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HEALTH TECHNOLOGY ASSESSMENT & TRANSFER

Market approval processes for new types of spinal devices: challenges and recommendations for improvement

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Abstract
Background Spinal pathology and related symptoms are among the most common health problems and are associated with high health care costs and productivity losses. Due to the aging population, these costs are further increasing every year. Another important reason for the increasing costs is the market approval of new technologies, such as spinal devices that are usually more expensive than the existing technologies. Previous cases of medical device failure led to concern about possible deficiencies in the market approval process.
Objective The objective is to provide an overview of U.S. Food and Drug Administration (FDA) regulation regarding spinal implants to delineate the challenges and opportunities that spine surgery currently faces.
Methods In this paper, two cases of market entries of spinal devices are presented and evaluated to illustrate these deficiencies.
Results Spinal implant regulation is facing several challenges. New spinal devices should increase patient outcomes and safety at reasonable societal costs. The main challenge is to have a rigorous evaluation before dissemination, while still leaving room for innovative behavior that thrusts the healthcare practice forward.
Conclusion We have provided recommendations to enhance spinal implant regulation and improve and ensure the patient's safety and the future of spine surgery.

Keywords Spinal devices · Market approval

Introduction

Spinal pathology and related back and neck symptoms are among the most common health problems and number one with respect to years lived with disability [1]. Care for individuals with spinal pathology and related symptoms are associated with high health care costs and productivity losses [2] and, compared to those without, cost an additional 86 billion dollars in the United States in 2005 [3]. Due to the aging population, these costs are further increasing every year. Another important reason for the increasing costs is the market approval of new and expensive technologies, such as spinal implants. However, in the USA and Canada, 88 % of orthopedic surgeons believe that new orthopedic technologies are overpriced and add little value in terms of patient outcomes [4].

It is important to safeguard patients' and societal interests. The chances of success increase when physicians and policy-makers adhere to the principles of evidence-based medicine (EBM) and Health Technology Assessment (HTA). EBM is the process of integrating scientific evidence with clinical expertise and patients' preferences and expectations to optimize clinical care [5]. HTA is a multidisciplinary field of policy-analysis that examines the medical, economic, social and ethical implications of the incremental value, diffusion and use of a medical technology in health care (http://www.inahta.org). Both EBM and HTA offer rigorous frameworks in evaluating medical

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technologies and health care interventions for possible market approval.

Previous cases of medical device failure led to concern about possible deficiencies in the market approval process. Recently, spinal surgical practice was struck by a widely recognized scandal involving the use of rhBMP [6–9]. Such deficiencies may lead to avoidable patient harm.

Here we focus on the procedural justification of new techniques in spinal surgery. We believe that regulatory mechanisms must become more rigorous. Our goal is to provide an overview of U.S. Food and Drug Administration (FDA) regulation regarding spinal implants to delineate the challenges and opportunities that spine surgery currently faces. To do so, two cases, including the X-Stop® (Medtronic Inc., Minneapolis, MN, USA) and the Dynesys® (Zimmer Inc., Warsaw, IN, USA) are presented. We conclude with recommendations for improving regulatory processes.

Methods

A literature study was conducted. First, the FDA websites were visited. Regulations, protocols and guidelines on medical devices (including spinal implants) and specific documents on the X-Stop® and Dynesys® were retrieved. Secondly, randomized controlled trials (RCTs) and cost-effectiveness studies of the X-Stop® and Dynesys® were gathered in PubMed, Embase and the Cochrane Database. Abstracts were assessed to select randomized controlled trials (RCTs), economic evaluations and review articles. All other studies including in vitro biomechanical studies, in vivo biomechanical studies, finite element studies, imaging studies, meeting notes, expert opinions, technical notes and articles responses were excluded. Furthermore, non-English language literature concerning these devices was not discussed in this study. Published reviews were used to cross-check all available references to find possible missing RCTs or economic evaluations. No additional literature was found.

Results

FDA market approval processes

To be able to notice deficiencies, it is necessary to briefly introduce the conventional FDA processes that lead to market approval of a spinal implant.

The FDA oversees medical devices and is responsible for the protection and promotion of public health by regulating the marketing of devices such that only those with demonstrated reasonable assurance of safety and effectiveness are marketed [10]. Medical devices are categorized into three Classes. Class I devices are deemed to be low risk and are subject to the least regulatory controls. Class II devices are higher risk devices than Class I and require stricter regulatory controls to provide reasonable assurance of the device's safety and effectiveness. Class III devices are the highest risk devices and are subject to the highest level of regulatory control, because they pose a significant risk of illness or injury to a patient. Here, we focus on class II and III devices, since nearly all spinal implants fall under these regulations [10].

