FDA’s Final Rules Regarding Expanded Access and Charging for Investigational Drugs and CMS Payment Implications

On August 13, 2009, the Food and Drug Administration (FDA) published in the Federal Register two final rules amending FDA’s regulations governing investigational drugs. The first of these expands and clarifies FDA rules on expanded access to investigational drugs for patients with serious or immediately life-threatening diseases or conditions. The second revises FDA regulations governing charging patients for investigational drugs. The final rules largely mirror the proposed rules FDA published in 2006, but the agency has made several modifications to clarify portions of the proposed rule and implement requirements in the Food and Drug Administration Amendments Act of 2007 (FDAAA). Both rules take effect on October 13, 2009.

This alert summarizes the key provisions of the final rules and identifies potential implications regarding reimbursement for investigational drugs in the clinical trial context.

I. SUMMARY OF PREVIOUS STATUTORY AND REGULATORY REQUIREMENTS

A. Expanded Access to Investigational Drugs for Treatment Use

The Federal Food, Drug, and Cosmetic Act (FDCA) prohibits the introduction (or delivery for introduction) into interstate commerce of a “new drug” unless an approval under FDCA section 505 is in effect. FDCA section 505(i), and Part 312 of FDA’s regulations provide an exception to this requirement for distribution of investigational drugs for the purpose of conducting clinical trials. As originally promulgated in 1938, FDA’s regulations (known as the “IND regulations”), did not provide for access to unapproved drugs outside of the context of clinical trials.

In 1987, FDA amended the IND regulations to provide for one specific type of expanded access to investigational drugs. This expanded access use, known as the “treatment IND,” provided a process by which broad patient populations could gain access to investigational drugs outside of the context of a clinical trial if certain conditions were met. These conditions included that: (1) the drug is intended to treat a serious or immediately life-threatening disease; (2) no comparable or satisfactory alternative therapy is available for treatment; (3) the drug is under investigation in a controlled clinical trial under an IND or

2 Id. at 40872. These regulations, and the payment policies discussed below, apply to both drugs and biological products.
3 See 71 Fed. Reg. 75147 (Dec. 14, 2006); id. at 75168.
all clinical trials have been completed; and (4) the sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence. The 1987 regulations also provided that FDA may authorize distribution of a pre-IND investigational drug “in an emergency situation that does not allow time for submission of an IND” in accordance with the usual requirements.\(^5\) Although this “emergency use” provision implicitly contemplated expanded access to individual patients, it did not define the criteria that govern FDA’s decision to allow emergency access. Nor did it provide a specific procedure, or criteria that would need to be met in order to authorize individual treatment use.

These regulations provided a framework for a number of different mechanisms for patients to obtain access to investigational drugs for treatment purposes—rather than to study the safety and effectiveness of a drug. These mechanisms are known as “compassionate use INDs,” “single-patient protocol exceptions,” and “large open protocols.” The vast majority of these INDs were used to make investigational drugs available to individual patients, but some expanded access programs made particularly promising investigational drugs available to large populations. For example, more than 10,000 patients obtained access to the first cardioselective beta-blockers and the first calcium channel blockers for vasospastic angina through these INDs. One of the hallmarks of all of these procedures was the requirement to file an IND prior to distributing the investigational drug.

Congress amended the FDCA in 1997 to provide statutory authorization for expanded access use.\(^6\) The 1997 statutory provision, codified in section 561 of the FDCA, largely parallels FDA’s treatment IND regulations. However, it also explicitly permits an individual patient, acting through a physician, to obtain access to an investigational therapy if certain conditions are met. FDA subsequently proposed revisions to the treatment IND regulations in 2006. FDA’s new expanded access final rule completes that process.

**B. CHARGING FOR INVESTIGATIONAL DRUGS UNDER AN IND**

With two exceptions, FDA’s previous regulations generally prohibited sponsors from charging for investigational drugs. The first exception allowed a sponsor to charge patients if the sponsor received prior FDA approval. The second permitted a sponsor to charge patients under a treatment IND or protocol if certain criteria were met. In either case, FDA regulations prohibited charging more than was necessary to recover the costs of manufacture, research, development, and handling of the investigational drug. FDA’s new regulations expand the circumstances in which charging for an investigational drug may be permitted and describe the costs sponsors may recover from patients for use of such drugs.

