Which Rules Must We Follow?

Sorting out compliance laws, rulings, and regulations

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This article is an engineer's (or engineering manager's) abridged guide to the FDA, regulatory documents, and standards. It will explain the FDA's interest in one's device, the level of control it has over a company, and how to navigate the available regulations and documents. Please note this guide is abridged. There are many documents available from the FDA and standards groups that are not referenced here. This information is just the "tip of the iceberg" of which product designers should have at least a cursory knowledge.

For managers and engineers who are new to the medical device industry, regulated device engineering will seem like a strange new world. One can no longer simply design, release and sell products; a pre-market submission and acceptance are required from a government agency. Circuits and software can no longer be designed from a blank page, inventing the look, feel, and performance limitations as one draws schematics or creates source files. Instead, one must work within design controls that are subject to audit from the same agency.

Confusion sets in when determining what rules must be followed. The industry is an alphabet soup of acronyms, abbreviations, and standards numbers. Quality and compliance professionals speak in this abbreviated language. There are standards on the same topics that disagree with each other. Consultants will be hired who will give conflicting advice. How can one make sense of the dozens of documents out there so one can get back to engineering a product?

Historical Background of FDA

The FDA was originally was formed and has

Glossary of Abbreviations

CDRH	Center for Device and Radiological Health
FDA	Food and Drug Administration
IDE	Investigational Device Exemption
ODE	Office of Device Evaluation
ORA	Office of Regulatory Affairs
OST	Office of Science & Technology
Part 820	Quality Systems Regulation section of 21 CFR
PMA	Pre-Market Approval
PMN	Pre-Market Notification
QSR	Quality Systems Regulation
21 CFR	Code of Federal Regulations, Title 21
510(k):	Pre-Market Notification, refers to section 510(k) of the Food, Drug and Cosmetic Act
820.30	Design Control section of Part 820 of 21 CFR
820.70	Production and Process Control section of Part 820 of 21 CFR

subsequently evolved in reaction to a series of calamities. The Food and Drugs Act was passed in 1906 in response to poisonous food additives, ineffective patent medicines, and public outrage over unsanitary meat packing practices (described in Upton Sinclair's The Jungle). Not long afterwards, the Food Drug and Insecticide Administration was set up as an independent regulatory agency. Although medical device quackery was rampant, the FDA had no power to regulate medical devices until 1938, when the Food and Drugs Act was replaced with the Food Drug and Cosmetic Act.

The Food Drug and Cosmetic Act (FDCA) was also passed in a climate of outrage, when nearly 100 people died from ingesting an elixir prepared with diethylene glycol (a substance similar to antifreeze). The Agency's name was changed to the Food and Drug Administration and medical devices were added to its purview. Under the 1938 FDCA, the Agency only had the power of seizure "after the fact", if a device was shown to be unsafe, mislabeled or adulterated. Unscrupulous manufacturers could continue to send faulty or dangerous devices to market, in spite of FDA intervention. The number and complexity of medical devices increased in the 1950's and 1960's. However, the FDA had little power to prosecute fraudulent devices. In some cases the Agency had to go to court to have a device declared a "drug", in order to get the power to require proof of effectiveness (drugs have needed premarket approval since 1962, as a result of the thalidomide tragedy in Europe). In 1976, after thousands of women were injured by the Dalkon shield intrauterine device, the Medical Device Amendments (MDA) set in place a mechanism to require premarket approval of medical devices. Devices were assigned three classification levels according to the level of risk to the user. The manufacturer had to prove efficacy and safety if the device was assigned to a higher risk category. If the device was *substantially equivalent* to a device already around before 1976, the path to market was streamlined. The MDA also imposed the first Good Manufacturing Practices, as well as requirements for keeping records of medical devices. Most importantly, the FDA was given the power to recall devices, and to withhold premarket approval, when necessary.

In the 1970's and 1980's computer components became widespread in safety critical medical devices. In the late 1980's, six cancer patients received massive X-ray overdoses during radiation therapy with Therac-25 linear accelerator machines because of software error. This tragedy led to the publishing of the FDA Quality System Regulation (QSR) in 1996. The 1990s also saw the passage of the Safe Medical Device Act in 1990, requiring closer tracking and post-marketing surveillance of medical devices. Most recently, in 1997, the Food and Drug Administration Modernization Act was passed, accelerating review and release of safe and effective devices. Some of the 1997 revisions, as well as the QSR issues will be discussed below.

