

Complying With Expanded Access Policy Drug Laws

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On Dec. 13, 2016, President Obama signed the 21st Century Cures Act into law. While the act contains many provisions of interest to pharmaceutical (and medical device) companies, one provision that might easily have been overlooked is Section 3032.

Section 3032, entitled “Expanded Access Policy,” requires a manufacturer or distributor of one or more investigational drugs “for the diagnosis, monitoring, or treatment of *one or more serious diseases or conditions shall make available* the policy of the manufacturer or distributor on evaluating and responding to requests submitted ... [*for expand access*] ... for provision of such a drug.” (Emphasis added.) In plain English, Section 3032 requires that manufacturers or distributors of an investigational drug indicated for a serious disease or condition make publically available their policy regarding the drug’s availability for expanded access, otherwise known as compassionate use.



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Expanded access refers to:

1. The use of an investigational drug (e.g., a drug that has not been approved or licensed by the U.S. Food and Drug Administration (FDA));
2. Outside of a clinical trial.[1]

Expanded Access: Pros and Cons

Expanded access is an issue on which pharmaceutical companies often struggle to find the right balance. On one hand, pharmaceutical companies are deeply concerned with patient welfare and well-being. So, in an ideal world, pharmaceutical companies would be able to provide investigational drug to any patient, enrolled in a clinical trial or not, who might benefit from the drug. But the counterweights are significant.

Supplies of investigational drugs are usually limited, with pharmaceutical companies often having just enough investigational drug, with perhaps a small reserve, to complete clinical testing required for regulatory approval. Investigational drug supply and the expense associated with production are often significant barriers to providing wider experimental drug access to compassionate use patients.

A further issue is the significant adverse events (SAEs) that can arise under compassionate use. Patients who receive an experimental drug in a compassionate use program are often very sick patients whose diseases have significantly progressed. Thus, SAEs, including death (which may or may not have been

caused by the experimental drug), are likely to occur. SAEs must be promptly reported to the FDA (e.g., in 15 day reports[2]) and other regulatory authorities. SAEs will also likely necessitate a change in the drug sponsor's informed consent form (which would, in turn, necessitate further institutional review board review and approval of the revised informed consent form). New SAEs must also be disclosed to investigations sites, and investigators and in investigator brochures, which could significantly delay the initiation of new studies or the continuation of ongoing studies. SAEs from compassionate use can therefore slow or even halt a drug sponsor's development program and commercialization.

Additionally, if a pharmaceutical company is going to provide its experimental drug on a compassionate use basis, which patients get the drug? As discussed above, the number of patients requesting compassionate use almost always exceeds the available drug supply. This supply and demand imbalance creates an ethical dilemma: how to determine who gets (and who does not get) the experimental drug.

There is no easy answer. After serious consideration, to address the ethical dilemma, some pharmaceutical companies have used lotteries to determine which patients get the experimental drug.[3]

Lastly, what happens if there is an injury to a compassionate use patient? This raises potential liability issues, as well as questions regarding the scope of the company's insurance. Providing an expanded access drug to a patient outside of a clinical trial could result in significant financial liability for the company.

While we have not touched on all issues related to expanded access,[4] expanded access decisions require careful consideration. Section 3032 of the act now brings a further sense of urgency to this consideration.

Section 3032: A Requirement to Make Available an Expanded Access Policy

Section 3032 of the act deals with and is entitled: "Expanded Access Policy." It contains the following requirements:

1) A "manufacturer or distributor of one or more investigational drugs for the diagnosis, monitoring, or treatment of one or more serious diseases or conditions shall make available the policy of the manufacturer or distributor on evaluating and responding to requests submitted ... [for expanded access] ... for provision of such a drug." (Expanded access.)

The act does not define what is a serious disease or condition. However, the FDA has previously defined a serious disease or condition[5] as:

... a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.[6]

Thus, a pharmaceutical company should first determine if any of their investigational drugs are intended for a serious disease or condition. If the investigational drug is intended for a disease or condition that is not serious, drug sponsors are not obligated under Section 3032 to provide a policy.

2) Assuming the indication is for a serious disease or condition, the act further requires that the manufacturer's policy shall be made public and readily available, such as by posting such policies on a publicly available website.

The act also recites that a policy may be generally applicable to all investigational drugs of distributor or manufacturer.

3) the act further recites that: "The posting of policies by manufacturers and distributors under subsection (a) shall not serve as a guarantee of access to any specific investigational drug by any individual patient."

