REGULATORY APPROVAL OF NEW MEDICAL DEVICES: A CROSS SECTIONAL STUDY

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HJM and CJP had equal contribution, and act as guarantors. They were involved in the study conception, acquisition of data, analysis of data, and drafting the manuscript. AHH, and APM were involved in the study conception, acquisition of data, analysis of data, and critical revision of the manuscript. DN, GZY and AD were involved in the study conception and critical revision of the manuscript.

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All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: H.J. Marcus was supported by an Imperial College Wellcome Trust Clinical Fellowship, and C.J. Payne was supported by a Wates Foundation Fellowship; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval:

Ethical approval was not required as this study involved information freely available in the public domain.

Data sharing:

No additional data available.

Transparency:

The lead authors (the manuscript's guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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ABSTRACT

Objective: To investigate the regulatory approval of new medical devices.

Design: Cross sectional study of new medical devices reported in the biomedical literature.

Data sources: The PubMed database was searched to identify clinical studies of new medical devices. We searched between the 1st January 2000 and 31st December 2004 to allow time for regulatory approval.

Eligibility criteria for selecting studies: Articles were included if they reported a clinical study of a new medical device and there was no evidence of a previous clinical study in the literature. We defined a medical device according to the FDA as an "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article..."

Main outcome measures: For each clinical study we determined the type of device, target specialty, involvement of academia, and involvement of industry. The FDA medical databases were then searched for clearance or approval relevant to the device.

Results: 5,574 titles and abstracts were screened, 493 full-text articles assessed for eligibility, and 218 clinical studies of new medical devices included. In all, 99/218 (45.4%) of the devices described in clinical studies ultimately received regulatory clearance or approval. These included 510(k) clearance for devices determined to be substantially equivalent to another legally marketed device (78/99; 78.8%), premarket approval (PMA) for high-risk devices (17/99; 17.2%), and others (4/99; 4.0%). Of these, 43 devices (43/99; 43.4%) were actually cleared or approved before a clinical study was published.

Conclusions: We identified a multitude of new medical devices in clinical studies, almost half of which received regulatory clearance or approval. The 510(k) pathway was most commonly used, and clearance often preceded the first published clinical study.

WHAT THIS PAPER ADDS

What is already known about the subject:

- New medical devices have distinct regulatory approval pathways

What this study adds:

- Almost half of the new medical devices described in the literature ultimately receive regulatory clearance or approval
- The 510(k) pathway is most commonly used, and clearance often precedes the first published clinical study

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INTRODUCTION

The introduction of new medical devices is fundamental to the advancement of healthcare. Historically, such devices have been adopted with little scientific evidence to support their use.[1] Although many have greatly improved clinical outcomes, not all devices are beneficial and some may be harmful. To this end, most jurisdictions have developed regulatory bodies such as the Food and Drug Administration (FDA) that ensure the safety and effectiveness of new medical devices.[2] These regulatory bodies must also act in an efficient and timely manner such that patients are not deprived from beneficial innovations.

The process by which new high-risk medical devices find their way from bench-to-bedside is well established: (1) the development of the device resulting in a first-in-human study, (2) the evaluation of the device in clinical trials, culminating in a regulatory approval for use, and (3) the adoption of the device.[3] While high-risk devices warrant considerable scientific evidence for their safety and effectiveness prior to regulatory approval, the pathway for lower risk devices is less stringent, allowing for their more rapid approval.[4-6]

The aim of this study was to investigate the use of these distinct regulatory approval pathways for new medical devices.

METHODS

We performed a cross sectional study of new medical devices reported in the literature. We determined whether or not these devices received regulatory approval, and the relative contributions of academia and industry in this process. We identified clinical studies of devices before searching for evidence of regulatory approval, allowing us to capture those devices that failed to receive approval.

We defined a medical device according to the US Food and Drug Administration (FDA) as an "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other

similar or related article...” We considered a device as new if there was no evidence of a previous clinical study in the literature.

For each article reporting a clinical study of a new medical device, we defined academia and industry as involved with the development of the device if a relationship was described in the article. We considered a device as having regulatory approval if an entry could be found on the FDA medical device databases.

Patient involvement:

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Search strategy:

The PubMed database (NCBI, Maryland, USA) was searched using the Boolean term: (device OR instrument OR apparatus OR implant OR "in vitro reagent" OR system) AND ("first in man" OR "first in human" OR "first experience" OR "first clinical" OR "early clinical" OR "early experience" OR "early human" OR "initial experience" OR "initial clinical" OR "initial human" OR "preliminary clinical" OR "preliminary experience" OR "preliminary human" OR "Phase 1" OR "Phase I"). This search term was selected on the basis of efficiency and being able to identify the most relevant studies. We searched between the 1st January 2000 and 31st December 2004 to allow time for regulatory approval as previous studies have suggested a long lag between device development and subsequent regulatory approval.[7 8]

We included articles that reported a clinical study of a new medical device. We excluded articles if they only reported a laboratory study of a device because very few such devices ultimately result in a clinical study.[9] We also excluded articles if they reported on the novel use of an existing device, as we expected that most such devices would already have received regulatory approval.

