

# A Regulatory Primer

Critical Regulatory Issues, Hurdles, Myths, and Realities ...  
Examined, Explored ... Explained



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## Part 1: Consider Regulatory Early On

**Regulatory hold-ups can delay time to market for early-phase companies.**

**This is the first in a series of articles from Roger Gray at Donawa Consulting concerning the critical regulatory hurdles that have to be overcome before medical device products can be sold in the major world markets.**

### Consider Regulatory Issues Early On

It is easily understood that new companies developing innovative technologies to solve clinical problems concentrate their energies on optimizing the technology and keeping the company afloat financially.

Unfortunately, if issues relating to regulatory compliance are not considered early on, it can lead to problems when the product is ready for marketing.

This may result in substantial delays in having the product available for sale, with knock-on effects in meeting critical investment milestones and even to the company's survival.

The company's initial business plan should include a regulatory strategy that is closely aligned to the marketing strategy (indeed, the regulatory strategy may often drive the marketing strategy).

Having experienced, professional regulatory advice, even the company's early days, is essential in ensuring that the technological and clinical advances made are not wasted. Such advice may be provided either by employed staff or by consultants, but the advice they can provide can mean the difference between success and failure.

### Two Major Markets, Two Different Systems

Most early-phase companies aim to market their devices in the United States and Europe. Depending on the location of the clinical experts with whom

they are collaborating, one market is selected over the other as the place for market entry.

Unfortunately, the regulatory regimes in these two major markets are significantly different, so an understanding of both systems is important. Indeed, some devices may be more easily cleared for sale under one regime than the other, and this may have a significant effect on how the company moves forward.

Both regimes **classify devices on the basis of perceived risk to patients**, but this doesn't always result in similar classifications. Once the classification is established under each regime, the requirements and options for "route to market" become clearer, allowing the company to firm up its regulatory and marketing strategies, giving much needed confidence to its investors.

For example, the **majority of lower-risk (Class I) devices in Europe may be placed on the market without any pre-market oversight**. In simple terms, the company "self-certifies" the product as being in compliance with a set of "essential requirements" listed in the relevant medical devices directive, places a CE mark on the device, and makes it available for purchase.

In the United States, most **lower-risk devices (again Class I) are exempt from pre-market review**, while others will require successful completion of a 90-day pre-market notification process. In addition, compliance with certain quality system requirements will be required unless specific exemptions apply, although third-party certification is not required.

**Subsequent articles in this series will explore in greater detail both European and U.S. requirements and their differences, allowing managers and entrepreneurs of start-up companies to understand basic, but extremely important, regulatory issues and plan for their incorporation into business plans. ■**

## Part 2: Up Close: U.S. FDA Classes

In Part 1, Roger Gray of Donawa Consulting explained how device classification can play an important role in determining not only the quickest route to market, but can potentially affect which of the major markets, United States (U.S.) or Europe (EU), the product is likely to achieve first clearance for sale.

In this article, Roger looks at classification issues in the United States. His first words of advice: Determine device classification as early as possible.

### Start with the Class & Learn about the Controls

In degrees of increasing perception of risk, the U.S. Food & Drug Administration (FDA) divides medical devices into three groups:

**Class I:** General controls are deemed sufficient to demonstrate safety and effectiveness. General controls include —

- Manufacturer establishment registration (which currently costs \$1,706 per annum)
- Listing of devices
- Compliance with the **quality system requirements** (QSR) in Title 21 of the U.S. Code of Federal Regulations (CFR), Part 820 (21 CFR 820 or QSR)
- Labeling in accordance with 21 CFR 801 or 809
- Submission of a premarket notification [otherwise known as a 510(k)]

**Class II:** General controls and special controls are deemed sufficient to demonstrate safety and effectiveness. Special controls may include —

- Additional labeling requirements
- Conformity with mandatory or voluntary standards or FDA guidance documents
- Requirement to conduct specified post-market surveillance activities

**Class III:** General controls and **premarket approval** (PMA) are required to demonstrate safety and

effectiveness. Carried out by the FDA, PMA is a process of detailed scientific review of data submitted by the manufacturer. The process is intended to ensure device safety and effectiveness.

### Class I & the Important Exception to the (Regulatory) Rule

One very important exception, however, is that the **majority of Class I devices (around 75%) are exempt from the 510(k) requirement.**

This means that bringing one of these 510(k) exempt Class I devices to the U.S. market is relatively easy and inexpensive — all that is needed is a quality system meeting the requirements of QSR.

Many Class I devices are also exempt from the design control aspects (Section 820.30) of the regulation.

Furthermore, there is no certification or prior quality system inspection required from the FDA or a third party — compliance with the QSR is self-imposed, but may be subject to FDA inspection once the device is on the market.

