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Regulation and Access to Innovative Medical Technologies

A comparison of the FDA and EU Approval Processes and their Impact on Patients and Industry

June 2012

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Executive Summary

- There has been increasing scrutiny on the FDA and the impact of the agency's processes on the volume and pace of approvals for new medical technologies, especially as compared to the EU. It is in this context that this study examines the impact of and trends in approvals for the most innovative and potentially risky medical technologies, those approved by the Premarket Approval (PMA) process.

- This study examines all PMAs approved between 2000 and 2011 and uses FDA data and manufacturer data to examine differences in approval timing for devices approved in both the U.S. and Europe.

- We find that throughout this period, the same devices have been approved and made available to patients in Europe three or more years before devices are approved in the U.S. From 2000 through 2011 devices approved via PMA have been available in Europe for an average of 43 months before being made available in the U.S.

- The difference in approval times between the U.S. and Europe reflects fundamentally different approaches to the review and approval of these technologies. A detailed examination of approval processes and timelines for selected devices highlights challenges in an FDA process that is often time confusing and repetitive, both before and during approval.

- Delays in access to new medical technologies impact patients. By studying a cross section of recently approved devices, we highlight examples of lost patient benefits including limited access to new treatment choices, lack of access to devices that improve quality of life, and missed potential cost savings.

- Differences in approval timing also have substantial implications for innovator companies. By examining the economics of research-based innovation in medical technology, we show how sustained approval differences are encouraging companies to favor innovations that will serve European markets and reducing the incentive to innovate for the specific needs of the U.S.

- We encourage policy makers to carefully consider how the long-term effects of regulation can affect the incentives for innovation and have consequences for patients and competitiveness.

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I. Introduction and Goals of This Study

The current environment is rife with debate calling for FDA and EU reform of the regulatory process for medical devices. One side views the processes for reviewing new medical technologies in the U.S. and Europe as too industry-centric and believes that speed to approval is valued over risk. The other side of the debate worries that the slowing pace of device approvals in the U.S. is creating an increasing gap between Europe and the U.S. Yet there is relatively little robust, comprehensive data on the trends in medical device regulation. In particular, little information exists on whether the phenomenon of earlier approval of certain medical technologies in Europe is a new development, or whether this is something that has been in effect for some time.

Within the FDA, the Center for Devices and Radiological Health (CDRH) regulates two pathways by which medical devices can gain approval for marketing in the United States. Premarket Notification, known as the 510(k) submission, is used for low to medium risk devices where substantial equivalence to FDA-approved predicate devices can be shown.[1] Novel devices, for which no predicate exists and which potentially pose a higher risk to patients, are subject to the Premarket Approval (PMA), which serves as an application to request approval to market. As the risk of potential harm to patients increases, application requirements increase as well. PMAs thus maintain a higher standard than substantial equivalence and require sufficient scientific evidence proving the safety and effectiveness of a device for its intended use.

The regulatory approach taken by the FDA in the U.S. differs fundamentally from the approach taken in the EU. While the U.S. utilizes a centralized approach through the FDA, the European CE (Conformité Européene) marking process is much more decentralized. In the CE marking process the manufacturer works with a public or private organization called a Notified Body (NB) to demonstrate that the new device conforms with all applicable requirements. Across the EU, there are 74 NBs in 25 countries with the power to issue a certificate of conformity demonstrating compliance of the device with European Directives. Based on the risk classification of a device, manufacturers must submit materials such as literature reviews or clinical investigation to one of these NBs. If all assessments are approved, the manufacturer will then be awarded a CE mark for access to the EU market.

The separate regulatory structures in the EU and the U.S. have led to two unique approval processes with different requirements and timelines. As a result, in many cases manufacturers seek approval in Europe before the U.S. This study is intended to explore whether differences in the timing of approval of innovative technologies in the U.S. and Europe have increased, and to examine how these differences impact patients and the companies seeking to develop new medical devices.

