# Innovation in neurosurgery: Evaluation of neurosurgical innovation, related ethics, and solutions

Muskens, I.S.

II

# Part 2: Ethics of neurosurgical innovation

# 5

# Introduction of Novel Medical Devices in Surgery: Ethical Challenges of Current Oversight and Regulation

**Ivo S. Muskens BSc, Saksham Gupta BSc, Alexander Hulsbergen, Wouter A. Moojen MD PhD MPH, Marike L.D. Broekman MD PhD JD**

***Summary**: Medical devices are an essential part of innovation in surgery and have tremendously improved patient outcomes. However, several medical devices have proven to be non-beneficial or even harmful to patients. Various forms of oversight and regulation are in place both in the United States (US) and in Europe to balance medical device safety and availability. Medical devices that are deemed safe receive FDA (Food and Drug Administration) approval or a CE-marking (Conformité Européenne), in the United States and Europe respectively. Although these approval processes vary, they share multiple ethical challenges with regard to risk-benefit ratio, informed consent, scientific validity, societal value, and justice towards patients. These include a possible lack of scientific validity as a result of exemption from formal evaluation. This also compromises informed consent as no data on efficacy and safety are available. Post-market surveillance is not mandatory which may put patients at increased risk. The differences in the approval processes also have ethical implications. High risk devices do not necessarily require a formal investigation in Europe. This*

Parts of this chapter have been published in Journal of American College of Surgeon **225**, 558-565 (2017)

*may unjustifiably put European patients at risks as most devices are approved in Europe first. Off-label use, which is allowed both in the US and EU, may increase risks for patients and compromises scientific validity as no form of oversight is in place. Potential change to current oversight mechanisms and legislation and the creation of awareness about the responsibilities of all involved parties to address current ethical challenges could aid device introduction. These changes should be aimed at minimizing risks for patients, adequate informed consent, methodologically sound evaluation of medical devices, and limiting disparities in current oversight and regulation.*

## Introduction

Innovation is at the heart of surgery, and innovative medical devices have contributed to advancements in surgery since its inception. Medical devices are instruments, implants, or mechanical agents intended to prevent, diagnose, or treat disease.[1] While device development has been critical in advancing surgery, not every novel device is an improvement over existing standards and unsafe medical devices can have deleterious consequences. Various devices, for example Poly Implant Prothèse (PIP) breast implants, vaginal meshes, metal-on-metal hip prosthesis, and interspinous devices (IDs) have been approved and applied to patients for years before safety studies uncovered major unforeseen side effects.[2–10]

Several forms of regulation and oversight have been created to ensure the safety of medical devices and the protection of patients in cases of investigational use. Regulation on a national level in United States (US) and an international level in the European Economic Area (EEA: the European Union (EU), Switzerland, Lichtenstein, Norway, and Iceland) ensure that medical devices gain approval before entering the market.

Current national and international regulations related to the innovation of medical devices in surgery pose several ethical challenges. In this perspective opinion piece, we review the current regulatory environment for medical device introduction both in the US and in the EEA and address the ethical challenges it creates.

## Summary of current legislation

The Food and Drug Administration (FDA) and Conformité Européenne (CE) are government bodies that are responsible for medical device evaluation in the US and EEA, respectively. FDA approval and CE-marking are required for clinical application of medical devices in the US and EEA, respectively (**Table 5.1**).

Table 5.1: Overview of the approval process for CE-marking and FDA-approval

| *Approval process* | | *CE-Marking* | *FDA Approval* |
|---|---|---|---|
| ***Device classification*** | **Class I/II** | Approval by national competent authorities based on safety and efficacy studies | 510(k) |
| | **Class III** | Approval by Notified Bodies based on safety and efficacy studies | PMA study |
| ***Exemptions from approval*** | | Devices deemed by national competent authorities to have low risk | IDE, 510(k) exemption, humanitarian exception |
| ***Post-market evaluation*** | | EUDAMED | MAUDE Database, MEDSUN device, "522 study" |

Legend: Abbreviations: CE: Conformité Européenne; FDA: Food and Drug Administration; PMA: pre-market approval; MAUDE: Manufacturer and User Facility Device Experience; IDE: Investigational Device Exemption; EUDAMED: European Database on Medical Devices

