FDA-CFR Title 21-Food and Drugs: Parts 800 to 1299

Indumathy Jagadeeswaran, Nandhini Palani, and Ganesh Lakshmanan

1 Introduction

(a) *FDA and FD&C Act*

Federal Food, Drug, and Cosmetic Act (FD&C Act) is the legal authority of FDA that regulates the medical devices along with electronic radiation-emitting products. FDA's level of control over these products was provided in the FD&C Act where the act is comprised of regulatory requirements and provisions for FDA to control the products. FDA develops, publishes, and implements regulations and provisions of FD&C Act over medical devices and radiation-emitting products [1].

(b) *Federal Register (FR)*

The FR is an official standard register of FDA, where official daily publication for rules, proposed rules, and notices of Federal agencies and organizations are documented. In addition, executive orders and other crucial presidential documents are encompassed in the register. Initially, all the rules proposed were made available in the FR for availing public comments, and the finalized rule will be documented in the Code of Federal Regulations (CFR). After the respective modifications, if any, according to public and professional comments, the final regulations will be placed

I. Jagadeeswaran (✉)
Department of Biological Sciences, Southern Methodist University, University Park, TX, USA

N. Palani
National Reference Laboratory, National Institute for Research in Tuberculosis, Chennai, Tamil Nadu, India

G. Lakshmanan
Department of Anatomy, Asan Memorial Dental College and Hospital, Chengelpetu, Tamil Nadu, India

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_12

or codified into the printed edition of the Code of Federal Regulations (CFR) on an annual basis [1, 2]. Specific website for finding recently published FR's is Regulations.gov [3].

(c) *Code of Federal Regulations (CFR)*

The CFR is a codification where executive departments and agencies of the federal government publish the general and permanent rules in the FR [4]. The CFR was categorized into 50 title heads which epitomize broad areas subject to Federal regulation [5]. The highly important title of CFR is Title 21 Parts 800-1299 in which most of the FDA's medical device and radiation-emitting product regulations were comprised. The CFR codifies final regulations of various aspects of design, clinical evaluation, manufacturing, packaging, labeling, and postmarketing surveillance of medical devices. Regulations addressing standards and product reports implicating radiation-emitting products were addressed in CFR [1]. Various fields of products are categorized into the parts as mentioned in Table 1.

(d) *Electronic Code of Federal Regulations (e-CFR)*

The e-CFR is a current updated version of CFR, which is an unofficial editorial compilation of CFR material and FR amendments produced by the national archives and Records Administration's Office of the Federal Register (OFR) and the Government Printing Office. However, it is an official legal edition of the CFR. On a daily basis, the new materials will be updated by the OFR in the e-CFR. The current update status appears at the top of all e-CFR webpages [6].

2 FDA-CFR Title 21-Food and Drugs: Parts 800 to 1299

Title 21 CFR-FDA Parts 800 to 1299 were comprising of many essential regulations of medical devices and radiation emitting products [7]. The parts from 800 to 898 related to medical devices and their responsibilities were tabulated [7] in Table 2.

In this chapter, we will discuss in detail all the parts pertinent to medical devices in FDA-CFR Title 21.

Table 1 Respective parts of CFR dealing with specific products and responsibilities

S.No.	CFR parts	Products and responsibilities
1	1–99	Product jurisdictions, protection of human subjects, institutional review boards, etc.
2	100–799	Food, human and animal drugs, biologics, cosmetics
3	800–1299	Medical devices and radiation emitting products
4	1300–1499	Controlled substances

Table 2 Parts of FDA-CFR Title 21 which carry responsibilities of medical devices

S.No.	CFR Title 21 part no.	Products and responsibilities
1	800	General [8]
2	801	Labeling [9]
3	803	Medical device reporting [10]
4	806	Medical devices; reports of corrections and removals
5	807	Establishment registration and device listing for manufacturers and initial importers of devices
6	808	Exemptions from federal preemption of state and local medical device requirements
7	809	In vitro diagnostic products for human use
8	810	Medical device recall authority
9	812	Investigational device exemptions
10	813	[reserved]
11	814	Premarket approval of medical devices
12	820	Quality system regulation
13	821	Medical device tracking requirements
14	822	Postmarket surveillance
15	830	Unique device identification
16	860	Medical device classification procedures
17	861	Procedures for performance standards development
18	862	Clinical chemistry and clinical toxicology devices
19	864	Hematology and pathology devices
20	866	Anesthesiology devices
21	868	Cardiovascular devices
22	870	Dental devices
23	872	Ear, nose, and throat devices
24	874	Gastroenterology-urology devices
25	878	General and plastic surgery devices
26	880	General hospital and personal use devices
27	882	Neurological devices
28	884	Obstetrical and gynecological devices
29	886	Ophthalmic devices
30	888	Orthopedic devices
31	890	Physical medicine devices
32	892	Radiology devices
33	895	Banned devices
34	898	Performance standard for electrode lead wires and patient cables

2.1 Part 800: General Requirements for Specific Medical Devices [8]

All the preparations that were offered or intended for various ophthalmic purposes including contact lens solutions should be sterile, as per the informed medical opinion. If the ophthalmic preparations are nonsterile and fall below their avowed standard of purity or quality, then the preparation was considered as adulterated under Section 501(c) of the FD&C Act and may also be misbranded according to Section 502(j) of the Act. This ruling is applicable to all ophthalmic preparations which are considered as medical devices, i.e., contact lens solutions, by this regulation and for the ophthalmic preparations that are regulated as drugs by the regulation in 200.50 of FDA. The containers or individual carton used should be at the time of filling and shall be sealed to ensure that the contents cannot be used without destroying the seal. Multiple-dose ophthalmic preparations should be packed in containers either comprised of one or more suitable and harmless substances for inhibiting the growth of microorganisms or proper labelling with duration of use and necessary warnings to minimize contamination during use.

The FDA has an authority and responsibility under the FD&C Act, to establishment of a uniform national standard for tamper-resistant packaging and labelling of the over-the-counter (OTC) healthcare products including contact lens solution and/or tablet or other dosage form used for preparing ophthalmic solutions in accordance with 800.12 regulation of the FDA. Tamper-resistant packages have an indicator or a barrier to entry, which if breached or missing gives a visible evidence to the consumers that the tampering has occurred. This act improves the security of OTC products vulnerable to malicious adulteration and assure the safety and effectiveness of the product contained therein. The indicator or barrier is required to be distinctive by design or by using identification characteristics like pattern, name, registered trademark, logo, or picture in order to reduce the likelihood of substitution of the tamper-resistant feature. The term "distinctive by design" indicates that the package cannot be duplicated with commonly available materials or processes. A statement on the temper-resistant feature of the package is required to be placed in a way that it will be unaffected if the temper-resistant feature of the package is breached or missing. For example, statement on a bottle with a shrink band might say "For your protection, this bottle has an imprinted seal around the neck." All the ophthalmic solutions intended for retail sale that is not packaged in a tamper-resistant package and not labelled in accordance with this section of FDA regulation shall be considered adulterated under Section 501 and/or misbranded under Section 502.

Given the prevalence of human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS) and other blood-borne infectious diseases, FDA had started to regulate the quality of barrier devices such as medical gloves (i.e., surgeons' gloves and patient examination gloves) in order to control the risk of disease transmission in the healthcare context. Healthcare workers are recommended to wear medical gloves while handling blood or other body fluids, mucous membranes, or non-intact skin of all patients by the Centers for Disease Control and Prevention (CDC) to reduce the risk of transmission of blood- and

fluid-borne pathogens. Hence, FDA defined adulteration for patient examination and surgeons' gloves, as a means of assurance of the safety and effectiveness of the devices through this regulation. FDA collects sample from lots of medical gloves based on sample sizes, sample inspection levels, and acceptable quality levels (AQLs) as per International Standard Organization (ISO) 2859, "Sampling procedures for inspection by attributes." The lots of medical gloves that are sampled, tested, and rejected using the test methods such as general test method, leak test materials, and visual defects and leak test procedures are considered adulterated as per the 501(c)act. A lot of medical gloves is considered adulterated by FDA, if the number of defective gloves found in the tested sample meets or exceeds the applicable rejection number at 1.5 AQL for surgeon's gloves or the 2.5 AQL for examination of patient gloves.

Administrative Practices and Procedures
The medical devices intended for human use may be ordered detention in accordance with Section 704 of the FD&C Act by an authorized FDA representative, during an inspection, if the device is believed to be adulterated or misbranded, as defined in Section 201(h) of the Act. Administrative detention prevents the distribution or use of adulterated or misbranded medical devices to ensure public safety, until the FDA considers the action to be carried out concerning the devices and to initiate legal action, if appropriate. The medical devices ordered detention by FDA may not be used, moved, altered, or tampered during the detention period. The detention period is usually 20 calendar days. However, if the FDA determines that a greater period is required to seize the device or to evaluate the legal action required, the total detention period may not exceed 30 calendar days.

2.2 Part 801: General Labeling Provisions [9]

The label of the device in package form shall specify the name and place of business including city, State, and/or zip code of the manufacturer, packer, or distributor. If medical devices are manufactured or packed or to be distributed at a place other than the principal place of business of the manufacturer, packer, or distributor, then the label may specify the principal place of business, unless such statement would be misleading. The labelling of a device is considered misbranded, if it represents a false or misleading representation with respect to another device or food or cosmetic or a drug. If the label of the medical device includes a printed expiration date, date of manufacture, or any other date intended to be brought to the attention of the medical device user, the date should be presented in the following format: year (YYYY), followed by month (MM) and day (DD), i.e., 2020-11-03. Labelling of a device should also supply adequate directions for use, which ensures a layman can use a device safely for its intended purposes. Directions for use may be considered inadequate because of omission (either in whole or in part) or incorrect specification of:

(a) Statements on the conditions, purposes, or uses for the intended common use of medical device, for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising
(b) Quantity of dose for persons of different ages and different physical conditions
(c) Frequency of administration/application
(d) Duration of administration/application
(e) Time of administration/application, in relation to time of meals, time of onset of symptoms, or other time factors
(f) Route or method of administration or application
(g) Preparation for use, i.e., adjustment of temperature or other manipulation or process

These statements are required to appear on the label, and no exemption due to insufficiency of label space will be allowed by the FDA under Section 502(c)act. All the statements and other information on the label shall appear in English language or replaced by the predominant language of the territory, where the device is distributed.

Labeling Requirements for Unique Device Identifier

The label/package of every medical device shall bear a unique device identifier (UDI) that meets the requirements of Section 801.20 and Part 830 of the FDA. In addition to the UDI on label, each device must also carry a permanent direct marking UDI on the device itself, which can be identical to the UDI on the label of the device or a different UDI that can be used to distinguish the unpacked device from any device package containing the device. Direct marking of UDI on the device shall be exempted in conditions such as interference with the safety and effectiveness of the device, technologically not feasible for direct marking, and in single-use devices. Every UDI must be presented in both easily readable plain text and automatic identification and data capture (AIDC) technology. The UDI must include device identifier segment that conveys the information such as a lot or batch number, a serial number, a manufacturing date, and an expiration date. Stand-alone software regulated as a medical device must display its UDI as a readable plain-text statement either when the software starts or through a menu command or both. Once the UDI is assigned to a device, then National Health-Related Item Code (NHRIC) or National Drug Code (NDC) number may no longer be required to be on the label/package of the medical device. However, medical devices including class I device with a universal product code (UPC), single-usage devices, combination product with NDC numbers, and shipping containers are excepted from the requirement to bear a UDI according to Sections 801.30, 801.45, and 801.128(f)(2) of this FDA regulation. Section 801.55 provides a means to request an exception or alternative not provided by those provisions.

Labeling Requirements for Over-the-Counter Devices

The term principal display panel in over-the-counter devices in package form refers to the part of a label that is usually displayed, presented, shown, or examined under customary conditions of display for retail sale. The principal display panel should

accommodate and display all the mandatory label information with clarity and conspicuousness, and without obscuring designs, or crowding. In medical device packages with alternate principal display panels, the label information shall be duplicated on each principal display panel. To ensure uniform font size in declaring the contents of principal display panel for all packages, the term area of the principal display panel is defined as the area of the side or surface that bears the principal display panel. For example, in case of rectangular package, one entire side (product of height times the width of that side) shall be principal display panel side. The principal display panel shall bear a statement of identity of the commodity, followed by an accurate statement of the principal intended action(s) of the device. Statement of identity is one of the principal features of the principal display panel and shall be in size reasonably related to the most prominent printed information on such panels. The label of these over-the-counter medical device in package shall bear a declaration of the net quantity of contents expressed in terms of weight, measure, numerical count, or its combination. All over-the-counter devices containing or manufactured with chlorofluorocarbons, halons, carbon tetrachloride, methyl chloride, or any other class I ozone-depleting substance designated by the Environmental Protection Agency (EPA) shall carry a warning statement. In accordance with the requirements of 40 CFR part 82, this warning statement should be legible, prominent, and conspicuous on the product, its immediate container, its outer packaging, or other labeling to be easily read and understood by consumers.

