



CONSULTING MEMORANDUM:

DEALING WITH A MEDICAL DEVICE IN THE U.S.

This memorandum outlines the basics the United States of America's (USA's) Food and Drug Administration (FDA) medical device compliance requirements. Unfortunately this is a subject that cannot be answered completely in any one short communication. In fact, our book, "**Mastering and Managing the FDA Maze – Medical Device Overview**," is almost 300 pages, and it is only an introductory work! However, we will attempt to be brief and outline the important elements you need to understand.

First, we would like to provide a very brief overview of the organization of the FDA:

In our Federal government, the **Department of Health and Human Services** oversees the **FDA**. The FDA is an organization of about 10,000 employees.

The FDA is made up of a number of "Offices," including the **Office of the Commissioner**, under which there are a number of "**Centers**." Under the Office of the Commissioner are two (2) with which most medical device companies deal, **the Center for Devices and Radiological Health (CDRH)** and **the Center for Biologics Evaluation and Research (CBER)**. See the attached diagram, page 4.

CDRH is the Center to which **Registration and Listing** (see #1 below) forms are sent. CDRH actually oversees the largest number of medical device manufacturers, including those that make radiology devices, chemistry analyzers, hematology analyzers, and surgical equipment, among thousands of other devices. CBER is the Center that oversees the biological medical devices and medical device software used in "blood establishments" and reviews biologics and blood establishment premarket notifications or 510(k) submissions. See diagram on page 4.

There are four (4) main compliance elements you need to understand:

1. Registration and Listing
2. Premarket Notification Submissions, the so-called 510(k)
3. Compliance with FDA Quality System Regulations
4. Preparation for FDA Inspection

1. Registration and Listing

To market any medical device in the U.S. as a U.S.-based medical device manufacturer or foreign medical device manufacturer, your firm must register on FDA Form 2891, Initial Registration of Device Establishment, and must list your Medical Device product(s) on FDA Form 2892, Device Listing. Additionally all manufacturers must identify an "Official Correspondent," and all foreign manufacturers must identify a "U. S.-based Foreign Agent." Oracle Consulting Group is an authorized official U.S.-based Foreign Agent. All the information submitted on these forms must be in English and FDA requires your company's actual street address. If you request, we would be happy to have the appropriate forms and specific instructions forwarded to you by mail. Foreign firms can also request information specific to their U.S. Foreign Agent requirement and Agreements.

Once you send in your completed forms, you are subject to inspection for compliance with all applicable FDA regulations. If you are introducing a medical device that requires a premarket submission and have not previously registered, we recommend that you delay submitting the registration and listing forms until you are within 6-8 weeks of making any Premarket Notification or 510(k) submission. This will ensure that you are reasonably prepared for any FDA inspection.

If you decide to register, several months (or more) after you have submitted your FDA forms (2891 and 2892) you will receive notification of a Registration Number and Owner/Operator Number. Annually thereafter, FDA will

mail to your company FDA Form 2891a, Annual Registration of Device Establishment, for completion. This form is used to keep your company information up-to-date with FDA.

2. Premarket Notification Submissions, the so-called 510(k)

If your device requires a premarket notification or 510(k), this will be your greatest challenge. The entire submission must be in English. 510(k) submissions assume that there is a legally distributed “predicate” device. A predicate device is a device that was legally marketed prior to May 28, 1976, the date the device amendments were made to the Food, Drug, and Cosmetic Act (the Act). Preamendment devices are those legally marketed devices that existed prior to May 28, 1976.

FDA is sent between 4,000 – 5,000 510(k)s each year. FDA, generally, classifies 510(k) submissions into Class I and Class II devices. Very few Class I devices require 510(k) submission and not all Class II devices require submissions. Class III devices do not have a preamendment predicate and, generally, require a premarket approval or PMA submission, see below.

We can supply a copy of any available CDRH or CBER “guidance” documents electronically. These guidance documents describe, step-by-step, of what CDRH or CBER requires from manufacturers in order to comply with the agency’s premarket notification expectations. Not all devices have a corollary guidance document.

We have assisted a variety of different kinds of medical device manufacturers with the 510(k) submissions. These submission complexity and size will vary with the type of device for which the submission is made.

510(k) submission support is tailored to each client. For those clients that need overall editorial management, we start out with establishing a “Style Guide” for the submission to ensure that all parties providing materials provide their material in the same style and format. Next we identify what materials a client already has (in English) and what materials need to be created or translated to comply with any existing FDA guidance document. This is sometimes referred to as a “Gap Analysis.” The missing materials must then be created, most retrospectively, to comply with FDA expectations.

