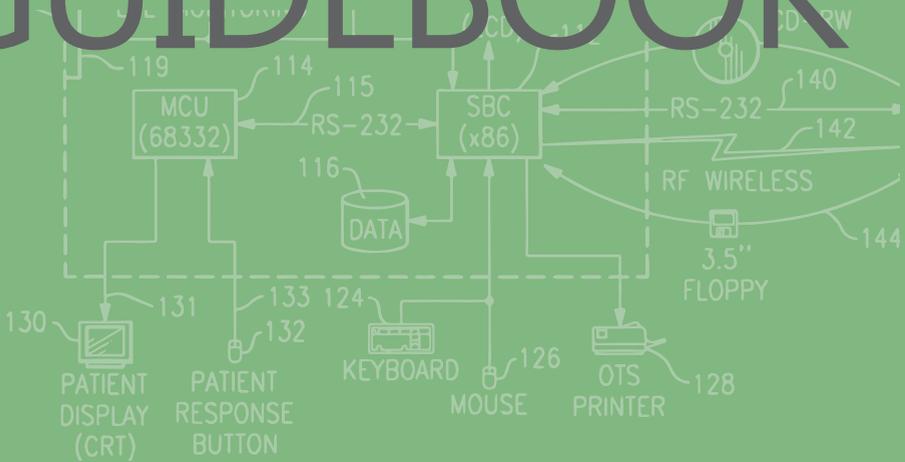
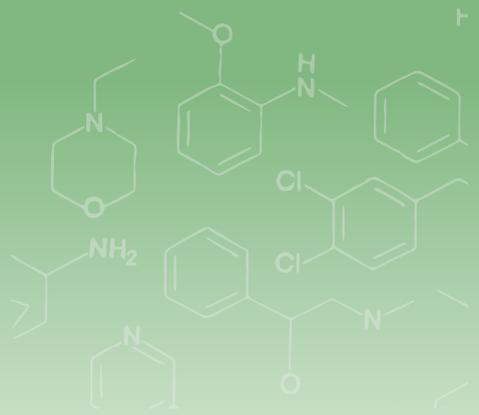


FDA GUIDEBOOK



Device	Pad, He
Regulation Description	Power
Regulation Medical Specialty	Physica
Review Panel	Physica
Product Code	IRT
Premarket Review	Office o Division Physica
Submission Type	510(K)
Regulation Number	<u>890.574</u>
Device Class	2



NYS SCIENCE+TECHNOLOGY

LAW CENTER

AT SYRACUSE UNIVERSITY COLLEGE OF LAW

About the FDA Guidebook:

This guidebook was compiled by the New York State Science & Technology Law Center to assist individuals working to commercialize a new medical device, drug, or substance for use in food. While inventors and researchers traditionally have a strong command of the science and engineering required to develop a new product, a lack of familiarity with the Food and Drug Administration's approval and oversight procedures often leaves companies under-equipped to pursue the financially onerous time commitment necessary to bring a product to market.

This guidebook addresses some of the common questions and procedures that companies with drugs, medical devices, and substances for use in food will encounter during the early regulatory process. Topics include the difference between a drug and a device, how to determine the classification of a medical device and submit a device for approval, an overview of the investigational new drug process, an explanation of the over-the-counter drug monograph system, and GRAS policy.

About the NYS STLC:

The New York State Science & Technology Law Center (NYS STLC) has been a leading resource in technology commercialization for nearly a decade. Since its inception, the NYS STLC has assisted with hundreds of commercialization projects across New York State. It was established at the Syracuse University College of Law by Empire State Development's Division of Science, Technology and Innovation (NYSTAR) to facilitate New York State's economic development by leveraging the experience and expertise of law faculty and SU College of Law students to assist New York businesses and institutions in delivering new and emerging technologies to the marketplace.

Advisement:

The information contained in this pamphlet is intended to be an introductory guide for businesses with a drug, medical device, or substance for use in foods. For further reading, literature from the FDA is cited in the Acknowledgments section.

No part of the guidebook, attachments, or related discussions constitutes legal advice or written opinion of counsel. For legal advice, please consult with an attorney.

Any opinions, findings, conclusions, or recommendations expressed are those of the author and do not necessarily reflect the views of the New York State Department of Economic Development.

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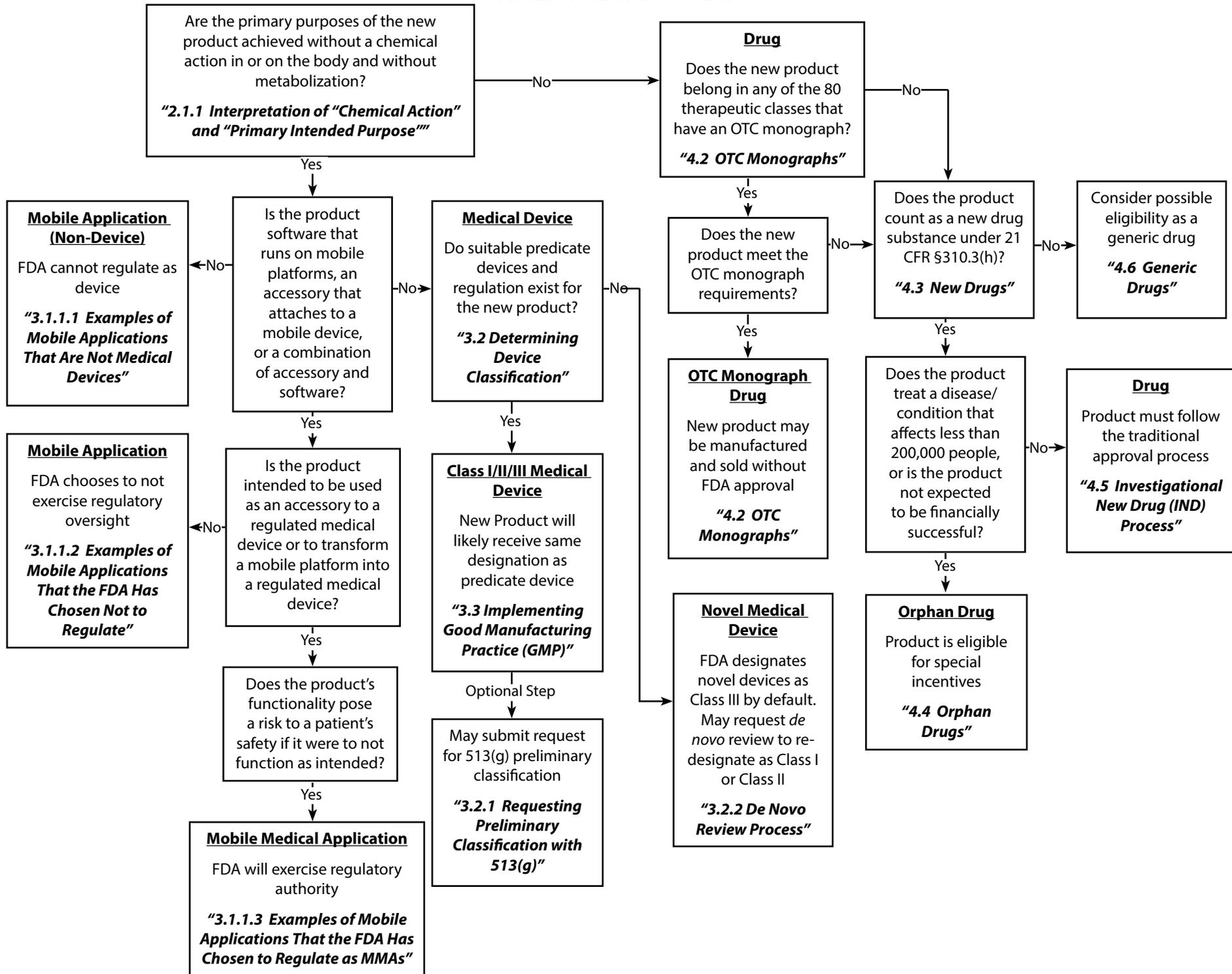
1 Introduction

The Food and Drug Administration regulates some of the most critical aspects of our daily lives. Whether it is the foods we eat, the drugs we take, or the appliances we purchase, the FDA's regulatory fingerprints are everywhere. For researchers and inventors focused on science and technology, it should come as no surprise that the FDA will often play a role in the commercialization pathway of an innovation. This guidebook primarily seeks to answer the question of what the agency's involvement will be, rather than if the agency will be involved.

