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U.S. Food and Drug Administration (FDA) Regulatory Pathways for Medical Devices

Abstract

There has been an explosion of new and innovative medical device products launched in the US and global markets over the last 5 years. The medical device industry is now capable of using 3D printers to produce everything from prosthetic parts to artificial knees to surgical tools. In addition to the use of 3D printers, the advancement of mobile health (mHealth) applications for smart phones and other electronic communication devices has seen an upsurge in usage and availability. mHealth applications are now used for collecting community and clinical health data, delivering patient healthcare information to doctors, as well as monitoring patient vital signs real-time. Medical device users, consumers, and patients expect medical device manufacturers to consistently develop and launch contemporary, state-of-the-art products and technologies that are cheaper, easier to use, and achieve greater benefits for the patient that ultimately result in more effective and efficient patient care and outcomes. To ensure these products are safe and effective, the FDA and other global Regulatory Authorities place a heavy burden on the medical device industry to demonstrate that such products are designed, developed, tested, and manufactured according to

Current Good Manufacturing Practices (cGMPs) and other applicable Standards and Guidances. Obtaining regulatory clearance or approval for new medical device products and technologies has historically been a complex and challenging process for many manufacturers. However, in recent years the FDA has taken a more proactive approach to collaborate with industry and streamline the evaluation process of these innovative medical devices to bring safe, effective, and novel products to market faster for the ultimate goal of advancing of public health.

Regulatory Compliance Associates Inc. has developed this white paper to help our clients understand the current regulatory pathways for medical devices intended for registration in the US in light of the advancements being made in the medical device field and the FDA's goal of ensuring the safety and effectiveness of novel devices and technologies.

Introduction

Medical technology innovators are continually focusing on new products that deliver better, faster, and less costly patient care. Advancements being developed in the medical device field include the use of 3D printers for surgical tools and medical equipment, mHealth applications for monitoring

patient vital signs, electronic aspirin using a handheld remote controller, needle free diabetes care using patch technology, the development of a transcatheter aortic valve for insertion in patients not suitable for open-heart surgery and brain-machine interfaces for amputees and potentially for spinal cord injury treatment.

Regulatory Strategy

The first step in determining the most appropriate regulatory pathway to obtain clearance or approval of a new or modified medical device in the US market is to develop a robust regulatory strategy that aligns the business objectives and the regulatory requirements necessary for market launch of the product. It is critical to accurately describe the device in terms of its intended use, indications for use, target population of users and/or patients, functional and/or performance characteristics, labeling and desired marketing claims for the device. These factors, when coupled with the determination of the device classification, applicable product code(s) for the device, and whether a predicate device(s) exists, will serve as the foundation to determine the most appropriate submission type and regulatory pathway.

Inventors face a smoother clearance or approval process if they are informed and prepared with a regulatory strategy prior to engaging with the FDA. Understanding the various device classifications and controls, as well as, the various regulatory pathways to obtain clearance or approval establishes the foundation for a cooperative partnership and with the USFDA and helps ensure expeditious clearance or approval of your medical device product.

Device Classifications and General & Special Controls

Understanding the different USFDA device classifications and the level of control applied to them helps the applicant determine the correct clearance or approval pathway. The FDA has established approximately 1,700 different generic types of devices that are grouped into 16 medical specialties. The product code and device classification of the medical device is designated under 21 CFR Parts 862-892.

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Determining which category a medical device falls into is defined by indications for use, the intended use, and the risk of the device, which drives the level of control a manufacturer must put in place at their facility and throughout their distribution chain to ensure that the device is safe and effective for its intended use. Lower risk medical devices have the least regulatory control applied to them whereas higher risk medical devices have the most stringent regulatory control applied to them because they may be life supporting and/or life sustaining devices.

There are three classifications for medical devices recognized by the USFDA.

