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 leave companies under-eguipped to pursue the financially onerous time commitment necessary to bring a product to market.

About the New York State Science & Technology Law Center:

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.

Notice:

The information contained in this pamphlet is intended to be an introductory guide only. No part of the guidebook, attachments, or related discussions constitues 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 Overview of FDA Law

The FDA regulates food (including food additives), dietary supplements, drugs, medical devices, cosmetics, and tobacco products. Food and drug law is based on the Federal Food, Drug, and Cosmetic Act (FDCA), which was enacted in 1938, and is codified in Title 21, Chapter 9, of the United States Code of federal statutes. The FDA has promulgated regulations that set out the specific requirements for complying with the FDCA, and these regulations are set out in Title 21 of the Code of Federal Regulations (21 CFR). In addition to its regulations, the FDA has issued many guidance documents, which describe how the agency interprets and plans to enforce the regulations on a particular subject. Although the guidance documents are not regulations, and do not have legal effect in and of themselves, they are often one of the best references for understanding FDA regulations and should be carefully considered whenever they are relevant to a particular regulatory issue. This guidebook provides a very brief introduction to FDA's regulation of medical devices, drugs, food additives, and dietary supplements.

FDA's regulation of products within its jurisdiction can be allocated among five general areas:

1) pre-market review and authorization to sell certain regulated products;
2) registration of manufacturing facilities and listing of regulated products with FDA;
3) good manufacturing practices for production of regulated products;
4) content of labeling, directions for use, and marketing claims for regulated products; and
5) monitoring customer feedback relating to regulated products to identify, report, and remediate adverse events.

The overriding purpose of regulation is to assure that regulated products are safe for use or consumption, and that drugs and

devices are not only safe, but also effective for the intended use described in the labeling for the drug or device.

There are three principal types of violations of the FDCA, which are in turn based on failure to follow the specific requirements set out in the FDA regulations in 21 CFR:

1) adulterated product violations,
2) misbranded product violations, and
3) violations based on marketing a product without the required premarket review and permission from FDA.

For example, if products are manufactured in a way that does not comply with prescribed current good manufacturing practices, the products are deemed to be adulterated, whether or not they are actually defective. A product is misbranded if it does not satisfy the performance or quality specifications in its labeling, or if the product is marketed for an intended use that is not included in its labeling. There are several types of remedies/penalties for violations of the FDCA, including government seizure of adulterated/misbranded product, required recall of adulterated/misbranded product, misdemeanor criminal prosecution of companies or executive management for unintentional violations, and felony criminal prosecution for intentional violations.

The remainder of this guidebook is organized into four parts. The first part covers medical devices, including the definition, classification, and premarket review framework that applies to devices. The second part covers drugs, including the definition, classification, and premarket review framework that applies to drugs. The third part covers several areas of regulation that apply to both devices and drugs, including good manufacturing practices, restrictions on promotion and marketing, and post-market requirements relating to reporting adverse events to FDA. The last part covers FDA's regulation of the food additive and dietary supplement portions of the food industry, including the premarket notification requirements and good manufacturing practices required for food additives and dietary supplements. The food additive and dietary

supplement segments of the food industry are covered in this guidebook because they typically involve more new technologies, as compared to the traditional whole food industry, and FDA's regulation of them is analogous to the regulation of drugs and devices.

2 Medical Devices: Definition, Classification, and Premarket Review

2.1 Definition

A general working definition of a medical device is an instrument, apparatus, or similar article that is either:

1) intended for use in the diagnosis or treatment of disease or other conditions in humans or other animals, or
2) intended for use to affect the structure or function of some part of the body of humans or animals, and which achieves its effect without chemical action and without being metabolized. (The complete definition is set out in section 201 (h) of the FDCA.)

In contrast, products that achieve their effects through chemical action or through metabolism are regulated as drugs. Medical devices span the range between simple products, such as tongue depressors and bandages, to complex products such as physiologic monitors, heart pacemakers, and other types of implants.

The definition of medical devices involves the concept of intended use, which means the general purpose or function of the device. The intended use of a device is determined by the design and functionality of the device itself, together with the device's labeling, which must inform the user what the device is for and how to use it. The intended use of a device covers one or more indications for use of the device that are described in the labeling. Indications for use are the condition(s) or disease(s) that are intended to be diagnosed or treated with a device, or the population of patients on which the device will be used. For example, a laser produces a beam of light that can have varying levels of power, and the design

of the laser determines its range of illumination intensity or power. The directions for use of a laser medical device will specify the intended use, meaning its general purpose and function, such as cutting or coagulating tissue in surgical procedures (high power) or modifying tissue in dermatology procedures by selective destruction of parts of skin tissue (low power). The indications for use of a medical laser (also set out in the directions for use) would specify the procedures for which it is used, such as neurologic or gynecologic surgery, ophthalmic procedures for the cornea or lens of the eye, or dermatology procedures for removing hair, treating wrinkles, or tattoo removal.

2.2 Device Classification

The classification of a medical device consists of two parts:

1) a level of control classification, and
2) a type classification.

2.3 Levels of Control

There are three levels of control device Classes, which are based on the degree of risk associated with use of the device. (Section 513 (a), FDCA, 21 USC 360 (c)(a)). Class I devices are associated with low risk, Class II devices are associated with moderate risk, and Class III devices are associated with high risk. As the name implies, the level of control classification determines the methods and extent of regulatory controls that are applied by FDA to a particular device. There are three methods of control used by FDA to regulate devices, which are described in the regulations as general controls, special controls, and premarket approval. Class I devices are subject only to general controls, Class II devices are subject to general controls and special controls, and Class III devices are subject to general controls and premarket approval.

General controls consist of all of the general requirements applicable to the manufacture and marketing of medical devices, including registration of manufacturing facilities with FDA, listing

medical devices marketed in the U.S. with FDA, compliance with good manufacturing practices, pre-market clearance (unless an exemption applies), creating and maintaining records documenting that devices meet their specifications before shipment, and investigating all adverse events involving devices and reporting to FDA those that caused, or could cause, serious harm to patients. Special controls consist mainly of specific requirements that must be met in order to obtain 510 (k) clearance to market a particular type of device. Special controls include product design standards/ performance standards that are recognized by FDA to ensure safety and efficacy for a particular type of device; prescribed labeling requirements such as warnings, cautions, or contraindications; and types of clinical testing that are required for clearance. Premarket approval is the most rigorous form of obtaining permission from FDA to market a new type of medical device product, and it requires comprehensive technical and clinical proof that the new device is safe and produces good clinical outcomes with acceptable side effects/risks. Both the 510(k) clearance and premarket approval processes are described in this section.

In practice, the level of control classification of a device is most important for determining the type of premarket permission that will be required before the device can be marketed and sold. FDA has exempted most Class I devices from the requirement to obtain premarket clearance, and therefore most Class I products typically can be marketed and sold without a clearance letter from FDA. Most Class II products require premarket clearance via the 510 (k) process, which in many cases will require compliance with special controls established for the type of device for which clearance is sought. Premarket clearance via the 510(k) process requires a substantial investment in money and time required for designing the device and obtaining clearance. Class III products require premarket approval, which requires an even more substantial investment in money and time required for designing the device and conducting the clinical studies necessary to obtain approval to sell the product. It should be noted that all devices, whether Class I, II, or III must comply with the general controls. (While most Class I

devices are exempt from premarket clearance, most Class I devices are subject to the other general controls.)

2.4 Product Classification

In addition to the level of control classification, devices are assigned a product code and most devices are assigned to a descriptive generic type classification. (Section 513 (d) FDCA, 21 USC 360 (c)(d). The generic type classifications of medical devices are set out in 16 parts of the medical device regulations between 21 CFR 862 and 21 CFR 892. Hundreds of types of devices are catalogued in these parts of the device regulations. Each part covers the devices used in a specific medical specialty; for example, part 870 covers cardiovascular devices and part 882 covers neurologic devices. (A few medical devices are "unclassified", meaning they are not assigned to a generic type classification in 21 CFR 862-892, but all devices are assigned a product code and level of control class.)

FDA makes available a product classification website (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm) that can be used to determine the classification of a device by entering the generic type of device or a known product code. The classification information provided by the FDA product classification website includes the product code, the section of the device classification regulations that covers the device, the level of control classification of the device, and any special controls that apply to the device. For example, if you search the product classification database using the term electrocardiograph, the product classification returned consists of:

1) the product code DPS;
2) the "Regulation Number" 870.2340, which means that electrocardiographs are defined in 21CFR 870.2340;
3) level of control Class II; and
4) a list of the special control performance standards that must be satisfied to obtain clearance of an electrocardiograph.

2.5 Medical Devices Exempted from Regulation

The FDA has exempted from the medical device regulations several groups of medical devices that are low risk, both in terms of how they function and their intended use. These groups of products include: General Wellness Products, Medical Device Data Systems (MDDS), and certain Mobile Medical Applications. Each of these groups of devices are briefly described in this section. The conditions that must be met to qualify for exemption from regulation are set out for each of the foregoing groups in guidance documents issued by FDA. A medical device that qualifies for one of these exemptions is not subject to regulation via any of the three methods of control employed by FDA (i.e., no general controls, special controls, or premarket approval).

2.5.1 General Wellness Products The exemption for General Wellness Products is explained in the FDA Guidance Document General Wellness: Policy for Low Risk Devices. The essential requirements that must be met to qualify for the General Wellness Product exemption are:

1) the device must be low risk, and
2) the intended use of the device must relate to practicing healthy lifestyles to maintain a general state of health or to reduce the impact of living with a chronic condition.

Low risk typically means that the General Wellness Product is not used in any invasive procedure (e.g., drawing blood), does not introduce energy into the body (e.g., neurostimulation with electric current or treatment of skin with laser or ultraviolet radiation), and is not used for diagnosis of any health condition or intervention to treat a health condition. Intended uses of General Wellness Product would include facilitation of weight management, physical fitness, sleep management, relaxation or stress management, mental acuity exercises, and other similar healthy lifestyles. In all cases, the labeling of the General Wellness Product would describe its purpose to be facilitation of maintaining a general state of good health or improving the ability to live with chronic conditions such as high

blood pressure or diabetes (not to treat them).

2.5.2 MDDS The exemption for an MDDS is explained in the FDA Guidance Document Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices. The MDDS exemption is available to devices that meet the definition set out at 21 CFR 880.6310 for Medical Device Data Systems. A working definition of an MDDS is hardware and software that provides one of the following uses:

1) electronic transfer of data collected with a medical device,
2) electronic storage of data collected with a medical device,
3) converting electronic medical device data from one format to another, and
4) displaying medical device data on a display screen.

The MDDS must not be capable of controlling the functions or parameters of any medical device that is connected to the MDDS. In a nutshell, MDDS are communications systems that take electronic/digital input from medical devices, transmit it to a storage database, and retrieve it from storage and display it when needed.

2.5.3 Mobile Medical Applications The exemption for Mobile Medical Applications is explained in the FDA Guidance Document Mobile Medical Applications. Mobile Applications are software programs that run on commercially available mobile computing platforms, such as smart phones or tablet computers. Mobile Medical Applications are Mobile Applications that meet the definition of a medical device, as described above. The Mobile Medical Application exemption applies to a subset of Mobile Medical Applications that fall within the following seven categories:

1) software applications that promote behavioral changes by providing “coaching” to patients
2) software tools to track health information that can be used in a treatment plan
3) software applications that are reference tools for health

care providers, such as treatment guidelines or drug interactions
4) software applications that facilitate providing remote healthcare, such as camera or video systems that enable a physician to see and interact with a patient at a different location
5) software applications that are medical calculators, e.g,. body mass index, Glasgow coma scale, NIH stroke scale
6) software applications that enable patients to interact with their electronic medical records
7) an MDDS that runs on a mobile platform.