Exemptions from Adequate Directions for Use

Devices with potentiality for harmful effect, or its common method of use known to ordinary individual or requires collateral measure such as supervision of a practitioner licensed by law for its use, are exempted for the requirement of "adequate directions for use" in the label. Medical devices used for processing or repacking in the manufacture of another drug/device or as in vitro diagnostic product (use in diagnosis of disease) or shipped or sold to persons regularly and lawfully engaged in teaching, law enforcement, research, and analysis, or any device held by the Strategic National Stockpile, shall be exempted from Section 502(f)(1) of the FDA Act, if the device meets the following conditions:

(a) If the device is in the possession of a person or his employees or agents manufacture, transportation, storage, or wholesale or retail distribution of such device; or a practitioner, such as physicians, dentists, and veterinarians, licensed by law to use or order the use of such device.
(b) Is sold only to or on the prescription or for use by a licensed practitioner in the course of his professional practice.
(c) Label of the medical device (except surgical instruments) bears symbol "Rx only" or "℞ only" or caution statement to restrict the sales of the device by or on the order of a state law licensed practitioner; and a method of its use or application.
(d) Labeling on or within the package of the dispensed medical device should bear the information for use, including indications, effects, routes, methods, frequency, and duration of administration, and any relevant hazards, contraindica-

tions, side effects, and precautions for the purpose it's advertised or represented.

(e) All the labelling bearing the information for use of the device also bears the date of issuance or the date of latest revision of such labelling.

2.3 Part 803: Medical Device Reporting [10]

This part delineates the requisites for medical device reporting to the facilities where the device will be used, to manufacturers, importers, as well as distributors. The device user facility should register and notify the deaths and serious injuries contributed and suspected from the device usage. Device malfunctions and adverse events should be recorded and maintained. These ensures the devices are not adulterated or misbranded and are used safely and effectively. The distributor must also maintain the records of incidents, though they may not report the same. Any report submitted can be disclosed to the public in accordance with §803.9. It includes FDA report of telephone records. But trade secrets, confidential commercial and financial information, personal medical information like serial numbers of implanted devices, and names and information identifying a third party that voluntarily submitted an adverse event report can all be deleted before public disclosure.

Reporting Requirements That Applies to Device User Facility

The device user facility must submit individual adverse events within 10 working days including device-related deaths and serious injuries to the manufacturer and FDA. The importer should submit annual report on adverse events, device-related deaths, or serious injuries to FDA and the manufacturer. Any device-related malfunction should be reported to the manufacture, and the manufacturer should report about individual adverse events in 30 calendar days. Any reportable event requiring remedial action or upon a written request over any reportable event and to submit supplemental reports to a submitted initial report can be submitted within 5 working days. The manufacturer or importer must report individual adverse events in electronic format in accordance with §803.11.

The manufacturer or importer must report initial, supplemental, or follow-up reports in electronic format that FDA can process, review, and archive. User facilities must submit their reports and additional information in electronic format in English to FDA as "User Facility Report" or "Annual Report." Confrontations with public health emergencies can be brought to FDA's attention at 301-796-8240 or toll free at 866-300-4374, followed by the submission of an email to *emergency.operations@fda.hhs.gov*. When further additional information is required, the FDA will notify in writing about the required additional information if protection of the public health requires additional or clarifying information for medical device reports submitted and in cases when the additional information is beyond the scope of FDA reporting forms or is not readily accessible to FDA. All such request will state the reason or purpose for the information request, specify the due date for submitting

the information, and clearly identify the reported event(s) related to our request. Verbal request for additional information will be followed by request in writing. Any report or information submitted to FDA following the written request does not necessarily reflect a conclusion that the device, or manufacturer or their employees, caused or contributed to the adverse event.

Requirements for Developing, Maintaining, and Implementing Written MDR Procedures

Any user facility, importer, or manufacturer must develop, maintain, and implement written MDR procedures for internal systems that provide for identification, communication, and evaluation of events with a standardized review process and timely transmission of the report to the FDA or manufacturers with evaluation of reportable event including all medical device reports and information submitted to manufacturers or FDA along with evaluated information for annual reports and systems that ensure access to information that facilitates timely follow-up and inspection by the FDA.

Requirements for Establishing and Maintaining MDR Files or Records

A user facility, importer, or manufacturer must establish and maintain MDR event files and keep accessible with all information in possession with copies of report submitted and copies of all electronic acknowledgements from FDA and permit any authorized FDA employee to access and verify the same. An MDR file has to be retained for 2 years from the date of event. A device distributor must maintain a device complaints records of all incident information related to identity, quality, durability, reliability, safety, effectiveness, or performance of a device along with distributor evaluation of the same at least for 2 years even if the distributor no longer distributes the device.

Exemptions, Variances, or Alternative Forms of Adverse Event Reporting Requirements

A licensed practitioner is an individual, who manufactures devices intended for use in humans solely for this person's use in research or teaching and not for sale. Dental laboratories or optical laboratories are exempted from adverse event reporting. A manufacturer, importer, or user facility, may request an exemption or variance from any or all of the reporting requirements, with the information necessary to identify the device and a complete statement of the request for exemption, variance, or alternative reporting along with proper justification. However, this has to be granted by FDA and can be revoked at any time.

Applicable Requirements for Individual Adverse Event Reports

A health professional or consumer or any other entity can submit their voluntary reports to the FDA regarding their devices or products using form FDA 3500A including a mandatory report in written form. An e-submission from a user facility, importer, or manufacturer must have information about the patient, the event, the device, and the "initial reporter" along with information from blocks G and H as well as including any corrected or missing information. Within 10 days of an adverse event, the user facility should report to the manufacturer or to the FDA. The

manufacturer should report to the FDA in 30 calendar days. All the adverse reporting codes to use with form FDA 3500A can be obtained from The MedWatch Medical Device Reporting Code Instruction Manual available at https://www.fda.gov/medical-devices/mandatory-reporting-requirements-manufacturers-importers--and-device-user-facilities/mdr-adverse-event-codes. Any additions and modifications to the existing codes will be made available to all reporters from time to time. Multiple information of the same patient and same event can be submitted as a single report. If the information received is determined as erroneous, it need not be reported by user facility, importer, or manufacturer. However, the documentation of these reports would be mentioned in MDR files for the time periods specified in §803.18. Any reporting to the wrong manufacturer or importer should be reported to the FDA by the receiver of such report.

User Facility Reporting Requirements

For a user facility, reports of death and serious injury must be submitted in 10 days to the manufacturer and the FDA as required by §803.32. Reports sent to the Agency must be submitted in accordance with the requirements of §803.12 (b). This should include information found in documents possessed by the user facility and any information that becomes available as a result of reasonable follow-up within the facility. An annual report should be submitted on form FDA 3419 by January 1 of each year and should include CMS provider number used for medical device reports, reporting year, name and complete address, total number of reports attached, date of the annual report, and details of the person reporting, and all information of the reportable events should be noted.

Importer Reporting Requirements

Reports of deaths and serious injuries as well as reports of malfunctions should be reported to the FDA. Reports should be prepared and submitted in 30 calendar days. Importer should correspond generally to the format of form FDA 3500A with the necessary patient information, adverse event or product problem, all necessary device information, and initial reporter information as well as the importer information.

Manufacturer Reporting Requirements

In case of a suspected death or grievous injury caused by the device or upon any malfunction of the device, it should be reported within 30 calendar days. All sorts of information obtained by contacting a user facility, importer, or other initial reporter as well as by analysis, testing, or other evaluation of the device should be submitted to the FDA. It is the responsibility of the manufacturer to get and submit all the details and also to investigate each event and evaluate the cause of the event. All patient information, complete adverse event or product malfunction information, detailed device information, manufacturer details, and initial reporter information are to be furnished by the manufacturer in the form FDA 3500A from Block A to Block H. An MDR reportable event necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health, and upon receiving a written request for the submission of a 5-day report from the FDA, a manufacturer

should submit a 5-day report within 5 working days. It can be extended upon a written interest and is in the interest of the public. Every foreign manufacturer whose devices are distributed in the United States shall designate a US agent to be responsible for reporting. The US-designated agent accepts responsibility for the duties that such designation entails. US-designated agents of foreign manufacturers are required to report to the FDA, conduct and obtain necessary information on investigation and evaluation of the event, forward MDR complaints to the foreign manufacturer, and maintain documentation of this requirement and complaint files and register.

2.4 Part 806: Medical Devices, Reports of Corrections and Removals [11]

This part implements the provisions of Section 519(g) of the Federal Food, Drug, and Cosmetic Act that mandates device manufacturers and importers to report on any of the device corrections and removals as well as to maintain records of those corrections and removals. However, actions taken by manufacturers to enhance the performance or quality of a device which do not pose a health threat, market withdrawal of the device, routine servicing, and stock recovery can be exempted from reporting requirements.

Reports of Corrections and Removals
For any correction or removal of a device, the device manufacturer or importer should submit a written report. This can be aimed at reducing a health risk posed by the device or to remedy a violation of the act caused by the device, and it should be done within 10 working days of the initiation of the correction or removal. In the submitted report, the manufacturer or importer should include the 7-digit registration number of the entity responsible for submission of the report of corrective or removal action (if applicable); the month, day, and year that the report is made; a sequence number (i.e., 001 for the first report, 002 for the second report, 003, etc.); and the report-type designation "C" or "R". Firms that do not have a 7-digit registration number may use seven zeros followed by the month, date, year, and sequence number (i.e., 0000000-6/1/97-001-C for corrections and 0000000-7/1/97-001-R for removals). Reports received without a 7-digit registration number will be assigned a 7-digit central file number by the district office reviewing the reports. It should also include the details of the manufacturer, details of the event giving rise to the information reported, and the corrective or removal actions that have been done and are expected to be taken, details of the production including date, no. of devices produced, details of all consignees of the devices, and how many was distributed by each of them. A copy of all communications regarding correction or removal should be added to the report. To amend any submitted report, it should be done within 10 working days of initiating the extension of the correction or removal and amended by submitting an amendment citing the original report number assigned.

Records of Corrections and Removals Not Required to Be Reported
All correction or removal of a device that is not required to be reported to the FDA should be maintained as a separate record. Such records shall contain details of the device including a unique device identifier (UDI) or the device identifier, universal product code (UPC), model, catalog, or code number of the device and the manufacturing lot or serial number of the device or other identification number and description of reported events and justification for not reporting the event. All communications toward this should be recorded. This should be maintained for a period of 2 years beyond the expected life of the device. Upon request of an officer or employee designated by the FDA and under Section 704(e) of the Act, each device manufacturer or importer should allow them to have access to, and to copy and verify, such records and reports maintained toward the cause. All reports under this part are available for public disclosure, but before disclosing, the FDA will remove any information that constitutes trade secret or confidential commercial or financial information as well as any personnel, medical, or similar information, including the serial numbers of implanted devices, which would constitute a clearly unwarranted invasion of personal privacy. However, if a patient requests all the information in the report concerning that patient, it will be released by the FDA.

2.5 Part 807: Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices [12]

Any distribution of a device intended for human use which is held or offered for sale is termed as commercial distribution (except of those internally transferred/exempted/introduced before May 28, 1976), and the place of business/one general physical location where the device is manufactured/assembled/processed is the establishment. The designated person for annual registration of the establishment and contact person with the FDA for device listing, maintenance, and submission of records and corresponds between FDA and owner/operator is the office correspondent.

Procedures for Device Establishments
(a) *Who Must Register and Submit a Device List?*

The term "device" can be used for all in vitro diagnostic products and in vitro diagnostic biological products. An owner or operator shall register its name, places of business, all the establishments while listing. In addition, registration shall pertain to any person who initiates or develops specifications for a device, makes a device on behalf of specifications provided, repackages or relabels a device, reprocesses a single-use device that has previously been used on a patient, and the initial importer.

