Lack of Publicly Available Scientific Evidence on the Safety and Effectiveness of Implanted Medical Devices

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IMPORTANCE Under the 510(k) process, the US Food and Drug Administration (FDA) clears about 400 implanted medical devices that are considered moderate to high risk for market each year without requiring clinical testing. Instead, the FDA requires the applicant to provide scientific evidence that the new device is “substantially equivalent” to a device or devices already on the market (predicate devices). Companies are legally required to submit the evidence to the FDA and to make publicly available at least a summary of the evidence.

OBJECTIVE To assess the types of scientific evidence used to determine substantial equivalence, safety, or effectiveness for a representative sample of implanted medical devices; the number of predicates for each implant; and whether this evidence was publicly available.

DESIGN Using FDA databases, we determined the device categories of the first 5 implanted medical devices cleared through the 510(k) process in 2008: cardiovascular, dental, general and plastic surgery, neurological, and orthopedic. We then identified the first 2 implanted medical devices approved in each of the 5 categories for each year from 2008 through 2012. The sample of 50 devices included, for example, total hip implants, vascular embolization devices, and surgical mesh. We also identified the 1105 predicates the manufacturers listed for these devices.

MAIN OUTCOMES AND MEASURES For each implanted medical device and its predicates, we determined whether clinical or nonclinical scientific evidence was provided to the FDA to support the claim of substantial equivalence and whether this evidence was publicly available. We also determined if safety or effectiveness data were provided.

RESULTS Scientific data to support the claim of substantial equivalence were publicly available for 8 of the 50 newly cleared implants (16%) and 31 of their 1105 listed predicates (3%). Most of the evidence was nonclinical data; some of the data also evaluated safety or effectiveness.

CONCLUSIONS AND RELEVANCE Despite the legal requirement that scientific evidence of substantial equivalence be publicly available for medical devices cleared by the FDA through the 501(k) process, such information is lacking for most implanted medical devices cleared between 2008 and 2012, as well as for their predicates.
Prescription drugs cannot be sold in the United States until the US Food and Drug Administration (FDA) determines they are safe and effective based on clinical trials and inspections of the manufacturing facilities. The FDA requires similar standards for approximately 1% of medical devices that are designated “highest risk” because they are implanted, life sustaining, or life saving.2 About two-thirds of medical devices (such as crutches and scalpels) are considered “low risk,” usually with no testing required. The FDA designates about one-third of devices “moderate to high risk” and reviews most of them through the 510(k) process; before a device is marketed, clinical trials or inspections of manufacturing facilities are rarely required.3

The 510(k) review is used for many diagnostic tests, robotic systems that aid in surgery, joint replacements, implants, and other life-saving devices if the FDA determines that “special controls would provide adequate assurance of safety and effectiveness.”3 Special controls may include safety data or physician training. The determination of whether a new, potentially risky device requires clinical trials to establish its safety and effectiveness reflects the judgment of FDA staff. This judgment is not necessarily based on scientific data.4

The Safe Medical Devices Act of 1990 requires that the scientific evidence submitted for 510(k) reviews be publicly available in a summary provided by the manufacturer to the FDA. The summary must include “sufficient detail to provide an understanding of the basis for a determination of substantial equivalence”6 to a product that is already marketed. If substantial equivalence is based on performance data, “the summary shall contain a brief discussion of nonclinical and clinical tests submitted, and the conclusions drawn from those tests.”6 If a summary is not provided, a company official must agree in writing to “make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person.”7

The FDA refers to devices as “cleared for market” through the 510(k) process rather than “approved.” In 2011, an Institute of Medicine report stated that “510(k) clearance is not a determination that the cleared device is safe or effective” but rather is based on evidence that the device is “substantially equivalent” to a “predicate” device already on the market that was itself “never systematically assessed for safety and effectiveness.”2 Research has documented fatalities and recalls for high-risk safety concerns associated with flawed devices cleared through the 510(k) process; however, there are no published analyses of the types of scientific evidence used to support FDA clearance decisions.