### Class II and the 510(k): Notification, Timelines & Guidelines

#### Well-Documented Exceptions

As with most regulatory rules, there are exceptions in each case. This overview does not cover many of these, but the exceptions are well-documented on the FDA website ([www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpd/315.cfm](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpd/315.cfm)).

The purpose of the 510(k) is to establish that the new device is “substantially equivalent” to the predicate(s).

When a 510(k) is required, mainly for Class II devices, in addition to requiring compliance with the QSR (including design controls), a notification has to be made to the FDA at least 90 days before the company intends to introduce the device to the U.S. market.

## Assembling the 510(k) Data: Allow the Necessary Time & Follow the FDA Format

Assembling the data for a 510(k) can take many weeks.

Although there is no specific format required by law for a 510(k), the FDA publishes guidelines on what should be included. It suggests the submission should have **20 chapter headings**, even if some of these are indicated as “not applicable.”

**What it includes:** A detailed description of the device, and a comparison with one or more existing devices already on the U.S. market (predicate devices), results of bench tests, animal tests and clinical data.

**Submission fee:** \$3,404, reduced to \$1,702 for “small businesses.” The discount is available to non-U.S. companies and domestic U.S. organizations.

**FDA response time:** The FDA is required to respond to a 510(k) within 90 days, but it may seek clarification of certain aspects or require additional data, in which case, officially, the 90-day “clock” starts again.

In practice, the FDA reviewers adopt an “interactive” relationship with the submitter to (1) reduce any delays in clearing the device for sale or (2) establish that the product is not “substantially equivalent” to the selected predicate(s).

### Class III: A Process All on Its Own

With only a few exceptions, Class III devices are required to go through the PMA process.

**What it includes:** A very detailed submission must be assembled. It will include the provision of clinical data to demonstrate safety and effectiveness, with the likelihood that specific clinical studies will have to be planned and carried out in compliance with a study protocol that has been agreed by the FDA.

**Submission fee:** \$185,000, reduced to \$46,250 for companies meeting the “small business” criteria.

There is, however, an important waiver of the fee for the first PMA submitted by a company (as long as its turnover is less than \$30 million), which is very useful for start-ups with high-risk devices.

**FDA response time:** Although there is no regulatory time limit on PMA review, FDA is targeted with completing its review with 180 working days from receipt if it is approved as received, or 320 days if additional information is required.

Prior to giving approval of a device via the PMA process, the FDA may schedule an inspection of the manufacturer’s facility to check compliance with the QSR. Marketing approval will not be forthcoming until an acceptable response to any observed nonconformities has been lodged with the FDA.

### Class Distinctions

It can be seen that the difference between the marketing authorization processes for Class I, Class II, and Class III devices is considerable both in terms of time and cost.

**Classification is based on the “intended use”** of the device. It may be possible to achieve initial market clearance under a lower classification if the intended use is restricted at first to allow more rapid market access, with income from initial sales then being used to support additional claims that may push the device into a higher classification.

### Recommended Reading

The FDA website is very comprehensive. If a manufacturer seeks to establish the classification of its device, the best place to start is on the site’s “Classify Your Medical Device” page (<http://www.fda.gov/cdrh/devadvice/313.html>). ■

## Part 3: Up Close: The European Rules-Based System

In Part 1, Roger Gray of Donawa Consulting explained how device classification can play an important role in determining not only the quickest route to market, but can potentially affect which of the major markets, United States (U.S.) or Europe (EU), the product is likely to achieve first clearance for sale.

In part 2, Roger looked at classification issues in the United States in greater detail.

This article provides details on the European classification system. Roger's first words of advice: Determine device classification as early as possible.

### A Rules-Based System

The European system is "rules-based," making the manufacturer responsible for determining the classification of its own devices. Although the rules are written in a numerical sequence, they can be considered as a decision tree. The official European guideline to applying the classification rules, **MEDDEV 2.4/1** ([ec.europa.eu/enterprise/medical\\_devices/meddev/meddev\\_index\\_en.htm](http://ec.europa.eu/enterprise/medical_devices/meddev/meddev_index_en.htm)), includes a set of flowcharts to aid manufacturers in reaching the correct classification decision.

In contrast, the U.S. Food and Drug Administration (FDA) system assigns a classification to each type of medical device within three classes, where Class I is the lowest risk category and Class III the highest. A database on the FDA website allows manufacturers to determine the relevant classification of their devices.

Similar to the U.S. system, medical devices in Europe are classified in four classes, depending on the degree of perceived risk:

- **Class I:** Lowest risk
- **Class IIa:** Intermediate risk
- **Class IIb:** Higher intermediate risk
- **Class III:** Highest risk

Although active implantable devices are covered by their own directive, for the purposes of this overview, they can be considered as Class III devices.

