

Medical Device Regulation

United States v. European Union

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Introduction

The United States and European Union occupy approximately 74 percent of the global medical device market, and are the leaders in innovative health care product development.¹ Internationally, a medical device is defined as “any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purposes of:

- Diagnosis, prevention, monitoring, treatment or alleviation of disease or injury
- Investigation, replacement, modification, or support of the anatomy or of a physiological process
- Supporting or sustaining life
- Control of conception
- Disinfection of medical devices
- Providing information for medical purposes by means of in vitro examination of specimens derived from the human body and which does not achieve its primary 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.”²

The United States (US) has always been a leader in the industry but the European Union (EU) occupies a significant share of the market. With the Federal Drug Administration (FDA) often characterized as a stifling force for the industry, many experts argue for outsourcing US operations to the EU, where regulatory standards foster more flexibility. It is important to examine the evolution of regulation in both markets in order to develop policy that supports business opportunities as well as safety for consumers.

Regulatory Practices

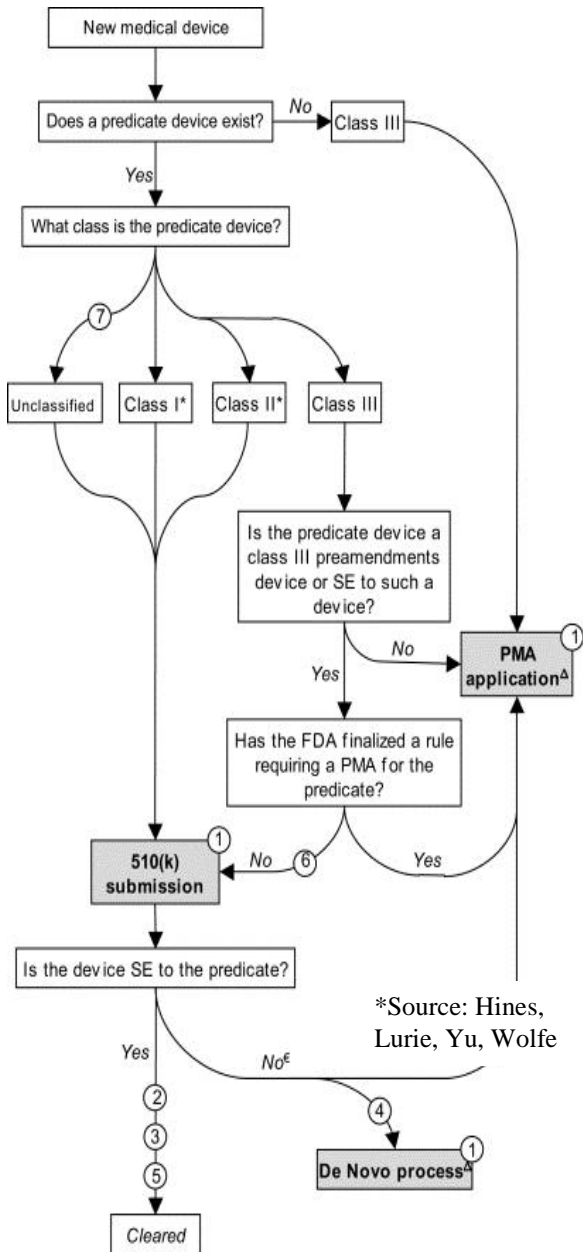
In the United States, medical device regulation falls under the jurisdiction of the Center for Devices and Radiological Health, which is a department of the Federal Drug Administration (FDA). Medical device regulation has been in practice since 1938 with the Federal Food, Drug, and Cosmetic Act, yet the European Union only adopted uniform regulation in 1990. The European Union’s move to create medical device regulation stemmed from the growth of “New Approach” directives, which were enacted to make trade easier within EU member states. Directives establish essential requirements, but allow for voluntary standards.³ If they follow the directives, devices will receive a Conformance Europeenne (CE) marking and can be sold in any EU country. The Directorate General of Health and Consumers under the European Commission controls the final CE process.⁴

¹ “Medical Equipment and Supplies Manufacturing-Industry Index.” *Hoovers*.

² “Medical Device Regulations-Global overview and guiding principles.” *World Health Organization*. 2003.

