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# **Guidance for Industry**

# **Available Therapy**

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**July 2004  
Clinical Medical**

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## **Guidance for Industry<sup>1</sup> Available Therapy**

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

### **I. INTRODUCTION**

This document is intended to provide guidance to industry on the meaning of the term *available therapy* as currently used by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) in the Food and Drug Administration (FDA) in the specific circumstances described in this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

### **II. BACKGROUND**

*Available therapy* and related terms, such as *existing treatments* and *existing therapy*, appear in a number of regulations and policy statements issued by CDER and CBER, but these terms have never been formally defined by the Agency. Some confusion has arisen regarding whether *available therapy* refers only to products approved by FDA for the use in question, or whether the term could also refer to products used off-label or to treatments not regulated by FDA, such as surgery. This guidance is intended to inform the public of the Agency's interpretation of *available therapy* as used in the regulations and policy statements described in Part III.

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<sup>1</sup> This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

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### III. AFFECTED REGULATIONS AND POLICY STATEMENTS

The regulations and policies described below incorporate the concept that the Agency can regulate a particular product in a certain manner because of a lack of available therapy or because of the product's advantage over available therapy. The language incorporating this concept is printed in bold italicized print for emphasis.

#### A. Treatment INDs

FDA's regulations allow the use of an investigational drug for treatment under a treatment protocol or treatment investigational new drug application (IND). According to 21 CFR 312.34(b), the investigational drug can only be used for this purpose if the following criteria are met:

- The drug is intended to treat a serious or immediately life-threatening disease.
- ***“There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population”*** (312.34(b)(ii)).
- The drug is being investigated under an IND in effect for the trial, or all clinical trials have been completed.
- The sponsor of the clinical trial is actively pursuing marketing approval of the investigational drug.

#### B. Subpart E Regulations

The Agency's procedures in subpart E of 21 CFR part 312, which expedite the development, evaluation, and marketing of promising therapies to treat individuals with life-threatening and severely debilitating illnesses, reflect that the Agency must make a medical risk-benefit judgment in deciding whether to approve a drug or biological product. As part of this risk-benefit analysis, the Agency will "tak[e] into consideration the severity of the disease and the ***absence of satisfactory alternative therapy***" (21 CFR 312.84).

#### C. Accelerated Approval Regulations

FDA's accelerated approval procedures and restricted distribution provisions in 21 CFR subpart H are available for new drug and biological products (1) that have been studied to treat serious or life-threatening illnesses and (2) "that provide meaningful therapeutic benefit to patients ***over existing treatments (e.g., ability to treat patients unresponsive to, or***

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*intolerant of, available therapy, or improved patient response over available therapy)"* (21 CFR 314.500 and 601.40).

### **D. Fast Track Drug Development Programs**

FDA's fast track drug development programs are designed to facilitate the development and expedite the review of drug and biological products that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical needs (FDA guidance for industry on *Fast Track Drug Development Programs: Designation, Development, and Application Review*). In the guidance, the Agency defined an unmet medical need as a "medical need that is *not addressed adequately by an existing therapy*."

As described in the guidance, *where there is no available therapy for a condition (or the only available therapy is approved under the accelerated approval regulations), a product in a drug development plan designed to evaluate the drug's potential to address the condition would meet the factors to address an unmet medical need. Where there is available therapy for the condition, the drug development program would address unmet medical needs if it evaluated any of the following:*

- *Improved effects on serious outcomes of the condition that are affected by alternate therapies*
- *Effects on serious outcomes of the condition not known to be affected by the alternatives*
- *Ability to provide benefits in patients who are unable to tolerate or are unresponsive to alternative agents, or ability to be used effectively in combination with other critical agents that cannot be combined with available therapy*
- *Ability to provide benefits similar to those of alternatives, while avoiding serious toxicity that is present in existing therapies, or avoiding less serious toxicity that is common and causes discontinuation of treatment of a serious disease*
- *Ability to provide benefits similar to those of alternatives but with improvement in some factor, such as compliance or convenience, that is shown to lead to improved effects on serious outcomes.*

### **E. Priority Review Policies**

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CDER and CBER have established review classifications and review policies and procedures for new drug applications (NDAs), biologics license applications (BLAs), and efficacy supplements to prioritize and speed their review. Most of these Agency policies and procedures are intended to encourage the development and expedite the review of innovative drug products (i.e., subpart E regulations, accelerated approval regulations, fast track drug development programs, priority review policies), while one (treatment INDs) provides early access to investigational therapies.

