Evaluation of the medical device approval lag between the United States and the European Union

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Abstract

The United States is the world leader in development and manufacture of medical devices. Even with this leadership position, there is evidence that the US is often not the first country to have new medical technology approved for patient use. In many cases, the European Union is the first geographic region to approve a new medical technology for sale, with US approval coming later. This delay in approval of new devices between the EU and US is referred to as the “device lag.” However, the extent or history of this lag over time and for different device types has not been examined.

This thesis evaluated if a device approval lag has developed between US and EU at any time over the past 20 years and whether a device lag continues to exist today. US and EU regulatory approval data for 135 medical devices in three innovative medical device segments were collected and analyzed to evaluate the extent and history of the approval lag between the European Union and the United States.

The collected approval data revealed a consistent approval lag between the US and EU in each of the three medical device segments explored in this study. Throughout the entire 20+ years of study, the United States had an average approval lag to the European Union in each of the three device segments, and an average lag for all devices of 21 months or almost 2 years ($H_0: \mu = 0, p = 8.2E-12$). Furthermore, the device lag in these three segments has grown in recent years. These data are striking because they show, perhaps for the first time, that an approval lag has existed for medical devices between the US and EU for the past 20 years – since the beginning of the pan-European device regulatory system in the mid-1990s.

The device lag is a useful metric for comparing the attractiveness of two markets for medical technology and may signal important changes in the medical technology industry. Furthermore, the existence of a persistent device approval lag in the United States may have significant implications for patients and their caregivers.

Thesis Supervisors: Ernst Berndt Ph.D. and Howard Golub M.D., Ph.D.
Dedication

To my wife, Rodi, for her endless love, support and encouragement.

To my children, Olivia and William, for all of their distractions and for reminding me of the best things in life.

To my parents, Dileep and Jeanne, and sister, Maya, for their constant love, advice and guidance throughout my life.
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INTRODUCTION AND BACKGROUND:

What is a Medical Device?

There are over 500,000 medical devices available in the world today [6, 70]. Devices range from everyday objects such as Band-Aids® and contact lenses to lifesaving technologies such as pacemakers and MRI scanners to pain alleviating artificial knees and spine implants that improve the quality of life for patients and their families.

Medical technology is all around us and medical devices are one of the oldest, if not original, forms of medical therapy used by humans. In fact, records indicate that Egyptians performed bladder catheterizations using metal tubes in 3000 BCE [17]. The availability of medical technology has exploded over the past century, contributing significantly to people’s quality of life. For example, medical technology has played an important and unique role in the increase in human life expectancy. Along with advances in surgical technique and drugs, medical technology helped create an increase in life expectancy of three years from 1980-2000 in the US, [31] while the EU saw an increase of six years from 1980 to 2006. [6, 70]

A medical device is a mechanical device used for treating, diagnosing or monitoring a medical condition in humans or animals. Another good definition is that provided by the California Healthcare Institute (CHI), the industry association for California’s biomedical industry: “The medical device sector encompasses all mechanical means for improving or diagnosing human health and mobility. Medical devices can be further sorted into two general categories: instruments, which includes scalpels, lasers, and heart monitors, and implants, which includes artificial hips or heart valves or products that are surgically placed in a patient’s body to perform a function that the body cannot provide or adequately perform for itself.” [22]

Medical devices go by many names. Because they are often complex, advanced instruments, medical devices are often also referred to as medical technology or “medtech”. As an example, the medical device industry is typically referred to as the medtech industry. Additionally, devices are called medical equipment, instruments, tools or supplies as well.
Today, medical devices continue to be a very important part of the armamentarium used by doctors, nurses and other professionals to provide healthcare to patients around the world. As medical technology is used to diagnose conditions and deliver treatment, medical devices are subject to regulations and review prior to being available for use. To ensure that patients and their caregivers have access to safe, well-made medical technology that improves their condition, devices are regulated the world over by various bodies, each with common themes and processes but with distinct differences.
**United States Definition**

In the United States, medical technology is regulated by the US Food and Drug Administration (FDA). FDA determines the need to regulate a device using the following definition (Section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act [21 U.S.C. 321]). A device is:

"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is –

(1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."
European Union Definition

In Europe, the European Commission (EC) defines the regulatory requirements for medical technology throughout the European Union (EU). The EC considers a medical device to be (Council Directive 93/42/EEC):

"Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means”

Furthermore and distinct from FDA, the EC specifies in separate legislation an active implantable medical device as the following (Council Directive 90/385/EEC):

“‘active implantable medical device’ means any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure”

Where an active medical device is:

“‘active medical device’ means any medical device relying for its functioning on a source of electrical energy or any source of power other than that directly generated by the human body or gravity”
Medtech Industry Overview

*United States*

Medical technology is a major industry in the United States, one in which the US is currently the world leader [37]. The US is one of the originators of modern medical technology and has nurtured many device companies from small operations (what today would be called start-ups) to large, multinational firms. In fact, the US is home to most of the leading medical device companies as well as an impressive number of small to midsize medtech companies. Seven out of the world's top ten device manufacturers are based in the US [65]. According to a 2010 report, the US is home to 1,023 active medical device companies, each working on creating new medical technology for patients in need [53].

The economic impact of the medtech industry on the US is significant. In 2006, the US medtech industry employed over 357,000 workers and paid $21.5 billion in salaries [63]. This amounts to an above-average nationwide annual salary of $60,000 for medtech workers [63]. Nationally, almost 1.6 million jobs are created by the medtech industry, as each direct medtech job generates 4.5 additional jobs across the US [63]. Finally, the device industry shipped $123 billion worth of products worldwide in 2006 [63].

The US is also the largest market for medical technology, estimated at $94.9 billion in 2010 or roughly 1/3 of the estimated $290 billion global market in 2009 [58, 65]. Finally, the United States is the third largest country in the world, having a population of 307 million in mid-2009 [68].
Europe

Europe is also home to many innovative medical device companies. The medtech industry is an important part of the EU economy and her 27 member states.

The medical technology industry in Europe generated annual sales of approximately €64 billion in 2005 ($77.3 billion in 2005), putting almost 6%, or €3.8 billion ($4.6 billion in 2005) back into R&D [6, 70]. It employed almost 435,000 people in 2005 and had almost 11,000 companies in its ranks [5, 6, 70]. As in the US, the medtech industry is a major piece of the economy, generating substantial R&D investments and creating many well-paying high tech jobs.

The EU market for medical technology is the second largest globally, behind that of the US [66]. The size of the EU market for medical devices was estimated to be approximately $70 billion in 2010 ($85.6 billion in 2010), or 25% of the global market [72]. Three of the five largest medical device markets in the world are in the EU: Germany, France and the UK [66]. Also, the EU population was approximately 500 million in 2009 – over 50% larger than that of the United States [13]. This makes the EU the largest market by population for medical technology in the world.
Medical Technology in Both Markets

At first blush, it appears that the EU has a larger medtech industry than the US by some measures. However, one potential discrepancy between the economic numbers for the US and EU may lie in how a medical device company is defined, and the subsequent effects of this definition on other numbers. The stated 11,000 medical device companies in the EU most likely contains suppliers, contract research and manufacturing vendors and other organizations that do not directly produce medical devices [31]. In comparison, if you expand the US count to include these types of companies, the FDA has over 16,000 medical device companies registered in the United States [31].

Medical devices have been and will continue to be a vital part of providing safe and effective care to patients. Moreover, it is interesting to note that medical devices constituted only 4.2% of the EU healthcare expenditure over the three-year period 2005-07 [70] and 5.5% of that in the US in 2005 [63]. Because healthcare is an important topic that will surely always be on the agenda for policymakers the world over, the exceptional economic and therapeutic value that medical devices provide to patients and the healthcare system in general is quite salient.
The Role of Device Regulations

Devices are used to diagnose conditions and deliver treatment to patients in need, often when there is no other alternative. They must be safe, reliable, function as intended and provide the therapy that they claim. Government regulations on medical technology provide this assurance.

Regulation provides a benefit for both patients and the medtech industry. It gives patients and their doctors confidence that the therapies will be effective and safe to use. In addition, regulations create a level playing field for all devices. Without a system of standards and regulations against which all devices can be compared, products of questionable utility could become available, which is exactly the situation that caused the United States Congress to pass the Medical Device Amendments in 1976 [54].

There are a number of regulatory agencies around the world, each with a different process for reviewing devices. In Australia, the Therapeutic Goods Agency (TGA) is the regulatory body. Canada’s Ministry of Health refers to itself as Health Canada. China created the State Food and Drug Administration, P.R. China or SFDA to administer its regulatory laws for medical devices. In fact, many of these regulatory systems are based on the US and its FDA [15]. One such regulatory system is that of the European Union [15]. The EU system had the benefit of being developed well after FDA and could not only learn from their experience but also build upon the solid foundation laid by FDA. Notably, the EU system was designed to be more efficient than that of the US as well as to be an economic driver for the EU [15]. Indeed, the Europeans recognized the competitive advantage that a streamlined regulatory system could create for the European medical technology market and created their regulatory framework in that spirit [7, 15].

