Humanitarians, Compassion, and the Food and Drug Administration: Guidance for the Practitioner

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EDITORIAL

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Without approval for marketing by the US Food and Drug Administration (FDA), even the most brilliant new medical device has essentially no economic value. Any strategy for bringing a novel device to the market must focus on the "regulatory pathway." The federal government has developed several such pathways, the choice of which has substantial effect not only on the expense required to gain approval but also on how the device can later be marketed and used. We suspect that many interventional neuroradiologists pay little attention to the nuances of "regulatory pathways." However, the advisability of regulatory naïveté has diminished with the advent of the now often-used "Humanitarian Device Exemption (HDE)" regulatory pathway.[1] It is the purpose of this paper to briefly review the HDE regulatory pathway and, more importantly, to focus the physician on the constraints, regulations, and practitioner responsibilities associated with these Humanitarian Use Devices (HUDs).

Regulatory Pathways

In general, there are 4 primary methods for marketing a medical device, including premarket approval (PMA)/product development protocol (PDP), premarket notification (510(k)) clearance, exempt devices, and HDE. The FDA defines several "classes" of devices, ranging from class I devices (for which potential harm is minimal) to class III (which support or sustain human life; are of substantial importance in preventing impairment of human health; or which present a potential, unreasonable risk for illness or injury). The regulatory path to market is primarily dictated by these device classifications. PMA/PDP devices are class III and typically carry the burden of large clinical trials to establish safety and efficacy. The 510(k) devices are class II, and the application process requires the submitter to establish that the device is "substantially equivalent" to a previously marketed class II device. Exempt devices, on the market before 1976 with a long history of use, are typically class I and do not require an application to be submitted to the FDA. An HDE represents an exemption to permit marketing of HUDs. This type of exemption stems from a waiver of burden of proof for efficacy. For an HDE, there is limited burden other than to demonstrate that the device is safe and that there is "probable benefit" in a population affected with a disease or condition that is manifested in fewer than 4000 patients per year.

The amount of clinical data required, and thus the expense incurred, to gain approval plummets when moving from PMA to HDE.[2] However, as in most of life, there is no free lunch at the FDA because the less onerous pathways are associated with greater restrictions than the more onerous pathways. For example, the 510(k) clearance process requires that the new device be "substantially equivalent" to an existing device. As such, the company must rely on effective marketing to convince us that we should use, and potentially pay a premium for, a device that is "substantially equivalent" to existing devices. Fortunately for industry, physicians have a strong track record in succumbing to such marketing. In comparison with both the PMA-approved and 510(k)-cleared devices, though, the restrictions on use of HUD are severe and, whether or not they know it, may affect physicians' responsibilities and liabilities.

HDE-Associated Constraints

No one likes to be labeled. Medical devices, unfortunately, have no choice in the matter. Each device is approved or cleared for a specific indication or indications, which are reflected in the "label." PMA-approved and 510(k)-cleared devices may be freely used "off-label," which means that these devices may be applied for an indication not listed on the label. Indeed, a physician could put one of these devices in someone's eyeball without any oversight, if such physician deems it appropriate. As is well reported even in the lay press, the company cannot specifically promote this "off-label use." Companies may choose to gain PMA approval or 510(k) clearance for a relatively uncommon "usage" while anticipating that physicians will take it upon themselves to use the device (frequently, off-label) for a more common condition than that on the label.

HUDs do not enjoy such liberties as those enjoyed by PMA-approved and 510(k)-cleared devices. HUDs must be reviewed by an Institutional Review Board (IRB) before use, though specialized, individual patient consent is not required by the regulations for their on-label use. In some cases, however, the IRB may require individual patient consent. Furthermore, the Principal Investigator for an HUD study needs to ensure that everyone who will use the device is listed on the protocol and that any serious and unanticipated adverse events that occur with use of the device are reported to the IRB and to the company. Failure to follow the rules could place those using the device, as well as their institution, not only at risk for loss of human research privileges but also subject to other liabilities. Not only are companies limited in how many devices they can sell annually (typically on the order of 4000), but also the off-label use of HUDs is severely limited. Physicians cannot simply use the device in an off-label fashion and move on. Instead, federal law outlines specific recommendations and recommendations for both the physician and company when off-label use of HUDs is considered (Table).