2.6 Assistance in Classifying a Device

There are a number of "informal" ways to get help from FDA with respect to classifying a medical device product, including contacting the Office of Device Evaluation or the Division of Small Manufacturers International and Consumer Assistance. If informal inquiries are not sufficient to enable classification of a device, Section 513 (g) of the FDCA provides a formal method for obtaining FDA's view on how a device will be classified, which is referred to as a Section 513 (g) Request for Information.

FDA has issued a Guidance Document explaining in detail how to submit a 513 (g) Request, entitled FDA and Industry Procedures for Section 513 (g) Requests for Information under the FDCA. A 513 (g) Request consists of:

1) a cover letter,
2) a detailed description of the device, including diagrams, pictures of the device, and an explanation of how the device operates,
3) a description of what the device is to be used for, i.e., the intended use and the indications for use, and
4) the proposed labeling for the device.

FDA is to respond to the 513 (g) Request within 60 days and provide its determination of the generic type to which the device

would be assigned, the level of control classification, and the product code for the device.

2.7 Premarket Review of Devices

This section provides an overview of the 510 (k) Premarket Notification process, the Premarket Approval Process, and the Design Control Regulations that must be followed in creating the design, testing, and other technical documentation that is submitted for both 510 (k) clearance and Premarket Approval.

2.7.1 510 (k) Premarket Notification As mentioned in the explanation of device classification, premarket notification is one of the general controls that technically applies to all devices. However, FDA has exempted almost all Class I devices from the premarket notification requirement, excluding only a few "Reserved" Class I devices, most of which are lab testing kits. A number of Class II devices have also been exempted from the premarket notification requirement, but most Class II devices require 510(k) clearance before they can be offered for sale. A list of the exempted Class II devices can be accessed via the FDA's website "Medical Device Exemptions 510 (k) and GMP Requirements". Nearly all Class III devices require Premarket Approval, and are therefore excluded from the Premarket Notification requirement, with exceptions for a few Class III devices that can be cleared with a 510(k). As a practical matter, Premarket Notification is associated with Class II devices. A device that requires 510 (k) clearance cannot be offered for sale until FDA issues a clearance letter (21 USC 360 (k)).

The 510 (k) process requires showing that the device for which clearance is sought (new product) is safe and effective by virtue of being substantially equivalent to one or more legally marketed "predicate devices". The 510 (k) process involves a detailed comparison of the new product to the selected predicate devices. Substantial equivalence of a new product to its predicate(s) requires showing that both products have:

1) the same intended use, and

2) technological characteristics that are either the same or similar enough that any differences do not raise issues of safety or efficacy that are different from those that are associated with the predicate.

It is possible to use more than one predicate to show substantial equivalence, but a primary predicate must be designated. Secondary predicates are used only to the extent that the primary predicate includes most, but not all, of the types of technology that are present in the new product, and the secondary predicates are used to cover the types of technology that are missing from the primary. Secondary predicates must have the same intended use as the primary predicate and the new product.

FDA has issued an excellent guidance document that explains substantial equivalence: The 510 (k) Program: Evaluating Substantial Equivalence in Premarket Notifications. The 510 (k) regulatory framework is based on the idea that acceptable clinical outcomes and the safety and efficacy of legally marketed medical devices have been established by historical use in the market, and therefore when a new product is shown to be substantially equivalent to a legally marketed predicate, it will also be safe and effective, in so far as its design is concerned. (Of course, manufacturing defects can cause problems even when a design is sound, and manufacturing defects are addressed through enforcement of good manufacturing practices.)

The format and information required for a 510 (k) submission are specified in 21 CFR 807.87, 807.90, 807.92, and 807.93. The contents include the following:

1) Applicant name, address, and registration number for applicant's manufacturing facility.
2) Device name and classification, meaning the generic classification name and product code as well as the contemplated trade name, and level of control classification.
3) Detailed description of the device, including a physical

and technical description, and its intended use and indications for use.

4) Performance Standards that are satisfied by the device; these must include all standards that are mandated by special controls for the device, and may include standards that are recognized for prescribing performance of the generic device type of the new product.
5) Information about verification and validation of any software in the device. These requirements are explained in the guidance document Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices.
6) The Substantial Equivalence Comparison between the new device and its predicate(s). This is the key section of the submission, and it will discuss the similarities and differences between the new device and its predicate(s), including showing conformity to the same performance standards that are satisfied by the predicate(s). In some cases, it may be necessary to do direct comparison testing (typically engineering lab testing) between the new device and its predicate to show equivalent performance on a set of test cases.
7) The final labeling to be used for the new device must be submitted. Labeling includes the directions for use and performance specifications for the product.
8) For devices whose use involves contacting body surfaces, information demonstrating biocompatibility must be presented. In a nutshell, materials used in parts of the device that contact the body must either be present in a predicate, or laboratory biocompatibility testing results must be provided to demonstrate safety in terms of allergic reactions.
9) Devices that are labeled as sterile must describe the sterilization method and information on validation of the sterilization method.
10) Clinical studies are not required for most 510 (k)

> submissions, but in some cases clinical studies are necessary to show that a new device and its predicate exhibit equivalent performance on patients in the same use cases. This type of clinical comparison testing between a new device and its predicate involve small populations of subjects (typically less than 100 subjects).

The foregoing description covers what are known as traditional 510 (k) submissions. There are two additional types of 510(k) submission that are available in limited circumstances. The Special 510 (k) and Abbreviated 510(k) are described in the guidance document: The New 510 (k) Paradigm-Alternative Approaches to Demonstrating Substantial Equivalence in Premarket Notifications-Final Guidance. The details of these alternative types of 510 (k) submissions are beyond the scope of this guidebook, and the traditional form is by far the most common. However, it is worth noting that the Special 510 (k) is used by a manufacturer that is developing a new version of one of its existing cleared devices. The manufacturer's existing cleared product is the predicate for the new device, and clearance is often obtained very quickly as compared to the traditional submission.

It takes significant work, time, and expense to develop the design of a medical device that meets the requirements for 510 (k) clearance and to prepare the 510 (k) submission. The design work typically will require many months to complete, and the preparation of the submission typically requires a few additional months. After the 510 (k) submission is accepted by FDA, the time for review and clearance by FDA will typically take between 4 and 12 months. It is essential for medical device manufacturers to accurately estimate the time and expense required for clearance when developing business plans and company budgets.

A new 510 (k) clearance is required if significant changes are made to a device as compared to its state at the time of original clearance. Significant changes are those that could affect the safety or effectiveness of the device, and include changes in design of the

device and the materials or manufacturing process used to make the device. Changes in intended use or indications for use also will require a new 510 (k) clearance. FDA has issued a guidance document explaining in detail when changes to a device require a new 510 (k): Deciding When To Submit a 510 (k) for a Change to an Existing Device.

2.7.2 The Premarket Approval Process The Premarket Approval Process (PMA) is the highest level of control exercised by FDA over medical devices, and it is used for Class III devices, which are new types of devices that are associated with inherent risks of serious harm or side effects. Class III devices usually incorporate new technology or an adaptation of existing technology to new intended uses or new indications for use, and it is often the case that there are no recognized performance standards for some parts of the technology deployed in Class III devices, and no legally marketed predicates. The PMA can be best understood by comparison to 510 (k) clearance. The 510 (k) framework requires showing substantial equivalence to a predicate, and substantial equivalence is presumed to be a proxy for safety and efficacy, because of the historically good clinical outcomes associated with all such predicates in the market. There are no predicates for Class III devices, and so the PMA must contain all scientific evidence that is necessary to demonstrate the safety and efficacy of the new Class III device. The PMA will therefore include extensive engineering lab testing to establish or justify the technical performance characteristics of the device, animal testing to establish enough safety to justify testing on humans, and extensive clinical studies in humans to demonstrate the safety of using the device on a large population of human subjects, as well as an acceptable benefit/risk profile for this population.

The format and information required for a PMA are outlined in 21 CFR 814.20, and include the following:

1) Applicant name, address, and registration number for applicant's manufacturing facility.
2) A summary of the application and background

information that is relevant to the new device. The summary will contain the generic classification of the device and its trade name, a brief description of the device, the intended use and indications for use of the device, history of the device in any foreign markets, and the existing practices and procedures that are used in the U.S. for diagnosis and treatment of the conditions for with the device is intended. The summary also must contain an abstract of the nonclinical and clinical studies conducted with respect to the device and a discussion of the key results of the studies that constitute scientific evidence that the device is safe and effective for its intended use.

3) A complete description of the device, including pictures and engineering schematic diagrams, list of materials and components used to make the device, principles of operation of the device and the key properties of the device relative to its diagnostic or therapeutic functions, the processes, equipment, methods of control to be used in making the device, and a list of all the performance standards that are relevant to the operation of the device. Samples of the device must be provided to enable testing and evaluation by FDA.
4) Technical sections that provide the data and information generated by nonclinical laboratory studies, animal studies, and clinical investigations on human subjects. The nonclinical laboratory studies would focus on demonstrating that the design and manufacture of the parts of the device that perform critical functions ensure good performance. The clinical investigations section must include the study protocols used, the performance measurements used, number of subjects and their characteristics, adverse events that occurred during the study, and a discussion of the results and conclusions drawn from the results. All studies on human subjects must be approved by an Institutional Review Board and all subjects must provide informed consent to

participate.

5) A bibliography of all known published articles and reports that are relevant to the potential safety and efficacy of the device for which PMA is sought.
6) The final labeling to be used with the Class III device.
7) A benefit/risk analysis that addresses expected side effects and the risk of unexpected adverse consequences arising from use of the Class III device.
8) Other information that FDA may request.

The time required to develop the design of a Class III device and compete the nonclinical and clinical testing that must be included in a PMA is measured in years, with commensurate costs. The time required for FDA to review and issue the PMA will probably be more than a year. The time and cost involved in obtaining a PMA is therefore much greater than the time and cost required for a 510 (k) clearance, and device manufacturers must account for the cost and time required to obtain a PMA in any realistic business plan or budget. In practice, a modular approach is used for the process of FDA review of PMAs because of their complexity and the high costs involved. It would be disastrous to complete a PMA and discover that it was not "approvable" by FDA. In essence, the modular approach involves FDA and the applicant meeting to agree on a phased plan for preparation and review of the PMA so that issues can be identified and addressed early.

FDA may issue a PMA subject to post-approval requirements, including requiring a plan for post-market surveillance, under which adverse events and other complaints or problems associated with the device are investigated and reported to FDA regularly. A PMA Supplement submission is required for any changes to a Class III device covered by a PMA to the extent that the changes could affect the safety or effectiveness of the device. The types of changes that require a PMA Supplement include:

1) new indications for use;
2) changes to labeling;
3) changes in design specifications, materials or methods

used in production;
4) changes in packaging; and
5) if the device is sterile, any change in the sterilization procedure.

2.7.3 De Novo Classification Process Section 513 (a) of the FDCA provides that a new type of generic device that has not been classified by FDA is automatically classified as Class III, even if the device is low or moderate risk. The PMA level of control is intended only for high-risk devices, and therefore a mechanism was needed for classification of new types of generic devices that are of low or moderate risk and which can be satisfactorily regulated with general and special controls applicable to Class I and II devices.

Section 513 (f)(2) of the FDCA was modified in 2012 to provide for a De Novo Classification Process pursuant to which new generic types of devices that present low or moderate risk can be classified by FDA as Class I or Class II devices and regulated by general and special controls. The De Novo Process is explained in the guidance document: De Novo Classification Process (Evaluation of Automatic Class III Designation). The De Novo Process can be used before any 510 (k) submission is made, or after a 510 (k) submission has been rejected because of the lack of a predicate. Failure to find a predicate typically results when the new device differs from potential predicates in intended use or incorporates technology that is not similar enough, even though it has the same functionality.