## FDA



The manufacturer of a medical device must register with the FDA to apply for approval and each device receives a classification.[11,12] According to the FDA: "Device classification depends on the intended use of the device and also upon indications for use." ... "In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned."[13]

However, the Product Code Classification Database provides classifications for specific devices, but does not create strict guidelines for the classification of novel devices.[14,15] Class I devices generally consist of relatively noninvasive products such as surgical gloves and instruments. Examples of class II devices are surgical meshes, absorbable sutures, and joint or vascular prostheses. Finally, class III devices are invasive devices that generate or modulate biological signals such as spinal stimulators and cochlear implants.[16]

The manufacturer must provide premarket notification (510(k)) of request for approval to the FDA for class I and II devices.[17] The 510(k) communication must contain evidence that compares the safety and efficacy of a novel device with a device regarded by the FDA to be "substantially equivalent" without further specification.[17] However, class I and II devices may be exempt from the 510(k) process by the FDA.[14,18] Conversely, the manufacturer must provide pre-market approval (PMA) studies to the FDA for class III medical devices.[11,19], Medical devices may be altered after approval through the PMA supplement pathway, which are rarely accompanied by a trial.[20-23]

The FDA may demand post-market surveillance known as "522 studies" after device approval to identify possible long-term complications and rare adverse events.[24-26] However, the FDA may only remove an approved device from the market because of concerns of safety, but not due to lack of efficacy.[23] The FDA's Manufacturer and User Facility Device Experience (MAUDE) is a registry that allows physicians, manufacturers, and patients to report complications from registered medical devices independently.[27] Also, 280 hospitals work together with the FDA and provide data to the online adverse event program "Medical Product Safety Network" (MedSun) to identify adverse events from medical devices.[28,29]

There are several circumstances in which FDA approval is not necessary to bring

a device to market. For instance, Investigational Device Exemption (IDE) allows the usage of a device for investigation in a clinical trial, in an emergent case, or in the compassionate use setting.[15,30-32] Furthermore, devices manufactured by surgeons for sole usage in their own practice do not require approval.[11] Finally, a medical device may receive a "humanitarian device exception" for treatment of rare disorders.[28]

### CE-marking

Manufacturers must obtain CE-marking before a medical device is allowed onto market in the EEA and Turkey.[33-36] Furthermore, non-EEA based manufacturers require an authorized representative within the EEA to have their devices approved.[37] Three classes of medical devices based on associated risk related to invasiveness, reusability, potential use as an implant, use of a power source, and use near a critical anatomical location.[38,39]

The EU appoints national Competent Authorities, such as the Medicines and Healthcare Products Regulatory Agency (MHPRA) in the United Kingdom, to grant the CE-mark for low risk devices.[28] For higher risk devices, medical device companies are obligated to seek review for CE-marking by private, EU-authorized, third-party Notified Bodies, which review the efficacy and safety of the device.[28,40,41] CE-marking differs from FDA-approval as it does not require a trial to demonstrate safety and efficacy, even for class III devices.[28,33] Finally, the European Database on Medical Devices (EUDAMED) serves as a repository for (post-market surveillance) data of medical devices collected by national Competent Authorities.[42]

The CE-marking review process has been suggested to be inconsistent.[28,43] Notified Bodies operate independently of each other and only one Notified Body has to give approval for the device in question.[28,43] This can result in medical device companies approaching Notified Bodies known to have less stringent approval protocols. Indeed, a group of Dutch reporters received a reported likelihood of approval greater than 90% for a tangerine net that was to be used for prolapse repair.[44]

### Off-label use

Both in the US and Europe, an approved medical device may be used for indications other than those it was initially approved for as long as the goal of its usage is to "practice medicine".[32,45] Studies have not compared off- and on-label use of medical devices, but the off-label usage of medical pharmaceuticals is independently associated with a higher rate of adverse events than on-label usage.[46] Risks may be even greater for medical devices due to different anatomical features and biophysical tissue properties in different pathologies. For instance, off-label use of rhBMP, which is also registered as a device, in anterior cervical spine surgery resulted in several adverse events such as heterotopic ossification, osteolysis, hematomas, and dysphagia.[47] This ultimately resulted in a formal FDA Public Health Notification Warning.[48,49]

## Ethical considerations

The gaps in current legislation in the US and EEA risk undermining the ethical principles of risk-benefit ratio, informed consent, scientific validity, societal value,

and justice.