[1] While the FDA has responsibility for ensuring the safety and of both drugs and medical devices it should be noted that the regulatory approaches for the two differ substantially. Devices are typically designed and engineered for a given use. A learning curve is climbed over time as prior versions are incrementally improved. Such changes often yield results that are more predictable. In contrast, altering the molecular structure of drugs is more confounding as it changes the way in which it works in the body. Such modifications require new clinical trials to ensure safety is maintained. While repeat trials to prove equivalence are thus relevant for drugs, they are less useful for devices. Treating every modified version of a device as if it were an entirely new product would increase development costs, extend time to market, and discourage innovation.

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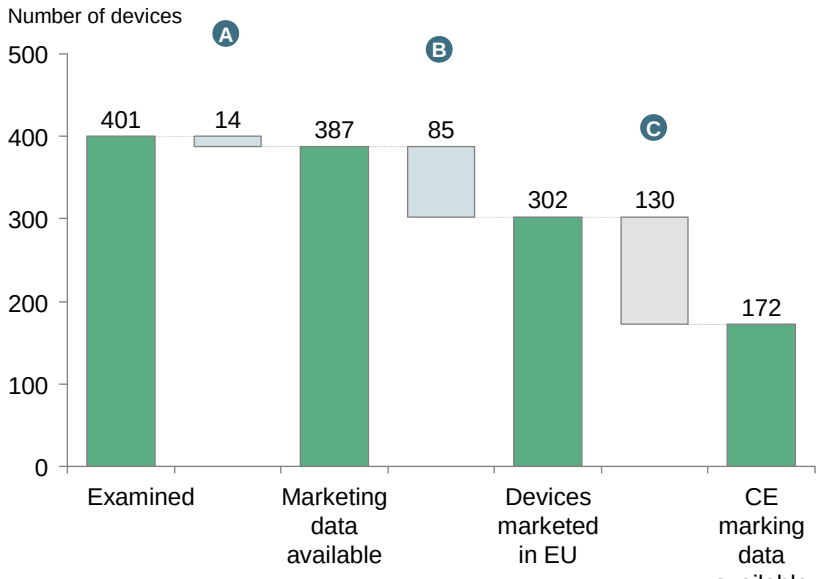
II. Methodology

This study used three approaches to evaluate trends in EU-U.S. approval times and the impact on patients and companies. The first approach was to develop a transparent and comprehensive data set of all original PMA approvals from 2000 through 2011. The marketing history of each device was reviewed to identify the corresponding CE mark date for the same indication approved in the U.S.[2] All data were collected using public information from FDA applications and company press releases. The approval delay between the EU and U.S. was then calculated for all devices with available FDA approval and CE mark dates. All 401 original PMA approvals from 2000 through 2011 were considered in the analysis. Of these, 85 devices (22%) were excluded, as they were marketed in the U.S. only. Of the remaining 302 devices, comparable approval timing data was found for 172 devices (57%). We believe this sample is representative and allows long-term trend analysis (see Exhibit I).

Exhibit I – 172 devices identified with data on CE marking

Dataset includes marketing history of 401 devices and CE marking data for 172 devices



1. Devices approved in the US without EU approval
Note: Represents original PMA approvals
Source: FDA Database, public press releases and company inquiries

Filter applied

A Devices without available marketing history excluded
- 11 of 14 devices in this category gained FDA approval from 2000-2002 with applications that did not include a marketing history description

B Devices never marketed in Europe excluded
- 85 devices with no EU marketing history[1]

C Devices w/o CE marking dates
- 130 devices marketed in Europe without public CE marking dates
- Includes devices approved for other indications than those approved in the US

[2] EU approved indications were matched to FDA submissions as best as could be determined based on marketing history information in FDA data.

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To better understand the cause of differences in approval timing and the implications these have for patients, we developed case studies of all recently approved PMA devices. Detailed device profiles were developed for original PMAs approved from October 2007 (FY 2008) to August 2011. Of the 89 devices approved during this time period, 62 devices contained CE marking information. Ten PMA-approved devices and two devices in the process of attaining PMA approval were then selected for a more detailed assessment. The devices selected represent a cross section of therapeutic areas, patient benefits, and types of companies. Several companies agreed to interviews from which further information was collected on the regulatory process, marketing history, and patient benefit of recently approved devices. Publicly available clinical information was also gathered to provide further detail on the benefits of using a particular device.