Both the US and the EU rely on medical device companies to contribute to the well-being of their citizens and economies. Both markets are interested in having cutting-edge devices available for physicians and their patients. However, the two economic areas have taken different approaches to medtech regulation and to encouraging the introduction of new medical technology within their borders.
United States Medical Device Regulations

History

Food and drugs started being regulated in the United States at the federal level just over a century ago. In 1906, Congress passed the Food and Drugs Act [42, 54]. This Act gave the US Bureau of Chemistry the ability to ensure food and drugs in the US were safe. Realizing the importance of safe products, Congress created the Food and Drug Administration (FDA) in 1930 [54]. In 1938, the Federal Food, Drug, and Cosmetic Act (FD&C Act) was enacted [42]. This legislation largely covered food and drugs but also gave the government limited authority over medical devices. Under the FD&C Act, FDA could regulate marketed medical devices and remove them from the market if they were deemed to be unsafe or ineffective. But at the same time FDA did not have authority to review devices before being placed on the market. [54, 67]

As technology advanced, it became apparent that medical devices required their own regulations. The Drug Amendments of 1962 established premarket approval of the safety and efficacy of all new drugs [54, 67]. Devices were originally included in this 1962 legislation, but were removed from the final bill [54]. Over the next 14 years, medical device regulation was discussed by Congress and endorsed by several Presidents, leading to the formation of the Cooper Committee. The Committee’s 1970 report discussed the need to regulate devices differently from drugs and recommended the tiered risk-classification system that is in use today [54, 67]. In 1976, these recommendations were incorporated into the Medical Device Amendments (MDA) to the FD&C Act, creating separate regulatory pathways for devices and drugs in the United States and marking the beginning of pre-market review of devices by FDA [30, 54, 67].

The MDA marked the beginning of more comprehensive device regulation in the US. Additional medical device regulations have been enacted in the past 35 years, but the MDA still form the foundation of medical device regulations in the United States.
In 1990, the Safe Medical Devices Act (SMDA) required adverse events to be reported to FDA, mandated manufacturers to conduct post-market surveillance on permanently implanted devices whose failure might cause serious harm or death, and authorized FDA to order device recalls [42, 54]. The FDA Modernization Act in 1997 included “least burdensome” measures to streamline device reviews and regulate device advertising [30, 41, 54]. Finally, the Medical Device User Fee and Modernization Act (MDUFMA) in 2002 imposed user fees for device evaluations by FDA but also placed performance criteria for review times on FDA [21, 54]. MDUFMA also established The Office of Combination Products to oversee products that fall into multiple jurisdictions within FDA, such as drug-eluting stents (a device and drug combination product) [54].

MDUFMA was reauthorized in 2007 (MDUFMA II) and is up for renewal in 2012 by the 112th Congress, contingent on FDA performance [15].

MDUFMA reauthorization in 2012 is part of the larger current discussion regarding medical technology regulation in the US. In the late 2000s, several high-profile device recalls and lawsuits drew criticism that FDA was not doing its job and that the device review process in the US was not stringent enough [15, 57, 69]. Changes to the device review process, and its two main pathways are currently under evaluation and are being discussed at several levels of the government [2, 15, 67].

Process and Risk Classifications

Medical devices in the US are reviewed by the Center for Devices and Radiological Health (CDRH), one of three Centers at FDA. As specified in the 1976 Medical Device Amendments, devices are organized into three classes based on potential risk, with the regulatory control increasing from Class I to III. There are two typical pathways for device premarket review: Premarket Notification or 510(k) and Premarket Approval or PMA. In general, Class I devices are exempt from both 510(k) and PMA, most Class II devices require 510(k) and Class III devices require PMA [11, 30].
Class I (low risk) – Most are exempt from 510(k) and PMA but are subject to General Controls (i.e. Good Manufacturing Practices, manufacturer registration with FDA, proper labeling). Examples include bandages, surgical instruments and tongue depressors.

Class II (moderate risk) – Most require General Controls and Special Controls (i.e. 510(k) Premarket Notification). Examples include X-ray machines, surgical needles/suture and fluid infusion pumps.

Class III (high risk) – Require General Controls and PMA. Class III devices are typically new and therefore insufficient safety and efficacy information exists to use General and Special Controls alone. Examples include pacemakers, artificial spinal discs and coronary stents.

There are four main pathways to gain regulatory allowance to sell a medical device in the United States, with PMA and 510(k) being the most common [50, 51]. The other, less-used pathways are the Humanitarian Device Exemption (HDE) and Product Development Protocol (PDP) [18, 48]. Full descriptions of these four pathways are found in Appendix A.
European Union Medical Device Regulations

History

The history of common European Union device regulation under the EU New Approach began in 1990 with the enactment of the Active Implantable Medical Device Directive (AIMDD) by the European Commission [5]. The European Commission (EC) is the executive body of the EU and is responsible for proposing legislation, including EU directives, upholding EU treaties and economic policies and running the day-to-day business of the EU [12]. The EC was set up in the 1950s along with the creation of the European Union itself and European Economic Community or “common market” [12]. The goal of the EU is to create a single market to guarantee freedom of movement of people, goods, services, and capital among member states [73].

Following the enactment of the AIMDD, the EC introduced the Medical Device Directive (MDD) in 1993. This directive further codified the pan-European process for regulation of all medical devices. The last of the three directives regarding medical technology was introduced in 1998. The In Vitro Diagnostic Medical Devices Directive (IVDMD) covers in vitro means used to diagnose and monitor medical conditions [3, 5, 10].

Before the 1990s and the passage of these three Directives, device regulatory efforts varied from country to country across the EU [15].

Since their original introduction there have been several technical revisions to the Directives, the latest of which was enacted in 2007 and came into force in March 2010 [5]. In addition, the EC is currently considering a recast of the Directives in order to strengthen the system. Revisions under consideration include measures to address concerns that the current system does not offer uniform public health protection across the EU, that expertise may not exist to properly evaluate emerging medical technology and that the current legal framework is fragmented and varies across the member states [5, 35, 56].

The European Union system for medical technology regulation was in fact modeled after the US regulatory system [15]. But its creators realized the impact that regulation has on investment and economic growth, and recognized the advantage that the EU would attain by offering an
improved system over that of the US [5, 15]. Indeed, the European Commission states that “Enhancing competitiveness is one of the key objectives of the European Commission. Accordingly, our services are in permanent contact with industry associations in order to verify what can be done to facilitate the activities of enterprises and to ensure that the high growth rates to be observed in the medical devices sector can be maintained [7].”

Process

The European system is much more decentralized than that of the US. The three Directives outline the approval system for the entire EU, but the actual regulatory process takes place at the country level. Each EU member country creates a Competent Authority (CA), which is responsible for ensuring compliance with the Directives, adverse event reporting and removing unsafe devices from the market. The CA also is responsible for authorizing private organizations known as Notified Bodies (NB) to conduct the actual premarket reviews and conformity assessments of devices. If the NB determines a device is in conformance with the appropriate Directive, the device is granted a “Conformité Européenne” (CE) mark [41, 71]. The CE mark is affixed to the device packaging and allows a medical device to be legally sold and distributed across the entire EU market [10, 26, 41].

There are a total of 74 Notified Bodies that are authorized to approve medical devices in the EU [10]. A device company may choose any one of these Bodies to review a device, with the NB determining the device performance information required (e.g., benchtop testing, clinical data, etc.) in order to grant a CE mark and approve a device, based on the device classification [3]. The Notified Body is paid by the device manufacturer to perform the conformance assessment, a potential conflict of interest.

This diverse system creates a system of checks and balances between the various CAs and NBs throughout the EU, ensuring that the MDD spirit of timeliness and consistency is upheld [10, 15].
Once a device is properly CE marked, it may be legally sold throughout the entire EU, European Economic Area (EEA) and Switzerland without any additional approval or certification. However, the national competent authorities may request device registration in their country or have specific language requirements for the device labeling. [71]

**Risk Classifications**

The EU system organizes devices into four classes – I, Ila, IIb and III, with III being the highest risk devices. As in the US, product classification as well as level of control for a device increases with the perceived risk associated with the device [4]. Several factors are considered when classifying a device in the EU, including:

- “how long the device is intended to be in continuous use
- whether or not the device is invasive or surgically invasive
- whether the device is implantable or active
- whether or not the device contains a substance, which in its own right is considered to be a medicinal substance and has action ancillary to that of the device [4].”

All devices except for Class I require a Notified Body to assess compliance with the appropriate Directive and issue a CE mark prior to sale [4].

