Successfully Navigating the FDA Regulatory Process

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Section 1 - Introduction

For most devices and products, identifying unmet market needs followed by resolving production, marketing, and distribution issues is sufficient to have a chance of being successful.

However, for medical devices sold in the US there are additional regulatory considerations as governed by the Food & Drug Administration (FDA). Most devices require approval or clearance before they can be sold commercially. Determining the regulatory strategy early in the development process is critical so that the product can be brought to market as quickly as possible.

It is important to determine the regulatory strategy.

The regulatory path will be determined by the device classification and the claims that are being made. The FDA classifies devices based on the intended use, risk, and regulatory controls. Tools to help determine device classification are available on the FDA website: https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medicaldevice.

Section 2 - FDA Definitions of Commonly Used Regulatory Terms

Class I - These devices present minimal potential for harm to the user and are often simpler in design than Class II or Class III devices. Examples include enema kits and elastic bandages. 47% of medical devices fall under this category and 95% of these are exempt from the regulatory process. (This is the FDA definition)

Class II - Most medical devices are considered Class II devices. Examples of Class II devices include many implantable devices, powered wheelchairs, and some diagnostic test kits. 43% of medical devices fall under this category. (This is the FDA definition)

Class III - These devices usually sustain or support life, are implanted, or present a potentially unreasonable risk of illness or injury. Examples of Class III devices include implantable pacemakers, selected orthopedic implants, and breast implants. 10% of medical devices fall under this category. (This is the FDA definition)

Exempt – If a device falls into a generic category of exempted Class I devices, a premarket notification application and FDA clearance are not required before marketing the device in the U.S. However, the manufacturer is required to register their establishment and list their generic product with the FDA. Examples of exempt devices are manual stethoscopes, mercury thermometers, and bedpans.

510(k) - Section 510(k) of the Food, Drug, and Cosmetic Act requires those device manufacturers who must register to notify the FDA of their intent to market a medical device. This is known as 510(k) submission, and is only intended for devices for which a substantially equivalent to an already legally marketed device (predicate device, see below). If the FDA rules

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the device is "substantially equivalent," the manufacturer can market the device. If the device being researched has been in commercial distribution before 1976 or is substantially equivalent to a device already on the market, there should be available information via a search of the FDA's 510(k) releasable database.

A claim of substantial equivalence (SE) does not mean the device(s) must be identical. Substantial equivalence is established concerning the: intended use, design, energy used or delivered, materials, performance, safety, effectiveness, labeling, biocompatibility, standards, and other applicable characteristics. One can claim SE to either a pre-amendments or post amendments device that is or was legally marketed. Legally marketed means that the predicate cannot be or was in violation of the Federal Food Drug & Cosmetic (FD&C) Act. An applicant may claim SE for a device that is no longer being marketed in the U.S

De Novo- The De Novo request provides a marketing pathway to classify novel medical devices for which general controls alone, or general and special controls, provide reasonable assurance of safety and effectiveness for the intended use, but for which there is no legally marketed predicate device.

Predicate Device - A legally marketed device referred to in a Premarket Notification [510(k)] submission made to the FDA to demonstrate that the candidate device is safe and effective by proving substantial equivalence (SE) to it. Submitters must compare their 510(k) device to a similar legally marketed U.S. device(s). A device recently cleared under 510(k) is usually used as a predicate device. However, any legally U.S.-marketed device may be used as a predicate so long as it falls into one of several categories. These include a device that has been cleared through the 510(k) process; a device that was legally marketed before May 28, 1976 (preamendments device); a device that was originally on the U.S. market as a Class III device (Premarket Approval) and later down classified to Class II or I; or a 510(k)-exempt device.

PMA (Pre-Market Approval) - A primary safeguard in the way the FDA regulates medical devices is the requirement that manufacturers must submit to the FDA a Premarket Approval (PMA) application if they wish to market any new products that contain new materials or differ in design from products already on the market. A PMA submission must provide valid scientific evidence collected from human clinical trials showing the device is safe and effective for its intended use. If the device being researched is life-sustaining or presents a potential, unreasonable risk of illness or injury, the FDA's Premarket Approval (PMA) releasable database should be searched.

Investigational Device Exemption (IDE) - An IDE allows the investigational device to be used in a clinical study to collect safety and effectiveness data required to support a Premarket Approval (PMA) application and in some rare situations a Premarket Notification (510(k)) submission. Only a small percentage of 510(k)s require clinical data to support a marketing clearance by the Food and Drug Administration (FDA). An IDE limits the distribution of an investigational device only to the sites identified in the IDE application. In addition to FDA requirements, clinical studies of devices are also monitored by Institutional Review Boards (IRB) located at hospitals or

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other facilities where the clinical studies are conducted. An IRB is composed of medical experts and laypersons.