We assessed the number of predicates for a representative sample of implanted medical devices cleared through the 510(k) process between 2008 and 2012. We then determined the types of scientific evidence used to evaluate substantial equivalence, safety, or effectiveness and the extent to which this evidence was publicly available.

Methods

Each year, the FDA clears about 400 implants through the 510(k) process.10 Using FDA databases,11 we selected the device categories for study by determining the categories of the first 5 implants cleared in 2008: cardiovascular, dental, general and plastic surgery, neurological, and orthopedic. We selected for analysis the first 2 implants cleared in each of those 5 categories every year from 2008 through 2012. The sample was 50 implants: 10 per year and 10 in each category, including, for example, total hip implants, vascular embolization devices, and surgical mesh. Institutional review board approval was waived for this study.

We used FDA databases to calculate the number of predicates for each of the 50 newly cleared implants, and the predicates of those predicates, going back as many iterations as available.12 For each new implant and predicate listed, we analyzed the type of scientific evidence the company provided to the FDA and the public to support the claim of substantial equivalence to a device already on the market or to establish safety or effectiveness. We identified the predicates; a summary, if available; the type of evidence (clinical or nonclinical); and whether scientific data were provided or merely mentioned as existing (eg, “required testing was completed,” without listing test results).

The summaries specified by law were not available for 5 of the newly approved implants and 75 of the predicates. Therefore, we wrote to a subsample of 20 companies, selecting all 10 that had statements promising to provide information on request, plus the companies with the 10 most recent applications that had provided neither the summary nor the required statement.8 We requested that these companies provide evidence of substantial equivalence within 30 days, as they are required to do.7

Results

Our sample consisted of 50 newly cleared implants and their predicates, as listed by the manufacturers (Table in the Supplement). For 7 of the implants, the companies’ 510(k) documents did not specify the name or 510(k) number of the predicate(s). The 43 implants that identified predicates listed between 1 and 8 predicates each, totaling 97. As those 97 predicates were previously cleared as equivalent to other predicates, we created a “family tree” for each newly approved implant, resulting in a total history of 1105 predicates. The mean number of unique predicates per implant was 26; the median was 9. The general and plastic surgery implants had the most predicates (mean, 43; median, 38); orthopedic and neurological implants each had a mean of 28 and a median of 8 and 28, respectively; dental implants had a mean of 16 and median of 3; and cardiovascular implants had a mean of 11 and median of 7. Two implants (5%) had more than 100 predicates. The Figure shows the family tree lineage of a bladder sling mesh implant used in the treatment of stress urinary incontinence; this is an example of a commonly used type of implant with relatively few predicates. Table 1 shows the 10 implants with the most predicates.

Public Availability of Scientific Evidence for New Implants

We analyzed all publicly available scientific evidence that was used to determine substantial equivalence, safety, or effec-
tiveness for the 50 implants and their 1,105 listed predicates. The summaries for 8 (16%) of the 50 new implants provided scientific evidence to support substantial equivalence: 1 (2%) provided clinical and nonclinical data; 4 (8%) provided clinical data only, and 3 (6%) provided nonclinical data only. Of the 8 summaries that included clinical or nonclinical data, 3 also included data on safety or effectiveness. An additional 27 (54%) mentioned nonclinical evidence of substantial equivalence in their summaries but did not provide the data; 11 of these also mentioned nonclinical evidence of safety or effectiveness without providing data. Two (4%) mentioned clinical evidence but did not provide data. No information on scientific evidence was available for 13 of the implants (26%); 8 summaries (16%) did not mention or provide any scientific evidence, and for 5 implants (10%), no summaries were found.

We analyzed the 10 implants cleared in 2012 to determine if more recent applications included more scientific evidence; only 2 provided such evidence (Table 2). For example, Synthes’ summary for the SyntheCel Dura Replacement Device briefly described a randomized trial with 99 patients, with successful treatment evaluated by an absence of cerebrospinal fluid fistula for 6 months following the operation. In contrast, D.N.E., LLC specified in their summary for the External Fixation System to repair broken bones, “No [nonclinical] testing” and “no clinical studies were performed.”