## Risk-benefit ratio

Expected benefits should outweigh the estimated risks of introducing any innovation to be beneficial to patients. Medical devices used in the operating room are no exception. Benefits and risks have traditionally been defined in large comparative clinical trials and prospective follow-up studies, but preclinical studies and extrapolation from experience with other pathologies provide an estimate of benefit and risk with some inherent uncertainty. The knowledge of the risk-benefit ratio may be limited by a possible lack of standardization of clinical studies, varying quality of trials, and ineffective post-market surveillance.[19,26]

Several legislative loopholes allow the usage of medical devices with poorly defined risk-benefit ratios. Class I and II devices introduced in the US through the 510(k) exemption process do not have to undergo any clinical evaluation, preventing the rigorous definition of efficacy and risk.[14,18] For countries where devices receive a CE-marking, defining the risk-benefit ratio may be even more challenging as approval of all devices - including class III devices - do not necessarily require any clinical evidence of safety and efficacy.[28,33,38] Furthermore, the involvement of Notified Bodies in the approval process may introduce inconsistency and bias into the approval process, due to suggested variation in the approval process.[28,33,38] Also, off-label use with little or no previous experience may compromise patient outcomes as efficacy and safety are unknown. While surgeons may estimate benefit and risk through analysis of device usage for other indications, preclinical studies, and assessment of compatibility to a patient's anatomy, inter-provider variation may still cause the use of medical devices that are not beneficial for patients.



## Informed consent

Patients must be adequately informed of the potential risks and benefits involved with a treatment to make autonomous decisions about their health care. Uncertain risk-benefit ratios obfuscate the informed consent process and do not respect patient's autonomy. For instance, low-quality clinical trials producing weak data limit patients' ability to evaluate treatment options adequately enough to provide informed consent.[19,26,28,33,38] The inaccessibility and incomprehensibility of many of the databases for registration of adverse events limit the ability of patients and surgeons to evaluate outcomes of a certain device for themselves.[29,42,50] Furthermore, there is currently no legislation in place that requires a patient to be informed that a device is being used off-label during surgery. The CE-marking of class III devices without proper investigation effectively eliminates the need to discuss the untested nature of the device during the informed consent procedure.[28]

### Scientific validity

Scientific validity forms the basis of evidence-based practice and motivates the trust patients have in their surgeons. Clinical study of medical devices may range from pre-clinical study to randomized control trials (RCTs) comparing an innovative device to the standard of care. RCTs provide the highest quality clinical evidence from

a single trial, but are expensive and time-intensive to conduct. An RCT for every medical device is increasingly unfeasible and may stifle innovation altogether by increasing expense and decreasing speed of device introduction. Nevertheless, medical devices should have scientifically valid evidence justifying their introduction. The 510(k) exemption from FDA approval and the lack of requirement for trials in the CE-marking process do not guarantee evidence-based practice and may lead to patient harm.[14,18,28,33,38]

The Idea, Development, Exploration, Assessment, Long-term Follow-up (IDEAL) consortium of surgeons, statisticians, and epidemiologists has proposed the IDEAL-Device Framework (IDEAL-D) to introduce medical devices ethically.[51] It also suggests that after prospective investigational trials, a randomized comparison should be performed with the current standard of care as reference.[51] However, these requirements are rarely met, as seen with IDs that were compared with other devices instead of the gold standard lumbar decompression, as comparison with the gold standard is not required by the FDA.[2,23,52] In addition to problems during approval process, the quality of PMA studies varies greatly.[19] Off-label use of devices complicates the picture even more. The tempting logical leaps of using devices off-label for similar indications as those they have been approved for provide no evidence of the efficacy of the device.