The FDA's Relationship with Medical Devices

It is important to understand that, despite the

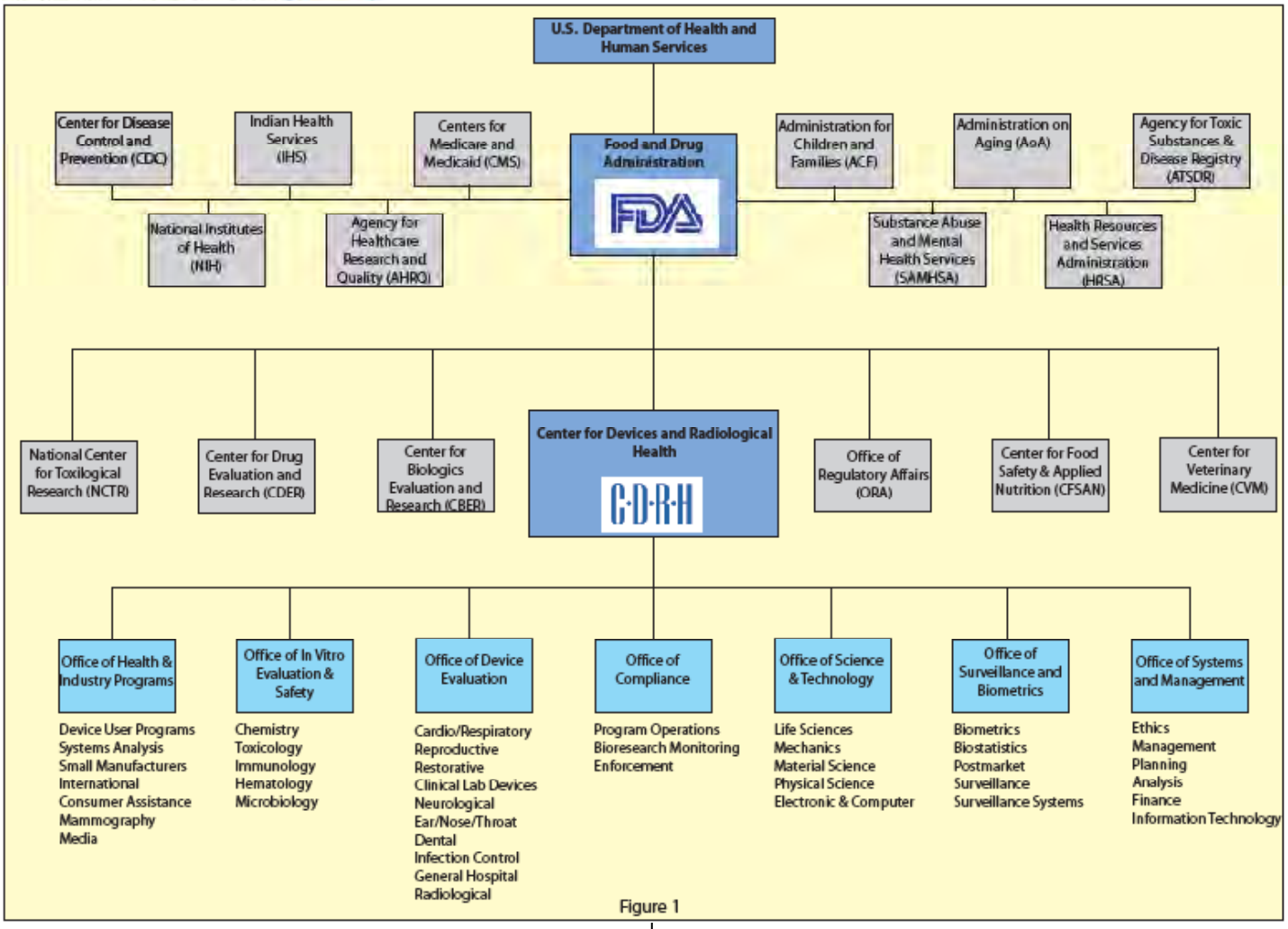

Figure 1

apparent complexity and number of Centers and Offices within the FDA, the mission of the agency is quite simple. As simply stated in the FDA Mission Statement, the mission of the FDA is to assure the *safety* and *efficacy* of the products within their purview. That mission of the agency extends down to each of the centers within the FDA, most notably (for device engineers), the Center for Devices and Radiological Health (CDRH). The mission also extends to each office within the center. FDA staff members who examine pre-market submissions are interested in assuring the *safety* and *efficacy* of devices before they get to market. Compliance auditors (inspectors) are interested in assuring the *safety* and *efficacy* of the design and quality systems used to create and maintain the devices.