- **Class I Medical Devices:** The least restrictive category for a medical device is Class I. Medical devices categorized as Class I are considered the lowest risk devices and include items such as dental floss, elastic bandages, disposable gloves, and tongue depressors. Devices in this category are subject to General Controls and must have certain mechanisms in place that address issues of preventing adulteration, assuring the product is not misbranded, procedures in place for notifying customers in the event of a problem or recall, and supporting documentation that the products were manufactured according to cGMPs. General Controls also include premarket notification, establishment registration and device listing.
- **Class II Medical Devices:** Class II devices are low to moderate risk devices that must comply with both General and Special Controls. Special Controls include performance standards, postmarket surveillance, patient registries, special labeling requirements, postmarket data requirements and guidelines based on the specific type of device. Examples of Class II devices include non-invasive blood pressure monitor, knee prosthesis, or pulse oximeter devices.
- **Class III Medical Devices:** Class III devices are the highest risk devices and include life supporting and/or life sustaining devices. Examples of a

Class III device include a transcatheter heart valve, spinal cord stimulation system, or thoracic endoprosthesis. Class III devices are subject to the most stringent regulatory controls and requires Class III General Controls and Premarket Approval.

Traditional Regulatory Pathways

The appropriate regulatory pathway to obtain US market clearance or approval for your product is determined primarily by the intended use, indications for use, risk and the classification of the device. The most common pathways to market for devices in the US include:

- **Premarket Notification [i.e., 510(k)]**
Required for some Class I devices and most Class II devices. There are three types of 510(k) submissions including:
 - **Traditional 510(k):** The Traditional 510(k) may be used when a new device is substantially equivalent to a predicate device already cleared for marketing in the US, or for a modification to a previously cleared 510(k) device.
 - **Special 510(k):** The Special 510(k) is used for device modifications to a previously cleared 510(k) device that do not affect the intended use of the device or alter the fundamental scientific technology of the device and utilizes the design controls aspect of the Quality System (QS) regulation (21 CFR 820.30).
 - **Abbreviated 510(k):** The Abbreviated 510(k) may be used when a guidance document exists, special controls for the device have been established, or when the FDA has recognized relevant consensus standards. Summary reports on the use of guidance documents and/or special controls or declarations of conformity to FDA recognized standards must be included with the submission.

Companies intending to market a Class I, Class II and some Class III devices, must submit a Premarket Notification or 510(k) to FDA at least 90 days before marketing the device. Most Class I devices and some Class II devices may be exempt from 510(k) regulations, therefore confirmation must be made at the beginning of the submission process to determine

whether or not the device to be marketed in the US is exempt.

- **Premarket Approval (PMA)**
Required for Class III devices. The FDA's typical review cycle for a Premarket Authorization (PMA) is 180 days. There are several types of PMAs and PMA Supplements including:
 - **Traditional PMA:** An original PMA application is an extremely comprehensive submission that includes a considerable amount of objective evidence to support the safety and effectiveness of the device including the device description, indications for use, intended use, nonclinical and clinical studies, case report forms, manufacturing methods, and labeling.
 - **Modular PMA:** A Modular PMA is often an appropriate route for products in the early stages of a clinical study. The contents of a Modular PMA are submitted to the FDA in separate modules (i.e. preclinical, clinical, manufacturing) upon the applicant's completion of each separate module and collectively constitute the entire Modular PMA.
 - **Product Development Protocol:** The Product Development Protocol route is typically used for well established products in industry and it requires an agreement between the Sponsor and the FDA as to the objective evidence that will be required by the FDA to demonstrate the safety and effectiveness of a new device. Once agreement with the FDA is reached with the Sponsor regarding the design and development activities, outputs, and acceptance criteria for the outputs, the Sponsor must comply with reporting milestones and submit the supporting documentation and milestone reports to the FDA for their review. Once the FDA declares the Product Development Protocol to be completed, it is considered to have an approved PMA.