We estimated based on a pilot study (between 1st January 2000 and 31st July 2000) that this search strategy would select sufficient articles to allow for meaningful analysis.

Titles and abstracts were initially screened to identify relevant articles (HJM and CJP, checked by AHH and APM). Articles were excluded if the title or abstract explicitly stated that: the article was not original research, related to drug development, related to an existing medical device, or was a laboratory study. Full articles were subsequently obtained and further assessed for eligibility. In each instance, we reviewed the reference list and searched the PubMed database using the device name to ensure that we did not miss a related previous clinical study (that would result in their exclusion). Discrepancies were resolved by consensus.

Medical devices:

For each clinical study of a new medical device we determined the type of device, the target specialty, the involvement of academia, and the involvement of industry (HJM and CJP, checked by AHH and APM). The types of device were based on the FDA definition and the target specialties were drawn from the FDA databases. We considered academia and industry to be involved in the development of a device if relevant author affiliation, financial support, or provision of technology was described in the author affiliations, main text, or acknowledgements of the article. Discrepancies were resolved by consensus.

Regulatory approvals:

For each new medical device we searched the FDA databases for a relevant regulatory clearance or approval. The FDA recognises several types of regulatory pathway depending on the nature of the device. Premarket notification [510(k)] is the regulatory pathway if the device is "substantially equivalent" to a predicate device, and does not necessarily require clinical data. Premarket approval (PMA) is the regulatory pathway if the device is "not substantially equivalent", and requires reasonable evidence of safety and effectiveness. Other regulatory pathways include humanitarian device exemption (HDE) if the device is for use in patients with rare diseases or conditions. We searched the FDA 510(k), PMA, and HDE databases using the device name, applicant name, and relevant keywords (HJM and CJP, checked by AHH and APM). We also searched Google™ (Google Inc., California, USA) for devices that may have been discontinued, withdrawn, or recalled. Search results were not limited to a date range, allowing for the identification of regulatory clearance or approval before the first published

clinical study. All the searches were performed in August 2015, allowing a minimum of 10 years from publication to regulatory clearance or approval. Discrepancies were resolved by consensus.

Statistical analysis:

We used the Chi-square test to compare differences in regulatory clearance or approval between the following groups: devices developed by industry alone versus academia alone; devices developed by both industry and academia versus academia alone; and devices developed by both industry and academia versus industry alone. First, we compared the proportion of devices receiving any regulatory clearance or approval (versus no clearance or approval). Second, we compared the proportion of devices receiving 510(k) clearance (versus any other approval). We considered differences to be statistically significant if P was less than 0.05. All statistical analyses were performed using SPSS 22.0 (IBM, New York, USA).

RESULTS

Search strategy:

In all, 5,574 titles and abstracts were screened, 493 full-text articles assessed for eligibility, and 218 clinical studies of new medical devices included (Figure 1). The corresponding authors originated from 28 countries, but the majority were located in the USA (70/218; 32.1%) and Germany (43/218; 19.7%).

Medical devices:

Most of the medical devices reported were instruments (86/218; 39.4%) or implants (79/218; 36.2%) (Table 1). Devices were developed by industry alone (140/218; 64.2%), academia alone (46/218; 21.1%), or both (32/218; 14.7%).

Regulatory approvals:

Of the 218 devices described in clinical studies, 99 (45.4%) ultimately received regulatory clearance or approval (Table 2). These included 510(k) clearance (78/99; 78.8%), PMA, (17/99; 17.2%), and HDA (4/99; 4.0%).

Regulatory clearance or approval was granted between April 1997 and September 2014. The median lag between publication of the clinical study and regulatory clearance or approval was 2 months (interquartile range -10.8 months to 26.3 months). Of these, 43 devices (43/99; 43.4%) were actually cleared or approved before a clinical study was published; the median lag in these devices was -12.5 months (interquartile range -23.3 months to -6.3 months).

Published clinical studies of devices that received regulatory clearance or approval were mostly case series' comprising Level 4 evidence (89/99; 89.9%).

Statistical analysis:

Devices were more likely to receive regulatory clearance or approval if developed by industry alone compared to academia alone (57.9% vs. 10.9%; p <0.001), or by both industry and academia compared to academia alone (40.6% vs. 10.9%; p = 0.003). There was no significant difference in clearance or approval between devices developed by industry alone compared to both industry and academia (57.9% vs. 40.6%; p = 0.114).

There was no significant difference in the proportion of 510(k) clearance and other approvals that were awarded to industry alone, industry and academia, or academia alone (p >0.1 in all cases).

DISCUSSION

Principal findings:

We identified a multitude of new medical devices in clinical studies, almost half of which received regulatory approval. The 510(k) pathway was most commonly used, and devices often received regulatory clearance before the first published clinical study. The corollary is that many devices cleared for use in patients had no clinical data accessible in the literature to support their use. Published clinical studies were mostly case series' comprising Level 4 evidence. Without high quality clinical data available, informed shared decision-making on the use of new medical devices is difficult if not impossible.