The FDA is an agency of the Department of Health and Human Services of the Federal government. The organization chart of Figure 1 shows how the FDA is organized. Of the Offices within CDRH, three are of particular interest to device designers.

1. The Office of Device Evaluation (ODE) is the office to which new products are submitted for their pre-market notification or approval.
2. The Office of Compliance has enforcement as one of its main responsibilities. The FDA audits (or investigations) of medical device manufacturers are prompted and coordinated by this office.
3. The Office of Science and Technology (OST) is where specialists are found

within the FDA in specific areas of science and technology. These specialists are called upon by the FDA to assist in writing guidances for the industry and to assist ODE and the Office of Compliance on technically complex submission and audit situations.

The powers of the FDA over medical device manufacturers, granted by the Food, Drug and Cosmetic Act of 1938, can be summarized as *pre-market approval powers* and *post-market audit powers*. The pre-market approval powers are exercised by requiring medical device manufacturers to submit their devices to the FDA for review prior to release.

Submissions fall in one of three major categories:

1. Investigational Device Exemptions (IDE) – these submissions are for devices whose *efficacy* has not yet been proven. They are not for sale, and generally are to be used in the early phases of device research.
2. Pre-Market Approvals (PMA) – these submissions are for devices whose therapeutic or diagnostic value are new and unproven. The *efficacy* of the device must be proven to the examiner prior to market release. It usually involves clinical trials, and statistical treatment of trial results. *Safety* must also be addressed through testing or reference to design controls and quality systems that assure the safety of the device.
3. Pre-Market Notification (PMN) – addressed in Section 510(k) of the Food, Drug and Cosmetic Act, usually referred to as a 510(k) or 510k submission. These submissions are for devices whose *safety* and *efficacy* can be proven to be substantially equivalent to a predicate device that is already legally marketed in the US. The examiner only needs to be convinced that the new device is at least as effective as the predicate device. *Safety* must also be addressed through testing or reference to design controls and quality systems that assure the safety of the device.

The post-market power of the FDA is exemplified by the audit. The Code of Federal Regulations (21 CFR 810) gives the FDA power to demand that a manufacturer recall or cease distribution of a device. The audit and the inspection are the tools that the agency uses to collect the information to support a demand for recall.

Manufacturers have a responsibility to maintain a quality system (QSRs). Implicit in this system is a responsibility for documentation of quality efforts appropriate to the type of device. The law requires a manufacturer to conduct internal audits at regular intervals, and to have a documented audit procedure.

Product designers and engineers need to understand that the FDA instructs its inspectors, during a quality audit, to choose any Class II or III device design project (as well as certain Class I devices) and to verify that Design Control Quality requirements under 21 CFR 820.30 have been met and have been documented. Furthermore, if software is part of the device, the inspector may look for documented evidence of its validation. For this reason, any project needs to be controlled and documented with the assumption that it may be subject to close scrutiny.

The Regulatory Maze

The FDA was created and given powers by Congress in the Food Drug and Cosmetics Act. The law can be found in Title 21 of the United States Code. The Regulations of the FDA are contained in the Code of Federal Regulations, Title 21 (referred to as 21 CFR). The regulations

that are of particular interest to medical device manufacturers are in Parts 800-1299 of 21 CFR. There are also regulations in Parts 11 and 211 that relate to electronic records and signatures and to the preparations of finished drug products, respectively, which are beyond the scope of this article. Medical device design engineers should read closely 21 CFR Part 820 on Quality System Regulations (the QSRs), particularly Section 30 (820.30) which regulates Design Controls and to a lesser extent Section 70 (820.70) which regulates Production and Process Controls. Some of the requirements of 820.70 relate to quality systems and the validation of automated process software that can include design tools such as test software, compilers, or code generators which might be used by product designers.

All designers should be familiar with the QSRs. Part 820 that defines the QSRs is only 13 pages long; however, the entire Title 21 is over 700 pages long and is available online or in printed form from the US Government Printing Office. The FDA usually has a stock of the printed versions available for the asking at medical device trade shows.

Documents for the Designer

The Design Controls (21 CFR 820.30) state that designers need to plan design activities, identify design inputs and outputs, verify and validate the design, plan for the transfer to manufacturing and the maintenance of the device design, and keep records of these activities. It sounds easy on the surface, but what *exactly* does it mean?

To help answer that question, the FDA has produced a large collection of publications. Figure 2 shows the relationship of the legislation to the regulations, guidances, and to industry standards. Of specific use to device designers are *Guidances*, which are methods proposed by the FDA for meeting the regulations. A manufacturer can propose any other method for meeting the regulatory intent, subject to acceptance by the FDA. The FDA also allows public web access to the inspection guides used by FDA auditors, including the Quality System inspection guides.