A Class II device, typically requiring 510(k) clearance, cannot be commercially distributed until the FDA acknowledges that the device is 'substantially equivalent' to a previously approved device. A 510(k) pathway is by far the most common track for market entry [11]. For a 510(k), the FDA often relies upon well-designed bench and/or animal testing rather than clinical studies, unless there is a specific rationale for requesting clinical information to support a determination of substantial equivalence. However, the FDA may recommend a supporting clinical study if there are new indications for use.

Class III devices require premarket approval (PMA). The PMA process is more extensive and complicated and includes the submission of clinical data to support claims made for the device. A PMA will only be granted on the basis of substantial pre-clinical and clinical data from research conducted under an investigational device exemption [12]. This allows the investigational device to be used in a clinical study to collect the necessary safety and effectiveness data. The clinical studies submitted to support PMA applications should be designed and conducted in a manner that provides valid scientific evidence. When developing a trial to demonstrate safety and effectiveness for spinal systems, FDA recommends a multi-center, randomized controlled trial. There are no specific requirements for types of control groups, but guidance is often provided to sponsoring companies. The FDA recommends a 5- to 10-year follow-up period (http://www.fda.gov).

Finally, a device will be recommended for approval by an FDA advisory panel if the panel judges that benefits outweigh the risks. The panel also holds the right to demand additional data, before recommending approval. The FDA might decide to grant approval of a device with a requirement for additional post-approval study. In practice, only a limited number of companies are enforced to present post-market study requirements. The FDA also has the legal right to perform post-market surveillance and to recall medical devices if they are judged to jeopardize patient safety. Although these regulatory mechanisms seem sound, still, medical devices granted with a 510(k) or PMA that are distributed to the market may sometimes fail within years.

Case studies

Manufacturers generally claim that their new techniques contain features that are superior to standard care. Two recently developed techniques were the X-Stop® (Class III; PMA) and the Dynesys® [Class II; 510(k)]. These implants are used to illustrate regulatory processes for new spinal devices. A reconstruction of events is provided to emphasize market approval deficiencies. Note that similar deficiencies may also apply to market approval processes of other new techniques.

The X-Stop®

According to the FDA, the X-Stop® is designed to limit extension of the spine in the affected area, which may relieve the symptoms of lumbar spinal stenosis. Compared to the surgical standard, the X-Stop® claims to be less invasive, thereby reducing surgical trauma. The first FDA filing date of the X-Stop® was on the 6th of January 2004. Before final approval, the initial protocol was amended on April 1st, May 20th, August 2nd and December 27th, 2004, and on June 22nd and November 14th, 2005. The X-Stop® was finally granted approval with a PMA for clinical use on the 21st of November 2005.

A total of 167 publications were identified for the X-Stop®. Prior to its PMA, only five studies on the X-Stop® were published. These included a prospective randomized multi-center study (191 patients) [13], a study on preliminary experiences in ten patients only [14] and three in vitro studies [15–17]. Up to now a total of ten RCTs [13, 18–25] and three cost-effectiveness studies [26–28] were published.

The first study by Zucherman et al. was a multi-center RCT in which the X-Stop® (100 patients) was compared with non-operative treatment (91 patients) for lumbar spinal stenosis [13, 21]. The authors concluded that the X-Stop® offers a significant improvement in The Zurich Claudication Questionnaire over non-operative treatment after 1-year and 2-year follow-up [13, 21] and in improving quality of life [20]. Furthermore, the authors stated that, at 1-year and 2-year follow-up, results were similar to published reports on decompressive laminectomy, with considerably lower morbidity [13, 21]. However, the X-Stop® was only compared with non-operative treatment in this trial and the conclusion regarding similarity to decompressive surgery was not supported by a direct comparison with the current surgical standard.

Anderson et al. concluded in a small RCT (42 patients) that the X-Stop® was more effective after 2-year follow-up than non-operative treatment (33 patients) for the management of symptoms secondary to degenerative lumbar spondylolisthesis [19]. An RCT by Miller et al. compared the X-Stop® (86 patients) with a novel interspinous technique, the Superion® (80 patients) (Vertiflex Inc., San Clemente, CA, USA) [18]. This new technique was found to be similar to the X-Stop® for treating lumbar stenosis. Again, no comparison with the current surgical standard was provided. Finally, the most recent RCT by Stromquist et al. reported no statistically significant difference between decompressive surgery (50 patients) and implantation of the X-Stop® (50 patients) after 2-year follow-up [22]. However, they found a significantly higher re-operation rate compared to non-instrumented surgery, as was, among others, also reported by Verhoof in 2008 [29] and Deyo in 2013 [30].