The 510(k) pathway is a fast-track system that allows the regulatory approval of a device that is "substantially equivalent" to a predicate device. A device is considered substantially equivalent

if: (1) it has the same intended use as the predicate device and (2) it has the same technological characteristics or, if it has different technological characteristics, information is provided that demonstrates that it is at least as safe and effective as the predicate device. Clinical studies are therefore not usually required.

The introduction of a device after it has been cleared through the 510(k) pathway is usually unstructured and variable.[2] A device may be introduced in the form of a research study but, more frequently, may be published as a non-comparative trial without special institutional board review. Although many such devices are safe and effective, the dangers of this process are obvious and have been reported.[10-13] The Balliol Collaboration has proposed the IDEAL model for safe innovation to address this shortfall, the central tenet being that innovation and evaluation can and should proceed together in an ordered and logical manner. [2 14-18] Moreover, the FDA has recognised the need for reform and has announced a new vision for post market surveillance of new devices.[19]

Industry was found to have a role in the development and regulatory approval of the majority of devices identified. For devices developed in academia collaboration with industry was associated with greater regulatory approval. Interestingly, the proportion of 510(k), PMA and other approvals that were awarded to industry and academia were comparable, suggesting that the greater regulatory approvals of devices developed by industry did not simply reflect a propensity for less disruptive and lower risk innovations. This finding supports efforts such as the Medical Device Innovation Consortium (MDIC) that facilitate collaboration among academia and industry in order to foster technology transfer.[20] Collaboration between academia and industry may also contribute to improved surveillance of devices after they receive regulatory approval.

Comparison with other studies:

In keeping with the present study, several other groups have also found limited publically available evidence to support the regulatory clearance and approval of new devices. Zuckerman et al evaluated the types of scientific evidence used to support devices cleared using the 510(k) pathway.[5] Of the 50 devices included, 8 had data to support the claim they were substantially equivalent to a predicate device, and only 3 had data on safety or effectiveness. Chang et al found that even devices approved using the PMA pathway, which require considerably more

scientific evidence, often had no published clinical trials.[21] When trials are published, comparators are often absent, and details may differ substantially from the data submitted to the FDA.[21 22]

In a previous study we investigated the translation of new devices from the laboratory to first-in-human studies[9]. In contrast to the present study we found that clinical rather than industry collaboration was the most important predictor of success; devices developed with clinical collaboration were over six times more likely to lead to a first-in-human study than those without. It is likely that this incongruity is the result of the varying role of clinical and industry collaboration through the device development pathway; early clinical studies may be more reliant on clinicians, and later regulatory approval more reliant on industry.

Limitations:

We recognise several limitations to this study. We restricted our analysis to clinical studies of new medical devices reported in the biomedical literature. It is likely that the publication practices of academia and industry vary. We speculate that academia may be more motivated to publish early clinical studies.

Our analysis may also have favoured more novel devices, which clinicians might have thought warranted publication in the biomedical literature. The proportion of devices cleared through the 510(k) pathway was therefore likely to be an underestimate.

We determined whether a device had regulatory approval using only the FDA medical device databases. The proportion of medical devices receiving regulatory approval was therefore also undoubtedly an underestimate, in particular it is likely that licenses were granted from the European Union which does not require any evidence of clinical value.[11] The reason for selecting the FDA, rather than other licensing authorities, was because the FDA provides public databases and search engines that allowed for a systematic search strategy, the FDA acts as the central body for all medical devices receiving regulatory approval in the USA, and the USA represents the largest medical device market in the world. We hypothesise that most of the manufacturers of devices that received regulatory approval from another jurisdiction would have ultimately sought and obtained FDA approval within the timeframe of this study if they were successful.

We evaluated the contributions of academia and industry in the development of a device if a relationship was described in the author affiliations, main text, or acknowledgements of the first published clinical study. We acknowledge that our cross-sectional study design does not capture potential interactions between academia and industry during the early device development phase, such as the creation of spinout companies, or the licensing of intellectual property to industry. This study does not identify why industry was superior in obtaining regulatory approval compared to academia alone. One possible explanation is that the profit-seeking motive of industry hones their choice as to which devices are pursued.

Conclusions:

The optimal framework for the regulatory approval of medical innovations remains unclear. This study suggests that many new devices do receive regulatory approval, but often lack clinical trial data supporting their safety and effectiveness.

The IDEAL model makes several proposals for the staged introduction of innovations in surgery (and other disciplines that offer complex interventions), including randomised controlled trials to assess safety and effectiveness. At present, few relevant randomised controlled trials are published, and fewer still meet current quality standards for optimal reporting. Changes in the regulatory approval of devices that would require trials for proof of safety and effectiveness might promote adherence to the IDEAL model.

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TABLES

Table 1. Characteristics of new medical devices, and whether they ultimately received regulatory clearance or approval, or not.