³ “CE Marking FAQs.-What is the EU’s New Approach to Product Certification?” *Export.gov*, http://export.gov/cemark/eg_main_017285.asp

⁴ Altenstetter, C. “EU and Member State Medical Devices Regulation.” *International Journal of Technology Assessment in Health Care*, 2003- <http://www.ncbi.nlm.nih.gov/pubmed/12701954>



In the United States, due to the Medical Device Amendments of 1976, medical devices are classified into three classes, Class I for low risk, Class II for medium risk, and Class III for high risk devices. Class III devices are defined by the FDA as “those that support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury.”⁵ This allowed different approvals for devices before they entered the market. The European Union similarly divides devices into four classes.

Class I and Class II devices acquire 510(k) approvals if they prove that the device had “substantial equivalence” to an already existing device, or predicate. A predicate device is a legally marketed device that has been approved by the FDA in the past. Applicants must also include the necessary user fee with the Pre-Market Notification 510(k). Devices intended for pediatric use are not required to pay the user fee.⁶

Currently every year, around 3,000 devices are approved through the 510(k) process. The FDA has met their current goal of reviewing over 90% of 510(k) submissions within 90 days, but that does not take into account the total time between submission and approval. The FDA frequently asks for additional information or a resubmission, and their definition of review time does not take that waiting period into account.

Therefore, from FY2005-FY2010 the average time to a final decision on an application has increased from 100 days to 161 days.⁷

Class III devices require premarket approval (PMA) from the FDA, that consists of clinical trial data proving the device is safe and effective. For a PMA, companies must submit clinical evidence that the device is safe and effective for its uses. If a device needs to be approved for use in the clinical trials, it needs to gain an Investigational Device Exemption (IDE). When the high risk device is the first of its kind, the FDA

⁵ “Device Advice: Comprehensive Regulatory Information.” *U.S. Food and Drug Administration*, September 20, 2012: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/default.htm>

⁶ “Premarket Notification [501(k)] Review Fees.” *U.S. Food and Drug Administration*, September 28, 2012: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/ucm134566.htm>

*Hines, J., Lurie, P., Yu, E., Wolfe, S. “Left to Their Own Devices: Breakdowns in United States Medical Device Premarket Review.” *Plos Medicine*, July 2010: <http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000280>

⁷ Seligman, P. “Healthcare: Products & Supplies.” *Standard & Poor’s Industry Surveys*, August 9, 2012.

will refer the submission to an outside panel of experts, and ask for their recommendation. The FDA then makes the final decision based on the outside recommendation, supporting data, and their own opinion.⁸

PMA user fees are significant, but the fee is waived if it is the first PMA submission from a company who makes less than \$30 million.⁹ The review time for PMAs is supposed to be 180 days, but the norm is usually much longer. The average review time has increased from 462 days in FY2003 to 627 days in FY2008.¹⁰

Decentralization

Unlike the American use of the FDA, the European Union currently operates its medical regulation through decentralized premarket controls. Every country has a Competent Authority, which is usually the main governmental health body, such as the Medicines and Healthcare Products Regulatory Agency in the United Kingdom. For all low risk devices, manufacturers must submit applications to their respective Competent Authority detailing the product. The Competent Authority can conduct inspections and review technical files, but usually after review it is sent to the European Commission (EC) for the CE mark.¹¹ For medium and high risk devices, companies must contract through one of the 78 notified bodies, which act as an outside reviewer and tester. For a fee, the notified body completes a conformity assessment to establish that the benefits of the device outweigh any risks. The notified body fee ranges from \$10,000-\$15,000, and often includes post market surveillance and support services.¹² The conformity assessment is then sent to the Competent Authority for review, then to the EC for the CE mark. The notified bodies are for profit entities, while the Competent Authorities play a public health role, balancing the approval for safety and effectiveness.

Similar to EU Notified Bodies, the FDA created a pilot program in 1997 to validate the use of third parties to approve devices. In attempt to speed up the approval times for 510(k) approvals, Accredited Persons conduct the primary reviews for the devices, and then send it to the FDA for final approval. The FDA is required to provide a decision within 30 days of that submittal. The third party review exempts companies from paying the user fees, but they then have to pay the Accredited Persons for their services.¹³ The third party fees are estimated to be between \$7,000 and \$12,000.¹⁴ The Third Party Review program mimics the strongest aspect of EU regulation, and attempts to relieve the FDA of cumbersome responsibilities. It allows companies to gain

⁸ "PMA Review Process." *U.S. Food and Drug Administration*, June 8, 2011:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm047991.htm>

⁹ "PMA Review Fees." *U.S. Food and Drug Administration*, September 28, 2012:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm048161.htm>