Patel et al. published two separate RCTs [23, 24]. In 2014 the X-Stop®, being a FDA-approved interspinous spacer, was used as a control for the Superion® device. The authors included 250 patients at baseline. Finally, after 2 years 192 patients (77 %) were analyzed. In 2015, a similar comparison was made. However, the number of included patients was substantially larger ($N = 391$). The latter study was part of an FDA Investigational Device Exemption (IDE) pivotal trial. In both trials, The Zurich Claudication Questionnaire scores significantly improved for both types of surgical care compared to conservative care. The rates of complications and reoperations were similar between groups.

Lønne et al. published the most recent RCT regarding the X-Stop® in the beginning of 2015 [25]. The investigators compared the X-Stop® with minimally invasive decompression. The study was terminated after a midway interim analysis because of significantly higher reoperation rate in the X-Stop group (33 %). Besides Stromquist's RCT, the trial by Lønne is the only one that compared the X-Stop® with a form of standard surgical care.

Three studies were identified evaluating the cost-effectiveness of the X-Stop®. Skidmore et al. focused primarily on cost-effectiveness alongside a RCT (sponsored by Medtronic Inc.) comparing the X-Stop® with conservative care and laminectomy [27]. The authors used clinical outcomes, quality-of-life and economic data. They found that the X-Stop® yielded favorable cost-effectiveness ratios over both conservative care and decompressive laminectomy. However, the economic evaluation was based on a small study sample and the authors did not report the uncertainty of their incremental cost-effectiveness ratios. In contrast, Burnett et al. compared similar treatment options in a review study and found that laminectomy appears to be the most cost-effective treatment strategy for patients with symptomatic lumbar spinal stenosis [26]. Finally, Lønne et al. [28] found that there was a 50 % likelihood that X-Stop is cost-effective over minimally invasive decompression. The significantly higher cost of X-Stop® was ascribed to implant cost and significantly higher

reoperation rates. However, as stated above the study was terminated after a midway interim analysis because of significantly higher reoperation rate in the X-Stop group (33 %).

Deficiencies in the approval process of the X-Stop®

Zucherman et al. compared implantation of the X-Stop® with conservative treatment [13, 21]. Based on this study the FDA granted approval to the X-Stop® with a PMA. Such a decision can be considered incomplete, since the X-Stop® was not compared with standard decompressive surgery. Superiority of conventional decompressive surgery over non-operative care was previously established in many studies [31]. Therefore, it would be erroneous to infer that X-Stop® is equivalent to decompressive surgery, that is not what could be concluded on the basis of the original study by Zucherman et al. [13, 21]. Basically, it might be argued whether the scientific basis provided enough justification to build a PMA upon.

After PMA approval, nine additional RCTs were published comparing the X-Stop® with alternatively decompressive surgery, other instruments and non-operative treatment strategies [13, 18–25]. The RCTs of Stromquist's and Lønne were the only studies that compared the X-Stop® with decompressive surgery, the standard surgical procedure. As stated, no statistically significant difference between decompressive surgery and implantation of the X-Stop® was found on clinical outcomes, but the X-Stop® showed a significantly higher reoperation rate compared to non-instrumented surgery [22, 25]. Interestingly enough, in some studies the X-Stop® was even used as a control as part of a FDA-IDE study [23, 24].

In addition, it was striking that up to 2012 all RCTs, with exception of the trial by Anderson [19] came from the same research group. Furthermore, one or more of the author(s) received benefits for personal or professional use from a commercial party related directly or indirectly to the subject of the study: e.g., royalties, stocks, stock options, decision-making position [21]. It is well known that industry-sponsored research is generally more favorable over independent research [32].

Finally, the approval was contingent upon post-approval follow-up data submission for safety and efficacy at 2 and 5 years. The Condition of Approval Study (COAST), a prospective Phase IV 5-year post-approval study of the X-Stop® device was completed in 2012, but these results have not been published. Currently, the X-Stop® is still PMA approved although post-market surveillance and post-market studies have clearly contradicted the findings of the first study by Zucherman et al. and recommendations seem unfavorable due to a lack of long-term follow-up, regarding efficacy and adverse effects.[1] On the other hand, none of the studies cited actually contradict the finding that the X-Stop® produced greater symptom relief than conservative care. It could still be argued that the X-Stop® may have a role in elderly high-risk patients for whom symptom relief is sought and decompression surgery could be seen as risky intervention. For this population, long-term results may also have a different type of importance. It may be a situation where patients need to be well informed about multiple treatment options, and engaged in the decision-making. However, as stated the FDA may recommend a supporting clinical study if there are new indications for use, this has not been executed for this possible new indication and corresponding target-population of the X-Stop®.

