Marketing Authorization Of Medical Device De Novo For USFDA

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Abstract:

The Food and Drug Administration Modernization Act of 1997 included the de novo categorization option as a substitute method of classifying new medical devices which had been automatically categorized as Class III after receiving a "not Substantially Equivalent" (NSE) decision in response to the submission of a Premarket Notice [510(k)]. De novo means a new, different device which was never available in the market before. There should be no subsequent equivalent device in the market as the new device. A de novo request must be given for acceptance with its 510(k) application and PMA application. De Novo provides a unique commercialization option of new medical devises medical devices are any products which is used alone or sometimes with some other devices and software for illness detection, diagnosis, treatment, monitoring, inspection, concepts, record keeping etc. Lifecycle period of a medical device is explained. What is the adverse event of medical device and how we can report is also explained. A detailed comparison study of medical device regulation in different major countries is done.

Keyword: De Novo, Medical device, commercialization, categorization, devices, equipment,

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1. INTRODUCTION:

The Food and Drug Administration Modernization Act of 1997 included the de novo categorization option as a substitute method of classifying new medical[1]. The de novo (meaning 'of new') is a Latin word that means 'from the beginning' or 'anew' in English.[2] The Merriam-Webster dictionary defines de novo as "as if for the first time; or anew." The FDA uses the phrase "De Novo" to designate market approval submissions for new medical devices or technology where there's not an equivalent established device on market.

DE NOVO Classification:

It Includes 3 categories:

Class 1: Low risk devices-> e.g.: - bandages, dental floss

Class 2: Medium risk devices-> e.g.: - needles, catheters, contact lenses

Class 3: High risk devices -> e.g.: - artificial heart valves, defibrillators, ventilators. [3].

2. WHAT REALLY IS A DE NOVO CATEGORIZATION APPEAL?

De Novo appeal is a process which creates a commercialization path for a unique and new type of medical device. In de novo categoryzation, a risk-based classified technique is applied. Equipment classified as -class 1 or -class 2 by a De Novo classification appeal may be commercialized.

3. HOW A DE NOVO MUST BE SUBMITTED AND WHEN:

There are 2 different ways to submit a De Novo application to FDA for a risk-based examination of a device's classification as class I or class II.

Options 1: Upon receipt of a greater-level NSE conclusion in reaction to a 510(k) application. to reach a substantial equivalence decision, we recommend that sponsors file a Pre-

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Option 2: If an applicant determines that legally marketed device can't be used Submission to elicit feedback from the relevant premarket evaluation unit before filing a De Novo appeal to the FDA.

4. CONTENT OF DE NOVO REQUEST:

To be accepted, a De Novo request must include all the content elements listed in Appendix A of FDA guidance paper document. The FDA will reject a De Novo request that lacks the following key requirements:

- The request is clearly identified as a 513(f)(2) De Novo "Request for Evaluation of Automatic Class III Designation" on the coversheet.
- Regulatory information
- Device information,

5. HOW A DE- NOVO APPEAL MUST BE SUBMITTED:

The de- novo appeal which can also be presented electronically to the appropriate document Control Center (eCopy). De Novo requests may also be sent out to CDRH via the electronic Submissions Template and Resources Request Form (eSTAR).[4]

A De Novo request may be made regardless of a prior 510(k) premarket notice, according to the guidelines, and the regulatory procedures for De Novo applications are outlined in 21 CFR 860.220. If the producer fails to post an eCopy in time, which must be filed collectively with an eCopy below the relevant procedure, the overview of the software might no longer start, unless a legitimate eCopy is provided.[5]

3

Figure 1: De Novo Eligibility

TABLE 1: USER FEES FOR APPLICATION IN DE NOVO

ECONOMICAL YEAR	De Novo requests Accepted	Percentage of requests ended in 150 days	User Fees	Small-scale Business Fees
2018-	56;	50 %	-$ 93229	-$ 23307
2019-	61;	55 %	-$ 96644	-$ 24161
2020-	69;	60 %	-$ 102299	-$ 25575
2021-	63;	65 %	-$ 109697	-$ 27424
2022-	-	70 %	-$ 112457	-$ 28114

