.R. § 814 (1986). <https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-814>

Roshanov, P. S., Eikelboom, J. W., Sessler, D. I., Kearon, C., Guyatt, G. H., Crowther, M., Tandon, V., Borges, F. K., Lamy, A., Whitlock, R., Biccard, B. M., Szczeklik, W., Panju, M., Spence, J., Garg, A. X., McGillion, M., VanHelder, T., Kavsak, P. A., de Beer, J., ... Devereaux, P. J. (2021). Bleeding independently associated with mortality after noncardiac surgery (BIMS): An international prospective cohort study establishing diagnostic criteria and prognostic importance. *British Journal of Anaesthesia*, 126(1), 163–171. <https://doi.org/10.1016/j.bja.2020.06.051>

Sharfstein, J., Miller, J., Davis, A., Ross, J., McCarthy, M., Smith, B., . . . Kesselheim, A.

(2017). Blueprint for Transparency at the U.S. Food and Drug Administration: Recommendations to Advance the Development of Safe and Effective Medical Products. *Journal of Law, Medicine & Ethics*, 45(S2), 7-23.

doi:10.1177/1073110517750615

Swann J. P. (1997). Drug abuse control under FDA, 1938-1968. *Public health reports* (Washington, D.C. : 1974), 112(1), 83–86.

The Food and Drug Administration: The Continued History of Drug Advertising. Weill

Cornell Medicine Samuel J. Wood Library. Retrieved from

[https://library.weill.cornell.edu/about-](https://library.weill.cornell.edu/about-us/snake%2%A0oil%2%A0social%2%A0media-drug-advertising-your-health/food-and-drug-administration-continued#:~:text=1911,or%20identity%20of%20a%20drug)

[us/snake%2%A0oil%2%A0social%2%A0media-drug-advertising-your-health/food-and-drug-administration-](https://library.weill.cornell.edu/about-us/snake%2%A0oil%2%A0social%2%A0media-drug-advertising-your-health/food-and-drug-administration-continued#:~:text=1911,or%20identity%20of%20a%20drug)

[continued#:~:text=1911,or%20identity%20of%20a%20drug.](https://library.weill.cornell.edu/about-us/snake%2%A0oil%2%A0social%2%A0media-drug-advertising-your-health/food-and-drug-administration-continued#:~:text=1911,or%20identity%20of%20a%20drug)

U.S. Congress. (1934) *United States Code: Federal Food, Drug, and Cosmetic Act*, 21

U.S.C. §§ 301-392 Suppl. 5. [Periodical] Retrieved from the Library of Congress,

[https://www.loc.gov/item/uscode1934-006021009/.](https://www.loc.gov/item/uscode1934-006021009/)

U.S. Dept. of Health and Human Services, Food and Drug Administration, Center for

Food Safety and Applied Nutrition, FDA and Industry Procedures for Section

513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act

(2019).

U.S. Food and Drug Administration, 2021 Monthly PMA Listings (2022). Retrieved from <https://www.fda.gov/medical-devices/pma-approvals/devices-approved-2021>.

U.S. Food and Drug Administration, 510(k) Devices Cleared in 2021 (2022). Retrieved from <https://www.fda.gov/medical-devices/510k-clearances/510k-devices-cleared-2021>.

U.S. Food and Drug Administration, Listing of CDRH Humanitarian Device Exemptions (2021). Retrieved from <https://www.fda.gov/medical-devices/hde-approvals/listing-cdrh-humanitarian-device-exemptions>.

U.S. Food and Drug Administration. (2019, June 21). Statement on agency's efforts to increase transparency in medical device reporting. FDA. Retrieved from <https://www.fda.gov/news-events/press-announcements/statement-agencys-efforts-increase-transparency-medical-device-reporting>.

U.S. Food and Drug Administration. (2021). Draft guidance for Industry and Food and Drug Administration Staff. <https://www.fda.gov/media/149346/download>

Yang, P. J. (n.d.). De Novo Final Rule: Overview and Guidance Updates. U.S. Food and Drug Administration. Retrieved from <https://www.fda.gov/media/155111/download>.