Quality Management System (QMS) - A Quality Management System (QMS) is a collection of business processes focused on achieving quality policy and quality objectives to meet customer requirements. The technique is used in a wide range of businesses, including those that manufacture medical devices.

CFR 820 - Quality system regulation. Quality system means the organizational structure, responsibilities, procedures, processes, and resources for implementing quality management. *Note – efforts are underway to substantially revise this to more closely match ISO 13485. See Quality Management System Regulation: Final Rule Amending the Quality System Regulation – Frequently Asked Questions | FDA*

Section 361 - Prescription drugs for human use generally recognized as safe and effective and not misbranded; drugs used in research. This only applies to biologics that are exempt from FDA review and not to a medical device that contains a drug.

BLA - Therapeutic Biologics Applications (BLA) The therapeutic biological products include:

1. Monoclonal antibodies for in-vivo use
2. Cytokines, growth factors, enzymes, immunomodulators; and thrombolytics
3. Proteins intended for therapeutic use that are extracted from animals or microorganisms, including recombinant versions of these products (except clotting factors)
4. Other non-vaccine therapeutic immunotherapies
5. Autologous or allogeneic cell therapies that fall under Section 351 of the Code of Federal Regulations, Part 1271.

CRO (Contract Research Organization) - In the life sciences, a contract research organization (CRO) is a company that provides support to the pharmaceutical, biotechnology, and medical device industries in the form of research services outsourced on a contract basis. A CRO may provide such services as biopharmaceutical development, biological assay development, commercialization, clinical development, clinical trials management, pharmacovigilance, outcomes research, and real-world evidence. This description is from Wikipedia quoting Nick Lucas (2021-04-09). "Contract Research Organizations: Key Partners In The Drug Development Journey". *Forbes.com*.

Section 3 - Financial Considerations

Scott Bruder has prepared the following overview of the financial requirements to bring a product to market, once the final design has been established and efficacy has been demonstrated in the appropriate non-clinical models:

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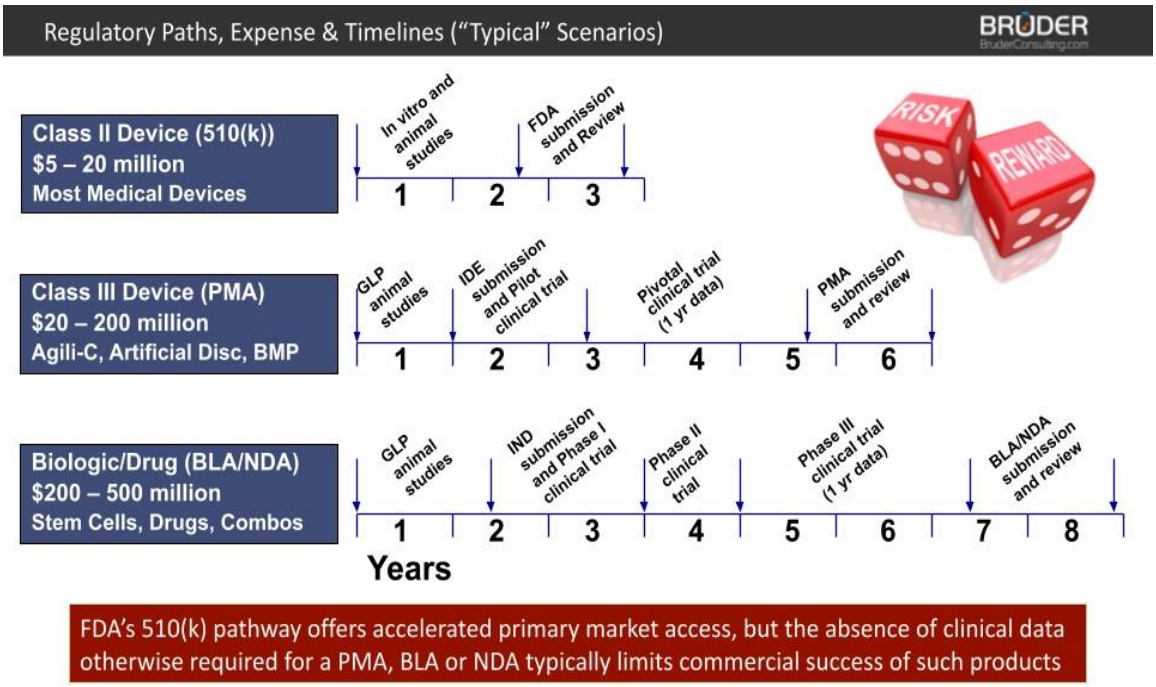