Our third and final analysis involved developing economic models to determine the impact of EU-U.S. regulatory delays on U.S. companies. Illustrative cash curves for devices marketed in the U.S. and the EU were then created to model the broader economic impact of delayed approval on a device manufacturer. The differential effect of delays on small versus large companies was also considered. In addition, second order effects of delay were incorporated.

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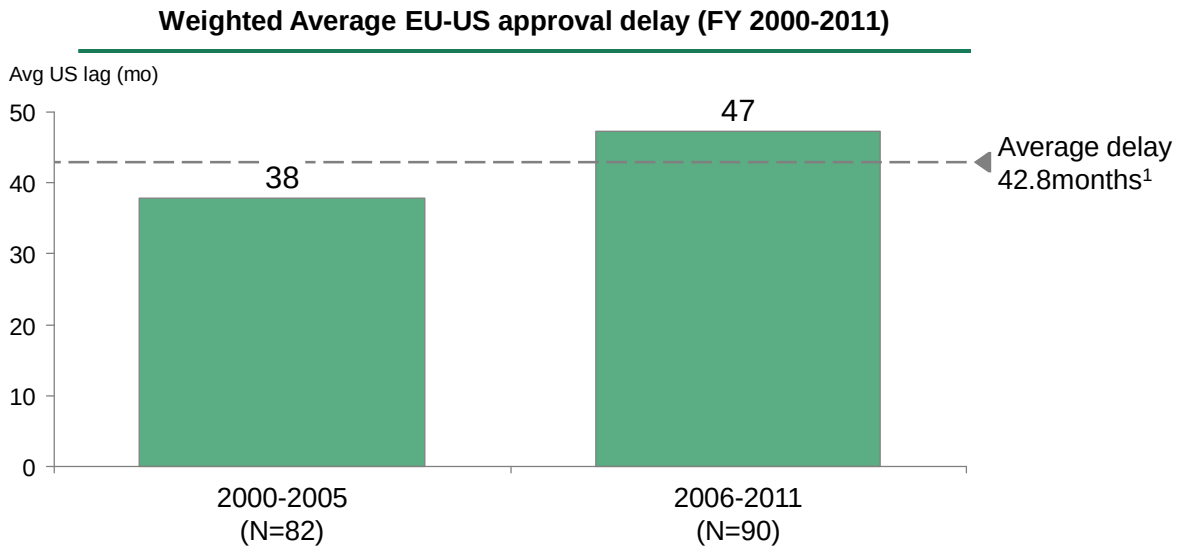
III. Trends in PMA Approval and Delay

Where devices are approved in both the U.S. and the EU, U.S. approval occurs on average 43 months after EU approval (see Exhibit II).

Exhibit II – Average PMA delay by approval year



1. Median (rather than average) delay over the same period is 35 months. Removing effect of delays from FDA warning letters that restrict application submissions for Class III products does not change in the overall average.
Note: EU-US lag calculated for 160 devices with available CE mark dates from 2000-2011. If year of CE mark provided without detailed month and date, December 1st of listed year used as a conservative estimate to calculate EU-US lag. Difference between 2000-2005 and 2006-2011 found to be statistically significant at the 5% significance level.
Sources: FDA database, public press releases and company inquiries

The median difference in approval between the US and EU is 35 months. The distribution of delay varies widely, with some devices experiencing approval delays of six years or more. Delays also seem to be worsening with average approval delays of 38 months for 82 devices approved between 2000 and 2005, compared with 47 months for 90 devices approved between 2006 and 2011.

Part of the trend to worsening delays can be explained by a 135% increase in PMA approval times over 10 years, from just over one year (12.5 months) in 2000 to over two years (29.3 months) in 2010. This compares with an average 3.4-month review time for equivalent devices in Europe.[3] Along with increases in approval time, variability has also increased since 2006.

[3] EU approval times calculated from BCG/CHI survey of 46 PMAs from 11 CHI (California Healthcare Institute) member companies approved in the U.S. and EU between 2004 and 2010 for which sponsor companies provided data on filing and approval times.