Usually we create and maintain a submission control document, typically in tabular form, that helps management and submission participants understand what is required, by whom and when. It is difficult to assess how big a job it will be to prepare your firm for FDA oversight and assist you with a premarket notification submission. However, the job required to make a premarket submission cannot be under-stated. It is a challenge.

3. Compliance with FDA Quality System Regulations and Other Regulations

Additionally, submitters must document that they comply with applicable parts of the FDA’s Quality System Regulation, 21 CFR 820. This regulation can also be provided to you electronically. This regulation has over 210 “shalls.” Usually, not all of these “shalls” will apply to your firm and your medical device, however, most or many will apply. These are only some of the FDA regulations that medical device manufacturers are inspected against.

As part of the premarket submission “Gap Analysis,” we can also provide a Quality System Regulation “Gap Analysis.” That part of the Gap Analysis compares each device manufacturers’ Quality Manual and written procedures, work instructions and forms against the Quality System Regulation expectation. Our analysis will provide a list of procedures that must be implemented to comply with these FDA regulations. This can be as few as 5 or 6 or as many as 25 – 30, or more. We have about 30 procedural templates that can be tailored for specific client requirements to ensure you implement compliant procedures.

Usually, it is our intent is to provide a copy of a manufacturer’s entire FDA compliant Quality Manual and applicable SOPs as evidence of their complete control of the design, development, verification, validation, distribution when submitting a 510(k).

Other applicable regulations include 21 CFR 806 Corrections & Removals, 21 CFR 7 Recalls, and 21 CFR 803 Medical Device Reporting, and, for all foreign device manufacturers, all regulations relative to importing medical devices into the U.S.

4. Preparation for FDA Inspection

Manufacturers of all medical devices distributed in the USA are subject to FDA inspections, even foreign manufacturers. Typically, foreign manufacturers are provided with about 30 days of prior notice before an

inspection. We generally try to provide some information for clients on what to expect during a FDA inspection, what to do, and what not to do. Our goal is to provide sufficient consulting services and support to help ensure no major nonconformances with FDA regulations are identified during an FDA inspection, but compliance is the individual manufacturer's responsibility.

Consulting Services and Costs

We are often asked to provide an estimate of consulting service costs. That is a difficult thing to do without understanding, in detail, the current state of your firm in terms of FDA compliance. It is much like trying to tell someone what a software application or new medical device will cost to develop and deliver without any knowledge of the application's requirements or specifications, or what a medical device will cost to deliver without any preliminary design descriptions.

Our GUESS is that the cost in consulting service fees will range between (US) \$7,500 - \$35,000, depending upon the consulting services for which you contract. FDA will expect that you have individual written procedures that control every step in the design, development, verification, validation, documentation, installation and support of your medical device(s). The FDA will expect that you have written procedures applicable for all their regulations, for example, the quality system regulations, device recalls, medical device reporting, corrections and removals, labeling and importing. Some compliance services may take a few hours or less than a day, while others, like complex submissions, may take hundreds of hours.

The FDA will expect that you have a risk analysis for each of your listed devices. That risk analysis must identify every known hazard associated with your device, including all hardware, any software operating system, operational software and any network(s) specified for the device's operation. That risk analysis must identify all known hazards, assess their likelihood, level of concern [how bad is the hazard], what step(s) you have taken to mitigate or eliminate the hazard, and how well that mitigation or elimination has worked. Your risk analysis should have a summary report that has been reviewed and approved by management.

If your company is procedurally controlled and extremely well documented, and if you have done significant "risk analysis" documentation, our services will probably cost less than \$9,000, but only a Gap Analysis can determine that situation. However, if you have poor procedural control, poor records, little or no "risk analysis," poor user manuals, etc., etc., and we are charged to provide some or most of the services to correct those problems, the costs could be over \$10,000 and might exceed \$25,000.

You should understand that if you have multiple devices to submit, you will have significantly lower costs with each subsequent submission. You will have a "learning curve" associated with your first submission. You will learn a lot with the first submission. Some times you will need NO ADDITIONAL SERVICE for any subsequent submission. If that first submission is ranked a 10 in terms of OCG's services, your next submission may only require a 2-6 level of service, your third submission may only require a 0-4 level of service, and any subsequent submission might require a 0-3 level of service. The level of service you require for subsequent submission will depend upon your company and the people you dedicate to those submissions.