The contents of a De Novo submission will include:

1) a detailed description of the device,
2) a summary of the search for potential predicate devices and an explanation of the differences between the potential predicates and the new device that make the potential predicates unsuitable,
3) a recommendation of the classification of the device (level of control and generic type or medical specialty in which the device will be used),

4) if Class II is recommended, an identification of the special controls that should apply and any data and analysis that demonstrates that the special controls will be adequate to ensure the safety and efficacy of the device, and
5) an analysis of the risk/benefit profile of the device.

The De Novo process provides for an optional pre-submission meeting with FDA, which involves providing FDA with an outline of a proposed De Novo submission and obtaining FDA's input on structuring the actual De Novo submission in a way that will address FDA's requirements and streamline the classification process.

2.7.4 Design Controls 510 (k) submissions and PMA submissions both require demonstrating that the design of the device covered by the submission will actually meet the performance requirements that are set out in the submission and will meet user expectations of utility and reliability. FDA has promulgated the Design Control regulations, 21 CFR 820.30, which prescribe quality practices and activities that must be applied in designing and developing a medical device, and therefore govern the R&D activities of medical device manufacturers. Design controls apply to the development of all Class II and Class III devices and a few Class I devices. Design controls do not apply to vetting product concepts and early stage prototypes that are used to demonstrate feasibility, but they are applied to all activities in creating the design/specification of the device that will be commercialized. All design control activities must be documented in a Design History File, which is one of the most important quality system records. A large amount of the documentation that is included in 510 (k) and PMA submissions is taken from or based on the Design History File, and most importantly, that documentation must have been created by activities that conform to the design control requirements.

The design control requirements are explained in the guidance document: Design Control Guidance For Medical Device Manufacturers. Design control activities consist of:

1) design and development planning,
2) development of design inputs,
3) development of design outputs,
4) design verification,
5) design review,
6) design transfer, and
7) design validation.

The development of a medical device must be structured as a series of iterative cycles, each of which has well-defined design input requirements, work activities to generate a variety of design outputs that are intended to satisfy the design inputs, and testing or analytic work to verify that the outputs do in fact satisfy the inputs. An overview of some of the design control activities is provided to enable entrepreneur device manufacturers to get some familiarity with the extent of work required to develop a medical device.

Design inputs are the physical and performance requirements of a device, and typically they are derived from user requirements. User requirements are stated in terms of qualitative features or functions of a device, using clinical terminology. User requirements are translated into design inputs by hypothesizing and analyzing the physical embodiments that would satisfy the user requirements, anticipating and mitigating the risks of these embodiments, and taking into consideration the environmental use cases and human factors associated with the device. Each user requirement will generate a hierarchy of design inputs that need to be satisfied to realize the user requirement. There are separate design inputs for software that must be developed by defining in detail the functions of the device that will be implemented in software, the inputs to and outputs from the software, the interfaces among software modules and wireless communication, and the required processing speed and data throughput. Clear and measurable design inputs are crucial, because they are the acceptance criteria used to judge the design outputs of each cycle of development of a device.

Design outputs consist of the work product created during each

cycle of development. Design outputs include the product specifications and drawings, new or updated design inputs that resulted from the development work, prototypes of the device and its parts and subassemblies, packaging and labeling, and plans for testing prototypes to establish design verification. Design verification amounts to showing that a design output satisfies its associated design inputs. Traceability matrices are required to map associated sets of design inputs and outputs and to document design verification. Design outputs evolve during the development process from preliminary drawings and prototypes to production drawings and documentation. Production documentation includes the list of all components and materials to be used to make the device, and the production process. The latter can range from simple assembly to complex production using automated equipment with precise operating controls. The design outputs for each cycle of development must be documented in the Design History File.

At predetermined intervals during development, design reviews must be conducted in which a qualified independent reviewer evaluates the design outputs for a design cycle and discusses them with the personnel who did the design work in order to identify oversights and mistakes. An independent reviewer can be someone who works for the manufacturer, so long as he/she did not do any of the work being reviewed. Design reviews are used to identify problems as soon as possible after they are created so that they can be eliminated or mitigated before being relied upon for further development. Problems discovered late in development often require a large amount of wasteful redesign work, because a change to fix one design defect will secondarily affect all parts of the device that interface or communicate with the part affected by the design defect. Design reviews must be documented in the Design History File.

Design transfer consists of building the production line on which the device will be made, putting the line in service, and making the adjustments necessary to achieve an operational state in which all (or a high percentage) of units made on the production line are de-

fect free and meet specification. The Device Master Record is the complete set of documents that are necessary to make the device, including the product specifications, bill of materials and components used to make the product, production line specifications (automated equipment and control parameters, work instructions for all production work done by hand), and final acceptance testing criteria that each unit must pass before being released for shipment. The Device Master Record is created by R&D in the product development process and design transfer essentially is the activities necessary to put the device into production by the manufacturing department.

As described above, for each cycle of development, design verification is performed to demonstrate that design outputs satisfy inputs. As the product development project progresses, design verification evolves from engineering testing of modules and subassemblies, to testing of the user interface, to testing the complete product in the engineering laboratory. Design validation goes a step further and involves testing of production units of the device (made after design transfer) by the end users for whom the device is intended (physicians, nurses, medical technicians) under actual or simulated clinical environments. This final step shows that the device in fact meets the requirements and expectations of the end users who will use the device.

2.8 Use of Devices in Clinical Studies

Devices used on human subjects for purposes of testing that is necessary to obtain premarket clearance or premarket approval are classified as investigational devices, and of course they cannot conform to the regular device regulations because they are under development. The use of investigational devices is governed by the Investigational Device Exemption (IDE) regulations at 21 CFR Part 812. The IDE regulations define three types of clinical investigations of devices, based on the risk associated with use of the device; significant risk investigations, non-significant risk investigations, and nominal risk/exempt investigations. Each type of

investigation is subject to a set of conditions and restrictions.

Significant risk investigations are defined in 21 CFR 812.3 in terms of devices whose intended uses present a potential for serious risks to the health and safety of patients, specifically including implants, life support equipment, and devices "of substantial importance in diagnosing … or treating disease" for which the means of diagnosis or treatment themselves create risk of harm. Non-significant risk investigations are defined by default as any investigation that is neither significant risk nor nominal risk/exempt. Nominal risk/exempt investigations include:

1) investigations of diagnostic devices that are not invasive and do not require an invasive sampling procedure, do not introduce energy into a patient's body, and are not used for diagnosis without confirmation by another established (i.e., FDA cleared or approved) method,
2) investigations on animals, subject to good laboratory procedures, and
3) testing to validate usability or certain modifications of an existing product.

Significant risk investigations must satisfy the following requirements:

1) The sponsor must submit to FDA an IDE application and obtain FDA's approval of the clinical study before it begins. The IDE application must contain a number of elements, including 1) the investigational plan, which will contain the study protocol, patient population, risk analysis, and monitoring procedures, 2) a description of the device and its construction, and the 3) the principal investigator.
2) The sponsor must obtain approval of the investigational plan by the Institutional Review Board (IRB) of each facility at which the investigation will be conducted, which will include review and approval of the informed consent materials that will be used for subjects participating in the study.

3) The investigational device must be labeled as such and its distribution and control must be limited to the qualified investigators who will conduct the investigation.
4) The investigational study must be monitored to protect the safety of participants, and there are prescribed records that must be created and maintained as well as reports that must be made to FDA.

Non-significant risk investigations do not require submission of an IDE application, nor approval by FDA before the study begins. The sponsor must however, obtain approval of the investigational plan by the IRB of each facility at which the investigation will be conducted, and the investigational device must be labeled and its distribution limited to the qualified investigators who will conduct the investigation. Non-significant risk studies are subject to monitoring and abbreviated record keeping and reporting requirements. Nominal risk/exempt investigations typically will require only IRB approval.

2.9 Regulation of Devices Used on Animals

Medical devices are defined to include veterinary devices, and FDA does have regulatory oversight of the manufacture and marketing of veterinary devices. However, FDA does not require premarket authorization to market any veterinary device, and FDA does not require manufacturers of veterinary devices to register their establishments or list their veterinary devices with FDA. FDA does require that veterinary devices be reasonably safe and effective for their intended use, and can take enforcement action against misbranded or adulterated veterinary devices. In practice, this means that veterinary device manufacturers should have in place good manufacturing practices to ensure that veterinary devices satisfy specifications set out in the devices' labeling and perform as described in the directions for use.

3 Drugs: Definition, Classification, and Premarket Approval

3.1 Definition

Drugs are defined in section 201 (g) of the FDCA, and for our purposes the working definition of drugs is: articles intended for use in the diagnosis, treatment, or prevention of disease, and articles intended to affect the structure or function of the body. The definition of drugs is broad enough to encompass the definition of medical devices as discussed in the prior section, but devices are defined to be limited to articles that achieve their effects without chemical action and without being metabolized. The resulting interpretation is that drugs are articles intended to diagnose or treat medical conditions or affect the structure or function of the body by means of chemical or metabolic action. Chemical or metabolic action involves interaction of the drug at the molecular level with substances produced by the cells of the body. The concept of indications for use applies to drugs in the same way as it did for devices; the indications for use of a drug are the diseases or medical conditions that the drug is designed to diagnose or treat.

Biologics or biologicals are medical products that are very similar to drugs and are regulated in a manner that parallels the regulation of drugs. Biologics are medical products produced by or derived from living organisms, such as vaccines, blood components or derivatives, antitoxins, and allergenic products (e.g., antibodies). Biologics will not be specifically covered in this section but the regulatory framework that applies to them is analogous to the drug regulatory framework.

3.2 Drug Classification

There are two broad categories of drugs:

1) New Drugs and
2) Drugs that are generally recognized as safe and effective (GRAS).

New drugs consist of all drugs that were marketed for the first time in the U.S. after 1938, excluding only those drugs that have been generally recognized as safe and effective via the Over-The-Counter (OTC) Review Process. New Drugs require premarket approval before they can be marketed, and there are two types of such premarket approvals. New Drug Application approvals (the basic type of New Drug approval) are required for all New Drugs, unless the New Drug qualifies for approval under the Abbreviated New Drug Application process (the second type of approval). The New Drug Application and Abbreviated New Drug Application processes are described in this section. Premarket approval is not required before marketing OTC drugs that have been recognized as safe and effective (GRAS) via the OTC Review Process. The OTC Review Process is also described in this section.

There are general requirements that apply to the production and marketing of all drugs, both New Drugs and OTC Drugs that have GRAS status, and these general requirements are analogous to the general controls that govern medical devices. The general requirements that apply to production and marketing of all drugs include:

1) registration with FDA of facilities at which drugs are produced,
2) listing drugs marketed in the U.S. with FDA,
3) production of drugs in compliance with current good manufacturing practices,
4) labeling OTC drugs consistent with OTC labeling requirements and labeling New Drugs consistent with the requirements established in the premarket approval,
5) advertising drugs using marketing claims that are consistent with the drugs' labeling, and
6) post market monitoring of use of the drug by patients to identify and investigate adverse events.

Most of the general requirements are covered in the next section of this guidebook. New Drugs must conform to the general requirements, and also to all specific requirements that are established in the premarket approval of the New Drug. OTC Drugs must con-

form to the general requirements, and also to the specific requirements that are established as a result of the OTC Review Process.

3.3 OTC Review and Conditions for GRAS Status

A drug must satisfy the following three conditions in order to achieve GRAS status:

1) there must be consensus among experts who are qualified by scientific training and experience to evaluate drugs that the candidate drug is safe and effective for use described in proposed labeling for the candidate drug,
2) the evidence for safety and efficacy must be in the form of published information, and
3) the candidate drug must have been used to a material extent and for a material time in connection with specific labeling that described the dosage and purposes for which the drug was used.