Table 5.2: Responsibilities for all parties involved to improve regulation and oversight for the use of medical devices

| *Involved party* | *Possible means of improvement* |
|---|---|
| ***Legislator and oversight bodies*** | - Create financial incentive for manufacturers to produce more safety and efficacy data.<br>- Demand for clinical data showing efficacy and safety for devices that are currently approved through exemption.<br>- Improve requirements for class III device evaluation in Europe.<br>- Create alternative funding for device development (e.g. NIH).<br>- Introduce oversight for off-label use of medical devices (e.g. a mandatory registry). |
| ***Medical device manufacturer*** | - Change business model to produce more safety and efficacy data.<br>- Introduce medical devices simultaneously in the US and Europe.<br>- Introduction of industry guidelines for ethical introduction of medical devices. |
| ***Surgeon*** | - Present conflicts of interest to the patient through a mandatory statement.<br>- Participate in registries and Surgical Innovation Committees for off-label use of medical devices. |
| ***Patient*** | - Active participation in device development.<br>- Allow sharing of their data to aid evaluation of medical devices. |

### Societal value

For an innovation to be ethical from a societal perspective, the net benefit derived from an innovation has to outweigh the costs for society. No rigorous peer-reviewed studies have estimated the benefit and costs of medical device introduction for society, although an industry report suggests $34 million for 510(k) approved devices and $94 million for PMA approved devices.[53] Moreover, current oversight mechanisms do not provide an infrastructure to assess societal value. FDA bylaws prohibit analysis of cost-effectiveness in the approval process altogether.[23] That 50% of side effects in drugs are discovered after FDA approval suggest that some adverse effects that reduce the societal value of devices would not be discovered until after approval.[23] Therefore, patients may continue to suffer increased health care costs associated with innovative technologies without any appreciable benefit.

### Justice

Justice in innovation requires that the availability and associated risks are shared equally between all potential patients. The majority of medical devices is introduced in Europe first as a result of lower costs associated with the less strict regulation compared to the US.[54] This provides European patients with earlier access to medical devices compared to patients in the United States. In theory, this earlier access could lead to better outcomes for European patients due to improved standards of care. On the other hand, European patients may face increased risks due to the use of relatively untested medical devices compared to American patients.[54]



## Recommendations for improvement of oversight and regulation

All involved parties - the device manufacturer, the regulation authority, the surgeon, and the patient - could improve current oversight environment for the introduction of medical devices and accept their respective responsibilities (**Table ??**). Shared goals could include patient safety, patient autonomy, surgeon support, and the facilitation of evidence-based practice in a climate of continuous innovation.

### Legislator and oversight bodies

Legislators and oversight bodies could create legislation targeted towards removing the lapses in device introduction legislation. Incentives for manufacturers could be shifted from financial gain to patient safety and device efficacy by creating a financial incentive to conduct and publish pre-clinical and methodologically sound trials. For instance, FDA and CE-approval could require at least Level 2 evidence prior to approval and provide funding for manufacturers organizing Level 1 evidence studies, perhaps similar to the IDEAL-D framework.[51] This could also reduce the disparity in regulation between the US and Europe, ending the current practices of earlier introduction of devices in Europe, that may be associated with earlier access to potentially beneficial devices or increased harm for European patients.[54] These oversight bodies would also benefit from more organized structures to monitor the long-term outcomes and evaluation of rare adverse events to minimize risks faced by patients and

ensures scientific validity.

Alternatively, grants by government bodies could motivate financially-driven decisions by manufacturers away from the short-term aims encouraged by venture capital and towards long-term patient benefit.[51] Financial incentives may be limited by a cap on the funding by private parties, as this type of funding has been shown to influence outcomes in pharmaceutical trials.[55,56]

Legislative authorities could introduce oversight for off-label use of medical devices that treats medical devices as separate entities from pharmaceuticals. One solution could be to allow off label-use only if the procedure is registered with an oversight body and outcomes are reported. This offers the possibility to study outcomes in a systematic fashion, while at the same time respecting the judgment of the surgeon.

Stronger centralized systems that automatically store all data relevant to adverse outcomes, such as the "National Evaluation System for Health Technology," could greatly aid identification of unwanted and long-term outcomes as an adjunct to existing databases.[57,58] For example, a centralized registry recently showed that a cardiac medical device offered inferior outcomes after identification of adverse events.[59] An increase of post-market surveillance studies and implementation of registries could limit the duration a medical device is allowed onto the market.