Reduce Paperwork by Complying with Standards

Recently Section 514(c) was added to the Food, Drug and Cosmetic Act under FDA jurisdiction. This addition allows for proof that a device conforms to acceptable industry standards

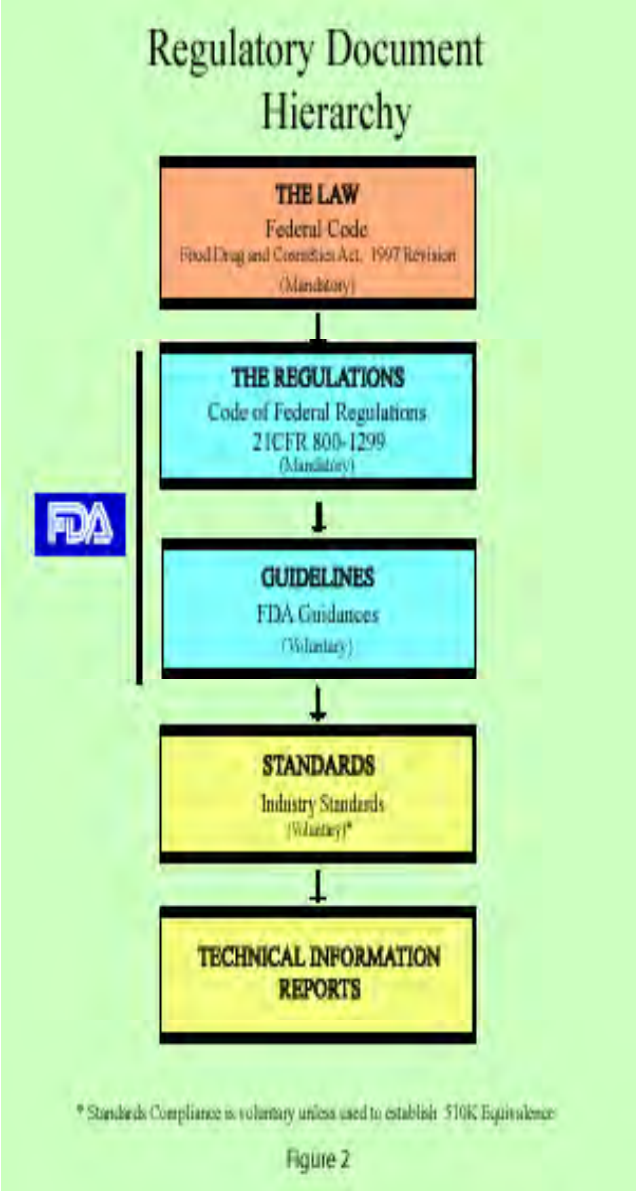

Figure 2

to replace detailed descriptive information or performance data, significantly reducing paperwork. Though not evident to a first time submitter, it is not the FDA's goal to create paperwork of no value. Instead its aim is to provide reasonable assurance that design engineering and quality practices are being followed that are appropriate for the development of safe and effective devices.

To an FDA reviewer, conformity with a standard means a new device has been developed to be compliant with industry accepted performance specifications, and/or uses processes generally accepted by the industry for successful development of medical devices. This recognition is sometimes referred to as the use of standards in *substantial equivalence determination.*

So, what standards should a designer use? If the FDA is unfamiliar with a standard, if there is a lack of specificity, or existence of device features not addressed in the standard, the FDA may reject substantial equivalence determination as sole 510(k) submission information. The best way to avoid this problem is to use the overall list of acceptable standards given by the FDA. Currently, over 500 standards are recognized, including: AAMI, ANSI, ASME, IEEE and ISO standards. Normally, if an FDA-recognized standard is applicable to a device, the device is identified in the standard's Supplemental Information Sheet on the Center's Website that lists FDA-recognized standards.

A Guide to Documents for Designers

The first task for a medical device manufacturer is registering its business with the FDA. A high level strategy for bringing a medical device to market is also critical. Small businesses are particularly challenged by the regulatory overhead, and need special consideration.

The potential device's classification will determine the design control rigor that will be required. The submission strategy will be determined by how novel the potential device is compared to similar devices already on the market. The manufacturer must decide if the device is exempt, whether it must submit a 510k PMN, or file a PMA. The design of the device can be affected by the submission strategy, especially if the manufacturer plans to make a substantial equivalence claim.