Due in large part to consumer familiarity with the types of products regulated by the FDA, innovators often apply incorrect interpretations of FDA terminology. This can lead to radically inaccurate expectations regarding outlook, cost, and time. An innovation that a layperson would reasonably consider to be a device might be a drug, while an agency notification process that is perceived to be mandatory may, in fact, be completely optional.

The decision tree on the following page is provided to help determine which sections of the guidebook will be most relevant to readers with a particular technology in mind. These readers are encouraged to work through the decision tree first, stopping to read relevant sections of the guidebook when posed with a question. When readers take this proactive approach to understanding the role of the FDA, an innovation's commercialization pathway should become clearer and more efficient.

FDA Involvement Decision Tree



2 Drug vs. Device Designation

2.1 Statutory Definitions

The FDA's determination of whether to classify a product as a device or drug is based on the definitions set out in Food, Drug, and Cosmetic Act (FD&C Act) sections 201(h) and (g), respectively. A device is defined as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is:

- (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,
- (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or;
- (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes."

In comparison, drugs are defined as:

- "(A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
- (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and
- (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)."

The FDA recognizes that the broad drug definition can include the narrower device definition. In cases where a product could meet both definitions, the FDA will generally classify it as a device, unless there is particular uncertainty regarding whether the product meets the device

definition.

Additionally, the FDA includes a classification for a “combination product,” which is defined in 21 Code of Federal Regulations 3.2 (e) as:

- “1. A product comprised of two or more regulated components (i.e., drug/device, biologic/device, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
2. Two or more separate products packaged together in a single package or as a unit and comprised of drug and device products, device and biological products, or biological and drug products;
3. A drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device, or biological product where both are required to achieve the intended use...; or
4. Any investigational drug, device, or biological product packaged separately that... is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.”

Despite not being explicitly stated in the definition, a combination product does not include same-type product pairings (such as drug with a drug).

2.1.1 Interpretation of “Chemical Action” and “Primary Intended Purpose”

Determining whether a product meets this portion of the device definition is often a key issue in determining classification. This consideration has two prongs: (1) determining what counts as chemical action, and (2) whether that chemical action is part of the product’s primary intended purpose.

A chemical reaction is present if a product either:

- (1) Mediates a bodily response at the cellular or molecular level,
or
- (2) Combines with or modifies an entity (including chemicals and living things, such as microbes) so as to alter that entity’s

interaction with the body of man or other animals.

The FDA provides a variety of examples to better determine what qualifies as a chemical action for the purpose of this consideration. Additional examples can be found in the FDA's *Guidance on the Definition of "Chemical Action,"* cited in the Acknowledgments section.

- A product that binds to a receptor through intermolecular force and initiates or inhibits a signaling cascade counts as a "chemical action" because it facilitates a bodily response at the cellular or molecular level.
- A product that binds to a chemical agent through a chemical reaction which inhibits the agent's impact on the body qualifies as a "chemical action" because the product combines with an entity (chemical agent) in order to alter the agent's interaction with the body.
- A dental device used to fill hollowed out spaces in teeth that depends on covalent bonding or intermolecular forces to change from a paste to a solid does not qualify as a "chemical action" because it does not mediate a bodily response at the cellular or molecular level or combine/modify an entity for the purpose of altering that entity's interaction with the body through chemical interaction.

The mere fact that a product is part of a chemical action does not automatically disqualify it from falling under the designation as a device. This is contingent on the chemical action not being part of the product's "primary intended purpose." If the product's chemical action has an effect other than the designated primary intended purpose, the product could still meet the definition of a device under §201(h). However, if the product depends even slightly on a chemical action within or on the body to achieve any of its primary intended purposes, it would not be considered a device. Additionally, if a product has multiple therapeutic effects, each would be considered a primary intended purpose. If any one of those purposes is dependent on a chemical action, the entire product would fall outside the scope of the device definition.

2.2 Obtaining a Formal Classification Determination

If a product's classification as a drug, device, or combination product is unclear or under dispute, a product's sponsor may submit a request for designation (RFD) with the FDA's Office of Combination Products to obtain a formal classification. While the FDA aims to respond

with a written determination to all RFDs within 60 days, the lack of a written response indicates that the sponsor’s recommended determination is considered to be the agency’s final determination. Regardless of if the product’s determination comes from a written agency response or a lapse of the 60-day reply window, the determination cannot be changed by the FDA without the sponsor’s consent, unless the change is due to a public health concern supported by scientific evidence. Additional information can be found in the FDA’s Guidance on Writing an RFD, cited in the Acknowledgments section.

2.3 Impact of the Regulation of a Constituent Part

A product or a constituent part of a combination product may fall within the scope of an existing classification issued by an FDA regulation, such as a monograph for over-the-counter drugs. When reviewing the RFD, the FDA may determine that the product or constituent part meets the definition of a device, even though the ingredients in the product or the constituent part are included in an OTC drug monograph.

2.4 Effect of Prior Agency Determinations

Product sponsors commonly argue that because similar products have been classified or regulated in a particular way in the past, that the current product should receive a similar determination. While the FDA recognizes that the classification of previous products can help inform the current determination process, the agency still chooses to utilize a “case-by-case approach based on the specific characteristics of the product, including its intended uses(s), and the current state of scientific knowledge.”

3 Medical Device Registration

The FDA is tasked with the regulation of medical devices to ensure their safety for consumers. The agency’s oversight power is established through the FD&C Act. Each year, countless medical devices and radiation-emitting electronic products are submitted to the FDA, while preexisting products and companies are reviewed for quality assurance compliance to ensure continued consumer and patient safety.

This section is designed to give a broad overview of the FDA medical device registration process for the United States. By highlighting critical aspects of the registration procedure, relevant federal statutes, and various paths to establishing a proper device classification, this sections provides a general framework to help a potential registrant to understand the nature of the device registration process, recognize its various financial implications, and strategize for an orderly and efficient registration plan.

3.1 Establishing Whether FDA Oversight Applies

To be subject to FDA oversight, a technology must meet the definition of a medical device. 21 U.S. Code § 321 lists the definition of a medical device as:

“an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

- (1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.”

Additionally, the FDA’s Center for Devices and Radiological Health has oversight and sets performance standards for technologies that emit radiation for diagnostic, therapeutic, and surgical purposes, as well as for industrial, commercial, and consumer purposes. Due to this

expansive oversight, many common household products fall under FDA oversight, including electric blankets, massagers, television receivers, and microwaves. The pertinent definitions related to radiation-emitting products are found in §531 of the FD&C Act:

“Electronic product –

(A) any manufactured or assembled product which, when in operation

(i) contains or acts as part of an electronic circuit and

(ii) emits (or in the absence of effective shielding or other controls would emit) electronic product radiation, or

(B) any manufactured or assembled article which is intended for use as a component, part, or accessory of a product described in clause (A) and which when in operation emits (or in the absence of effective shielding or other controls would emit) such radiation.”