The FDA established the OTC Review Process in 1972 to systematically evaluate active drug ingredients, which were classified into a number of drug ingredient categories in order to establish the drug ingredients that qualified for GRAS status. For each drug ingredient category subjected to the OTC Review Process, the FDA issued (or will issue) a call for data notice, and interested drug manufacturers and other parties can submit clinical and marketing data about the active ingredients in drugs that they make or use. A panel of experts is convened to review the information submitted, and the panel issues a report to FDA that classifies the ingredients that were reviewed as either:

1) GRAS,
2) not safe or effective, or
3) of uncertain status, because insufficient data was presented to determine safety or efficacy.

The report is published in the Federal Register for comment by the public, and after considering public comment, the FDA issues a Tentative Final Monograph, which includes, for each GRAS ingre-

dient, the dosages and labeling for which the GRAS determination was made. The Tentative Final Monograph is published for public comment, and after review of the comments on the Tentative Final Monograph, the FDA issues a Final Monograph for the designated category of drug ingredients. The Final Monograph is published in the Federal Register and becomes effective on a designated date, usually one year after publication. After their effective dates, the Final Monographs are administrative rules, which are a form of regulation. (Unlike most regulations, the Final Monographs are contained in the Federal Register instead of the Code of Federal Regulations.) After a Final Monograph becomes effective, a drug with active ingredients covered by the monograph qualifies as GRAS only if it conforms to the requirements prescribed in the monograph, including dosages and labeling claims. Existing Final Monographs can be amended and updated by following the OTC Review Process.

The categories of drug ingredients that are covered by the OTC Review Process are listed in 21 CFR 330.5 and are comprised of 26 categories, including, for example, analgesics, antacids, anti-microbial products, cold remedies, sedatives, and stimulants. If a manufacturer aims to market a drug without premarket approval by qualifying it for GRAS status, the active ingredients in the drug must be covered by one of the 26 ingredient categories listed in 21 CFR 330.5 and the corresponding Final Mongraph. The drug also must satisfy the conditions set out in 21 CFR 330.1, which include:

1) the drug must be produced in compliance with current good manufacturing practices,
2) the production facility at which the drug is made must be registered with FDA and the drug must be listed with FDA,
3) the dosage of active ingredients in the composition of the drug must conform to the Final Monograph,
4) the labeling for the drug must comply with the Final Monograph, as well as the labeling requirements prescribed by 21 CFR 201.66 and 330.1,
5) advertising for the drug must be consistent with the

conditions and indications for use stated in the labeling,
6) post-market use of the drug must be monitored and adverse events reported to FDA.

In some cases, Tentative Final Monographs may be issued and remain in effect for many years before the corresponding Final Monograph is issued. If a Tentative Final Monograph has been issued, a manufacturer may market and sell a drug in conformity with the Tentative Final Monograph, but the manufacturer assumes the risk that if the Final Monograph differs from the Tentative Final Monograph, the drug will be considered adulterated if its ingredient dosage does not conform to the Final Monograph and will be considered misbranded if its labeling does not conform to the Final Monograph.

The OTC Review Process remains open, and certain drug ingredient categories are in the review process. However, the basic OTC Review Process does not apply to New Drugs that were initially marketed in the U.S. after 1972. It is important to understand that the terms GRAS drugs and OTC drugs are not synonymous; all GRAS drugs can be sold OTC but not all OTC drugs are GRAS. A New Drugcan be approved for sale only by prescription or for sale over the counter. There is therefore a group of New Drugs that were initially marketed in the U.S. after 1972 under a New Drug approval that permitted sale over the counter. There is a process, known as the Time and Extent Application process, through which a New Drug in this group (initially marketed in the U.S. after 1972 pursuant to a New Drug approval) can achieve GRAS status after it has been marketed OTC for at least five years. The process also applies to drugs marketed outside the U.S. for sale without a prescription for at least five years. (See Guidance for Industry: Time and Extent Applications for Nonprescription Drug Products.) The Time and Extent Application process consists of two parts: first, the Time and Extent Application is submitted, and based on a review of the application, FDA decides if the drug is eligible to be considered for inclusion in the OTC drug monograph system of GRAS drugs; and second, if FDA decides that the drug is eligible,

it will issue a call for data notice and the drug will be evaluated using the OTC Review Process described above. The Time and Extent Application must provide information on several aspects of the candidate drug, including:

1) description of the active ingredients and their pharmacologic classes,
2) intended OTC uses,
3) strength, dosage, and route of administration information,
4) directions for use, and
5) the Final Monograph in which the drug would be included.

As indicated above, any drug marketed in the U.S. for the first time after 1938 that is not designated as GRAS by virtue of the OTC Review Process is classified as a New Drug for which premarket approval is required. The next section provides an overview of premarket approvals for New Drugs.

3.4 Premarket Approval of New Drugs

There are four types of applications for premarket approval of New Drugs.

1) The comprehensive New Drug Application (NDA) is used for a drug that has never before been sold in the U.S. for any indication for use. The applicant must provide all evidence of safety and efficacy for the NDA (FDCA Section 505 (b)(1)).
2) A somewhat less comprehensive type of New Drug Application can be used in some cases when a manufacturer seeks approval of a new indication for use for a drug that has previously been sold in the U.S. for a different indication for use. In these cases, the information on the safety of the drug from the prior application may be used in the follow-on application (FDCA Section 505 (b)(2)).
3) An Abbreviated New Drug Application (ANDA) is used

for a drug that is a generic duplicate of a previously approved drug that will have the same indication for use as the previously approved drug. However, the ANDA process is available only if the previously approved drug has been designated as a Reference Listed Drug by FDA (FDCA Section 505 (j)). Reference Listed Drugs are a group of New Drugs that FDA has determined have a history of safe and effective clinical use for a significant number of years.

4) A variant type of Abbreviated New Drug Application can be used for a drug that is equivalent to, but not a duplicate of, a Reference Listed Drug (FDCA Section 505 (j)(2)).

The second type of application is a variant of the first type, and the two will be described together, and similarly, the fourth type of application is a variant of the third type, and the two types of application will be described together.

3.5 The New Drug Application Process

The comprehensive information on safety and efficacy that must be submitted in a New Drug Application is developed through preclinical and clinical investigations. These investigations are briefly described, since they must be completed before any New Drug Application can be prepared and submitted.

The preclinical investigation of a New Drug involves laboratory experimentation and animal testing to understand the chemical structure and mechanism of action of the drug, and most importantly, to investigate the drug's side effects, in order to determine if it is reasonably safe to begin preliminary clinical investigations of the drug in humans. It is not necessary to notify FDA before starting preclinical investigations of New Drugs, but the preclinical investigations must be conducted in conformity with FDA's Good Laboratory Practice (GLP) regulations (21 CFR Part 58). The FDA also inspects laboratories at which preclinical investigations are done to

ensure compliance with the GLP regulations. At the conclusion of the preclinical investigation, if the drug developer wants to proceed with a clinical investigation in humans, an Investigational New Drug (IND) Application is prepared, based on the results of the preclinical investigation, and the IND is submitted to FDA. Unless FDA objects to the IND Application within 30 days, the clinical investigation can begin.

The requirements for an IND application are set out in 21 CFR Part 312. The IND application contains two types of information:

1) information on the drug itself, and
2) a description of the investigative plan.

Information about the drug includes its chemical composition, pharmacology (mechanism of action in the body), and toxicology, as well as a description of the manufacturing process for the drug that will be used in the clinical investigations. The investigative plan includes:

1) the rationale for the investigation and the expected benefits versus risk,
2) identification of the principal investigators,
3) description of the protocols for administering the drug to subjects (dose and routes of administration) and the measurement of outcomes and safety measures,
4) a description of the number and type of subjects who will participate in the investigation, and
5) a commitment to conduct the investigation under the supervision of an Institutional Review Board (IRB). IRBs include independent clinicians who must agree that the proposed investigation does not expose subjects to unreasonable risks, in light of their medical conditions and existing alternative treatments for the condition that the new drug is intended to treat.

The clinical investigation typically consists of three parts—phase 1, phase 2, and phase 3—and patients who participate in any phase of the investigation must provide informed consent before they

are enrolled and begin their participation. The risks and benefits of participation in the study must be explained to patients, and their decision to participate, after the explanation is provided to them, must be entirely voluntary (e.g., no inappropriate inducement to participate such as compensation). Each patient's consent must be documented in writing.

The phase 1 investigation involves a small population of subjects (fewer than 100) who are usually healthy, i.e., not affected by the condition that will be treated by the drug. Phase 1 focuses on verifying the safety of the contemplated drug dosage and characterizing side effects of the drug. Phase 2 of the investigation involves a medium-sized population of subjects (perhaps a few hundred) who have the condition to be treated by the drug. Phase 2 focuses on the effectiveness of the drug treatment as compared to the side effects. The drug developer and FDA will meet at the end of Phase 2 to review the results and determine whether phase 3 clinical trials are appropriate. Phase 3 clinical trials will involve many clinical sites that are geographically dispersed, and up to several thousand subjects. The focus of phase 3 clinical trials is to prove the safety and efficacy of the drug in a large and heterogenous population that represents the patients who will be treated after the drug is approved. Use of the drug on large numbers of subjects can expose side effects and variations in the range of effectiveness that have a low rate of occurrence and therefore may not be seen in the small "sample populations" that are used in phases 1 and 2. The IRB periodically reviews all phases of the clinical investigation and may suspend the investigation if adverse side effects are more serious than anticipated.

3.6 Contents of a New Drug Application (NDA)

The required contents of a comprehensive NDA (a Section 505 (b)(1) application) are set out at 21 CFR Part 314, and cover the following areas:

1) The preclinical data from laboratory and animal studies that describe the chemical structure of the drug and

explain the drug's pharmacology and toxicology.

2) Results from clinical investigations that explain the bioavailability and metabolism of the drug in humans, and demonstrate that when the drug is used as directed it is reasonably safe and is an effective treatment for the medical condition for which it will be prescribed.
3) A description of the methods by which the drug will be manufactured, processed, and packaged.
4) The labeling and directions for use of the drug, including all contraindications and warnings.
5) A statement of whether any patent claims the drug or method of manufacture or use of the drug.
6) If required by FDA, a Risk Evaluation and Mitigation Strategy (REMS). A REMS is required when a drug has an "acceptable" risk of serious side effects, and is approved because its expected clinical benefits justify the risk. The REMS requires periodic reporting of the occurrence and management of serious side effects, so that the benefit/risk profile of the drug can be closely monitored and remedial action taken if the profile is worse than anticipated at the time of approval.

FDA will approve an NDA if FDA determines that the NDA provides substantial evidence, based on relevant science that:

1) the drug is an effective treatment for the medical condition for which it will be prescribed, and
2) the benefits of the drug's demonstrated effectiveness as a medical treatment outweigh the risks of expected adverse (serious) side effects.

The risk/benefit analysis requires consideration of the seriousness of the disease being treated and the availability of existing alternative treatments. Before approving an NDA, the FDA will verify by inspection that the manufacturing process to be used to produce the drug conforms to the current good manufacturing practice (cGMP) regulations for drugs (described in the next main section of this guidebook) and will ensure the purity and quality of the drug. Fi-

nally, the labeling of the drug must clearly set out the directions for use, indications for use, contraindications, and warnings.

A detailed discussion of FDA's review process for NDAs is beyond the scope of this basic introduction, but in general the initial cycle of review of an NDA should be completed in a period of time between six and 10 months. FDA's initial response likely will be a list of additional information that will be required for approval. If the additional requirements are minor, the approval may be obtained in two-three additional months. If the additional requirements amount to a significant resubmission, another 6–10-month review cycle is initiated.