In vitro diagnostic devices are categorized in a different manner and will be covered in a later article.

The class of a device also provides manufacturers with a choice of routes to market ("conformity assessment routes"), as will become apparent.

In common with the FDA system, increasing perception of risk brings with it an increased scrutiny prior to a device being allowed onto the European market. Essentially, under the Medical Devices Directive (MDD) (93/42/EEC), Class I devices may be CE marked in a self-declaration process, according to Annex VII of the MDD (EC Declaration of Conformity) once the manufacturer has satisfied itself that the Essential Requirements (ERs) contained in Annex I of the MDD have been met.

### A Notified Body

Third-party oversight from a **notified body** (NB) designated by one of the EU member states is necessary for Class I devices only if they are marketed as sterile devices, or if they have a measuring function. Even then, the NB activity is limited to those particular aspects of the device.

For devices in Classes IIa and IIb, involvement of an NB is mandatory, either to

(1) assess the manufacturer's quality system against the requirements of Annex II (full quality assurance, with similar requirements to ISO 13485), Annex V (production quality assurance) or Annex VI (product quality assurance); or

(2) verify that devices have been "type tested" and conform to a specified device design, Annex III (EC type examination); or

(3) to ensure that each device or batch of devices are tested before release to market, Annex IV (EC verification).

Manufacturers of Class IIa devices may also use Annex VII, as long as either Annex V or Annex VI has been additionally selected for quality system certification. In contrast, Annex VII cannot be used by manufacturers of Class IIb devices because of their higher risk.

An NB must also be involved in the CE marking process of Class III devices in two different ways:

(1) The manufacturer may choose to apply to an NB for certification of its full quality assurance system (Annex II), but must also submit a design dossier for NB review and approval (Annex II, section 4); or

(2) it can go through the type-testing process (Annex III) coupled with the EC verification process (Annex IV) or the certification of its production quality system (Annex V). This effectively means that Class III device design is subject to a formal evaluation before the product can be marketed.

### Areas of Applications

The rules-based European classification system divides devices into a number of areas of application, which are based on the level of invasiveness and duration of use. There are additional rules for “active” devices (devices whose operation depends on any source of power other than that directly generated by the human body or gravity, and which acts by converting this energy), and certain other product types, such as combination devices, contraceptives, and blood bags, plus breast implants and certain orthopedic implants (reclassified into Class III by Directives 2003/12/EC and 2005/50/EC).

**If two different rules are found to apply to a device,** then the rule resulting in the higher classification must be used. Comprehensive guidance to

application of the classification rules, including examples, is provided in MEDDEV 2.4/1.

Manufacturers should include a classification rationale within the technical documentation retained for each device type.

### Making the Complex Simple

To the uninitiated, the choice of routes through the conformity assessment system may seem bewilderingly complex, so a diagrammatic representation is often used to help manufacturers determine the options available (see Table 1 below).

In terms of timescales, if a Class I manufacturer considers compliance with the appropriate European directive at the beginning of the design process, taking the relevant ERs into account at each stage of development, the CE marking process and the automatic market clearance that goes with it can be achieved relatively quickly.

**If an NB needs to be involved, it is best to select one as early as possible** to allow time for a pre-audit visit to assess the readiness of either the manufacturer’s quality system or type-testing route to market. For Class III devices needing design dossier examination or type-testing, it is advisable to obtain timescale estimates from a number of potential NBs before making a selection. ■

**Table 1: European Conformity Assessment Routes for Medical Devices**

MDD Annex	Device Classification					
	Class I	Class I S/M*	Class IIa	Class IIb	Class III	
II plus Sec 4					√ or	
II minus Sec 4			√ or		√ or	
III					√ +	√ +
IV		√ or		√ or	√ or	√ or
V		√ or		√ or	√ or	√
VI		√		√	√	
VII	√	+ √		+ √		

\*Sterile or Measuring

## Part 4: Understanding Quality System Requirements

In Part 1, Roger Gray of Donawa Consulting explained how device classification can play an important role in determining not only the quickest route to market, but can potentially affect which of the major markets, United States (U.S.) or Europe (EU), the product is likely to achieve first clearance for sale.

The second article looked in more detail at classification issues in the United States; the third provided detail on the European classification system.

This article focuses on the quality system requirements for the United States and Europe, highlighting the major differences between the two.

### Laws or Standards?

**In the United States:** The detail of the U.S. system is set by law, with the basic **quality system (QS)** requirements for medical device manufacturers being included in Title 21 of the Code of Federal Regulations, Part 820 (21 CFR 820), known as the **quality system regulation (QSR)** or **current good manufacturing practice (cGMP)** requirements.

**In Europe:** In contrast, the European system includes an outline of the requirements in the Annexes of the medical devices directives, but the majority of the detail is described in Harmonized European Standard EN ISO 13485:2003, “Medical devices — Quality management systems — Requirements for regulatory purposes.”