	Total (n = 218)	Clearance or approval (n = 99)	No clearance or approval (n = 119)
Type of device			
Imaging	31	11	20
Implant	79	37	42
Instrument	86	47	39
Laboratory analysis	3	1	2
Monitor	10	3	7
Physical therapy	7	0	7
Other	2	0	2
Target specialty			
Anesthesiology	5	2	3
Cardiovascular	67	40	27
Clinical Chemistry	2	0	2
Clinical Toxicology	1	0	1
Dental	2	0	2
Ear, Nose and Throat	12	3	9

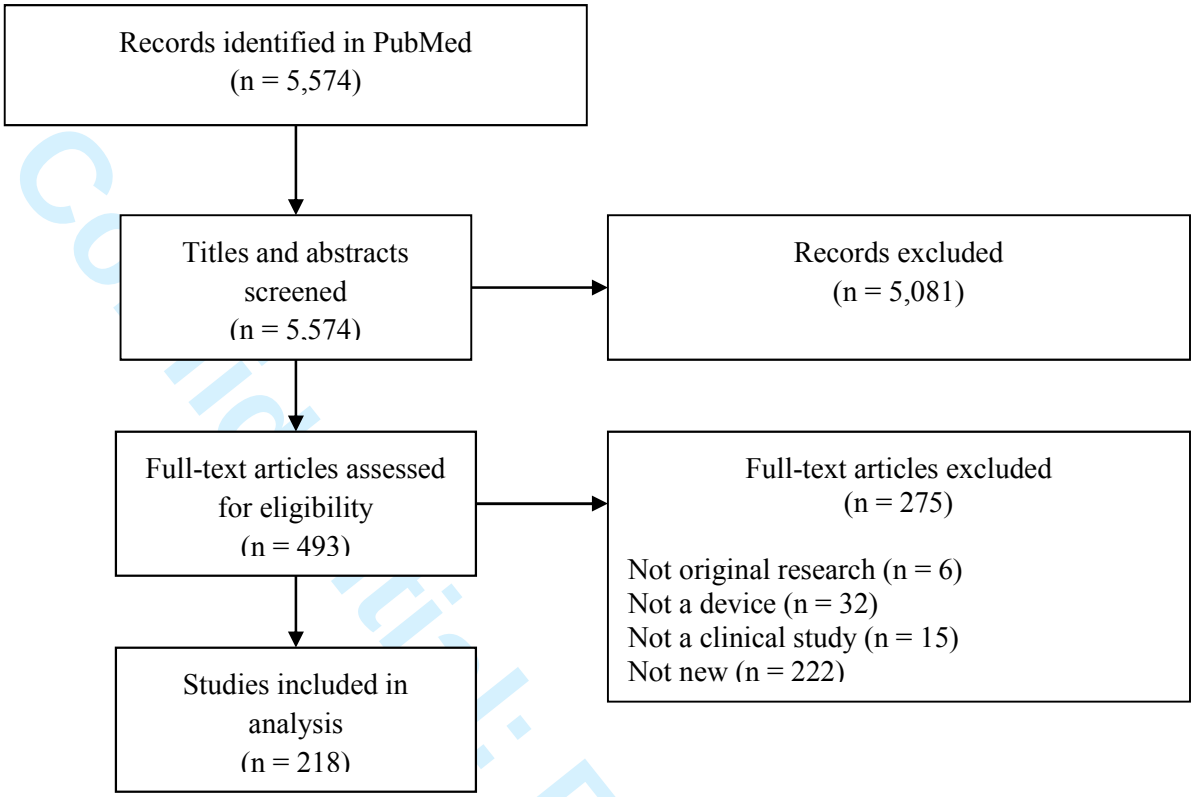
Gastroenterology and Urology	19	7	12
General and Plastic Surgery	22	11	11
General Hospital	8	2	6
Hematology	2	1	1
Neurology	15	6	9
Obstetrics and Gynaecology	11	6	5
Ophthalmic	11	5	6
Orthopaedic	22	10	12
Physical Medicine	6	0	6
Radiology	13	6	7

Table 2. Development of new medical devices, whether they ultimately received regulatory clearance or approval, and the regulatory pathway used.

	Total (n = 218)	**Clearance or approval (n = 99)**	**510k (n = 78)**	**PMA (n = 17)**	**HDA (n = 4)**
Academia alone	46	5	5	0	0
Academia and Industry	32	13	10	1	2
Industry alone	140	81	63	16	2

FIGURES

Figure 1. Flow chart demonstrating the selection of clinical studies of new medical devices.



SUPPLEMENT

Table 1. Devices identified that received regulatory approval. * The Oxford 2011 Levels of Evidence

Device	Article title	Journal	Year	Evidence	Level of evidence*
Talent abdominal stent graft system	Early experience with the Talent stent-graft system for endoluminal repair of abdominal aortic aneurysms.	Tex Heart Inst J	2000	Case series (n > 120)	Level 4
Cryogen cryosurgical system	Endometrial cryoablation with ultrasound visualization in women undergoing hysterectomy.	J Am Assoc Gynecol Laparosc	2000	Case series (n = 10)	Level 4
Debakey VAD	First clinical experience with the DeBakey VAD continuous-axial-flow pump for bridge to transplantation.	Circulation	2000	Case series (n = 2)	Level 4