The Dynesys®

The FDA indicates that the Dynesys® (Zimmer Inc., Warsaw, IN, USA) is intended to provide immobilization and stabilization of spinal segments as an adjunct to fusion in the treatment of and following acute and chronic instabilities or deformities and failed previous fusion. The claimed advantage of the Dynesys® is its motion preservation capacity and its ability to prevent adjacent segment degeneration [33]. Because fusion is not the end-point, no bone grafts are used, offering less invasive surgery and less surgical trauma. In March 2004, the Dynesys® received a 510(k) market approval, since it was considered to be 'substantially equivalent' to the Silhouette® spinal fixation system (also Zimmer Inc., Warsaw, IN, USA). The Dynesys® as a stand-alone device for non-fusion stabilization was later recognized by the FDA as a new type of treatment, and consequently Zimmer© had to apply for a PMA. On the 4th of November 2009, the PMA application for this device was rejected.[2] Withdrawal from the market might be argued being a success of the FDA, albeit delayed. Although a comprehensive review executed by the National Institute for Clinical Excellence (NICE) of the National Health Service (NHS) in the United Kingdom in 2009 based on available data found that the Dynesys is both safe and efficacious as a dynamic stabilization technique for some patients with intractable lumbar pain,[3] the gold standard for disc and facet joint degeneration with symptomatic instability still remains a rigid fusion technique [34, 35]. Currently, the Dynesys® is still globally the most

[1] https://wcis.ceiwc.com/dev60html/Pguide/MedicalGuides/Interspinous_Decompression_Device_X-STOP.pdf.

[2] http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM188734.pdf.

[3] http://www.nice.org.uk/guidance/ipg366/evidence/nonrigid-stabilisation-techniques-for-the-treatment-of-low-back-pain-overview2.

used dynamic stabilization system, although now used in the USA in patients with an 'off-label' indication only.

A total of 154 publications were identified for the Dynesys®. The approved 510(k) for the Dynesys® in March 2004 consisted of a review [36], a single prospective, non-randomized, non-controlled multi-center study (83 patients) [37] and an in vitro study [38]. None of these studies were performed primarily in the USA, which is one of the FDA's requirements.

Post-approval, one RCT by Yu et al. was published which included a total of 53 patients, allocated to a posterior lumbar interbody fusion (26 patients) or Dynesys® (27 patients) [39]. Patients in both groups clinically improved, but no statistically significant differences between groups were found after 3-year follow-up. Complications were similar between groups. In addition, in 2007 1-year preliminary results as a part of a multicenter randomized FDA-IDE clinical trial including a number of 101 patients were published [40]. However, this study had a non-comparative design. To our knowledge, no data on cost-effectiveness of the Dynesys® has been published.

Deficiencies in the approval process of the Dynesys®

It might be argued, considering the assumed equivalence of this device to the Silhouette®, that surgeons and the manufacturer were not specifically interested in publishing data on indications and patient selection criteria for the Dynesys®. However, from a clinical point of view, the Dynesys® is no ordinary posterior instrumentation technique because of the dynamic component of it.

The limited amount of published research before the Dynesys® was granted 510(k) clearance is especially disappointing because the Dynesys® was introduced on the European market in 1999. Over 40,000 patients have been implanted with this device since then [41], but with little published research. Thus, physicians did not report their clinical outcomes, even though the Dynesys® was new and its safety and efficacy had not yet been demonstrated.

The Dynesys® received its 510(k) approval long before the first and sole RCT was published [39]. Although this device has been in clinical use for more than a decade, there was insufficient evidence in the period between the 510(k) approval and the rejected PMA application to determine whether this device resulted in improved health outcomes compared to standard treatments. Although short-term clinical results seemed favorable, long-term complications arose, including screw loosening, late infections and adjacent segment degeneration [42–44]. It appears that these complications were not recognized and specifically addressed until 2005 [45]. Thus, this was an example of a new technique that was widely used without the results being scientifically scrutinized.

As stated, Yu et al. found no significant differences between the Dynesys® and the surgical standard in terms of clinical outcomes [39]. If a new technique is proven to be non-inferior, then it should be proven to be safer and or more cost-effective, otherwise, no additional value is created. Cost-effectiveness of the Dynesys® was not only not confirmed, it was not even investigated.

Finally it is important to note that a 510(k) pathway instead of a PMA procedure was chosen. The Dynesys® was considered to be of substantial equivalence, while basically, this should have been regarded as a new dynamic stabilization technique instead of a new type of posterior technique.

Discussion

New techniques should be as safe, effective and cost-effective as possible to optimize healthcare. Optimizing patient care should be the primary purpose of market approval of new spinal implants. The presented cases briefly introduced deficiencies in the PMA and 510(k) market approval processes. This study provides a comprehensive overview of available literature and reconstruction of events concerning the period before and after the market entry of the X-Stop® and Dynesys®.

Challenges in market approval processes of spinal devices

To optimize patient care, manufacturers, policy-makers and last but not least, physicians need to change their current practice. Long-term safety and effectiveness data should be required before physicians start working routinely with a new technique. Not only are spinal surgeons directly involved in patient care, they also are vital for the accessibility of clinical data. Physicians should aim on reviewing every patient with a new product to define its success or failure. Still just a fraction of clinical outcomes and adverse events is reported.

