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PERSPECTIVE

# Bill would bring drugs that treat serious conditions to market faster

**By Georgia Ravitz, David Hoffmeister, James Ravitz, Vern Norviel, Prashant Girinath and Charles Andres**

Recently, Sen. Mike Braun (R-Ind.), introduced the Conditional Approval Act (S.3133). The act would amend the Federal Food, Drug and Cosmetic Act (21 U.S.C. 351 et seq.) to allow for a shorter pathway to market — that is, to allow for an early, provisional, and time limited approval — for drug candidates that meet six criteria.

In proposing the act, Braun noted: "Patients with fatal diseases are fighting for their lives every day while real, meaningful, life-extending treatments sit on the shelf just beyond their reach. " "For those who are so courageously battling these terrible diseases, the least we can do is not stand in their way."

**Conditional Approval**

Conditional approval, if granted, would initially be effective for 1 year, renewable for up to four additional one-year terms. Conditional approval, as the name suggest, indicates a drug has conditionally been found to be safe and effective, and therefore may be introduced (sold) into interstate commerce in the United States.

The act recites a conditional approval shall be in effect for "not more than five years from the date on which conditional approval is first granted." The act also requires that any conditionally approved drug be brought to market within three years of conditional approval (delays of up to three years would, of course, require an initial grant and several renewals). Failure to meet this three year deadline, as recited in the act, will result in any conditional approval being "deemed invalid."

**Conditional Approval Criteria**

A drug candidate may be conditionally approved if six criteria are met. First, it must be "likely that the sponsor will be able to provide comprehensive clinical trial data after [the] drug is conditionally approved." This provision will require appropriate clinical development planning and budgeting, in advance, for the expense of conducting confirmative clinical trials. In the case of startup companies, this may require the raising of additional funds, for example, by going public, or raising additional rounds of capital (e.g., raising a series D or E round).

Second, the drug must be "intended for the treatment, prevention, or medical diagnosis of a seriously debilitating disease, a life-threatening disease, or a chronic condition." The act defines a seriously debilitating disease as "a disease or condition that causes major irreversible morbidity." A life-threatening disease is one "where the likelihood of death is high unless the course of the disease is interrupted" or "a disease or condition with potentially fatal outcomes, where the end point of clinical trial analysis is survival." A chronic condition is a disease or condition that "usually lasts for 3 months or longer" and "requires ongoing medical attention" or "limits activities of daily living."

Third, the "expected benefits of the drug outweigh the potential risks to patients," taking into account that "additional data are still required to assess the drug."

Fourth, there must be "no existing meaningful treatment for the disease or condition that the drug is intended to treat." The act does not define the term "meaningful treatment." Interestingly, the fifth criteria that "such drug is intended to treat a disease for which no more than two meaningful treatments currently exist" might be viewed, through one lens, as contradicting the fourth criteria.

The last criteria is that "confirmatory clinical trials [be] difficult and costly to conduct." As most clinical trials (e.g., phase 3 trials) that support drug approval could be classified as difficult and costly to conduct, this last criteria may not create a significant gating issue.

**Use of Real World Evidence**

Real world evidence is defined as "data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials." (Emphasis added.) The 21st Century Cures Act created a requirement for establishment of a draft framework for evaluating real world evidence to: (1) "help support the approval of a new indication for a drug approved under section 505(c) of the FDCA"; and to "help support or satisfy postapproval study requirements." Sources of real world evidence include "registries, observational studies, ongoing safety surveillance, and patient centered outcomes." The act allows "the use of real world evidence ... collected by a sponsor of a drug during the duration of conditional approval ... to supplement an application for full approval."

**Liability Limitation**

The act provides for limitations on liability for drug sponsors. "With respect to any claim under State law alleging that a drug sold or otherwise made available pursuant to a grant of conditional approval [under the act] is unsafe or ineffective, no liability ... shall lie against a manufacturer. The liability limitation protection does not apply to conduct that "constitutes reckless or willful misconduct, gross negligence, or an intention tort under any applicable state law." The limitation on liability is potentially significant, as we discuss below.