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However, while delays are caused in part by lengthening review times, another important factor is the time needed before the PMA review process commences: on average, 52% of the EU-U.S. approval lag can be attributed to the pre-FDA review period[4]. Pre-submission statistics are difficult to come by, so this metric serves as an indicator for the pre-review process. Lags in the pre-submission process may be caused by a variety of factors such as sponsor management decisions or the long and often repetitive Investigational Device Exemption (IDE) process.

One unexpected consequence of the long term-pattern of earlier approval in Europe has been a decline in the numbers of new devices developed for the U.S. only. Between 2000 and 2007, 24% of all PMAs were intended for the U.S. only, i.e., devices for which no equivalent was ever approved in the EU. Since 2008, however, this proportion has fallen substantially, to only 15% between 2008 and 2011[5].

[4] For PMAs approved in the US between 2000 and 2011 the average EU-U.S. approval lag was 42.8 months. If the same devices took 17 more months in approval in the U.S. than in the EU (20.4 months rather than 3.4) then 22.4 months of the difference was pre-submission.

[5] Of 387 devices for which PMA approval was granted between 2000 and 2011 and for which marketing history was available, 85 (22%) had no equivalent in the EU. Between 2000 and 2007 an average of 8 devices were approved per year for which there was no EU equivalent, Since 2008 less than 2 devices have been approved each year for U.S. only marketing

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IV. Impact of PMA Approval and Delay on Patients

What is the impact on patients, if these innovative technologies are available to U.S. patients over three years later than patients in Europe? Do U.S. patients suffer from delayed access to technologies to which their peers in Europe have access, or are they protected from technologies that are potentially risky and unsafe?

Does the PMA process improve safety?

Some have argued that additional review time is necessary to ensure the safety of a device. However, separate studies by Prof. Ralph Hall at the University of Minnesota, by the Batelle Memorial Institute, and by The Boston Consulting Group suggest not only that recall rates are low, but also that there is little difference in the rates of serious recalls under the EU and U.S. regulatory systems[6]. While some have suggested that European patients are "guinea pigs" and subject to working out the kinks in new medical technologies, we found no evidence of this in our sample of 89 PMAs approved between 2008 and 2011. Examining all original PMAs during this period with CE marking information we found only two in which there were any recalls or safety issues in the period between European and U.S. approval.

A recent FDA Publication has suggested that the US regulatory approval system protects patients from "unsafe and ineffective devices" that are approved in Europe and cited twelve case examples from the 1990s and 2000s in which devices, or classes of devices, were approved in Europe but were not approved in the US, and in some cases subsequently withdrawn in Europe[7]. The study did not however provide any information on the rate at which such problems were identified, nor even indicate whether the devices were submitted as 510(k) or PMA. Conservatively, if we were to assume that all 12 were considered as PMA then they represent <2% of approvals in the period, or a much lower proportion if 510(k) clearances were also included.

If a lengthy PMA review process does not bring a significant safety benefit, the question then becomes whether it imposes a substantial efficacy or quality of life burden on patients. To examine this we looked at 89 original PMAs submitted between FY 2008 to August 2011. CE marking information was available on 62 of these devices. Of these 62, approximately half of the devices fell into the cardiovascular segment, with the remaining half covering a range of therapeutic areas. Ten devices across a wide range of therapeutic areas and company sizes were selected for further analysis. Two additional devices currently pursuing PMAs were also included in the deep dive analysis. Research conducted included company interviews, analysis of clinical studies, and review of press releases.

[6] Prof. Hall's study ("Using Recall Data to Assess the 510(k) Process", 2010) examined rates of Class I recalls of medical devices approved in the US and found recall rates of ~1:500 the majority of which (55%) were for issues that would not have been identified in clinical testing. The BCG study ("EU Medical Device Approval Safety Assessment—A comparative analysis of medical device recalls 2005-2009," January 2011) found both similar rate, therapeutic mix and reason for recalls in Europe as in the US.

[7] "Unsafe and Ineffective Devices Approved in the EU that were Not Approved in the US", FDA, April 2012. This study examines 12 case examples four of which were from the 1990s, and one of which related to a class of devices (dermal fillers) and instances in which issues were as much arising from differences in whom and how the product is used (filers being Rx only in the US versus more widely administered in Europe)

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What causes PMA approval delays?