**II. DEVELOPMENT OF THE REVISED RULES**

FDA’s initiative to revise its rules largely was prompted by pressure from patient advocacy groups, who claimed that the criteria for obtaining a treatment IND were unclear and led to disparate access. In particular, concerns had been raised that access to investigational drugs for treatment uses focused primarily on cancer- and human immunodeficiency virus (HIV)-related conditions and that patients with other serious diseases or conditions did not have comparable access to appropriate treatment use of unapproved drugs. Patient groups also claimed that barring charging for investigational drugs deters drug manufacturers from making their products available for compassionate use. In 2003, the Abigail Alliance and Washington Legal Foundation (WLF) filed a lawsuit claiming FDA’s policies limiting access to life-saving investigational drugs were unconstitutional.

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Ultimately, however, the U.S. Court of Appeals for the District of Columbia sitting en banc held in 2007 that terminally ill patients have no constitutional right to unapproved drugs.\(^7\)

### III. FDA’s New Expanded Access and Charging Rules

#### A. Expanded Access to Investigational Drugs

The expanded access final rule deletes the current regulations on expanded access to investigational drugs (21 C.F.R. §§ 312.34-.36) and adds a new subpart I to Part 312. The new subpart I allows for expanded access to investigational drugs in three categories of patient populations: (1) individual patients (including specific provisions for emergency and non-emergency use), (2) intermediate-size patient populations (smaller than those typical of a treatment IND or treatment protocol), and (3) widespread use under a treatment IND or treatment protocol. This third category, treatment IND or treatment protocol, was the only option for expanded access provided for broad populations under the old regulations. As under the old rule, the emergency use provisions apply only to individual patients; the final rule does not provide for emergency use in larger patient populations. Subpart I outlines general requirements (including submission criteria and safeguards) for all expanded access populations, then provides additional criteria specific to each of the three patient populations. The specific criteria required to justify treatment use become more burdensome as the size of the patient population increases.

1. **Requirements for All Expanded Access Populations**

To permit any type of expanded access, FDA must make the following determinations: (1) the patient(s) seeking treatment use must have a serious or immediately life-threatening disease or a condition with no comparable or satisfactory alternative therapy; (2) the potential patient benefit must justify the potential treatment use risks, and those risks must not be unreasonable in the context of the disease or condition to be treated; and (3) the expanded access must not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use.\(^8\) The term “serious or immediately life-threatening disease or condition” is defined as a disease or condition associated with morbidity that has a substantial impact on the patient’s day-to-day functioning, or renders patients reasonably likely to die within a matter of months or likely to die prematurely without early treatment.\(^9\)

The final rule requires an individual or entity to submit a new IND or a protocol amendment to an existing IND before patients can obtain expanded access to an investigational drug. For all three patient populations, a new IND application for expanded access takes effect 30 days after FDA receives the IND (or upon earlier notification by the agency). For protocol amendments to existing INDs, use may begin after institutional review board (IRB) approval and submission of the protocol to FDA, with two exceptions. First, protocol amendments to existing INDs that are submitted for expanded access in large patient populations take effect 30 days after FDA receives the IND (or upon earlier notification by FDA). Second, for protocol amendments submitted for emergency use, treatment may begin as soon as the FDA reviewing official authorizes use (which may take place over the phone).

An individual or entity that submits an expanded access IND or protocol is considered a sponsor. The sponsor must submit IND safety reports and provide treating physicians with the necessary information to minimize the risk and maximize the potential benefits of the

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\(^8\) 74 Fed. Reg. 40943; 21 C.F.R. § 312.305(a).

\(^9\) Id.; 21 C.F.R. § 312.300(b).
investigational drug. Physicians who administer or dispense the investigational drug are considered investigators and are responsible for reporting adverse drug events to the sponsor, ensuring that informed consent requirements are met, ensuring that IRB review of the expanded access use is obtained as required, and maintaining accurate case histories and drug disposition records.

Additional requirements, based on the size of the patient population to be treated, are described in greater detail below. These criteria must be met in addition to the general criteria for all expanded access uses.

2. Additional Criteria for Individual Patient and Emergency Use

The final rule requires that for an investigational drug to be used for expanded access in an individual patient, the following criteria must be met in addition to the general criteria discussed above: (1) a physician must determine that the probable risk from the drug is not greater than the probable risk of the disease it is meant to treat; and (2) FDA must conclude that the patient could not obtain the drug under another type of IND or protocol (such as through participation in a clinical trial). If the drug is the subject of an existing IND, either the sponsor or the patient’s physician can submit a request. Access to treatment under this option generally will be limited to one course of therapy for a specified time period, unless FDA authorizes otherwise. The physician or sponsor is required to report to FDA the results of the expanded access use at the conclusion of the treatment.