Section 4 - Categories of FDA Approval

Erin Cosgrove summarizes the categories as follows:

Device Classification	**Risk**	**Regulatory Path**	**Exemptions**
Class I	Low	510k (if the device is substantially equivalent to the predicate) De Novo (if no substantially equivalent predicate exists)	Yes – some devices are 510k exempt and may be sold without FDA clearance
Class II	Medium	510k (if the device is substantially equivalent to the predicate) De Novo (if no substantially equivalent predicate exists)	Yes – some devices are 510k exempt and may be sold without FDA clearance
Class III	High	PMA (Pre-Market Approval)	No – all devices must be FDAapproved to sell commercially

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One can view the FDA guidance on how to classify a device here - https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medicaldevice#:~:text=Class%20I%20includes%20devices%20with,I%2C%20II%2C%20and%20III

Data required to support submission

Performance and safety data for the medical device need to be provided. Depending on the device classification, intended use, and indications for use one may need to provide clinical data and additional test data such as performance in more than one animal species, biocompatibility, or sterility.

An overview of FDA requirements can be found here:

https://www.fda.gov/medical-devices/premarket-notification-510k/content-510k#:~:text=The%20data%20may%20include%20test,the%20device%20will%20be%20used.

Process controls required for medical devices

The FDA requires medical devices to be designed and manufactured under a Quality Management System (QMS) that meets CFR 820. An overview of the FDA requirements can be found here:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820

Scott Bruder states that many companies commercializing products are exempt from FDA review under Section 361. To qualify for an exemption under Section 361, the product must meet four rigorous criteria: 1) The human tissue must not be more than minimally manipulated. 2) It must be used for the same homologous purpose (i.e. One could take fat from one part of the body and put it in another part of the body for the same purpose and function that it originally served.). 3) It cannot be combined with something else (except for water and a few other items). 4) It does not have a systemic effect and does not rely on other metabolic activity of the cells or tissue to function. This is unlike 510(k), PMA or BLA products which are subject to review.

Some individuals are marketing products as Section 361 exempt, even though they have not received confirmation from the FDA that such products are exempt, and they do so until they are told to stop by the FDA. Unfortunately, many companies attempt to liberally interpret these four guidelines, and the FDA is forced to issue Warning Letters and other sanctions to compel them to cease. The biological community refers to these firms and physicians using such products as “bad actors”. For example, more than one company is marketing amniotic fluid at $2,000 per cc to inject into the knee joint to treat osteoarthritis. Their “argument” is that it is for “cushioning” the way it provides cushioning for a baby. The company markets it to physicians and says that it is Section 361 exempt even though the FDA has clearly stated that amniotic fluid should be regulated as a drug. The DOJ and the FTC are going after these companies because

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they do not have FDA approval, have caused the medical system such a great expense, and could cause harm to patients.

BCVG's work with large multinational conglomerates focused on areas such as tissue repair, protection, and healing. These are related to musculoskeletal issues, advanced wound care, and plastic as well as reconstructive surgery. They also work with investigators coming out of universities, who have their first $500,000 to get started. and with large companies as well. The needs of each client partner will vary as a function of maturity along the development journey. Some of these client products are devices requiring a 510(k) or a PMA, and some are biologics that need a BLA. Finding external resources can be very helpful for smaller companies that have an idea for a product but do not know how to convert work done in the laboratory to a patented product that can be manufactured and navigated through the FDA.

In the case of certain products that are eligible for a de novo clearance as noted above, the sponsor may need both animal data and human clinical trials. One recent example is Bone Support, who negotiated with the FDA that their bone graft substitute combined with an antibiotic could pursue a de novo 510(k) path. The FDA required a clinical trial since this product was not based entirely on a predicate product. There are certain advantages of a de novo 510(k) over a PMA. The review cycle for a PMA takes longer (PMA is close to a year but 90 days for a de novo 510(k)) and for a PMA one is obligated for post-market surveillance, postmarket reporting, and annual reporting of manufacturing. However, once one has obtained de novo 510(k) clearance, the way has been paved for someone else to follow up with this product serving as a predicate. To decrease the chances of a "fast follower", one would try to write the Special Controls that define the product in a way that is narrow so that someone else cannot slip their product into the traditional 510(k) pathway without the extra effort needed for a de novo 510(k).