To successfully apply for a PMA, one successful trial is sufficient to receive marketing approval. In case of a 510(k), requirements are even less substantial. In relatively small trials, not all potential adverse effects are found. Within the framework of EBM, the highest level of evidence for effectiveness is a systematic review or a meta-analysis of multiple RCTs [5]. A single RCT is usually not considered as sufficient prove for effectiveness of a clinical intervention, especially not when the sample size is small, potential risk of bias high and/or the study authors have a conflict of interest. In surgical studies in which patients, care providers and outcome assessors are not blinded risk of bias is always present. Replication of results in another

RCT performed by another research group (preferably without any conflict of interest) is required. Within the FDA, this philosophy is not adopted. Interestingly enough, an FDA drug approval does typically require two RCTs. One could argue that device approval should simply require similar standards.

In light of HTA, economic evaluations in the field of orthopedic surgery are direly needed to facilitate well-informed policy decisions. These studies entail systematic comparisons of two or more health technologies, services or programs in terms of both costs and consequences [2]. The best comparator for new technologies is usual care, in case of orthopedic surgery the standard surgical technique for the same indication. Simultaneous comparison of the costs and consequences provides insight into whether the new intervention is worth doing over the standard technique or whether the additional costs of a new intervention are worth the effects. If an intervention is more effective than another intervention but associated with higher costs, the intervention may still be cost-effective [2]. Of course, economic evaluations are only useful if they are based on valid, reliable and precise effectiveness data. In view of increasing health care expenses [3], it is of utmost importance to provide high-quality healthcare for an affordable prize. Regulatory processes are a key element in limiting these costs. It was striking that no data on cost-effectiveness for the Dynesys® were available, while only two studies with conflicting results were published for the X-Stop® [26, 27]. From a cost-effectiveness point of view, these new devices might not have been approved. In addition, not only are physicians and policy-makers obliged to provide the best clinical care possible, they should also protect the availability of healthcare resources by addressing the economic perspective.

The main target for a physician should not be a weak demonstration of 'substantial equivalence' of a new, more expensive device compared to a previously approved device. It should be improving patient safety and effectiveness. However, manufacturers often use the 510(k) pathway [11]. Yearly, the FDA evaluates thousands of new medical devices. Of all applications, 99 % are cleared via the 510(k) process, directly leading to insufficient evidence of the safety and clinical superiority at the time of dissemination in clinical practice.

From a scientific point of view it has been argued that the FDA is generally too quick to approve new devices [46]. On the other hand, public opinion often demands quick approval of new and promising techniques, making it a politically challenging issue. The FDA also functions within a legal framework, affecting (and limiting) its decision-making. For example the FDA is forbidden by law to consider the cost of drugs and devices. In other words, the FDA is legally prevented tot consider cost-effectiveness in their approval deliberations. Only by an amendment, cost-effectiveness can be put on the FDA's agenda, basically making it a political issue again.

Compared to other countries, the FDA is considered one of the most stringent authorities when it comes to approval of medical devices.[4] In addition, the USA market is the single largest market for medical devices and is widely acknowledged as leading in device approval, accounting for 38 % of the total market share.[5] Ideally, other countries should argue the clinical outcomes of medical devices approved by the FDA by generating their own high-quality scientific data. The higher the standards of approval in these countries, the more likely developers/manufacturers are pressured into more rigorous studies.

Recommendations for market approval processes of spinal devices

We believe that every new type of spinal implant should be evaluated in at least one RCT. It should not be compared with non-operative treatment but with the standard surgical technique. RCTs should take place in a multi-center setup to limit bias. In addition, a multi-center setup may reduce potential conflicts of interest and increase sample size [47, 48]. After obtaining successful results in a first trial, a second confirmatory trial should be performed by another group before a new device is approved for clinical use and widely disseminated. Furthermore, to address adverse events and long-term results, follow-up is key. We recommend that follow-up through clinical registries should be obligatory for at least 5 years after initial approval. Although it has a restrictive outcome on clinical practice, we believe that off-label use should always be included in studies, since evidence only applies for the investigated and approved indications. Publishing off-label use will finally support patient care. In case a medical device is frequently used for a new indication or subgroup, then a new RCT needs to be performed. In a situation regarding an exemption, good clinical practice and corresponding case-reports suffices. Furthermore, in concordance with the AllTrials Initiative (http://www.alltrials.net), all clinical trial protocols of ongoing and future studies should be registered in the clinical trial database (http://www.clinicaltrials.gov). To this end, other research groups are able to see which trials are ongoing and therefore no unnecessary harm is done to patients due to an overkill of similar trials. Finally, all data resulting from registered clinical trials should be obligatorily published.