Boston Scientific’s summary for their Interlock-35 Fibered IDC Occlusion System, a vascular embolization device to treat aneurysms, did not mention whether any testing was conducted, and their summary for the Exxcel Soft ePTFE Vascular Graft stated that “the results of these nonclinical tests met the specified accep-
tance criteria,” but they did not name the tests or describe results. Three other summaries, for the Dentium Co Ltd Slim One-body System dental implant, Synovis Orthopedic and Woundcare Synergy Tissue Matrix mesh, and CryoLife, Inc, ProPatch Soft Tissue Repair Matrix mesh, listed the specific nonclinical tests conducted but did not provide data.

**Public Availability of Scientific Evidence for Predicates**

There was no publicly available scientific evidence mentioned for 733 (66%) of the 1105 predicates; only 503 had summaries, and 131 summaries (26%) did not mention scientific evidence. Summaries for 31 predicates (3%) included data to support the claim of substantial equivalence; 12 (1%) provided clinical data indicating equivalence and 19 (2%) provided nonclinical data. Most of these summaries also provided data indicating safety or effectiveness. In addition, 48 predicates (4%) mentioned clinical evidence and 324 (29%) mentioned nonclinical evidence; these summaries did not provide data, however. For example, Boston Scientific’s summary for their Neurovascular GDC 360 Coils cardiac device, cleared in 2004, listed names of nonclinical tests and stated, “meets acceptance criteria” or “no change made which would affect this test.”

Most summaries that mentioned clinical evidence either did not provide data or referred to an unspecified study, such as “clinical experience in several hundred patients in Europe.”

At least 264 of the 602 predicates (44%) that lacked summaries were cleared for market before the Safe Medical Devices Act of 1990, which required such summaries, was implemented on March 14, 1995. An additional 262 of the predicates that lacked summaries were not identified specifically enough to determine if they were cleared before or after the law was implemented. Of the 578 predicates that were recorded as cleared for market after the Safe Medical Devices Act was implemented, 75 (13%) lacked summaries.

After March 14, 1995, companies that did not provide a summary were required to release their 510(k) submission within 30 days of a written request. We requested that information for 20 of the 80 implants in this category. Four companies (20%) provided detailed evidence: Micrus Corpora-
tion, Sterngold-ImplaMed, Straumann USA, and Vascutek. In contrast, 3M, Intervascular, and Neovasc Inc provided redacted documents that did not include any scientific evidence. Zimmer Dental provided summary information that did not include scientific evidence. S. Jackson, Inc, explained that they had submitted no data to the FDA, “as the device itself was essentially unchanged from the original device” (written communication, October 9, 2013).

### Summaries That Included Detailed Data

Thirty-nine of the summaries provided scientific data: 8 from new implants and 31 from predicates. These often included useful information on the safety and effectiveness of implants, as illustrated by the examples in this section.

#### LeMaitre Vascular's Albograft Vascular Prosthesis

LeMaitre Vascular’s Albograft Vascular Prosthesis, made of polyester fabric impregnated with bovine collagen, was cleared in 2011 to repair or to replace diseased arteries. The summary compared preoperative and postoperative aggregate data on patency and limb salvage rates for 57 patients with gangrene and other diseases.17

#### Integra LifeSciences Corporation's DuraGen Dural Graft Matrix

Integra LifeSciences Corporation's summary for DuraGen Dural Graft Matrix, cleared in 1999 as a dura substitute to repair the membrane covering the brain and spinal cord, briefly summarized their clinical evaluations of more than 1000 patients: “No incidences of graft encapsulation, neomembrane formation, delayed hemorrhage, or foreign body reactions.” It also included a chart comparing the new device with 4 predicates on key factors such, as materials and whether they were resorbable.18

### Table 2. Public Availability of Scientific Evidence for the 10 Implants Cleared Through the US Food and Drug Administration 510(k) Process in 2012