The EU risk classes are the following:

**Class I (low risk)** – Must meet and self-declare compliance with Essential Requirements of the Directive. Sterile products and devices with a measuring function must use a Notified Body rather than self-declaration

**Class Ila (lower moderate risk)** – Must comply with provisions and Essential Requirements of the Directive. Notified Body must then perform conformity assessment of device and may conduct quality assurance testing or audit of quality assurance system
**Class IIb (higher moderate risk)** – Must meet Class Ila requirements, as well as have full quality assurance system audit

**Class III (high risk)** – Must meet Class IIb requirements as well as submit device design dossier (a complete technical file detailing all device testing, manufacturing and clinical data) to Notified Body for conformance assessment

Depending on the device classification, the manufacturer would either self-declare conformity with the Directive or have a Notified Body assess Directive conformance, perform quality assurance audits and review a design dossier, as required. Following certification of the device by the Notified Body, the device may be CE marked and placed on the market [3, 71].
Comparison of US and EU Regulatory Systems

Both the US and the EU rely on medical device companies to contribute to the well-being of their citizens and their economies. Both markets are interested in having useful, cutting-edge devices available for physicians and their patients. However, the two economic areas have taken different approaches to medtech regulation and to encourage the introduction of new medical technology within their borders.

One major difference is the organizational structure of each system. The US system is centralized, with the FDA implementing all regulatory guidance, actions and reviews before allowing a device to be sold. The EU system is more diverse, with the European Commission creating all regulatory guidance and each member state authorizing private companies to conduct reviews of medical technology. These private bodies are then allowed to perform regulatory reviews for the entire EU prior to a device being placed on the market.

Moreover, the most discussed and fundamental difference between the US and EU medtech regulations is the criteria for approval of higher-risk devices. Devices in the EU must be proven to be both safe and to perform in a manner consistent with the manufacturer’s intended use (i.e., must have truth in advertising) prior to being allowed on the EU market [26]. In the US, devices must be proven to be both safe and effective before being allowed on the US market, often requiring much larger clinical data sets and trial sizes than those needed for EU approval [26].

Regulatory review times are different as well. For example, the EU has considerably shorter review times for approval to sell a medical device than the US [10, 26, 31]. The decentralized nature of the EU process makes it difficult for performance metrics across all 74 Notified Bodies to be determined, unlike FDA which publishes performance reports. However, competition among Notified Bodies creates incentives for the NBs to have enough resources to meet the 90-day review time for Class III medical devices, as laid out in the EU regulations [15]. In comparison, FDA’s approval database indicates that Pre-Market Approvals or PMAs (the longer, more complex pathway) had average review times of 27 months in FY 2010, while 510(k)s had average review times of 4.5 months in FY 2010 [15].
Not surprisingly, these differences between the regulatory systems have also translated to a larger number of devices being approved in Europe to treat patients [10]. Despite this difference, a 2011 study [10] showed the rate of medical device recalls for serious issues between 2005-2009 to be essentially identical between the US and EU, even with the different approval criteria, shorter review times and larger number of approved devices in the EU.
ISSUE: DEVICE APPROVAL LAG

The United States is the world leader in development and manufacture of medical technology and medical devices [37]. In fact, medical devices are one of the few areas in which the United States runs a trade surplus [37]. Even with this leadership position, there is evidence [15, 26, 31] that the US is often not the first country to have new medical technology approved for patient use. In many cases, the European Union is the first area to approve a new medical technology for sale, with US approval coming later. This delay in approval of new devices between the EU and US is referred to as the “device lag.”

With the United States being the leader in creating medical technology, the lagging devices are often invented, developed and manufactured in the US – in many cases with initial scientific funding and tax breaks provided by Federal and State governments.

The results of a 2010 industry survey [31] indicate that over the past 10 years a device lag has emerged. This survey indicates that a decade ago, medtech companies would first look to the US for approval; whereas survey respondents indicate that there is now an average lag of almost two years [31]. However, the extent or history of this lag over time and for different device types has not been examined.

Interestingly, an approval lag between the US and EU is not unprecedented. In the late 1970s and 1980s a drug lag between the US and EU existed [15]. This US-EU drug approval lag is well documented [24, 61] as is the presumed role of regulatory agencies in contributing to the lag [1, 20, 32]. In fact, Congress created the Prescription Drug User Fee Act (PDUFA) in 1992 in part as a mechanism to address and reduce the drug lag [15, 34].

A similar user fee system was extended to medical devices in 2002 through the Medical Device User Fee and Modernization Act (MDUFMA) due to its success on the drug side, although a device approval lag was not established prior to MDUFMA introduction [15, 54]. However, given the recognized existence of a drug lag it is plausible that similar forces and circumstances have led to the existence of a device lag as well.
While differences in regulatory environments between the two markets may primarily drive the device lag, it is recognized that company strategy also plays a role. Device manufacturers may contribute to a lag by choosing not to seek approval in a certain market for a variety of reasons, including regulatory requirements, physician preferences, legal issues, licensing agreements, pricing/reimbursement precedents (e.g., “reference pricing”) and competing products.

Finally, the device lag only pertains to the difference in approval dates between different areas — it does not describe device availability in those areas. It is recognized that device approval and availability are not the same thing. Just because a device is approved for sale does not mean that that device is made available to patients and physicians for their use. Numerous factors such as reimbursement coverage, sales and distribution arrangements and physician training play a role in the actual availability of a device after it has been approved.

In this thesis I do not aim to parse out the complex factors behind the lag and determine a root cause but instead take the first step by establishing and documenting the presence and extent of a device approval lag between the US and EU. My objective is to examine (1) if a device approval lag has developed between the US and EU over the past 20 years, (2) whether it has varied over that time, and (3) if it is similar for different device types.

Changes to both the US and EU medical device regulatory systems are currently under consideration [5, 67, 75]. As the two largest global systems for medical device regulation, the US and EU systems are often compared — especially when revisions to regulations are being discussed. As such, the device approval lag is a useful metric to compare the attractiveness and performance of the two systems in relation to each other.

A 2011 study demonstrated that the US and EU have an identical risk of medical device recall for serious issues and adverse events [10]. Given this fact, there are many obvious and serious effects resulting from a device lag. Patients and their doctors have delayed approval for cutting-edge technology and procedures. Payors also do not have these less-invasive and potentially less costly technologies approved and must continue to cover older procedures. Finally, the lag may signal that device manufacturers view the US market with less importance, perhaps moving jobs, manufacturing and the creative equity that goes along with them to
newer, more efficient markets. While the costs of these consequences are difficult to quantify, they are nevertheless important factors to take into account as both the US and EU consider changes to their device regulatory processes.

On the other hand, it is important to mention that the device lag may have positive effects as well. In some cases, a later approval in the US may prevent a technology that has undesirable side-effects from prematurely entering the US market. While it is unfortunate that any patient in another country may be harmed by this new technology, this initial device experience yields invaluable information on the performance and reliability of a device.
HYPOTHESIS

A device approval lag has developed between US and EU over the past 20 years and continues to exist today.

In examining the hypothesis, the following questions were considered for several medical device segments:

1. When did the approval lag begin in each of the device segments?
2. Was the EU always first to approve a device, i.e. was there ever a reverse lag in which the EU lagged the US?
3. If there is a lag, has it stayed steady over the study period? Did it ever go away?
4. If there is a lag, is it similar for different device segments?
5. If there is a lag, are there any common patterns between device segments?
6. If there is a lag, was it impacted by industry events?

The study data were compiled and analyzed with these questions in mind and these questions are addressed in the Results and Discussion sections.
METHODOLOGY

To examine the device approval lag, US and EU approval dates for particular medical devices were compiled and analyzed.

The method for calculating the lag time between a device’s EU and US approval date is not complex: simply compare the date of US approval to the CE mark grant date in the EU. For this study, a US date occurring after an EU date represents a positive lag. Therefore, to determine the approval lag between the EU and US for a particular device, the EU date was subtracted from the US date.

However, determining approval dates is not as clear cut. US approval data are readily available, as the FDA maintains all approval records and makes certain details, such as filing date and approval/clearance date, available for all PMA and 510(k) devices on the FDA website (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Databases/default.htm).

In the EU, approval data are neither collected nor maintained at a central body or location, due to the decentralized nature of the EU device approval process [8, 10, 46]. There is no requirement in the medical device directives for approval dates to be published or appear in device labeling [8]. A Notified Body (NB) does determine compliance with the device directives but all information exchanged between a device manufacturer and a NB is confidential and not made public [8]. Finally, the approval date does appear on the certificate of conformity that must be drawn up before a CE mark can be applied to a device, but these certificates are not publically available either [8].

Fortunately, companies themselves typically disclose some details regarding EU approvals. For EU approval dates, I used company press releases, SEC filings and secondary sources such as analyst and industry reports.

For US approval dates, I used FDA approval data in addition to the sources listed for EU dates.
If a device was approved in one market but not yet in the other, one of two methods was used to estimate an approval date for lag calculations. If a projected approval date was available from the company or secondary sources, 1) that estimated date was used. However, in most cases a projected date was not available and 2) May 1, 2011 was used as the approval date for lag calculations.

Finally, devices that were available in one of the studied markets but will never be available in the other market were not included in the approval lag analysis. For example, if a company announced its intent not to seek regulatory approval for a device in a particular market, the device was not used in the analysis. To the best of my knowledge, all devices included in the lag analysis have been or will potentially be submitted for regulatory approval and no announcements to the contrary have been made publicly.

