



The Honorable Henry A. Waxman
House of Representatives
Washington, D.C. 20515-0530

JUL 18 2011

Dear Mr. Waxman:

Thank you for your request for the Food and Drug Administration's (FDA or the Agency) comments on two industry-sponsored studies regarding FDA's performance on the review and approval of medical devices. Over the past few months a number of reports have been issued by or supported by the medical device industry regarding the Agency's performance on the review and approval of medical devices, especially as compared to that of the European Union (EU). Many of these studies employ questionable methodologies and report data that differs significantly from that which is collected as part of FDA's obligations under the Medical Device User Fee Act (MDUFA).

You asked for FDA's comments on the November 2010 report entitled "FDA Impact on US Medical Technology Innovation" by Josh Makower, MD, Consulting Professor of Medicine, Stanford University and CEO, ExploraMed Development, LLC, which was also supported by the Medical Device Manufacturers Association (MDMA) and the National Venture Capital Association (NVCA) (Makower Survey); and the February 2011 Report entitled "Competitiveness and Regulation: The FDA and the Future of America's Biomedical Industry," by the California Healthcare Institute and the Boston Consulting Group (CHI/BCG Survey).

We have restated your questions in bold, followed by our responses.

Makower Survey

1. What are the major methodological issues (whether positive or negative) of this study?

Of the more than 1,000 companies asked to complete the survey, only 204 responded. For some of the individual survey questions, fewer than 100 companies responded. Therefore, the response rate for the survey overall is 20.4 percent, and for some of the questions it is less than 10 percent. These reporting rates are likely to produce an inherently biased result because they are not based on a representative sample of all medical device companies. In fact, research has shown that the persons most likely to respond to a survey are those who are dissatisfied. It is also important to note that PwC (formerly PricewaterhouseCoopers LLP), which was retained to ensure quality control of the survey, did not assess the study methodology.

In addition, the claim that survey respondents include "approximately 20 percent of all public and venture-backed medical device manufacturers in the U.S. that are focused on

bringing innovative new technologies to market to improve the public health” is a gross overstatement. The authors note that 90 percent of the companies that responded were privately-held, venture-backed companies with a median of 33 employees. The remaining 10 percent of respondents (i.e., 20 companies) do not make up 20 percent of all public medical device firms in the United States. In fact, the study was not sent to the majority of U.S. medical device manufacturers. Instead, the survey was sent primarily to “small, early-stage entities, focused on a single product family,” who had limited experience with the FDA review process, which is reflected by the fact that only 55 percent of survey respondents had completed a traditional premarket notification (510(k)) and only 32 percent had gone through the premarket approval (PMA) process. These numbers indicate that some respondents had never gone through the process of getting a product reviewed by the FDA.

2. Please comment on the response rate for the survey overall, and for the time to first contact subgroup.

As noted in response to Question 1 above, the response rate for the survey overall is 20.4 percent, and for some of the questions it is less than 10 percent. For the time to first contact subgroup, only 15 respondents answered the questions with regard to a 510(k) submission. The authors do not give the response rate for the data they report regarding PMAs, but since only 32 percent of all respondents had gone through the PMA process, if the authors had a 100 percent response rate to these questions (which is unlikely given that they admit that some questions had an overall response rate of less than 10 percent), the maximum number of respondents would be 65.

3. Please discuss the methodology used in the study to compare EU and U.S. approval times.

The authors note that “the earliest interaction between company and regulatory body was used as the starting point for evaluating U.S. and European review timelines relative to one another.” However, communications between FDA and a sponsor occur far earlier in the device development pathway, when clinical data is required, than they do in the EU, generally before an Investigational Device Exemption (IDE) is submitted to FDA for approval. Therefore, this is an “apples to oranges” comparison that will show an artificial disparity in review times.

Devices submitted to FDA under a PMA are high-risk devices. These devices generally require data from a pivotal clinical trial to demonstrate safety and effectiveness to support their marketing applications, unlike in the EU. Sponsors most often begin interacting with FDA before they even begin designing their clinical trials so as to ensure that the clinical trials are designed to yield scientifically valid and useful results. These interactions are critical to a successful device approval. By contrast, in the EU, sponsors typically meet with a Notified Body (a private company) before or around the time of submitting a premarket application. The difference in starting points for communications between the United States and the EU can be years. The same circumstances apply for 510(k)s that require clinical data, where sponsors may meet with FDA prior to submitting

an IDE. Regardless, sponsors will communicate with FDA by the time they submit their IDE. As such, the statement that “American patients have to wait on average a full two years longer than their European counterparts for many life-saving and life-enhancing technologies” is misleading.

