
Medical Device Regulatory Practices

An International Perspective

Val Theisz



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*To my partner Günther Theisz, founder and CEO of
Certification Body Australia,
and my lovely daughter, Nadine*

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Preface

“This is a culture war.” These comments by the Food and Drug Administration (FDA) consultant Steve Grossman, reported in a November 9, 2014, article by AP Health Writer Matthew Perrone, refer to the cultural divide between the highly regulated medical device industry and the Silicon Valley tech industry “used to just bringing their products straight to the market” and for whom “any regulatory scheme that involves scrutiny and delay is alien”. The article tells the story of two Silicon Valley companies and their very different experiences with getting medical apps through the FDA regulatory hoops (1).

23andMe, a Mountain View, California, based company became the poster child for tech companies’ dysfunctional relationship with the FDA in 2013, when the company was ordered to stop selling its medical app for genetic testing. In a warning letter, the FDA said that despite “hundreds of email exchanges” the Google-backed company failed to demonstrate the effectiveness of its saliva-based kit, which claimed to tell customers if they were at risk for more than 250 health conditions.

Since then, the article said, 23andMe has brought in four new executives with experience in the drug and medical testing fields and submitted an FDA application for the first in a series of genetic health tests. The company’s CEO, Anne Wojcicki, compared the process of working in healthcare to doing business in a foreign country. “You need to understand that language and the way that they do business there almost in the same way you would going into China or India,” she said.

On the other end of the spectrum is Alivercor, a San Francisco company selling a hand-held device that attaches to a smartphone

to detect dangerous heart rhythms. Alivercor submitted its FDA application in August 2012 and received clearance four months later. The company's CEO, Euan Thomson, said tech industry people exaggerate the difficulties of regulation because they don't understand it.

But this is not just about Silicon Valley tech struggling in a highly regulated environment. It is also the story of medical technology start-ups striving to transition to financially viable businesses and that of big companies held back by ineffective internal systems and processes. Obtaining regulatory approvals in the United States and the European Union (EU), the two largest and most lucrative markets, is a sort of Darwinian make or break for developers of medical devices, including the latest medical apps for smart phones.

In my 20 years of experience working on both sides of the regulatory divide – as an EU notified body reviewer and auditor, as well as managing regulatory affairs in various medical device companies – I have seen this happening again and again. Some organizations struggle for many months trying to obtain marketing authorizations even for “me too”, lower-risk products, while others manage to breeze through with innovative, complex, high-risk products. Whilst many companies find themselves in the former category, they all aspire to be in the latter. To get there, though, it takes a thorough understanding of the terminology and processes governing the healthcare product industry.

It is my hope that this book will demystify the “alien” world of medical device regulations and help organizations get to market faster and smoother.

I finished writing the book at the end of 2014, a year that saw the enactment of major reforms of medical device regulatory regimes in China and Japan and the introduction in Europe of unannounced audits by notified bodies in the aftermath of the Poly Implant Prothèse (PIP) scandal. For many years the French company PIP, one of the world's biggest suppliers of breast implants at the time, had fraudulently used industrial silicone instead of the approved medical-grade silicone in many of its breast implants that were marketed worldwide, and it concealed this fact during the

pre-announced audits of its EU notified body. PIP breast implants were withdrawn from the market in 2010 after it came to light that they'd been deliberately manufactured with a much cheaper industrial-grade silicone and were far more prone to rupture than other breast implants.

Also in 2014, Frances Oldham Kelsey, the pharmacologist and FDA reviewer who famously refused to authorize thalidomide for the US market in 1960, celebrated her 100th birthday. Thalidomide had been used as a sedative and to reduce morning sickness in pregnant women in many countries since the late 1950s. Despite a constant and increasing pressure from the pharmaceutical company, Dr. Kelsey refused to approve the application for marketing authorization without adequate evidence that the drug was safe, a decision that prevented thousands of babies in the United States being born with crippling birth defects. In 1962 Dr. Kelsey received the President's Award for Distinguished Federal Civilian Service from President J. F. Kennedy in recognition of her "exceptional judgment in evaluating a new drug".