## Medical device manufacturer

The manufacturer has the primary responsibility to provide a product proven to be reliable and effective. Financial incentives do not align with this responsibility: most incentive structures encourage companies to acquire reimbursement for their medical devices to pay back investors and make profits.[60] The Medical Device Manufacturers Association could introduce guidelines and standards for the ethical introduction of devices together with an associated trademark as a form of self-regulation to achieve safer medical device introduction, as is seen in the food industry.[61] The medical device industry could also collaborate with oversight bodies, surgeons, and patients to work more transparently by generating and providing extensive safety and performance data, comparable to the aviation industry.[62]

## Surgeon

Surgeons are the most direct participants in medical device innovation. They make conscious and creative decisions to innovate, and in the process, they weigh the balance between the benefits and risks of innovation. Financial and professional conflicts of interest (COIs) may influence the risk-benefit calculations surgeons make. Especially in Europe, more uniform legislation on an international level could limit financial gains from COI as regulation varies among EU countries.[51,63,64] A publicly accessible registry that includes all financial contributions could improve transparency towards patients.[51,63,64] In the US, the Sunshine Act mandates that all payments from the industry to physicians are registered in a transparent database. This database showed that, on average, neurosurgeons received $30,718.02 from companies in 2014.[65, 66] A cap on the amount a surgeon receives from the industry could limit COI. Another solution could be a requirement for surgeons to register the use and outcomes of a device for which potential COIs exist.

Surgeons may alter their informed consent process as well. A statement that includes the manufacturer, the amount of compensation, and alternative treatment options within the informed consent process could increase transparency towards the patient. Furthermore, an informed consent procedure that includes description of all available scientific evidence could ensure that the patient is truly informed.[28,33]

Registries created by surgeons to track outcomes from off-label use of devices could help to ensure patient safety and scientific validity on a hospital level. Within this registry, surgeons could be responsible for the evaluation of factors that government administrators and manufacturers cannot intuit, including surgical learning curve, long-term functional outcomes, and device-specific adverse events. Professional societies could create Surgical Innovation Committees (SIC) to provide a forum for surgeons to discuss and evaluate device-related innovation.[67] The SIC could be made responsible for appropriate oversight of innovation and a discussion panel on an institutional level as an adjunct to national oversight by the FDA.

### Patients



Finally, patients have an essential role in the ethically sound introduction of medical devices. Patients who benefit from innovations carry some responsibility towards future patients, as the quality of their care is partially the result of risks taken by patients that preceded them.[68,69] Patients could participate in patient organizations that collaborate with manufacturers and legislators in setting priorities for medical devices. Patients could help define the limits of acceptable risk to safety as they will be the actual participants for the required trial. In addition, patients should be open to sharing their (electronic health record) data for safety monitoring.[68] At the same time, we recognize that patients can have an optimism-bias, resulting in over-optimistic expectations of devices, which could make them inclined to accept more risks. Therefore, we believe that patients should not be made responsible for the clinical evaluation of the devices for approval or for post-approval surveillance.

## Conclusion

The oversight and regulation for the introduction of medical devices in surgery carries many unique ethical challenges. The need to strike a balance between patient safety and innovation and circumstances in which oversight or regulation may be lacking form the basis of many of these challenges, that relate to risk-benefit ratio, informed consent, scientific validity, societal value, and justice. We outline the current legislation oversight and its ethical challenges for the surgeon to consider. Potential changes of current oversight mechanisms and legislation and creating awareness about the responsibilities of all involved parties to address current challenges to the introduction of medical devices, could aid ethically sound introduction of medical devices in surgery. In the end, improving quality of patient care should be ultimate shared goal.

## References


1. US Food and Drug Administration. What is a medical device? https://www.fda.gov/AboutFDA/Transparency/Basics/ucm211822.htm.AccessedApril10,2017.

2. Moojen WA, Arts MP, Jacobs WC, et al. Interspinous process device versus standard conventional surgical decompression for lumbar spinal stenosis: randomised controlled trial. Br J Sports Med. 2015;49(2):135.

3. Moojen WA, Arts MP, Jacobs WC, et al. Interspinous process device versus standard conventional surgical decompression for lumbar spinal stenosis: randomized controlled trial. BMJ. 2013;347:f6415.

4. Griffin WL, Nanson CJ, Springer BD, Davies MA, Fehring TK. Reduced articular surface of one-piece cups: a cause of runaway wear and early failure. Clin Orthop Relat Res. 2010;468(9):2328-2332.

5. Langton DJ, Jameson SS, Joyce TJ, Hallab NJ, Natu S, Nargol AV. Early failure of metal-on-metal bearings in hip resurfacing and large-diameter total hip replacement: A consequence of excess wear. J Bone Joint Surg Br. 2010;92(1):38-46.