Many years are required to complete the preclinical and clinical investigations necessary to create the information necessary to prepare an NDA and then to complete the process of obtaining approval of the NDA. This approval time would consume a significant part of the life of any patent issued for the drug covered by the NDA, which would discourage drug development. To partially address this problem, a patent term extension provision for new drugs was enacted in 1984. The length of the extension is calculated according to a set of detailed rules, but essentially the extension consists of two parts:

1) the time required for clinical testing, from the date on which the IND became effective until submission of the NDA, and
2) the time required to obtain approval, from the date of submission of the NDA until approval is issued by the FDA.

As mentioned in the introduction to this section on premarket approval of new drugs, a variant of the NDA can be used in certain circumstances described in FDCA Section 505 (b)(2). The two main circumstances to which Section 505 (b) (2) applies are:

1) an NDA for a drug that has been approved, but for a therapeutic indication for use that is different from the therapeutic indication covered by the subsequent NDA,

or

2) an NDA for a drug that has been approved, but for a dosage or route of administration that is different from the dosage or route of administration covered by the subsequent NDA.

In both cases the 505 (b)(2) is available only after the patent on the previously approved version of the drug has expired. The 505 (b)(2) NDA content parallels the content for the comprehensive NDA discussed above, but the applicant is not required to repeat:

1) the preclinical studies to demonstrate the pharmacology and toxicology of the drug, or
2) the clinical studies regarding the safety of the drug in humans for a particular range of dosages and routes of administration, if that information exists in published literature or FDA's records from processing prior NDAs. To the extent that such published literature or FDA records exist and cover the dosages contemplated in the 505 (b)(2) application, the applicant is permitted to rely on this "outside information". The practical effect is that the clinical investigations for a 505(b)(2) NDA can be limited to showing the therapeutic effectiveness for the new indication for use or the new dosage and route of administration.

3.7 The Abbreviated New Drug Application (ANDA) Process

The ANDA process is used to obtain approval of generic drugs (FDCA Section 505(j)). Generic drugs are duplicates of previously approved New Drugs that will be administered in the same dosage and by the same route for treatment of the same medical conditions that were previously approved for the New Drug. The ANDA Process can be used only if three fundamental conditions are satisfied:

1) the predecessor drug which is duplicated by the "ANDA generic" must be listed by FDA as a Reference Drug,
2) the ANDA generic must be shown to be bioequivalent to

the Reference Drug that it purports to copy, and

3) the effective date of approval of the ANDA generic cannot precede expiration of the patent on the Reference Drug, unless the applicant makes a certified declaration to FDA that it believes the patent on the Reference Drug is invalid.

FDA publishes a list, which is updated monthly, that lists all approved New Drugs and identifies those approved New Drugs that FDA considers to be safe and effective based on history in the market. The latter group of approved New Drugs are designated as Reference Drugs. The continuously updated list of approved New Drugs and Reference Drugs is known as the Orange Book. All ANDA submissions are based on comparison to a Reference Drug.

The key requirement that must be met to obtain approval of an ANDA is proving that the proposed generic drug is bioequivalent to the Reference Drug. The FDCA allows the presumption that if the proposed generic is bioequivalent to the Reference Drug, it will be as safe and effective as the Reference Drug for therapeutic use on patients. The essence of the bioequivalence concept is that the active ingredients of the generic drug and the Reference Drug become equally available at the site of drug action in the body, when administered at the same dose under similar conditions. The site of drug action is usually defined in terms of the molecular parts of cells in one or more types of tissue in the body with which the drug reacts to produce its effects on the body. However, in most cases bioequivalence is shown by measurements of the concentrations of the generic drug and Reference Drug in some body fluid that is in contact with the site of drug action. For example, for drugs that are delivered throughout the body via the blood, bioequivalence requires showing that total and peak blood concentrations of the generic and Reference Drug are equal when the two drugs are administered in the same way. It is assumed that if the concentrations of the drugs are the same in the blood, they are equally available at the site of action that is in contact with the blood.

ANDAs must include a certification regarding the status of the patent(s) that cover the Reference Drug, which facilitates coordination with the patent extension for the Reference Drug. The certification identifies the date on which the Reference Drug patent will expire, and FDA's approval of the generic drug covered by the ANDA will be the later of the patent expiration date or successful completion of the ANDA review process. The statute on patent extension also provides that development of a generic drug in accordance with the ANDA process will not constitute infringement of the Reference Drug patent. The applicant filing an ANDA also has the option of making a certification that it believes the Reference Drug patent is invalid or that the generic drug will not infringe the Reference Drug patent. In this case there is a complex set of rules that are applied to determine the status of the Reference Drug patent in relation to the generic drug.

The required contents of an ADNA are set forth in 21 CFR Section 314.94, and include the following:

1) Identification of the Reference Drug.
2) Proof that the generic drug has the same active ingredients, dosage form, and route of administration (e.g., oral or intravenous) as the Reference Drug.
3) Demonstration that the labeling for the generic drug regarding therapeutic indications for use and contraindications are the same as the Reference Drug.
4) Proof that the generic drug is bioequivalent to the Reference Drug.
5) Technical information including the chemical composition of the generic drug (both active and inactive ingredients) and a detailed description of how the generic will be manufactured, processed, and packaged.
6) Samples of the generic drug and labeling.
7) A certification of the status of the patent covering the Reference Drug.

An ANDA application will be approved if the content requirements are satisfied, and if the facility and manufacturing process for the

generic drug are found to conform to the cGMPs for drugs. The review period for ANDA applications should be in the 6-10 month range, similar to the review time for NDAs. Of course, the NDA approval will require much longer to obtain and will be much more expensive because of the time and cost for preclinical and clinical investigations and clinical trials.

The Section 505(j)(2) variant of the ANDA that was mentioned in the introduction to the drug approval process is very similar to the standard ANDA described above, except that the applicant can submit an ANDA "suitability petition" before submitting the ANDA itself, to request permission to make changes to the generic drug, as compared to the Reference Drug, that can be shown not to affect its safety and efficacy. These changes typically are limited to changes in inactive ingredients, a combination of active ingredients, and changes in dosage form or route of administration. If the suitability petition is approved, the ANDA can be submitted based on a comparison to the Reference Drug as modified by the changes that were approved via the suitability petition.

3.8 Regulation of Drugs Used for Animals

FDA's regulation of drugs for animals is analogous to the regulatory framework described above regarding drugs for human use, and this section provides a few highlights on how the animal drug regulatory scheme is different.

Drugs for animal use can be classified into two broad categories. New Animal Drugs are analogous to New Drugs for use in humans, and New Animal Drugs must be approved before marketing. Unapproved animal drugs that are recognized as the "standard of care" for certain veterinary uses are analogous to drugs that are GRAS under the human drug regime. However, there is no process like the OTC Review Process to formally recognize animal drugs that are GRAS. Instead, FDA has adopted an informal policy of enforcement discretion for animal drugs that it believes are generally recognized as the standard of care for medical conditions

in animals but which have not been approved. These unapproved drugs are adulterated and misbranded, but FDA has informally suspended or waived enforcement of the drug regulations against the manufacturers. Unapproved standard of care drugs comprise a significant segment of the animal drug market, and the regulatory status of these unapproved drugs is uncertain, because the policy on enforcement discretion could be rescinded.

There are two fundamental approval processes for New Animal Drugs:

1) the New Animal Drug Application (NADA) process, and
2) the Abbreviated New Animal Drug Application (ANADA) process.

The NADA is analogous to the NDA for human drugs, and the ANADA is analogous to the ANDA for human drugs.

3.9 The New Animal Drug Application (NADA) Process

The contents required for a NADA depend on whether the animal(s) to which the drug will be given are used as food or not. The NADA for drugs to be used in non-food animals will include several technical sections, including:

1) Identification of the species of animals for which the drug will be used, and evidence of the safety of the drug in the target species, with respect to the dosages prescribed in the labeling.
2) Evidence of the effectiveness of the specified drug dosage in the target species for the designated therapeutic intended use.
3) A description of the chemistry and composition of the drug, as well as the manufacturing process used to produce and package the drug.
4) The labeling to be used for providing instructions on prescribing and administering the drug.

The NADA for drugs to be used in food animals includes all of

the foregoing sections, plus a section on human food safety and a description of any non-therapeutic indication for use. A key requirement that the section on human food safety must satisfy is to establish an acceptable daily intake amount of the drug that humans can safely ingest by eating meat that contains residual amounts of the drug from treating the food animal. This section requires completion of a battery of tests that prove the safety of human consumption of meat from animals treated with the drug. Animal drug safety testing typically includes administering dosages that significantly exceed the proposed labeled dose (e.g., 3-5 times) and the proposed labeled time of treatment. Study animals are tested extensively, and full necropsies are performed to study the residual amounts of drug remaining in tissue after treatment, as well as its effects on the animal's anatomy and physiology. The NADA for food animals also must explain any non-therapeutic indication for use. The main non-therapeutic indication for use of animal drugs such as antibiotics is increasing the efficiency of animal's conversion of feed grain into weight gain. It may be more difficult to prove the safety and efficacy of drug treatment to enhance weight gain, due to the more questionable risk/benefit profile of this indication for use.

Pre-clinical and clinical testing will be required to generate the information necessary to complete the NADA, just as it was required to enable preparation of the NDA for human drugs. All animal testing done to produce information to be used in an NADA must be performed in accordance with the GLP regulations. In addition, all animal studies done in connection with an NADA must be overseen and monitored by an Institutional Animal Care and Use Committee, which is the counterpart to the IRB in human studies. The committee ensures the humane and ethical care and use of animals used in the studies.

3.10 The Abbreviated New Animal Drug Application (ANADA) Process

The ANADA process is used for generic drugs that are duplicates

of New Animal Drugs that were previously approved under the NADA process. The ANADA process closely follows the ANDA process previously described for human drugs. It is based on a comparison of the proposed generic animal drug to the designated reference animal drug that it duplicates. The ANADA process allows reliance on the safety, efficacy, and human food safety information contained in the NADA for the reference drug, and therefore the ANADA application does not require new clinical investigations to duplicate that information. The ANADA must include a technical section that proves the bioequivalence of the generic animal drug to its reference animal drug. Bioequivalence is defined in the same way as described for human drugs.

4 Regulation of Production and Distribution of Devices and Drugs

FDA regulates most aspects of the business operations of manufacturers of devices and drugs. These regulations cover three broad areas:

1) Quality System Requirements for devices and Good Manufacturing Practice (GMP) Requirements for drugs,
2) marketing and advertising of devices and drugs, and
3) Post Market Requirements regarding monitoring customer feedback and complaints to identify adverse events and report the adverse events to FDA.

Compliance with these regulations requires implementation of business systems that are unique to device and drug manufacturers and impose significant overhead costs. Familiarity with these regulations is essential for any entrepreneur that intends to be a device or drug manufacturer, because the business plan for the manufacturing business must include realistic estimates of the costs of compliance. This section provides a high-level overview of these three areas of FDA regulation.

4.1 Quality System / GMP Requirements

The Quality System Requirements for device manufacturers are set out in 21 CFR Part 820, and GMPs for drug manufacturers are set out in 21 CFR Part 211. A detailed discussion of these regulations is beyond the scope of this guidebook; however, the two sets of regulations have many similarities at a system level, and they will be discussed together in terms of a generic Quality System that is representative of what is required of a device or drug manufacturer. The Quality System prescribes how regulated work must be performed by the manufacturer's personnel. Regulated work is comprised of all activities that affect the development and production of regulated product (including purchasing materials and components used in production), as well as sales and service (where applicable) of regulated product. The generic Quality System used as our example consists of four subsystems:

1) Management Responsibility,
2) Resource Acquisition and Development,
3) Production Process Controls, and
4) Corrective and Preventive Action (CAPA).