CHI/BCG Survey

1. What are the major methodological issues (whether positive or negative) of this study?

The study uses the wrong data set to measure the time to a decision. The data expressed in the CHI report are based on clearance or approval decisions for 510(k)s and PMAs made during each year (decision cohort). While sometimes informative, using decision cohorts is contrary to how FDA has been reporting its performance on MDUFA goals to Congress for almost a decade. The difference has to do with decision cohorts (the year in which a decision is made) versus receipt cohorts (the year in which a submission is received). Receipt cohorts are generally more informative about performance because most of the work on an application occurs in its year of receipt. On the other hand, if FDA makes good progress on older applications by making decisions on them in a given year, what might otherwise be improved performance would be reflected as a longer review time for that year if a decision cohort is used.

For example, a PMA application may be received by the Agency in 2006, but a decision on that submission may not occur until 2008. When using decision cohorts to assess FDA’s performance on this PMA, it would be included in the performance data for 2008, rather than being compared to how FDA performed on all other PMAs received in 2006. Performance metrics based on decision cohorts compare applications that were received in many different years; therefore, there is no baseline upon which to make a comparison.

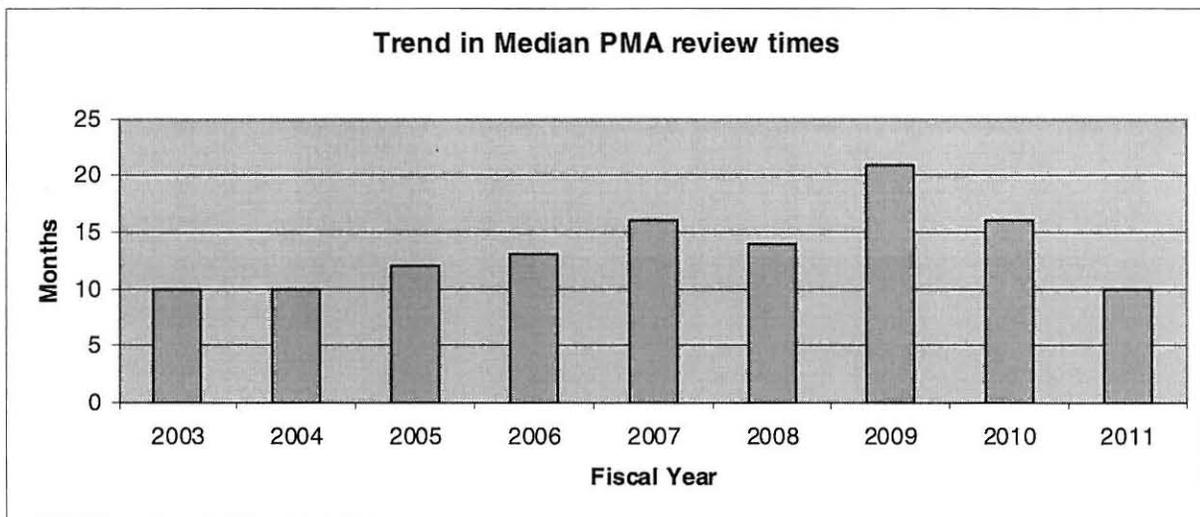
When FDA tracks its performance, we use receipt cohorts so that we know how we performed on applications we received in each year and we can identify the outliers. We also can track other performance trends by keeping track of how we review applications we received in a given year, because that metric allows us to gauge our work during the time we were actively reviewing an application. We can see how much time we took to review an application as compared to how much time industry took to respond to requests for information. We can also better assess the impact of reviewer attrition rates during those years, overall submission volume, and other factors on review times. Using decision cohorts, as is done in the CHI/BCG survey, eliminates these subtleties from the data and paints a less meaningful picture of the Agency’s review performance.