(b) *How to Register Establishments and List Devices?*

Owners or operators of establishments must electronically register the device of interest with initial establishment information, updates to registration information,

initial device listing information, and updates to device listing information (including updates to reflect the halt of commercial distribution of previously listed device). If electronic submission is not possible, a waiver may be requested for reasonable explanations by providing information on name and address of device establishments and information about the company and reason for request.

(c) *Times for Establishment Registration and Device Listing*

If the owner or operator of an establishment is newly entering the device in listing, they shall register within 30 days after entering into an operation and submit the device listing information at that time. If already registered, they shall review and update any changes that were not previously reported. Failure to submit any required information on time will be noted as "failed to register" or "failed to list," and the list of device may not be put on the FDA website till complete submission.

(d) *Information Required for Device Establishment Registration and Device Listing*

Registration information includes the name, mailing address of the device establishment, website address, contact details of the owner, establishment, and all trade names used by the establishment. The listing shall include all officers, directors, and partners to furnish to FDA upon request. The official correspondent would serve as a point of contact with FDA on all matters relating to the registration of device establishments. He/she would be responsible for providing the FDA all required registration and listing information electronically, receiving all correspondence from FDA, and supplying the list of officers/directors/partners upon request. The information required for each device listed includes current registration number, name of each establishment, product code of each device, proprietary or brand name(s), FDA-assigned premarket submission number of approved application, and list of each activity or process that is conducted on or done to the device at each establishment.

(e) *Additional Listing Information*

Each owner or operator shall maintain a historical file containing labeling and advertisements in use on the date of initial listing, location of files including currently existing records, historical files, copy of certification, and disclosure statements. Upon specific request, each owner or operator shall provide a copy of all labelling for the device, a copy of all advertisements, label and package insert of the device, a statement of the basis to determine the device is not a restricted one, and list of all distributors for whom the device is manufactured.

(f) *Updating Device Listing Information*

Updating of device listing information is required if an additional establishment begins to engage or if it begins performing another activity on or to the device or ceases to perform an activity on or the device that had previously been identified on the device listing. However, a new device listing is created if device is not currently listed by the owner or operator, if the device is a non-exempt one with new FDA premarket submission number, or if the device is imported or offered into United Sates from a foreign establishment. A device listing is discontinued if all devices

under an exempt product code have been discontinued or all devices associated with an FDA premarket submission number have been discontinued.

(g) *Summary of Requirements for Owners or Operators Granted a Waiver*

An owner/operator who has been granted a waiver from electronic filing must send a letter containing all of the registration and listing information to the Imports and Registration and Listing Team, FDA, and shall update their establishment registration and device listings annually during the period between October 1 and December 31 of each fiscal year. Failure to submit any required information on time will be noted as "failed to register" or "failed to list," and the list of devices may not be put on the FDA website till complete submission.

(h) *Notification of Registrant*

The FDA will assign each device establishment a registration number after verifying the initial registration information that has been submitted along with an identifying number for the owner/operator. Both these numbers will be sent to official correspondent by email or by post. Validation of registration and device listing does not ensure the legal qualification of registration until further scrutinization.

(i) *Public Availability of Establishment Registration and Device Listing Information*

Establishment registration and device listing information is made available for public inspection with exception of certain information including contract manufacturers, contract sterilizers, private label manufacturers, proprietary or brand names, and FDA-assigned listing numbers.

(j) *Misbranding by Reference to Establishment Registration or to Registration Number*

Any representation intended to create an impression of official approval because of registration approval is misleading and may be misbranded.

Procedures for Foreign Device Establishments

(a) *Establishment Registration and Device Listing for Foreign Establishments*

Any establishment in a foreign country importing or offering the device into the United States shall undergo electronic device registration, and the official correspondent of the foreign establishment shall facilitate communication with the FDA on behalf of the owner or operator. Each foreign establishment shall designate only one agent in the United States to act as an official correspondent who resides in the United States and shall maintain a place of business. The correspondent shall assist the FDA by responding to all questions raised, for onsite inspections, and by reporting changes within 10 business days of the change.

(b) *Identification of Importers and Persons Who Import or Offer for Import*

Upon initial registration, annually at time of any changes, each foreign establishment is required to register through FDA electronic device registration and listing system with details of importers of persons who imports or offers for import.

(c) *Exemptions*

The following classes of persons are exempted from registration by the Commissioner of Food and Drugs: a manufacturer of raw materials or components to be used for the device; a manufacturer of a device solely for veterinary purposes or chemical reagents; licensed practitioners, pharmacies, or surgical supply outlets; persons who manufacture, prepare, and propagate devices solely for use in research, teaching, or analysis; and carriers of devices or who dispense devices to consumers.

Premarket Notification Procedures

(k) *When a Premarket Notification Submission Is Required*

Each person who has to register their establishment must submit a premarket notification submission to the FDA at least 90 days before initiating the introduction of commercial distribution of a device intended for human use. This includes all devices being introduced into commercial distribution for the first time or reintroduced with significant changes or modifications in designs, components, method of manufacture, or intended use.

(l) *Exemption from Premarket Notification*

A custom device is exempted from premarket notification requirements if it is intended for use by a patient named in the order of the physician or dentist or solely for use by a physician or dentist or if a distributor who places a device into commercial distribution for the first time under his own name and a repackager who places his own name on a device if the premarket notification submission was filed by another person or if the device was in commercial distribution before May 28, 1976.

(m) *Information Required in a Premarket Notification Submission*

The premarket notification submission shall include the device name, establishment registration number, class of the device, statement of classification, action taken by the person required to register to comply with the requirements, proposed labels, labeling, advertisements, a statement indicating the device is similar or different from other products if any, and a financial certification or disclosure statement or both. The submission should be supported by clinical investigations conducted inside or outside the United States, statement that the submitter believes to best of his/her knowledge about the truthful, and accurate information provided. If any information is requested by the Commissioner, the same has to be submitted promptly, and failure of submission within 30 days will make the premarket notification withdrawn.

(n) *Format of a Premarket Notification Submission*

Each premarket notification submission shall be submitted to respective sections like Center for Devices and Radiological Health or Center for Biologics Evaluation and Research, and all inquiries should be sent as a single version electronically, separately for each product with the designated "510|(k) notification in the cover letter."

(o) *Content and Format of a 510(k) Summary*

A 510(k) summary shall contain details to provide an understanding of the basis for a determination of substantial equivalence, and it shall include the submitter's name, address, and contact details; name of the device trade or proprietary name (if applicable); identification of the legally marketed device to which the submitter claims equivalence; description of the device, its functioning, scientific concepts, and physical and performance characteristics; and a statement of the intended use of the device that is the subject of the premarket notification submission. In addition to it, it shall also include a brief discussion of clinical and nonclinical tests submitted, conclusions drawn from these tests, and an exclusive summary with any other information necessary to be attached.

(p) *Content and Format of a 510(k) Statement*

A 510(k) statement signed by the certifier shall state that "I certify that, in my capacity as (the position held in company by person required to submit the premarket notification, preferably the official correspondent in the firm), of (company name), I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness information, but excluding all patient identifiers, and trade secret and confidential commercial information, as defined in 21 CFR 20.61."

(q) *Format of a Class III Certification*

A class III certification submitted as a part of a premarket notification signed by the certifier shall state that "I certify in my my capacity as (position held in company), of (company name), that I have conducted a reasonable search of all information known or otherwise available about the types and causes of safety or effectiveness problems that have been reported for the (type of device). I further certify that I am aware of the types of problems to which the (type of device) is susceptible and that, to the best of my knowledge, the following summary of the types and causes of safety or effectiveness problems about the (type of device) is complete and accurate."

(r) *Confidentiality of Information*

The FDA will disclose publicly whether the device is on the market and whether the person submitting the premarket notification submission has disclosed his intent to market the device, analyses, or not. But FDA shall not disclose the existence of premarket notification submission for a device that is not in the market or if requested to hold the intent as confidential commercial information up to 90 days from the date of the receipt of submission.

(s) *Misbranding by Reference to Premarket Notification*

Submission of a premarket notification and subsequent determination by the Commissioner that the device intended is substantially equivalent to a device in the

commercial distribution. However, any representation that creates an impression of official approval of a device because of complying with the premarket notification regulation is misleading and can lead to misbranding.

(t) *FDA Action on a Premarket Notification*

After review of premarket notification, FDA will an issue an order declaring the device to be substantially equivalent/not equivalent to a legally marketed device, request more information, withhold decision until certification or disclosure statement is submitted, or inform the applicant that the premarket notification is not required. FDA will determine whether the device of interest is substantially equivalent to a predicate device if it has the same technological characteristics or if the device is as safe and as effective as a legally marketed device.

2.6 Part 808: Exemptions from Federal Preemption of State and Local Medical Device Requirements [13]

This part sets forth the procedure for submission, review, and approval of applications for exemptions from Federal preemption of State and local requirements applicable to medical devices under Section 521 of the FDA Act. The FDA is responsible for determining whether a State or local requirement is equal or substantially identical or different or in addition to the Federal requirements with respect to a device. However, if any State or political subdivision whose requirements relating to a device are preempted in accordance with Section 521(a), they may petition the Commissioner of the FDA for exemption from preemption.

(a) Section 521(a) of the Act prescribes special provisions that after May 28, 1976, no State or political subdivision of a State may establish or continue in effect any requirement with respect to a medical device intended for human use having the force and effect of law, which is different from, or in addition to, any requirement applicable to such device under any provision of the act and which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under the Act.
(b) In accordance with Section 521(b), the Commissioner of the FDA may, upon application by a State or political subdivision, allow imposition of a requirement which is different from, or in addition to, any requirement applicable under the Act to the device (and which is thereby preempted) by promulgating a regulation.

Exemption Procedures
A signed letter from an authorized State or political division in accordance with §808.20 (if not, they will be returned for corrections) may request exemption to the Commissioner of the FDA. For each requirement for which an exemption is sought shall include all the information and explanation to justify the requirement. Upon receipt of the application meeting the requirements of §808.20, the Commissioner shall review such application and will issue in the FEDERAL REGISTER a

proposed regulation to either grant or deny an exemption from preemption for each requirement. An exemption from preemption in accordance with §808.25 shall remain effective until the Commissioner revokes such exemption.

2.7 Part 809: In Vitro Diagnostic Products for Human Use [14]

In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. Data and information submitted shall be treated as confidential by the FDA and any person to whom the data and information are referred.

Labelling for In Vitro Diagnostic Products
The label for an in vitro diagnostic product shall have its proprietary name, established name, and its intended use. For reagents, its established name, its source, and measure of activity should be labelled. A statement of warning and precautions along with a statement "For In Vitro Diagnostic Use" should be added. Any other limiting statement can also be added and shall bear the symbol statement "Rx only" or "℞ only" or the statement "Caution: Federal law restricts this device to sale by or on the order of a ___", the blank to be filled with the word "physician," "dentist," "veterinarian," or the descriptive designation of any other practitioner licensed by the law of the State in which the practitioner practices to use or order the use of the device.

Appropriate storage instructions including temperature, light, humidity, and other factors should be added. For products requiring manipulation, such as reconstitution and/or mixing before use, appropriate storage instructions shall be provided for the reconstituted or mixed product which is to be stored in the original container. The basis for such instructions shall be determined by reliable, meaningful, and specific test methods. An expiration date, net quantity of contents, and a statement of an observable indication of an alteration of the product can be added for a reagent. The details of the manufacturer and lot number with ability to tracing individual units can be added.

Labelling accompanying each product should also have all the abovementioned details.

Summary and explanation of the test including a short history of the methodology with pertinent references and a balanced statement of the special merits and limitations of this method or product should also be added. In case of reagents, established names and a statement indicating the presence of and characterizing any catalytic or nonreactive ingredients, e.g., buffers, preservatives, and stabilizers, can be added. A statement of warning and precautions with a statement "For In Vitro

Diagnostic Use" should be added. Adequate instructions for reconstitution, mixing, dilution, etc. should also be included. In case of instruments, use or function, installation procedures and special requirements, principles of operation, performance characteristics and specifications, operating instructions, calibration procedures including materials and/or equipment to be used, operational precautions and limitations, hazards, and service and maintenance information should be included.