The Management Responsibility Subsystem provides that executives of device and drug manufacturers are directly responsible for establishing a Quality System that satisfies the regulations. While the work of establishing the Quality System can be delegated, the ultimate responsibility for compliance remains with executive management (the CEO and the CEO's direct reports). The Quality System usually consists of:

1) A Quality Manual that describes the overall system (typical length 20-50 pages);
2) High-level procedures that describe how the manufacturer will control all activities that are governed by the regulations, generally a procedure for each regulatory requirement (typically 20-50 procedures);
3) A set of several WorkInstructions for each high-level procedure, which describe how personnel must perform each work task that is part of the activity covered by the

parent procedure; and

4) Templates or forms for Quality Records that, when completed properly, will prove that Work Instructions were followed for each regulated product or batch of regulated product that was made, serviced, or processed subject to the Work Instructions.

Developing the Quality System is a major sunk cost for a device/drug manufacturer and requires a significant period of time. Operation of the Quality System will generate numerous records, and the Management Responsibility Subsystem requires that these records be evaluated by trending and appropriate statistical methods to produce quality metrics. Quality metrics reflect how the Quality System is operating and the level of quality of the regulated product that is made under the Quality System. Periodic management reviews of the quality metrics are required by the Management Responsibility subsystem. Executive managers must participate in a reasonable number (typically 2-4) of these management reviews annually, and problems identified by the quality metrics must be investigated and fixed.

The Resource Acquisition and Development Subsystem covers the requirements that must be satisfied by personnel employed by the manufacturer, facilities, and equipment used in the manufacturer's operations, and the relationships between the manufacturer and the suppliers from whom the manufacturer purchases goods and services.

1) Employees who are hired to perform regulated work must be qualified, meaning they have been taught and know the regulations, Quality System Procedures, and Work Instructions that govern their work. (Remember that regulated work broadly covers design and development of product, production of product, sales and customer service, and repair and maintenance of devices.) Continuing education in the form of periodic training is required to maintain employee knowledge and skills. Training Records are required for employees who

perform regulated work to document their qualifications, as well as their completion of the periodic refresher training.

2) Production of drugs and devices typically requires precision equipment that must be calibrated and maintained, and the production environment requires clean and hygenic, sometimes sterile, conditions. The requirements for facilities and equipment are designed to ensure that these physical resources are adequate for production of high-quality products that are free from contamination.
3) All manufacturers will purchase materials and components that are used to make their drugs or devices, and they may engage independent contractors to perform regulated work. The regulations on Supplier Controls require that suppliers of materials used in production and suppliers of services that involve performance of regulated work must be qualified, monitored, and controlled by the manufacturer. Initial qualification of suppliers requires an interview or audit to verify that the supplier has the knowledge and capability to meet the Quality System Requirements or GMPs. Written contracts that include adequate performance standards must be used to govern the manufacturer-supplier relationship. Most importantly, the supplier's performance must be monitored by the manufacturer, and any deficient performance must be corrected and steps taken to prevent the deficiency from occurring again. Examples of deficient performance include delivery of material that does not meet specification, or performance of contracted services in a way that does not comply with the regulations.

The Production Process Control Subsystem requires manufacturers to implement procedures that both proactively ensure production of products that satisfy their specifications and also verify and document that each batch of production units satisfied their specification

before they are released for sale. Some of the main requirements that Production Procedures must address include the following:

1) Materials and components to be used in production must be inspected to verify that they meet specification before they are used in production. The inspection plan for each material or component will require sampling and inspection by the manufacturer at some frequency, which will depend on the reliability of the supplier and whether the supplier inspects and certifies conformity of each shipment of material/components.
2) A final acceptance test or analysis must be created for each product, which will be used to determine whether the product meets specification and can be released for sale. All products must be tested to verify conformity to specification, unless the products are made on a "highly validated" production line (described next) which justifies inspection of only a designated number of samples from the batch of production.
3) The manufacturing process for each product will consist of a sequence of steps that are followed to construct a device or compound a drug. The steps may be performed manually by a production worker or by a piece of automated equipment that is operated by a production worker. Validation of manufacturing processes is complex, but the underlying idea is that the combined automated and manual steps for making a device or drug must designed so that, when it is in operation, the units of devices or drugs that it produces will consistently pass final inspection testing. Work instructions are required to describe in detail how to perform each manual step, and how to verify that the step was properly completed (in process inspection). Work instructions for automated steps must specify control parameters that define the range in which the equipment must be operated in order to produce good product. (Examples of control parameters are temperature, pressure, and variability in a particular

measurement, such as + / - 1 millimeter.)

4) Records must be written for each batch of production to demonstrate that all equipment in the production line was operating within acceptable ranges for all control parameters and that all sampled units passed final acceptance testing.
5) Procedures must be provided for how to handle all materials, components, partially finished product, and finished product that were rejected during production, because they failed to meet specification, failed to satisfy in process testing, or failed final acceptance testing. Such non-conforming materials or product must be clearly marked as non-conforming and segregated from good product so that it is not shipped out by mistake.

The Corrective and Preventive Action (CAPA) Subsystem is one of the features of device and drug manufacturers that most clearly differentiates them from manufacturers in other industries. The CAPA Subsystem requires implementation of procedures for systematically analyzing the records that are generated through the Quality System to identify non-conformities. Remember that the records describe the operation of the Quality System as well as its output in the form of device or drug products. Records include customer feedback/ complaints, non-conforming materials or product, supplier performance reports, and the results of self audits. Non conformities are any quality metric or outcome revealed by the records that is outside of the range that would be expected, based on the collective knowledge of the manufacturer's personnel who designed the product or Quality System Procedure to which the record relates.

The CAPA Subsystem requires Procedures for comprehensive investigation of non-conformities. These investigations must be pursued until the root cause of the problem is revealed. The concept of root cause means identification of the essential problem that is the first event which causes a non-conformity. Root causes can be difficult to identify, because they can act through a series of in-

termediate causes. When any cause is identified in an investigation, it must be determined whether it is the root cause or merely an intermediate cause. For example, assume the investigation of a failed circuit board finds that cracked solder joints caused the failure. This is an intermediate cause; the investigation must be pursued further to determine why the solder cracked. Alternatives include defective solder material, incorrect soldering temperature, or latent damage to the solder joints caused by handling of the board.

Fixing the root cause of a non-conformity will prevent its recurrence, but fixing an intermediate cause will not. Manufacturers are required to take corrective action to prevent the recurrence of non-conformities, and to verify that the corrective action was in fact effective in eliminating the root cause of the non-conformity. Manufacturers also are required to correct non-conformities that affect their products, both in inventory and in the market, if the non-conformity creates a significant risk of harm to patients, or if the non-conformity consists of a failure to meet a specification of the product that was not detected before it was shipped.

FDA enforces the Quality System/GMP requirements by periodically inspecting manufacturers. Regular inspections are performed every couple of years. For-cause inspections are conducted when FDA has reason to believe that a manufacturer's product may be adulterated or misbranded, typically based on reports of problems that FDA obtained via the adverse event reporting system, which is described at the end of this section. Inspections are conducted by FDA investigators, and involve review of the manufacturer's Procedures, Work Instructions, and records that relate to a particular regulation or suspicious product, as well as interviews of the manufacturer's personnel whose work is covered by those documents. When a problem/non-conformity becomes evident during an inspection, the CAPA Subsytem will be evaluated for its effectiveness in dealing with it. The CAPA Subsystem is usually a focal point of inspections, especially in terms of whether Management Reviews are being utilized effectively to monitor CAPA investigations and to allocate resources to take corrective actions to prevent

recurrence of problems and to correct any problems with products that are in the market that create significant risk of harm to patients.

The investigator will provide a list of violations observed during the inspection, and the manufacturer has a short period of time to remedy the violations and provide written evidence to FDA that the violations were fixed. If FDA finds that the manufacturer's response does not prove that it has addressed the observed violations, it will issue a warning letter that is made public. The manufacturer has a final opportunity to respond to the warning letter and convince FDA that it has adequately addressed the observed violations. If the warning letter response is not acceptable to FDA, it will initiate legal proceedings against the manufacturer.

4.2 FDA Regulation of Marketing and Advertising

FDA regulates manufacturers' public communications about their products, including marketing materials, advertising, and more general communications such as press releases. The regulations on marketing and advertising for drugs can be found at 21 CFR Part 202 and for devices at 21 CFR Part 801. The underlying principles of the regulation of marketing and advertising of drugs and devices are the same and will be discussed together. For purposes of this description, marketing materials are all communications about a drug or device that are published by a manufacturer for use in connection with the product's promotion and distribution, other than the package insert or directions for use/user manual. Marketing materials include, for example, brochures, catalogues, and direct mail pieces, as well as verbal sales presentations by the manufacturer's personnel or representatives. Advertising, on the other hand, is material that a manufacturer pays to have placed in another publication, such as a magazine, or in other media such as television. Note that FDA does not regulate communications about devices or drugs that are published by third parties who are independent of the manufacturer, such as health care providers. However, if a manufacturer disseminates third-party statements or publications,

they are treated as communications of the manufacturer. FDA regulates marketing materials, advertising, and more general communications such as press releases (Regulated Communications) by applying two main principles, which are described below.

The first principle is that Regulated Communications must be consistent with the labeling for the device or drug that was included in the submission to FDA and cleared or approved by FDA as part of the premarket authorization. This approved labeling consists of the package insert for drugs and the user manual and directions for use of a device, which state the indications for use. In the case of devices and drugs that do not require premarket clearance or approval, the Regulated Communications must be consistent with the intended use and indications for use that are authorized by regulation. For devices, the authorized indications for use are found in the generic type classification, and for GRAS drugs the authorized indications for use are found in the associated Final Monograph.

Regulated Communications that are not consistent with the cleared labeling (or the authorized labeling for products that do not require clearance or approval) are referred to as Off Label claims. For example, the claim that a drug approved for hypertension can be used to treat migraines is Off Label, and the claim that a robotic surgical instrument approved for joint surgery can be used for abdominal surgery is Off Label. Off Label claims are deemed problematic by FDA for two reasons. First, by definition, no evidence that the device or drug would be safe and effective for the Off Label indication for use was presented as part of the premarket authorization process, and the Off Label use was not approved by FDA. Second, FDA expects manufacturers to supplement and update the approvals and clearances for their products to encompass new indications for use. These updates require new submissions that prove that the drug or device is safe and effective for the new indication for use through the results of additional clinical studies. If Off Label claims were permitted, it would undermine the need for manufacturers to conduct the additional clinical studies that are necessary to prove safety and efficacy for new indications for use.

The second principle is that Regulated Communications must be accurate, complete, and not misleading. This requires a fairly-balanced presentation of the benefits, risks, and limitations of the drug or device. The concept of fair balance with respect to drugs focuses on full disclosure of side effects, and with respect to devices fair balance focuses on disclosure of the risks of the procedures performed with the device, or the limitations that are inherent in the indications for use of the device.

Medical and scientific journals often publish peer-reviewed articles that involve clinical studies of devices or drugs for Off Label uses that were conducted by third parties who are independent of the manufacturer. The FDA has developed a policy regarding how manufacturers can respond to inquiries about Off Label uses that are covered in peer reviewed articles, and the extent to which manufacturers can distribute reprints of such articles. Reprints about Off Label use can be provided only in response to inquiries from customers. Although the policy is complex, it permits manufacturers to respond to inquiries about Off Label uses by providing reprints of the articles that report favorable results regarding the Off Label use only if:

1) the article is published in a peer-reviewed journal,
2) the response includes reprints of, or a bibliography that lists, known articles that report unfavorable results regarding the Off Label use, and
3) the response includes a copy of the approved labeling and a statement that the manufacturer has not determined the safety and efficacy of the drug or device for the Off Label use.

If FDA becomes aware of a violation of the rules on Regulated Communications, it deems the product described in the violative communication to be misbranded. FDA typically will send the manufacturer a warning letter that includes a demand for remedial action. Remedial action may be limited to eliminating the violation prospectively, or it may require publication of a correction, including sending correction letters to health care professionals to whom

the violative Regulated Communication was distributed.