On- and Off-Label Use

Scrutiny of recent HDE approvals for aneurysm devices, including the Enterprise (Cordis, Miami Lakes, Fla) and Neuroform (Boston Scientific, Natick, Mass) stents as well as Onyx 500 (ev3, Irvine, Calif), may shed light on specific aspects relevant to the physician. What exactly comprises "off-label use" of one of these devices may not be as simple as it seems. It is certain that use of an Enterprise stent as a bailout maneuver in a patient with acute stroke is off-label and thus mandates that the physician and company comply with federal regulations regarding patient consent, IRB, and FDA notification.[3] Several other applications would seem to be less clear with regard to being "off-label." For example, the use of HDE-approved aneurysm devices as stand-alone devices, without intention to place coils, as might be considered for fusiform or blister-type aneurysms, probably constitutes off-label use. Placement of the stent across the aneurysmal neck after an uneventful coil

Task list for off-label use of Humanitarian Device Exemption (HDE)–Approved Devices (2)	
Emergent HDE Off-Label Use*	**Compassionate HDE Off-Label Use†**
Obtain IRB chairperson's concurrence. If unable to obtain, must report within 5 days.	Provide HDE holder (company) with the following:
Obtain informed consent of patient or legal representative, if possible.	A description of the patient's condition.
Provide documentation of independent assessment by uninvolved physician (not referring physician).	The circumstances necessitating the use of the device.
Obtain institutional clearance, written notice that the IRB acknowledges the off-label use.	A discussion of why alternative therapies of diagnostics are unsatisfactory.
Obtain authorization from HDE holder (company).	A follow-up plan to HDE holder for their submission to the FDA.
Obtain submission of a follow-up plan to HDE holder for their submission to the FDA.	FDA approved for compassionate use with help of HDE holder.‡

Note:—IRB indicates Institutional Review Board; FDA, US Food and Drug Administration.
* Emergent HDE use: to save life or protect the physical well-being of a patient.
† Compassionate HDE: not an emergency, but no alternative device for the patient's condition exists.
‡ This task is a requirement, whereas all other tasks listed for both emergent and compassionate use are recommendations.

procedure, for whatever reason, probably constitutes off-label use. As such, use of the devices in these instances requires special consent and reporting rules to be followed, as outlined in the accompanying table.

Additional areas may be even less clear regarding on- or off-label use. For example, the package insert for the Enterprise stent notes that "The Cordis Enterprise . . . is intended for use with embolic coils for the treatment of wide-neck, intracranial, saccular or fusiform aneurysms arising from a parent vessel with diameter of >/ = 2.5 mm and </ = 4 mm." It seems likely that the Enterprise would often be used in carotid arteries of 4.5 mm or so. Is that use considered "off-label?"

Uncertainties about off-label use are also relevant for the Wingspan stent (Boston Scientific). The standard practice of some practitioners for treatment of an intracranial stenosis is to perform balloon angioplasty alone, if possible, and place stents only in the setting of abrupt or impending arterial closure. This practice pattern seems rational in light of high rates of restenosis reported with the Wingspan stent.[4] However, the Wingspan is marketed as a "system," in which both the Gateway balloon (Boston Scientific, Fremont, Calif) and the Wingspan stent are used together. Is one using the Gateway "off-label" when choosing not to place the stent? Is one required to report all such cases to the IRB and FDA?

A Missed Opportunity?

"Postmarket surveillance" is a fancy name for prospective data collection from patients treated with an approved or cleared device. In some cases, including carotid stents, the FDA might mandate that prospective registries be applied as a condition of approval or when collection of "real world" data are considered valuable. Especially in instances where limited clinical data are available before approval, as in the case of essentially all HUDs, it seems that routine postmarket surveillance would be of especially great relevance. Indeed, physicians are already required to get IRB approval before use of HUDs and to send continuing review reports to the IRB no less often than once a year. One might anticipate that IRB approval of prospective registries of these devices would be easily obtained, yet no such registries are required.

How much information are we learning about HUDs from the literature, in the absence of postmarket surveillance guidelines? In the case of the Enterprise stent, the entire literature from domestic sites comprises 5 cases, with an additional 55 cases from European centers. Given that the Enterprise was approved for use in the United States in May 2007, likely hundreds of Enterprises have been sold to date, and thus we are capturing only a tiny fraction of cases in the literature. This seems relevant because the HDE itself was based on a series of only 28 patients. Should physicians demand a systematic process for prospective data collection of devices such as these?

Summary

Once an HUD finds its way to the shelves in a hospital's procedure room, there is a possibility that the practitioner will find applications for the device beyond its intended use. In many or most of these cases, the patient would probably benefit from its use, but the practitioner should be cognizant of FDA recommendations and requirements surrounding such off-label applications. It is strongly recommended that practitioners work closely with their local IRBs for any intended off-label use. It is hoped that this brief review not only will focus proper attention on these federal recommendations but also will bring to light ongoing shortcomings in accumulation of published data on these HUDs.

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