### Sections & Subsections

The QSR is divided into 15 sections, whereas ISO 13485 has 8. (See Table 2 on page 10 for the section headings.) The majority of the EN ISO 13485 requirements are in section 7 of the standard, which includes subsections for design and development, purchasing, production and servicing, all of which are considered under separate sections in the QSR.

**Depending on the classification of the device, all, some, or none of the QS requirements are mandatory.**

Fortunately, the European QS requirements are similar to the U.S. QSR; however, the wording used is

sometimes different. Some of the more significant differences are shown in Table 3 (see page 11).

#### A History Lesson

EN ISO 13485 is based on the international general quality system standard ISO 9001:2000. The QSR is more similar to the previous versions of ISO 13485 and ISO 9001, as the U.S. requirements were largely aligned with the international standards in the late 1990s, before the international community agreed to rewrite ISO 9001, which was effective from 2001.

### Design Controls

**In the United States:** Design controls are not mandatory for Class I devices (see Part 2: “Up Close: U.S. FDA Classes”), with the following exceptions:

- Devices automated with computer software
- Tracheobronchial suction catheters
- Surgeons’ gloves
- Protective restraints (i.e., for limiting a patient's movements to the extent necessary for treatment, examination, or protection of the patient or others)
- Manual radionuclide applicator systems
- Radionuclide teletherapy sources

**In Europe:** No QS is necessary for Class I devices; design controls are optional for Class IIa, IIb and III devices. (See Part 3: “Up Close: The European Rules-Based System.”) For Class IIb and III devices, however, in the absence of design controls, it will be necessary for a notified body to assess a representative sample of the product in accordance with Annex III of the **medical device directive (MDD)**, in order to issue an EC-type examination certificate or to carry out the EC verification process in accordance with MDD Annex IV.

However, most companies find that following the QS approach, including design controls, provides commercial and financial advantages, as well as quality advantages and regulatory compliance. An effective QS will **minimize the chances of**

releasing nonconforming products into the marketplace and facilitate the effective handling of complaints and quality problems, should they arise.

## Other Differences

There are a number of other differences between the two systems. Table 3 (on page 11) highlights the differences from the overall approach to packaging design.

### “Management Responsibility”

The top management of a start-up company needs to have an overview of the “management responsibility” aspects of the QSR and ISO standard. In this respect, both include a need for a “quality policy” to be established. The QSR includes a requirement for “quality objectives,” but doesn’t expand on this, whereas ISO 13485 requires these to be “*established at relevant functions and levels within the organization,*” and that they must be “*measurable and consistent with the quality policy.*”

## Meeting Company Objectives and Regulatory Requirements

Depending on whether new companies have decided to focus their first marketing activities in the United States or Europe, **they should select and install a QS that meets the company’s objectives and regulatory requirements.** If this includes design controls, then clearly these particular systems or processes should be in place sufficiently early to allow manufacture of

a device for which design controls have been applied.

## The Difference Is in the Detail

Although it is perfectly achievable to have one QS that fully meets both the QSR and ISO 13485, there are specific differences that must be taken into account when developing a QS that meets both sets of requirements. **If device sale is to be extended to the other main markets,** then a **gap analysis** should be carried out to determine what must be added to the QS to allow compliance with both sets of requirements.

Emphasis may differ on certain aspects by ISO 13485 auditors or FDA QSR inspectors. For example, process validation is generally reviewed more stringently by FDA inspectors, whereas risk management will be a focus of ISO 13485 auditors.

It must also be remembered that the QS annexes of the European MDDs include particular “administrative requirements” beyond ISO 13485, so these need to be taken into account in a manufacturer’s QS.

Finally, there are guideline documents in Europe that provide non-binding guidance on certain aspects of regulatory compliance, including post-market vigilance (equivalent to 21 CFR 803, “Medical Device Reporting”), which must be written into a manufacturer’s QS. ■

**Table 2: QSR & ISO 13485 Sections**

<b>United States: 21 CFR 820</b>		<b>Europe: EN ISO 13485</b>	
<b>A</b>	General Provisions	<b>1</b>	Scope
<b>B</b>	Quality System Requirements	<b>2</b>	Normative References
<b>C</b>	Design Controls	<b>3</b>	Terms and Definitions
<b>D</b>	Document Controls	<b>4</b>	Quality Management System
<b>E</b>	Purchasing Controls	<b>5</b>	Management responsibility
<b>F</b>	Identification and Traceability	<b>6</b>	Resource Management
<b>G</b>	Production and Process Controls	<b>7</b>	Product Realization
<b>H</b>	Acceptance Activities	<b>8</b>	Measurement, Analysis and Improvement
<b>I</b>	Nonconforming Product		
<b>J</b>	Corrective and Preventive Action		
<b>K</b>	Labeling and Packaging Control		
<b>L</b>	Handling, Storage, Distribution and Installation		
<b>M</b>	Records		
<b>N</b>	Servicing		
<b>O</b>	Statistical Techniques		

