**Many Newer Cardiac Devices Approved Without Clinical Data**

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January 22, 2014

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\*Irritable Bowel Syndrome with Constipation.
†Chronic Idiopathic Constipation.

Information from Industry

BOSTON, MA — Many cardiac implantable electronic devices (CIEDs) in use today were approved by the US **Food and Drug Administration** (FDA) based on earlier versions without additional human clinical trials[1].

This does not mean that these newer cardiac devices—including pacemakers, implantable cardioverter defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices—are inherently unsafe, the researchers say, but it does "reinforce the importance of rigorous postapproval surveillance."

"We're not trying to argue that there are any [devices] out there that are particularly dangerous," senior author **Dr Aaron S Kesselheim** (Harvard Medical School, Boston, MA) told [**heart*wire***](http://www.medscape.com/cardiology/news) . However, physicians should be skeptical of hype surrounding new devices, he said.

The article aims "to educate cardiologists and patients that a lot of the devices that are out there are being approved through this supplement process and to be wary if there is a change to a device and the device is being promoted as 'new and improved.' . . . Those kinds of statements may not be based on comparative data," he said.

The study is published in the January 22/29, 2014 issue of the *Journal of the American Medical Association.*

**PMA-Supplement Pathway**

The US FDA "reviews high-risk medical devices—those that support human life, prevent illness, or present an unreasonable risk—via the premarket approval [PMA] pathway, through which manufacturers collect preclinical and clinical data as necessary to provide 'reasonable assurance' of the device's safety and effectiveness," Kesselheim and colleagues explain.

When the design of an approved device is changed, instead of submitting a new PMA application to the FDA, the device manufacturer can submit a "supplement" to the original PMA application that may have been submitted decades earlier. This supplement-approval pathway is frequently used for devices, but it has not been well studied.

To investigate this, the researchers performed an in-depth study of PMA supplements related to CIEDs, which are useful to study since they have evolved substantially over the past 30 years.

They reviewed PMAs for CIEDs that were approved from 1979 to 2012.

**77 Original Devices, More Than 5000 Iterations**

During the studied 23-year period, the FDA approved 77 original applications for CIEDS—46 pacemakers, 19 ICDs, and 12 CRT devices—and 5829 supplement PMA applications for CIEDs.

Each device generated a median of 50 supplements during a median of 15 years.

More than one-third of the supplement PMAs (37%) were for design changes, and in the vast majority of cases, the FDA deemed that new clinical data were not needed for approval.

It was surprising that the applications reached so far back, Kesselheim said, "especially if you take [for example] a device that was marketed in 1999 and compare it with a device that you're looking at now in 2014; the difference . . . is going to be pretty stark, and yet the new device is still relying on that old device in its approval process."

The supplement-approval process can benefit patients. It "allows manufacturers to update devices via incremental innovations rather than encouraging them to wait and release a package of more substantial changes that might necessitate a new PMA application . . . [so] useful technological advances can be rapidly integrated into clinical care," the authors write.

On the other hand, the recalled Medtronic [**Sprint Fidelis**](http://www.medscape.com/viewarticle/564253)and St Jude [**Riata**](http://www.medscape.com/viewarticle/755585)ICD leads were both PMA supplements, and neither lead was studied in human trials prior to FDA approval. "The FDA's approval of many supplements without new human trials, as in the case of these recent ICD changes, highlights the importance of collecting rigorous postapproval performance data," they note.

"What we suggest . . . is maybe there should be a process where every [five to seven] years of a device being iteratively supplemented, there's an expert look back to ask whether or not it is reasonable to continue do that or whether a new, original PMA is necessary," Kesselheim said.

**Preclinical Data May Not Spot Problems**

In an accompanying editorial[2], **Dr Steven N Goodman** (Stanford University, Stanford, CA) and *JAMA Internal Medicine* editor **Dr Rita F Redberg** (University of California, San Francisco) write that this study evaluates "a process that has received relatively little attention . . . an underexamined third way for a device to reach the market." The other two ways are the (original) PMA route, which requires clinical effectiveness and safety evidence—although only 14% of high-risk devices have been assessed in a randomized controlled trial. The second way is the 501(k) route, in which a low-or moderate-risk device needs to show 'substantial equivalence' to an existing device—an approval pathway that a 2010 **Institute of Medicine** committee recommended be eliminated," they explain.

Citing the same example of the recalled leads, Goodman and Redberg note that these problems "were not predictable based on engineering insights or in vitro studies." This illustrates that "more empirical work is needed to assess the validity of reviewer judgments about whether clinical data are needed prior to certain types of device approval."

Asked to comment on this study, **Janet Trunzo**, senior executive vice president, technology and regulatory affairs, at **AdvaMed**, the advocacy organization for medical devices in the US, said in an email that "the FDA's [PMA] process is a rigorous, evidence-based review process designed to provide reasonable assurance of the safety and effectiveness of complex, high-risk medical devices before they are allowed to market," and the supplement-PMA process also requires manufacturers to submit extensive safety and effectiveness data.

"It is important to understand that the PMA-supplement process is intended for a change to an already-approved PMA that has met the agency's requirements for safety and effectiveness," she noted.

*Kesselheim reports previously publishing research funded by the FDA on comparative medical device regulation. Disclosures for the coauthors are listed in the paper. Redberg reports being a member of the US Food and Drug Administration Circulatory System Devices Panel and a member of the California Technology Assessment Forum. Goodman reports having no conflicts of interest.*