6. 510(K):

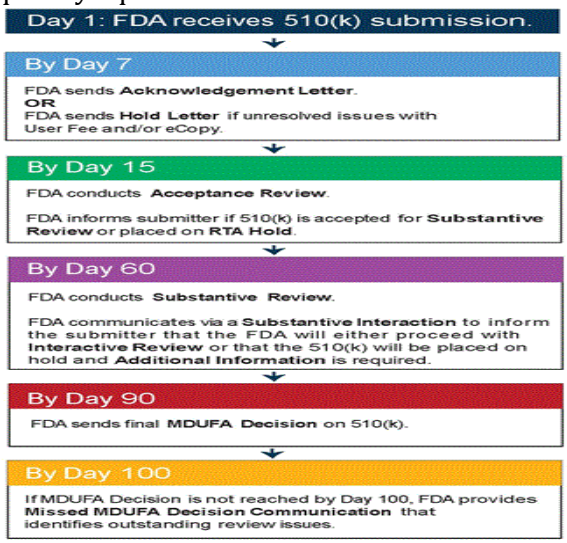
The 510(k) is often the most expeditious path to market approval in the United States, because you establish your device is safe and effective based on this substantial equivalence requirement, rather than presenting more detailed clinical trial data. There are three types of 510(k)s: traditional, abbreviated, and special.

I. when 510(k) is requires:

A 510(k) is essential for new devices that have a predicate on the market that may be utilized to demonstrate their safety and effectiveness. A PMA is necessary for high-risk or revolutionary devices that require more scrutiny to be proven safe and effective. This could include alterations to the: Materials, Materials, Chemical structure, Manufacturing procedure. Energy source, intended application, you must register your device at least 90 days before you intend to release the device.[6]

II. 510(k) submission process:

Once the device is determined to be subsequently equivalent it can be marketed in US.



7

Figure 2: 510(k) submission process

7. EVALUATION OF DE NOVO:

Device manufacturers needed the federal law to inform the FDA of their intention to commercialize a medical device at least 90 days before commercializing. Historically, if an industry developed a novel medical device that was not based on a similar device (no substantial equivalent), the FDA automatically classified the device as Class III, regardless of the device's nature. It might be an adhesive patch, but it would still be classified as an implanted device that requires a lengthy PMA process. This frequently resulted in a lengthy back-and-forth with the FDA, which may last well over 200 days. Because the industry needs a better process, the FDA established the de novo pathway.[8]

8. WHY ITS NEEDED:

De Novo offers a commercial option for unique medical devices about which basic control alone, or normal plus special controls, provide assurance of safeties and effectiveness for the intended purposes, but for which no lawfully commercialized reference equipment exists.[9]

9. HOW IT WORKS:

DE NOVO takes place when there is no substantial equivalent device is there in market. It is a process to register a newly invented medical device in market which where clinically proven as safe.[10]

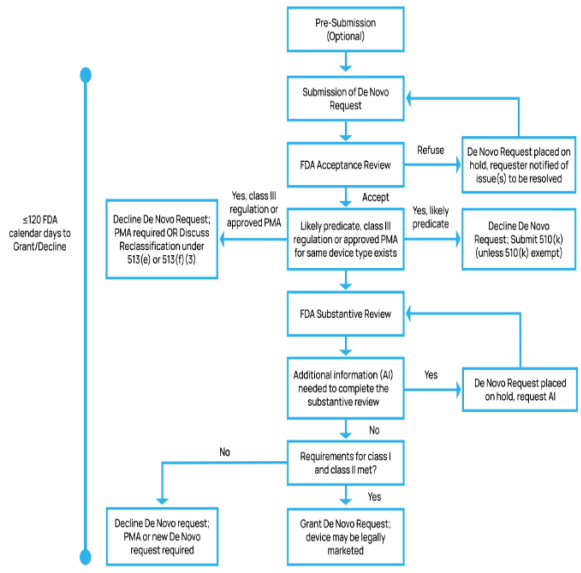


Figure 3: working process of de novo

10. BENEFITS OF DE NOVO:

The de novo road is a speedier path to regulatory approval; but, how quickly a company gets to market is determined by its level of preparedness to traverse the regulatory pathway. One of the primary advantages of the de novo is less interactions with the FDA.[11]

11. MEDICAL DEVICES:

Medical Devices DEFINITION: - Medical device is an integral element of patient protection and supervision. Because of their difficulties, as well as the presence of strength considerations in most of the medical equipment, stricter safety standards and procedures are required.