A priority designation is intended to direct overall attention and resources to the evaluation of applications for products that have the potential for providing a significant treatment, preventive or diagnostic therapeutic advance, as compared to standard applications.<sup>2</sup>

Products regulated by CDER are eligible for priority review if they provide a ***significant improvement compared to marketed products in the treatment, diagnosis, or prevention*** of a disease.

Products regulated by CBER are eligible for priority review if they provide a ***significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention*** of a serious or life-threatening disease.

#### **IV. POLICY: DEFINITION OF AVAILABLE THERAPY**

The regulations and policies described above do not explicitly define *available therapy*. CDER and CBER have determined that in regulations and policy statements where the terms are not otherwise defined,

*available therapy* (and the terms *existing treatments* and *existing therapy*) should be interpreted as therapy that is specified in the approved labeling of regulated products, with only rare exceptions.<sup>3</sup>

FDA recognizes that there are cases where a safe and effective therapy for a disease or condition exists but it is not approved for that particular use by FDA. However, for purposes of the regulations and policy statements described in Section III, which are intended to permit prompt FDA approval of medically important therapies, only in exceptional cases will a treatment that is not FDA-regulated (e.g., surgery) or that is not labeled for use but is supported by compelling literature evidence (e.g., certain established oncologic treatments) be considered *available therapy*.

Most of the Agency programs that use the term *available therapy* are intended to encourage the development and expedite the review of innovative drug products. By defining *available therapy* to

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<sup>2</sup> CDER Manual of Policies and Procedures (MaPP) 6020.3 explains the priority review policy and procedures. CBER Manual of Standard Operating Procedures and Policies 8405 explains the process for Complete Review and Issuance of Action Letters.

<sup>3</sup> Approved labeling refers to claims approved conventionally or under FDA's accelerated approval procedures.

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focus on approved products with labeling for use in the disease or condition at issue, FDA (1) emphasizes the importance of the approval process for establishing that a drug is safe and effective for a particular use and (2) provides the greatest opportunity for development and approval of appropriately labeled drugs. For these programs, products that are used off-label for the indication at issue and products that have not had formal FDA review are rarely considered *available therapy*; the definition of *available therapy* in this guidance provides only a limited exception for particularly well-documented therapies.

Questions also have arisen concerning how the term "meaningful therapeutic benefit to patients over existing treatments" in the accelerated approval regulations (21 CFR 314.500 and 601.40) should be interpreted when the only available therapy is another treatment approved under the accelerated approval regulations. This question arises when several drugs are under investigation or application review for a specific indication based on a surrogate endpoint, or when the only product on the market has restrictions on distribution. Specifically, when one drug is approved under the accelerated approval regulations, can additional therapies be approved under the accelerated approval regulations?

We have determined that the approval of one therapy under the accelerated approval regulations (either on the basis of a surrogate endpoint or with restricted distribution) should not preclude the approval under the accelerated approval regulations of additional therapies. As a general matter, it is preferable to have more than one treatment approved under the accelerated approval provisions, because there are more bases on which an approval under these provisions may be withdrawn, and thus the availability of the therapy is less certain than it is with a conventional approval. Approval under the accelerated approval provisions may be withdrawn if, for example, post-approval studies fail to verify clinical benefit or the postmarketing restrictions are inadequate to assure safe use of the drug product (21 CFR 314.530). Such a withdrawal of approval would leave no treatment available.

Accordingly, we intend to interpret *existing treatment* under the accelerated approval regulations to mean, in the context of approval based on a surrogate, a treatment that has demonstrated a clinical benefit under conventional approval standards (21 CFR 314.105, 314.125, 601.2). In the context of a prior approval based on restricted distribution, *existing treatment* means a treatment approved for the same indication without restricted distribution.



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**REFERENCES**

FDA, *CDER Manual of Policies and Procedures (MAPP) 6020.3, Priority Review*

FDA, *CBER Manual of Standard Operating Procedures and Policies 8405, Complete Review and Issuance of Action Letters*

FDA guidance for industry on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*

FDA guidance for industry on *Fast Track Drug Development Programs: Designation, Development, and Application Review*