Innovative Regulatory Pathways

- **De Novo Application**
The De Novo pathway is most appropriate for novel, low to moderate risk devices, presumptively designated as Class III devices due to no

identifiable predicate device for a substantial equivalence comparison. The de novo process provides a pathway to classify a low to moderate risk device for which general controls or general and special controls provide reasonable assurance of safety and effectiveness, but for which there is no legally marketed predicate device. The FDA's typical review cycle for a De Novo Application is 120 days.



HUD is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals.

- **Humanitarian Use Device (HUD)/Humanitarian Device Exemption (HDE)**

A Humanitarian Use Device (HUD) is a unique device with no other comparable devices available, that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. To obtain approval for an HUD, a humanitarian device exemption (HDE) application is submitted to FDA which must contain sufficient information to demonstrate that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. An HDE application is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA and the applicant is not required to include the results of scientifically valid clinical investigations. The FDA's typical review cycle for a Humanitarian Device Exemption Application is 75 days.

Regulatory Plan

Predicated upon the regulatory strategy, the second step is to define a very detailed and device-specific regulatory plan that includes a comprehensive list of all of the submission deliverables, the applicable FDA guidance documents, and/or testing standards that are relevant for the specific type of device, if any. FDA guidance documents provide industry with invaluable information about the required documentation that must be included in a regulatory submission (including the performance, bench, animal testing and/or clinical data that may be required for certain types of devices according to their device classification).

Between 2010 and 2016, the FDA Office of Device Evaluation issued 40 final guidance documents and 66 draft guidance documents. Consideration of the applicable FDA guidance documents that are relevant to your specific type of medical device product must be addressed early in the concept and development process. For example, the FDA expects manufacturers to follow human factors or usability engineering processes during the development of new medical devices to ensure that devices are safe and effective for the intended users, uses, and use environments and that the device user interface has been designed such that use errors that occur during use of the device that could cause harm or degrade medical treatment are either eliminated or reduced to the extent possible. The FDA expects that for certain types of medical devices with the potential for serious harm resulting from user error, human factors data must be included in the premarket submissions for the FDA to evaluate the safety and effectiveness and substantial equivalence of these devices.

The following list includes examples of FDA's recently issued Final and Draft Medical Device Guidance documents:

Relevant FDA Final Guidance

- Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling issued 8/24/2016

- Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications issued 8/24/2016
- FY 2018 Medical Device User Fee Small Business Qualification and Certification issued 8/29/2017
- Adaptive Designs for Medical Device Clinical Studies issued 7/27/2016
- Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" issued 6/16/2016
- Applying Human Factors and Usability Engineering to Medical Devices issued 2/03/2016
- Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile issued 1/21/2016
- eCopy Program for Medical Device Submissions issued 12/03/2015
- Intent to Exempt Certain Unclassified, Class II, and Class I Reserved Medical Devices from Premarket Notification Requirements issued 8/14/2015
- Unique Device Identification System: Form and Content of the Unique Device Identifier (UDI) issued 7/26/2016
- Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies issued 6/20/2016
- Dissemination of Patient-Specific Information from Devices by Device Manufacturers issued 6/10/2016
- List of Highest Priority Devices for Human Factors Review issued 3/03/2016
- Postmarket Management of Cybersecurity in Medical Devices issued 1/22/2016
- Manufacturing Site Change Supplements: Content and Submission issued 10/21/2015
- General Considerations for Animal 1 Studies for Medical Devices issued 10/14/2015

Relevant FDA Draft Guidance

- Deciding When to Submit a 510(k) for a Software Change to an Existing Device issued 8/08/2016
- Deciding When to Submit a 510(k) for a Change to an Existing Device issued 8/08/2016
- Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices issued 7/27/2016

Manufacturers may not be fully aware of the potentially excessive costs and long-lead time required to complete product testing and/or to obtain clinical data that may be necessary for the regulatory submission, nor may they account for the time frame required for the FDA's review cycle during their evaluation of the device. Therefore, the regulatory plan must include a projected timeline and the costs and resources associated with performing or obtaining the testing and/or clinical data that may be required for the submission.