As previously discussed on page 24, to my knowledge no comprehensive examination of the evolution of the device lag is available. Therefore, this work set out to evaluate devices over approximately the last 20 years in three high-profile device segments that had seen dramatic growth over that timeframe. These three devices were chosen as a proxy for the entire medical technology market because of their rapid adoption and impact on the practice of medicine. The 20 year period was chosen because this corresponds with the introduction of the EU medical device directives.

For each segment, all devices approved in either the US or EU during the study timeframe were included in the study. If the device was known to be approved in a particular market, but complete approval information could not be determined, the device was not included in the final analysis. In all, data on 135 devices were analyzed to evaluate the approval lag between the US and EU markets.

In order to keep the comparison more straightforward, all devices used in the study were Class III devices in both markets at the time of approval – subject to the PMA route in the US and
likely requiring a full design dossier in the EU. This allowed for a cleaner comparison of the data across the markets as well as across device segments.

Class III devices were chosen because they represent major, new device types that are fundamentally different than those currently available and therefore without predicate. In comparison, Class II devices can vary substantially in terms of risk and accordingly the 510(k) and Class IIa/b regulatory processes can also vary, both between the US and EU as well as within each economic area. Using only Class III devices in the study helped to mitigate variability and inconsistency that could have potentially been introduced by using lower risk class devices.

In this 20 year timeframe, I was able to identify three segments in which a radical, game-changing device was introduced to the market. These three devices had widespread adoption, led to continued innovation and have heralded growth in the practice of medicine in each of the segments. In addition, these devices have each led to rapidly expanded treatment options and availability for patients. These devices are:

1. Coronary Stents
2. Implantable Cardioverter Defibrillators
3. Spinal Fusion Cages (and the spine market)

Indeed, two of these devices (coronary stents and ICDs) were cited by D. Bruce Burlington, M.D., the former director of Center for Devices and Radiological Health at FDA, as “breakthrough devices,” stating that their approvals marked significant accomplishments of CDRH during his tenure [43].
Coronary Stents

Coronary stents are expandable scaffolds that prop open arteries in the heart and are placed through minimally invasive means. They were a follow-on improvement to coronary angioplasty, which was introduced in the late 1970s and early 1980s. Introduced in the early 1990s, stents quickly became standard-of-care because they increased the chance of the treated artery remaining open and not collapsing after the angioplasty procedure. The first stent was approved in the United States in 1993, with the second stent being approved in 1994.

Coronary stents have seen rapid growth and development since their introduction, with both start-ups and the largest global device firms being involved throughout their history. In fact, coronary angioplasty and later stents are largely responsible for the growth in the field of interventional cardiology.

In the initial decade of their use, it was not uncommon for successive generation stent systems to be approved and introduced each year. Stents have gone from being simple bare-metal coils or meshwork to more sophisticated bare-metal stents (BMS) that provide more reliable results and are easier to implant. BMS then led to the development of drug-eluting stents (DES), which incorporate drugs that elute from the stent to keep the vessel from re-narrowing after stent placement. The latest advance in stent technology is constructs that are fully absorbable into the body after they have accomplished their job.
Implantable Cardioverter Defibrillators

Implantable Cardioverter Defibrillators (ICDs) are electronic devices placed in the body to monitor the heart and shock it back to a normal rhythm if it is beating irregularly. ICDs are particularly effective for treating sudden cardiac arrest (SCA), in which the heart stops beating normally and frequently leads to death [23]. Similar to pacemakers in appearance and implantation, these devices were first approved in the US in 1985, but it was not until the mid-1990s that they were approved in the US for their current indications and implantation method [40]. ICDs have experienced rapid development and product introduction, becoming smaller, more powerful and better at detecting irregular heart rhythms. Before the advent of ICD technology, patients at risk for sudden cardiac arrest had no real preventative options [33, 74].

Similar to coronary stents, companies both large and small have played a role in advancing ICD therapy over the past 20+ years. ICDs have played a role in the expansion of the electrophysiology medical specialty and also helped lead to the development of cardiac resynchronization therapy (CRT), a similar therapy that helps a weak heart to function better by coordinating heart rhythm[28, 29]. CRTs are also sometimes equipped to shock the heart back into normal rhythm, like an ICD.
Interbody Fusion Cages, Dynamic Stabilization and Motion Preservation Spine Devices

As of 2011, the spine market is the least developed of the three device segments included in this study, but like the others has rapidly grown and evolved over the past 20 years.

Interbody fusion cages, dynamic stabilization devices and motion preservation devices represent the innovative spine technology introduced in the modern spine market, beginning approximately 20 years ago.

The modern history of spine device technology begins with interbody cages. First approved in the US in 1993, threaded interbody fusion cages revolutionized spinal fusion procedures—taking success rates from 56% to 93% in one study [59, 60]. Interbody cages are hollow screw-like devices that during a fusion procedure are filled with bone graft and screwed into adjacent vertebrae. The purpose of spinal cages is to secure vertebrae together and promote bone growth or “fusion” between them. Before cages, spinal fusion was a classic, invasive surgical procedure that had changed little since its introduction in the 1940 and 50s [59, 60]. Cages allowed a fusion procedure to become less invasive and traumatic.

Before cages, the spine market was largely ignored by the major orthopaedic companies, with only a few smaller players making spine devices [27]. When spinal cages were introduced in the early 1990s, they were rapidly adopted and made spine the fastest growing segment in orthopaedics [27]. Cages were compared to stents both in their growth projections and similarities as less-invasive, disruptive technologies revolutionizing current treatment [27, 55]. As a result of this growth, the large orthopaedic device companies quickly began to pay more attention to the spine segment. Indeed, the two small companies that split the spinal cage market were both acquired by major orthopaedic companies [27].

Interbody fusion cages led the spine revolution but unfortunately were not a panacea. Fusion is a far from perfect solution to back pain because it permanently ends motion at the vertebrae where it is performed, changing biomechanics and potentially leading to pain at neighboring areas of the spine.
A more elegant solution to spine degenerative disease is to support the spine and alleviate pain, while still allowing motion. Following the approval of interbody cages, other spinal devices began to be introduced that stabilized the spine but also allowed movement. Devices using this approach were termed “dynamic stabilization” devices [25, 44]. During the study period, a number of dynamic stabilization devices were developed and tested, with many being approved.

Another approach that allows the spine to move involves implants that recapitulate the natural function of the spine. These approaches are called “motion preservation.” Examples of motion preservation devices include artificial discs, nucleus replacement and annulus repair devices [25, 45]. Several motion preservation spine devices were approved during the study period as well.

Spine surgery is often undertaken to alleviate pain, which is a subjective end point that requires longer follow-up to prove utility of a procedure than other devices that provide an immediate result, such as coronary stents. As a result, the development timeline is longer and spine technology does not evolve as quickly as many other devices. Therefore the spine market is less settled than the other markets in the study, with the superior approach and technology not yet understood.

The spine segment has nevertheless seen incredible growth and rapid introduction of new technologies over the past 20 years. However, in order to obtain a complete picture of the approval lag in the spine area over the past 20 years, interbody fusion cages, dynamic stabilization and motion preservation devices were included in the data set.
RESULTS

Data were compiled, analyzed and charted using Microsoft Excel 2007. All calculations were performed using the standard arithmetic and statistical functions available in Microsoft Excel 2007.

In all, US and EU regulatory approval data for 135 Class III devices in the coronary stent, ICD and spine markets were analyzed to evaluate the approval lag between the European Union and the United States. For calculation purposes, a positive lag was defined as an US approval at a date after an EU approval (i.e. Lag = US approval date - EU approval date).

An overall picture of the lag, followed by results for each device segment is below.

Approval Lag Overview

The total average approval lag for all devices in the study was 21.3 months (Table 1 and Figure 1). Again, a positive lag indicates a later approval in the United States. This means that over the approximate 20 year period if this study, patients and physicians in the United States had to wait an average of almost two years longer than their counterparts in the Europe for these 135 devices to be approved.

A total of 34 devices in the full data set of 135 devices were approved in the EU but not yet approved in the US. Approval dates for these devices in the US were estimated using the method previously described on page 29. Excluding these 34 devices, the average approval lag for the remaining 101 devices with complete approval data was 13.8 months, with a median of 7.1 months.

An independent one-sample t-test of the hypothesis $H_0: \mu = 0$ was conducted on the full data set of 135 devices. The two-sided $p$ value of 8.23E-12 clearly rejects the null hypothesis and therefore the average device approval lag between the US and EU is significantly greater than zero.
Data for 135 Class III devices: 52 Coronary Stents, 54 ICDs, 29 Spine devices approved between Sept '88 and Jun '14 (projected). Lag = US approval date - EU approval date

Figure 1: Device approval lag in US and EU for three device segments (1988 - 2014). Positive lag = US lag; Negative lag = EU lag. All average and median lags over the study period were US lags.

For the three device segments evaluated, spine devices had the highest average lag (55 months) over the study period, with coronary stents having an average lag of 17 months and implantable cardioverter defibrillators (ICDs) having the smallest average lag (7 months) over the approximate 20 year period (Table 1 and Figure 1).