Such lessons are a reminder of why therapeutic goods are so highly regulated. The main role of regulatory agencies is to protect the health and well-being of patients, consumers, healthcare workers and the community at large. They strive to strike a balance between preventing unsafe or ineffective products from being distributed in the market and enabling fast access to innovative technologies that improve patients' health and quality of life.

I would like to express my gratitude to those who have reviewed and contributed valuable comments and content to sections of this book: Dr. Sean Williams, BE (Elec.) (Hons.), PhD, on design controls (Chapter 4) and configuration management (Chapter 6); Dr. Sylvia Roins, PhD Pharm., on combination products (Chapters 2 and 5); Ms. Kathy Wang, APAC Regulatory Affairs Expert, on China and Association of Southeast Asian Nations (ASEAN) regulations (Chapter 5); and Mr. Phillip Prather, BSc (Biology, Economics), MComm (Marketing), on the product launch process for medical devices (Chapter 6).

Also, this book has benefited from the many questions I had to find answers to and the challenges encountered during the course

of my work, as well as from the expertise and insights of people I have worked with and learned from in the past 20 years – too many to mention here. My thanks and appreciation goes to all of you.

Val Theisz

Reference

1. Perrone, M., Associated Press. *Silicon Valley Struggles to Speak FDA's Language*. Thu, 09/11/2014, Washington: s.n., 2014.

Introduction

This book is intended to serve as a reference for professionals in the medical device industry, in particular those seeking to learn from practical examples and case studies. Medical devices, like pharmaceuticals, are highly regulated and the bar is raised constantly as patients and consumers expect the best-quality healthcare and safe and effective medical technologies. Obtaining marketing authorization is the first major hurdle that med techs need to overcome in their pursuit of commercial success. In today's competitive environment a few months delay in time to market can cost millions of dollars in missed opportunities.

Start-up companies in particular may find that bringing innovative medical technologies to market is daunting and fraught with difficulty. Growing and larger companies may also struggle to meet product launch deadlines and keep compliance costs under control. A product recall can tarnish the reputation of a medical device company within weeks. However, the cost of development and regulatory compliance can be significantly reduced, and delivery of new medical devices that are safe and effective to patients around the world can be accelerated, if sponsors and manufacturers understand the regulatory requirements and processes involved.

In addition to the expertise required to design and manufacture a medical device, a manufacturer needs to have an understanding of how to test and clinically evaluate medical devices, how to identify and address the root causes of adverse events and device malfunctions and, in general, how to apply regulatory requirements throughout the product life cycle.

Many problems faced by medical device manufacturers are a result of a lack of understanding of the intent rather than the letter of regulations, poor business processes or deficient implementation

of regulatory controls. It is a common misconception, for instance, that to be compliant one must have lots of procedures, forms and templates. Nothing is further from the truth. Too much bureaucracy, overly complicated and opaque processes, a lack of structure, clarity and visibility throughout the business – all these have a negative impact on the ability to obtain marketing approvals quickly and to maintain regulatory compliance. Worse still, overly complicated systems and processes are prone to frequent non-conformities and are difficult, time-consuming and expensive to maintain. Robust regulatory controls co-exist a lot better with streamlined, agile and effective systems and processes.

Another frequently encountered issue is an insular approach to applications for marketing authorizations. Often regulatory professionals receive engineering documents full of technical jargon, which they then “translate” into submission documentation that an external reviewer can understand without requiring substantial prior product knowledge. This is then usually repeated for every country or region where marketing authorizations are sought. After going through multiple and exhausting cycles of questions and answers with the various authorities lessons learned are lost and mistakes repeated, efforts duplicated and deadlines missed. Regulatory requirements are taken out of context, misunderstood or misinterpreted, and bureaucracy takes over, sucking the life out of projects and bringing down teams’ motivation and energy.

In this book the reader will find examples and practical recommendations on how to implement statutory requirements applicable throughout the life cycle of a medical device: design and development, clinical evaluation, manufacturing and the post-market phase. Although the case studies are fictional, they are based on real-world scenarios and depict common errors. The proposed solutions are pragmatic, tried and tested in both large and small medical device companies, but there is no intention to suggest they are the best or the only solutions.