There is also a direct cost associated with the filing fee for certain types of regulatory submissions pursuant to the FDA's Medical Device User Fee Program. The table below outlines the Medical Device User Fees for Fiscal Years 2017 – 2018.

FDA Medical Device User Fees for Fiscal Years 2018 - 2019

Submission type	FY 2018 (Valid from October 1, 2017 through September 30, 2018)	FY 2019 (Valid from October 1, 2018 through September 30, 2019)
Premarket Notification 510(k)		
Standard Fee	\$10,566	\$10,953
Small Business Designation Fee	\$2,642	\$2,738
Premarket Approval (PMA) – Original PMA		
Standard Fee	\$310,764	\$322,147
Small Business Designation Fee	\$77,691	\$80,537
Premarket Approval (PMA) Annual Report		
Standard Fee	\$10,877	\$11,275
Small Business Designation Fee	\$2,719	\$2,819
Panel-Track PMA Supplement		
Standard Fee	\$233,073	\$241,610
Small Business Designation Fee	\$58,268	\$60,403
180-Day PMA Supplement		
Standard Fee	\$46,615	\$48,322
Small Business Designation Fee	\$11,654	\$12,081
Real-Time PMA Supplement		
Standard Fee	\$21,753	\$22,550
Small Business Designation Fee	\$5,438	\$5,638
30-Day Notice		
Standard Fee	\$4,972	\$5,154
Small Business Designation Fee	\$2,486	\$2,577
De Novo Application		
Standard Fee	\$93,229	\$96,644
No fees required by FDA	\$23,307	\$24,161

Determining the Right Pathway for Your Device

Navigating through the various regulatory pathways to obtain market clearance or approval for your device can be a challenging and overwhelming process for many medical device manufacturers. Let Regulatory Compliance Associates Inc. assist you in determining the right pathway for your device. RCA has extensive

subject matter expertise in developing regulatory strategies, regulatory plans and product submissions and has assisted countless manufacturers in the medical device industry gain market clearance and/or approval for their products.

Please visit our website www.rcainc.com or call Regulatory Compliance Associates® Inc. at 262-288-6300 for more information.

References

- 1) <https://3dprintingindustry.com/news/12-things-we-can-3d-print-in-medicine-right-now-42867/>
- 2) *FDA Guidance on Innovative Pathway*
- 3) *21 CFR 860*
- 4) *Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling*
- 5) *Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications*
- 6) *FY 2018 Medical Device User Fee Small Business Qualification and Certification*
- 7) *Adaptive Designs for Medical Device Clinical Studies issued*
- 8) *Use of International Standard ISO 10993-1, “Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process”*
- 9) *Applying Human Factors and Usability Engineering to Medical Devices*
- 10) *Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile*
- 11) *eCopy Program for Medical Device Submissions*
- 12) *Intent to Exempt Certain Unclassified, Class II, and Class I Reserved Medical Devices from Premarket Notification Requirements*
- 13) *Deciding When to Submit a 510(k) for a Software Change to an Existing Device*
- 14) *Deciding When to Submit a 510(k) for a Change to an Existing Device*
- 15) *Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*
- 16) *Unique Device Identification System: Form and Content of the Unique Device Identifier (UDI)*
- 17) *Evaluation and Reporting of Age, Race, and Ethnicity Data in Medical Device Clinical Studies*
- 18) *Dissemination of Patient-Specific Information from Devices by Device Manufacturers*
- 19) *List of Highest Priority Devices for Human Factors Review*
- 20) *Postmarket Management of Cybersecurity in Medical Devices*
- 21) *Manufacturing Site Change Supplements: Content and Submission*
- 22) *General Considerations for Animal 1 Studies for Medical Devices*