In case of a specimen collection, a description of special precautions regarding specimen collection including special preparation, additives, preservatives, known interfering substances, recommended storage, and handling details can all be included. In the case of a procedure, a step-by-step outline of recommended procedures from reception of the specimen to obtaining results with stressing anything that may improve the precision and accuracy can be added. List of materials provided, list of materials required but not provided, description of reagents quantity needed, and a statement on the stability of the final reaction and other details of calibration and quality control procedures should be stated. The procedure for calculating the results in a detailed manner along with limitations of the procedure covering the known extrinsic factors and interfering substances, with the expected values and a final note on bibliography, should all be included. Apart from this, other standard labelling norms should be followed.

Exceptions or Alternatives to Labeling Requirements for In Vitro Diagnostic Products for Human Use Held by the Strategic National Stockpile

The appropriate FDA Center Director may grant an exception or alternative, if a strategic National Stockpile official posts a written request for an exception or alternative. The center director may grant an exception or alternative described in paragraph (a) of this section on his or her own initiative with the identity of the thing explaining why compliance with such labeling provision(s) could adversely affect the safety, effectiveness, or availability of the specified lots, batches, or other units of the in vitro diagnostic product for human use that are or will be held in the Strategic National Stockpile with proposed safeguards or conditions. A grant of an exception or alternative under this section will include any safeguards or conditions deemed appropriate by the Center Director to ensure that the labeling of the product subject to the exception or alternative includes the information necessary for the safe and effective use of the product, given the anticipated circumstances of use. For a Premarket Approval Application (PMA)-approved in vitro diagnostic product for human use, the submission and grant of a written request under this section satisfy the provisions relating to submission of PMA supplements.

Restrictions on the Sale, Distribution, and Use of Analyte Specific Reagents

In vitro diagnostic products shall be manufactured in accordance and compliance with the good manufacturing practices requirements. Analyte specific reagents (ASRs) are restricted devices and may be only sold to clinical laboratories regulated under the Clinical Laboratory Improvement Amendments of 1988 and to Organizations that use the reagents to make tests for purposes other than providing diagnostic information to patients and practitioners.

Advertising and promotional materials for ASRs should include the statement for class I exempt ASRs, “Analyte Specific Reagent. Analytical and performance characteristics are not established,” and for class II or III ASRs, “Analyte Specific Reagent. Except as a component of the approved/cleared test (name of approved/cleared test), analytical and performance characteristics are not established,” and should not make any statement on its analytical and clinical performance.

The laboratory that develops an in-house test using the ASR shall inform the ordering person of the test result by appending to the test report the statement: “This test was developed and its performance characteristics determined by (Laboratory Name). It has not been cleared or approved by the U.S. Food and Drug Administration.” This statement would not be applicable or required when test results are generated using the test that was cleared or approved in conjunction with review of the class II or III ASR.

Restrictions on the Sale, Distribution, and Use of OTC Test Sample Collection Systems for Drugs of Abuse Testing

Over-the-counter (OTC) test sample collection systems for drugs of abuse testing are restricted devices. Sample testing should be performed in a laboratory using screening tests that have been approved, cleared, or otherwise recognized by the FDA as accurate and reliable for the testing of such specimens for identifying drugs of abuse or their metabolites. The laboratory where the tests are performed should have been a recognized one and proven to have adequate capability to perform integrity checks for possible adulterations in the biological samples.

2.8 Part 810: Medical Device Recall Authority [15]

This part of the regulation describes the procedures that the FDA will follow in exercising its medical device recall authority under Section 518(e) of the FDA Act. If, after providing the appropriate person with an opportunity to consult the agency, FDA finds that there is reasonable probability that the device intended for human use would cause serious, adverse health consequences or death, the agency may issue a notification for immediate order to:

(a) Cease the distribution of the device
(b) Notify and instruct the health professionals and the device user facilities to cease the use of the device

A written request for regulatory hearing under §810.11 may be submitted to the FDA for review of cease distribution and notification order. Such requests shall be addressed to agency employee identified in the order and shall submit within the stipulated timeframe under §16.22(b) (usually 3 working days from receipt of cease order) specified by the FDA. Within the 15 working days of receipt of the written request, the agency shall provide written notification (a statement) on its decision to affirm, modify, vacate, or amend the order to the requestor. If a regulatory hearing

or agency review of the order is not requested, or within 15 working days of denying a request for a hearing, or within 15 working days on completion a regulatory hearing under §810.11, or within 15 working days of receipt of a written request for review of a cease distribution and notification order under §810.12, then the FDA shall amend the order to require a recall or a mandatory recall of the device within 15 working days of issuance of a cease distribution and notification order. A descriptive listing of each new mandatory recall issued will be available to the public in the weekly FDA Enforcement Report by the agency.

If cease distribution and notification order or a mandatory recall order is issued, then the person mentioned in the order should submit a periodic report (as specified in the order) to the FDA on his progress in complying with the order. On compliance with order, the person mentioned in the cease distribution and notification order may submit a written request to the FDA for termination of the order. After assessing the person's progress in complying with the order, FDA may deny or grant the termination of device recall order within 30 working days of its receipt.

2.9 Part 812: Investigational Device Exemptions [16]

Discovery and development of useful devices intended for human use is encouraged, and optimum freedom is given for scientific investigators for this purpose. In conduct of clinical investigations of devices, approved investigational device exemption (IDE) permit is given to such devices which otherwise would be subjected to comply all the performance standard or premarket approval to be shipped lawfully. An IDE approved under or considered approved exempts a device from the requirements of the following sections of the Federal Food, Drug, and Cosmetic Act and the regulations issued from the agency.

Applicability

- General: In this part, all the clinical investigations of devices which determine safety and effectiveness will be proved except the exempted investigations.
- Abbreviated requirements: The following are categories of investigations to get approval of applications for IDEs:

  (i) An investigation of a device including labelling, IRB approval, a brief explanation of why the device is not a significant risk device, documents proving the collection of informed consent unless documentation is waived by an IRB, and maintenance of records

- Exempted investigations: This part does not apply to investigations of the following devices:

  (a) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time

(b) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, the FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976
(c) A diagnostic device, if the sponsor complies with applicable requirements and if the testing is noninvasive, which does not require an invasive sampling procedure that presents significant risk, does not by design or intention introduce energy into a subject, and is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure
(d) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not the purpose of determining safety or effectiveness and does not put subjects at risk
(e) A device intended solely for veterinary use
(f) A device shipped solely for research on or with laboratory animals and labeled in accordance animal research caution labelling format
(g) A custom device as per Federal Food, Drug, and Cosmetic Act unless the device is being used to determine safety or effectiveness for commercial distribution

Labeling of Investigational Devices

The contents shall bear label with information including name, place of business of manufacturer, packer or distributor, and quantity of contents, with CAUTION notice with following statement if appropriate "CAUTION-Investigational device. Limited by Federal (or United States) law to investigational use." Other labels shall also be displayed for describing relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Labeling of an investigational device shall not bear any statement that is false or misleading in any particular and shall not represent that any device is safe or effective for the purpose for which it is being investigated. Any device shipped solely for research on or with laboratory animals shall bear on its appropriate detailed label.

Prohibition of Promotion and Other Practices

A sponsor, investigator, or any person shall not promote or test market an investigational device, until after FDA has approved the device for commercial distribution. They shall not commercialize by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling. They shall not unduly prolong an investigation or represent it as safe or effective for the purposes for which it is being investigated.

Waivers

A sponsor shall request the FDA to waive any requirement, and this request with supporting documentation may be submitted separately or as a part of an application. FDA may grant a waiver of any requirement if it is not required by act or is unnecessary to protect the rights, safety, or welfare of human subjects. Any requirement shall continue to apply unless and until FDA waives it.

Import and Export Requirements

A person who imports or offers for importation an investigational device shall be the agent of the foreign exporter with respect to investigations of the device and shall act as the sponsor of the clinical investigation or ensure that another person acts as the agent of the foreign exporter and the sponsor of the investigation. A person exporting an investigational device shall obtain FDA's prior approval before proceeding.

Address for IDE Correspondence

All applications, reports, request for waiver, request for import or export approval, or any other correspondence must be sent to the appropriate address mentioned in the official website with a submission title mentioned on the outside wrapper.

Application and Administrative Action

1. Submission: A sponsor shall submit an application to the FDA if the sponsor intends to use a significant risk device in an investigation or to conduct an investigation that involves an exception from informed consent or if FDA notifies that an application is required for an investigation. FDA needs to approve an application from the sponsor to conduct an investigation after which sponsor shall submit a signed "Application for an investigational Device Exemption" (IDE application), with accompanying materials in electronic format. FDA shall provide a written determination 30 days after FDA receives the IDE or earlier.
2. The investigational plan shall include purpose, protocol, risk analysis, description of device, monitoring procedures, labeling, consent materials, IRB information, and other additional records and reports.
3. The report of prior investigations will include general reports of all prior clinical, animal, and laboratory testing along with specific contents including bibliography of all publications, published or unpublished adverse information, nonclinical laboratory studies, and data from clinical investigations.
4. Acceptance of data from clinical investigations conducted outside the United States will need additional conditions to be met based on good clinical practice (GCP) which includes review, independent ethics committee (IEC), and supporting information.
5. FDA action on applications: FDA will notify the sponsor in writing of the date it receives an application. FDA shall provide a written determination 30 days after FDA receives the IDE or earlier. DA takes 30 days' time to approve an investigation as proposed, approve with modifications, or disapprove it or withdraw approval an application. FDA shall consider the use of an investigational device under category "treatment IDE" to facilitate the availability of promising new devices to desperately ill patients as early as possible. FDA will not disclose the existence of IDE unless its existence has been previously been publicly disclosed or acknowledged until approval of device. FDA will make a detailed summary of information concerning the safety and effectiveness of the device after approval upon request.
6. Supplemental applications: (a) Changes in investigational plan shall include changes requiring prior approval, changes effected for emergency use, changes

effected with notice to FDA within 5 days (developmental changes, changes to clinical protocol, definition of credible information, notice of IDE change), changes submitted in annual report, or IRB approval for new facilities.
7. Treatment use of an investigational device: FDA shall consider the use of an investigational device under a treatment IDE if the device is intended to treat or diagnose a serious or immediately life-threatening disease; no comparable or satisfactory alternative device or other therapy is available to treat or diagnose the stage of the disease.
8. Confidentiality of data and information will be maintained unless its existence has previously been publicly disclosed or acknowledged.

Responsibilities of Sponsors
Sponsors shall not begin investigation until both IRB and FDA have approved the application. The responsibilities of sponsors are the following:

(a) Selecting investigators and monitors
(b) Informing investigators
(c) Monitoring investigations

IRB Review and Approval
An IRB shall review and have authority to approve, require revisions on, or disapprove all investigations, and if there is no IRB or FDA finds IRB review is inadequate, a sponsor shall submit an application to FDA directly. IRB can demand an investigation for devices involving a significant risk through the sponsor prior to approval.

Responsibilities of Investigators
An investigator is responsible for ensuring a proper conduct of investigation as per the signed agreement. The conduct shall be according to investigational plan and FDA regulations, after obtaining informed consent, and they also will be liable for protecting the rights, safety, and welfare of subjects and for control of devices under investigation. The specific responsibilities of investigators include the following:

(a) Awaiting approval
(b) Compliance
(c) Supervising device use
(d) Financial disclosure
(e) Disposing of device

A clinical investigator can be disqualified if FDA has information that an investigator has deliberately failed to comply with the requirements or repeatedly submitted false information in any required report. In such cases, the Centre of Devices and Radiological Health, the Centre for Biologics Evaluation and Research, or the Centre for Drug Evaluation and Research will furnish a written notice on matter of complaint and offer to provide the investigator's explanation in writing or through an informal conference. If the explanation provided is accepted, disqualification

proceeding will be discontinued, otherwise will be examined with test articles to support his explanation.

Records and Reports (a) *Records*

- Investigator records: A participating investigator shall maintain all the correspondence with another investigator, an IRB, the sponsor, a monitor, or the FDA. They preserve the records of receipt, the use of device including the type and quantity of device, batch number or codes, and the name of all persons who received or used the device and details of units. He/she shall also hold records of each participant's case history, date and time of each use, exposure details, signed and dated consent forms, medical records, hospital charts, and nurses' notes.
- Sponsor records: A sponsor shall maintain all correspondence with another sponsor, a monitor, an investigator, an IRB, or the FDA. They record the shipment and disposition including the name and address of the consignee; type and quantity of device; date of shipment; batch number or code mark; details if any devices were returned to the sponsor, repaired, or disposed; and signed investigator agreements. They shall preserve records of name and intended use of device, objectives of the investigation, explanation of non-risky aspects of the device, statements of good manufacturing practice regulations, and notes of adverse device effects.
- Retention period: All the records of investigator or sponsor shall be maintained for a period of 2 years after the date on which the investigation is terminated or completed or the date that records are no longer required for purpose of supporting a premarket approval application.