12. MEDICAL DEVICE INTRODUCTION:

A medical device is any equipment, instrument, material, apparatus, or other product, used alone or in along with extra devices, including the software necessary by the maker for its intended function, which is meant to be used for humans for the following purposes:

- illness detection, prevention, surveillance, diagnosis, or alleviation
- inspection, substitution, or modification of physiological or anatomical processes
- control of conceptions, which does not accomplish its primary required task in or on the human by pharmacologic, immunologic, or metabolic processes, but whose function may be supported by such ways.

Medical devices are major aspect of patient supervision or protection. As a result, in addition to system working, the essential aspect of patient and their health care provider safety is included. Testing is a means of ensuring that the products meet the required standards. As a result, product testing provides an initial level of examination of a device's suitability and safety. People are willing to spend money on innovative technologies and solutions to boost their health. As a result, the use of medical devices in the healthcare business has increased dramatically. It should meet 3 conditions: -

i. it should be recognized by national formulary or pharmacopoeia
ii. it should be employed in illness treatment, prevention, and mitigation.
iii. It is meant to influence the structure and

function of the human body.

13. MEDICAL DEVICE TYPES:

Active Medical Device - Any medical equipment that is powered by a source other than the human body or gravity is considered an active medical device. Active implantable medical device - any active medical device that is meant to be entirely or partially implanted, surgically or medically, into the human body or through a natural aperture, and to survive after the surgery. In vitro diagnostic medical device — any type of medical equipment that is reagent, reagent material, vernier caliper, control materials, kits, equipment, instruments, or system designed by the producer to be utilized in vitro for the assessment of material derived from human beings' body. [12]

TABLE 2: MEDICAL DEVICE CLASSIFICATION:

Class	Categorization/classification	Exemplification
Class I	Lower risk level	Thermometers, Tongue depressors
Class IIA	Lower to Moderate risk level	Hypodermic needles
Class IIB	Moderate to High risk level	Lung ventilators and bone fixation plates
Class III	High risk level	Heart valves and implantable defibrillators

EXAMPLE OF MEDICAL DEVICE:

12

14. PRODUCT LIFECYCLE OF MEDICAL DEVICE:

The appropriate handling of medical devices during their lifespan is a critical activity that benefits both manufacturers and end users. As medical devices progress through their lifetime cycles, they are subjected to additional process, testing, and regulation constraints. Previously, medical equipment authorities centered quality regulations on the device development and design process, although enhancements such as ISO 13485 have only been accomplished.[13]

Stages of medical device life cycle: The concept of medical device product lifecycle is developed from the larger context of PLC. A medical device's life cycle may be split into six phases, each with its own regulatory requirements.

Phase 1: Concept: At this point, the medical device is merely a notion. A medical device manufacturer may begin to describe the product, examine funding options and possible approaches to commercialization, and establish device criteria during the idea stage.

Phase 2: Planning: This stage is distinguished by the collecting of user requirements and their conversion to technical specifications of the end product.

Phase 3: Design: A medical device begins this phase when the specifications have been identified. Engineers will repeat the product design process, collect feedback forms, do model validation and verification, and then start the writing of relevant documentation.

Phase 4: Validations: During validation stage of a life cycle of the product, medical device makers perform clinical verification procedures to guarantee that the equipment is both effective and safe. For the product to be marketed in the intended locations, it will be branded, and a needed regulatory filing will be made.