FDA may authorize expanded use prior to receiving a written submission in an emergency situation. The final rule, however, does not set forth any criteria regarding the type of showing necessary to establish an emergency. Requests may be submitted via telephone, fax, or by any other electronic means, and the regulation provides the relevant contact information for FDA’s drug and biologics centers. The requesting physician or sponsor must provide the written submission within 15 days of FDA’s authorization of the emergency use.

3. Additional Criteria for Intermediate-Size Patient Populations

Intermediate-size patient populations typically consist of several hundred patients. Under the final rule, expanded access to intermediate patient populations may be appropriate in the following situations: (1) the drug is not being clinically developed (e.g., due to a lack of study subjects with a particular rare disease); (2) patients requesting expanded access to a drug that is being developed are unable to participate in the trials; or (3) the drug requested is approved but no longer marketed for safety or other reasons. FDA also may ask a sponsor to consolidate individual patient requests under this category if the agency has received numerous requests for the same use.

In addition to the general criteria, expanded access in intermediate-size patient populations requires an FDA determination that (1) there is sufficient evidence that the drug is safe at the dose and duration proposed to justify a clinical trial in the approximate number of patients expected to receive the drug under expanded access; and (2) there is at least preliminary clinical evidence of effectiveness or a plausible pharmacologic effect to justify use as a treatment in the anticipated population. In the IND submission to FDA, the sponsor requesting expanded access must: (a) state whether the drug is or is not currently being developed and describe the intended patient population to be treated; (b) if the drug is not being developed, explain why it cannot be developed for this particular use and under what circumstances it could be developed; (c) if the drug is being studied in

\[10 \text{Id. at 40944; 21 C.F.R. § 312.310(a).} \]
\[11 \text{Id. at 40943; 21 C.F.R. § 312.315(a).} \]
a clinical trial, explain why the patients to be treated cannot be enrolled in the trial and under what circumstances the sponsor would conduct a trial in these patients.

Once expanded use has begun under an IND, the agency will review the IND annual reports to determine whether it is appropriate for expanded access to continue. Additionally, if the number of patients being treated increases, FDA may ask the sponsor to submit a treatment IND or protocol for widespread use.

4. **Additional Criteria for Widespread Use Under a Treatment IND or Protocol**

A treatment IND or protocol (the only expanded access category that existed under the previous regulations) enables widespread treatment use of an investigational drug. As was true under the previous regulations, the final rule permits a treatment IND or protocol only if: (1) the drug is under investigation in a controlled clinical trial, or all clinical trials have been completed, and (2) the sponsor is “actively pursuing,” with “due diligence,” marketing approval for the expanded use.\(^{12}\) In the preamble to the final rule, the agency explains that “such active pursuit of marketing approval with due diligence implicitly includes a determination that the treatment use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval for the investigational drug.”\(^{13}\) The sponsor must ensure that physicians comply with the protocol and regulations applicable to investigators.

According to the preambles to the proposed and final rules, FDA may begin reclassifying proposals for certain open-label (non-blinded) studies as treatment INDs. They note that open-label safety studies have been used improperly to make investigational drugs available to large patient populations for treatment use. Thus, a proposal for an open-label study for a serious or life-threatening disease or condition may be reclassified as a treatment IND if it provides broad access to a drug in the later stages of development and lacks systemic data collection and an appropriate design for safety evaluation.

B. **CHARGING FOR INVESTIGATIONAL DRUGS**

FDA’s previous regulation pertaining to charging for investigational drugs (21 C.F.R. § 312.7(d)) authorized sponsors to charge patients for treatment use of an investigational drug only under a treatment IND or treatment protocol, provided certain requirements were satisfied. The final rule on charging for investigational drugs replaces section 312.7(d) with a new section 312.8. The new provision clarifies the circumstances under which charging for an investigational drug is appropriate, sets forth the criteria for charging for an investigational drug for each patient population described in the expanded access final rule, and clarifies which costs sponsors may recover from patients who receive an investigational drug.