[4] http://www.euractiv.com/special-report-medical-devices-r/us-doctors-look-envy-europe-medi-news-529026.

[5] http://www.emergogroup.com/resources/research/annual-medical-device-industry-survey.

However, we acknowledge that the costs to perform a large and long-term trial are substantial. As stated, the FDA requires a 5- to 10-year follow-up period. For example, the market entry and clinical study of the Barricaid® (Intrinsic Therapeutics GmbH, Düsseldorf, Germany), a spinal implant to prevent recurring herniation after discectomy, cost over tens of millions of dollars.[6] Recently, Paradigm Spine GmbH (New York City, NY, USA), the producer of the Coflex® (an interlaminar stabilization device), announced a 75 million dollar secured debt financing.[7] Obviously, these costs will eventually be discounted in the price of the implant when it is introduced on the market, directly increasing healthcare expenses. However, it also shows how high stakes are. Another disadvantage of the high costs of these trials is that they limit innovation. Small innovative enterprises will only reach the point of market entry when being funded or acquired by large (orthopedic) enterprises. The latter possibly decreases market competition which might further increases the price per implant. In other words, an optimum should be sought in which patient safety is guaranteed while at the same time innovative behavior flourishes.

As stated, new techniques are often more expensive, without being superior to the clinical standard [4]. New devices, if they are more expensive than standard surgical techniques, should be clinically superior. Approving new devices that are equally effective but more expensive will only increase costs but not improve quality of health care. To serve not only a patient's interest but also the interest of society, we recommend that every 510(k) and PMA should be based on valid, reliable and precise effectiveness as well as cost-effectiveness analysis. The latter should, similar to data on effectiveness, be obligatorily made available.

Manufacturers prefer a 510(k) instead of a PMA due to its less extensive procedures. In a 510(k) procedure manufacturers claim that their new device is of substantial equivalence to a previously approved device. For new implants that are in line with comparable devices, it is reasonable to use the 510(k) approach. However, we believe that new techniques should not easily be considered to be of 'substantial equivalence'. In other words, new techniques should ideally more often be reviewed by PMA regulations. Considering the risk classification, we believe that in case of a Class III device, the FDA could use the GRADE System to evaluate the level of clinical evidence for new techniques [49]. The GRADE system has been adopted by national and international professional medical societies, health-related branches of government and health care regulatory bodies in most US academic medical centers [50].

Our recommendations are illustrated in Figs. 1 and 2. Figure 1 shows the Market approval process for a class II device requiring 510(k) clearance, while Fig. 2 focuses on a class III device requiring pre-market approval (PMA) clearance (based on: Dawnbreaker Medical Portal, April 2013).

Medicinal regulation could provide guidance for the regulatory processes of spinal implants. In many countries, regulations for new pharmaceutical interventions are strict, but none exist for medical devices or non-pharmaceutical interventions [2]. In many countries new drugs are only reimbursed in public health insurance systems if they are proven to be safe, effective, and cost-effective compared to existing drugs for the same disease or disorder [2]. The mission of FDA's Center for Drug Evaluation and Research (CDER) is to ensure that drugs marketed in this country are safe and effective. To introduce a new drug product into the USA market, a company needs to submit a new drug application (NDA). It is the responsibility of the company seeking to market a drug to test it and submit evidence that it is safe and effective. A team of CDER physicians, statisticians, chemists, pharmacologists, and other scientists reviews the sponsor's NDA containing the data. After obtaining promising data from laboratory studies, submission of an Investigational New Drug (IND) application to CDER is the first step. Once the IND application is in effect, the drug sponsor could begin their clinical trials. Clinical trials are experiments that use human subjects to see whether a drug is effective, and what side effects it may cause. The FDA provides regulations and guidelines that the clinical investigators must have used to conduct a successful study, and that protect their human subjects. After a sponsor (often a company) submits an IND application, it must wait 30 days before starting a clinical trial to allow FDA time to review the prospective study. If FDA finds a problem, it can order a 'clinical hold' to delay an investigation, or interrupt a clinical trial if problems occur during the study. When an IND application is successful, a company is allowed to start a clinical trial. A pharmaceutical clinical trial consists of four phases. During the first phase, healthy human subjects are included. The main goal of this phase is to determine dosages and whether the drug is safe to use. In the second phase, drugs are tested on patients to assess early efficacy and safety. The final step before market approval is the third phase. During this phase, efficacy and safety is tested in a large group of patients, preferably in a double-blinded randomized controlled trial comparing the investigational product with the current standard. After market approval, phase four is used to evaluate the medicinal product when it is already on the market and used in a large group of

[6] http://www.in-thera.com/en/news/intrinsic-raising-$21m-for-implant-to-improve-lumbar-disc-surgery.

