The NEW ENGLAND JOURNAL of MEDICINE

Perspective

AUGUST 9, 2012

Patient Access to Medical Devices — A Comparison of U.S. and European Review Processes

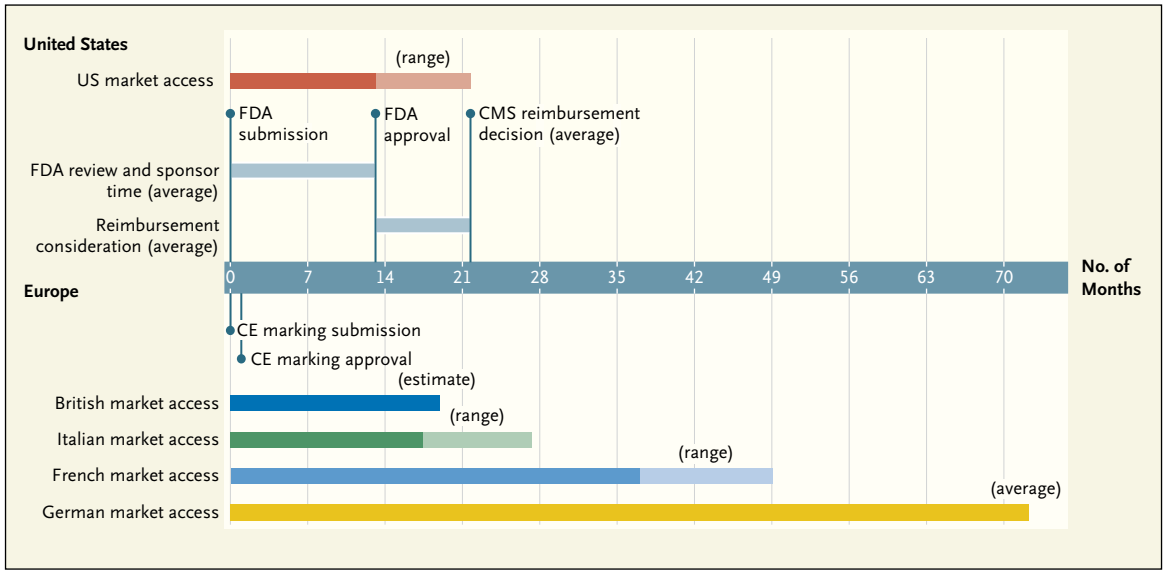
Saptarshi Basu, M.P.A., and John C. Hassenplug, M.Sc.

The U.S. process for approving innovative, high-risk medical devices has been criticized for taking longer than the European approval process.[1] This contention is often used to support the argument that the Food and Drug Administration (FDA) should lower its standards for approving medical devices, since a slow approval process is delaying Americans' access to innovative and lifesaving technology. But a review of the data, using appropriate end points, suggests instead that it takes the same amount of time or less for patients to gain access to innovative, high-risk medical devices in the United States as it does in the four largest European markets (Germany, France, Italy, and Britain)[2] — largely because patient access is generally delayed until reimbursement decisions are made, which often takes substantially longer in Europe than in the United States.

To compare the United States and Europe fairly on this front, three criteria must be considered: the level of device innovation, equivalent start and end points, and patient access as defined by time to reimbursement. First, we focused on innovative, high-risk devices because in the United States such devices require the strongest evidence of clinical benefit and are the subject of most debates about the relative effectiveness of approval processes in different countries. Furthermore, previous studies have shown that lower-risk devices achieve market access in a similar amount of time in the United States and in Europe.

Second, an accurate comparison of time to market access requires measurement of the total time that elapses between application submission and market access. Previous studies have compared the chronologic dates of application submission and market access, but the date an application is submitted varies from country to country.

Third, patient access should be equated with the availability of reimbursement rather than with device approval, because broad patient access to a new device doesn't occur until reimbursement by a national or third-party payer is available. Previous comparisons of the U.S. and European systems have used the approval date to measure process duration, but innovative, high-risk devices don't reach a market where most patients can benefit from them immediately after gaining regulatory approval, though they may be accessible to patients who can af-



Comparison of Time to Market in Premarket Approval and Reimbursement Processes.