¹⁰ Seligman, *op. cit.*

¹¹ Kramer, Xu, Kesselheim, *op. cit.*

¹² Halpaus, Y. "Something Funny Happened on the way to the Notified Body." *Qnet LLC*. <http://www.ce-mark.com/nbs.html>

¹³ "Third Party Review." *U.S. Food and Drug Administration*, April 26, 2006:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ThirdPartyReview/default.htm>

¹⁴ Mundy, A., Favole, J. "Third-Party Reviews of Devices Come Under Scrutiny at the FDA." *Wall Street Journal*, March 15, 2010:

<http://online.wsj.com/article/SB10001424052748703447104575117892340074732.html>

*Hines, J., Lurie, P., Yu, E., Wolfe, S. "Left to Their Own Devices: Breakdowns in United States Medical Device Premarket Review." *Plos Medicine*, July 2010:

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000280>

more guidance for device approval through non-governmental entities. By decentralizing device approval, the US is trying to learn from the EU's approval efficiency.

FDA Accredited Persons for the Third Party Review Program

Bsi Healthcare	Center for Measurement Standards of Industrial
Dekra Certification B.V.	Intertek Testing Services
NIOM-Nordic Institute of Dental Materials	Pharmalink Technical Group, LLC
Regulatory Technology Services, LLC	Tuv Rehinland of North America, Inc.
Tuv Sud America Inc.	Underwriters Laboratories, Inc.

Safety and Coordination

To maintain an effective American device industry, the FDA creates current good manufacturing practices (CGMP) that device makers should follow. These CGMP provide a framework for manufacturers to develop their own quality system that tailors to their work. The FDA also provides labeling guidelines.

American companies must comply with post market surveillance, which requires medical device companies to submit a report to the FDA within 30 days if there are any deaths or serious injuries. They must submit a report in 5 days if there is something that requires action to prevent any injury. User facilities must report any deaths to the manufacturer and the FDA, and any serious injuries just to the manufacturer. All of these reports are in a public database called Manufacturer and User Facility Device Experience. With this information, the FDA has the power to perform inspections if necessary and institute recalls.¹⁵ In addition any business involved with manufacturing and distribution of medical devices must register with the FDA. This establishment registration must be done electronically every year, and includes an annual fee, which for FY2013 is \$2,575. Also included with the registration is a list of all the devices made and any activities performed on devices.¹⁶

In the EU, safety is not addressed as thoroughly as in the US. Since the safety discretion is delegated to the Competent Authority, there is a lack of standards across Europe, with countries operating at different levels of scrutiny. There are no external experts involved, and no coordination throughout the EU for similar devices. This leads to a possibility of getting rejected in one country, but then going to another one that has a more lenient approval process. Once the Competent Authority sends the submission to the EC, they have no post market power, therefore leaving more opportunity for safety risks. No data exists to trace the devices, even though some countries have an electronic registry. The EC operates the European Databank on Medical Devices (EUDAMED), which is only available to competent authorities, but is not used appropriately. Even though countries have retained significant power, they all can achieve the CE mark in different ways, which indicates a prevalence of unfairness.¹⁷

Look to the Future

The US and EU are working to adapt changes that will make their regulatory systems safer and simpler. They are continuing to learn from each other and use similar principles that are successful. Although both systems are being updated, the US system is still much more advanced than the EU in many areas. The most recent updates to US medical device regulation are the Medical Device User Fee and Modernization Acts in 2002, 2007, and

¹⁵ Kramer, Xu, Kesselheim, *op. cit.*

¹⁶ "Device Registration and Listing." *U.S. Food and Drug Administration*, October 10, 2012: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/RegistrationandListing/default.htm>

¹⁷ Kramer, Xu, Kesselheim, *op. cit.*

2012. These laws require manufacturers to pay fees for approval applications, in the goal of reducing FDA burden. Most recently, the 2012 Act, which will be in effect until October 1, 2017, called for the hiring of 200 more full time employees to speed up approval time. The FDA is also mandated to decide on approval applications within 90 days of active review for 91% of the submissions.¹⁸ The amendments also solidify continued support for the third party review program. The program now includes ten accredited persons for a multitude of eligible devices.¹⁹ Most importantly the amendments authorize an independent consulting group to evaluate the pre-market review program and recommend changes to clarify substantial equivalence and Class II device requirements.