Siemens magnetom 0.2T concerto	Interventional MRI-guided brain biopsies using inductively coupled surface coils.	Magn Reson Med	2000	Case series (n = 26)	Level 4
Plateletworks	Clinical evaluation of a new, point-of-care hemocytometer.	Crit Care Med	2000	Cross sectional study (n = 345)	Level 2
SMART nitinol stent system	Endovascular stenting for carotid artery stenosis: preliminary experience using the shape-memory- alloy-recoverable-technology (SMART) stent.	AJNR Am J Neuroradiol	2000	Case series (n = 4)	Level 4
HomMed sentry, Model 1 sentry	Emergence of electronic home monitoring in chronic heart failure: rationale, feasibility, and early results with the HomMed Sentry-Observer system.	Congest Heart Fail	2000	Non-randomised controlled cohort study (n = 53)	Level 3

Smith & Nephew HandPort system	Hand-assisted laparoscopic surgery (HALS) with the HandPort system: initial experience with 68 patients.	Ann Surg	2000	Case series (n = 68)	Level 4
EBI Omega 21 system	Biomechanical evaluation and preliminary clinical experience with an expansive pedicle screw design.	J Spinal Disord	2000	Case series (n = 14)	Level 4
MR elastography	High-resolution tensor MR elastography for breast tumour detection.	Phys Med Biol	2000	Case series	Level 4

ATTAIN access 6218 left-heart delivery system, model 6218	Initial results with left ventricular pacemaker lead implantation using a preformed "peel-away" guiding sheath and "side-wire" left ventricular pacing lead.	Pacing Clin Electrophysiol	2000	Case series (n = 13)	Level 4
Biologic-DT system (biologic-DT-1000 with DT-1000-TK)	Push-pull sorbent-based pheresis and hemodiabsorption in the treatment of hepatic failure: preliminary results of a clinical trial with the BioLogic-DTPF System.	Ther Apher	2000	Case series (n = 4)	Level 4
Lap discs	Hand assisted laparoscopic radical nephrectomy for renal carcinoma using a new abdominal wall sealing device.	J Urol	2000	Non randomised controlled cohort (n = 6)	Level 3

Gore helex™ septal occluder	Helex Septal Occluder for Closure of Atrial Septal Defects.	Curr Interv Cardiol Rep	2000	Case series (n = 28)	Level 4
Atlantis anterior cervical plate system	The management of one-level anterior cervical corpectomy with fusion using Atlantis hybrid plates: preliminary experience.	J Spinal Disord	2000	Case series (n = 8)	Level 4
P.D. access (percutaneous doppler) vascular access device	Gaining vascular access in pediatric patients: use of the P.D. access Doppler needle.	Catheter Cardiovasc Interv	2000	Case series (n = 39)	Level 4
Photon DR implantable cardioverter defibreillator (ICD)	Initial clinical experience with a dual chamber rate responsive implantable cardioverter defibrillator.	Pacing Clin Electrophysiol	2000	Case series (n = 57)	Level 4

Aescula LV model 1055K	Initial clinical experience with a new self-retaining left ventricular lead for permanent left ventricular pacing.	Pacing Clin Electrophysiol	2000	Case series (n = 13)	Level 4
Vasca LifeSite Hemodialysis Access System	Initial clinical results with the LifeSite Hemodialysis Access System.	Kidney Int	2000	Case series (n = 23)	Level 4
Omniport	Laparoscopic hand-assisted surgery for hepatic and pancreatic disease.	Surg Endosc	2000	Case series (n = 14)	Level 4
Ophthalmic medical laser system	Laser trabeculodissection with a photopolishing scanning excimer laser.	Ophthalmic Surg Lasers	2000	Case series (n = 8)	Level 4
SimpliCT	Potential of a new laser target system for percutaneous CT-guided nerve blocks: technical note.	Neuroradiology	2000	Case series (n = 8)	Level 4

Easytrak coronary venous steroid-eluding single-electrode	Transvenous left ventricular lead implantation with the EASYTRAK lead system: the European experience.	Am J Cardiol	2000	Case series (n = 186)	Level 4
Medtronic AVE solstice temporary occlusion balloon system	Balloon-assisted coil placement in wide-necked cerebral aneurysms: preliminary clinical experience.	Neurol Med Chir (Tokyo)	2000	Case series (n = 7)	Level 4
Leksell gamma knife target system, model 24001	First clinical experience with the automatic positioning system and Leksell gamma knife Model C. Technical note.	J Neurosurg	2000	Case series (n = 50)	Level 4

Cordis Palmaz Corinthian Transhepatic Biliary Stent and Delivery System	Initial experience using the Palmaz Corinthian stent for right ventricular outflow obstruction in infants and small children.	Catheter Cardiovasc Interv	2000	Case series (n = 4)	Level 4
Dysis	A novel optical imaging method for the early detection, quantitative grading, and mapping of cancerous and precancerous lesions of cervix.	IEEE Trans Biomed Eng	2001	Case series (n = 16)	Level 4
Sculptor robotic guidance arm (RGA)	The first clinical application of a "hands-on" robotic knee surgery system.	Comput Aided Surg	2001	Case series	Level 4