Excluding the devices for which US approval dates were estimated, coronary stents had an average lag of 14.4 months, ICDs had an average lag of 6.3 months and spine devices had an average lag of 45.3 months over the 20+ years studied.
<table>
<thead>
<tr>
<th>Device Type</th>
<th>No. Products Studied</th>
<th>Average Lag (mo.)</th>
<th>Market with Lag</th>
<th>Time Period Studied</th>
<th>Lag Range (mo.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Stents</td>
<td>52</td>
<td>17.2</td>
<td>US</td>
<td>6/90 – 6/12</td>
<td>0 – 87.2</td>
</tr>
<tr>
<td>Implantable Cardioverter Defibrillators</td>
<td>54</td>
<td>7.2</td>
<td>US</td>
<td>9/88 – 9/11</td>
<td>-5.0 – 79.4</td>
</tr>
<tr>
<td>Spine Devices</td>
<td>29</td>
<td>55.0</td>
<td>US</td>
<td>9/93 – 6/14</td>
<td>-4.1 – 236.4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>135</strong></td>
<td><strong>21.3</strong></td>
<td><strong>US – all 3</strong></td>
<td><strong>9/88 – 6/14</strong></td>
<td><strong>-5.0 – 236.4</strong></td>
</tr>
</tbody>
</table>

Table 1: Device approval lag summary. Over the approximate 20 year study period, the US market lagged the EU market for approval of these 135 devices, having an average approval lag of at least 7 months. Future dates were projected.

**Comments on Overall Device Approval Lag**

Over the 20+ years of study, an approval lag was observed in each of the three device segments. Of course, the approval lags for each device segment varied over the period of study, as the range values in Table 1 indicate. However, in comparing the lag data across the three device segments, a general pattern of three distinct lag periods was observed for the devices included in the study (described below and in Figure 2). Interestingly, because the three markets each had an innovative, game-changing device initially approved at roughly the same time, each of the markets experienced these lag periods over approximately the same date ranges, as given below in parentheses:

First Generation Lag (1993-1996): For the devices in the study, the time between approval in the EU and the US for the first generation was characterized by a significant US approval lag. Although the spine market did not exhibit a strong first-generation lag compared to the succeeding period, it did nevertheless exhibit a large 1st generation lag for the initial cage devices. It could also be argued that spine market during the study period consisted of a series of first-generation lags given the newness of the segment and the multiple innovative device types that were approved over the period.
The 1\textsuperscript{st} generation lag period is likely the result of the difference in approval requirements between the two markets (i.e. safety and efficacy in the US vs. safety and intended function in the EU) – only magnified for these new types of devices. For our study period, the first generation lags occurred over the approximate years 1993-1996 (US approval dates).

**Middle Lag (1997-2008):** Following the first-generation, the approval lag between the US and EU decreased and normalized, with both markets having similar technologies approved in closer timing. For our study period, the middle lags occurred over the approximate years 1997-2008 (US approval dates).

**Recent Lag (2009-2014):** Over the more recent years of 2009 to 2014 the approval lag has grown. It is not known whether this is 3\textsuperscript{rd} lag period is typical of all devices after 15-20 years on the market or if outside factors have caused the recent uptick in approval lags across the three device segments. Coronary stents did not exhibit as strong a recent lag, likely due to the use of May 1, 2011 as the US approval date for investigational stent systems, per the study methodology. For our study period, the recent lags occurred over the years 2009-2014 (US approval dates).

![Figure 2: Average approval lags during each of the three lag periods identified in the study: First Generation Lag, Middle Lag and Recent Lag](image-url)
Outside of the three distinct lag periods noted over the lifetimes of the devices in the study, there were two other observations:

**Device Issues:** If a safety issue with a device arose, an approval lag for that device type was typically observed. A clear example of this lag is provided by later-generation drug eluting stents (DES). After the possibility of late stent thrombosis (ST) with the two US approved DES was revealed around May 2005 [9, 19], approval of successive DES systems slowed in the US, while DES systems continued to receive CE mark. Subsequent understanding of the issue led to approval for these next DES in the US, but after 2-3 years of lag.

**Lost Generations:** Lost generation devices are available in the EU but may never be approved in the US. As technology advances, lost generation devices are at risk of being leapfrogged by newer device technology before they are approved in the US. For that reason, device companies may choose not to seek US regulatory approval due to potential obsolescence of these devices. As such, this generation of more advanced technology is “lost” to US patients and their doctors even though available in the EU.

Lost generations were observed in each of the three markets, with several of these devices having been on the EU market for many years (Table 2). None of the lost generation devices identified in this study have been removed from the EU market for regulatory reasons. In total, 17 potential lost generation devices were identified with an average lag of almost 6 years. However, two examples had an approval lag of over 16 years and counting (Table 2).

| Device            | Segment | EU approval date | US lag (as of 5/1/11) | Notes:                                                                 
|-------------------|---------|------------------|-----------------------|------------------------------------------------------------------------
<p>| Cypher Select     | Stent   | Mar-04           | 87 mo.                |                                                                         |
| Cypher Select     | Stent   | Aug-06           | 58 mo.                |                                                                         |
| Plus              |         |                  |                       |                                                                         |
| Endeavor          | Stent   | Oct-07           | 44 mo.                |                                                                         |
| Resolute          |         |                  |                       |                                                                         |
| PRESILLION        | Stent   | Mar-08           | 39 mo.                |                                                                         |
| PROMUS Element    | Stent   | Oct-09           | 19 mo.                | Confirmed lost generation – Company instead releasing newer PROMUS Element Plus version in June 2012 (estimated) |</p>
<table>
<thead>
<tr>
<th>Device</th>
<th>Segment</th>
<th>EU approval date</th>
<th>US lag (as of 5/1/11)</th>
<th>Notes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Stent Lost Gen. Lag</td>
<td></td>
<td></td>
<td>49 mo. or 4.1 years</td>
<td></td>
</tr>
<tr>
<td>AnalyST Accel</td>
<td>ICD</td>
<td>Nov-08</td>
<td>30 mo.</td>
<td></td>
</tr>
<tr>
<td>Coflex Interlaminal Implant</td>
<td>Spine</td>
<td>Jun-94</td>
<td>206 mo.</td>
<td></td>
</tr>
<tr>
<td>Dynesys</td>
<td>Spine</td>
<td>Jan-95</td>
<td>199 mo.</td>
<td>Projected approval date 2014 after PMA advisory panel ‘no’ vote in Nov. 2009, but company may not release</td>
</tr>
<tr>
<td>Mobi-C Cervical Disc</td>
<td>Spine</td>
<td>Jun-04</td>
<td>84 mo.</td>
<td></td>
</tr>
<tr>
<td>ACADIA</td>
<td>Spine</td>
<td>Sep-06</td>
<td>56 mo.</td>
<td></td>
</tr>
<tr>
<td>Nflex</td>
<td>Spine</td>
<td>Sep-06</td>
<td>56 mo.</td>
<td></td>
</tr>
<tr>
<td>Perc. Dynamic Stabilization</td>
<td>Spine</td>
<td>Nov-06</td>
<td>54 mo.</td>
<td></td>
</tr>
<tr>
<td>(PDS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCI</td>
<td>Spine</td>
<td>Dec-06</td>
<td>54 mo.</td>
<td></td>
</tr>
<tr>
<td>Coflex F</td>
<td>Spine</td>
<td>Dec-06</td>
<td>53 mo.</td>
<td></td>
</tr>
<tr>
<td>PercuDyn</td>
<td>Spine</td>
<td>Apr-07</td>
<td>49 mo.</td>
<td></td>
</tr>
<tr>
<td>Superion ISS</td>
<td>Spine</td>
<td>Jun-07</td>
<td>48 mo.</td>
<td></td>
</tr>
<tr>
<td>Superion Intraspinous</td>
<td>Spine</td>
<td>Jun-07</td>
<td>48 mo.</td>
<td></td>
</tr>
<tr>
<td>Average Spine Lost Gen. Lag</td>
<td></td>
<td></td>
<td>83 mo. or 6.9 years</td>
<td></td>
</tr>
<tr>
<td>Total Average Lag</td>
<td></td>
<td></td>
<td>70 months or 5.8 years</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Lost generation devices approved for use in the EU but for which US approval may not be sought. Confirmed lost generation devices were not included in the approval lag calculations, but were included in Table 2.
Coronary Stent Approval Lag

To examine the coronary stent approval lag, approval data for 52 coronary stent systems were collected and the lag between the date of CE mark and US approval was calculated for each device. The approval period examined was 22 years – June 1990 to June 2012, with future approvals estimated as previously described.

The two initially approved stents and their corresponding first generation lags are shown in Figures 3 and 6. Following US approval of these first generation stents in 1993-94, the coronary stent approval lag remained at an average of 13.5 months from 1997-2007. After the late stent thrombosis (ST) concern with DES was resolved [9, 19, 47], several next generation DES systems were approved in 2008 after an average lag of 30.4 months – over 2.5 years (Figure 4, 2008 data). Omitting the 2008 DES approval data from lag calculations because of the ST issue, the years 2009-2012 had an average lag of 14.5 months (Figure 3).