(b) *Inspections*

A sponsor or an investigator shall permit authorized FDA employees, at fixed time and manner, to inspect the establishment where the devices/records are held (including sites where these are manufactured, packed, installed, used, or implanted). They shall permit FDA employees to inspect and copy all records related to this investigation, subjects, and the informed consents.

(c) *Reports*

- Investigator reports: An investigator shall prepare and submit complete, accurate, and timely reports including report of any unanticipated adverse effects, withdrawal of IRB approval, progress reports, deviations from the investigational plan, informed consents, and the final report.
- Sponsor reports: A sponsor shall prepare and submit complete, accurate, and timely reports including unanticipated adverse device effects, withdrawal of IRB approval, withdrawal of FDA approval, current investigator list, progress reports, recall and device disposition, final report, informed consent, and significant risk device determinations.

2.10 Part 814: Premarket Approval of Medical Devices [17]

The premarket approval (PMA) of medical devices applies to any class III medical device that was not on the market before May 28, 1976. The review process of premarket approval of medical devices facilitates the approval for those devices that have been shown to be safe and effective and that meets statutory criteria and approval and disapprove otherwise.

Confidentiality of Data and Information in a Premarket Approval Application (PMA) File
A PMA file includes all data and information submitted with or incorporated by reference in the PMA, any IDE incorporated into the PMA, or any PMA supplement related to submission. The PMA file may not be disclosed by the FDA before an approval order unless it previously has been publicly disclosed or acknowledged. After PMA decision, the following information are immediately available for public disclosure including safety and effectiveness data and protocol for a test or study unless the protocol is shown to constitute trade secret or confidential commercial or financial information, adverse reaction report, product experience report, consumer complaints, and all the correspondence and written summaries of oral discussions relating to PMA file. The FDA shall abandon PMA if the applicant fails to respond to a request for additional information within 180 days after the date FDA issues the request, or if all legal appeals after the denial of PMA have been exhausted, if PMA has been voluntarily withdrawn, if the device has been reclassified, or if the device is found to be equivalent to class I or class II device.

(a) Research conducted outside the United States: A PMA based solely on foreign clinical data may be approved if the data are applicable to US population and US medical practice and if the studies have been performed by clinical investigators of recognized competence. Applicants shall meet the FDA officials in a "presubmission" meeting when approval based solely on foreign data is sought.
(b) Service of orders: The orders issued will be served in person by a designated officer or employee of FDA on, or by registered mail to, the applicant or the designated agent at the applicant's or designated agent's last known address in FDA's records.
(c) Product development protocol (PDP): A class III device for which a product development protocol has been declared completed by FDA under this chapter will be considered to have an approved PMA.

A. *Premarket Approval Application (PMA)*

A. Application

The PMA shall be signed by the applicant residing within the United States or shall be countersigned by an authorized representative residing or maintaining a place of business in the United States. The PMA application shall include the name and address of the applicant, separate sections on nonclinical laboratory studies and on clinical investigations involving human subjects. The trade secret or confidential

commercial or financial information is provided but identified to be a confidential information.

(a) Summary: Details of summary shall include indications of use of the device to diagnose, treat, prevent, cure, or mitigate including a description of target patient population. The device is described in detail, functionally, physically, along with the manufacturing process and performance characteristics of the device. The generic name and the proprietary name or trade name of the device shall also be included. It should also describe the alternative practices or procedures for diagnosing, treating, preventing, curing, or mitigating the disease or condition. Summary of studies shall include description of objective of the study; description of experimental design of study; brief description of data collection; analysis results whether positive, negative, or inconclusive; nonclinical laboratory studies; clinical investigations involving human subjects submitted in the application along with the conclusion; and valid scientific evidence drawn from the study.
(b) Description of device shall include pictorial representations; functional components or ingredients of the device; properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition; principles behind operation of the device; and methods used for manufacture, processing, packing, storage, installation, and quality control.
(c) FDA shall determine whether to approve or deny approval of the application based on nonclinical and clinical laboratory studies. The results of nonclinical laboratory studies include microbiological, toxicological, immunological, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests as appropriate. The results of clinical investigations involve human subjects with clinical protocols, number of investigators, subjects per investigator, subject inclusion and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, complaints, device failures, replacements, tabulations of data from all individual subject report forms including of those who died during clinical investigation or who did not complete the investigation, results of statistical analyses of the clinical investigations, device failures and replacements, and contraindications and precautions for use of the device.

B. PMA Amendments and Resubmitted PMAs

An applicant may amend a pending PMA or supplement to revise the existing information or to provide additional supporting information. FDA also may request the applicant to amend a PMA to provide necessary information to complete the review. Such PMA amendment shall include the original submission details along with reason for submitting the amendment, and FDA may extend the time required for its review up to 180 days, and if not received, it shall consider pending PMA or PMA supplement to be withdrawn voluntarily by the applicant.

C. PMA Supplements

PMA supplement shall be submitted after FDA's approval of a PMA for making a change affecting the safety or effectiveness of the device. A supplement is required if there are new indications for use of the device; labeling changes; use of a different facility or establishment to manufacture, process, or package the device; and changes in sterilization procedures packaging, performance, specifications, circuits, components, ingredients, principle of operation, or layout. FDA will identify the information that needs to be included in the report or the supplement, and if change is required, it shall be made 30 days after FDA files the PMA supplement unless FDA requires the PMA holder to provide additional information or disapproves a supplement.

B. *FDA Action on a PMA*

(a) Time frames for reviewing a PMA

FDA will review the PMA within 180 days after receipt of an application and send an approval order, an approvable letter, a not approvable letter, or a denying approval. An applicant has the opportunity to amend or withdraw the application after receiving approvable letter and the not approvable letter.

(b) Filing a PMA

Within a time period of 45 days, FDA will notify the applicant, in writing, whether the PMA has been filed. The notice will include the PMA reference number and date filed. From the date of filing, the 180-day time period for review of a PMA starts. The filing of an application itself denotes a threshold determination about the completion of PMA to permit a substantive review. If FDA refuses to file, it will notify with reasons for refusal after which the applicant can resubmit the PMA with the necessary additional information. Upon request after resubmission, FDA shall hold an informal conference within 10 working days and will produce its decision of filing within 5 working days. If FDA does not reverse its decision, the applicant may request reconsideration to the directors of appropriate agency as applicable, and it shall be considered as a final administrative action. The refusal of a PMA is considered if the application is incomplete, has missing information or omission of any item, contains false statement of material fact, or is not accompanied by a statement of certification or disclosure.

(c) Procedures for Review of a PMA

FDA refers the PMA to each member of its own panel for review and communicates mediating the applicant and the panel to respond to additional information or questions raised during the review. The advisory committee shall hold a public meeting or a telephone conference and submit a report to FDA which will have recommendations and the basis for the same signed by the chairperson of the committee. This happens within the later of 180 days from the date of filing of the PMA. FDA will issue the approval of a PMA if there are no reasons for denying it and give the public notice of the order, including notice for any interested concerns to request review. FDA's homepage displays the notice of approval with a brief

summary of information regarding safety and effectiveness of the device, basis of approval, and adverse effects if any. The applicant shall receive an approvable letter if they need a specific additional information or conditions to be agreed by the applicant or a not approvable letter if it describes the deficiencies in application for one or more reasons. In response to an approvable or not approvable letter, the applicant may amend the PMA, file a petition in form for reconsideration, or withdraw the application. FDA will consider a PMA to have been withdrawn voluntarily if the applicant fails to submit a written request for an amendment needed within 180 days after FDA issues a request or if the applicant fails to respond in writing to an approvable or not approvable letter within the same time period or a written notice of withdrawal is submitted by the applicant.

(d) Denial of Approval of a PMA

FDA shall deny an approval if the applicant fails to meet the requirements in the application including various reasons: false statement of facts or labeling of the device without complying the requirements. FDA, if denied permission to inspect at a reasonable time or manner at the facilities, controls, or to access to verify any records pertinent to the application, shall propose denial of approval. Similar decision shall be recommended if conditions prescribed were not conducted in compliance with good laboratory practice regulations, or do not support the validity of the study. FDA shall deny approval for all the clinical investigations involving human subjects, if not accompanied by the institutional review board or informed consent regulations, or found in line with rights or safety of human subjects. The public notice of an order denying approval of the PMA will be placed on FDA's homepage with detailed summary of the reasons.

(e) Withdrawal of Approval of a PMA

An approval of a PMA shall be withdrawn if FDA determines that post-approval requirement has not met the regulations proposed or if the nonclinical/clinical laboratory investigations are found in compliance with the good laboratory practice regulations or adequately protected for maintaining the rights or safety of human subjects. FDA will decide to withdraw approval of a PMA after seeking advice of an advisory committee and after giving a notice of opportunity to the applicant for an informal hearing if requested. If still found unsatisfactory, FDA shall give the public notice of an order withdrawing approval of a PMA with appropriate explanation.

(f) Temporary Suspension of Approval of a PMA

FDA, if suspects the probability that a device would cause serious, adverse health consequences, or death, shall issue an order temporarily suspending approval of a PMA. If FDA issues such an order, within 60 days, the agency holds a hearing on whether a permanently withdraw an approval of PMA.

C. *Post-approval Requirements*

(a) General

After the PMA approval of a device, it is mandatory to manufacture, pack, store, label, distribute, or advertise as specified in the PMA application; hence post-approval requirements are important to follow.

(b) Post-approval Requirements

Post-approval requirements may include many clauses as conditions to approval of the device like the following: restrictions of sale; distribution of use of device on particular conditions; continuing evaluation and periodic reporting on safety, effectiveness, and reliability of the device; prominent display in the labeling of a device and in the advertising of any restricted device of warnings, hazards, or precautions regarding the device's safe and effective use, including patient information; inclusion of identification codes on the device or its labeling on cards to be inserted for patients; providing the identity of any patient be disclosed in records maintained to verify a record or a report; submission of periodic reports as specified during the application; batch testing of the device; and providing the records and reports required to inspect at a reasonable time or manner at the sites of producing/storing/shipping the device.

(c) Reports

The holder of an approved PMA shall comply with all the requirements as mentioned in the order of device approval. The periodic reports shall submit the changes if available along with summary and bibliography of unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices.

D. *Humanitarian Use Devices*

(a) Purpose and Scope

The discovery of devices intended to benefit patients in treatment or diagnosis of diseases or conditions that affect or are manifested in not more than 8000 persons in the United States per year is encouraged under HUD designation of a medical device. Obtaining marketing approval for a HUD involves obtaining designation of the device from FDA's Office of Orphan Products Development and submitting an HDE application to respective center as applicable.

(b) Designation and HUD Status

(i) Request for designation: The process starts with submitting a request to FDA's Office of Orphan Products Development which shall contain name and address and contact details of the applicant;

a statement of reason for HUD designation for a rare disease or condition or a valid subset of a disease or condition which shall be identified with specificity; proposed indications for use of the device, reasons why such therapy is needed; scientific rationale for the use of the device; and documentation with appended references to demonstrate the disease or condition and its relation to the people in the United States.

(ii) FDA action: FDA will take one of the following actions on request for HUD designation in 45 days: Approve the request and notify the applicant or return the application for further review or disapprove the request.
(iii) Revocation of designation: If the request for designation contained false statements/facts/omitted material information or if the device is not eligible for HUD designation based on evidences provided, FDA shall revoke a HUD designation.

(c) Original Applications

The applicant or an authorized representative shall sign the HDE; if he does not reside in the United States, it shall be countersigned by an authorized representative in this country. The application shall include a copy of reference to the determination of qualification of the device as a HUD made by FDA's Office of Orphan Products Development, explanation of why the benefit of health in the device usage outweighs the risk of injury or illness, summary of all clinical experience or investigations, and labeling requirements. If the price of the device is more than $250, a report made in accordance with the Statement on Standards for Attestation established by the American Institute of Certified Public Accountants is provided.