[7] http://investor.pdl.com/common/mobile/iphone/releasedetail.cfm?ReleaseID=826161&CompanyID=ABEA-6FA0L9&mobileid=.

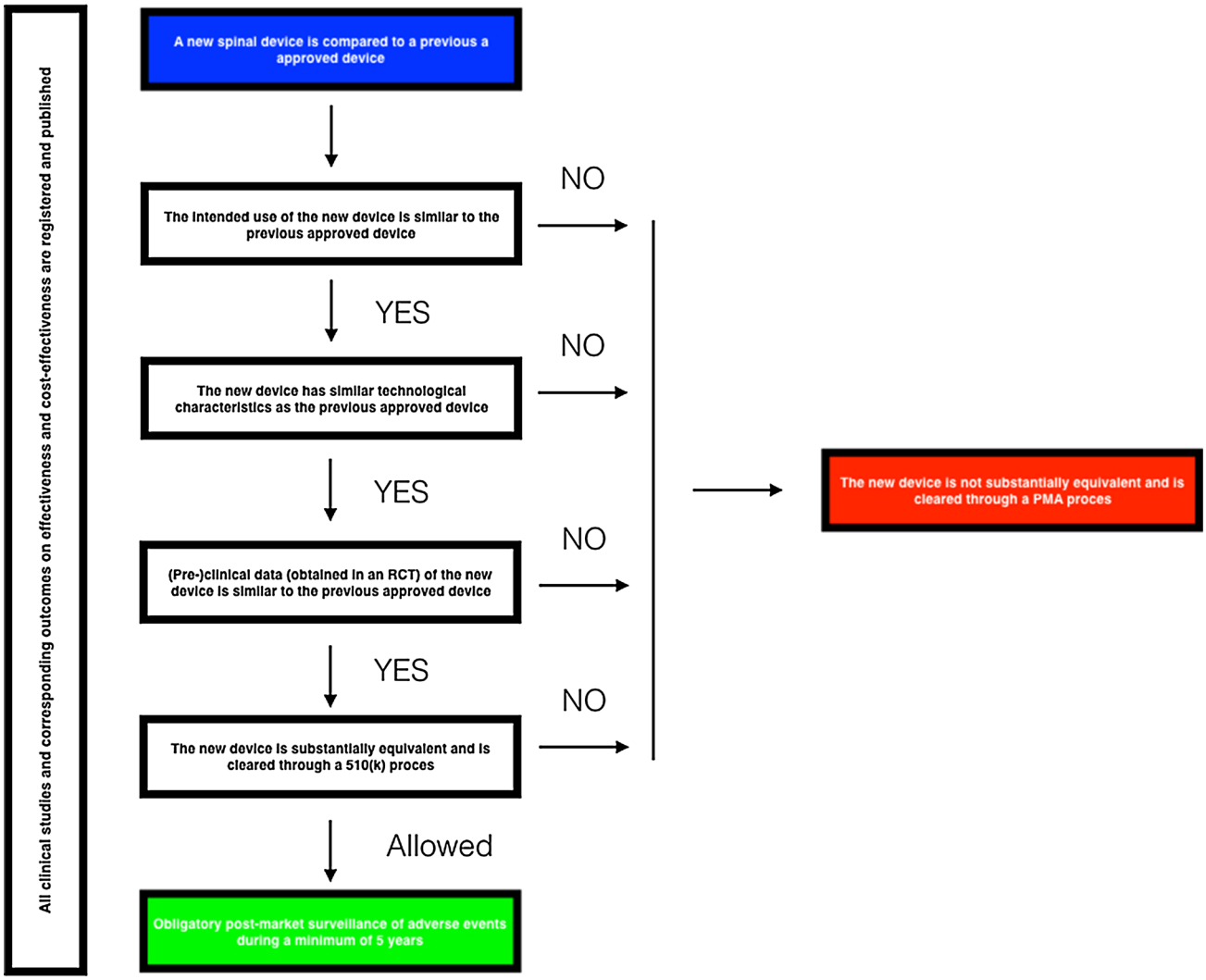

Fig. 1 Market approval process for a class II device requiring 510(k) clearance

patients, i.e., post-marketing surveillance. After the sponsor has analyzed the clinical trials data and concluded that enough evidence existed on the drug's safety and effectiveness to meet FDA's requirements for marketing approval, the sponsor submits an NDA with full information on manufacturing specifications, stability and bioavailability data, method of analysis of each of the dosage forms the sponsor intends to market, packaging and labeling for both physician and consumer.

This short description of pharmaceutical regulations for new drug development shows a striking difference with medical device regulation. The differences between market authorization approval of spinal implants and medicinal products are substantial. However, obviously these trials cannot be fully copied to spinal implant regulation. Still, we believe that the 'pharmaceutical mindset' can and will lead to improved regulatory processes for spinal devices.