Our first intent was to better understand why the process of PMA approval takes longer than approval via other routes and in other regions. Interviews with device manufacturers indicated that a primary cause of delay involved the FDA's uncertainty regarding submission requirements—the so-called pre-IDE (Investigational Device Exemption) process through which manufacturers seek the FDA's approval to initiate U.S. clinical studies of a new device; these studies that will ultimately form the basis of the PMA. The pre-IDE process is often long and complex. For example innovators reported additional requests for clinical data once the PMA process was underway which differed from original data requests presented in initial IDE meetings. Some companies noted that FDA personnel lacked the necessary scientific expertise to understand a specific device, or had to learn and get up to speed with the device following turnover in the FDA team. The lack of transparency in data needed for approval, high costs of clinical data and lengthy delays for correction are causes for concern for companies. The lack of predictability in information requested by the FDA can undermine the efficiency of the entire approval process.

Do PMA delays harm patients?

Delay in access to a new medical technology could harm patients in three distinct and different ways. These delays could:

- limit the treatment choices available to a patient by limiting access to technologies that offer superior efficacy over any approved alternatives
- limit access to a product that could potentially offer improved quality of life, even if it does not provide a clinical efficacy benefit
- reduce physician and patient choice and limit available treatments to other approved technologies that do not have the ideal combination of features needed for a given patient group

To understand the implications of these types of factors, we developed detailed case studies on a broad cross section of PMA-approved devices. A selection of examples demonstrate some of the ways in which slower approval of new medical technologies in the US affects patients.

For example in some cases patients in Europe may have access to superior treatment choices well in advance of the same patients in the U.S. Examples of this include:

- The Implantable Miniature Telescope from VisionCare Ophthalmic Technologies. The Implantable Miniature Telescope is the first device capable of restoring vision for patients with end-stage, age-related macular degeneration (AMD). This new technology offers a potential treatment for 500,000 U.S. patients with advanced AMD who previously had no real viable options. This device was approved in Europe eighteen months before the U.S.
- The SAPIEN Transcatheter Heart Valve from Edwards Lifesciences. The Edwards SAPIEN Transcatheter Heart Valve presents an option for patients who are considered to be high-risk or non-operable for conventional open-heart valve replacement surgery. The collapsible bovine aortic heart valve can be introduced into the body via a catheter-based delivery system. The device received CE marking in September 2007, but is still in the process of gaining approval in the U.S. The technology could potentially benefit approximately 75,000 patients who receive aortic valve replacements every year in the U.S.

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Even in cases where there is an alternative technology available new innovations can bring substantially improved quality of life for patients. For example:

- The Revo MRI SureScan from Medtronic is the first pacemaker designed to be safe for patients to receive MRI scans. The technology improves quality of life by reducing patient concern regarding future diagnostic needs as well as assuring that MRI diagnostic capabilities will be available to patients with pacemakers who need this advanced imaging tool . SureScan was approved in Europe 29 months before the U.S. Without access to this technology patients cannot benefit from MRI scans, which are critical for early detection, diagnosis, and treatment of many diseases.
- The Esteem Implantable Hearing System from Envoy Medical Corporation. This is the first implantable hearing system used to treat moderate to severe hearing loss. It was available in the EU almost four years before becoming available in the U.S. This product is medically necessary for patients who have moderate to severe sensorineural hearing impairment and cannot tolerate an ear mold because of medical conditions. A portion of the 10% of Americans suffering from hearing loss could have benefited from this device had it been approved earlier.

Finally, innovations also represent alternatives for physicians and for patients. Delayed approvals therefore can limit physician and patient choice, such as in the cases of:

- The Zenith TX2 Thoracic TAA Endovascular Graft from Cook Inc. This device presents a less invasive treatment for the repair of aneurysms of the aortic chest. In the three years following approval in the U.S., approximately 12,000 grafts were utilized by U.S. patients. Had the device not experienced a 44-month delay, a similar number of patients could have received access to this new technology.
- The T-SPOT.*TB* test from Oxford Immunotec. The T-SPOT.TB test is the first improvement to the over 100 year-old traditional tuberculin skin test, and allows for next day test results without requiring a follow up visit. Additionally, the simple and faster test is substantially more accurate and effective in controlling the spread of TB and minimizing costs of onward transmission. Despite these benefits, the T-SPOT.TB test faced a 49-month approval lag. Twenty million individuals tested for TB infection each year could have benefited from earlier approval.