“Electronic product radiation –

(A) any ionizing or non-ionizing electromagnetic or particulate radiation, or

(B) any sonic, infrasonic, or ultrasonic wave, which is emitted from an electronic product as the result of the operation of an electronic circuit in such product.”

3.1.1 FDA Oversight of Mobile Medical Applications

With the explosive proliferation of health-related applications for smartphones, tablets, and wearables, the FDA has sought to clarify what it will regulate. The agency’s stance is that it is focused on “only those mobile apps that are medical devices and whose functionality could pose a risk to a patient’s safety if the mobile app were to not function as intended.” The FDA uses a number of different definitions to clarify which products will fall under its jurisdiction.

- **Mobile Applications:** “software programs that run on mobile devices, accessories that attach to a mobile device, or a combination of accessories and software.”
- **Mobile Platforms:** “defined as commercial off-the-shelf (COTS) computing platforms, with or without wireless connectivity, that are

handheld in nature. Examples of these mobile platforms include mobile computers such as smart phones, tablet computers, or other portable computers.”

- **Mobile Medical Applications (MMAs):** “a mobile app that meets the definition of device of the FD&C Act that is either is intended:
 - (A) to be used as an accessory to a regulated medical device; or
 - (B) to transform a mobile platform into a regulated medical device.”

The FDA has provided examples of applications that would fall outside the scope of these definitions (Section 3.1.1.1), applications that could meet the definition but that the agency has chosen to not regulate (Section 3.1.1.2), and applications which the agency intends to regulate (Section 3.1.1.3). Additional examples can be found in Mobile Medical Applications: Guidance for Industry and Food and Drug Administration Staff, cited in the Acknowledgments section.

3.1.1.1 Examples of Mobile Applications That Are Not Medical Devices

- Applications that are meant to provide access to electronic copies of medical textbooks and reference materials that are not intended for diagnosing, treating, mitigating, or preventing a disease by assessing a particular patient in the judgment of a professional:
 - Medical dictionaries
 - Translations of medical terms
 - Encyclopedia of first-aid or emergency care information
- Applications that are meant for health care providers to use as educational tools for medical training or reinforcement of previously received training:
 - Medical flash cards
 - Interactive anatomy diagrams or videos
 - Surgical training videos
 - Medical board certification preparation applications
- Applications intended for general patient education and to facilitate access to commonly used reference information. These applications can include filters to provide patient-specific characteristics, but are intended to increase awareness and education.
 - Medical facility and doctor locator

- Information on gluten-free foods or restaurants
- Program that lets users enter pill shape, color, or imprint and displays pictures and names of pills that match
- Applications that automate health care office operations that are not intended for diagnosing, treating, mitigating, or preventing a disease.
 - Insurance claim analysis
 - Patient payment submission and tracking
 - Appointment reminder programs
- Applications that are generic aid or general purpose products that are not intended for diagnosing, treating, mitigating, or preventing a disease.
 - Audio recording and note-taking programs
 - Turn-by-turn navigation to medical facilities
 - Secure and protected communication system for health care providers

3.1.1.2 Examples of Mobile Applications That the FDA Has Chosen Not to Regulate

- Applications that help patients with diagnosed psychiatric conditions (e.g., post-traumatic stress disorder (PTSD), depression, anxiety, obsessive compulsive disorder) maintain their behavioral coping skills by providing a “Skill of the Day” behavioral technique or audio messages that the user can access when experiencing increased anxiety
- Applications that use GPS location information to alert asthmatics of environmental conditions that may cause asthma symptoms or alert an addiction patient (substance abusers) when near a pre-identified, high-risk location;
- Applications that use video and video games to motivate patients to do their physical therapy exercises at home;
- Applications that use patient characteristics such as age, sex, and behavioral risk factors to provide patient-specific screening, counseling and preventive recommendations from well-known and established authorities;
- Applications that record the clinical conversation a clinician has with a patient and sends it (or a link) to the patient to access after a visit;
- Applications that are intended to allow a user to initiate a pre-specified nurse call or emergency call using broadband or cellular phone

technology;

- Applications that enable a patient or caregiver to create and send an alert or general emergency notification to first responders;
- Applications that are intended for individuals to log, record, track, evaluate, or make decisions or behavioral suggestions related to developing or maintaining general fitness, health, or wellness, such as those that:
- Provide tools to promote or encourage healthy eating, exercise, weight loss or other activities generally related to a healthy lifestyle or wellness;
 - Provide dietary logs, calorie counters, or make dietary suggestions;
 - Provide meal planners and recipes;
 - Track general daily activities or make exercise or posture suggestions;
 - Actively monitor and trend exercise activity;
 - Help healthy people track the quantity or quality of their normal sleep patterns;
 - Provide motivational tips (via text or other types of messaging) to reduce stress and promote a positive mental outlook;
 - Use social gaming to encourage healthy lifestyle habits;
- Applications that provide drug-drug interactions and relevant safety information (side effects, drug interactions, active ingredients) as a report based on demographic data (age, gender), clinical information (current diagnosis), and current medications.

3.1.1.3 Examples of Mobile Applications That the FDA Has Chosen to Regulate as MMAs

- Applications that use a sensor or lead that is connected to a mobile platform to measure and display the electrical signal produced by the heart (electrocardiograph or ECG).
 - Possible product codes: DPS, MLC, OEY (21 CFR 870.2340), MLO, MWJ (21 CFR 870.2800)
- Applications that use a sensor or electrode attached to the mobile platform or tools within the mobile platform itself (e.g., microphone and speaker) to electronically amplify and “project sounds associated with the heart, arteries and veins and other internal organs”

- Possible product code: DQD (21 CFR 870.1875(b))
- Applications that use an attachment to the mobile platform to measure blood glucose levels.
 - Possible product code: NBW (21 CFR 862.1345)
- Applications that analyze an image of a skin lesion using mathematical algorithms, such as fractal analysis, and provide the user with an assessment of the risk of the lesion.
- Applications that are used to calibrate hearing aids and assess the electroacoustic frequency and sound intensity characteristics emanating from a hearing aid, master hearing aid, group hearing aid, or group auditory trainer.
 - Possible product code: ETW (21 CFR 874.3310)
- Applications that calibrate, control, or change settings of a cochlear implant.
 - Possible product code: MCM.
- Applications that are intended to display images for diagnostic review may be regulated as a picture archiving and communications system.
 - Possible product code: LLZ, (21 CFR 892.2050)
- Applications that connect to bedside (or cardiac) monitors and transfer the data to a central viewing station for display and active patient monitoring.
 - Possible product code(s): DSI, MHX, MLD (21 CFR 870.1025), DRT, MWI, MSX (21 CFR 870.2300)

3.2 Determining Device Classification

The FDA organizes all medical devices into three classes: Class I, II, and III. Items that fall into Class I are considered to be low-risk and are therefore only subject to baseline General Controls, while Classes II and III each come with further restrictions and more steps before products are permitted to be commercialized. Depending on a device's classification, premarket approval (PMA) or premarket notification (510(k)) may be required.

The 510(k) process requires that a device manufacturer give the FDA at least 90 days' notice of the intent to market a medical device. This advanced notification gives the FDA time to determine whether the new device is at least as safe and effective as a device already in the market that does not require premarket approval. The PMA process is much

more involved, requiring both human and laboratory or animal studies to scientifically prove the safety and effectiveness of a device.

To determine the proper classification for a device, the FDA maintains a list of predicate devices and their corresponding classifications to inform and educate new device applicants of how the FDA will most likely classify their product.