Conclusions

In conclusion, spinal implant regulation is facing several challenges. Previously marketed implants taught us valuable lessons. New spinal devices should increase patient outcomes and safety at reasonable societal costs. The main challenge is to have a rigorous evaluation before dissemination, while still leaving room for innovative behavior that thrusts the healthcare practice forward. We have provided recommendations to enhance spinal implant regulation and improve and ensure the patient's safety and the

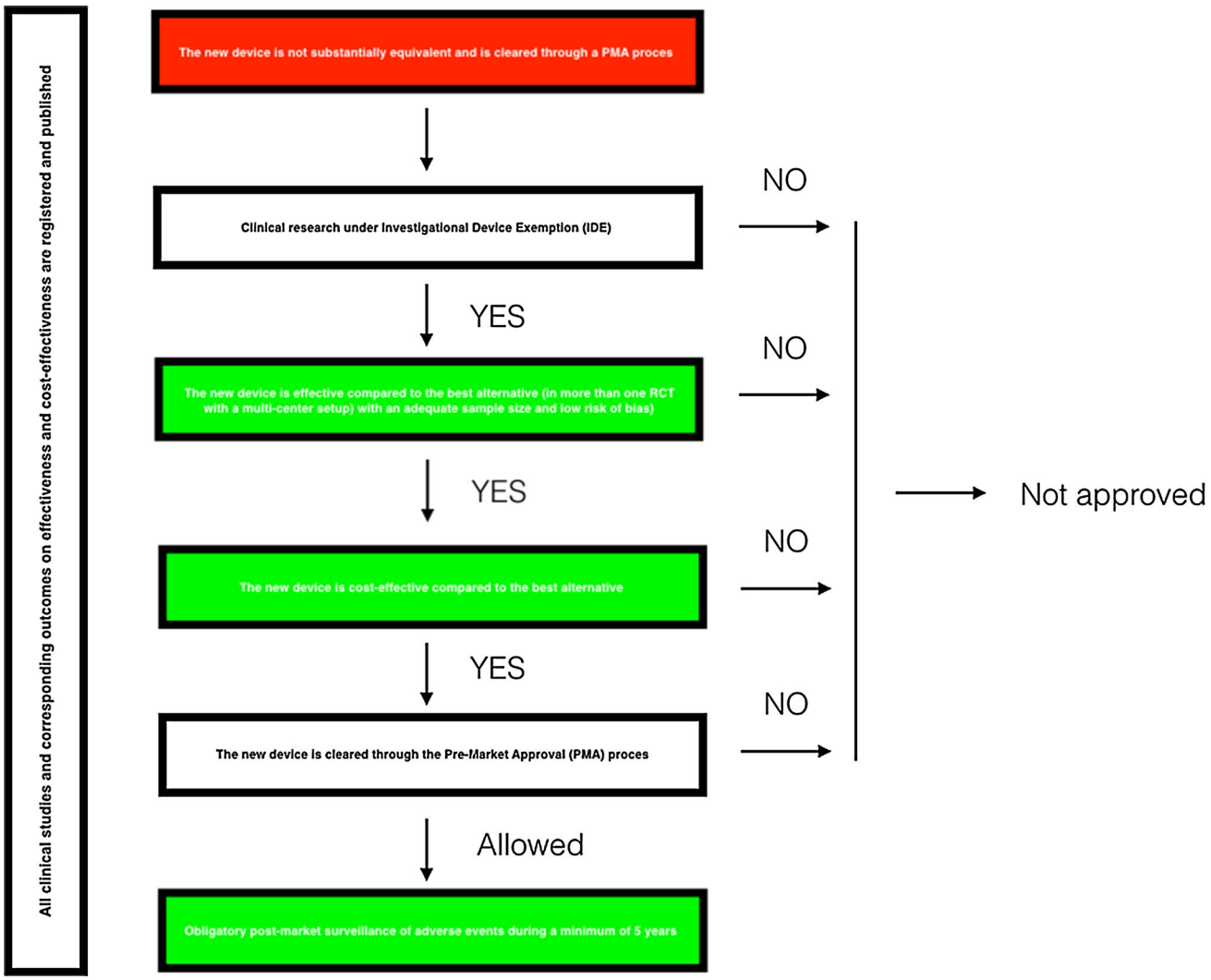

Fig. 2 Pre-market approval (PMA) clearance for a class III device

future of spine surgery. We do not suggest that the FDA should be required to prove efficacy over the long-term. Such a situation will not be realistic as these resources are not available at the FDA. The role of the FDA should be assessing whether there is sufficient evidence for the efficacy and cost-effectiveness for new interventions. Applicants (developers or manufacturers) should be responsible for providing adequate and sufficient data to facilitate the FDA in making a decision about market approval.

Compliance with ethical standards

Conflict of interest None.

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