**Table 3:** Comparison between QSR (21 CFR 820) and EN ISO 13485:2003

	<b>United States: QSR (21 CFR 820)</b>	<b>Europe: EN ISO 13485:2003</b>
Overall approach	Procedure-based, includes 36 requirements for documenting specific procedures	Process-based, follows ISO 9001:2000, includes 17 requirement for documenting specific procedures
Management reviews	Must ensure that the QS satisfies the 21 CFR 820 requirements, together with the manufacturer’s quality policy and objectives	Includes specific requirements for management review input and output
Human resources	All personnel must be trained to adequately perform their assigned responsibilities	Company required to determine necessary competence for personnel performing work affecting product quality (including training necessary to achieve this competence level) and effectiveness of the training must be evaluated
Specific quality records	Manufacturers must establish and maintain device master record (DMR), device history record (DHR), design history file (DHF)	Requirements for similar files as in the QSR, but uses different terminology
Design transfer	Specific requirement for procedure documenting transfer from development to production	No specific requirement
Product distribution	Records of finished device shipments must be maintained for all devices	Records of finished device shipments required only for active implantable devices; extent of traceability of other devices up to the manufacturer
Customer requirements	No specific requirement to meet anything other than regulatory requirements	Must meet customer and regulatory requirements
Risk management	No specific mention; however, effective risk analysis expected by FDA as part of design process	Output from a risk management process must be one of the design inputs
Complaints	Includes specific requirements; refers to regulations on Medical Device Reporting (21 CFR 803) and Reports of Corrections and Removals (21 CFR 806)	Includes specific requirement for authorization, if a complaint is not followed by corrective or preventive action
Labeling	Includes full set of requirements	No specific requirements; covered under process control
Packaging design and construction	Includes specific requirements	No specific requirements; covered under design control and process control

## Part 5: An Important Post-Market Requirement

In Part 1, Roger Gray of Donawa Consulting explained how device classification can play an important role in determining not only the quickest route to market, but can potentially affect which of the major markets, United States (U.S.) or Europe (EU), the product is likely to achieve first clearance for sale.

The second article looked in more detail at classification issues in the United States; the third provided detail on the European classification system; the fourth focused on quality system (QS) requirements.

This article looks at the post-market requirements in the United States and Europe.

### Terminology

It may be useful first of all to define what we mean by “post-market requirements.”

This is a term that covers **activities that manufacturers should undertake during the post-production phase**, including the proper management of adverse incidents involving one of their devices, and carrying out appropriate corrective and preventive actions related to devices that have already been sold.

Various terms are used to describe such activities, and the vocabulary itself varies between the United States and Europe.

#### In the United States

- **Medical device report (MDR):** Reporting of a qualifying adverse incident to the U.S. Food and Drug Administration (FDA).
- **Recall:** Used to describe any “removal or correction” of devices that do not meet regulatory requirements.
- **Correction:** Modification, adjustment, relabeling, destruction, or inspection (including patient monitoring) of a product without its physical removal to some other location.
- **Removal:** The physical removal of a device from its point of use to some other location for repair,

modification, adjustment, relabeling, destruction, or inspection.

- **Advisory notice:** Communication to customers advising of the need for post-market action.

#### In Europe

- **Medical devices vigilance system:** The system that applies (in Europe) to both adverse event reporting and post-market corrective action.
- **Vigilance report:** A report to a European Competent Authority providing details of an adverse incident.
- **Field safety corrective action (FSCA):** Any post-market activity that concerns devices that have already been sold, in order to reduce a risk of death or serious deterioration in the state of health.
- **Field safety notice (FSN):** Communication to customers in relation to a FSCA.

### U.S. Requirements

The actions that manufacturers must take in the United States, should there be a need to report an adverse incident or undertake other types of post-market activities, are covered by federal laws. The principal ones —

- 21 CFR Part 7: Recalls
- 21 CFR Part 803: Medical Device Reporting
- 21 CFR Part 806: Medical Devices; Reports of Corrections and Removals

### MDRs

The basic adverse event reporting requirement in the United States is that a report is required when a **manufacturer becomes aware of information that reasonably suggests that one of its marketed devices may have caused or contributed to a death or serious injury, or has malfunctioned**, and that the device or a similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. (See box, “What Is a Serious Injury?”)

In this context, “becomes aware” means when any employee of the manufacturer becomes aware of a reportable event from any information source. A “malfunction” is a failure of a device to meet its performance specifications or otherwise perform as intended; malfunctions are not reportable if they are not likely to result in death or serious injury.