2. Please comment on the time to decision data presented in the study.

As discussed above, the CHI/BCG survey notes that “complex PMA submittals saw review periods increase 75 percent over the MDUFMA I (2003-2007) average to 27 months in 2010.” However, over the past nine years, the average (mean) time to reach a

decision on an original PMA has varied. The number of PMAs FDA receives each year is relatively small. Therefore, the mean review time can be significantly affected by one or two outliers. Thus, it is most appropriate to use the median time (middle value) to a decision when looking at trends in PMA data to eliminate the effect of outliers. However, the CHI/BCG survey uses the mean time to a decision, which can be skewed by one or two outlier submissions.

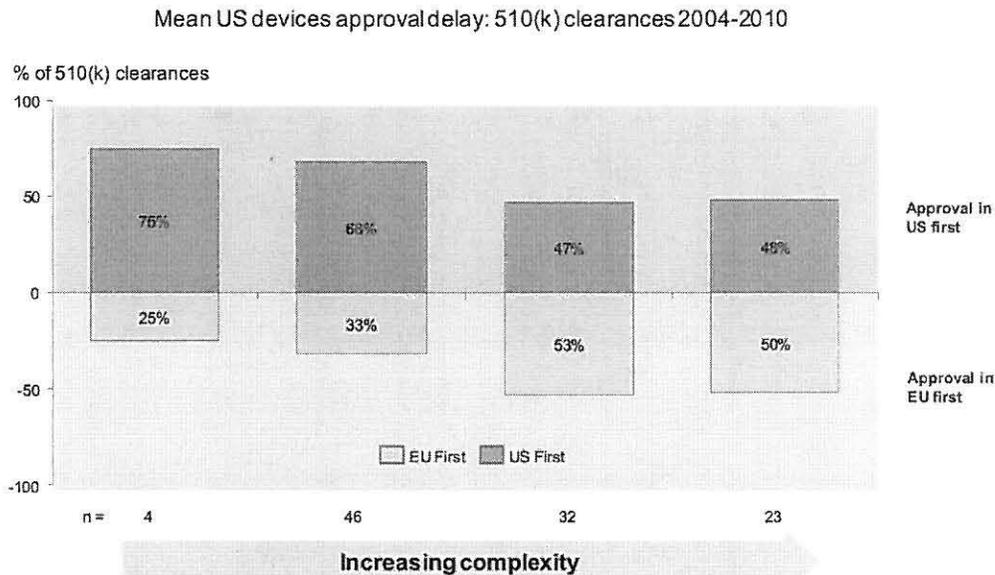
As is shown in the chart below, if the data used by CHI is presented using the median time to a decision (total time) rather than the mean time, it reflects that time to decision for PMAs in 2010 is not going up but rather is less than 2009 and closer to our performance in 2007.



The CHI/BCG survey also notes that “[f]or 510(k) submissions, the approval time has increased 43 percent to an average of 4.5 months in fiscal year 2010 over the average of about three months under the MDUFMA I years of 2003-2007.” While the percentage may sound high, the increase in total time to a decision is about six weeks. The increase in time to a decision described by the study is predominantly due to increases in the time it takes industry to provide the information necessary for FDA to make a decision. There are several reasons for this increase, including poor quality submissions from sponsors and FDA asking inappropriate questions.

3. Please discuss the methodology used in the study to compare EU and U.S. approval times.

The CHI/BCG survey claims that there is a clear trend that the more complex, and often cutting edge, a product is, the more likely it is to be approved first in Europe versus the United States. However, based on the following chart from the study, it is clear that 510(k)s without clinical data, which is about 90 percent of the 510(k)s we review and about 80 percent of the devices we review premarket, come on the market in the United States first as often or more often than in the EU.



Note: Represents original 510(k) applications without clinical data. Devices classified using EU standard I-IIa-IIb-III where classification I is least risky while Class III is most risky.
Source: Data collected from 10 different medical device companies, where total sample size n = 205 data based on 105 devices for which EU classification was available.

For more than a decade, Europe has often approved high-risk devices that would be subject to PMA applications in the United States more quickly for one simple reason: FDA, by law, requires that devices be both safe and effective. That is, devices must provide clinical benefit to American patients. Europe requires only that the device be safe and fit for its intended use with no requirement to demonstrate benefit. As discussed in response to this question regarding the Makower survey, comparing review times for the United States and EU is an “apples to oranges” comparison that does not take into account the difference in the review standards between the two regulatory regimes.