Sample FDA Classification

Device	Pad, Heating, Powered
Regulation Description	Powered heating pad.
Regulation Medical Specialty	Physical Medicine
Review Panel	Physical Medicine
Product Code	IRT
Premarket Review	Office of Device Evaluation (ODE) Division of Neurological and Physical Medicine Devices (DNPMD) Physical Medicine and Neurotherapeutic Devices Branch (PNDB)
Submission Type	510(K) Exempt
Regulation Number	890.5740
Device Class	2
Total Product Life Cycle (TPLC)	TPLC Product Code Report
GMP Exempt?	No

As part of the classifications, the FDA includes a link to the section of the Code of Federal Regulations that defines and classifies that particular medical device. It is critical that the new device seeking registration falls within the scope of the regulation number listed on its registration form. Moreover, the product code found to relate to the new medical device will be needed for several future steps in the registration process, making it critical that the code or codes used be appropriate.

Sample Regulated Device Definition

```
TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES

PART 890 -- PHYSICAL MEDICINE DEVICES
Subpart F--Physical Medicine Therapeutic Devices

Sec. 890.5740 Powered heating pad.

(a) Identification. A powered heating pad is an electrical device intended for medical purposes that provides dry heat therapy for body surfaces. It is capable of maintaining an elevated temperature during use.

(b) Classification. Class II (special controls). The device is exempt from the premarket notification procedures in subpart E part 807 of this chapter subject to 890.9.

[48 FR 53047, Nov. 23, 1983, as amended at 63 FR 59231, Nov. 3, 1998]
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3.2.1 Requesting Preliminary Classification with 513(g)

While the existence of predicate devices and a list of applicable regulations are often sufficient to guide new applicants through the device registration process, there are instances when a new device is similar but still outside of the scope of preexisting device listings. For these cases, an applicant may submit a 513(g) document, which requests a classification confirmation by the FDA. The FDA breaks down what a 513(g) request should include:

1. A cover letter containing:
 - a. the date of the request,
 - b. the name of the device,
 - c. your specific question(s) concerning the class in which a device has been classified and/or the regulatory requirements applicable to a device,
 - d. the requestor's name, address, telephone number, fax number, and email address, and
 - e. the 513(g) requestor's signature.
2. A description of the device, including:
 - a. a list of materials and components used in/with the device,
 - b. photographs, engineering drawings, and/or samples of the device,
 - c. a summary of the device's operational principles,
 - d. a description of the type and amount of energy to be used or delivered by the device, and
 - e. a description of similar devices in commercial distribution in the United States, if available.
3. Device uses, including:
 - a. the disease or condition with respect to which the device is to be used
 - b. prescription versus over-the-counter use,
 - c. part of the body or type of tissue applied to or interacted

- with,
- d. frequency of use,
 - e. physiological purpose (e.g., removes water from blood, transports blood, etc.),
 - f. patient population; and
 - g. any other labeling information related to the patient use of the device.
4. Any proposed labeling, including promotional material or labeling for any similar, legally marketed device.

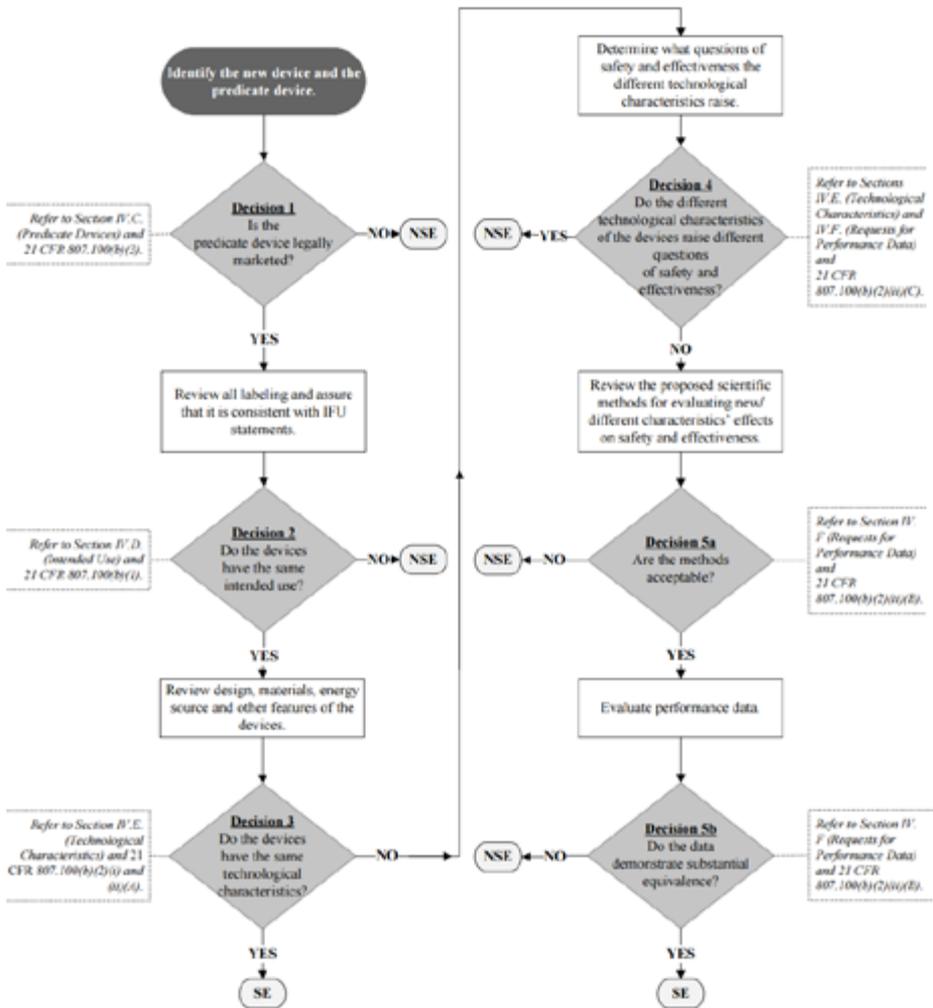
3.2.2 De Novo Review Process

Novel medical devices are automatically given Class III categorization by the FDA. However, the 1997 Food and Drug Administration Modernization Act created a de novo process for having a novel device reclassified as either Class I or Class II. A company can initiate the de novo process in two ways, depending on how far into the registration process a device is.

Option 1: If an applicant has submitted a 510(k) document and has received a “not substantially equivalent determination” (NSE) by the FDA, there is a 30-day window to submit a de novo request so that the FDA may perform a risk-based evaluation for classification as a Class I or Class II device.

Option 2: If an applicant has yet to submit a 510(k) and determines that there is no substantially equivalent device currently on the market in the United States, a de novo request can be submitted, requesting the FDA perform a risk-based classification of the device to potentially have it re-categorized as either Class I or Class II.

FDA Substantial Equivalency Determination



SE = "Substantially Equivalent"
 NSE = "Not Substantially Equivalent"
 IFU = "Instructions For Use"

3.3 Implementing Good Manufacturing Practice (GMP)

Under 21 CFR § 820, a company that manufactures a medical device is required to implement a quality assurance system. This requirement also applies to companies that outsource manufacturing. The vast majority of Class I devices are exempt, and a limited number of Class II devices are as well. When determining a device's classification, the FDA lists whether predicate devices qualify for GMP exemption. A GMP

exemption still requires a company to satisfy general recordkeeping and filing provisions.

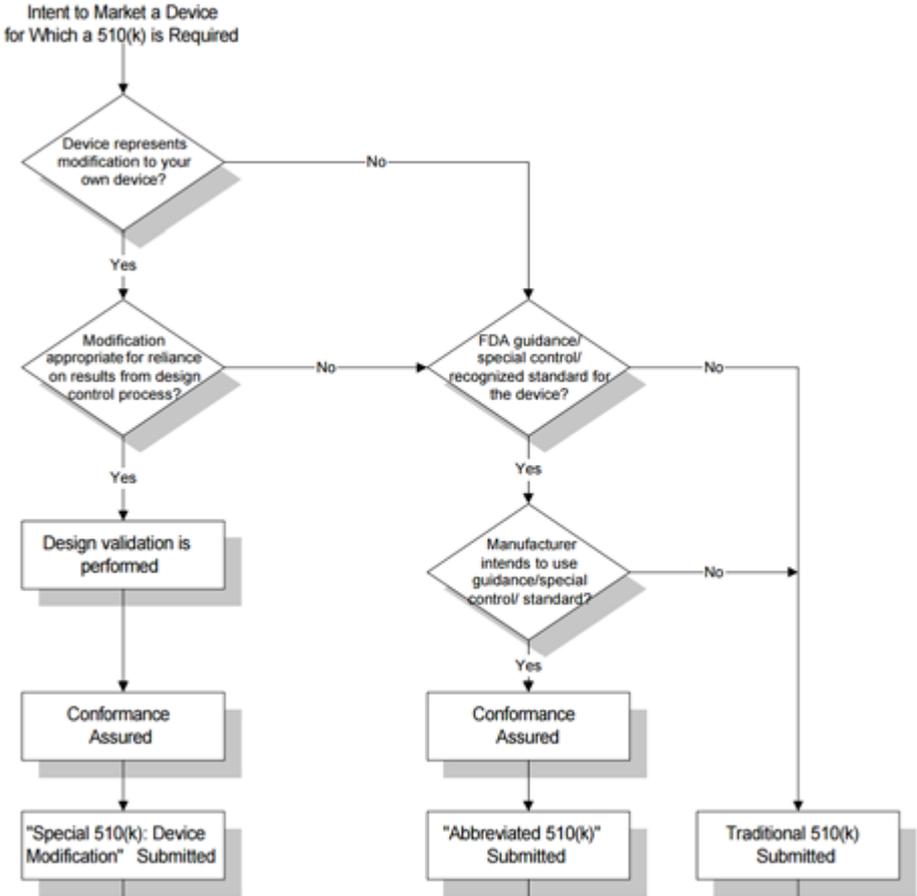
As part of its oversight responsibilities, the FDA will evaluate whether both domestic and foreign device manufacturers are in compliance with 21 CFR § 820. While the FDA will not inspect Class I or Class II manufacturers for compliance before the device's registration, it can conduct random inspections at any time after registration is completed. If an inspection takes place and the quality assurance measures are found to be insufficient, a Form 483 and/or Warning Letter from the FDA can be issued to the company. Form 483 notifies a company of "objectionable conditions" that are "clear, specific and significant" and sets a deadline for responding to the inspector's objections. While the Form 483 is not considered a final agency determination by the FDA, the egregiousness of the objections and/or the insufficiency of a company's written response to the objections can lead to further agency action deemed necessary to protect the public's health.

3.4 Premarket Notification Process - 510(k)

FD&C § 510(k) requires that device manufacturers notify the FDA of the intent to market a medical device at least 90 days in advance. The FDA defines a 510(k) filing as a "premarket submission made... to demonstrate that a new device is at least as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to premarket approval." The four groups that are required to submit a 510(k) are: (1) Domestic manufacturers introducing a device to the U.S. market, (2) Specification developers introducing a device to the U.S. market (3) Repackers or relabelers who make labeling changes or whose operations significantly affect the device, and (4) Foreign manufacturers/exporters or U.S. representatives of foreign manufacturers/exporters introducing a device to the U.S. market.

The FDA divides the 510(k) submissions into three subtypes: Traditional, Special, and Abbreviated. The Traditional 510(k) can be used for any "original 510(k) or for a modification to a previously cleared device under 510(k)." It may be utilized regardless of the circumstances. The Special 510(k) is used for device modifications and utilizes the "design controls aspect of the Quality System (QS) regulation (21 CFR 820.30)." An Abbreviated 510(k) may be used when "a guidance document exists, a special control has been established, or the FDA has recognized a relevant consensus standard."