Manufacturers must report using a specified format (Form FDA 3500A), although it is likely that online reporting will take over from the paper system within the next year. See the FDA Guidelines on Medical Device Reporting ([www.fda.gov/cdrh/devadvice/351.html](http://www.fda.gov/cdrh/devadvice/351.html)).

### What Is a Serious Injury?

*Serious injury* means an injury or illness that —

- is life threatening, even if temporary in nature;
- results in permanent impairment of a body function or permanent damage to a body structure; or
- necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

### Recalls

The word *recall*, when used in the context of U.S. medical device post-market activity, does not just refer to the physical removal of the product and its return to the manufacturer’s location, but also covers on-site and off-site modification, adjustment, relabeling, inspection or destruction.

Generic requirements that apply to any FDA-regulated products for the voluntary recall of items are provided in 21 CFR Part 7. Device-specific requirements for reporting corrections and removals are contained in 21 CFR 806. For example, if an action was taken to reduce a risk to health posed by a device, the correction or removal of that device is required to be reported to the FDA by the manufacturer.

Once the FDA is notified of a recall, it classifies it as Class I, II, or III to indicate the relative degree of health hazard presented by the product being

recalled, with Class I representing the highest risk (see box below, “FDA Recall Classification”).

The FDA recommends that the manufacturer develops a recall strategy that it shares with the FDA, addressing the following elements of the recall:

- **Depth of recall.** Depending on the degree of hazard and extent of distribution, the level in the distribution chain to which the recall is to extend.
- **Public warning.** The purpose of a public warning is to alert the public that a product being recalled presents a serious hazard to health. This is reserved for urgent situations where other means for preventing use of the recalled product appear inadequate.
- **Effectiveness checks.** The purpose of effectiveness checks is to verify that all consignees (at the specified recall depth) have received notification about the recall and have taken appropriate action.

See the FDA guidelines on Medical Device Recalls, Corrections and Removals ([www.fda.gov/cdrh/devadvice/51.html](http://www.fda.gov/cdrh/devadvice/51.html)).

### FDA Recall Classification

- **Class I:** Reasonable probability that the use of, or exposure to, the device will cause serious adverse health consequences or death.
- **Class II:** Use of, or exposure to, the device may cause temporary or medically reversible adverse health consequences, or where the probability of serious adverse health consequences is remote.
- **Class III:** Use of, or exposure to, the device is not likely to cause adverse health consequences.

### European Requirements

The three European medical device directives (for active implantable devices, “general” medical devices, and in vitro diagnostic devices) all include articles requiring post-market surveillance on the part of device manufacturers. All mandate that manufacturers establish systematic procedures to review experience gained from devices in the post-production phase, implement appropriate means to

apply any necessary correction, and conduct reviews of the post-production experience. In addition, they must notify the competent authorities should there be —

- any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the instructions for use which might lead to, or might have led to, the death of a patient or user or a serious deterioration in his state of health; or
- any technical or medical reason connected with the characteristics or performance of a device leading for the reasons referred to above to systematic recall of devices.

See the document, “Guidelines on a Medical Devices Vigilance System” (MEDDEV 2.12-1 rev. 5, updated April 2007) ([ec.europa.eu/enterprise/medical\\_devices/meddev/2\\_12\\_1-rev\\_5-2007-fin2.pdf](http://ec.europa.eu/enterprise/medical_devices/meddev/2_12_1-rev_5-2007-fin2.pdf)) for comprehensive guidelines on the application of the directives’ requirements for vigilance.

This document not only covers adverse incident reporting, but also the need to keep the relevant competent authorities up-to-date with any post-market actions the manufacturer may decide to take, as a result of either an adverse incident report or information from some other source, such as a service report.

Such actions are an FSCA, which may include —

- return of a medical device to the manufacturer;
- device modification;
- device exchange;
- device destruction;
- retrofit by purchaser of manufacturer’s modification or design change; and
- advice given by manufacturer regarding the use of the device.

In this context, device modification can include —

- permanent or temporary changes to the labeling or instructions for use;
- software upgrades, including those carried out by remote access;

- modification to the clinical management of patients to address a risk of death or serious deterioration in state of health related specifically to the characteristics of the device; and
- advice relating to a change in the way the device is used.

The MEDDEV document also includes a template for FSNs, which are the means of communicating the required FSCA to users.

Generic forms for initial and final reports are also included in the guidance, although many European competent authorities either have their own versions of the form or have online reporting systems.

## Conclusion

The types of adverse events that need to be reported to the regulatory authorities in the United States and Europe are very similar; the type of information to be provided is also comparable. The forms to be used have a number of significant differences; however, so separate forms will need to be used if parallel reports are required. Regulatory authorities around the globe now also exchange adverse incident and FSCA information, so reports sent to one authority will often result in enquiries from authorities in other parts of the world who want to know if suspect devices have been sold in their markets.