Upon request we can provide you with a Consulting Services Agreement and Non-disclosure Agreement for your review. In the Consulting Service Agreement, we will identify what services we propose to provide. In all cases, our clients define and approve our services. You should never receive an invoice for services that you have not understood and approved in advance. This is our way of helping our clients control their costs for our services.

To get started in further discussions, it would be appropriate to have an executed Non-disclosure Agreement. You can execute the one we can provide and we will sign it and return a copy to you by FAX. Alternatively, we would welcome an opportunity to review your Non-disclosure Agreement for our execution. We hope that this communication provides you with the information you need.

Final Note

Finally, a few complex or sophisticated devices may require compliance with FDA's Premarket Approval (PMA) or Investigational Device Exemption (IDE) regulations.

PMA's

Like 510(k)s, all PMA submissions must be in English. If your device requires a premarket approval submission, this is a greater challenge than a 510(k). In many respects a PMA submission for a medical device to CDRH is the

device equivalent to a submission for a new drug to the Center for Drug Evaluation (CDER). Typically, FDA receives less than 50 PMAs each year.

PMA submissions typically are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury. If FDA accepts your PMA submission, a minimum 180-day review period provided by the Act is initiated. FDA can issue, at any time during this review, a letter notifying you of any deficiencies. Within the 180-day review period, FDA will execute one of the following actions:

- Issue an approval order under 21 CFR 814.44(d), or
- Issue an approval order under 21 CFR 814.44(e), or
- Issue a not approved order under 21 CFR 814.44(f), or
- Issue an order denying approval under 21 CFR 814.45

PMA submissions require a scientific and regulatory review to ensure their safety and effectiveness. PMA approval is a private license granted by FDA to the applicant to market that device.

IDE's

Whenever manufacturers need to have their devices used in a clinical evaluation on or in human subjects, the Act authorizes FDA to exempt these devices from certain requirements of the Act that apply to normal commercial distribution. Clinical evaluations of these devices require, unless exempt, an approved investigational device exemption (IDE) either by the clinical facilities' institutional review board (IRB) or and IRB and FDA. The IRB will establish an approved protocol, ensure informed consent for all patients, provide and document adequate monitoring, records and reports.

Clients requiring assistance with PMAs and IDEs can expect significantly higher consulting service costs. Again, those costs will depend upon the level of documentation present in the firm and the level of services required in preparation for the PMA submission. Small or medium size firms should expect that additional consultants and technical service firms may have to be brought in to provide skills and technologies they do not presently have. Clients requiring PMA and IDE assistance must understand that accurate cost estimates are impossible to provide and will depend upon factors out of the consultant's hands. These include the:

- compliance status to the firm,
- sophistication and risk of the device,
- clinical evaluation requirement, and
- resources available within the firm.

Documents available electronically:

21 CFR 7, Recalls, Adobe Acrobat

21 CFR 803, Medical Device Reporting, Adobe Acrobat

21 CFR 806, Corrections and Removals, Adobe Acrobat

21 CFR 820 Quality System Regulations, Adobe Acrobat

OCG Consulting Memorandum: FDA Required Procedures and Records, Adobe Acrobat

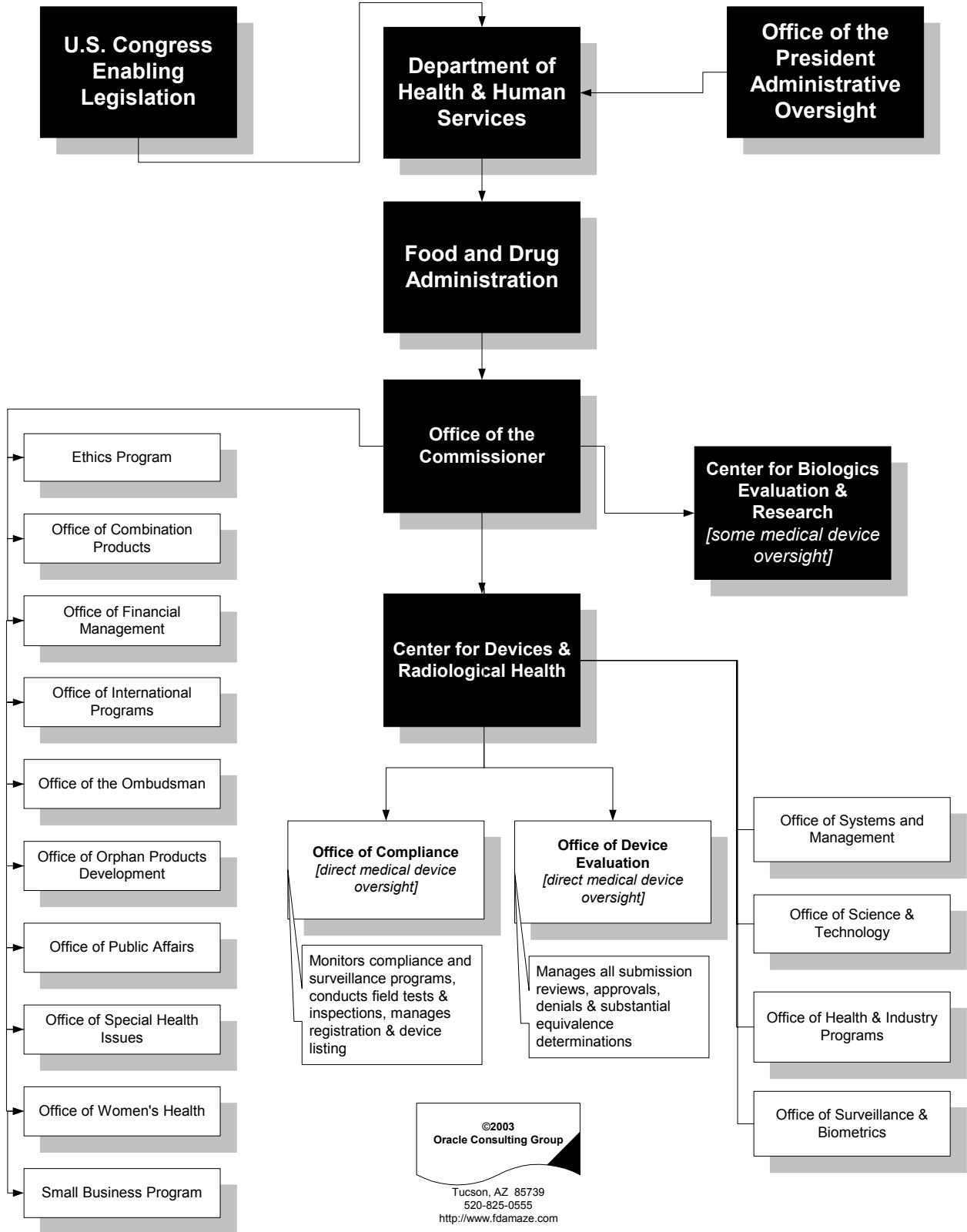
Glossary of Computerized System and Software Development Terminology, Adobe Acrobat

OCG Consulting Memorandum: QSIT Inspection Checklist

FDA Software Validation Guide, Adobe Acrobat

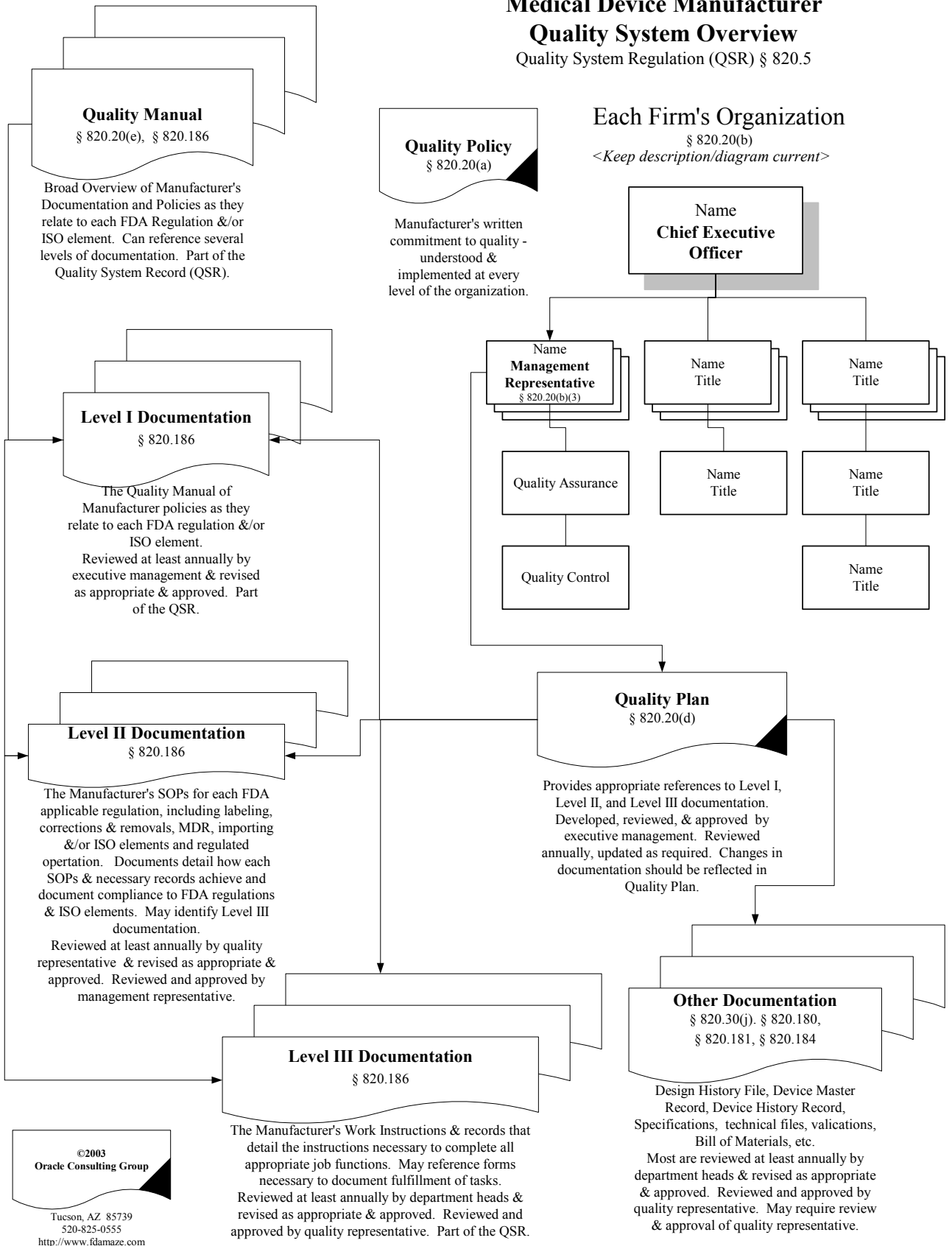
and others as are applicable for each client.