By including medical device manufacturers, public health organizations, and advocacy groups such as the National Venture Capital Association and Avamed, the FDA can have a better understanding of the implications of their actions. Most recently, within the Affordable Care Act, the Medical Excise tax was passed, which starting in 2014 will impose a 2.3% tax on all sales of devices. This has implications for transforming the market in the United States, since all manufacturers will have to pay regardless of their country of origin. Since the U.S. is still the most profitable medical device market in the world, everyone will shoulder the burden. It is estimated that at least 14,500 American jobs will be lost, since the ever increasing regulation and tax will be a huge hindrance to small and mid-size companies, which make up 91% of the US medical device market.²⁰ Contrary to perception, the tax will not force companies to move to different countries, but perhaps it will encourage them to look for different markets that can make up for the lost profits.

The EU is just now updating their rules to encourage better oversight. On September 26, 2012, the European Commission adopted a new proposal to amend the medical device directives. The new provisions include better supervision of notified bodies, and more power for them to impose standards on manufacturers. The EU is also looking to expand the EUDAMED database, which will allow better traceability of devices for reasons such as recalls. They want to ensure all the necessary clinical data is being collected before device approval, and to reinforce safety requirements through labeling.²¹ Most importantly, to address the problem of coordination between member states, the EC will establish a Medical Device Coordination Group, an expert group which will facilitate information between national competent authorities and the EC.

There is still no performance evaluation of their system, in regards to approval times and other data, but hopefully this legislation will be the first step in building a more robust system that thrives on the different national systems. Associations such as Eucomed, represent the medical device industry and are fighting for a more efficient system. Both the US and the EU will look to international standards being developed by the International Medical Device Regulators Forum for future guidance. This group includes Australia, Brazil, Canada, Europe, Japan, and the United States, with the World Health Organization overseeing their work. The Forum will hopefully allow global leaders adopt standards such as a unique device identifier (UDI) that will allow better post market surveillance all over the world.²²

¹⁸ Bauman, *op. cit.*

¹⁹ "MDUFA Performance Goals and Procedures." *U.S. Food and Drug Administration*, April 18, 2012: <http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM295454.pdf>

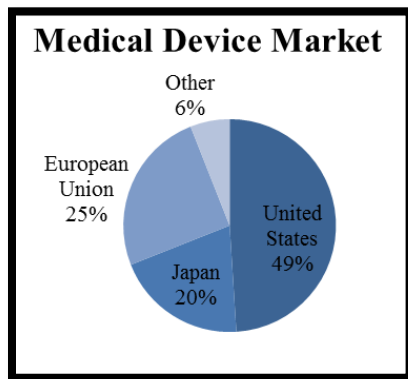
²⁰ Ramlet, M., Book, R., Zhong, H. "The Economic Impact of the Medical Device Excise Tax." *American Action Forum*, June 4, 2012: http://americanactionforum.org/sites/default/files/The_Economic_Impact_of_the_Medical_Device_Excise_Tax.pdf

²¹ "Questions and answers: Commission tables proposals for a new EU Regulatory Framework for Medical Devices and In Vitro Diagnostic Medical Devices." *European Commission*, September 26, 2012: http://ec.europa.eu/health/medical-devices/files/revision_docs/qa_20120926_en.pdf

²² "About IMDRF." *International Medical Device Regulators Forum*: <http://www.imdrf.org/about/about.asp>

Although the EU is often viewed as a better regulatory environment for the medical device industry, their only true advantage is in a decentralized review process. They still lag far behind in many other aspects such as safety and accountability, and it is important they continue to develop their system. The US should work to simplify its regulatory system and allow companies to have the freedom to develop innovative products which meet high standards of quality.

Business Case



Despite the United States' advanced regulatory system, misconceptions still exist regarding US market power. The global market for medical devices has now reached \$340 billion in sales. The biggest markets include the United States, Japan, Germany, France, and Italy, and those countries comprise more than 75% of device consumption. The United States is the largest market, accounting for around 11,000 companies that generated \$105.8 billion in 2011. The market is dominated by large companies, such as Baxter International and Medtronic, with 50 of the biggest corporations making up for 60% of the revenue.²³ Companies make gross margins anywhere between 50-70% and the larger ones invest 5% of their revenue in research and development. One of the biggest companies is Medtronic,

headquartered in Minnesota, who is the fourth largest American company. Medtronic generates \$16,184 million in sales, and employs 45,000 people.²⁴ The company focuses on developing devices for cardiac rhythm disease management, spinal and biologics, cardiovascular conditions, neuromodulation, diabetes, and surgical technologies. They have a 75.97% gross profit margin. 55% of their revenue is gained from the United States, while 26% is from Europe and Canada. Medtronic enjoyed a 4% growth in total revenue in FY2012, yet profits decreased by a substantial 25% because of litigation and expenses.²⁵ Medtronic also predicts that they could have to pay as much as \$145 million a year starting in 2013 to comply with the medical device excise tax.²⁶ In response to a more hostile American market, Medtronic has looked to emerging markets to compensate for lost profits. In 2012, they reported a 21% growth of sales in places such as the Asia Pacific and Latin America.