The New 510(k) Paradigm



This flow decision treechart was designed by the FDA to help registrants determine which 510(k) format should be submitted. Additionally, the FDA has also developed literature to assist registrants in preparing traditional, special, and abbreviated 510(k) filings, which are cited in the Acknowledgments section.

As with the GMP requirements, most Class I devices and select Class II devices are exempt from the 510(k) requirement. The FDA provides a list of all exempt Class I and Class II predicate devices to assist new registrants during their device's application process, as well as a searchable database with product codes. The accuracy of the product codes used for this process will not only expedite the 510(k) process, but will also be needed during the final self-registration stage for the device. The

FDA strives to complete 510(k) review within 90 days, but the process can go longer. Device registration cannot be completed without the 510(k) number assigned at the end of the premarket notification process, making an early and accurate submission critical to avoiding prolonged periods of waiting.

Alternatively, the FDA permits third-party 510(k) review for certain medical devices. If a device is eligible, an individual on the FDA's accredited persons list may conduct the 510(k) review in lieu of the FDA. The review performed by the accredited person is then forwarded to the FDA, which issues a final determination within 30 days.

3.5 Self-Registering a Facility and Medical Device

Once prerequisite filings have been completed, the final step is to complete the self-registration process for a medical device facility and new medical device. Under the 2007 Food and Drug Administration Amendments Act, all registration and listing information must be submitted electronically through the FDA Unified Registration and Listing System (FURLS). If requested, the FDA may grant a waiver, allowing registrants to file through other means. Regardless of the method used, an annual registration fee is required and must be paid prior to device registration. The fee is determined by the FDA and can change every fiscal year.

Once payment has been processed, registrants must first register their medical device facilities. These facilities may be located internationally, but must have a listed U.S. agent. The FDA maintains a list of the types of domestic and international establishments that must be registered. Registrants will also be required to input any related 510(k) numbers associated with the medical device or appropriate product codes if the device being registered was exempt from the 510(k) process. The process will also require a listing of all proprietary names under which the medical device will be marketed and activities that will be performed on or to the device. A similar process exists if a preexisting facility was purchased and resulted in the transfer of ownership. When the process is completed, an Owner/Operator number will be designated for the location.

With the facility registration complete, the final step is to register the medical device. At this stage, the product code based on the predicate device search that was completed before prior to registration will need to be entered by using the product code search built into the registration system. From there, all facilities where activities are performed on the

device must be selected from the registrants list, and the activities being performed by each facility must be designated. Once the registration process is complete, a device is ready to be marketed in the United States.

4 Early-Stage Application Process for Drugs

This section addresses the earliest stages of the regulatory approval process for new drugs. A common misconception is that the mere fact that a drug is available over-the-counter (OTC) as opposed to requiring a prescription speeds up the regulatory approval process. While the FDA does have a regulatory fast-track for certain classes of OTC drugs, many must still go through the traditional multi-phase approval process, which can cost millions of dollars over the course of several years.

4.1 Drug-Related Regulatory Terminology

Clinical Investigation: Any experiment in which a drug is administered or dispensed to, or used involving, human subjects.

Sponsor: The party that takes responsibility for and starts a clinical investigation. A sponsor may be an individual, pharmaceutical company, governmental agency, academic institution, private organization, or other organization. A sponsor cannot conduct an investigation unless the sponsor is classified as a sponsor-investigator.

Sponsor-Investigator: An individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. This term cannot include any person other than an individual.

4.2 OTC Monographs

More than 300,000 OTC drug products are marketed in the United States, and the FDA recognizes that requiring each new OTC drug to complete the traditional approval process would be a significant strain on resources. To create a more efficient regulatory process while ensuring that OTC products are safe for consumers, the FDA has developed an OTC monograph system. In these monographs, the FDA puts together a collection of acceptable ingredients, doses, formulations, and labels for certain therapeutic classes of drugs, such as acne, sunscreen, and hair growth products.

For a company with a drug that falls into one of those classes governed by an OTC monograph, the drug can be produced and marketed to consumers without any pre-approval from the FDA, as long as it meets monograph's various criteria. A drug that includes ingredients that are not included in the monograph, or is comprised of ingredients in doses

outside the range permitted in the monograph, would still need to complete the traditional drug application process. The rulemaking history for the different OTC therapeutic drug categories and ingredients is available on the FDA's Center for Drug Evaluation and Research website.

4.3 New Drugs

For drugs that fall outside the scope, or are in a class not governed by an OTC monograph, the drug must go through the new drug application process. The FDA considers a product to be a new drug substance if the “manufacture, processing, or packing of a drug causes that drug to be a new drug.” This definition goes on to specifically exclude “intermediates used in the synthesis of such [a] substance.”

For evaluating whether the manufacturing, processing, or packing causes a drug to be new, the FDA primarily uses five-pronged analysis in making a determination which can be found in 21 CFR §310.3(h), though other factors not enumerated may make a drug new:

1. The newness for drug use of any substance which composes such drug, in whole or in part, whether it be an active substance or a menstruum, excipient, carrier, coating, or other component;
2. The newness for a drug use of a combination of two or more substances, none of which is a new drug;
3. The newness for drug use of the proportion of a substance in a combination, even though such combination containing such substance in other proportion is not a new drug;
4. The newness of use of such drug in diagnosing, curing, mitigating, treating, or preventing a disease, or to affect a structure or function of the body, even though such drug is not a new drug when used in another disease or to affect another structure or function of the body; and
5. The newness of a dosage, or method or duration of administration or application, or other condition of use prescribed, recommended, or suggested in the labeling of such drug, even though such drug when used in other dosage, or other method or duration of administration or application, or different condition, is not a new drug.