The minimum time of 1 month was used for the Conformité Européenne (CE) marking process and does not include sponsor time (which is not publicly reported). Reimbursement times were obtained as follows: Britain, government report of the time to conduct 11 assessments in 2008; Italy and France, estimated ranges from a trade press report; and Germany, calculated average time to complete 23 assessments with clear start and end dates from the last 5 fiscal years (full references available from the FDA). In the United States, the majority of devices do not undergo further review after FDA approval. Reimbursement decisions for devices that do require further review are typically made within a few months by private insurers and an average of 8.6 months by the Centers for Medicare and Medicaid Services (CMS). The EU process includes both the CE marking process and the reimbursement process, which varies among countries.

ford to pay out of pocket. Rather, there is a second level of review through which public or private insurers decide whether and at what price they will pay for a device. Generally, public systems take longer than private insurers to make reimbursement decisions, and significantly more Europeans than Americans have public insurance. Two thirds of the U.S. population is covered by private health insurance, whereas only a fifth receives publicly funded reimbursement, primarily administered by the Centers for Medicare and Medicaid Services (CMS).

For both private and public systems in the United States, the pathway to patient access to a device starts with the submission of an application to the FDA. The FDA reviews innovative, high-risk devices for safety and effectiveness (clinical benefit) under the premarket approval (PMA) process, and information on the duration of reviews is publicly available. In fiscal year 2011, the FDA approved 40 applications for PMA. The average review time was 13.1 months, with 8.4 months attributed to FDA review time, and 4.7 months to the time the agency waits for the sponsor to address deficiencies in the application ("sponsor time").[3] CMS provides reimbursement for the majority of devices when they earn FDA approval. For a limited number of devices each year, however, CMS conducts a national coverage determination in response to external requests for validation or for devices that have limited or conflicting evidence of clinical benefit. This process averaged 8.6 months over the past 5 fiscal years.[4] Although it is difficult to obtain data on how long private insurers take to make coverage decisions, anecdotal information from private insurers suggests that decisions are made within a few weeks to a few months after FDA approval, depending on the amount and quality of evidence of clinical benefit.

In Europe, by contrast, most of the 27 member countries of the European Union (EU) have publicly financed health care systems; such systems cover approximately four fifths of the populations of the four largest device markets. All EU countries require devices to first obtain a Conformité Européenne (CE) marking, which refers to a symbol shown on products that indicates market approval throughout the EU. The CE marking process is conducted by for-profit, third-party "notified bodies" that have been accredited by a member country to assess de-

vice safety and performance but do not evaluate effectiveness (which requires more clinical data). Although publicly available data are limited, anecdotal information from notified bodies suggests that the process takes 1 to 3 months, excluding sponsor time.

Most European patients do not have access to innovative, high-risk devices as soon as the devices receive a CE marking. Each country must first make a decision about reimbursement, a process that varies substantially among countries.[5] Though a CE marking can be granted on the basis of fewer clinical data than are required for FDA approval, European standards for reimbursement are often similar to or higher than those that the FDA imposes for device approval. European countries may require additional data on the device's safety and effectiveness, as well as on cost-effectiveness.

In France, a centralized body makes reimbursement decisions after assessing the safety and effectiveness of individual devices. Reimbursement decisions in Italy are devolved to the various regions, and Britain and Germany conduct broader assessments of device types or procedures, rather than of individual devices. Typically, innovative devices not covered under an existing diagnosis-related group (DRG) require review under the lengthier Health Technology Assessment process, which assesses safety, clinical benefit, and cost-effectiveness. Government-provided information on time to reimbursement varies by country. Estimated time frames are an average of 71.3 months in Germany, a range of 36.0 to 48.0 months in France, a range of 16.4 to 26.3 months in Italy, and an estimated 18 months in Britain.

Comparison of Time to Market Access for Five Innovative Devices in France, Italy, and the United States.*

Device Name	Type of Device	France			Italy			United States		
		Submission for CE Marking	Reimbursement Decision	Months Elapsed	Submission for CE Marking	Reimbursement Decision	Months Elapsed	FDA Submission	FDA Approval	Months Elapsed
Endurant	Vascular stent graft	June 6, 2008	Aug. 25, 2011	38.6	June 6, 2008	Aug. 6, 2008	2.0	June 4, 2010	Dec. 16, 2010	6.4
Ovatio CRT-D (6750)	Implantable defibrillator	March 25, 2005	Jan. 8, 2008	33.5	March 25, 2005	Nov. 28, 2008	44.2	Oct. 3, 2006	May 15, 2008	19.4
Stratos LV-T	Implantable pacemaker	Aug. 14, 2002	Oct. 3, 2005	37.7	Aug. 14, 2002	Sept. 24, 2008	73.4	March 12, 2007	May 12, 2008	14.0
Taxus Liberté	Paclitaxel-eluting coronary stent	Aug. 8, 2005	Feb. 6, 2006	6.0	Aug. 8, 2005	June 6, 2008	33.9	March 8, 2006	Oct. 10, 2008	31.1
Valiant	Thoracic stent graft	Sept. 8, 2009	Jan. 6, 2011	15.9	Sept. 8, 2009	Sept. 30, 2009	0.7	Oct. 8, 2010	April 1, 2011	5.8
Average time to market access			26.3 mo			30.8 mo			15.3 mo	