The approval lag was always positive for coronary stents systems (Figures 3 and 4) meaning that the US lagged the EU in approval for each of the 52 stents included in the study. Figure 4 plots the average annualized data for the stent segment over the study period. In the United States,
an average of 2.6 stents was approved per year with an overall average lag of 17.2 months over the study period, including the 2008 DES approvals (Figure 4).

Figure 4: Annual approval count and lag for coronary stents. An average of 2.6 stents was approved per year over the study period.

Figure 5 is a histogram of the approval lag for all 52 coronary stents. US approval dates were estimated for 12 of the 52 total stent systems, as highlighted in Figure 5.
Data for 52 coronary stents approved between Jun '90 and Jun '12 (future approvals estimated). Any projected future approvals included in the analysis are shown in the upper portion of each bar separately from actual approvals.

Figure 5: Histogram of the coronary stent approval lag. The darker portions of the frequency bars indicate stents for which the US approval date was estimated because actual US approval has not yet occurred.

Figure 6 plots the approval history of all 52 coronary stent systems in both the US and the EU over the 22 year study period. The two first generation lags, the additional US approval lag caused by stent thrombosis concerns with DES and the potential lost generation stent technologies are highlighted in Figure 6 as well.

Comments on Coronary Stent Approval Lag

At first glance, it appears that following the first generation average lag of 44 months and omitting the 2008 data, the coronary stent lag remained relatively constant at approximately one year over the entire history of the coronary stent to date (Figure 3).

However, the high number of stents in the study recently EU approved yet still investigational in the US skew the lag data in 2011, artificially lowering the average lag over 2009-2012 (Figures 3, 5 and 6). In this study, 12 investigational stents use projected US approval dates. Six of these...
stents were approved in the EU in the past 14 months. Rather than omitting these newer-generation stents from the study, an understated projected US approval date was used but with the consequence of moving the approval lag in recent years downward. The estimated approval dates are understated because they occur earlier than the actual future approval dates. Therefore, the recent stent lag is likely higher than the reported 14.5 months.

The first generation DES systems each had a lag of approximately one year (12.2 months for Cypher in 2003 and 14.2 months for Taxus in 2004). It is interesting that this one year approval lag is exactly that expected for all coronary stents during these years (Figure 3). It has been noted [26] that the 12-month lag in US approval of drug eluting stent technology is a prime example of the substantial difference in the speed of interventional cardiology device introduction between the US and EU. While this is true, the approval lag for DES was not at all an isolated example (although a well-publicized one), as the data show that all stents over the entire history of the modality have been subject to the approximate one year average lag.
Coronary Stent Approval History in US and EU

Figure 6: European and US approval history for all 52 coronary stent systems included in the study. The 1st generation and potential lost generation devices are highlighted, as well as the period of increased approval lag during DES late stent thrombosis concerns.
ICD Approval Lag

For implantable cardioverter defibrillators, approval data for 54 products were collected and the approval lag between the date of CE mark and US approval was calculated for each device. The approval period examined was September 1988 to September 2011, with future approvals estimated as previously described.

Two ICD devices experienced significant first generation lags in the US early 1995 (with an average lag of 48 months), as shown in Figures 7 and 8. Following approval of these first generation devices, the ICD approval lag decreased to an average of 3.5 months for the middle period from 1996-2008. This lag of 3.5 months was the lowest average lag observed over any period in the study.

![ICD Approval Lag between US and EU chart]

**Figure 7:** Approval lag data for all 54 ICD systems

For the recent period, beginning in 2009 and continuing to September 2011 (estimated), the average approval lag for ICDs rose 360% to 12.6 months.

Figure 8 plots the average annualized data for the ICD segment over the study period. The approval lag for ICDs systems was occasionally negative over the period of study (Figures 7 and
meaning that the US was ahead of the EU in approval at these times. Over the 23 years examined for ICDs, the EU had an average approval lag to the US in three years as shown in Figure 8. In the United States, 3.2 ICDs were approved per year on average with an overall average lag over the 23 year study period of 7.2 months.

![Average ICD Approval Lag by Year](image)

**Figure 8:** Annual approval count and lag for ICD systems. An average of 3.2 ICDs was approved per year over the study period.

**Figure 9** is a histogram of the approval lag for all 54 ICD systems. US approval dates were estimated for 4 of the 54 total ICD systems, as highlighted in Figure 9.
Figure 9: Histogram of the ICD approval lag. The darker portions of the frequency bars indicate ICDs for which the US approval date was estimated because actual US approval has not yet occurred.

Figure 10 plots the entire approval history of all 54 ICD systems in both the US and the EU over the study period and highlights the two devices with a first generation lag and the potential lost generation ICD that had a 30 month lag as of May 1, 2011 (Table 2).

Comments on ICD Approval Lag

During the early part (1996-1999) of the middle lag period for ICDs there are several comments in company press releases applauding FDA for the speed and transparency in approving their ICDs and for decreasing the long approval times for ICDs [14, 39, 62]. Interestingly, these approvals and press announcements correspond exactly with industry criticism of long FDA review times and the passage of the FDA Modernization Act of 1997, a major goal of which was to accelerate device reviews in the US [30, 54]. Given the high 1st generation lag for ICDs that occurred just prior to the FDA Modernization Act, it makes sense that these devices would be
high on the list for accelerated reviews. This precedent of expedited reviews may also explain why the ICD segment has historically had a low approval lag following the 1st generation.

Also during this middle lag period, there were several well-publicized ICD recalls beginning in early 2005 [64]. However, these recalls did not appear to cause an additional approval lag for the entire segment similar to the one observed for DES. This is presumably because the recalls were focused largely on one manufacturer, Guidant, and not on ICD devices in general, as was the case with DES. Guidant, however, did not have any ICD devices approved in the US until early 2008 likely as a result.

As in the case of coronary stents, the recent ICD lag period beginning in 2009 saw an increase to 12.6 months even with four investigational ICDs and their understated estimated future approval dates included in the analysis (Figures 7, 9 and 10).

Finally, given the relatively low lag between the EU and US for ICDs over the study period, the three years with a negative lag (Figure 8) are not surprising.
Figure 10: European and US approval history for all 54 ICD systems included in the study. The 1st generation and potential lost generation devices are highlighted.
Spine Approval Lag

The spine market was the third market examined. To examine the approval lag over 21 years, approval data for 29 spine devices were collected and the lag between the date of CE mark and US approval was calculated for each device. The approval period examined was September 1993 to June 2014 (projected), with future approvals estimated as previously described.

Several device types that were approved during the study period were included in the spine market lag analysis. The two initially approved cages and their corresponding first generation lags (average 1st generation lag of 35 months for the two) are shown in Figures 11 and 14. Following US approval of these initial cages in late 1996, the spine market approval lag remained at an average of 37.5 months during the middle lag years from 1997-2008.

For the recent period, beginning in 2009 and continuing to June 2014 (estimated), the average approval lag in spine rose 350% to 130.9 months.

![Spine Approval Lag between US and EU](image)

Data for 29 spine devices approved between Sept '93 and Jun '14 (future approvals estimated). Lag = US approval date - EU approval date. Positive lag = US lag, Negative lag = EU lag. Average lag from 1997-2008 = 37.5 months. Average lag from 2009-2014 = 130.9 months.

Figure 11: Approval lag data for all 29 spine devices

The approval lag in the spine segment was negative only once during the study period – in 2002 (Figures 11 and 12). Figure 12 plots the average annualized data for spine over the study period.
period. In the United States, an average of 1.5 spine devices was approved each year with an overall average lag of 55 months over the 21 year study period.

Figure 12: Annual approval count and lag for spine devices. An average of 1.5 spine devices was approved per year over the study period.

Figure 13 is a histogram of the approval lag for all 29 spine devices. US approval dates were estimated for 18 of the 29 total ICD systems, as highlighted in Figure 13.
Data for 29 spine devices approved between Sept '93 and Jun '14 (future approvals estimated). Any projected future approvals are shown in the upper portion of the bar separately from actual approvals.

Figure 13: Histogram of the spine approval lag. The darker portions of the frequency bars indicate spine devices for which the US approval date was estimated because actual US approval has not yet occurred.

Figure 14 plots the entire approval history of all 29 spine systems in both the US and the EU over the study period. The two cage devices with a first generation lag and the 11 potential lost generation spine technologies, with an average lag of almost 7 years (Table 2), are highlighted in Figure 14 as well.

**Comments on Spine Approval Lag**

Similar to coronary stents and ICDs, the lag for the recent period beginning in 2009 saw a large increase even with estimated approval dates for 18 investigational products included in the analysis (Figures 11, 13 and 14).

In addition, while the spine market is less mature and contains many more technologies than the coronary stent or ICD markets, the approval history of the market still yields useful
information on the approval lag between the US and EU, given the number of innovative
technologies that were introduced over the study period.
Spine Approval History in US and EU

Data for 29 spine devices approved between Sept '93 and Jun '14 (future approvals estimated)

Figure 14: European and US approval history for all 29 spine systems included in the study. The 1st generation and numerous potential lost generation devices are highlighted.
OVERALL DISCUSSION

The EU and US approval data collected demonstrate that an approval lag has always existed and continues to exist for the coronary stents, ICDs and spine devices examined in this study. Over the entire 20+ years of study, the United States had an average approval lag to the European Union in each of the three device segments, with an average lag for all devices of 21 months or almost 2 years.