<table>
<thead>
<tr>
<th>510(k) No.</th>
<th>Company</th>
<th>Device Name (Purpose)</th>
<th>Date Cleared</th>
<th>Evidence Mentioned</th>
<th>Classification</th>
<th>Specific Scientific Data Provided</th>
<th>No. of Predicates/Generations</th>
</tr>
</thead>
<tbody>
<tr>
<td>K113101</td>
<td>Boston Scientific</td>
<td>Exxcel Soft ePTFE Vascular Graft-Standard Wall, Thin Wall (vascular graft prosthesis)</td>
<td>1/17/2012</td>
<td>Nonclinical</td>
<td>Cardiovascular</td>
<td>No. “The results of these nonclinical tests met the specified acceptance criteria and were substantially equivalent to predicate device.”</td>
<td>5/2</td>
</tr>
<tr>
<td>K111162</td>
<td>Dentium Co, Ltd</td>
<td>Slim Onebody System (supports artificial teeth)</td>
<td>1/13/2012</td>
<td>None cited</td>
<td>Dental</td>
<td>No. Listed specific tests but not specific data results.</td>
<td>1/1</td>
</tr>
<tr>
<td>K113651</td>
<td>Boston Scientific</td>
<td>Interlock-35 Fibered IDC Occlusion System (vascular embolization device to control hemorrhaging due to aneurysms)</td>
<td>1/11/2012</td>
<td>None cited</td>
<td>Cardiovascular</td>
<td>No. Change to direction for use.</td>
<td>8/4</td>
</tr>
<tr>
<td>K113460</td>
<td>Synovis Orthopedic and Woundcare</td>
<td>Synergy Tissue Matrix (surgical mesh to reinforce soft tissue)</td>
<td>1/11/2012</td>
<td>None cited</td>
<td>General and plastic surgery</td>
<td>No. Listed specific tests but not specific data results.</td>
<td>105/6</td>
</tr>
<tr>
<td>K111761</td>
<td>Neobiotech Co, Ltd</td>
<td>Neo Titanium Mesh, CTI-Mem (bone plate to stabilize fractured bone structures in the oral cavity)</td>
<td>1/10/2012</td>
<td>None cited</td>
<td>Dental</td>
<td>No.</td>
<td>2/2</td>
</tr>
<tr>
<td>K110581</td>
<td>CryoLife, Inc</td>
<td>ProPatch Soft Tissue Repair Matrix (surgical mesh to reinforce soft tissue)</td>
<td>1/10/2012</td>
<td>None cited</td>
<td>General and plastic surgery</td>
<td>No. Listed specific tests but not specific data results.</td>
<td>38/8</td>
</tr>
<tr>
<td>K113071</td>
<td>Synthes</td>
<td>SyntheCel Dura Replacement Devices (dura substitute to repair the membrane surrounding the brain)</td>
<td>1/9/2012</td>
<td>Both clinical and nonclinical</td>
<td>Neurology</td>
<td>Yes. Randomized clinical test (n = 99; 62 in the investigational treatment group and 37 in the control group). Patients evaluated 4 times during a 6-month period. Also specific nonclinical data.</td>
<td>20/3</td>
</tr>
<tr>
<td>K112557</td>
<td>Stryker Corporation</td>
<td>Stryker Universal Neuro 3 System (cranioplasty plate to repair a skull defect)</td>
<td>1/5/2012</td>
<td>None cited</td>
<td>Neurology</td>
<td>Yes. Provides specific data in Substantial Equivalence Tables.</td>
<td>48/6</td>
</tr>
<tr>
<td>K113106</td>
<td>D.N.E., LLC</td>
<td>DNE External Fixation System (fixation of fractures of long bones (femur)</td>
<td>1/4/2012</td>
<td>None cited</td>
<td>Orthopedic</td>
<td>No. “[nonclinical testing was performed] and “no clinical studies were performed.”</td>
<td>9/3</td>
</tr>
<tr>
<td>K113609</td>
<td>Exactech, Inc</td>
<td>Novation Integrip Acetabular Augments (hip joint replacement)</td>
<td>1/4/2012</td>
<td>None cited</td>
<td>Orthopedic</td>
<td>No.</td>
<td>7/3</td>
</tr>
</tbody>
</table>
Micrus Corporation provided detailed summaries for their Microcoil Delivery System, cleared in 2001, and their Modified Microcoil 18-System, cleared in 2005. Both devices stop blood flow to cerebral aneurysms. The 2001 summary included a technological comparison with the predicate based on the results of multiple tests. The 2005 summary also provided detailed test results.