For all of the devices mentioned above, U.S. patients did not have access to innovative technologies that would have resulted in reduced disability, improved quality of life, and/or superior treatment options. Not only do U.S. patients suffer, but U.S. clinicians also lose out on early clinical experience with new technologies. These devices represent only a subset of the numerous devices that are already marketed overseas. In some instances, second and third generation products are being used in Europe before the first generation product gains approval in the U.S.

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V. Impact of PMA Approval and Delay on Businesses

Beyond the effect on patients, EU-U.S. approval delays also impact device companies. One way to measure the impact is by evaluating the effect of delay on the investment and pay-back for a given device. We developed a detailed financial model of the costs and returns from a typical PMA-type device. This model is based on BCG experience of typical costs and product revenues for medical device companies with which BCG has experience.[8] The increase in approval times has impacted the returns to innovation. We modeled the costs and returns for the same device under approval times expected in 2007 and the same times today. The model used assumes a device with sales between a hip replacement (between $20 million and $50 million in sales) and a drug eluting stent (between $200 million and $500 million in sales). Our modeling suggested that the impact of increasing FDA uncertainty and regulatory delays had significantly reduced the returns on Medical Technology R&D and increased the uncertainty and cash needed to bring a new product to market.

For large medical technology companies, FDA delays extend product lifecycles and create cash flow fluctuations. The inability to prepare for product launches results in extended time before positive cash flow can be achieved. Moreover, difficulties in predicting cash flow for development hinder investment in new innovation. Future spending on R&D may also decrease due to costs of potential delay. Despite these concerns, large companies are able to endure regulatory uncertainty much better than smaller companies. In fact to some extent a high regulatory bar acts as a barrier to entry to new innovators and may even reduce competition. Thus while a large company may have to forgo near term revenues on a delayed PMA approval this can be offset by extended revenues on older products that face limited competition.

While FDA delays may cause some difficulties for large firms, delays are almost certainly destroying value for small firms. Often funded by venture capital firms, these companies receive funding based on clinical and regulatory milestones in both the EU and the U.S. Regulatory and marketing success in Europe is often required as a prerequisite for further support to enter the U.S. market. In fact, venture capitalists we interviewed suggested that they would not be prepared to invest in a company without confidence of an approval pathway and consequent revenues in Europe that would help offset long and uncertain U.S. development and approval. However, with limited resources to fully understand the EU regulatory environment and limited sales forces to tackle the numerous countries within Europe, smaller companies are altogether disadvantaged. Smaller medical technology companies, which often lack a portfolio of products to serve as alternative sources of cash flow, are thereby more affected by the increase in U.S. approval times and the recent variability in EU-U.S. approval delays. Faced with funding challenges, smaller firms may be forced to sell at low valuations or to discontinue development efforts. With medical technology innovation heavily driven by smaller companies, the ability for such firms to exist and continue to innovate in the long term is certainly at risk.

In conclusion, while longer U.S. approvals may reduce returns for larger companies, smaller companies encounter severe challenges. Funding problems due to extended EU-U.S. regulatory delays may prevent life-saving innovations from ever reaching the market. Due to the likelihood of undergoing a costly and lengthy regulatory process, companies may be less incentivized to innovate and may pursue less risky products in the future. The resulting decrease in innovation could jeopardize the competitive position of the U.S. in the medical technology sector.

[8] The model was developed from the assumptions documented in Lawyer et. al., "Medical Devices Ride the Cash Curve," *In Vivo,* 25, no. 3 (2007).

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VI. Implications

The EU-U.S. device lag results in real impact to U.S. patients and U.S. companies. U.S. patients, who experience over three-year delays in accessing new technologies, miss out on potential health benefits that include reduced disability, improved quality of life, and greater patient choice. Small device companies with limited resources suffer the most with approval delays, and many are unable to withstand the costs of long regulatory delays. With the majority of innovation stemming from small firms, the ability for the U.S. to maintain its competitive position and to produce technologies to address the needs of U.S. patients is put at risk.