Of course, the lag in each device segment varied over the 20+ years and there were instances in which the EU lagged the US in medical technology approval (a reverse lag), but these cases were rare. In the cumulative 56 years of US approvals studied (stents=20 years of data, ICD=17 years of data, spine=19 years of data), the US lagged the EU in 52 of those years, with the US having earlier average approvals in only four of those years. (Figures 4, 8, 12)

Furthermore, the data indicate that the US approval lag has grown in recent years (2009-2014) – dramatically in the cases of ICDs and spine (Figure 2). In each of the three device segments, the recent lag has grown, even though the use of estimated dates for unapproved devices artificially lowered the recent lag numbers. This is especially the case for coronary stents, with estimated approval dates for 12 investigational devices, and spine with estimated dates for 18 investigational devices.

The recent lags for the three segments range from 12.6 months for ICDs to 130.9 months (almost 11 years) for spine as shown in Figure 2. The recent lags for both spine and ICD have both grown by over 350% from the previous middle lag periods. Perhaps most striking though is the ICD recent jump because the middle lag for this technology was by far the smallest of all, at only 3.5 months. Users of ICD technology went from a lag of only a few months to over a year – a lag similar to that for their interventional cardiology colleagues.

Also interesting, European approval for the devices in the study has been relatively consistent throughout the entire 20+ year study period, following the initial 1st generation approvals. This is especially true for coronary stents and ICDs. Over the study period, the slope of European approval data for stents in Figure 6 as well as that for ICD approval data in Figure 10 are both
surprisingly constant. As the spine market has not developed as quickly as the other two segments, the EU spine approval history in Figure 14 has three distinct slopes over the 20 years as new types of spine technologies were introduced. On the other hand, over the study period US approvals were not as consistent in any of the three device segments.
IMPLICATIONS

1) The device approval lag has existed for at least the past 20 years, but has grown recently:

The most striking conclusion from these data is the history and longevity of the approval lag. Indeed, a lag has been present for the entire lifetime of each of these devices. One might speculate that a lag would be present briefly during the initial 1st generation and subside after that time, but in these three examples the lag has persisted for the last 20+ years.

Other reports [15, 26, 31] have remarked on the presence of a device approval lag in the 2000s. But no other studies have shown the level or longevity of the lag over a longer time period or over the course of a device’s lifetime. Those familiar with the medtech industry may have had a gut feel or anecdotal evidence of a lag based on certain case examples, but few could have guessed the pervasiveness or resilience of the actual approval lag between the US and EU for the devices in this study.

Furthermore, in recent years the approval lag appears to have grown in each device segment included in the study, with substantial increases observed in the ICD and spine markets.

2) Some lagging medical technologies may be lost to the US forever:

The study identified several technologies that have been approved in the EU for many years but are yet to be approved in the US (Table 2). These technologies may never be approved and would then be completely lost to the US market.

Alternately, lost generation technology may eventually be approved in the US, but not with the same frequency as in the EU. Instead, the technology may be held up and combined with other new technologies, and not approved as soon as it is developed.

The actual costs of the approval lag are difficult to estimate, but it unfortunately appears as though patients and their caregivers bear the strongest consequences of the lag – lack of access to new and potentially game-changing therapies. Payors may also suffer a consequence of an
approval lag, by not having newer, less-invasive and potentially less-costly procedures to help offset rising healthcare costs.

Also affecting patient care, a potential result of the lost generation and lack of availability of the newest devices is a divergence in the manner in which medicine is practiced in the US versus the EU. Without the latest medical technologies approved for use, US physicians are unable to learn advanced procedures and keep current on the most up to date therapies for their patients.

3) The lag is a useful metric for monitoring trends in the medtech industry:

The approval lag is a good barometer of the attractiveness of the US market for medical technology. However, it is not in and of itself a cause of device approval delay. The US lag is controlled by two forces – FDA regulations and by company decisions on when to seek US approval, although the exact role of each depends on the circumstance.

Whatever the predominant cause of the lag, a growing lag signals that US regulations are becoming more stringent or that medical device makers view the US as less important globally. In either case, a lag in most instances is not favorable for patients in the United States and could portend a loss of the medtech industry’s innovative edge in the United States. Similarly, US physicians may be at risk of losing their command of the practice of advanced medicine to clinicians in the same developing countries to which the US medtech industry may be losing ground in innovation.

Policy makers should familiarize themselves with the medtech approval lag and be mindful of recent trends in the lag when considering regulatory changes. A more stringent regulatory environment would likely have the side-effect of promoting the device approval lag in the US. Interestingly, recent reports [15, 57] indicate that FDA has become more rigorous in device reviews over the past two years, a timeframe that corresponds with the growing lag observed over the recent study period beginning in 2009.
In addition, as a useful metric of US attractiveness, the lag should be monitored for meaningful changes. The approval lag is a good way to keep a finger on the pulse of the medtech industry. In fact, a number of recent studies already indicate that the US advantage in medical technology is eroding [15, 16, 38]. Going forward, attention to the lag may help reveal and elucidate the latest device approval trends in markets outside of the US.

4) Emerging markets may impact approval lag in US:

One major trend that may impact the extent of the approval lag is the emergence of new markets for medical technology. These new markets have large populations with growing access to medical care and can be extremely nimble in developing their healthcare facilities and systems. As an example, these new markets may craft their regulatory systems to encourage healthcare investment and new technology introduction, just as the EU did in the early 1990s [7, 15].

One can imagine these new markets learning from the EU’s experience in creating device regulation based on the US system. These new markets will have the advantage of learning not only from the US but also from the experiences of the EU and its success in encouraging medical technology investment in the EU market area [7, 15]. As a result, medical device manufacturers may view these large and developing markets with greater enthusiasm, and choose to seek approval in these emerging areas ahead of the US.

Indeed, a recent study [36] reveals that device makers view emerging markets the greatest opportunity for medtech growth, but as having the most difficult regulatory systems. Furthermore, the study found that 68 percent of surveyed companies plan to enter international markets for the first time in 2011 [36]. If these developing countries revamp their regulatory systems to be more collaborative and transparent with industry, investment will surely grow even faster. Undoubtedly, the United States would be the biggest loser if medtech resources and investment begin move into these new markets as a result.
5) The device approval lag will likely continue in the future:

Given the number of devices that are approved in the EU but remain investigational in the US and the recent trend toward a longer lag, it appears as though the approval lag will continue into the future. The addition of more stringent device regulatory requirements in the US will also likely add to the approval lag, assuming that the EU does not radically change its system.

Furthermore, as new markets open and entire new populations have access to medical technology, the US market may become a less significant market. If other markets become more attractive and device approval is sought earlier in these markets, a new lag between the US and developing markets may emerge, giving the US approval lags on multiple fronts.

In addition, as new markets emerge, they may craft their regulatory systems to encourage development and new technology introduction, following the EU’s lead. If the United States becomes a less important market and earlier medical technology introduction shifts to these developing markets, the US lag may grow.

Finally, as knowledge of a device approval lag grows, it may begin to affect device approval and investment in the United States. Decision makers may alter their strategy simply because of the presence of a lag. This could potentially lead to a vicious cycle in which the lag itself creates further lag.
LIMITATIONS

1) This study only evaluates the lag in approval dates with the purpose of an apples-to-apples comparison of device regulatory approval between the US and EU. However, device availability to clinicians and patients can differ from approval date for a variety of reasons (such as reimbursement or company strategy). Furthermore, actual availability dates are extremely difficult to obtain. To eliminate the potential bias that may be introduced by evaluating availability dates, I focused only the legal right to market a device and did not attempt to compare actual product availability dates between the two markets. I believe that this is the proper place to start, by evaluating regulatory approval and not introducing the potential bias that company or reimbursement decisions may create.

Furthermore, an approval lag does not necessarily mean that device availability also lags between the US and EU. For example, device manufacturers may not make a device available as soon as it is approved in the EU, instead waiting for US approval before launching in both markets. However, it would be interesting to examine if this lag carries over to device availability. Indeed, the availability lag may be more pronounced than the approval lag due to the additional step of reimbursement approval in the two markets. It is also possible that a lag in device availability between the US and EU is small or nonexistent given the many factors besides reimbursement that are involved. Comprehensive availability data are likely extremely difficult to obtain, but an interesting follow-on to this study would be to examine if the approval lag carries over to device availability.

2) Devices were certainly missed. Because the EU does not publish a list of approved devices, there is no way to determine if all devices approved in the EU in these three device categories over the study period were included in my analysis. The PMA listings were reviewed for completeness on the US side, but this would not reveal devices that were approved in the EU and not the US. Therefore, my study may underestimate the
US lag because some devices approved in the EU but not yet or never to be approved (the “lost generation”) in the US were likely excluded from the study.