Helen Simons advises that the FDA classification of devices is subjective and relative to existing products. This is compared to the more straightforward approach adopted by the EU and Canada, where they use a rule-based system to ensure consistency. The FDA has 3 risk classifications of devices, from class 1 as the lowest risk to class 3 as the highest. The EU and Canada have similar categories but expand them to 4 levels (1, 2a, 2b, 3, and 1 to 4 respectively). The subjective nature of the FDA classification can prove a challenge for device developers and StarFish always recommends a pre-submission meeting to confirm classification with the FDA as any changes in classification can have a big impact on the development process. Any questions raised at a pre-sub will be answered by the team who will review the final product submission and who are well informed and educated about that category of device. The overlap in risk classifications means that one can utilize the same documentation generated to support an FDA application for other regions. Some smaller markets will also accept an FDA clearance or approval instead of an application within their region (e.g. Switzerland).

If the product is a class II device, one may be able to take advantage of the 510(k) program where a comparison is made to a predicate device that is deemed substantially equivalent to the device being developed. The FDA recently released a new guidance to help support the

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selection of predicate devices. Again, the pre-submission meeting can be a good time to confirm that the FDA finds the predicate choice acceptable. StarFish has found this to be useful time and time again. Once when involved with a dental device, the FDA suggested an additional reference device to support the predicate with additional functionality to match that of the device that is being developed. The discussions can also help if the FDA needs further explanation to understand how the device will function and provide clinical benefit. Presenting the methods that will be used to show safety and efficacy can mitigate the business risk that the FDA will reject the application. For another device in the diagnostic/monitoring field, StarFish had several pre-submission meetings working with the FDA review team to help them understand the statistical analysis being carried out on the captured patient data and what clinical benefit this provided to the practitioner using the device.

510(k) submissions are interesting as they do not require evidence of the ability to manufacture products consistently. Often it is said that 510(k)s represent an assessment of a technology rather than a final product. This can be seen on occasions when clearance is gained for a product that is never actually manufactured or marketed in volume. Gaining 510(k) clearance can be seen as an investor milestone or just as a pathway to develop the next generation of a product. Whether this is an appropriate approach or not is debatable. We have to rely on the initial submission data to be reassured that the product is safe and effective, rather than being able to confirm it more expansively with post-market data collection.

Section 5 - Special Considerations for Monitoring Devices

Monitoring devices are under the purview of the FDA. On October 19, 2023, the FDA issued a document entitled “Enforcement Policy for Non-Invasive Remote Monitoring Devices Used to Support Patient Monitoring”. Here is the link to that document:

https://www.fda.gov/media/136290/download

Section 6 - Marketing Considerations

Erin Cosgrove states that the intended use and indications for use are key pieces of the FDA submission. These are important business decisions that will determine what can legally be said to market the device once FDA approval or clearance has been obtained. They will also drive the device classification and impact the data and testing required to support the submission. Deciding on these early in the product development process will help streamline the team’s work.

The intended use statement summarizes what the device is intended to do. For example, let’s look at an electrosurgical device intended to seal tissue. In this case, the intended use could be something like, “Device X is intended to seal tissue”.

The indications for use clarify more specifically how the device will be used. For example, if the commercial plan is to sell the product for plastic surgery, the indications for use could be

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something like, “Device X is indicated for healthcare professionals to use in sealing skin tissue during plastic surgery”.

In some cases, changing the intended use or indication for use can change the device classification or the amount or type of data that will be needed to be provided to support the submission.

Key reminder: The commercial marketing & sales claims must be consistent with the intended use and indications for use.

The commercial strategy is an important driver for the regulatory strategy because one will only be able to promote the device based on what the intended use and indications for use say. For example, if the device indication says, “Device X is indicated for healthcare professionals to use in sealing skin tissue during plastic surgery” one can market to physicians and nurses who would use the device in plastic surgery.

Should there be a desire to market to additional customers – i.e. orthopedic surgeons, one would need to amend the intended use statement to include orthopedic surgery and provide supporting data for this. Many companies choose to get an initial FDA clearance or approval for a single indication and then broaden their claims with additional submissions over time.

Scott Bruder states that before dealing with the FDA one should also think in terms of the product’s marketability. This is easily accomplished by performing a survey of appropriately filtered and qualified physicians regarding the appeal of this product. Such a survey can assess their view of the benefits, the hurdles that they see as necessary for them to overcome before using the product if they are not currently using it, or what the switching criteria are if they are using a competitive product.

Section 7 - Considerations to be Taken into Account Before Starting the FDA Regulatory Process

Maria Shepherd, President of Medi-Vantage, emphasized the importance of Human Factors Usability Studies. The human factors and usability research process confirms that the product or device has been given the appropriate risk classification and explains how the person will be using the device or product.