4.3 Adverse Event Reporting Requirements

Device and Drug Manufacturers are required to establish procedures to monitor the experiences of clinicians and patients who use the manufacturer's products, identify the adverse events among those experiences, and report them to FDA. The monitoring procedures require logging and evaluating customer communications, such as complaints and customer service interactions, as well as adverse event reports that are filed by health care providers. Brief summaries of the adverse event reporting requirements for device and drug manufacturers are contained in this section.

Adverse event reporting for drugs is addressed primarily in 21 CFR 310.305, 314.80 and 314.98. An adverse drug experience is any situation in which a drug caused a side effect or failed to have its intended effect in a patient. Adverse drug experiences must be reported by the manufacturer for all drugs, whether GRAS or approved pursuant to the NDA or ANDA process, if they are serious and unexpected. An adverse drug experience is unexpected if it is not identified in the professional labeling for the drug, and an adverse drug experience is serious if it caused death or physiologic damage to a patient, or if a side effect required medical intervention to prevent death or physiologic damage. Unexpected serious adverse drug experiences must be reported by the manufacturer within 15 days after it receives information about the reportable event, using an Alert Report form published by FDA. The manufacturer must also conduct a comprehensive investigation of the reportable event and file a follow-up to the initial Alert Report within 15 days after the Alert Report was filed.

Manufacturers of drugs that are approved pursuant to the NDA or ANDA process also must file periodic reports covering all adverse drug experiences, including those that were not unexpected and serious. For the first three years after a drug is approved, periodic reports are filed for the first three quarters of each year and a summa-

tive annual report is filed for the fourth quarter. After the first three years, only the annual report is filed. All periodic reports contain a detailed evaluation of all adverse drug experiences, including those that are unexpected and serious as well as those that are expected. In addition, the annual reports include a summary of all significant new information that bears on the safety and efficacy of the drug, including published literature regarding studies of the drug.

Finally, if the manufacturer of an approved drug discovers that any batch of production of the drug is contaminated or does not meet the compositional specification for the drug, the manufacturer must file a field alert with FDA within three days of discovering the problem and take all remedial action necessary to prevent the defective drug from being dispensed to patients.

Adverse event reporting for devices is addressed in 21 CFR Part 803. A device manufacturer must submit a Medical Device Report (MDR) for any situation in which:

1) one of its medical device products may have caused or contributed to a death or serious injury (whether or not the device malfunctioned), or
2) one of its medical device products malfunctioned without causing injury, but if the malfunction were to recur there is a significant probability that it would cause serious injury or death.

The second of these reportable scenarios is therefore based on a hypothetical situation that requires evaluation of the probability that a particular malfunction could recur and cause a serious injury. In most cases, MDR reportable events must be initially reported within 30 days after the manufacturer receives information about the reportable event, using a form published by FDA. However, the MDR must be filed within five days if any further delay would result in an unreasonable risk of substantial harm to the public health.

MDR reportable events must be comprehensively investigated,

and the root cause of any malfunction involved in the event must be determined. If the root cause was caused by a design or manufacturing defect, the manufacturer must correct the problem in all affected devices in the market. Correction involves either fixing the defect (a recall) or providing supplementary instructions to end users on how to prevent the malfunction or mitigate the risk of harm that the malfunction might cause (a field safety alert). In addition, the manufacturer must take corrective action to ensure that the defect is eliminated to the extent feasible in future production of the medical device product.

5 FDA Regulation of Food Additives and Dietary Supplements

Regulation of food is arguably the most basic public health responsibility of FDA. This guidebook focuses on the regulation of food additives and dietary supplements, but a very brief overview of FDA's regulation of food is provided as context for the more specific coverage of additives and supplements. Section 201 (f) of the FDCA defines food as whole foods or drink consumed by humans or animals, and all components of any such food. FDA regulates food safety based on Section 402 (a) of the FDCA, which defines what constitutes the adulteration of food, including for example, food that contains harmful contaminants or is decomposed because of poor handling or storage. FDA has implemented Section 402 (a) of the FDCA by promulgating Good Manufacturing Practices for food at 21 CFR Part 110 (Food GMPS). Any food that is not manufactured in compliance with the Food GMPs is deemed to be adulterated, even if it is not actually contaminated or of poor quality.

The Food GMPs cover all aspects of food production, including inspection of raw materials, plant design, equipment specifications and cleaning, personnel training and hygienic practices, production controls, and quality control testing. The focus of the Food GMPs is:

1) ensuring that sanitary operations are used to produce food by requiring specified cleaning and disinfection

procedures to be applied to equipment, personnel, facilities, and raw materials; and
2) ensuring high-quality food by means of controlling the critical parameters that are important in the processing of food, such as temperatures, pressure, time of exposure, and pH (acidity or alkalinity).

In addition to the Food GMPs, food manufacturers are required to implement written plans to identify food safety hazards that could adversely affect their operations and then implement preventive controls to eliminate or mitigate the hazards.

The labeling of foods is also subject to extensive regulation by FDA, pursuant to 21 CFR Part 101. The labeling regulations require:

1) identification of the food by its recognized generic name,
2) specification of the quantity of food in the package,
3) identification of the company that makes or distributes the product,
4) identification of the ingredients comprising the food in descending order of percent by weight,
5) identification of the flavorings used in the food,
6) identification of the nutrition characteristics of the food in a prescribed format, and
7) creation of the nutrition information that is reported in the labeling through the use of standardized testing procedures.

Finally, any health claims that are made for a food must either be approved health claims or qualified health claims. Approved health claims are those that have been approved by FDA in a regulation, and they must be used verbatim in the form set out in the regulation. Qualified health claims are those deemed by FDA to be supported by credible evidence, but not enough to be approved. Qualified claims must be cleared for use by FDA and accompanied by a disclaimer that FDA has not approved the claim.

5.1 Food Additives

A food additive is defined as any substance that is added to food in order to achieve some technical effect, unless the substance is generally recognized as safe (GRAS). Technical effects include preserving food by inhibiting spoiling, changing the texture of food to improve processing or appeal to consumer preferences, enhancing the flavor of a food, or providing nutritional value to the food. The regulatory framework for food additives essentially classifies food ingredients that are added to food to achieve a technical effect into two groups:

1) GRAS ingredients, and
2) food additive ingredients.

Food additive ingredients can be used only if they are approved by FDA, while GRAS ingredients can be used without approval by FDA. Color additives are regulated in a way that is closely analogous to the regulation of food additives, except that there is no GRAS exception or group of color additives that can be recognized as GRAS. All color additives can be used in food only if they are approved by FDA.

Food additives that have been approved by FDA are set out in 21 CFR Parts 172-178. In addition, FDA has a searchable database, called EAFUS, Everything Added to Food in the U.S., which lists the approved food additives and provides a cross reference to the regulation number in 21 CFR Parts 172-178 where the food additive is addressed. For each approved food additive, the regulation sets out the conditions under which it is approved for use, including for example the foods in which it can be used, the range of concentrations permitted for the additive in the food, and any specific labeling requirements. Approved food additives must be used within their respective approved conditions for use.
If a food manufacturer wants to incorporate an ingredient into a food that has not been approved by FDA as a food additive, it will be necessary to determine if the ingredient has been recognized by FDA as GRAS. Food ingredients that have been recognized by

FDA as GRAS are set out in 21 CFR Parts 182-186. As with food additives, food ingredients are GRAS only for a set of specified conditions, and they are considered GRAS only when used within the bounds set by those conditions.

If a new ingredient that is under consideration for incorporation into a food has not been approved as a food additive or recognized as GRAS, the manufacturer must make an independent self-determination of whether the ingredient can be qualified as GRAS or must be approved by FDA as a food additive. If the ingredient can be qualified as GRAS, the manufacturer may utilize the GRAS notification procedure set out in 21 CFR 170.203-285 to notify FDA of its GRAS determination and discover whether FDA objects to it. The GRAS notification procedure is voluntary, but if the manufacturer does not notify FDA, it is assuming the risk that FDA could disagree with the GRAS determination. A consequence of FDA's disagreement with the GRAS determination would be that the foods in which the new ingredient was used are adulterated and could not be sold in the U.S. market. The GRAS notification procedure sets out the requirements that must be met to qualify as GRAS, and as such, even if FDA is not notified, the substantive requirements to qualify as GRAS that are set out in 21 CFR 225-255 must be used to make the self determination of GRAS status. FDA has published a helpful Guidance Document on GRAS determinations: Frequently Asked Questions about GRAS for Substances Intended for Use in Human or Animal Food; Guidance for Industry. A summary of the requirements to qualify as GRAS is provided in this section. Finally, if the new food ingredient cannot be qualified as GRAS, and must be approved by FDA as a food additive, 21 CFR Part 171 sets out a process that can be used to petition FDA to approve the new food additive and promulgate a regulation under its rulemaking authority that sets out the conditions for use of the new approved additive. The food additive petition process is also summarized in this section.

The determination that a food ingredient is GRAS must be made by experts who are qualified to evaluate the safety of foods and

must be based on published scientific information (or common use in food prior to 1958, which is unlikely for any new food ingredient). A manufacturer making a self-determination of GRAS will therefore need to engage a panel of qualified experts who will essentially conduct an extensive review of published literature on the biochemistry of the ingredient, its toxicologic testing in animals, and its use in humans. The panel of experts will decide whether the results of the studies demonstrate that there is a consensus among their peers that the ingredient is safe for use in food. Most GRAS determinations are made for specified uses of the ingredient in a specified range of concentrations.

The contents of a GRAS notice are set out in 21 CFR 170.225-255, and even if a manufacturer decides not to notify FDA of its GRAS self-determination, the self-determination must be based on information that satisfies these requirements, and the manufacturer must have documentation that demonstrates satisfaction of the requirements. The information that is necessary for a GRAS self-determination includes the following:

1) Scientific information that identifies the substance, its food grade specifications, and a description of the method of manufacture of the substance.
2) The technical effect that the substance is intended to produce and the conditions of use for the substance, including the quantity/concentration of the substance required to produce the technical effect, the foods in which the substance will be used, and the subpopulations of people expected to be primary consumers of foods containing the substance.
3) Information on dietary exposure of the substance, meaning the amount of the substance that a consumer is likely to ingest based on the number of foods in which the substance may be present and its concentrations in those foods. The dietary exposure evaluation will address any self-limiting levels of use of the substance, which are maximum amounts of the substance that can be incorporated into a food, based on constraints of taste

and processing requirements.

4) Citation to all of the published literature which was relied upon by the panel of experts in making the determination that the substance is GRAS.
5) A detailed narrative that discusses key results reported in the published literature and an explanation of how the results demonstrate that the substance is GRAS.

If a GRAS notice is submitted, FDA will respond within 180 days, and the response will indicate whether FDA objects to the GRAS status of the substance. If FDA does not object, the substance can be used without FDA approval subject to all of the conditions set out in the GRAS notice. GRAS notice submissions and FDA's responses to them are publicly available, but there is no index or listing of all substances that can be used in food based on a GRAS determination (because GRAS notification is voluntary). However, the FDA web site GRAS Notice Inventory does list the GRAS notices that have been acted on by FDA. If a substance was covered in a GRAS notice to which FDA did not object, it can be used within the bounds of the conditions set out in the GRAS notice; however, if that substance is to be used under a different set of conditions, a new GRAS self-determination is required.

A GRAS self-determination is not possible for a food ingredient/substance if there is insufficient published literature to support the determination. In that case, it is necessary to obtain FDA's approval of the substance as a food additive, based on chemical, toxicologic, and clinical studies performed by the manufacturer or published by third parties. Approval of food additives is obtained through the food additive petition process set out in 21 CFR Part 171. The requirements for a food additive petition include the following:

1) Description of the chemical identity of the food additive substance and the chemical methods that are used to detect the substance and measure its quantity or concentration in a food. This information must be developed and presented in a way that is consistent with

a Chemistry Guidance Document published by FDA.