**Predicates Recalled for Safety Reasons**

The FDA recommends that applicants identify the exact predicate(s) in their 510(k) application. For 7 of the 50 newly cleared implants (14%), information about predicates was unavailable; thus, we could not determine whether an implant’s predicate has been recalled for safety reasons. For 8 of the new implants (16%), we identified at least 1 permanently recalled predicate. For example, the ProteGen Sling (Boston Scientific) was an early predicate for the MiniArc Sling System (American Medical Systems) (Figure) and the other newly cleared mesh implants in our sample. The ProteGen Sling was permanently recalled in 1999 owing to vaginal erosion and chronic pain. Similarly, the earliest predicate of a newly cleared implant to repair heart valves, St Jude’s Attune Adjustable Flexible Annuloplasty Ring, Model AFR, was a silicone-coated ring recalled in 2000 owing to life-threatening leakage. A few weeks after that recall, another St Jude implant was approved as substantially equivalent to the recalled device. Acumed’s Ulnar Shortening Saw Blade was the direct predicate for Acumed’s Congruent Bone Plate System; a year before the Congruent Bone Plate System was cleared in 2011, the Ulnar Saw Blade was recalled because it could “contribute to bone necrosis.”

**Examples of Substantially Different Predicates**

Although some predicates seem similar to the newer implants, others were used in different parts of the body and made from different materials. For example, a set of titanium implants and instruments to treat scoliosis and spinal fractures, the DePuy Spine, Inc, Mountaineer Laminoplasty System was cleared in 2010 as substantially equivalent to a lineage of 15 predicates going back to a dental device consisting of a screw or wire “inserted into fractured jaw bone segments.” Although these predicates varied in materials, size, shape, and indication, DePuy’s summary did not provide clinical or non-clinical data supporting the substantial equivalence, safety, or effectiveness of the device. The summary stated, “test data is available in Exhibit D. Exhibit D, however, is not publicly available. None of the 15 predicates for this implant had publicly available scientific data.

**Discussion**

Most new implanted medical devices are cleared through the 510(k) process; fewer than 20 annually are approved through the more rigorous Premarket Approval process. Scientific evidence of substantial equivalence is important for 2 reasons. First, when a medical device in current use is substantially equivalent to a predicate device that has been recalled for safety reasons, use of the new medical device could raise safety concerns. Second, differences can accumulate from predicate to predicate. According to the FDA, as a result of “predicate creep,” little is known about certain devices because they “can be made from different materials, use different power sources, and have indications for different anatomical sites.”

An analysis of the predicate history for a metal-on-metal hip implant illustrated those risks.

Our study is limited by the lack of publicly available data for the implants and predicates we identified. Except when summaries provided data or specified that no testing was conducted, we could not determine whether manufacturers of medical devices provided the FDA with appropriate scientific evidence.

**Conclusions**

In the United States, manufacturers of medical devices are required by law to provide the public with “sufficient detail to provide an understanding of the basis for a determination of substantial equivalence” of a medical device to a product that is already marketed in online summaries or on written request. For implants cleared between 2008 and 2012, however, we repeatedly found that scientific evidence of the substantial equivalence, safety, or effectiveness of medical devices was not publicly available in accordance with the legal requirements. To protect the public health and allow for independent judgment of the quality of the scientific evidence that supports the marketing of medical devices, the FDA should enforce the law.
REFERENCES