6. Geller EJ, Babb E, Nackley AG, Zolnoun D. Incidence and Risk Factors for Pelvic Pain After Mesh Implant Surgery for the Treatment of Pelvic Floor Disorders. J Minim Invasive Gynecol. 2017;24(1):67-73.

7. Miklos JR, Chinthakanan O, Moore RD, et al. The IUGA/ICS classification of synthetic mesh complications in female pelvic floor reconstructive surgery: a multicenter study. Int Urogynecol J. 2016;27(6):933-938.

8. Oulharj S, Pauchot J, Tropet Y. PIP breast implant removal: a study of 828 cases. J Plast Reconstr Aesthet Surg. 2014;67(3):302-307.

9. Moschetta M, Telegrafo M, Cornacchia I, et al. PIP breast implants: rupture rate and correlation with breast cancer. G Chir. 2014;35(11-12):274-278.

10. Quaba O, Quaba A. PIP silicone breast implants: rupture rates based on the explantation of 676 implants in a single surgeon series. J Plast Reconstr Aesthet Surg. 2013;66(9):1182-1187.

11. US Food and Drug Administration. CFR - Code of Federal Regulations Title 21. 2016; http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=807.20. Accessed April 10, 2017.

12. Chohan MO, Levin AM, Singh R, et al. Three-dimensional volumetric measurements in defining endoscope-guided giant adenoma surgery outcomes. Pituitary. 2016;19(3):311-321.

13. US Food and Drug Administration. Classify Your Medical Device. 2014; https://www.fda.gov/medicaldevices/deviceregulationandguidance/overview/classifyyourdevice/. Accessed 2017, April 10.

14. US Food and Drug Administration. The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] Guidance for Industry and Food and Drug Administration Staff 2014; http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf. Accessed April 10, 2017.

15. US Food and Drug Administration. Device Classification Panels. 2017; https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051530.htm. Accessed April 10, 2017.

16. US Food and Drug Administration. Title 21–Food and drugs chapter I–Food and drug adminitration department of health and human survices subchapter H. 2016; http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=882. Accessed April 10, 2017.

17. US Food and Drug Administration. Code of Federal Regulations Title 21 Part 807: Establishment registration and device listing for manufacutrers and inittial importors of devices subpart E–Premarket Notification Procedures. 2016; http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=807&showFR=1&subpartNode=21:8.0.1.1.5.5.AccessedApril10,2017.

18. US Food and Drug Administration. Medical Device Exemptions 510(k) and GMP Requirements. 2016; https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm.AccessedApril10,2017.

19. Golish SR, Reed ML. Spinal devices in the United States-investigational device exemption trials and premarket approval of class III devices. Spine J. 2017;17(1):150-157.

20. Samuel AM, Rathi VK, Grauer JN, Ross JS. How do Orthopaedic Devices Change After Their Initial FDA Premarket Approval? Clin Orthop Relat Res. 2016;474(4):1053-1068.

21. Rome BN, Kramer DB, Kesselheim AS. FDA approval of cardiac implantable electronic devices via original and supplement premarket approval pathways, 1979-2012. JAMA. 2014;311(4):385-391.

22. US Food and Drug Administration. PMA Supplements and Amendments. 2002; https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050467.htm. Accessed May 24, 2017.

23. Carragee EJ, Deyo RA, Kovacs FM, et al. Clinical research: is the spine field a mine field? Spine (Phila Pa 1976). 2009;34(5):423-430.

24. US Food and Drug Administration. Current Postmarket Surveillance Efforts. 2014; http://www.fda.gov/MedicalDevices/Safety/CDRHPostmarketSurveillance/ucm348738.htm. Accessed April 10, 2017.

25. Rome BN, Kramer DB, Kesselheim AS. Approval of high-risk medical devices in the US: implications for clinical cardiology. Curr Cardiol Rep. 2014;16(6):489.

26. Reynolds IS, Rising JP, Coukell AJ, Paulson KH, Redberg RF. Assessing the safety and effectiveness of devices after US Food and Drug Administration approval: FDA-mandated postapproval studies. JAMA Intern Med. 2014;174(11):1773-1779.