4.4 Orphan Drugs

_____ Additionally, a new drug could qualify as an orphan drug, which

is intended to treat a “rare disease or condition.” 21 U.S.C. § 360ee(b)(2) classifies a rare disease or condition as something that either affects less than 200,000 people in the United States, or affects more than 200,000 people in the United States and for which there is not a reasonable expectation that the cost of developing and producing the drug in the United States will be recouped from domestic sales.

A classification as an orphan drug comes with a number of benefits. One of the most significant benefits are grants for Phase I – III funding through the FDA’s Office of Orphan Products Development in amounts that will significantly assist or result in market approval. Up to three years of Phase I funding is available at up to \$250,000 per year; studies in Phases II and III are eligible for up to four years of funding at as much as \$500,000 per year as of FY 2015. While these grants are not available exclusively to drugs with orphan status, an orphan drug designation is an important factor in the consideration of eligibility for a grant award. Furthermore, the sponsor of an orphan drug is granted “exclusive approval” from the FDA, which means that the agency will not approve other sponsors with the same drug for a period of seven years as part of a market exclusivity incentive to optimize revenue for a drug that might not be financially successful otherwise.

When submitting an application for an orphan drug designation, an application must contain the following:

1. A statement that the sponsor requests orphan-drug designation for a specific or condition;
2. The contact information of the drug sponsor, the drug’s generic and trade name, or the chemical name or a meaningful descriptive name of the drug, and the contact information of the drug’s manufacturer if being produced by a third party;
3. A description of the disease or condition which the drug is being or will be investigated, the proposed use of the drug, and the reasons why such therapy is needed;
4. A description of the drug, to include the identity of the active moiety if it is a drug composed of small molecules, or of the molecular structural features if it is composed of macromolecules, physical and chemical properties, and an explanation of the scientific rationale establishing a medically plausible basis for the use of the drug for the rare disease or condition;
5. If the drug is the same as an already approved drug for the same

rare disease or condition, an explanation of why the proposed variation may be superior to the already approved drug;

6. If a sponsor requests orphan-drug designation for a drug for that is only meant for a subset of people with a particular disease or condition that otherwise affects 200,000 or more people, a demonstration that the remaining persons with the same disease or condition would not be appropriate candidates for the drug;

7. A summary of the regulatory status and marketing history of the drug in the United States and in foreign countries; and

8. Documentation, with authoritative references, to demonstrate that:

a. The disease or condition the drug is intended to treat affects fewer than 200,000 people domestically or, if the drug is a vaccine, diagnostic drug, or preventive drug, the drug will be domestically administered to fewer than 200,000 per year. The specific data needed to support such a claim can be found in 21 CFR §316.21(b).

b. For a drug intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year domestically, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug domestically. The specific data needed to support such a claim can be found in 21 CFR §316.21(c).

4.5 Investigational New Drug (IND) Process

4.5.1 Application Process

Before starting a clinical investigation, a sponsor of a new drug must file an IND Application with the FDA. As part of the application, the sponsor must submit information related to animal pharmacology and toxicology studies, clinical protocols, investigator information, and manufacturing information.

A clinical investigation cannot begin until either (1) 30 days have passed since the FDA received the IND and no clinical hold has been placed on the investigation, or (2) the FDA has explicitly stated that a clinical investigation may begin. Additionally, a sponsor cannot ship the

drug until either 30 days have passed since the FDA has received the application unless the agency has given explicit permission to ship.

Once a clinical investigation has begun, the sponsor has the option to cease the investigation at any time and for any reason. Ceasing a clinical investigation does not preclude the sponsor from starting or continuing it in the future. Once an investigation is halted, all treatments must be stopped and the complete drug stock must be returned to the sponsor. Additionally, the FDA must be notified that the clinical investigation has been halted. If the investigation is halted due to a safety reason, that reasoning must be shared with the FDA and all interested parties, including review boards.

The FDA offers a Pre-IND Consultation Program, which is designed to help sponsors with questions related to a variety of matters:

- Data needed to support the rationale for testing a drug in humans;
- The design of nonclinical pharmacology, toxicology, and drug activity studies;
- The design and potential uses of any proposed treatment studies in animal models;
- Data requirements for an Investigational New Drug (IND) application;
- Initial drug development plans; and
- Regulatory requirements for demonstrating safety and efficacy

4.5.2 Phase Trials

The traditional clinical investigation model is broken up into four phases, each responsible for ensuring the safety of the drug for use by patients. Each phase differs in length and patient population, with the sample size getting larger as the drug progresses through the investigation process. 21 CFR §312.21 contains a more detailed explanation of the specific role of each phase of a clinical investigation and is excerpted below.

Phase 1 includes the introduction of an investigational new drug into human patients. Studies are closely monitored and may be conducted in both patients or volunteer subjects. Phase 1 studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. Additionally, information about the drug's pharmacokinetics and pharmacological effects should be obtained to

assist in developing effective Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies, but is generally within the range of 20 to 80 participants.

Phase 2 includes controlled clinical studies meant to evaluate the effectiveness of the drug for a particular indication(s) in patients with the disease or condition and to determine the common short-term side effects and risks associated with taking the drug. Phase 2 studies are typically conducted with no more than several hundred subjects.

Phase 3 studies contain both controlled and uncontrolled trials that are undertaken after preliminary evidence of drug effectiveness has been obtained. The trials in this phase are intended to gather the additional information about effectiveness and safety to better develop a cost/benefit evaluation of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include several hundred to several thousand subjects.

Once the drug has been approved by the FDA, Phase 4 commences with a continued focus on the drug's long-term safety and effectiveness. Phase 4 studies traditionally include several thousand patients and require substantial expenditure similar to the cost of Phases 1 and 2, despite the drug's regulatory approval.

4.5.3 Exploratory IND Studies