Not only does Medtronic have to deal with additional costs, they also face longer wait times for their products, in the US compared to the EU. Recently, on December 3, 2012, Medtronic received the CE mark for a new glucose monitoring system for diabetic patients. It is estimated that this product could be a part of a new potential \$1 billion global market. Yet, the system is still in clinical trials in the US.²⁷ Despite challenges in the US market, Medtronic has been in a leader in instituting improvements through areas such as post market surveillance. The company has assumed responsibility for monitoring more of its implantable devices, since the FDA lacks the efficient framework to do so.²⁸ Medtronic has also been a driving force in the newly formed

²³ "Medical Equipment and Supplies Manufacturing-Industry Index." *Hoovers*.

²⁴ "Medtronic, Inc.-Company Overview." *Hoovers*.

²⁵ "Transforming for Growth-2012 Annual Report." *Medtronic*, 2012:

http://annualreport.medtronic.com/wcm/groups/mdtcom_sg/@mdt/@corp/documents/documents/ar12_annual_report_final.pdf

²⁶ Edney, A., Cortez, M. "Medtronic Second-Quarter Profit Falls on Litigation Costs." *Bloomberg*, November 20, 2012: <http://www.bloomberg.com/news/2012-11-20/medtronic-second-quarter-profit-falls-on-litigation-costs.html>

²⁷ Garde, D. "Medtronic snags CE mark for critical-care glucose monitor." *Fierce Medical Devices*, December 3, 2012: <http://www.fiercemedicaldevices.com/story/medtronic-snags-ce-mark-critical-care-glucose-monitor/2012-12-03>

²⁸ Yukhananov, A. "Medtronic to boost safety monitoring of devices." *Reuters*, April 17, 2012:

<http://in.reuters.com/article/2012/04/16/us-medtronic-safety-idINBRE83F15120120416>

Medical Device Innovation Consortium, a new partnership that will bring government officials, industry professionals, and research experts together to improve device testing.

Europe also makes up a substantial part of the market, accumulating sales of \$132 billion in 2009, and investing 8% into research and development. Germany, the United Kingdom, and France make up 57% of all European sales. Europe's 22,500 medical device companies employ 500,000 people and are growing 5% per year.²⁹ Novo Nordisk is a powerful pharmaceutical company that also produces devices. They currently generate \$11,557.47 million and employ 32,000 employees around the world. Novo Nordisk has a 82.13% gross profit margin based on their 50% share of the world diabetes market.³⁰ Their medical device operations are mostly occupied by insulin delivery systems, as they are the first company to develop an insulin pen.³¹ In 2011, sales of protein-related products still increased by 5% in the US, despite negative growth of 5% due to the Affordable Care Act. It is evident that even with new health reform, the American medical device market still has better profit opportunities, as Novo Nordisk experienced a 1% decline in sales in the E.U.³² Although Novo Nordisk is still making profit despite regulatory burdens, many small medical device companies do not have that power. In the E.U., 80% of medical device companies employ less than 250 people; while small to medium companies comprise 91% of the American industry. These smaller entities struggle with complying with the complicated regulations, and now paying the significant medical device excise tax in the U.S.

Policy Recommendations

Critics so often have the prediction that American medical device companies will move to Europe because it is a less hostile environment for development and innovation. Yet, the biggest market is still the United States, and regulatory problems apply to everyone who tries to gain profits there. So even if a company moved to Europe, it would still have to go through FDA approvals to sell in the United States, which is their greatest opportunity for profit. As seen through companies like Asante Solutions, the US is still the premiere landscape for medical devices, but it is important to continue to cultivate these companies and encourage investors to seek them out because of their opportunity to save lives. Experts have recommended 510 (k) reforms to clarify requirements for Class II devices, and an improvement in post market surveillance. These are all necessary impending changes that could be better implemented by third party organizations, rather than further burdening the FDA.