* The date of submission for CE marking was estimated to be 1 month before the date of receipt of CE marking. This conservative estimate was used because data regarding actual CE marking review and sponsor-related time are not publicly reported. FDA approval was used as the end point for the U.S. process, since all the device types listed had already received National Coverage Decisions for CMS reimbursement and did not require further review. All devices had original premarket applications approved by the FDA between fiscal years 2006 and 2011, had not been recalled, were cross-referenced on publicly available reimbursement lists for devices in France and Italy, and were original devices with the same brand name and indication. Data on France are from the French government; data on Italy, from the Italian Ministry of Health; and data on the United States, from the FDA.

Using this information, we determined that the time it takes to bring innovative, high-risk devices to patients in the United States is similar to or shorter than that in the top four European markets (see figure). The public (CMS) process in the United States takes approximately as long as those in Italy and Britain, approximately half as long as that in France, and less than a third as long as that in Germany. The difference in time to market access is even greater when it comes to private insurers (covering the majority of the U.S. population), which often make reimbursement decisions within a few months after FDA approval.

To further illustrate this point, we compared the time to approval for five innovative, high-risk medical devices available in France, Italy, and the United States (see table). These case studies indicate that the average time to market access for these devices was 26.3 months in France, 30.8 months in Italy, and 15.3 months in the United States.

These numbers may not fully capture the reasons why a device reaches the market more quickly in one country than in another and do not reflect experiences with all innovative, high-risk devices. However, unless one uses equivalent standards in terms of the level of risk, the start and end points of the process, and the key end point of market access, accurate comparisons cannot be made.

The time it takes to bring innovative, high-risk devices to patients in the United States is similar to or shorter than that in the top four European markets.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Office of Planning, Office of the Commissioner, Food and Drug Administration, White Oak, MD.

This article was published on August 1, 2012, at NEJM.org.

1. Kramer D, Xu S, Kesselheim AS. Regulation of medical devices in the United States and European Union. N Engl J Med 2012;366:848-55.
2. Medical Device Network. Payback time. December 10, 2008 (http://www.medicaldevicenetwork.com/features/feature48597/).
3. FDA medical product approval times, fiscal year 2011: report in response to House report 2112. Silver Spring, MD: Food and Drug Administration, March 7, 2012.
4. Centers for Medicare & Medicaid Services. Coverage information exchange: reports for FY 2006–2010 (http://www.cms.gov/InfoExchange/04_reports.asp#TopOfPage).
5. Schreyögg J, Baumler M, Busse R. Balancing adoption and affordability of medical devices in Europe. Health Policy 2009;92:218-24. [Erratum, Health Policy 2010;94:90.]

DOI: 10.1056/NEJMp1204170

The Ethics of Early Evidence — Preparing for a Possible Breakthrough in Alzheimer's Disease

Justin Lowenthal, B.S., Sara Chandros Hull, Ph.D., and Steven D. Pearson, M.D.

Related article, p. 570

Being on the cusp of a potential medical breakthrough for a serious disease can pose substantial ethical challenges. One current example arises from a recent study demonstrating — in a single mouse model in one laboratory — that the drug bexarotene is effective in treating Alzheimer's disease (see article by LaFerla in this issue of the *Journal*, pages 570–572). Administration of bexarotene resulted in a greater-than-50% reduction of β-amyloid plaque at 72 hours and substantial reversal of neural, cognitive, social, and olfactory deficits, albeit with reduced effects as the mice aged.[1] A single report of this kind of preliminary evidence will require confirmation before Alzheimer's disease investigators even consider launching clinical trials in humans. But unlike many drugs under study for Alzheimer's disease, bexarotene is not a novel experimental drug; it is already approved by the Food and Drug Administration (FDA) for treatment of a cutaneous form of non-Hodgkin's lymphoma. Therefore, physicians could currently legally prescribe it for off-label indications.

Although the results in the mouse model are too preliminary to generate more than the most cautious optimism among researchers, they are already creat-