Medical Device Manufacturer Laws, Regulations & FDA Oversight



Medical Device Manufacturer Quality System Overview

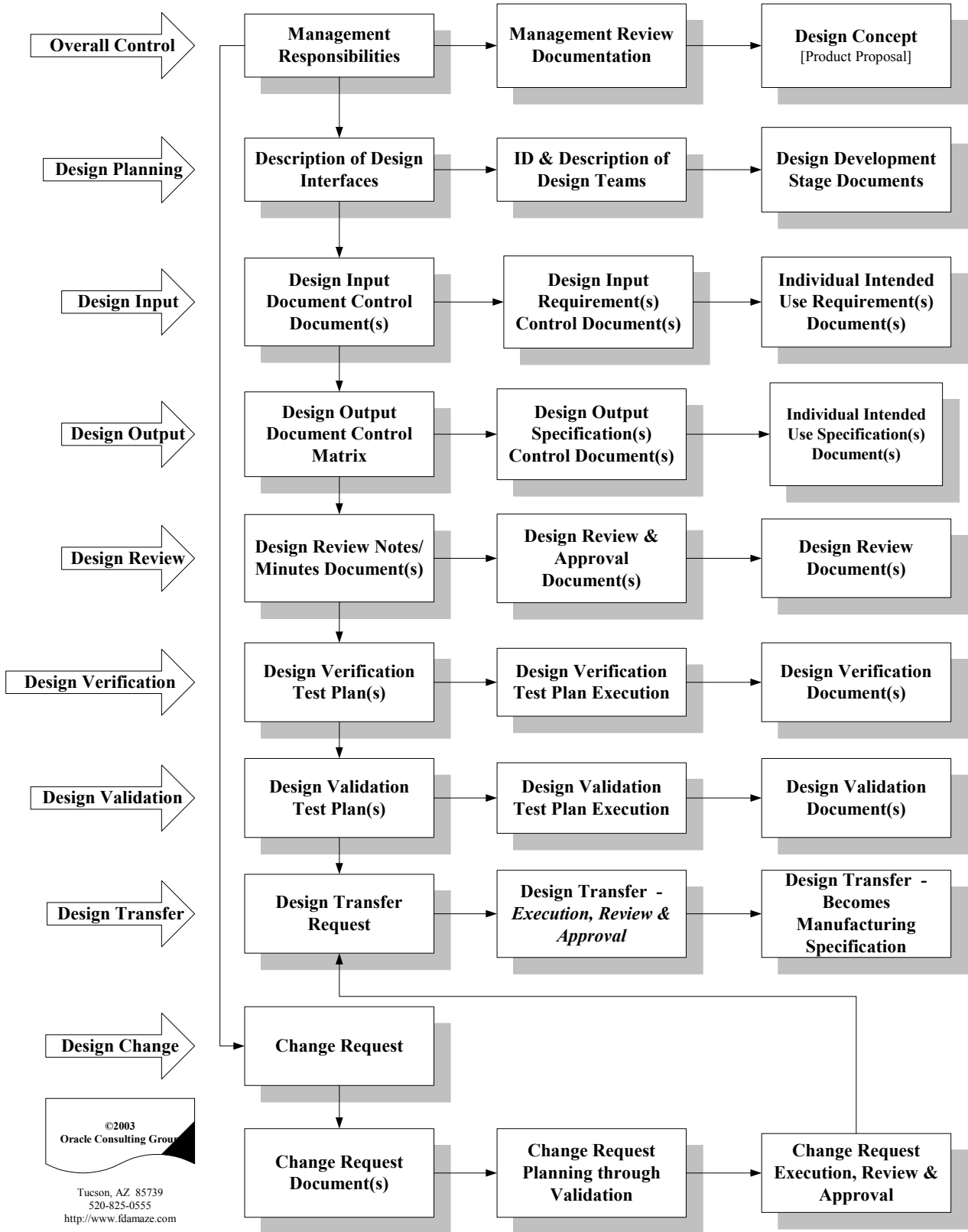
Quality System Regulation (QSR) § 820.5



Medical Device Manufacturer Design Controls

§ 820.30