3) Only Class III devices were used. The lag is likely most extreme for these device types because of the length of their review processes. However as discussed on pages 29 and 30, using these devices gives the most consistent picture of the lag will show the largest extent of the device lag. A further study could be conducted on 510(k) devices to determine if the approval lag carries over to that pathway.

4) Only three devices/segments were evaluated. Ideally, all device approvals (or perhaps just PMAs) during the 20+ year period would be compared between the US and EU to attain a complete view of all of medical technology. However, these three segments were chosen because of the pace of device introduction and their rapid growth over the study period, serving as a limited proxy of the entire medtech market.

5) The spine analysis was not simply one device as was the case for the others, but nevertheless gave a picture of a rapidly emerging device segment during the past 20 years – albeit not as robust as the data for the other markets, especially given the smallest sample size of 29.

6) Using May 1, 2011 as an estimated approval date for unapproved devices skews the data. If more accurate projected approval data could be collected then more correct future lags could be predicted. The approval lag estimates are likely lower than actual.

7) Only the US and EU markets were compared in this study. An interesting follow-on to this study would be to evaluate the state of the medical device lag in Japan, currently the third largest market for medical technology and one that traditionally lags both the EU and US.
CONCLUSION

This research revealed a consistent approval lag between the US and EU in each of the three innovative medical device segments explored in this study. This lag was present in each segment throughout the 20+ year period of study. Furthermore, the lag in these three segments has grown in recent years. Some studies have discussed the origins and presence of a lag in the past decade, but study data demonstrate that the lag has a much greater longevity in these device segments and will likely persist in the future.

These data are striking because they show, perhaps for the first time, that an approval lag has existed for medical devices between the US and EU for at least the past 20 years – since the beginning of the pan-European device regulatory system in the mid-1990s.

The lag is important because it is a useful metric for comparing the attractiveness of two markets for medical technology – in this case the US and EU. Given that the lag has existed over the entire lifetimes of the devices in the study, it seems as though a baseline lag is unavoidable as well as tolerated by the market. It is also reasonable that some lag exists given the differences in the regulatory requirements and processes between the US and EU. However, a growing lag is cause for concern. A growing lag may indicate a true sea change in the attractiveness of the US market for medical technology and signal a shift in investment from the US to new markets.

It is important to note that the lag is not in and of itself a cause of device approval delay. However, as awareness of the extent of the lag grows, so too may the decisions to seek approval in up-and-coming device markets rather than the US. The lag may start to influence strategic decisions and actually create a vicious cycle in which the lag itself creates further lag. In this case, the United States would have the most to lose if medtech resources and investment begin move into new markets as a result. Already, several studies have shown that the US is losing its medtech market attractiveness and is viewed as being less innovative as in the recent past.
Another component of the lag is the lost generation of products that may never reach US patients because the technology may be outdated by the time it can gain approval. The cost versus benefit of these technologies to the US healthcare system can be questioned. But the fact cannot be ignored that US patients and physicians do not have the latest technology approved for their use, and may never have the benefit of this generation of technology.

On the other hand, a lag in US approval may also be beneficial in some cases, delaying or preventing US approval of emergent but unproven medical technology that may experience adverse events in other markets. Unfortunately, there is no easy way to know which is ultimately better for the patient – the cost-versus benefit ratio for novel technology is neither easy nor straightforward to determine.

Finally, with proposed regulatory changes being discussed in both the EU and US, it is important for those involved to be mindful of the device approval lag, its significance as an indicator of the attractiveness of a market and the potential economic changes signaled by a growth in the lag.

Reasons for the lag as well as whether or not it has grown in recent years can be debated, but what is clear from this study is that an approval lag has been a permanent feature of medical device approvals in the US over the past 20 years and that American patients and physicians must wait longer for beneficial, innovative medical technology to be approved than their counterparts in the EU.
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Feb 2011.


66. The Outlook for Medical Devices in Western Europe. Espicom Business Intelligence. 2011.


APPENDIX A

FDA Device Review Pathways:

Premarket Approval (PMA) – “Premarket approval (PMA) is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices... under section 515 of the FD&C Act in order to obtain marketing clearance. PMA is the most stringent type of device marketing application required by FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. PMA approval is based on a determination by FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device. The PMA owner, however, can authorize use of its data by another. FDA regulations provide 180 days to review the PMA and make a determination. In reality, the review time is normally longer. Before approving or denying a PMA, the appropriate FDA advisory committee may review the PMA at a public meeting and provide FDA with the committee’s recommendation on whether FDA should approve the submission [50].”

The current user fees in FY 2011 for PMA submission are $236,298 for the standard fee and $59,075 for a small business [49].

Premarket Notification (510(k)) – So called because the regulation that covers this pathway is section 510(k) of the Medical Device Amendments to the FD&C Act [42].

“A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to PMA [51].”

“Before marketing a device, each submitter must receive an order, in the form of a letter, from FDA which finds the device to be substantially equivalent (SE) and states
that the device can be marketed in the U.S. This order "clears" the device for commercial distribution [51]."

"Submitters must compare their device to one or more similar legally marketed devices and make and support their substantial equivalency claims. A legally marketed device, as described in 21 CFR 807.92(a)(3), is a device that was legally marketed prior to May 28, 1976 (preamendments device), for which a PMA is not required, or a device which has been reclassified from Class III to Class II or I, or a device which has been found SE through the 510(k) process. The legally marketed device(s) to which equivalence is drawn is commonly known as the ‘predicate.’ Although devices recently cleared under 510(k) are often selected as the predicate to which equivalence is claimed, any legally marketed device may be used as a predicate. Legally marketed also means that the predicate cannot be one that is in violation of the Act [510k] [51]."

"A 510(k) requires demonstration of substantial equivalence to another legally U.S. marketed device. Substantial equivalence means that the new device is at least as safe and effective as the predicate.

A device is substantially equivalent if, in comparison to a predicate it:

has the same intended use as the predicate; and

has the same technological characteristics as the predicate;

or

has the same intended use as the predicate; and

has different technological characteristics and the information submitted to FDA; does not raise new questions of safety and effectiveness; and

demonstrates that the device is at least as safe and effective as the legally marketed device.

A claim of substantial equivalence does not mean the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design,
energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable [51].”

“Until the submitter receives an order declaring a device SE, the submitter may not proceed to market the device. Once the device is determined to be SE, it can then be marketed in the U.S. The SE determination is usually made within 90 days and is made based on the information submitted by the submitter [51].”

The current user fees in FY 2011 for 510(k) submission are $4,348 for the standard fee and $2,174 for a small business [52].

**Humanitarian Device Exemption (HDE)** – “An Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year. A device manufacturer’s research and development costs could exceed its market returns for diseases or conditions affecting small patient populations. The HUD provision of the regulation provides an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations [18].”

“To obtain approval for an HUD, an humanitarian device exemption (HDE) application is submitted to FDA. An HDE is similar in both form and content to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of a PMA. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable
devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market [18].”

“An approved HDE authorizes marketing of the HUD. However, an HUD may only be used in facilities that have established a local institutional review board (IRB) to supervise clinical testing of devices and after an IRB has approved the use of the device to treat or diagnose the specific disease. The labeling for an HUD must state that the device is a humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated [18].”

No user fees apply for the Humanitarian Device Exemption approval process [49].

Product Development Protocol (PDP) Pathway – Technically a PMA application method, the PDP pathway is the least employed method for device premarket review.

“In the product development protocol (PDP) method for gaining marketing approval, the clinical evaluation of a device and the development of necessary information for marketing approval are merged into one regulatory mechanism. Ideal candidates for the PDP process are those devices in which the technology is well established in industry. The PDP process provides the manufacturer with the advantage of predictability once the agreement has been reached with FDA [48].”

“The PDP allows a sponsor to come to early agreement with FDA as to what would be done to demonstrate the safety and effectiveness of a new device. Early interaction in the development cycle of a device allows a sponsor to address the concerns of the FDA before expensive and time consuming resources are expended [48].”

“The PDP is essentially a contract that describes the agreed upon details of design and development activities, the outputs of these activities, and acceptance criteria for these outputs. It establishes reporting milestones that convey important information to the
FDA as it is generated, where they can be reviewed and responded to in a timely manner. The sponsor would be able to execute their PDP at their own pace, keeping FDA informed of its progress with these milestone reports. A PDP that has been declared completed by FDA is considered to have an approved PMA (§814.19) [48].”

Typical PMA user fees apply for the Product Development Protocol approval process [49].
### APPENDIX B

Coronary Stent Approval Data:

<table>
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<tr>
<th>Device</th>
<th>EU approval</th>
<th>US approval</th>
<th>Lag (days)</th>
<th>Lag (mo.)</th>
<th>Lag (yrs)</th>
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<td>Gianturco-Roubin Flex-Stent</td>
<td>Jun-90</td>
<td>Jun-93</td>
<td>1096</td>
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*Denotes US investigational product and estimated US approval date
APPENDIX C

Implantable Cardioverter Defibrillator Approval Data:

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*Denotes US investigational product and estimated US approval date