Cooltouch "v" Nd:YAG surgical laser	Facial rejuvenation with a nonablative 1320 nm Nd:YAG laser: a preliminary clinical and histologic evaluation.	Dermatol Surg	2001	Case series (n = 10)	Level 4
Excluder bifurcated endoprosthesis	Update on the bifurcated EXCLUDER endoprosthesis: phase I results.	J Vasc Surg	2001	Case series (n = 29)	Level 4
Contak TR pacemaker	[Experiences with a new transvenous electrode for left ventricular stimulation].	Herz	2001	Case series (n = 16)	Level 4
Symmetry	Sutureless mechanical anastomosis of a saphenous vein graft to a coronary artery with a new connector device.	Lancet	2001	Case study (n = 1)	Level 4

Gyrus plasmakinetic Superpulse System	Electrovaporization of the prostate with the Gyrus device.	J Endourol	2001	Case series (n = 42)	Level 4
Voice master prosthesis	First results of the VoiceMaster prosthesis in three centres in the Netherlands.	Clin Otolaryngol Allied Sci	2001	Case series (n = 85)	Level 4
Parietex composite (PCO) mesh	Laparoscopic repair of ventral and incisional hernias using a new composite mesh (Parietex): initial experience.	Surg Laparosc Endosc Percutan Tech	2001	Case series (n = 20)	Level 4
Polestar N-10	Novel, compact, intraoperative magnetic resonance imaging-guided system for conventional neurosurgical operating rooms.	Neurosurgery	2001	Case series (n = 20)	Level 4

Soundtec® direct system	Semi-implantable electromagnetic middle ear hearing device for moderate to severe sensorineural hearing loss.	Otolaryngol Clin North Am	2001	Case series (n = 5)	Level 4
Nit-occlud PDA	The duct-occlud device: design, clinical results, and future directions.	J Interv Cardiol	2001	Case series (n = 821)	Level 4
Ems swiss orthoclast	Cement removal with an endoscopically controlled ballistically driven chiselling system. A new device for cement removal and preliminary clinical results.	Arch Orthop Trauma Surg	2001	Case series (n = 28)	Level 4

Corlink Automated Anastomotic Device (AAD)	Early clinical experience with a new sutureless anastomotic device for proximal anastomosis of the saphenous vein to the aorta.	J Thorac Cardiovasc Surg	2001	Case series (n = 17)	Level 4
Visian ICL (implantable collamer lens)	Collamer intraocular lens: clinical results from the US FDA core study.	J Cataract Refract Surg	2001	Case series (n = 686)	Level 4
Ligasure Vessel Sealing System	Initial results with an electrothermal bipolar vessel sealer.	Surg Endosc	2001	Case series (n = 98)	Level 4

Siremobil ISO-C 3D	[3-D imaging with a mobile surgical image enhancement equipment (ISO-C-3D). Initial examples of fracture diagnosis of peripheral joints in comparison with spiral CT and conventional radiography].	Unfallchirurg	2001	Cross sectional study	Level 2
Safe-steer guide wire system	Initial experience and safety in the treatment of chronic total occlusions with fiberoptic guidance technology: optical coherent reflectometry.	Catheter Cardiovasc Interv	2001	Case series (n = 6)	Level 4
Extracorporeal shock wave lithotripter	The first clinical results of "wide-focus and low-pressure" ESWL.	Ultrasound Med Biol	2002	Case series (n = 297)	Level 4

GE discovery LS system	Initial clinical experience using a new integrated in-line PET/CT system.	Br J Radiol	2002	Case series	Level 4
Shelhigh no-react tissue repair patch/uropatch.	The YAMA UroPatch sling for treatment of female stress urinary incontinence: a pilot study.	J Laparoendosc Adv Surg Tech A	2002	Case series (n = 22)	Level 4
Medtronic model 7272 InSync ICD	Initial experience with an implantable cardioverter-defibrillator incorporating cardiac resynchronization therapy.	J Am Coll Cardiol	2002	Case series (n = 84)	Level 4
Mammosite radiation therapy system (RTS) tray, mammosite HDR afterloader accessories tray	Dosimetric characteristics of the MammoSite RTS, a new breast brachytherapy applicator.	Int J Radiat Oncol Biol Phys	2002	Case control study (n = 12)	Level 4

Coalescent U-clip delivery and disposal device	Early experience of coronary artery bypass grafting with a new self-closing clip device.	J Thorac Cardiovasc Surg	2002	Case series (n = 14)	Level 4
X-sept transseptal sheath and transition catheter, model mv-03-09-90, mv-03-10-90, mv-03-11-90, mv-03-09-120, mv-03-10-1	Percutaneous left atrial appendage transcatheter occlusion to prevent stroke in high-risk patients with atrial fibrillation: early clinical experience.	Circulation	2002	Case series (n = 15)	Level 4
X-sizer catheter system	Early experience with a helical coronary thrombectomy device in patients with acute coronary thrombosis.	Am J Hematol	2002	Case series (n = 35)	Level 4
St. Jude medical regent mechanical heart valve (aortic)	Experimental evaluation and early clinical results of a new low-profile bileaflet aortic valve.	Artif Organs	2002	Case series (n = 30)	Level 4