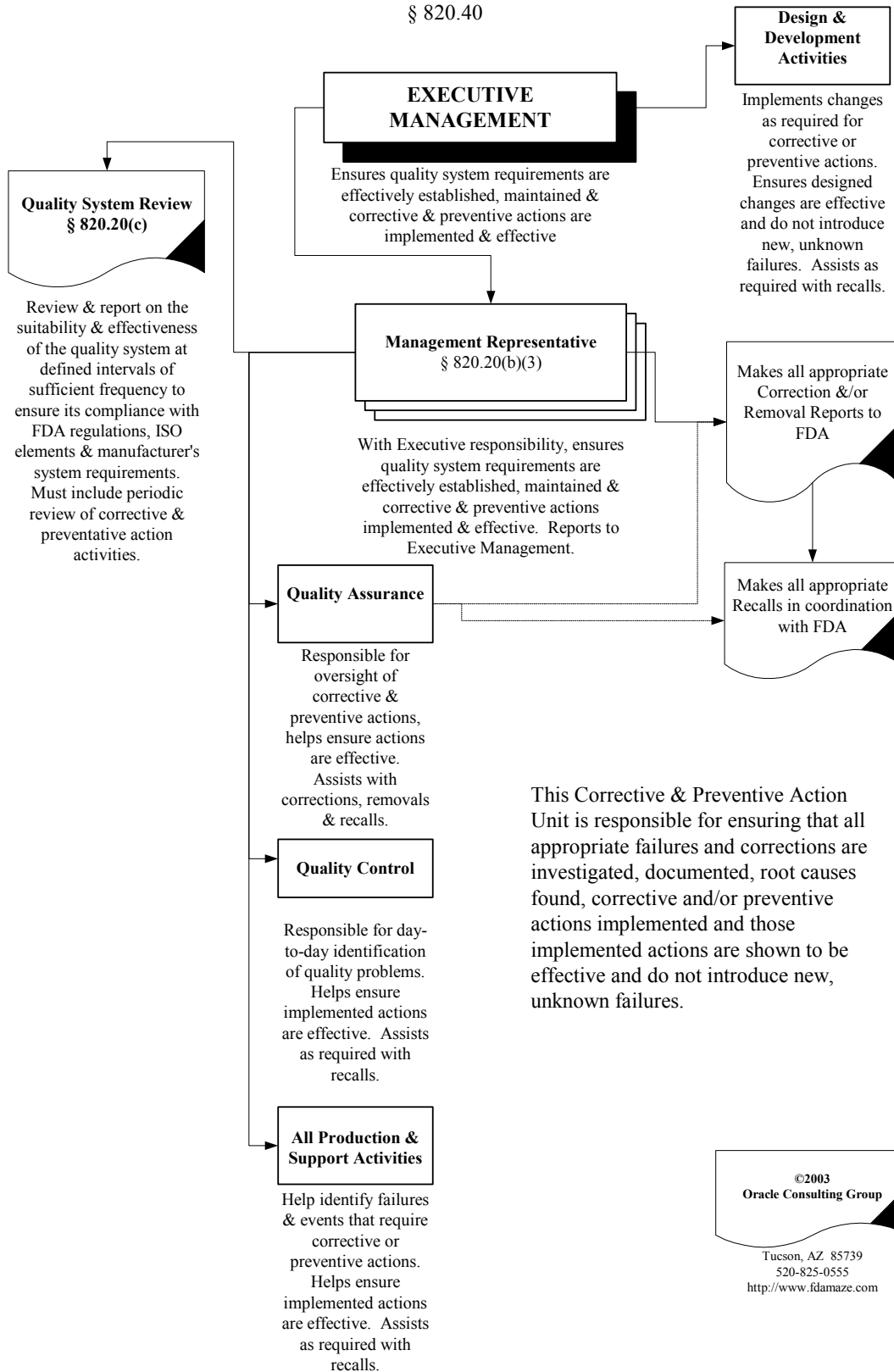
Expected FDA Oversight



©2003
Oracle Consulting Group
Tucson, AZ 85739
520-825-0555
<http://www.fdamaze.com>

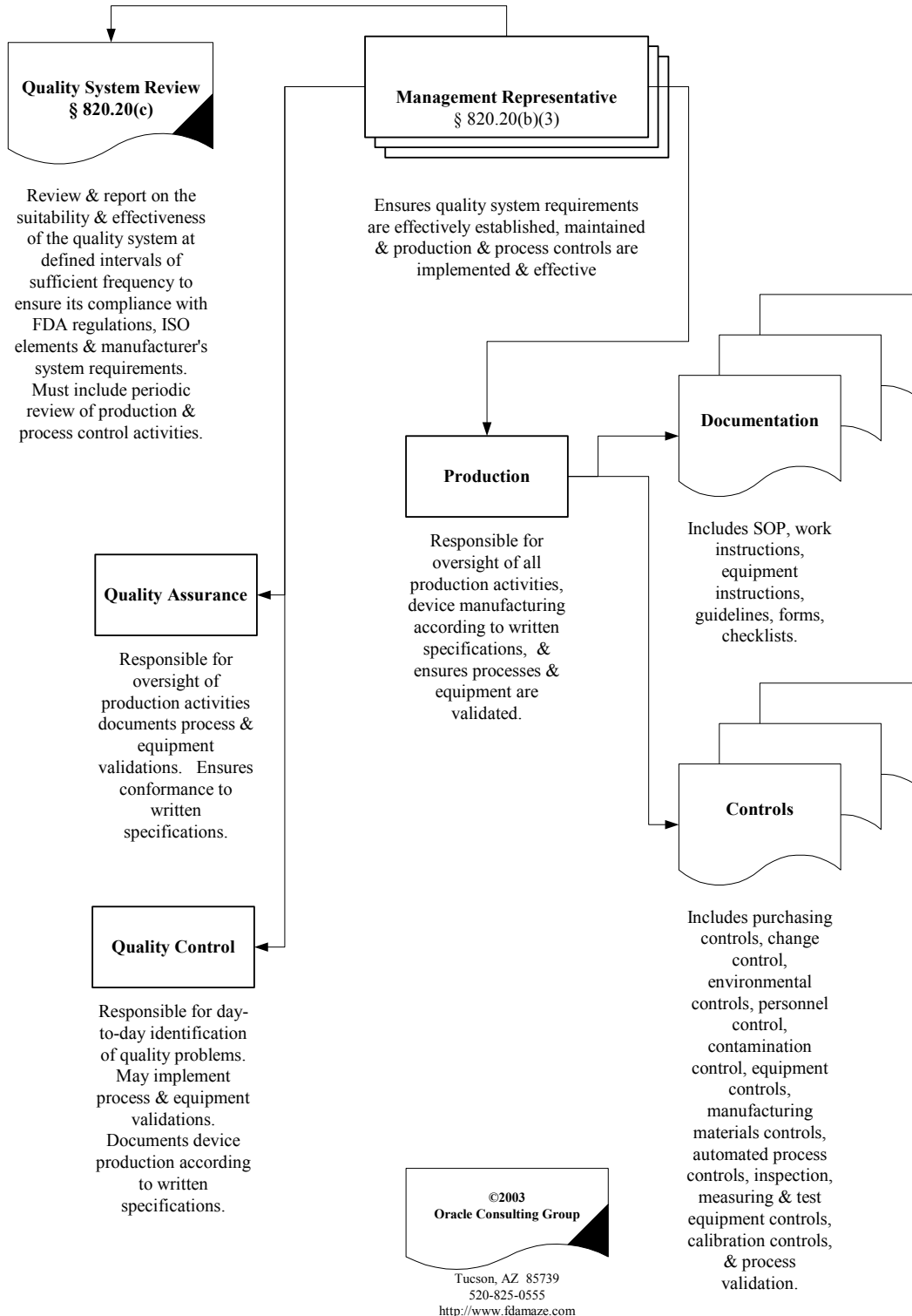
Medical Device Manufacturer Corrective and Preventive Action Unit