In addition, filing an incident or field action report with a regulatory authority may also trigger an on-site inspection to allow the authority the opportunity to assess the manufacturer’s competence in dealing with such problems effectively.

Despite an understandable reluctance on the part of manufacturers to admit any failings in design or manufacture by submitting a vigilance report, this must not delay or halt reporting, as the later discovery by a regulatory authority of information that should have been reported is likely to become a much more serious issue than making the initial report. ■

## Part 6: CEO Confidential: 14 Medical Device Myths and Realities

**In Part 1, Roger Gray of Donawa Consulting explained how device classification can play an important role in determining not only the quickest route to market, but can potentially affect which of the major markets, United States (U.S.) or Europe (EU), the product is likely to achieve first clearance for sale.**

**The second article looked in more detail at classification issues in the United States; the third provided detail on the European classification system; the fourth and fifth articles focused on quality systems and post-market requirements.**

**In this final article, Roger considers a number of popular regulatory misconceptions.**

### Introduction

Whether they lead early-phase or extremely mature companies, CEOs of medical device enterprises need to have sufficient knowledge to make informed regulatory, clinical study, and quality system decisions related to their companies and products. Unfortunately, many do not. As a result, either poor decisions are made or there is an unhealthy reliance on external support without any internal knowledge. CEOs do not need to be regulatory affairs experts in clinical affairs or quality systems; however, they should have a basic understanding of these areas.

In particular, CEOs of early-phase medical device companies need to grasp the basic concepts of design controls that apply to the products they are developing. If they lack this understanding, the wrong design decisions can have significant adverse effects on the success of the project and on the future of the company.

CEOs of more mature companies, operating under a certified quality system, have very specific responsibilities, which are not always clearly understood. These responsibilities are specified in the U.S. Quality System Regulation (QSR) (21 CFR 820) for “management with executive responsibility,” defined as “those senior employees of a manufacturer who have the authority to establish or make changes to the manufacturer’s

quality policy and quality system.” Similar responsibilities are found in the European harmonized standard for medical device quality systems, EN ISO 13485:2003, where “top management” is defined as a “person or group of people who controls an organization at the highest level.”

Sufficient regulatory, clinical study, and quality system-related knowledge will also help CEOs avoid believing and acting on incorrect assumptions that may have disastrous consequences for their companies and products. We’ll now take a look at 14 of these myths and their corresponding realities.

### Myths and Realities

**Myth: “I can meet with the FDA for a brainstorming session to identify our U.S. regulatory strategy.”**

**Reality:** The FDA is not a regulatory consultancy. The FDA is a regulatory agency that publishes regulations and guidelines. Manufacturers should read and understand these before engaging with the FDA. The FDA is willing to offer advice when a manufacturer has a strategy based on the regulations and guidelines, or to clarify any unclear points. However, meeting with the FDA to discuss aspects that are fully detailed in freely available publications is not a prudent use of the FDA’s time.

**Myth: “It’s easier to get approval in Europe than in the United States.”**

**Reality:** Although both U.S. and European regulatory systems provide risk-based market clearance routes, there are differences, and these work both ways. Some devices attract a higher risk classification in the United States; others have a higher classification in Europe. It is therefore important for manufacturers to establish the classification of their device in both of these major markets before deciding which to target first. It just may be that the United States offers a quicker route than Europe.

**Myth: “My marketing strategy will drive my regulatory strategy.”**

**Reality:** As a continuation of the previous “reality,” there may be significant differences in the time

necessary to achieve market clearance in the United States and Europe, because of, for instance, device classification or the acceptability of existing clinical data. It is therefore important to understand the full regulatory picture before making detailed marketing plans. Otherwise it is possible that the wrong target has been selected.

**Myth: “I’ve made a prototype, so now I can give it to a clinician to try it out.”**

**Reality:** The days when clinicians could decide on the suitability of prototypes for human use are long gone. Regulations in just about every country now require the use of new devices on patients to be subject to strict controls and approvals. Voluntary standard ISO 14155 describes the minimum procedural checks and safety requirements that must be achieved before use of pre-production devices on patients.

**Myth: “We don’t need design controls yet.”**

**Reality:** There are significant benefits when manufacturers control device design from the point when it moves from “concept” to “specification” (or “design input”), whether design controls are required or not. Useful guidance on the subject has been published by the FDA ([www.fda.gov/cdrh/comp/designgd.pdf](http://www.fda.gov/cdrh/comp/designgd.pdf)).