2) Description of the technical effect to be achieved with the food additive substance, the levels of the substance required to achieve the technical effect, and data showing that the substance does achieve the technical effect. All information must be developed in conformity with the Chemistry Guidance Document.
3) Evaluation and estimation of the dietary exposure of the food additive; the amount that is likely to be ingested by consumers based on the number of foods in which the food additive will be present and the concentrations in those foods.
4) Full reports on all animal and human studies that demonstrate the safety of the food additive. These studies will include studies in animals to establish the basic metabolism and any toxicity of the food additive as well as studies in humans to demonstrate tolerance of the food additive. This information must be developed and presented in a way that is consistent with Toxicology Guidance published by FDA.
5) An environmental assessment of the operations necessary for production of the food additive, unless a waiver can be obtained.

The petition will be subjected to FDA's rulemaking procedure, which includes:

1) an initial evaluation of the petition and supporting chemistry and clinical information to verify adequacy;
2) separate reviews by agency departments including Chemistry, Toxicology, and Environmental, as well as outside experts engaged by FDA; and
3) final review of all departmental reports by FDA, which may convene an advisory committee, followed by issuance of a decision on approval of the food additive.

If the food additive is approved, a proposed regulation setting out the conditions of use is drafted and published in the Federal Reg-

ister for comment by any interested parties, and after any revisions are made, based on comments received, the final regulation is published in the Federal Register.

5.2 Dietary Supplements

Dietary supplements were regulated as food ingredients until 1994, and as explained above, under that regulatory framework, they could be sold only if deemed to be GRAS or if they were covered by an approved food additive regulation. The FDCA was amended in 1994 to create a separate regulatory framework for dietary supplements.

Dietary supplements are defined in Section 201 (ff) of the FDCA to include substances that meet three criteria:

1) they contain one or more listed types of ingredients
2) they are sold in a form that is included in list of formulations, and
3) they are labeled for use as a dietary supplement.

The ingredients of a dietary supplement must be one or more of the following:

1) a vitamin;
2) a mineral;
3) an herb or botanical;
4) an amino acid;
5) any other substance that is found in conventional food, which is to be increased in the diet by making or extracting the substance and separately consuming it as a supplement; and
6) a combination of any of the foregoing types of ingredients.

The formulations permitted for dietary supplements are:

1) tablets, capsules, or gel caps;
2) powders;
3) liquids; or

4) bars.

Dietary supplements cannot be sold as conventional foods. Dietary supplements must be labeled solely for use to supplement the diet, and not for use to prevent or treat any medical condition or disease (which would require approval as a drug).

Dietary supplements can be classified in two groups. One group consists of supplements that are made of ingredients that were sold as dietary supplements in the U.S. before Oct. 15, 1994 (Grandfathered DS Ingredients), and one group that consists of supplements that include at least one ingredient that was not sold in the U.S. as a dietary supplement before Oct. 15, 1994 (New DS Ingredients). Supplements that are made of Grandfathered DS Ingredients must satisfy a general safety standard, whereas supplements that include at least one New DS Ingredient must satisfy a more specific safety standard which includes, in some circumstances, submitting a notification to FDA before the supplement with the New DS Ingredient is marketed. Both safety standards are summarized below. Unfortunately, there is no authoritative list of Grandfathered DS Ingredients, and classification of dietary supplement ingredients requires research of published materials, such as advertisements and other information published by manufacturers of supplements sold before Oct. 15, 1994.

The general safety standard that applies to dietary supplements that contain only Grandfathered DS Ingredients requires that the manufacturer make a self-determination that the supplement does not present a significant or unreasonable risk of causing illness or injury under the conditions of use suggested in the labeling. This self-determination is similar to the self-determination that a food ingredient is GRAS, but it is less stringent, because there is no requirement that the supplement be generally recognized as safe by qualified experts or that the data relied upon to determine safety is published. The self determination of safety for this group of Grandfathered supplements can be based on a history of use in food at the levels comparable to the supplement, results of studies

on animals or humans that are published in the scientific literature, or results of studies on animals or humans conducted or sponsored by the manufacturer. The information relied upon by the manufacturer to make the self-determination of safety must be documented and available for inspection by FDA, but the "level of evidence" required is not specified, and is therefore determined on an ad hoc basis.

The more specific safety standard that applies to dietary supplements that contain New DS Ingredients is set out in Section 402(f)(1)(B) of the FDCA. This section of the FDCA provides that a dietary supplement that contains a New DS Ingredient is adulterated unless there is adequate information to provide reasonable assurance that the supplement does not present a significant or unreasonable risk of illness or injury. This is essentially the same basic requirement of the general safety standard, but the level of evidence required, i.e., adequate information to provide reasonable assurance, is generally higher than that required in the self-determination of safety for Grandfathered supplements, because FDA determines what is adequate based on its experience in regulating supplements.

In addition, a notification must be submitted to FDA before marketing a supplement containing a New DS Ingredient (NDI Notification), unless each New DS Ingredient in the supplement qualifies for an exemption from notification. Two conditions must be satisfied for a New DS Ingredient to qualify for the exemption from NDI Notification:

1) the New DS Ingredient must have been present in conventional foods in the historic food supply chain at levels that are comparable to those in the supplement, and
2) the chemical form of the New DS Ingredient must be the same as its chemical form in the conventional food supply.

If all New DS Ingredients in a supplement qualify for the exemp-

tion, it is not necessary to submit an NDI Notification to FDA before marketing the supplement, but the supplement is of course subject to the specific safety standard set out in FDCA 402(f)(1)(B), and the information on which the exemption from NDI Notification is based must be documented (and is subject to inspection by FDA). FDA has published a draft Guidance Document that contains a comprehensive explanation of the NDI Notification process: Dietary Supplements: New Dietary Ingredients Notifications and Related Issues: Guidance for Industry.

To summarize, a substance is a New DS Ingredient if it was not sold in the U.S. as a dietary supplement before Oct. 15, 1994, and a substance that is a New DS Ingredient qualifies for the exemption from NDI Notification if it previously was in the conventional food supply in a chemically unaltered form. As an example, if a substance that is a New DS Ingredient is chemically the same as an ingredient in conventional food that was either recognized by FDA as GRAS or was covered by a GRAS notice to which FDA did not object, the supplement would qualify for the exemption from the NDI Notification requirement.

The procedure for submitting an NDI Notification for a New DS Ingredient that does not qualify for the exemption is set out in 21 CFR 190.6 (b). This procedure would be used by a manufacturer that plans to market a supplement containing a New DS Ingredient, as well as a manufacturer that plans to market a New DS Ingredient to other manufacturers of supplements. The contents of an NDI Notification include the following information:

1) A description of the New DS Ingredient, and if applicable, the supplement in which the New DS Ingredient will be used. The description would include the chemical or molecular composition of the New DS Ingredient, and if applicable, the chemical composition of the supplement in which it is incorporated, as well as their chemical and physical properties.
2) A description of the analytic tests or methods that are

used to identify and quantify the amounts of the ingredient that are present in a compounded mixture of many ingredients, and to prove the purity, quality, or bioactivity of the ingredient. The description would include the range of acceptable results for each analytic test, i.e., the acceptance criteria, that will be used to assure the quality of the ingredient and/or supplement in production.

3) A description of the process and equipment to be used to manufacture the ingredient and supplement.
4) The information relied upon to substantiate that the New DS Ingredient and the supplement containing it are reasonably expected to be safe when used as directed in the labeling for the supplement. This information can consist of a history of safe use, or the results of safety studies.
    a. A history of safe use will probably be based on the presence of the New DS Ingredient in a conventional food in a chemically altered form or in a composition that differs from the supplement. (If the chemical form and composition are unaltered, the NDI would not be necessary.) The history of safe use will therefore focus on showing that the differences in chemistry or composition do not adversely affect the safety of the ingredient or supplement.
    b. If a history of safe use does not exist, the results of toxicology and use case studies will be necessary to demonstrate safety. These safety studies can be taken from published peer-reviewed scientific literature, or they can be sponsored by the manufacturer. Toxicology studies are performed on animals and use case studies performed on human subjects in scenarios that are similar to the expected use by consumers. The NDI Notification Guidance document identifies the specific types of toxicology and

other safety testing that are required.

FDA has a 75-day period in which to review the NDI Notification, and it will respond by either accepting the determination of safety without objection, or objecting to the determination of safety and providing a list of deficiencies on which the objection is based.

There are two main differences between the NDI Notification regulatory regime and the GRAS Notice regime. First, NDI Notification is mandatory unless the exemption from notification applies, while the GRAS Notice process is voluntary. Second, if FDA did not object to a GRAS Notice, it indicates that the substance covered by the notice is GRAS when used within the scope of conditions described in the notice. The GRAS status applies to the substance and can be relied upon by other manufacturers, provided the GRAS conditions of use are satisfied. The NDI Notification is a requirement imposed on the manufacturer of a supplement that contains a New DS Ingredient, and no prior NDI Notification for the same New DS Ingredient can be relied upon to relieve the manufacturer of the requirement to file its own NDI Notification.

Production of dietary supplements and dietary supplement ingredients are subject to a set of good manufacturing practice regulations contained in 21 CFR Part 111. These dietary supplement GMPs are similar to the Food GMPs with respect to the sanitation requirements for facilities, equipment, and personnel. However, the dietary supplement GMPs are more extensive and prescriptive with respect to the requirements for production process controls. For example, a master manufacturing record is required for each dietary supplement. The master record identifies each step in the production process that is critical to the quality and purity of the supplement, and establishes a control point for each critical step. Each control point includes a specification of the chemical composition of the intermediate form of the supplement as it proceeds through that stage of its production, and a test, with acceptance criteria, that will be used during production to ensure that it meets specification. The dietary supplement GMPs require creation of a record for each

batch of production, which documents that samples taken from the batch satisfied final acceptance testing before shipment. Manufacturers are also required to take "reserve samples" of each batch of production, which are kept in inventory for testing in the event that any complaints are received regarding the quality of the batch.

A system of adverse event reporting was established for dietary supplements in 2006 (by the Dietary Supplement and Nonprescription Drug Consumer Protection Act). The basic requirement is that serious adverse events must be reported to FDA within 15 days. Serious adverse events are situations in which a supplement caused an illness that required medical intervention to prevent a serious outcome, a significant incapacity or disability, or death.

Dietary supplements are subject to comprehensive labeling requirements that include:

1) the ingredients contained in the supplement;
2) nutrition information on content of carbohydrates, fat, protein, vitamins, dietary fiber, and other types of nutrients in terms of both amount and percent of daily requirements;
3) identification of, and contact information for, the manufacturer; and
4) a statement of the contents of the package measured by weight or number of units (tablets or capsules).

There are restrictions on health claims and "structure-function" claims for dietary supplements. Structure-function claims consist of the following types:

1) claims that describe the role or mechanism by which a supplement affects the structure of some tissue or organ in the human body or some physiologic function (e.g., antioxidants maintain cell integrity),
) claims that describe a benefit related to prevention of a recognized nutrient deficiency by consumption of the supplement, or
3) claims improving general well-being by consumption of

the supplement.

A structure-function claim can be made only if the manufacturer notifies FDA of the claim and submits evidence that it believes substantiates the claim. If FDA does not object to the proposed claim, it can be used to market the supplement, but the claim must be accompanied by a prominent disclaimer that states that the claim has not been evaluated or approved by FDA, and that the supplement is not intended to prevent or treat any disease. Health claims characterize the relationship between a supplement to a disease or medical condition, and are permitted only if the health claims have been approved by FDA in an issued regulation. Regulations for approved health claims for dietary supplements are contained in 21 CFR Part 101.