An expansion in the American third party review program could aid all medical device companies. By allowing more personal and quicker support in pre-market review, bigger companies could gain more profit and smaller companies could better navigate the FDA process. By allowing private companies to train experts in medical devices, the approval process could cater to each individual company's needs. Concerns exist regarding the use of third parties to push unsafe devices through regulation by unqualified companies, but the FDA should develop the power to grant certification to the third parties. Like it is done in the E.U., the third parties should be subject to frequent surveillance and inspections. By opening this market, companies would have incentive through competition to develop quality services that encourage safety. Attempts have already been made by the US to develop this system internationally, by recognizing the work done by European notified bodies. The Mutual Recognition Agreement between the E.U. and U.S. would have allowed a process for notified body approval to be considered by the FDA. Although this program never came to fruition, it shows how a developed American third party review system could work alongside the E.U. notified bodies, influencing each other to

²⁹ "Medical Technology-key facts and figures." *Eucomed Medical Technology*:

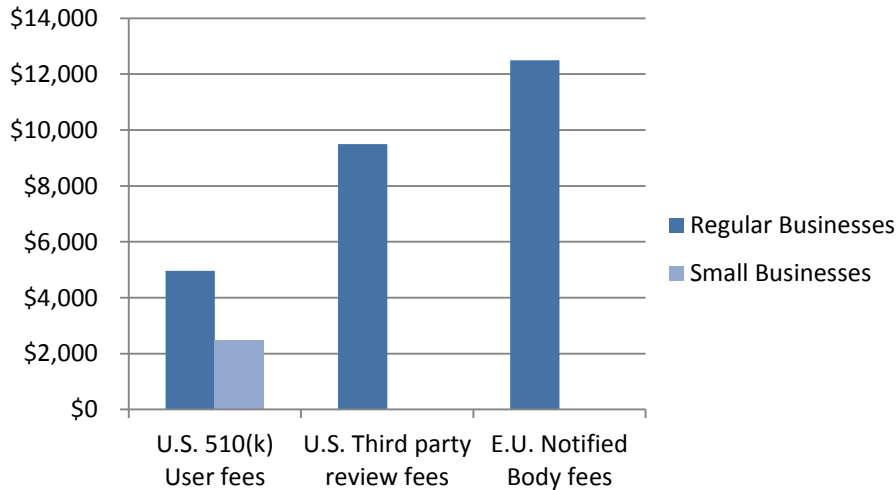
<http://www.eucomed.org/medical-technology/facts-figures>

³⁰ "Novo Nordisk A/S-Company Overview." *Hoovers*.

³¹ "Diabetes Care." *Novo Nordisk*, 2012: http://www.novonordisk-us.com/documents/promotion_page/document/diabetes_care.asp

³² "Novo Nordisk Annual Report 2011." *Novo Nordisk*, 2012: <http://annualreport.novonordisk.com/web-media/pdfs/Novo-Nordisk-AR-2011-en.pdf>

develop better services and lower costs.³³ The EU also needs to update their third party process, and ensure that safety is a priority. By improving both the US third party review and the EU notified bodies, they can compete and learn from each other. Right now, regular FDA user fees are substantially lower than using third party services, but by cultivating a competitive market, it would encourage rates to drop. Even so, arguably the customer service provided by third parties is worth the extra money.



The United States has also considered taking ISO 13485 into account, which is the International Standards Organization list of requirements for medical devices. Meeting these requirements is usually the first step in European approval, but the U.S. continues to ignore them. Third parties can develop to understand those guidelines, and use them to better prepare applications for FDA approval. The FDA is still one of the only regulatory bodies in the world that relies on inspections from its own staff for medical devices, and it is essential that they adopt more international friendly regulations.³⁴ The U.S. has already started evaluating its system and receiving recommendations for improvements. Among many suggestions, some have asked “that CDRH explore the feasibility of requiring each manufacturer to provide regular, periodic updates to CDRH listing any modifications made to its device without the submission of a new 510(k) and clearly explaining why each modification noted did not warrant a new 510(k).”³⁵ Improvements such as these could be better implemented by third parties, who understand the situations of each client, and can adapt to their needs. As emerging markets develop, third parties provide an opportunity for the US to update their regulatory process in order to maintain their medical device market power.

³³ Winter, M. “Will FDA recognize ISO 13485 registration? Draft Guidance Document May Open the Door.” *LNE/G-MED*, October 2010: http://www.lne-america.com/fileadmin/user_upload/LNE_FILES/PDF/Progress_Report_-_October_2010_-_FDA_Report_on_ISO_13485.pdf

³⁴ Winter, *op. cit.*

³⁵ Bauman, *op. cit.*