The book has two parts:

Part 1, comprised of three chapters, gives an overview of the international regulatory framework for medical devices and introduces basic concepts and terminology (Chapter 1); covers

compliance with requirements for safety and effectiveness of medical devices (Chapter 2); and provides recommendations for the content and structure of technical documentation required by regulations (Chapter 3).

Part 2, also comprised of three chapters, goes into more detail, outlying the regulatory controls applicable in each of the main phases of a medical device's life cycle: the pre-market phase (Chapter 4); regulatory submissions, approvals and registrations (Chapter 5); and the post-market phase (Chapter 6).

The major established markets – the European Union, the United States, Australia, Canada and Japan – have center stage, but significant developments in international harmonization and emerging markets such as China, ASEAN countries and Brazil are mentioned as well. Various national and regional regulations are presented as they apply to major topics such as compliance with safety and effectiveness requirements, and in alignment with the typical medical device life cycle: the pre-market phase, regulatory approvals and registrations, and the post-market phase. The reason behind choosing such a structure is that in reality this is how regulatory knowledge is used and applied (see Fig. I.1).

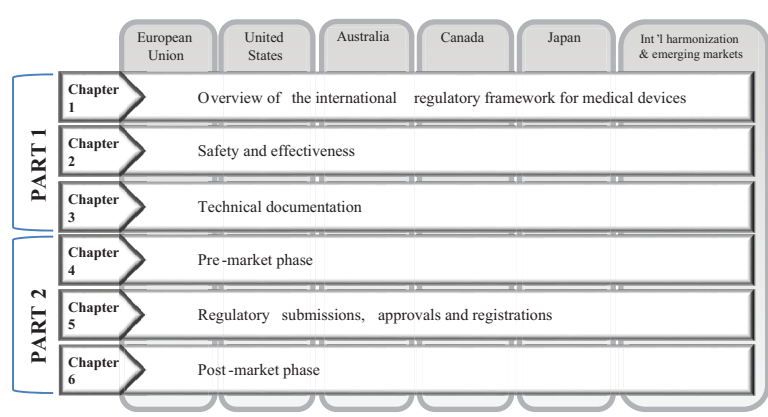


Figure I.1 This book's structure: rows represent chapters, and columns represent regulatory jurisdictions covered.

Table I.1 Orientation guide

Steps	What to do	Useful reading
Step 1	Confirm that the product is indeed a medical device.	Chapter 1, Section 1.4, "Medical Devices"; Section 1.6, "Components, Spare Parts, Accessories, Device Families, Kits, Systems and Procedure Packs"
Step 2	Determine the risk classification of the medical device.	Chapter 1, Section 1.5, "Risk-Based Classification"
Step 3	Identify the applicable regulatory controls in the target market(s).	Chapter 1, Section 1.7, "Risk-Based Approach for Regulatory Controls and Conformity Assessment"
Step 4	Implement regulatory controls during the pre-market phase.	Chapter 2, "Safety and Effectiveness"; Chapter 3, "Technical Documentation"; Chapter 4, "Pre-Market Phase"
Step 5	Submit regulatory application(s) and obtain marketing approval(s) in the target market(s).	Chapter 5, "Regulatory Submissions, Approvals and Registrations"
Step 6	Maintain compliance until product obsolescence.	Chapter 6, "Post-Market Phase"

Part 1 should be read by anyone involved in developing, manufacturing or marketing medical devices, and especially by novices in the regulatory affairs space, as it explains relevant terminology and the basics required to understand medical device regulations.

Part 2 chapters can be used as a reference according to the reader's needs. For instance, a company developing, manufacturing and marketing medical devices would need to know about the regulatory controls applicable in all phases of a product's life cycle, but an importer may only need to concentrate on the regulatory submission and post-market phases.

For those new to medical device regulations, asking the question, What do I need to do and where do I even start?, here is, in a nutshell, a quick orientation guide (Table I.1).

There was no intention to reproduce entire texts of regulations and guidelines in this book, as these are already publicly available from the official websites of relevant agencies, but some of the

most important definitions and excerpts have been included for convenience, along with explanations and discussions.

Moreover, every effort has been made to ensure that the latest information is used in writing of this book; however, regulations and guidelines are often being revised and some information may be already outdated at the time of publishing. By providing detailed references the reader can refer directly to the information source to confirm the latest status.