27. US Food and Drug Administration. How the FDA will Create an Integrated National Postmarket Surveillance System. 2014; http://www.fda.gov/MedicalDevices/Safety/CDRHPostmarketSurveillance/ucm348751.htm. Accessed April 10, 2017.

28. Kramer DB, Xu S, Kesselheim AS. Regulation of medical devices in the United States and European Union. N Engl J Med. 2012;366(9):848-855.

29. US Food and Drug Administration. MedSun: Medical Product Safety Network. 2016; https://www.fda.gov/MedicalDevices/Safety/MedSunMedicalProductSafetyNetwork/. Accessed April 10, 2017.

30. Blumenthal S, McAfee PC, Guyer RD, et al. A prospective, randomized, multicenter Food and Drug Administration investigational device exemptions study of lumbar total disc replacement with the CHARITE artificial disc versus lumbar fusion: part I: evaluation of clinical outcomes. Spine (Phila Pa 1976). 2005;30(14):1565-1575; discussion E1387-1591.

31. US Food and Drug Administration. Code of Federal Regulations; Title 21–Food and drug, Chapter I–Food and drug administration department of health and human servises subchapter H–Medial devices part 812 investigational device exemptions. 2016; http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812&showFR=1. Accessed April 10, 2017.

32. US Food and Drug Administration. Guidance on IDE Policies and Procedures. 2015; http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080202.htm. Accessed April 10, 2017.

33. European Commission. Clinical evaluation: a guide for manufacturers and notified bodies (MEDDEV. 2.7.1 Rev.3). 2009; http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_7_1rev_3_en.pdf. Accessed April 10, 2017.

34. Fraser AG, Daubert JC, Van de Werf F, et al. Clinical evaluation of cardiovascular devices: principles, problems, and proposals for European regulatory reform. Report of a policy conference of the European Society of Cardiology. Eur Heart J. 2011;32(13):1673-1686.

35. Schweizerische Eidgenossenschaft. Abkommen zwischen der Schweizerischen Eidgenossenschaft und der Europäischen Gemeinschaft über die gegenseitige Anerkennung von Konformitätsbewertungen. 1999; https://www.admin.ch/opc/de/classified-compilation/19994644/index.html. Accessed April 10, 2017.

36. European Commission. Interpretation of the customs union agreement with Turkey in the field of medical devices. 2010; http://ec.europa.eu/DocsRoom/documents/10270/attachments/1/translations/en/renditions/native. Accessed April 10, 2017.

37. European Commission. Interpretative document of the commision's placing on the market of medical device. 2010; http://ec.europa.eu/consumers/sectors/medical-devices/files/guide-stds-directives/placing_on_the_market_en.pdf. Accessed April 10, 2017.

38. Hulstaert F, Neyt M, Vinck I, et al. Pre-market clinical evaluations of innovative high-risk medical devices in Europe. Int J Technol Assess Health Care. 2012;28(3):278-284.

39. European Commission. MEDICAL DEVICES: Guidance document - Classification of medical devices 2010; http://ec.europa.eu/consumers/sectors/medical-devices/files/meddev/2_4_1_rev_9_classification_en.pdf. Accessed May 24, 2017.

40. Kramer DB, Xu S, Kesselheim AS. How does medical device regulation perform in the United States and the European union? A systematic review. PLoS Med. 2012;9(7):e1001276.

41. Heinemann L, Freckmann G, Koschinsky T. Considerations for an institution for evaluation of diabetes technology devices to improve their quality in the European Union. J Diabetes Sci Technol. 2013;7(2):542-547.

42. The Eudamed Working Group. Evaluation of the "EUropean DAtabank on MEdical Devices" 2012; http://ec.europa.eu/growth/sectors/medical-devices/market-surveillance_nl. Accessed April 10, 2017.

43. Cohen D, Billingsley M. Europeans are left to their own devices. BMJ. 2011;342:d2748.

44. RADAR. Mandarijnennetje als implantaat: goedkeuring implantaten is een farce. 2014; http://radar.avrotros.nl/nieuws/detail/

mandarijnennetje-als-implantaat-goedkeuring-implantaten-is-een-far
Accessed April 10, 2017.

45. US Food and Drug Administration. "Off-Label" and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices - Information Sheet. 2016; http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm. Accessed April 10, 2017.