**The Act Compared to Accelerated Approval**

The act is similar to, but also differs from, the process for accelerated approval. Accelerated approval allows for a drug — indicated for a serious condition — and that fills an unmet medical need, to be approved based on the drug's effect on a surrogate endpoint or an intermediate clinical endpoint. A surrogate endpoint is a "laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit" that is considered "reasonably likely" to "predict the clinical benefit of a drug." We previously wrote about the U.S. Food and Drug Administration's, or the FDA's, publication of a list of surrogate endpoints that have been used to support approval. As required by the 21st Century Cures Act, the list is updated every six months.

Accelerated approval allows for

the use of a surrogate endpoint as a primary endpoint in a clinical trial to support approval, and the act does not. Additionally, accelerated approval is reserved for drug candidates indicated for a serious condition. The act allows for drugs to treat chronic conditions, thus making the scope of drugs available to be conditionally approved broader than the potential drug approval scope of accelerated approval. Also, the act does not appear to preclude seeking both conditional approval and accelerated approval to see if one, or the other, or both, are realistically possible.

**Issuing Guidance(s) and Regulations**

The act additionally requires, within one year of enactment, that final regulations and guidance(s) be issued by the FDA. Thus, early conditional analysis requesters should be prepared to engage in some degree of "trail blazing."

**Full Approval and Eligible Drug Candidates**

The act is unambiguous about when a sponsor of a conditionally approved drug may seek full approval. A sponsor may, "at any point, submit an application for full approval as described under section 505 of the Federal Food, Drug and Cosmetic Act or Section 351 of the Public Health Service Act, as applicable." This language would also appear to indicate that the Act contemplates being applicable to small molecule drugs (FDCA) and biologics (PHSA).

**Our Thoughts**

The act is applicable to a broad set of drug candidates. For example, many drugs are in development to treat chronic conditions. Additionally, the act could be made stronger, and a potential contradiction could be mooted, by removing the fourth criteria (e.g., no existing meaningful treatment for the disease or condition that the drug is intended to treat) and simply relying on the sixth criteria, in combination with the remaining criteria, for seeking conditional approval. Finally, most larger scale clinical trials arguably are difficult and costly to conduct. Thus, the act, with some fine tuning, could be a broad pathway to get drugs into the hands of patients faster.

Additionally, conditional approval, like accelerated approval, presents a potential alternative funding model. If drugs can be sold earlier in time, profits from the sale of the drugs can, at least in part, be used to fund the subsequent, required, clinical trial to confirm drug safety and efficacy.

From one perspective, the act, like accelerated approval, could be viewed as an extension of, and a partial remedy for, the deficiencies of the compassionate use or expanded access program. Expanded access refers to the use of drug by a patient while the drug is pending regulatory approval. While in some instances, drug candidates are provided to patients outside of an expanded access program, doing so is not the norm.

For example, 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. Conditionally allowing drugs could obviate these supply issues.

Additionally, if a pharmaceutical company is going to provide its experimental drug on a compassionate use basis, which patients get the drug? 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. Conditionally allowing drugs could remove this ethical dilemma.

Also, the limitation on liability provision of the act is important. Drug companies may be discouraged from taking a drug to market under an expanded access program because, in the absence of a larger scale clinical trial, the drug company may not sufficiently understand the drug's risks. The removal of liability could lower this barrier to getting drug to patients who need the drug.

One downside is that at least some conditionally approved drugs may fail to show statistically significant safety and efficacy in larger clinical trials. In those cases, patients may see no or limited benefit, and could be harmed.

**Conclusion**

Comments and questions can be submitted to ConditionalApproval@Braun.Senate.gov. The act, if made into law, could be a significant mechanism to get drugs into the hands of patients faster. Interested stake holders should consider submitting comments and questions, and contacting their elected federal representatives. ■

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