Pre-submission interaction with the FDA is important to ensure that regulatory submissions and human factors studies being done are designed to provide the information that the FDA will be seeking. The usability studies are an important part of the pre-submission process.

Patrick O’Donnell of NanoHive Medical which produces 3D-printed spinal interbody implants brought up several important points. Among the early decisions necessary is determining what the regulatory pathway will be, by way of input from consultants and partnering early in the process via communication with the FDA. From there the company can structure a plan to ensure clinical, regulatory, and reimbursement considerations are “hand-in-glove” upon product approval and commercialization. With this information, the company can craft its

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capital raise story with a very good handle on the amount of time and money it will need to achieve the milestones that properly position the company on a pathway to liquidity. Because the clinical and regulatory decisions and subsequent clinical stage execution are so critical, it makes sense to collaborate with a consultant or firm that has experience with the FDA (as a prior employee ideally) in the specific division that the technology will be working through. Another issue to be mindful of is that a product is only approved for the indication that was studied. Hence, the commercial opportunity and business plan must reflect the market for the product's indication and generally be well thought through.

Scott Bruder clarifies that his firm does not execute the clinical trials as a Contract Research Organization (CRO) might do. CROs monitor sites, ensure that the data has high integrity, enter it into the database, and do the analysis. BCVG represents sponsor companies at the FDA, writes the submissions, and designs the trials, but doesn't execute the actual clinical trials.

Helen Simons states that a key area the FDA is currently focusing on is cybersecurity. They released a draft guidance in 2022 which was finalized in September 2023, and lays out a steep change in the expectations for the content to be included in submissions for a wide range of devices. They are looking to ensure that patient safety is being protected against tampering or intervention by external parties and that health data is being protected from exploitation. This is an example of where it is important to stay on top of what is going on within the area of regulatory affairs so that one can plan the development accordingly and not be hampered by upcoming changes in requirements.

Section 8 - Considerations To Be Taken into Account During The FDA Regulatory Process

Scott Bruder says that in general, working with the FDA can be a positive experience. In unusual circumstances, however, in the middle of the application process, the FDA review team might say "Our views have evolved", meaning that what the company was told to do will no longer be considered acceptable. This could cost the company years and a tremendous amount of money in clinical trials that need to be redone. The way to avoid this problem is to have meetings with the FDA that are "binding" which precludes any changes. There could also be initial disagreements where certain data is expected to be shown that are not expected of similar products. In both disagreement scenarios, after one has gone through the reviewer, the assistant director, and the director, one can appeal the situation to the Ombudsman whose function is to adjudicate disagreements between sponsors and the FDA. The most important advice is to go to the FDA early and clarify the intentions, get them to understand what the company is trying to do, and get their feedback so that there are no surprises later. Some startup companies have done studies before going to the FDA and when they made their presentation were told that what the FDA is looking for is different. They lost a year and $500,000 on an animal study that was not useful.

Section 9 - International Considerations

Maria Shepherd noted that a company's marketing and regulatory strategies must be coordinated. Failure to understand regulatory requirements' ramifications could put the entire marketing strategy at risk. The regulatory plan must consider the requirements of the FDA for

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the United States and any regulatory bodies in the foreign country where studies are being performed. Countries such as the United States, China, and India have high regulatory barriers while countries such as Chile, Paraguay, and Israel have changing regulatory barriers. For example, Chile is part of the Asia-Pacific Economic Cooperation (APEC), developed to help members of APEC economies create robust regulatory systems for medical devices[1]. In Israel, the Ministry of Health is responsible for the regulation of medical devices. All companies wishing to import medical equipment must be registered with the Ministry of Health and have a local agent or distributor. Medical device companies are required to provide certification issued by a competent authority to show that the device has obtained USA FDA approval, EU CE marking, or Australian, Canadian, or Japanese regulatory approval. In addition, all products will require labelling and instructions in the local language.

It should be remembered that if one wants to market the innovation in the United States, the studies must meet FDA standards even if the clinical trials are performed overseas. Within the marketing strategy, a company must consider the profiles of the potential product or device users since the success of the product or device is directly related to the user acceptance rate which is dependent on the potential user's approach to innovation in addition to the superior performance of the device or product. The specific regulations in each potential target area regarding marketing must be considered.

[1] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3326589/

Section 10 - Conclusion

The FDA regulatory procedures are complex. Proper preparation and guidance from people with experience navigating the agency's process for protecting the public tremendously improve the probability of a successful outcome.

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