Our study does not prescribe EU regulatory processes for the U.S. or suggest that the EU process is perfect. It does however suggest that the regulatory delays are detrimental to U.S. patients and companies and that more rapid approval times in the EU offer significant health benefits to European patients and to industry. Policy makers should be aware of the consequences of increasing FDA delays and elongating the EU-U.S. device lag and of the potential negative impacts of reforms to the EU process that would elongate European review times. If approval requirements for complex medical devices are to be increased, they must be done so in a transparent and predictable fashion that does not further jeopardize the efficiency of the regulatory process and reduce future innovation.

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Appendix

I. Assumptions and Limitations

Assumptions

1. Difference between regulatory approval dates approximates difference in market launch dates

2. Regulatory timing is presumably similar for companies with and without publicly listed CE mark

3. Conservative calculations of EU-U.S. approval lag accurately reflects degree of delay
    - If year of CE marking provided without detailed month and date, December 1st of listed year used as a conservative estimate to calculate EU-U.S. approval lag

Limitations

1. Internal company decisions contributing to approval lags not included in calculations
    - Strategy of individual firms not evaluated

2. Standardized metrics of patient impact, such as QALYs, not utilized due to inability to calculate changes in survival rates or conduct quality of life surveys
    - Incremental benefits often seen in medical devices limits types of potential assessment
    - Length of study limits ability to conduct primary patient analysis

3. Differences between clinical practices and alternative treatments in the EU and U.S. not incorporated

4. While marketing history provides information on whether a device was marketed in Europe, full disclosure of approved indications in Europe is not always provided
    - Further follow up with individual companies may be required to fully understand differences by country

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II. Economic Model Assumptions

We modeled the costs and returns for the same device under approval times expected in 2007 and the same times today. The model used assumes a device with sales between a hip replacement (between $20 million and $50 million in sales) and a drug eluting stent (between $200 million and $500 million in sales). In 2007, a PMA-approved device could reasonably attain an internal rate of return (IRR) of 15%. However, launching the product today would reduce the IRR to 13%.

Categories	US	Assumptions	EU	Assumptions
Revenues	$230M[a]	Sales between a hip replacement ($20-50M) and a drug eluting stent ($200-500M)	$115M[d]	1/2 of US revenues based on 2009 Medtech revenues by region in E&Y report
Costs	$100M[a]	Burdened with pre-regulatory failures and 30% chance of FDA rejection	$25M[4]	1/4 of US costs as suggested in VC interviews and E&Y Report
Ideation, clinical, development	2.5 years, 80% of costs[a]	Responsible for most of the pre-launch expenses and time	1 yr, 80% of costs	Shortened due differing requirements
Regulatory approval	1.80 years, 10% of costs[b]	Actual average from 2008-2010, Includes cost of $740,000 per month of delay[c]	11 months, 10% of costs[c]	As reported in Makower study
Commercialization	0.5 years, 10% of costs[a]	Marketing, training and inventory build-up	1 yr, 10% of cost	Twice as long as a result of increased requirements of a centralized system
On market	Peak sales after 2.5 yrs[a]	Follow-ups to extend life to 8 years, 30% operating margin	Peak sales after 2.5 yrs	Same

a. BCG Report - Payback II: Medical Devices Ride the Cash Curve, Mar 2007
b. FDA Database
c. Makower, Josh. "FDA Impact on U.S. Medical Technology Innovation," Nov 2010
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The Boston Consulting Group (BCG) is a global management consulting firm and the world's leading advisor on business strategy. We partner with clients in all sectors and regions, including many of the leading medical-technology and medical-device companies, to identify their highest-value opportunities, address their most critical challenges, and transform their businesses. Our customized approach combines deep insight into the dynamics of companies and markets with close collaboration at all levels of the client organization. This ensures that our clients achieve sustainable competitive advantage, build more capable organizations, and secure lasting results. Founded in 1963, BCG is a private company with 71 offices in 41 countries.

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