Makower Survey and CHI/BCG Survey

1. Are there issues not addressed at all in either study that might be helpful in a comparison of the EU and U.S.?

As discussed above, neither the Makower survey nor the CHI/BCG survey account for the significant differences in the regulatory requirements of the United States versus EU systems. These differences include:

- In the EU, manufacturers do not have to demonstrate that their products are effective at treating or diagnosing the disease or condition for which they are approved;
- In the EU, manufacturers pick and pay for private companies, of which there are over 70, to review and approve devices by giving them a CE mark. These decisions are kept confidential and are not released to the public or EU regulatory bodies. These private companies, called Notified Bodies, are each

certified by any one of the 27 member countries of the EU, but the decision to approve a device by one Notified Body applies to the entire EU. There has been near unanimous agreement in the EU that the oversight of Notified Bodies is inadequate and in need of significant improvement; and

- In the EU, there is little to no publicly accessible, centralized system for collecting and monitoring information about device approvals or safety problems.

Furthermore, comparisons between the U.S. and EU systems are challenging because the European device review process is less transparent than FDA's, due to the absence of publicly available information about device approvals and safety problems.

The difficulty in making robust comparisons has recently been highlighted by several prestigious European medical journals. These journals have noted that it is nearly impossible to assess the public health impact of the lack of an efficacy requirement, because there is no centralized source of data in the EU. Notified Bodies are not required to make their conformity decisions public and there is not a main database of recall information. There is anecdotal evidence that products reach the EU market that are later shown to be unsafe or ineffective, often when they are undergoing pivotal clinical trials to support U.S. approval.

The European Society of Cardiology (ESC) recently issued a “case for reform” of the European medical device regulatory system and their recommendations included creating a unified system, stronger clinical data requirements, and more accountability for notified bodies.¹ The ESC cites examples of many different cardiovascular technologies that were implanted in patients in the EU that were then proven to be unsafe and/or ineffective through clinical trials required under the U.S. system and removed from the European market. A recent article in the *British Medical Journal* discusses the opacity of the European medical device regulatory system, with regard to access to decisions regarding device clearances.² The article cites the FDA system's transparency as helping physicians to make informed decisions on which devices to use and giving patients access to information on devices that will be used on them.

In 2010, the clinical director of the UK's regulatory body overseeing devices said “I'm appalled at how many devices are brought to market with a lack of appropriate clinical data. ... A lot of devices have given me cause for concern because of the lack of adequate clinical evidence...”³ She went on to point out that many Notified Bodies do not know how to adequately assess, or challenge, clinical data. “These are commercial

¹ See “Clinical evaluation of cardiovascular devices: principles, problems, and proposals for European regulatory reform,” Fraser, et al., *European Heart Journal*, May 2011.

² See “Medical-device recalls in the UK and the device-regulation process: retrospective review of safety notices and alerts,” Heneghan, et al., *British Medical Journal*, May 2011.

³ See “EU must tackle clinical trial shortfalls as current lack of evidence is ‘appalling’,” Maxwell, Amanda, *Clinica*, July 2010.

organizations, many of whom are reluctant to challenge because they fear losing their clients and for their survival.”

Based upon identified weaknesses of the EU system, the European Commission has undertaken a review of its device regulatory system. As the Commission stated in 2008, “Experience indicates that the current system does not always offer a uniform level of protection of public health in the European Union. New and emerging technologies have challenged the current framework, highlighting gaps and pointing to a certain scarcity of expertise And finally, the legal system has been criticized as being too fragmented and difficult to follow and fraught with national variation.”⁴ Additionally, a report released by the Belgian Health Care Knowledge Centre⁵ calls upon the European Commission to implement reforms to make the EU review process for high-risk devices more like that of the United States.

Thank you again for your interest in this matter. If we can be of further assistance, please let us know.

Sincerely,


fo) Jeanne Ireland
Assistant Commissioner
for Legislation

⁴ See “Recast of the Medical Devices Directives: Summary of Response to the Public Consultation,” European Commission, December 2008.

⁵ See “The pre-market clinical evaluation of innovative high-risk medical devices,” KCE reports 158C, Belgian Health Care Knowledge Centre, 2011.