Getting a Product Approved by the FDA

An introduction to the pathway from idea to approval or clearance.

BY EUGENE DE JUAN JR, MD

Many important steps are required to take a product from its initial concept to market, including design, building, packaging, testing, and sales. In medicine, an increasingly complex yet critical part of the process is the FDA's approval or clearance of the drug or device.

Major lapses in safety prompted the passage of the 1906 Pure Food and Drugs Act. One such disaster involved a mascara called Lash Lure, the use of which caused blindness. Public awareness of tragedies such as the deformation of limbs by the use of thalidomide in the 1960s led to tighter regulations. Today, the FDA regulates roughly $1 trillion of commerce (approximately 25% of the US gross domestic product).[1] The agency's budget is nearly $4 billion, of which about one-half is provided by companies seeking approval/clearance.[1] The FDA is a law enforcement arm of government. The agency's operations and rules are not easy to understand or inexpensive to comply with, but it is essential to work with the FDA to make safe and effective products available to patients. This article serves as an introduction to that process.

WHAT IS THE IDEA?

What sort of product is it? The FDA regulates drugs, devices, diagnostic instruments, biologics, cosmetics, and food.

DRUGS

All new active chemical agents are drugs, and there is a clearly delineated path to demonstrating their safety and efficacy. Generally, when the drug (even an established, well-known agent) is combined with a device or a new formulation, it requires new testing. Not all drug-device combinations are true combined products; some are determined to be primarily a drug (eg, a drug-eluting punctal plug) or primarily a device (eg, a drug-coated cardiac vessel stent).

DEVICES

The 510(k) Process

A new device may bear similarities to a product made available before 1976. If so, the manufacturer can submit a Substantially Equivalent 510(k) application. The pathway to FDA clearance is shorter for these products than for a device not in this category.

Of course, the agency reserves the right to overrule these guidelines. For example, daily wear contact lenses are 510(k) devices. When one of these products is to be sold for extended wear (ie, overnight or longer), however, the FDA has decided that the associated risks are higher and that more extensive testing and controls are needed to support this use and claim. Extended-wear contact lenses require premarket approval, even though it is the manufacturer's claim—not the device—that is different.

A femtosecond laser can be a 510(k) device. Although lasers were not available prior to 1976, keratomes to cut the cornea were. It was demonstrated to the FDA that a femtosecond laser cuts the cornea in a way that is "substantially equivalent" to how a keratome does.

Implants

IOLs are designed to remain in a patient's eye for the rest of his or her life. These implants are all classified as high-risk (Class III) devices and require a premarket approval regulatory path.

Occasionally, an implant is for use under special conditions identified by the FDA as requiring more limited testing, thus allowing a 510(k) pathway. Glaucoma shunts for use after a failed trabeculectomy are an example.

Rarely (once in ophthalmology), a Humanitarian Device Exemption can be applied to a product. After the device's 5-year clinical trial in 30 patients, the FDA cleared Second Sight's Argus II ocular prosthesis for use in blind patients with retinitis pigmentosa. The reasons behind the decision were an absence of other such devices and a demonstra-

ACOS AND INNOVATION

The pathway to new and innovative technology goes through the FDA.

BY STEPHEN SLADE, MD

We members of the American-European Congress of Ophthalmic Surgery (ACOS) have been fortunate with regard to the ACOS' relationship with the FDA. As individuals, many of us had appeared before the FDA numerous times and worked on multiple projects with the agency. As members of the ACOS and as individuals, we did not always agree with the FDA, but we always maintained our respect for the personnel at the agency and their mission. The FDA employees dedicated, hard-working, intelligent scientists, physicians, and experts in many fields in a very challenging, high-workload environment. As the ACOS, we knew working with the FDA in any way we could would deliver valuable results for both our members and our patients. Ophthalmology is, of course, technology dependent, and most of our technologies must pass through the FDA. The ACOS made it a goal of the society to interact with the FDA in any way we might.

COLLABORATION

At the very first ACOS Winter Meeting, we invited Malvina Eydelman as a special guest speaker. Dr. Eydelman attended and graciously participated in a frank discussion with the group of the FDA's positions and future direction.

Encouraged, in August 2011, as ACOS, we approached the Drug Division of the Center for Devices and Radiological Health with a unique idea for an ACOS-sponsored clinical trial. We recognized the value of corneal cross-linking to arrest the blinding diseases of keratoconus and related corneal dystrophies. Working with Wiley Chambers, MD, we were able to begin the largest FDA trial of corneal cross-linking within 1 year of our initial contact, a shining example of a society and the FDA's working together quickly and efficiently. This trial grew into the largest FDA trial of corneal cross-linking. To date, 84 investigators have enrolled more than 800 patients, with keratoconus and ectasia diagnoses.

A DIALOGUE

We at the ACOS have continued our dialogue with the leadership of the FDA by inviting Jeff Shuren, head of the Center for Devices and Radiological Health, as a special guest, to our Deer Valley, Utah, Summer Meeting in 2012. There, Dr. Shuren met with ACOS leadership, gave a keynote lecture at the meeting, and took on all questions, answering frankly. After the meeting, Dr. Shuren invited us to Washington, DC, as a society, to explore further ways to work together.

In September 2012, an ACOS leadership team went to Washington, DC, and met with Dr. Shuren, Dr. Eydelman, and their team. We discussed different ways to work together, and we were challenged by the FDA to come back with a project of value that would be centered on the FDA and the ACOS. We created an idea for an expedited pathway for device approvals and have continued to develop that with the agency. We believe we can create an efficient approach in the case of specific devices.

Most recently, we have continued to work with the FDA by becoming one of the first ophthalmic societies to enter into a "network-of-experts" agreement with the FDA. This is a resource group for the agency to gather timely information. As a result, a number of ACOS leaders have participated with the FDA in discussions on LASIK, as an example.

For a working relationship of less than 3 years, we at the ACOS have been very pleased. We expect to disagree on some issues, but we know the pathway to new and innovative technology routes through the FDA. We know it is in our patients' best interest and foremost in our goals as a society to continue to work with and build a relationship with the FDA.

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tion of reasonable safety, as judged by a panel of experts and interested persons. Generally speaking, clinical data on at least 300 patients is required for implants to allow a reasonable assessment of their safety at the 1% incidence level.

CONCLUSION

The process of obtaining FDA approval or clearance of a product can be complex. The determination of a device's level of risk (Class I-III) can be helped by the FDA or by a regulatory consultation. The field of ophthalmology will benefit from the recent addition of highly experienced people as consultants and as the heads of the regulatory division on the drug and device arms of the FDA. Those interested in bringing new ideas to market should give them a call. ■

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1. Food and Drug Administration. Wikipedia website. http://en.wikipedia.org/wiki/FDA. Accessed January 22, 2014.