**Myth: “Software designed to European standards will be OK for the FDA.”**

**Reality:** Although the requirements for the control of software design and validation are similar between the United States and Europe, the depth of review of software documentation during market clearance can be significantly different.

For example, for Class II devices subjected to pre-market or 510(k) notification, the FDA has published two documents, “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices” ([www.fda.gov/cdrh/ode/guidance/337.pdf](http://www.fda.gov/cdrh/ode/guidance/337.pdf)) and “General Principles of Software Validation; Final Guidance for Industry and FDA Staff” ([www.fda.gov/cdrh/comp/guidance/938.html](http://www.fda.gov/cdrh/comp/guidance/938.html)). These explain in detail what software documentation is expected to be provided to allow review of the safety and effectiveness of the device.

Software developers who do not follow these guidelines during the design phase will probably find that a significant part of the software risk analysis, development, validation, and verification testing will have to be redone to satisfy the FDA, even if the device is already CE marked for sale in Europe.

**Myth: “Class I devices don’t need clinical data.”**

**Reality:** While this may often be true for the United States because Class I devices are exempt from premarket notification, the 2007 European directive revising the Active Implantable Device Directive (90/385/EEC) and the Medical Device Directive (93/42/EEC), which takes effect from March 2010, clarifies that clinical data are expected for all classes of device.

**Myth: “You can’t use clinical data gathered outside of the United States for the FDA.”**

**Reality:** Non-U.S. clinical data can be used for U.S. submissions as long as certain criteria are met, which are defined in the premarket approval (PMA) regulations 21 CFR 814.15, but is also applicable to clinical data in support of a 510(k), when needed. For example, the non-U.S. clinical study data must be applicable to the U.S. population and U.S. medical practice. The studies must be performed by clinical investigators of recognized competence and other criteria. However, having the FDA review the study protocol before it is final to ensure FDA acceptance is highly recommended. Not to do so is extremely risky with regard to the FDA acceptance of clinical study data.

**Myth: “Only the first part of the clinical study needs to be monitored.”**

**Reality:** Whenever clinical studies are conducted, whether during the pre-market stage to determine safety and effectiveness or performance, or for post-market purposes, monitoring of the study must take place, otherwise the results may be considered invalid.

**Myth: “510(k)s and PMAs must be filed by a U.S. organization.”**

**Reality:** 510(k)s and PMAs can be submitted by anyone, from any country. All that the FDA requires of non-U.S. manufacturers is that at the time of first making devices available for sale in

the United States, a “U.S. Agent” is designated. The U.S. Agent is someone, locally based, who is responsible for assisting the FDA in communications with the non-U.S. manufacturer, responding to questions concerning the company’s products that are exported or offered for export to the United States, and assisting FDA in scheduling inspections of the company. The FDA does not require the U.S. Agent to report adverse events under the Medical Device Reporting regulation (21 CFR Par 803) or submit 510(k)s or PMAs.

**Myth: “I’m just a one-person start-up – I don’t need regulatory support yet.”**

**Reality:** Even at the earliest stage in the life of a device company, good regulatory advice can be critical to its future success. Making the wrong strategic decisions early on, based on bad regulatory understanding or advice, can lead companies into blind alleys, hindering their ability to meet investor milestones and raise additional funds.

**Myth: “I’ve read the regulations. I don’t need to do all that, do I?”**

**Reality:** Yes, you do! Companies should approach regulatory compliance in a pragmatic manner. Some companies seem to think that the regulations don’t apply to them when, in fact, they do. Sometimes, a tremendous amount of energy is spent on trying to avoid compliance with a

regulation when the same energy could be used in achieving compliance. Companies should certainly avoid doing what is unnecessary, but they should not try and “get round” the regulations. Investing in the infrastructure to “do it right” will pay dividends in the long run.

**Myth: “I don’t need to understand about QA/RA. I’ve got a QA/RA manager to do that.”**

**Reality:** As mentioned in the introduction to this article, CEOs, when their companies operate under a certified quality system, have very specific responsibilities, which are not always clearly understood. Even if the company has an experienced QA/RA manager, the CEO needs to understand the “basics,” especially with regard to those aspects of U.S. and European quality system requirements that refer to “management responsibility.”

**Myth: “We don’t need to audit the CEO during our internal audits.”**

**Reality:** As covered in the previous “reality,” the CEO has specific responsibilities within certified quality systems. A further requirement of these quality systems is that all aspects of compliance with the quality system must be regularly audited, to ensure continued compliance. It follows that internal audits of responsibilities allocated to the CEO must be included. ■

## About the Authors

**Trendlines International** ([www.trendlines.com](http://www.trendlines.com)) is Israel’s premier international marketing consulting and business development firm. Trendlines consults to businesses of all sizes – from small one-person start-ups to large public companies – across a number of industries. Trendlines International is a member of The Trendlines Group.

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