Phase 5: Launch: Once a medical device company wins clearance to market a product, the product enters the release phase of its life cycle. The device will be supplied to physicians,

hospitals, and clinics, and the manufacturer will provide training and support to ensure the technology is utilized efficiently.

Phase 6: Post Market: When medical equipment is introduced to the market, it enters the post-market stage of its product lifespan. There will be efforts to ensure that unpleasant occurrences related with medical devices are recorded through post-market surveillance. If product is successful, it could be presented to an additional market.[14]

15. GLOBAL MEDICAL DEVICE NOMENCLATURE:

I. Importance of consistent naming:

- Medical devices are traded internationally.
- Regulatory need to approve the device by identifying the product group and related hazards and find systemic failures.
- Hospitals can identify the products they need and manage their inventory

II. Why it is needed:

- Existing nomenclature: National systems and single language; Poor definition; Difficult to recent technologies and Duplication & Uncontrolled

III. What is GMDN:

- GMDN is international standard (ISO 15225) for naming medical device
- It is Used by 65 national medical device regulators
- There are over 4000 manufacturers worldwide
- Translated in 25 languages& it is internationally accepted process

IV. Global acceptance

- GHTF proposed GMDN for UDI
- Ethical committee proposed GMDN for EUDAMED
- EUCOMED supports use of GMDN to fulfil needs of European manufacturers.
- WHO & MSF use GMDN for developing countries

a) PROCESS: process includes:

- Identify the GMDN code from GMDN database, Provide the GMDN to you distribute, Use the GMDN code to register product, Use with Unique Identification Device

b) UDI:

- Product marking, Production identifiers, Machine readable & linked to other product data

c) RELATIONSHIP OF GMDN AND UDI:

- Device- UDI, Generic device group- GMDN

d) EXAMPLES:

- Post marketing surveillance and better regulation[15]

16. ADVERSE EVENT REPORTING SYSTEM:

Introduction:

The aim of reporting adverse reactions and end-user evaluations is to reinforce patient and user health and safety. The second study group consists of members from regulatory agencies in the United States, Europe, Canada, Japan, and Australia, as well as representatives from European, American, Canadian, and Japanese organizations. Existing regulative policies of SG2 member states want scientific tool producers to tell NCAs of precise unfavorable occurrences. This evaluation highlights a worldwide version that gives hints at the types of unfavorable reactions associated with scientific gadgets that makers must file again with a National Competent Authority (NCA). It was designed to shape the regulatory requirements of the nation. There are two types to do this reporting:

Decision process:

Any incident that explicitly meets the 3 basic reporting criteria following will be classified as an undesirable incident and must be reported to the appropriate NCA.

I. The occurrences listed below are examples of typical occurrences.
a) A glitch or degradation in the functionality or characteristics
b) Poor manufacturing design and threat to public health.
c) Inaccurate in labelling, usage directions, and/or advertising materials.

II. The incidence is related with the

manufacturer' device: -
The manufacturer should consider the relationship between the device and the event when assessing the link, A healthcare professional's assessment supported on the availability of the information; - data about prior, similar events; & different information maintained by the manufacturer.

III. The occurrence resulted in one among the subsequent outcomes: -
a) Death of a patient. Severe bodily harm to a patient/individual or different subject
b) There were no fatalities or significant injuries, however this event could result in serious harm AND death to a patient/individual or other subject if it recurs.
Examples of reportable adverse events:

i. Losses of detection after the pacemaker has reached the end of its useful life. The elective replacements prompt did not appear when it should have appeared despite the device specifications.
ii. Patients sustained burns to surrounding organs undergoing uterine endometrial ablation.
iii. The patient died because of an unprotected ECG cable becoming entangled in the main power source.