Nomos corvus 5.0m	Clinical implementation of intensity-modulated arc therapy.	Int J Radiat Oncol Biol Phys	2002	Case series (n = 50)	Level 4
Boston keratoprosthesis or Boston KPRO	Seoul-type keratoprosthesis: preliminary results of the first 7 human cases.	Arch Ophthalmol	2002	Case series (n = 7)	Level 4
Valleylab ligasure precise instrument vessel sealing system-model # ls1200 & sligaure generator	Use of a bipolar vessel-sealing device for parenchymal transection during liver surgery.	J Gastrointest Surg	2002	Case series (n = 27)	Level 4
Intrastent doublestrut stent	Initial experience with intratherapeutics Intrastent Doublestrut LD stents in patients with congenital heart defects.	Catheter Cardiovasc Interv	2002	Case series (n = 22)	Level 4

Niti-s stent & introducer, model eoxxxx	Polyurethane-covered self-expandable nitinol stent for malignant biliary obstruction: preliminary results.	Cardiovasc Intervent Radiol	2002	Case series (n = 10)	Level 4
Artifical cervical disc	Preliminary clinical experience with the Bryan Cervical Disc Prosthesis.	Neurosurgery	2002	Case series (n = 60)	Level 4
The auto suture MIBB system	Stereotactic breast biopsy with an 8-gauge, directional, vacuum-assisted probe: initial experience.	Eur Radiol	2002	Case series (n = 138)	Level 4
Biorigid nail femur (BNF)	["Biorigid" interlocking after unreamed intramedullary nailing of tibial shaft fractures].	Unfallchirurg	2002	Case series (n = 76)	Level 4

Macropore hydrosorb spine system	Resorbable polymer implants in unilateral transforaminal lumbar interbody fusion.	J Neurosurg	2002	Case series (n = 60)	Level 4
Boston scientific filterwire ex embolic	Initial clinical experience with distal protection using the FilterWire in patients undergoing coronary artery and saphenous vein graft percutaneous intervention.	Catheter Cardiovasc Interv	2002	Case series (n = 35)	Level 4
Storz millennium microsurgicl system high speed vitrectomy system	Initial experience using the transconjunctival sutureless vitrectomy system for vitreoretinal surgery.	Ophthalmology	2002	Case series (n = 33)	Level 4

Eg-3630ur, ultrasund video gastroscope	Initial experience with an electronic radial array echoendoscope: randomized comparison with a mechanical sector scanning echoendoscope in humans.	Gastrointest Endosc	2002	Cross sectional study (n = 14)	Level 2
Bodyfix	A novel vacuum device for extremity immobilisation during digital angiography: preliminary clinical experiences.	Eur Radiol	2002	Non randomised controlled cohort (n = 100)	Level 3
Setpoint endovascular temperature management system	Initial experience with a novel heat-exchanging catheter in neurosurgical patients.	Anesth Analg	2002	Case series (n = 8)	Level 4
HTS coil	Superconducting RF coils for clinical MR imaging at low field.	Acad Radiol	2003	Cross sectional study	Level 2

Safe-cross deflecting catheter, model c114nd1	Initial experience and safety in the treatment of chronic total coronary occlusions with a new optical coherent reflectometry-guided radiofrequency ablation guidewire.	Am J Cardiol	2003	Case series (n = 13)	Level 4
Tissuelink monopolar floating ball	Early experience employing a linear hepatic parenchyma coagulation device.	J Hepatobiliary Pancreat Surg	2003	Case series (n = 7)	Level 4
Endoscopic plication system	Endoscopic full-thickness plication: the device, technique, pre-clinical and early clinical experience.	Gastrointest Endosc Clin N Am	2003	Case series (n = 6)	Level 4

Surgical sealant	Feasibility study of NeoMend, a percutaneous arterial closure device that uses a nonthrombogenic bioadhesive.	AJR Am J Roentgenol	2003	Case series (n = 26)	Level 4
Daum-lectric MRI drilling machine	Magnetic resonance-guided transcortical biopsy of bone marrow lesions using a magnetic resonance imaging-compatible piezoelectric power drill: preliminary experience.	Invest Radiol	2003	Case series (n = 17)	Level 4
Spy intra-operative imaging system: sp2000	Preliminary experience with a novel intraoperative fluorescence imaging technique to evaluate the patency of bypass grafts in total arterial revascularization.	Ann Thorac Surg	2003	Case series (n = 84)	Level 4

CV232 sre pre-rolled acrylic intraocular lens	Deep sclerectomy with a nonabsorbable implant (T-Flux): preliminary results.	Can J Ophthalmol	2003	Case control study (n = 25)	Level 4
Reform peripheral catheter system, model 02200; reform peripheral cathetercatheter, model 02406	Initial experience with a new 8 French-compatible directional atherectomy catheter: immediate and mid-term results.	Catheter Cardiovasc Interv	2003	Case series (n = 77)	Level 4
Surgifrost 10 cm cryosurgical device plus frostbyte clamp and cryosurgical console	Intraoperative left atrial ablation (for atrial fibrillation) using a new argon cryocatheter: early clinical experience.	Ann Thorac Surg	2003	Case series (n = 28)	Level 4
Attain 6218a-am amplatz guide catheter for left-heart delivery	New catheter design for cannulation of the anomalous right coronary artery arising from the left sinus of valsalva.	Catheter Cardiovasc Interv	2003	Case series (n = 5)	Level 4