(d) HDE Amendments and Resubmitted HDEs

An HDE or HDE supplement may be amended or resubmitted by the applicant itself or provided at the request of the FDA as similar to PMA but without the timeframes. If a written response is not received within 75 days of date of the request, the pending HDE or HDE supplement is proposed for voluntary withdrawal by the applicant.

(e) Supplemental Applications

Once the original application of HDE is approved by the FDA, an applicant must submit supplements as similar to PMA's as per HUD requirements.

(f) New Indications for Use

An applicant seeking a new indication for use of a HUD shall obtain a new designation of HUD status and submit an original HDE as explained earlier.

(g) Filing an HDE

The filing of an HDE means that FDA has found that the application is sufficiently complete to subject it for further review. Within 30 days, FDA shall notify the applicant about the filing review result.

(h) Timeframes for Reviewing an HDE

Within 75 days after a filing of an HDE, for which there is no major amendment pending, FDA shall send the applicant an approval order, an approvable letter, a not approvable letter, or an order denying approval.

(i) Procedures for Review for an HDE

FDA shall begin a substantive review of an HDE after filing by constituting a panel for reviewing process, and this advisory committee shall recommend and report within 75 days from the date of filing of an HDE. An approval order is given if none of the reasons for denying is pointed after review except for minor deficiencies in final draft labeling. The notice of approval will be published in the Federal Register. An approvable letter will be sent if the agency believes that it can approve if specific additional information is submitted or specific conditions are agreed by the applicant. A not approvable letter is provided if the application may not be approved for one or more reasons due to deficiencies in the application and opportunity is given for submitting an amendment within 75 days.

(j) Denial of Approval or Withdrawal of Approval of an HDE

FDA may deny the approval or withdraw approval of an application, if the application fails to meet the requirements of an HDU or any condition of approval imposed by an IRB or by the FDA. Denial of approval suggests the following:

(i) Lack of showing a reasonable assurance that the device is safe as prescribed, recommended, or suggested in the labeling
(ii) Lack of reasonable basis to conclude the probable benefit to health which should outweigh the risk of injury or illness
(iii) Evidence of untrue statement of material fact, or omission of information
(iv) Clinical or nonclinical laboratory studies not conducted in compliance with the good laboratory practice or informed consent regulations

(k) Temporary Suspension of Approval of an HDE

An HDE or HDE supplement may be temporarily suspended for the same reasons and the same manner.

(l) Confidentiality of Data and Information

The HDE file includes all the data and information submitted with or referenced in the HDE including amendments, supplement related to submission. Any record in the HDE file will be available for public disclosure in accordance with the FDA's norms. The disclosure by FDA shall subject to the same rule like that of a PMA.

(m) Institutional Review Board Requirements

Once a HUD is approved, the HDE holder is responsible for attending to requirements of the Institutional Review Board (IRB). A HUD shall be administered only if the use of device is approved by an IRB; however, in an emergency situation, to prevent serious harm or death of a patient, a HUD may be administered without prior approval by an IRB, where the physician shall provide a written notification within 5 days after the use to the chairman of the IRB with the explanation with the details of the patient involved and date of usage and the reason for its use. A HUD holder shall notify FDA of any withdrawal of approval for use of HUD by reviewing IRB within 5 working days after being notified of the withdrawal of approval.

(n) Post-approval Requirements and Reports

All the HUD approved devices shall be subjected to post-approval requirements and reports in a complete, accurate, and timely manner. The periodic reports shall include an update of information regarding the device, number of devices shipped or sold since initial marketing approval, number of devices used per patient, or if a single device is used for multiple patients. This shall include information describing clinical experience, safety instructions, statement of contraindications, warnings, precautions, and adverse reactions in the device's labeling. In addition to it, an HDE holder shall maintain records of the names and addresses of the facilities to which the HUD has been shipped, and such records shall be maintained in accordance with the HDE approval order.

2.11 Part 820: Quality System Regulation [18]

Quality system regulation is in line with current good manufacturing practice (CGMP), and these govern the methods, facilities, controls used in design, manufacture, packaging, labeling, storage, and servicing of any finished device intended for human use. This system shall ensure that the device will be safe and effective in compliance with the FDA and Cosmetic Act. This part shall inform the basic requirements applicable to manufacturers of the finished device manufactured, imported, and offered in the United States, and this system also is applied to the manufacturer from a foreign country. Anyone who wishes to apply for an exemption or variance from any device quality system requirement has to request to the FDA, and the agency may initiate and grant the variance in the best interest of the public health.

For any device, its manufacturers shall develop and maintain a unique quality system that is specific for the device and ensure that it meets the requirement as per the quality system regulations as follows:

(a) *Management responsibility:* The management with executive responsibility is responsible for the development of its policy with "quality" as the main component. The same management shall ensure that the quality policy is made available, implemented, and maintained at all levels. The manufacturer shall be responsible for all the personnel who manage, perform, and assess work quality through proper training, and they will provide adequate resources for quality performance including internal quality audits. These shall be managed by a representative who shall be appointed from the members of the management to ensure the requirements of the quality system regulations. He/she will head the review of suitability and effectiveness of the system at defined intervals and with sufficient frequency, and these dates and results are to be documented. A quality planning and framework of quality system procedures form the initial outline of this part.
(b) *Quality audit*: The manufacturer of the device shall start the process by developing procedures for the quality audits whereby it is assured that the system is

in compliance with the quality system requirements. These audits shall be conducted by individuals who are not in direct responsibility for the matters being audited. A report of the audits and the re-audits (if conducted) shall be made and reviewed by the management.

(c) *Personnel*: The manufacturer shall ensure the availability of adequate personnel with qualified education, background, training, and experience to assure the activity of quality system regulations. The training of all the personnel shall be conducted to make them aware of all the device defects or errors that may be encountered during the improper performance.

(d) *Design controls*: Each manufacturer shall establish and maintain procedures to control the design of the device of any class (class I–III). The design and development is planned with different groups which shall be reviewed, updated, and approved as it evolves. The basis of the design input is to ensure that it's appropriate for the intended use and needs of the user or the patient. These input requirements shall be documented and reviewed and approved by appointed designated individuals, which shall be documented with date and signature. Based on this input requirements of the device designed, device output procedures shall contain and make reference to acceptance criteria which are essential for the proper functioning of the device of interest, and again this device output shall be documented, reviewed, and approved before release. These designs produced are reviewed by an individual who is not in direct responsibility for the design state, and the results shall be documented in the design history file (DHF). Each manufacturer shall also develop and maintain procedures for validation of the device design. This validation shall include software validation and risk analysis (if appropriate) and is documented in the DHF file with date and method. Hence each manufacturer shall establish and maintain a DHF for each type of device, and each DHF shall contain all the records necessary to demonstrate that the design was developed in accordance with the approved design plan.

(e) *Document controls*: Each manufacturer shall develop and maintain procedures to control all the documents established to meet the requirements of the quality system regulations. The approvals including the date and signature shall be documented, and all the changes in the documents shall be reviewed and approved by the individuals in the organization in a timely manner. The change records shall include the description of change, identification of affected documents, signature of the individual, the approval date, and the effect date.

(f) *Purchasing controls*: Each manufacturer shall establish and maintain procedures to ensure that all the purchased or received the products are in line with specific requirements. This involves evaluation and documentation of potential suppliers, contractors, or consultants. The producing documents shall include an agreement that the suppliers and contractors agree to notify the manufacturer in case of any change in the product or service that may affect the quality of the finished the device.

(g) *Identification and traceability*: Each manufacturer shall establish and maintain the procedures for identification and traceability of each product during each

stage including the receipt, production, distribution, and installation. This is important for the devices used to support or sustain life like surgical implants. These procedures shall facilitate corrective actions.

A. *Production and Process Controls*

This part includes the documented instructions or standard operating procedures (SOPs) and methods to define and control the production system, the monitoring and control process parameters, and the approval of these parameters. Any change from the specification shall be verified and approved and validated, and these will be documented in accordance with the quality system regulations. For some of the devices, the production will be affected by the different environment conditions, and hence the environmental control systems shall be in place, and it is periodically inspected and documented. Each personnel involved in the manufacturing shall maintain the requirements of health, cleanliness, and personal protective practices which can affect the product quality adversely. Adequate training of these personnel is given through our trained professional before involving them into the process. Steps to prevent any contamination of the equipment should be available in the buildings of production and storage. The buildings and equipment used in the manufacturing process shall meet the design to facilitate the specific requirements, and a maintenance schedule should be available; the details of inspection and adjustments made during inspections shall be documented. The source material used for the manufacturing should be of good quality, and the details of it shall be documented in DHF. Even though automated data processing system is used for production, the manufacturer shall validate the software before approval and shall be documented.

(a) *Inspection, measuring, and test equipment*: Each equipment used in the process shall be tested by mechanical, automated, or electronic inspection methods, and it is routinely calibrated, inspected, checked, maintained, and documented. The calibration procedures of each equipment shall check the accuracy and precision in accordance with national or international calibration standards. The equipment identification, calibration dates, and the next calibration date shall be documented on the equipment.
(b) *Process validation*: Each manufacturer shall ensure that the validation processes is performed by qualified individuals. The monitoring and controlling methods and the date performed shall be documented. If changes or deviations are observed, the revalidation can be conducted if appropriate.

B. *Acceptance Activities*

(a) *Receiving, In-process, and Finished device acceptance*: Each incoming product shall be inspected and tested before acceptance or rejection. Documentation of finished device acceptance ensures each production run and batch or number of devices as per the design criteria. Hence, finished devices shall be held until all

the data, documentation, and authorization are completed. The records shall include the acceptance activity, dates, results, and signatures in the DHR.

(b) *Acceptance Status*: The acceptance identification shall be maintained throughout manufacturing, packaging, labeling, and installation of each product produced.

C. *Nonconforming Product*: If a product doesn't conform to the specified requirements, details procedures to address the identification, documentation, evaluation, segregation, and disposal shall be followed and documented. This shall be followed by rework, retesting, and reevaluation of the products as per current approved specifications.

D. *Corrective and Preventive Action*: Appropriate corrective and preventive actions shall be in place for analysis of the process, work operations, concessions, quality audit reports, complaints, and returned product, and all other quality problems and appropriate statistics shall be employed to detect the recurring quality problems. The corrective and preventive actions are validated to ensure that the action is effective and does not affect the finished device in any manner. These relevant information on identified quality problems are submitted for the review of the management.

E. *Labeling and Packaging Control*

(a) *Device labeling*: Labels of the device shall be printed and displayed legibly and with appropriate details about processing, storage, handling, and distribution. Labels are released after inspection for the accurate details, including the unique device identifier (UDI) or universal product code (UPC), expiry details, control number, storage instructions, and other processing instructions. Labels are designed for proper identification and to prevent mix-ups.

(b) *Device packaging*: The material used for packaging the device and the shipping containers are designed and developed for protection of the device of interest from any alteration or damage from the time of production till distribution.

F. *Handling, Storage, Distribution, and Installation*

The handling of device is critical, and issues like mix-ups, damage, deterioration, and contamination can occur during handling and should be managed appropriately. Any product or device deteriorates over a fixed time duration, and hence it shall be stored to facilitate the safe and proper condition before distribution. The stock sheets with details of storage areas and stock rooms are maintained with the manufacturer. Before the distribution, the purchase orders are approved and checked to ensure the errors are resolved if any before the devices are released for distribution, and those devices which have deteriorated beyond acceptable fitness are not distributed. The distribution details include the location planned, name and address of initial consignee, quantity of devices shipped, date, and numbers of contact for the distribution. Once distributed, the manufacturer shall establish and maintain installation and appropriate test procedures and demonstrate the device to the end user or the patient.

G. *Records*

(a) *General requirements*: All records are maintained by the manufacturer and provided accessible to the responsible officials or FDA for in-depth inspections. Therefore, the records are maintained legibly and stored from any damage and also backed up in automated data processing systems. These records are maintained in confidential and are disclosed only when specified by the producers and the agency.
(b) *Device master record*: The device master records (DMRs) shall be available with the manufacturer which shall contain device specifications including drawings, composition, formulation, and component and software specifications; production specifications including methods, procedures, and environment specifications; quality assurance procedures like acceptance criteria and equipment used for audits; *and* packaging and labelling specifications and installation and servicing methods.
(c) *Device history record*: The device history records (DHRs) shall contain the batch, lot, or unit, dates of manufacture, and quantity manufactured and distributed. It shall also contain the primary identification label, unique device identifier (UDI), or universal product code (UPC) specific for the device.
(d) *Quality system record*: The quality system record (QSR) shall include location of documents and procedures following for assuring the quality of the device which shall be in accordance with the quality system regulations.
(e) *Complaint files*: Complaint files shall contain all documents pertaining to receipt, review, and evaluation of the complaints. The procedures shall ensure that all the complaints shall be processed in a uniform and timely manner and documented upon receipts including oral complaints if any. In case of unattended complaints, the reason for the same and details of the individual responsible for decision shall be noted. Once a complaint is registered, the date of complaint, unique device identifier (UDI), or universal product code (UPC) shall be recorded, including the nature and details of complaint, date of results of the investigation, any corrective action taken, and any reply to the complainant.