Exemption Rules:

once any of the subsequent exemption rules are met, the manufacturer isn't needed to report the adverse incidence to NCA-

i. Defect in new device found by the user prior to its use-> whether limits within the manufacturer's instructions to use exist, defects in devices that will commonly be recognized by the user, and where no significant damage has happened do not require notification.
ii. The medical device' service life-> If the sole cause of the unpleasant reaction was that the instrumentation outlived its service life as specified by the
iii. manufacturer, and the failure mechanism was not exceptional, the adverse reaction is not necessary to be documented.[16]

TABLE 3: COMPARATIVE STUDY OF MEDICAL DEVICE IN MAJOR COUNTRIES

COUNTRY	USA	EU	INDIA	CANADA	AUSTRALIA
REGULATORY AUTHORITY	USFDA	EMA (European Medicine Agency)	CDSCO	Health Canada	TGA (Therapeutic Good Administration)
CLASSIFICATION	3 Categories Class 1 Class 2 Class 3	4 Categories Class 1 Class 2a Class 2b Class 3	4 Categories Class A- Class B- Class C- Class D-	4 Categories Class 1- Class 2- Class 3- Class 4-	4 Categories Class 1 Class 2a Class 2b Class 3
LEGISLATION AND GUIDELINES	1. 21 CFR part 807 2. 21 CFR part 807 Subpart E 3. 21 CFR part 812 21 CFR part 814	3 Directives 1.AIMD- 93/385/EEC 2.MDD- 93/42/EEC 3. IVD-98/79/EC	1. DCGI 2. IMRDA 3. D&C Act 1940 AND Rules 1945	1.TPD Therapeutic product directorate)	1. ARGMD 2. TGA 1989 Act 3. TGA regulation 2002
PRE-MARKET APPROVAL APPLICATION	• 510(k): most class II devices • PMA- most class III device	• class 1 device self - declaration •QMS and technical construction file	1.wholesale forms (form 20B,21B/21C 2.Form of medical device- form 15	Medical device License: class 2, 3 and 4 MD	• Conformity assessment document • GMDN code
MD REGISTRATION FEES	1.$5,672 2.510(K)- $3,529 3.PMA- $261,388	1)Class 1- 350 EUR 2)CLASS 2a,2b-700 EUR 3)CLASS 3- 1000 EUR	CLASS A – PMF - $1000 DMF- $50 CLASS B- PMF- $2000 DMF- $1000 CLASS C & D PMF- $3000 DMF- $1500	1. CLASS 2 - $450 2. CLASS 3- $7477 3. CLASS 4- $24345	1 Class 1 - $640 2 Class 2a- $940 3 Class 2b- $940 4. Class 3- $1200
PROCESSING TIME	One to Eight months	For MD Class 1 and 2a – 6 months For MD class 2b & 3- 12 months	Six to Nine months	For MD class 1&2 – approx. 2 months For MD class 3&4- approx. Four to Eight months	Before 255 days of submission of application
LICENSE VALIDITY TIMING	------	5year	5 Years	Every license should be re-registered by November 1 of every year	5 Years
REGULATORY REQUIREMENTS	-21 CFR PART 820,812,56,54,50	- EN ISO 14155	-ISO 13485	-ISO 14155	-ISO 13485
ADDITIONAL DOCUMENT REQUIREMENTS	-listing of medical devices -Registration establishment -requirements for labelling -QSR	-conformity assessment procedure -technical doc	-certificate of declaration -details of manufacturer -power of the attorney	-license establishment -investigational testing -reporting of MD, labelling of QSR	-reference and details of client -procedure for conformity assessment -details of manufacturer

CONCLUSION:

In this paper, de novo is described briefly. How can a newly invented medical device launch into the market if there is no subsequently equivalent device before. For acceptance, the device goes through 510(k) submission and PMA. And a brief discussion of medical devices i.e., a medical device is any equipment, instrument, material, apparatus, or other product, used alone or in along or in conjunction with other devices, including the software necessary by the maker for its intended function. Medical devices are a major aspect of patient supervision or protection. Medical devices' product life cycle, i.e., handling of a medical device through its lifespan id described above. How a medical device is named by global medical device nomenclature and how it will have a unique name are narrated in above. And what will be the adverse events of the medical device and its types, i.e., decision process and exemption rule are describes. A comparative study of major countries i.e., the USA, the European Union, India, Canada, and Australia, is briefly explained with appropriate information.

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Ethical approval

Since this work does not involve any animal studies it does not require Ethical approval

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