The medical device manufacturer must have a formal quality system in place. If the manufacturer is already familiar with the ISO 9000 quality standards, it may be relatively easy to map the ISO 9000 quality system the QSRs. The FDA also offers some advice to small businesses on how to comply with the QSRs.

If the device contains software, it receives increased scrutiny from the FDA. There are special considerations when applying the QSR design controls to software developed for a medical device, especially as it relates to the validation and verification (V&V) of the software. If off-the-shelf software is embedded in the device, it, too, falls under the design controls of the QSRs.

FDA studies of device incidents and recalls have shown that a significant number of incidents are reported every year, because users of devices are confused or misled by the user interface to the device. There are special guidances for the industry to suggest methodologies for developing user interfaces appropriate for the intended use of the device.

Special devices such as blood banks and imaging systems deserve special treatment, and as such have a special guidance to assist manufacturers of those devices. The CDRH website has numerous documents for ODE reviewers to guide them on their evaluations of specific device types.

In preparing device submissions it can be useful for the manufacturer to understand how the FDA reviewers are trained to review submissions. Likewise, it is also useful, in preparing for an FDA audit, to understand how the FDA inspectors are trained to inspect manufacturers and to inspect quality systems.

Manufacturers who wish to comply with accepted industry standards can choose from a number of standards that deal with specific devices, and with development and quality processes. The AAMI and ANSI standards are generally accepted in the US market; ISO standards are internationally recognized. For standards specific to dealing with software, the IEEE has a large collection of standards that provide detail down to the document level.

FDA Center for Devices & Radiological Health Direct links to helpful sections of the FDA website

Supplemental Information Sheet:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm

Registering Your Establishment (who must register, how, why):
http://www.fda.gov/cdrh/devadvice/341.html

Getting to Market with a Medical Device:
http://www.fda.gov/cdrh/devadvice/3122.html

Small Business Guide to the FDA:
http://www.fda.gov/ora/fed_state/Small_Business/sb_guide/default.htm

Classify Your Medical Device:
http://www.fda.gov/cdrh/devadvice/313.html

Design Control Guidance for Medical Device Manufacturers:
http://www.fda.gov/cdrh/comp/designgd.html
http://www.fda.gov/cdrh/comp/designgd.pdf

How to tell if your device is exempt:
http://www.fda.gov/cdrh/devadvice/3133.html
http://www.fda.gov/cdrh/devadvice/ide/index.shtml

Should you submit a 510k PMN?:
http://www.fda.gov/cdrh/devadvice/314.html

Should you file a PMA?:
http://www.fda.gov/cdrh/devadvice/pma/

Do It By Design; An Introduction to Human Factors in Medical Devices:
http://www.fda.gov/cdrh/humfac/doit.html
http://www.fda.gov/cdrh/humfac/doitpdf.pdf

ISO 9001 Comparision to the Quality System:
"Comparison Chart: 1996 Quality System Regulation Versus 1978 Good Manufacturing Practices Regulation Versus ANSI/ISO/ASQC Q9001-1994 and ISO/DIS 13485:1996"
http://www.fda.gov/cdrh/dsma/133.pdf

"ISO 9001:2000 and FDA Quality System"
http://www.fda.gov/cdrh/devadvice/ISO9001.pdf

Medical Device Quality Systems Manual: A Small Entity Compliance Guide:
http://www.fda.gov/cdrh/dsma/gmpman.html

Inspection of Medical Device Manufacturers:
http://www.fda.gov/ora/cpgm/7382_845/pdf/7382_845.pdf

Guide to Inspections of Quality Systems:
http://www.fda.gov/ora/inspect_ref/igs/qsit/qsitguide.pdf

ABOUT THE AUTHOR:

David Vogel is the founder and president of Intertech Engineering Associates, Inc.

Dr. Vogel was a participant in a joint AAMI/FDA workgroup to develop a standard for Critical Device Software Validation which was subsequently included in the IEC 62304 Software Lifecycle Standard. He was also a participant on the joint AAMI/FDA workgroup to develop a Technical Information Report (TIR) for Medical Device Software Risk Management. Currently, Dr. Vogel is a member of the AAMI/FDA workgroup developing a TIR on Quality System Software Validation.

A frequent lecturer for workshops and seminars on topics related to medical device development and validation, Dr. Vogel also is the author of numerous publications and holds several patents.

Dr. Vogel received a bachelor's degree in electrical engineering from Massachusetts Institute of Technology. He earned a master's degree in biomedical engineering, a master's degree in electrical and computer engineering, and a doctorate in biomedical engineering from the University of Michigan.

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