The act specifically notes that posting of a policy is not a guarantee of access. Accordingly companies should consider adding language to this effect to their policies.

4) the act also recites the content of a compassionate use policy, which must include:

- Contact information for the manufacturer or distributor to facilitate communication about requests ... ;
- Procedures for making such requests;
- The general criteria the manufacturer or distributor will use to evaluate such requests for individual patients, and for responses to such requests;
- The length of time the manufacturer or distributor anticipates will be necessary to acknowledge receipt of such requests; and
- A hyperlink or other reference to the clinical trial record containing information about the expanded access for such drug ...

Some companies may elect to not provide an experimental drug on a compassionate use basis. These companies could craft their policies to indicate that the companies will not provide experimental drug to patients outside of company sponsored clinical trials and that the companies do not have a compassionate use program. However, it is important to consider that this could result in some backlash from socially and politically connected activists, patients, protestors upset with such policies, patient sympathetic politicians, and human interest news stories. On the other hand, companies who provide experimental drug on a compassionate use basis may see delays, or even a halting, of their drug development processes. Companies should therefore carefully consider the pros and cons of compassionate use before providing a policy.

5) Revisions to the policy are allowed.

This provision is generally good for companies. Companies should consider adding language to this effect in any posted policy.[7]

6) Finally, this provision of the act shall *apply on the later of* (emphasis added):

(1) "the date that is 60 calendar days after the date of enactment of the 21st Century Cures Act [the act was enacted on Dec. 13, 2016]; or

(2) the first initiation of a phase 2 or phase 3 study (as such terms are defined in section 312.21(b) and (c) of title 21, Code of Federal Regulations (or any successor regulations)) with respect to such investigational drug."

Given the "apply on the later of" language above, several companies may need to post a policy soon.

A Further Consideration

It is currently unclear, based on the statutory language alone, whether the policy requirement only applies to companies that are conducting clinical trials in the United States, and with U.S. citizens. In other words, it is not completely clear if a U.S. company, that does not have a U.S. investigational new drug application (IND), and is not testing an investigational product on U.S. citizens, is required to comply with this requirement. For example, is a U.S. company that is conducting a phase II clinical trial in Europe required to post a policy? Further guidance from the FDA would be helpful.

Conclusion

Section 3032 of the act requires timely posting of an expanded access policy when a serious disease or condition is indicated. Timely complying with Section 3032 is important, when required. But multiple and often opposing considerations go into determining what a company's expanded access policy should be. Such policy may change depending on clinical development stage of a company. And any policy may have negative repercussions for a company. Companies should carefully weigh these considerations when deciding how to comply with the act Section 3032.

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[1] "Expanded Access (Compassionate Use)," FDA, (updated Jan. 27, 2017), available at <http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm>, last accessed Feb. 12, 2017.

[2] 21 C.F.R. § 312.32(c).

[3] For a good primer on expanded access relating to experimental cancer drugs, see <http://www.canceractionnow.org/living/gettingdrug.php>, last accessed Feb. 12, 2017.

[4] For example, every expanded access use of an experimental drug outside of a clinical development program must be approved by FDA, either on an individual use basis or through an expanded access program. FDA permits sponsors to amend INDs (e.g., to an expanded access IND) to grant patients access to experimental drugs for treatment purposes. The amendments should demonstrate that patients: i) have serious or life-threatening conditions, ii) do not qualify to participate in an on-going clinical trial, iii) have no other treatment options available, and iv) that potential benefits of the experimental drug, provided on a compassionate use basis, are likely to outweigh the experimental drug's potential risks.

But, patients cannot self-apply for such access to experimental drugs; requests on behalf of the patient must come from the sponsor (see above), a physician investigator, or the patient's treating physician.

These requirements, while intended to address patient safety, also provide examples of how FDA regulations create significant hurdles that impede patient compassionate use access to experimental drugs.

[5] “Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics,” FDA, (May 2014), available at <http://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf>, last accessed Feb. 12, 2017. 21 C.F.R. § 312.300(b)(1).

[6] 21 C.F.R. § 312.300(b)(1).

[7] For example, while it may not make sense for a company sponsoring a phase I to provide experimental drug on a compassionate access (e.g., because of very limited experimental drug supply), this could change when the company, later in time, is contemplating phase III clinical trial(s) and has a more abundant experimental drug supply.