§ 820.40

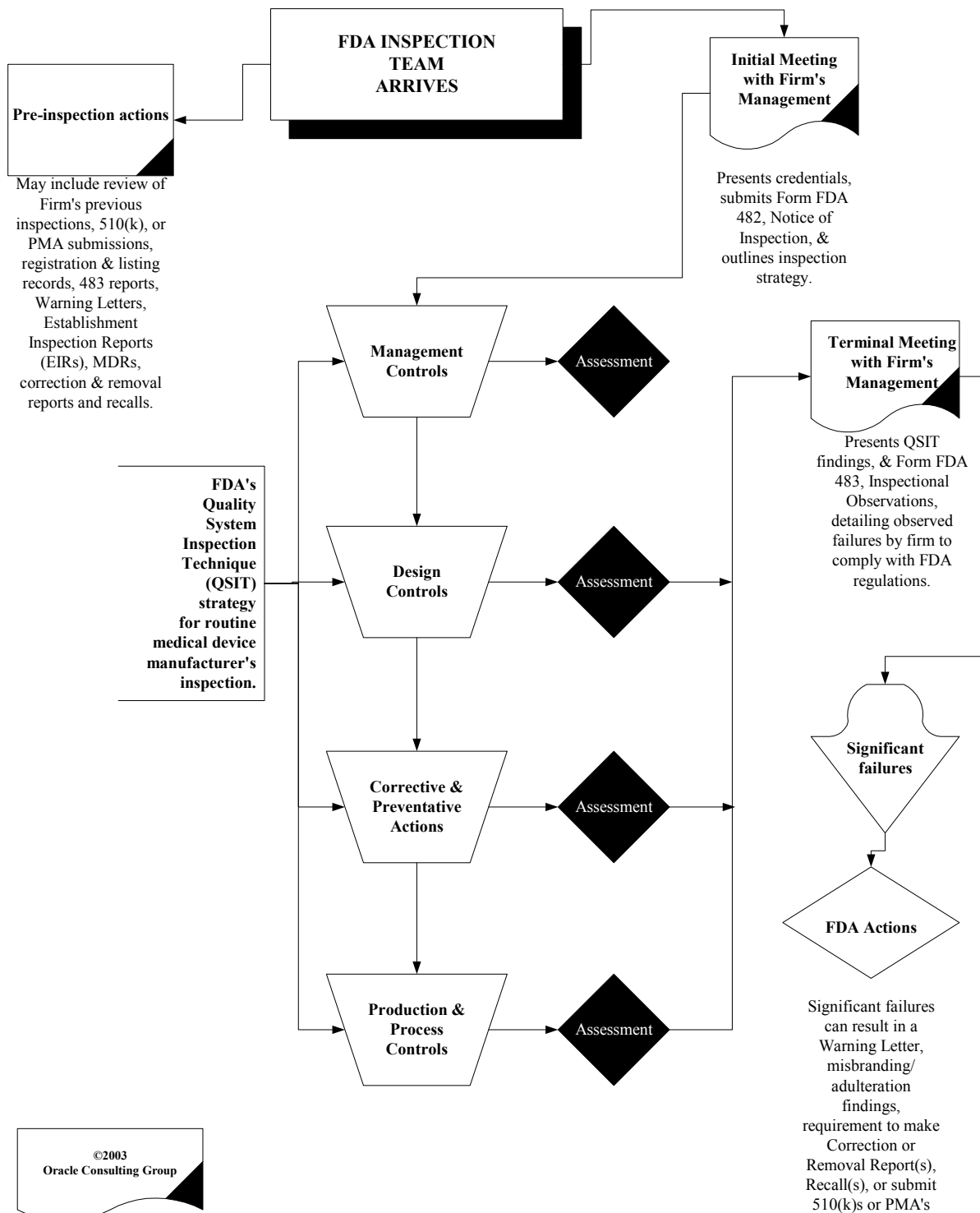


Medical Device Manufacturer Production and Process Controls

§ 820.40



Medical Device Manufacturer FDA Inspections § 820.180



©2003
Oracle Consulting Group

Tucson, AZ 85739
520-825-0555
<http://www.fdamaze.com>