Rossmax automatic blood pressure monitor, model cardiocare 1000i	Validation of the ROSSMAX blood pressure measuring monitor according to the European Society of Hypertension International Protocol for Validation of Blood Pressure Measuring Devices in Adults.	Blood Press Monit	2003	Cross sectional study (n = 33)	Level 2
Tonoport V	Validation of the TONOPORT V ambulatory blood pressure monitor according to the European Society of Hypertension International Protocol for Validation of Blood Pressure Measuring Devices in Adults.	Blood Press Monit	2003	Cross sectional study (n = 33)	Level 2

Neuroform™ microdelivery stent system	Preliminary experience using the Neuroform stent for the treatment of cerebral aneurysms.	Neurosurgery	2004	Case series (n = 18)	Level 4
Trellis infusion system (10cm infusion length); trellis infusion system (20cm infusion length)	Clinical and economic evaluation of the trellis thrombectomy device for arterial occlusions: preliminary analysis.	J Vasc Surg	2004	Case series (n = 26)	Level 4
ATS 3f aortic bioprosthesis	Early clinical experience with a new tubular equine pericardial stentless aortic valve.	Heart Surg Forum	2004	Case series (n = 24)	Level 4
Portaclamp	Early experience with a new aortic clamping system designed for port access cardiac surgery: the PortaClamp.	Heart Surg Forum	2004	Case series (n = 20)	Level 4

Silverhawk peripheral plaque excision system, models 02550,04800, 05200, 02406, 04706, 04300	Early experience with a novel plaque excision system for the treatment of complex coronary lesions.	Catheter Cardiovasc Interv	2004	Case series (n = 10)	Level 4
Corlink AAD (3.5 to 6.0 m m outer diameter vessels),model 200-064, corlink aad (2.0 to 4.0 mm outer diameter vessels), m	Initial experience of an automated anastomotic distal device in off-pump CABG.	Heart Surg Forum	2004	Case series (n = 14)	Level 4
Abiocor® Implantable Replacement Heart	Initial experience with the AbioCor implantable replacement heart system.	J Thorac Cardiovasc Surg	2004	Case series (n = 7)	Level 4
Medamicus flowguard peelable introducer	Preliminary evaluation of a valved introducer sheath for the insertion of tunneled hemodialysis catheters.	Semin Dial	2004	Case series (n = 15)	Level 4

Levitronix centrimag extracorporeal blood pumping system, model l-100	The CentriMag: a new optimized centrifugal blood pump with levitating impeller.	Heart Surg Forum	2004	Case series (n = 11)	Level 4
Outback catheter	The outback catheter: a new device for true lumen re-entry after dissection during recanalization of arterial occlusions.	Cardiovasc Intervent Radiol	2004	Case series (n = 10)	Level 4
Gambro prismaflex and gambro prismaflex m60 & m100 sets	First clinical trial for a new CRRT machine: the Prismaflex.	Int J Artif Organs	2004	Case series (n = 13)	Level 4
Impella recover LP 2.5 percutaneous cardiac support system	Initial experience with miniature axial flow ventricular assist devices for postcardiotomy heart failure.	Ann Thorac Surg	2004	Case series (n = 6)	Level 4

Biopsy handy, MRI biopsy handy	A new safe and stable spiral wire needle for thoracoscopic resection of lung nodules.	Chest	2004	Case series (n = 13)	Level 4
Contegra® Pulmonary Valved Conduit, Models 200 (unsupported) and 200S (supported)	Contegra pulmonary valved conduits cause no relevant hemolysis.	J Card Surg	2004	Case series (n = 60)	Level 4
Microcuff pediatric endotracheal tube	Tracheal sealing characteristics of pediatric cuffed tracheal tubes.	Paediatr Anaesth	2004	Randomised trial (n = 80)	Level 2
Cardiovention corx system, model FG 0001	A new cardiopulmonary bypass circuit with reduced foreign surface (CorX): initial clinical experience and implications for anaesthesia management.	Eur J Anaesthesiol	2004	Case series (n = 10)	Level 4

ACMI vista CTR bipolar loop electrode	First clinical experience with new transurethral bipolar prostate electrosurgery resection system: controlled tissue ablation (coblation technology).	J Endourol	2004	Case series (n = 36)	Level 4
MO.MA ultra proximal cerebral protection device, model mus0130069x6	First clinical experiences with an endovascular clamping system for neuroprotection during carotid stenting.	Eur J Vasc Endovasc Surg	2004	Case series (n = 42)	Level 4
1.5T 32-channel head coil and 3T 32-channel head coil	New partially parallel acquisition technique in cerebral imaging: preliminary findings.	Eur Radiol	2004	Case series (n = 6)	Level 4

Box 1. FDA processes.

510(k) is a premarketing submission to demonstrate that a device is as safe and effective, that is "substantially equivalent", to a legally market device.

Premarket Approval (PMA) contains sufficient valid scientific evidence to provide reasonable assurance that the device is safe and effective for its intended use or uses.

Humanitarian Use Device (HUD) is similar to PMA, but is exempt from the effectiveness requirements; it is intended for devices that benefit patients with rare disease.