H. *Servicing*: In case the device supplied needs servicing, the manufacturer shall establish and maintain the instructions and procedures for performing and verifying it as per specified requirements. All the service reports shall be analyzed and documented with the name of device, UDI, or UPC, control numbers, date of service, service personnel details, and method of testing used.
I. *Statistical techniques*: The manufacturer shall develop procedures for identifying valid statistical techniques required for establishing, controlling, and validating the processes and device characteristics. Sampling plan can be made based on a valid statistical understanding, and these shall be documented.

2.12 Part 821: Medical Device Tracking Requirements [19]

A. *General Provisions*

(a) *Scope*: As per the Federal Food, Drug, and Cosmetic Act of the FDA, the manufacturer shall adopt a method of tracking a class II or III device, if failure of the device would be reasonably likely to have serious adverse health consequences, or intended to be implanted in the human body for more than a year, or if the device is a life-sustaining one, it is referred to as a "tracking device." In case of a tracking device, it can be traced from the manufacturing facility through the distributor networks including distributors, retailers, rental firms, and other commercial enterprises and device user facilities. The tracking system is the responsibility of the manufacturer, and any person who permanently closes the business of the device shall notify the FDA and provide the complete set of its tracking records and information. In that case, the other person who acquires the right to manufacture or distribute the tracking devices will be responsible for continuing the tracking responsibility.
(b) *Exemptions and variances*: A manufacturer or a distributor shall request exemption or variance from medical device tracking responsibility by providing a petition containing the name of device, class type, reasons and justification explaining why tracking is unnecessary, and alternate steps if available. This petition shall be approved by the Director, Office of Compliance, CDRH, before deemed effective.
(c) *Imported devices*: In case of a device manufactured in a foreign country, the importer of the tracked device in the United States shall be considered as the manufacturer and shall comply to all requirements as applicable.

B. *Tracking Requirements*

(a) *Devices subject to tracking*: A manufacturer of any class II or III device must track that device in accordance with FDA requirements if the agency notifies the need for tracking during the premarket notification submissions and premarket approval applications.
(b) *Devices tracking system and content requirements*: The manufacturer shall adopt a method of tracking as per each type of device. Upon FDA's request, the UDI, lot number, batch number, model number of the device, date of shipment, contact details of the patient, location of the device, and name and details of the treating physician who recommended the device are provided within 10 days of request. A standard operating procedure of device tracking shall be established and shared to the FDA upon request. This SOP shall include the data collection and recording procedures, methods for recording all modifications, or changes to the tracking system if any. A quality assurance program which includes audit procedures with statistical relevant sampling to ensure the accuracy of data and functioning of tracking system shall be established.

C. *Additional Requirements and Responsibilities*

(a) *Tracking obligations for persons other than device manufacturers*: Apart from the manufacturers of the device, upon purchasing or acquiring any interest of the same, the distributor(s) are obliged to provide the following details: name and address of the distributor (final/multiple distributors), UDI, lot number, batch number, model number or serial number of the device, date of receipt, end user, and return date or permanent disposal date (if appropriate). The distributor(s) shall maintain all records to be made available for the manufacturer during audits.

D. *Records and Inspections*

(a) *Availability*: Manufacturers or distributor(s) shall make a document of each information collected and maintained from all the records and related events and persons identified. This shall be provided to the FDA personnel upon issuance.
(b) *Confidentiality*: Any patient receiving a device shall be subjected to tracking requirements but however may refuse to release or refuse permission to release the patient's name, address, telephone number, social security number, or other information for the tracking purpose. FDA shall protect the records and other information submitted and shall not be available for public disclosure. However, patient names and other identifiers shall be disclosed to the manufacturer or to treating physician to pursue the health aspects of the patient.
(c) *Retention of records*: The manufacturer or the distributor shall maintain records about useful life (time when the product is in use) of the tracked device. These records shall be retired only when the device is no longer used, explanted, or returned, or when the patient using it is no more existing.

2.13 Part 822: Postmarket Surveillance [20]

Postmarket surveillance as per section 522 of the Federal Food, Drug, and Cosmetic Act is required for all class II and III devices which upon failure would result in serious adverse health consequences or are implanted in the human body for more than 1 year or used to sustain life of the user. The purpose of postmarket surveillance is to collect useful data which can reveal unforeseen and anticipated adverse events or any information that protects the public health aspect of the device usage.

A. *Notification*: The FDA shall send a letter called "postmarket surveillance order" which notifies the requirement to conduct the postmarket surveillance. Before issuing this order, FDA requests the manufacturer to submit information about the device to specify the subject of the surveillance order and reason for the requirement of the surveillance. Once considered necessary, the FDA shall notify the postmarket surveillance based on the surveillance question. In case the manufacturer decides not to conduct the postmarket surveillance, a request shall be submitted with the Director, Office of Surveillance and Biometrics,

seeking internal review of the order and requesting an informal hearing or review by the Medical Devices Dispute Resolution Panel of the Medical Devices Advisory Committee.

B. *Postmarket surveillance plan*: Once the postmarket surveillance order is received, the manufacturer shall submit the plan to conduct the same within 30 days to the respective agency in-charge. Upon receiving the plan, the agency shall send an acknowledgement letter with unique document number assigned for any further correspondence. The initial details to be included in the submission are the following: organizational information, name, address, generic/trade names, address of contact person, premarket application/submission, description of device, product codes, and indications for use. The postmarket surveillance plan shall include the following: the objective addressing the question put forth in the FDA order, study subject details, clinical parameters/outcomes, methodology of surveillance, sample size and units of observation, sources of data, data collection plans and forms, consent document (if applicable), Institutional Review Board information, patient follow-up plan, procedures for monitoring conduct and progress of the surveillance, estimate of duration of surveillance, data analyses, and statistical tests planned. The duration allowed for postmarket surveillance shall be mentioned in the order usually for a period of up to 36 months, longer if needed. If the prospective period is not agreeable between the manufacturer and the FDA, the matter shall be resolved through Medical Devices Dispute Resolution Panel.

C. *FDA review and action*: FDA shall review the submission if it's received complete as per the requirements, and after which a designated person with essential qualifications and experience shall be assigned to conduct the surveillance. The review shall be completed within 60 days of receipt, and decision or identification of actions needed shall be notified. FDA shall send an approval order/approvable letter/disapproval letter. If the manufacturer fails to submit a revised or new plan after the review, the device shall be misbranded, and these devices can be seized. The personnel involved shall pay civil money penalties or prosecuted. If changes required in the plan are suggested, resubmission shall be proceeded; however, the changes should not affect the nature or validity of the data collected in the initial device approval order. If the manufacturer disagrees to the review of the FDA, they shall request a meeting with the authority responsible for the postmarket surveillance, seeking internal review and informal hearing through Medical Devices Dispute Resolution Panel. The content of the postmarket surveillance plan submission shall be maintained confidential until approved; however, the trade secret and commercial information (if any) shall be protected.

D. *Responsibilities of manufacturers*: Once notified about the requirement to conduct postmarket surveillance, the manufacturer shall submit the plan within 30 days. The manufacturer shall ensure that the surveillance is initiated and conducted diligently, until the submission of reports, required in a timely manner. In case of any change in the ownership of the device's company, it shall be notified, and the new owner shall be obliged to conduct the surveillance. Similarly,

if manufacturers decide to close the business or stop marketing of the device of interest, it shall be notified, and plans to complete the postmarket surveillance or terminate it should be discussed.

E. *Waivers and exemptions*: The manufacturer shall request to waive any specific requirement under postmarket surveillance with supporting document with explanation of why it is believed an exempt is applicable for the device, and this shall be submitted separately or with the postmarket surveillance submission document.

Records and Reports The manufacturer shall maintain copies of all correspondence with the investigating team or FDA including reports, signed agreements, plan, approval order, data collected and analyzed for conducting the postmarket surveillance plan, or any other records involved during the postmarket surveillance. Similarly, the investigators shall keep all the correspondence between them, the FDA, and the manufacturer and the plans approved for conducting the surveillance. All these records are preserved for a period of 2 years after acceptance of final report. In case of any change in plan, FDA shall be notified within 10 working days; otherwise once initiated, the program is regularly inspected by authorized FDA employees in the facility where the device is held. FDA shall be permitted at a reasonable time and manner to inspect the copy of any records related to this surveillance, or it shall be provided upon request within 72 hours of initiation of the inspection. The records of the individual subjects shall be inspected if the reports are found incomplete, inaccurate, false, or misleading. The manufacturer shall submit interim and final reports as per the postmarket surveillance plan and additional information if found necessary.

2.14 Part 830: Unique Device Identification [21]

A unique device identifier (UDI) means an identifier that adequately identifies a device through its distribution and use. An UDI is composed:

(a) Device identifier, a mandatory, fixed portion of UDI that identifies the specific model or version of the device and the device label
(b) Production identifier, a conditional, variable portion of UDI that might include the lot or batch of manufacture, serial number of specific device, expiration date, and specific date of device manufactured

It is required that the UDI must:

(a) Be issued under a system operated by the FDA or an FDA-accredited issuing agency
(b) Conform to the following international standards:

(i) ISO/IEC 15459-2:2006, Information technology-Unique identifiers-Part 2: Registration procedures
(ii) ISO/IEC 15459-4:2008, Information technology-Unique identifiers-Part 4: Individual items
(iii) ISO/IEC 15459-6:2007, Information technology-Unique identifiers-Part 6: Unique identifier for product groupings

(c) Only use characters and numbers from the invariant character set of ISO/IEC 646:1991, Information technology-ISO 7-bit coded character set for information interchange

Only one device identifier from any particular system for issuance of UDI shall be used to identify only one particular version or model of a device. When a change is made to the device, a new UDI must be assigned to distinguish the new version or model device from its previous one. In case the model or version of the device is discontinued, its UDI will not be reassigned to another device. On re-introducing the discontinued version or model of the device with no change, then the same UDI can be used. For relabeling a device, a new device identifier can be assigned to the device, but its relationship with previous device identifier should be kept in record.

Responsibilities of FDA-Accredited Issuing Agency
A private organization is eligible to apply for FDA accreditation, or FDA by itself can act as an issuing agency. For initial accreditation, the applicant shall notify their desire to be accredited by sending a notification by email or by correspondence to the FDA. If approved, the initial term of accreditation for an issuing agency shall be for 3 years and can be periodically renewed for 7 years. To maintain its accreditation as an issuing agency, they must operate:

(a) To meet the requirements of UDI to adequately identify a device through its distribution and use.
(b) Conform to international standards: ISO/IEC 15459-2, ISO/IEC 15459-4, ISO/IEC 15459-6.
(c) Only use characters and numbers from the invariant character set of ISO/IEC 646.
(d) With single set of consistent, fair, and reasonable terms and conditions to all users.
(e) To protect against conflicts of interest between the issuing agency (and its officers, employees, and other agents) and labelers (and its officers, employees, and other agents).
(f) Make available information concerning its system for UDI assignments.
(g) List of labelers using their system for UDI assignment should be maintained, and an electronic copy of the same must be submitted to FDA upon request anytime or at end of each year.