For sponsors that are still in the process of determining which drug might be best suited for further development, the FDA's Exploratory IND process allows sponsors to engage in studies with limited human exposure with no therapeutic or diagnostic intent. The FDA suggests the Exploratory IND process for sponsors seeking to:

- “Determine whether a mechanism of action defined in experimental systems can also be observed in humans (e.g., a binding property or inhibition of an enzyme);
- Obtain important information on pharmacokinetics;
- Select the most promising lead product from a group of candidates designed to interact with a particular therapeutic target in humans, based on pharmacokinetics or pharmacodynamic properties; and
- Explore a product's biodistribution characteristics using various imaging technologies.”

An Exploratory IND study involves either sub-pharmacologic

doses or doses expected to produce a nontoxic pharmacologic effect. Since a study with this limited scope has fewer potential risks, the FDA allows for more flexibility in the preclinical testing requirements needed before initiating such a study. For sponsors who may be interested in an Exploratory IND, reviewing the preclinical requirements helps to avoid a common issue when more supporting information than is required is submitted to the FDA.

4.6 Generic Drugs

Most consumers are familiar with generics, as they play a critical role in making innovative drugs more financially accessible to a broader population. The FDA defines a generic drug as a drug that is identical (or bioequivalent) to a brand name drug in dosage form, safety, strength, path of administration, performance, intended use, and quality. More specifically, when compared to a brand-name drug, a generic drug must:

- Use the same active ingredients, though different inactive ingredients are permissible;
- Be manufactured under the same good manufacturing practices;
- Meet the identical batch requirements for strength, purity, quality, and identity;
- Be bioequivalent;
- Have identical use indications; and
- Use the same dosage form, method of administration, and strength.

Despite being identical to their brand-name counterparts, generic drugs must still go through a regulatory approval procedure. However, those similarities mean that the process can be substantially shortened through the Abbreviated New Drug Application (ANDA) Process.

The ANDA Process generally does not require the drug sponsor to supply animal or human data to establish safety and effectiveness. Alternatively, the goal of the application process is to determine whether a drug is in fact identical to a brand-name version. This bioequivalence focus was established in 1984 by the Drug Price Competition and Patent Restoration Act, which is more commonly referred to as the Hatch-Waxman Act. While there are multiple ways to determine bioequivalence that would pass regulatory scrutiny, the FDA has supplied the method most commonly used in the ANDA Process. This method requires giving 24 to 36 healthy patients the drug product and measuring the time it takes to

reach the bloodstream. This study provides the drug's rate of absorption, which can be used to ensure that the drug supplies the same quantity of active ingredients in the same amount of time as the brand-name drug.

Further information on generic drugs and the ANDA Process can be found in the FDA guidance document, *Abbreviated New Drug Application (ANDA): Generics*, cited in the Acknowledgments section.

5 Generally Regarded As Safe Designation (GRAS)

This section discusses GRAS designation, the regulations that govern it, and the FDA's evaluation process. This section also highlights the uniquely decentralized nature of the GRAS ecosystem and how it varies from more rigid and traditionally structured safety programs.

5.1 GRAS Purpose

GRAS is a determination that indicates that a particular chemical or substance is generally considered by qualified experts to be safe under the conditions of its intended use and thereby exempt from the traditional PMA process.

Unlike most safety designations when a federal agency independently investigates and determines safety, the study that leads to the finding of a substance as GRAS is completed by a private entity or industry association. The party that completes the safety study has no obligation to publish it or submit it to the FDA for review, as the notice system is purely voluntary. Of course, the data and methods used to make the safety determination must be archived in the event the substance in question comes under scrutiny from the FDA.

If the data related to a GRAS determination is sent to the FDA and currently under review, the substance may still be marketed without informing the FDA. Additionally, even if the FDA is informed while it is still reviewing the GRAS notification, the substance may be marketed. This self-reporting system came into effect in 1998 after the FDA determined that it no longer had the resources to perform research required to make GRAS designations. Since then, there have been more than 500 notices related to GRAS designations.

Share of FDA GRAS Notices by Category

GRAS Substance Category	Share of Filings
Lipids	24%
Enzyme Preparations	20%
Chemicals	18%
Carbohydrates	13%
Protein	10%
Extracts	8%
Other	7%

GRAS notifications sent to the FDA are under the purview of the Office of Food Additive Safety. GRAS notices need to include a concise description of the substance, its use conditions, and the basis of the safety determination. The FDA strongly recommends arranging a meeting before submitting a GRAS notification, as it tends to substantially improve the quality of submissions.

Since there is no obligation to submit a GRAS notice to the FDA, many industry stakeholders keep a private list of substances that have been internally tested for safety, while other associations such as the Flavor and Extract Manufacturers Association (FEMA) offer their own GRAS reviews and publications as an alternative to the FDA's system. Each system is operated independently with no FDA oversight over third-party systems, which means that a GRAS designation made by FEMA's panel of expert scientists can be challenged by the FDA. Additionally, the FDA can reverse its own opinion on substances that previously went through its own GRAS procedure, as the FDA admits to not performing independent analysis on these substances and that scientific consensus can change over time. The June 2015 revocation of the GRAS designation for partially hydrogenated oils is a prime example of the continuing scrutiny GRAS-designated substances face from the FDA.

This decentralized GRAS ecosystem leaves a variety of choices for parties seeking to have a substance evaluated. Certain stakeholders may require a substance go through a particular GRAS notification process as part of a licensing negotiation, but in the end, the regulatory effect is the same, regardless of the method used.

5.2 GRAS Regulations and Procedure

The GRAS designation was initially introduced by the Food Additives Amendment of 1958. Today, GRAS designation is governed by §201 and §409 of the FD&C Act, as well as the Code of Federal Regulations under 21 CFR §170.30. The FDA has two primary methods of proving that a chemical or substance is GRAS: recognition of safety through scientific procedures, and recognition of safety through experience based on common use in foods. Lists of substances with GRAS designation are found in 21 CFR sections 182 (Substances Generally Recognized as Safe), 184 (Direct Food Substances Affirmed as GRAS), and 186 (Indirect Food Substances Affirmed as GRAS). Additionally, a complete database of GRAS notices and FDA responses is available online.

The foundational definition related to GRAS is that of a food additive, which is defined as:

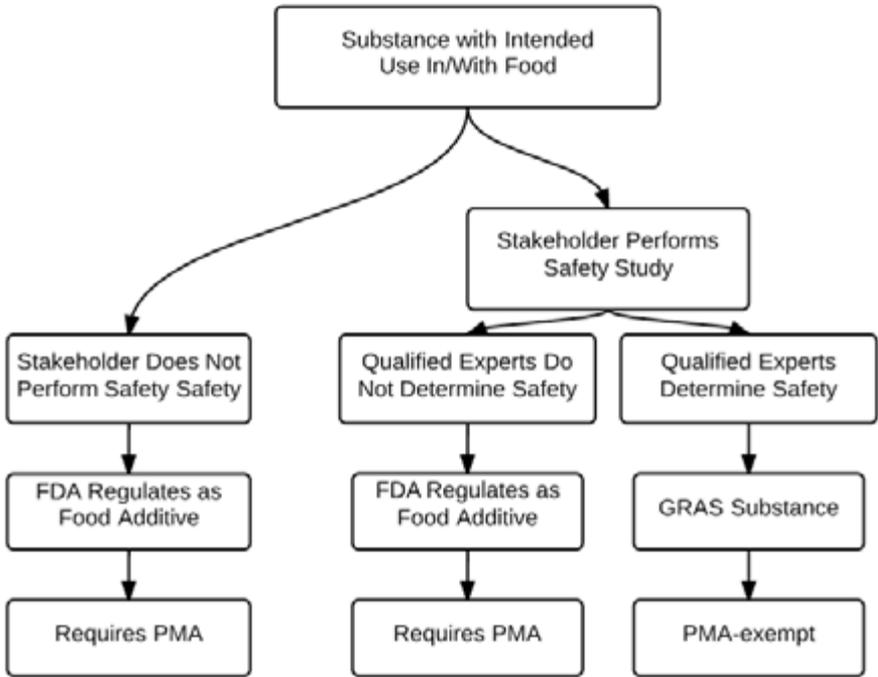
“Any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food. [This] include[es] any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food...**if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety**” (emphasis added).

The definition of “food” used in the preceding paragraph, is fairly straightforward, and includes:

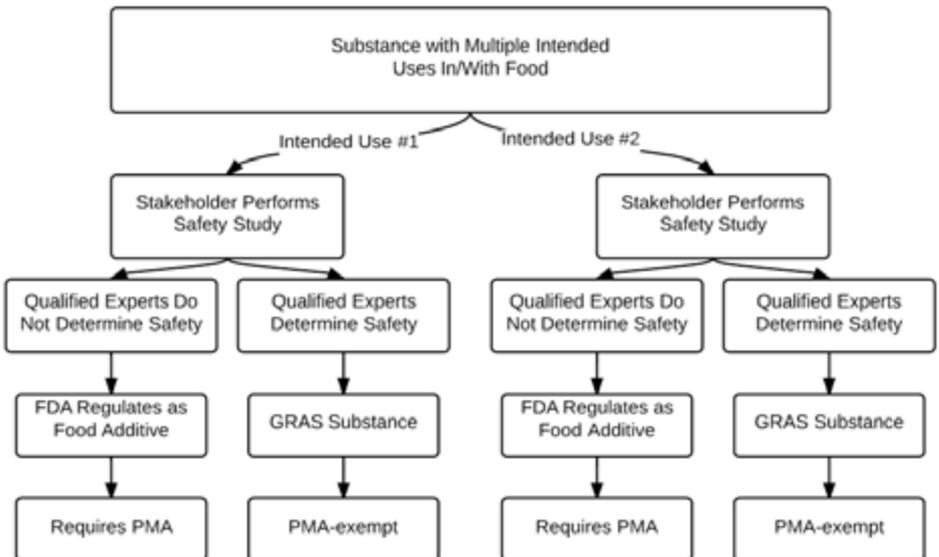
- “(1) articles used for food or drink for man or other animals;
- (2) chewing gum, and;
- (3) articles used for components of any such article.”

If a substance meets the definition of a food additive, it must go through the FDA’s PMA process. However, if a substance meets all of the criteria in the food additive definition but has been generally recognized as safe by qualified experts, than the substance is considered GRAS by the FDA and may bypass the PMA process. It is important to note that a substance can be considered GRAS for one intended use and as a food additive for another. This depends on a variety of factors, including the food it is intended for use with or the amount of the substance expected to be ingested by a consumer.

Food Additive vs GRAS Flow Chart (Single Intended Use)



Food Additive vs GRAS Flow Chart (Multiple Intended Uses)



5.3 FDA Submission Requirements

This section broadly outlines the notification requirements that must be met in every GRAS notification that is sent to the FDA. Requirements specifically related to the method of determining safety are addressed in sections 5.3.1 and 5.3.2. The FDA's GRAS Notification Database is available online and provides access to submissions and the FDA's response, which is useful in determining best practices for filings. The FDA's lists of food additive statuses and Everything Added to Food in the United States (EAFUS) provide additional information about prior-approved substances. Additionally, the FDA's *Redbook: Toxicological Principles for the Safety Assessment of Food Ingredients* provides in-depth guidance on structuring safety assessments and is cited in the Acknowledgments section.

The FDA requires that all voluntary notices include detailed information about the GRAS substance, including which foods it is intended for use in, the levels of use for those foods, and the purpose of the substance's use. When appropriate, a description of the population that is expected to consume the substance is expected. Additionally, notice formalities require that the method of GRAS determination (scientific or common-use experience) must be explicitly referenced, along with a statement indicating that the FDA can review information and data used to make the safety determination.

5.3.1 Scientific Procedures

Most GRAS notifications require evidence collected through scientific procedure, as outlined in 21 CFR §170.30(b). The FDA requires the same quantity and quality of scientific evidence that would be required if the substance was being submitted through the more rigorous food additive regulations. This scientific evidence used to prove a substance's safety must be generally available, which is often accomplished through published studies.

More specifically, a GRAS notice should include a discussion of scientific procedures used to make the safety determination, including the data, methods, and principles relied on. A key part of this data that must be included is a consideration of how probable consumption of the substance is and in what quantity it will likely be consumed. This analysis also needs to take into consideration consumption that may occur because the substance is used on surfaces or equipment that may come in contact with food.

Additionally, the notice must include a comprehensive discussion of any reports, investigations, or data that appear to be inconsistent with the GRAS determination. A conclusion that a substance is safe must include the basis for such a finding in light of all the information presented in the notice, including any data or information to the contrary.

5.3.2 Common Use in Food

This method of making a safety determination is only applicable for substances used in foods before 1958, as outlined in 21 CFR §170.30(c) and (f). For common use in food determinations, a notice must include a comprehensive discussion of, and citations to, generally available data and information used to establish a safety determination. This includes evidence of a substantial history of consumption of the substance by a significant number of consumers.

5.3.3 Substantial Equivalence

The FDA does not formally recognize substantial equivalence considerations in GRAS notices. However, the principle can be used as part of the data used to prove a substance's safety. The FDA's preferred terminology includes phrasing such as "similar" or "indistinguishable," as substantial equivalence is primarily associated with the FDA's medical device division. It is worth noting that while the FDA has used the term "substantial equivalence" in its response to a GRAS notice in the past, this is considered an anomaly. Additionally, since GRAS notifications submitted to the FDA are not independently validated and industry-specific databases have no FDA oversight, the concept of substantial equivalence does not necessarily add significant credence to a safety determination. The GRAS notifier should not predominantly depend on similarities to other GRAS substances when making a submission to the FDA.

5.4 FDA Responses to GRAS Notifications

The FDA has two main responses for a GRAS notice that completes the submission process: (1) The FDA has no questions, and (2) Notice does not provide a basis for a GRAS determination. A response that the agency has no questions indicates a successfully completed submission. However, since the FDA does not independently validate the data and research in the submission, this response does not function as the agency certifying that the substance is GRAS; it merely indicates that the conclusion is sound, based on the current data presented.

If the FDA finds that the notice does not provide a basis for

a GRAS determination, the letter written by the FDA will address the deficiencies in the reasoning or scientific process that led to this conclusion. For example, the FDA takes issue with toxicity studies that lack sufficient animal testing if the projected human consumption of the substance reaches certain levels. Additionally, the testing conditions for determining how much of the substance is being consumed should seek to closely emulate how the substance would be used in applicable consumer products, taking into account both environmental factors and different types of foods.

6 Acknowledgements

2 Drug vs. Device Designation

- Special thanks to Diana M. Yoon, Ph.D., FDA Office of Combination Products, Office of Special Medical Programs.
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- *Guidance on Writing an RFD*, FDA, available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM251544.pdf>.
- *Guidance on the Definition of “Chemical Action”*, FDA, available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM259068.pdf>.

3 Medical Device Registration

- *Evaluation of Automatic Class III Designation (De Novo) Summaries*, FDA, available at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm232269.htm>.
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4 Early-Stage Application Process for Drugs

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5 Generally Regarded As Safe Designation (GRAS)

- Special thanks to Leah Rosenfeld, Ph.D., Consumer Safety Officer, FDA Office of Food Additive Safety, Division of Biotechnology and GRAS Notice Review.

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