46. Eguale T, Buckeridge DL, Verma A, et al. Association of Off-label Drug Use and Adverse Drug Events in an Adult Population. JAMA Intern Med. 2016;176(1):55-63.

47. Epstein NE. Complications due to the use of BMP/INFUSE in spine surgery: The evidence continues to mount. Surg Neurol Int. 2013;4(Suppl 5):S343-352.

48. Schnurman Z, Smith ML, Kondziolka D. Off-label innovation: characterization through a case study of rhBMP-2 for spinal fusion. J Neurosurg Spine. 2016;25(3):406-414.

49. US Food and Drug Administration. FDA Public Health Notification: Life-threatening Complications Associated with Recombinant Human Bone Morphogenetic Protein in Cervical Spine Fusion. 2008; http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062000.htm. Accessed April 10, 2017.

50. Coelho DH, Tampio AJ. The Utility of the MAUDE Database for Osseointegrated Auditory Implants. Ann Otol Rhinol Laryngol. 2017;126(1):61-66.

51. Sedrakyan A, Campbell B, Merino JG, Kuntz R, Hirst A, McCulloch P. IDEAL-D: a rational framework for evaluating and regulating the use of medical devices. BMJ. 2016;353:i2372.

52. Moojen WA, Bredenoord AL, Viergever RF, Peul WC. Scientific evaluation of spinal implants: an ethical necessity. Spine (Phila Pa 1976). 2014;39(26):2115-2118.

53. Makower J, Meed A, Denend L. FDA impact on U.S. medical technology innovation a survey of over 200 Medical Technology Companies. November 2010 2010.

54. Hwang TJ, Sokolov E, Franklin JM, Kesselheim AS. Comparison of rates of safety issues and reporting of trial outcomes for medical devices approved in the European Union and United States: cohort study. BMJ. 2016;353:i3323.

55. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. BMJ. 2003;326(7400):1167-1170.

56. Lundh A, Sismondo S, Lexchin J, Busuioc OA, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev. 2012;12:MR000033.

57. Shuren J, Califf RM. Need for a National Evaluation System for Health Technology. JAMA. 2016;316(11):1153-1154.

58. US Food and Drug Administration. National medical device postmarket surveillance plan. 2012; http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm301912.htm. . Accessed April 10, 2017.

59. Resnic FS, Majithia A, Marinac-Dabic D, et al. Registry-Based Prospective, Active Surveillance of Medical-Device Safety. N Engl J Med. 2017.

60. Nelsen LL, Bierer BE. Biomedical innovation in academic institutions: mitigating conflict of interest. Sci Transl Med. 2011;3(100):100cm126.

61. Sharma LL, Teret SP, Brownell KD. The food industry and self-regulation: standards to promote success and to avoid public health failures. Am J Public Health. 2010;100(2):240-246.

62. Lewis GH, Vaithianathan R, Hockey PM, Hirst G, Bagian JP. Counterheroism, common knowledge, and ergonomics: concepts from aviation that could improve patient safety. Milbank Q. 2011;89(1):4-38.

63. Perlis RH, Perlis CS. Physician Payments from Industry Are Associated with Greater Medicare Part D Prescribing Costs. PLoS One. 2016;11(5):e0155474.

64. Arie S. The device industry and payments to doctors. BMJ. 2015;351:h6182.

65. Institute of Medicine Committee on Conflict of Interest in Medical Research E, Practice. The National Academies Collection: Reports funded by National Institutes of Health. In: Lo B, Field MJ, eds. Conflict of Interest in Medical Research, Education, and Practice. Washington (DC): National Academies Press (US) National Academy of Sciences.; 2009.

66. Babu MA, Heary RF, Nahed BV. Does the Open Payments Database Provide Sunshine on Neurosurgery? Neurosurgery. 2016;79(6):933-938.

67. Biffl WL, Spain DA, Reitsma AM, et al. Responsible development and application of surgical innovations: a position statement of the Society of University Surgeons. J Am Coll Surg. 2008;206(6):1204-1209.

68. Faden RR, Kass NE, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics. Hastings Cent Rep. 2013;Spec No:S16-27.

69. Faden RR, Beauchamp TL, Kass NE. Informed consent, comparative effectiveness, and learning health care. N Engl J Med. 2014;370(8):766-768.