Suspension or Revocation of FDA Accreditation as an Issuing Agency
Accreditation of an issuing agency can be suspended or revoked by the FDA with a notice and opportunity for informal hearing, if FDA finds an issuing agency or any officer, employee, or other agent of the issuing agency:

(a) Is guilty of misinterpretation or failed to disclose potential information during accreditation
(b) Failed to fulfill the responsibilities as an issuing agency
(c) Failed to protect against conflict of interest
(d) Engaged in any anticompetitive activity to restrain trade
(e) Violating or aided and abetted in violation of any regulation under section 510(e) or 519(f) of the FDA Act

2.15 Part 860: Medical Device Classification Procedures [22]

This part of the regulation sets forth the criteria and procedures in accordance with Sections 513, 514(b), 515(b), and 520(l) of the FDA Act, used for classification and determination of class of regulatory control (class I, class II, and class III) appropriate to provide assurance for the safety and effectiveness of the medical devices. Three categories of regulatory control for medical devices are:

(a) Class I (general controls): This class of device is subjected to only general control authorized by or under Sections 501 (adulteration), 502 (misbranding), 510 (registration), 516 (banned devices), 518 (notification and other remedies), 519 (records and reports), and 520 (general provisions) of the Act. The general controls are adequate to assure the safety and effectiveness of these class I device.
(b) Class II (special controls): This class of device will be or will eventually be subjected to special controls. The general controls alone are inadequate for safety and effectiveness assurance in class II devices; therefore, special controls including promulgation of performance standards, postmarket surveillance, patient registries, guidance on premarket notification submission (in accordance with section 510(k) of the FDA Act), and other appropriate recommendations are required for such assurance.
(c) Class III (premarket approval): This class of device will require premarket approval in accordance with Section 515 of the FDA Act. A device is in class III if general controls provide insufficient information for safety and effectiveness assurance or if a need for special control is required or if the device is life-supporting or life-sustaining or if the device presents a potential unreasonable risk of illness or injury.

Determination of Safety and Effectiveness
The Commissioner of the FDA refers the device to the appropriate classification panel, which is one of the advisory committees established by the Commissioner under Section 513 of the FDA Act for making recommendations on the classification and reclassification of devices. The recommendation will include:

(a) Summary of reasons for the recommendation
(b) Summary of data upon which the recommendation is based
(c) Report on the health risks (if any) presented by the device

Manufacturers may submit evidence to FDA to substantiate the safety and effectiveness of device; however, the FDA relies only on the valid scientific evidence generated from well-controlled investigations, partially controlled studies, and objective trials conducted by qualified experts. Based on the scientific evidence using laboratory animals, clinical studies on human subjects, and analytical studies, FDA ensures the absence of unreasonable risk of illness or injury associated with intended uses and usage conditions of the device. A device is considered safe and effective when its intended use of the device, adequate directions for use, and warnings against unsafe use are proven in a significant portion of target population by clinically significant results. The classification panel reviews the evidence concerning safety and effectiveness and prepares advice to the commissioner, and the commissioner will apply rules for determining safety and effectiveness of a device. The panel recommendation is regarded preliminary until the Commissioner reviews and publishes it in the FEDERAL REGISTER, together with the proposed regulation for device classification for comments. The Commissioner reviews the comments and issues the final regulation for classifying the device and other devices of that generic type.

Exemptions from Sections 510, 519, and 520(f) of the FDA Act

In case of recommendation for a medical device to be classified as class I, recommendations on the exemption of one or more requirements of the following sections of the FDA Act can be made: Section 510 (registration, product listing, and premarket notification), section 519 (records and reports), and section 520(f) (good manufacturing practice requirements of the quality system regulation). In the case of a recommendation for classification of a medical device into class II, whether the device should be exempted from the premarket notification requirement under section 510, will be decided in accordance with §860.15. For the purposes of classification, establishment of special controls for class II devices, and premarket approval of class III devices, the Commissioner and the classification panels consider the following factors:

(a) The person for whose use the device is represented or intended
(b) Conditions of use including prescribed or recommended or advertised or suggested in the labelling for the device
(c) Health benefits from device usage outweigh the probable injury or illness as a result of such use
(d) Reliability of the device

Reclassification

Under Sections 513(e) and (f), 514(b), 515(b), and 520(l) of the FDA Act, an interested person or manufacturer or importer may submit a petition for reclassification of a device. Unless provided in writing by the commissioner, any petition for reclassification of the device shall include:

(a) Specification for the type of device requested for reclassification
(b) A statement on action requested, such as “It is requested that….. device(s) be reclassified from class III to class II”

(c) A statement on the basis of disagreement with the present device classification
(d) A full statement of reasons supported the reclassification and how the proposed classification assures the safety and effectiveness of the device
(e) Relevant data and new information with source documents relevant to the petition

Within 180 days after the filing of a petition for reclassification under this section, the Commissioner will either deny the petition by order published in the Federal Register or give notice of the intent to initiate a change in the classification of the device. The Commissioner may initiate the reclassification of the device, by either referring a reclassification petition to the panel under §860.134(b) or consulting with panel regarding the petition under §860.130(d) or received in a proceeding under §860.133(b), or the Commissioner chooses to consult with a panel with regard to the reclassification of a device initiated by the Commissioner under §860.134(c) or §860.136. If a device is reclassified under this section, it may revoke any special control or premarket approval requirement that was previously applied to the device. In addition, reclassification of specific device will result in reclassification of all devices within the same generic type.

2.16 Part 861: Performance Standards Development [23]

The FDA may determine performance standards of class II devices in accordance to special controls described in Section §860.7(b) to ensure safety and effectiveness of the device. This part implements Section 514 of the FDA Act for establishment, amendment, and revocation of performance standards applicable to medical devices.

Contents of Standards
Such performance standards established by FDA will address, but not be limited to:

(a) Device performance characteristics
(b) Design, components, and properties of device and its compatibility with other components
(c) Manufacturing and quality control procedures applicable to the device
(d) Testing all the devices by the manufacturer or testing by FDA or a third person to ensure conformity of the device to standard
(e) Publication of the results of test or tests of the device to show their conformity to standard
(f) Manufacturers' certification to purchasers or FDA for device conformity to standards
(g) Restrictions on the sale and distribution of the device, in accordance to Section 520(e) of the FDA Act
(h) Use of proper form and content of the label for installation, maintenance, operation, warnings, storage, transportation expiration dates, concerning statements for appropriate patient population, and for safe usage of devices

Performance Standards Development and Publication
The FDA will publish in the FEDERAL REGISTER a notice of a proposed rulemaking for the establishment, amendment, or revocation of any performance standards for a device. The FDA might either develop or may accept an existing or proposed standard to be published in their FEDERAL REGISTER. This notice will set forth the findings that the performance standards are appropriate and necessary for the safety and effectiveness of the device and/or for the reduced risk of illness or injury associated with the device. A notice under this section will be available for comments from interested persons not less than 60 days. If FDA receives a request for a change within 60 days of the publication of notice, upon consultation with the appropriate panel, it will either deny the request or give a notice for its intent to initiate a change in the classification.

Amendment or Revocation of a Standard
The FDA will provide for periodic evaluation of performance standards to determine their ability to reflect the recent advances in medical, scientific, or other technologies. FDA may amend or revoke by regulation the standard established, on its own or upon petition of an interested party. Any petition or proceedings to amend or revoke a performance standard shall be conducted in accordance with the rulemaking procedures of §10.30. This notice of proposed rulemaking to amend or revoke the standard, in addition, shall also set forth the proposed evidences for reduced risks or health benefits or illness to be eliminated from the proposed amendment or revocation.

Standards Advisory Committees
The FDA will establish advisory committees, to which proposed regulations may be referred for reports and recommendations. The members of the advisory committees established under this section shall include:

(a) Members selected in accordance with §14.82 and §14.84, except that no member may be a full-time FDA employee
(b) Nonvoting member representative of consumer interests
(c) Nonvoting member representative of interests of device manufacturing industry

The FDA will furnish the advisory committee with the data and information upon which the referred proposed regulation is based. After independently reviewing the materials provided, advisory committee shall submit a report and statement of reason/or basis for the recommendation on the proposed regulation, within 60 days of the referral. In the office of the Division of Docket Management, FDA, a copy of the report and recommendation will be publicly displayed.

2.17 Part 862-898: Medical Device Listing and Premarket Approval [7]

These parts of the Chapter I of Title 21 of FDA regulation sets forth the classification of medical devices that are in commercial distribution intended for human therapeutic or diagnostic use. A premarket notification is required to be submitted by a manufacturer for a device under Part 807, for establishment registration and device listing. This notification should identify the device for its description and section title in this part of the regulation. The classification of devices may not show precise description of every device that is or will be subjected to the regulation. In such instances, as required by §807.87, a manufacturer shall state why the device is substantially equivalent to other devices. To avoid duplicative listing, devices with more than one type of use (i.e., both as therapeutic and as diagnostic use) shall be listed only in one subpart. A device included in this part of regulation classified into class III (premarket approval) shall not be commercially distributed after the date mentioned in the regulation classifying the device, unless the device has been approved by FDA Act under Section 515.

Exemption from the Requirements of Premarket Approval
The requirement of premarket notification for a generic type of class I or II device as per Section 510(k) of the Act is exempted only if applicable to device with existing or reasonably foreseeable characteristics of commercial distribution within the generic type or, in the case of in vitro diagnostic devices, only if the misdiagnosis as a result of using the device would not be associated with morbidity or mortality. FDA has granted exemption for these class I and II devices from the requirement of premarket notification. However, the manufactures of these commercially distributed devices must still submit a premarket notification to FDA before introducing the device into interstate commerce.

Bibliography

1. U.S. Food and Drug Administration. 19 Sept. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPartFrom=800&CFRPartTo=1299. Accessed 22 Jun. 2020
2. FEDERAL REGISTER. The Daily Journal of the United States Government, www.federalregister.gov/agencies/food-and-drug-administration. Accessed 2 June 2020
3. Regulations. gov. www.regulations.gov. Accessed 13 Mar. 2020
4. Code of Federal Regulations. 18 Aug. 2016, www.archives.gov/federal-register/cfr. Accessed 24 Apr. 2020
5. Code of Federal Regulations list of Subjects. 1 Oct. 2019, www.archives.gov/federal-register/cfr/subjects.html. Accessed 18 May 2020
6. Electronic Code of Federal Regulations. 18 Jun. 2020, www.ecfr.gov/cgi-bin/ECFR?page=browse. Accessed 22 June 2020
7. CFR Title 21 – Food and Drugs: Parts 800 to 1299. 1 Apr. 2019, www.document-center.com/standards/show/21CFR(800-1299). Accessed 17 Jun. 2020

8. CFR Title 21 – Food and Drugs: Parts 800: General. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=800&showFR=1. Accessed 23 May 2020
9. CFR Title 21 – Food and Drugs: Parts 801: Labeling. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=801&showFR=1. Accessed 20 Jun. 2020
10. CFR Title 21 – Food and Drugs: Parts 803: Medical device reporting. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=803&showFR=1. Accessed 7 Apr. 2020
11. CFR Title 21 – Food and Drugs: Parts 806: Medical devices; reports of corrections and removals. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=806&showFR=1. Accessed 14 Mar. 2020
12. CFR Title 21 – Food and Drugs: Parts 807: Establishment registration and device listing for manufacturers and initial importers of devices. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=807&showFR=1. Accessed 18 Apr. 2020
13. CFR Title 21 – Food and Drugs: Parts 808: Exemptions from federal preemption of state and local medical device requirements. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=808&showFR=1. Accessed 20 Jun. 2020
14. CFR Title 21 – Food and Drugs: Parts 809: In vitro diagnostic products for Human use. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=809&showFR=1. Accessed 3 Jun. 2020
15. CFR Title 21 – Food and Drugs: Parts 810: Medical device recall authority. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=810&showFR=1. Accessed 9 May 2020
16. CFR Title 21 – Food and Drugs: Parts 812: Investigational device exemptions. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812&showFR=1. Accessed 26 May 2020
17. CFR Title 21 – Food and Drugs: Parts 814: Premarket approval of medical devices. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=814&showFR=1. Accessed 19 Apr. 2020
18. CFR Title 21 – Food and Drugs: Parts 820: Quality system regulation. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820&showFR=1. Accessed 23 May 2020
19. CFR Title 21 – Food and Drugs: Parts 821: Medical device tracking requirements. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=821&showFR=1. Accessed 9 Jun. 2020
20. CFR Title 21 – Food and Drugs: Parts 822: Postmarket surveillance. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=822&showFR=1. Accessed 17 May 2020
21. CFR Title 21 – Food and Drugs: Parts 830: Unique device identification. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=830&showFR=1. Accessed 11 May 2020
22. CFR Title 21 – Food and Drugs: Parts 860: Medical device classification procedures. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=860&showFR=1. Accessed 8 Jun. 2020
23. CFR Title 21 – Food and Drugs: Parts 861: Procedures for performance standards development. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=861&showFR=1. Accessed 11 Jun. 2020