1. **General Criteria for Charging**

The final rule includes general criteria all sponsors must follow in order to charge for an investigational drug, whether the drug is being used in a clinical trial or for expanded access. Specifically, sponsors must: (1) comply with the specific requirements that apply to the type of use for which charging is requested (i.e., clinical trial or expanded access); (2) demonstrate that the amount to be charged reflects only those costs that are permitted to be recovered; and (3) obtain prior written authorization from FDA.\(^{14}\)

\(^{12}\) *Id.* at 40945; 21 C.F.R. § 312.320(a).

\(^{13}\) *Id.* at 40915.

\(^{14}\) *Id.* at 40899; 21 C.F.R. § 312.8(a).
2. **Charging in Clinical Trials**

Exceptional circumstances must exist to justify charging for an investigational drug in a clinical trial. A sponsor that wishes to charge for its own investigational drug, including an investigational use of its own approved drug, must: (1) provide evidence of a potential clinical benefit that would provide a significant therapeutic advantage over available products; (2) demonstrate that the data to be obtained are essential to establishing that the drug is safe or effective for initial approval or would support a significant labeling change; and (3) demonstrate that clinical development of the drug could not otherwise proceed, due to the extraordinary cost of the drug. In response to comments on the proposed rule, the final rule clarifies that extraordinary costs will be determined by considering the financial resources of the sponsor. In a change from the proposed rule, the final rule does not require sponsors to obtain prior authorization to charge patients for use of approved drugs obtained from another entity.

3. **Charging for Expanded Access for Treatment Use**

The final rule expands the circumstances under which sponsors are allowed to charge for investigational drugs provided for treatment use. In any expanded access case (i.e., in any expanded access population), a sponsor must provide “reasonable assurances” to FDA that charging will not interfere with the development of the drug for marketing approval.15 For treatment INDs, the final rule requires additional assurances because of the greater potential that widespread treatment use would interfere with drug development. Treatment IND sponsors are required to provide evidence of sufficient enrollment in any ongoing clinical trials needed for marketing approval, demonstrate adequate progress in the development of the drug for marketing approval, and submit information under their general investigational plan specifying the drug development milestones they plan to meet in the coming year. Authorization to charge for expanded access for treatment is valid for one year (unless FDA specified a shorter period), but it can be renewed.

4. **Recoverable Costs**

Sponsors may only recover the direct costs of making an investigational drug available. Allowable costs include costs per unit to manufacture the drug, costs to obtain the drug from another manufacturing source, and costs to ship and handle the drug. Expenditures to produce the drug for commercial sale, research and development, or administrative, labor, or other costs that would be incurred even if the clinical trial or treatment use for which charging is authorized did not occur are not recoverable.

**IV. Reimbursement Implications of the Final Rules**

Although FDA’s final rules expand the circumstances under which trial sponsors may charge subjects for investigational drugs, it is important to note limitations on payment for such charges for Medicare beneficiaries, as specified by the Centers for Medicare & Medicaid Services (CMS). Medicare and, in turn, many private payers will generally pay only for drugs that have been approved by FDA for at least one indication. Thus, in most cases, charges for new investigational drugs will be paid by patients, although Medicare will generally pay for certain “routine costs” for particular types of trials.

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15 *Id.*; 21 C.F.R. § 312.8(c)(1).
A. Physician-Administered Drugs and Medicare’s Clinical Trials Policy

Physician-administered drugs are typically reimbursed under Medicare’s Part A (hospital services) or Part B (physician’s services) programs.16 To be eligible for reimbursement under these provisions, a drug must be “reasonable and necessary.”17 In treatment settings (i.e., outside of clinical trials), CMS has interpreted this statutory “reasonable and necessary” requirement to mean that the drug must be both “safe and effective” and “otherwise reasonable and necessary.”18

Physician-administered drugs are subject to Medicare’s Clinical Trials Policy (CTP), which permits Medicare coverage in a broader set of circumstances than the “reasonable and necessary” requirement would otherwise permit.19 The CTP permits Medicare reimbursement for “routine costs” of qualifying clinical trials, which are costs that are “otherwise generally available to Medicare beneficiaries” and not subject to an exclusion from the CTP. The CTP excludes “the investigational item” from the definition of “routine costs” unless it is “otherwise covered outside of the clinical trial.”

1. Unapproved Drugs

Drugs that have not yet received FDA approval are generally not considered “safe and effective” for Medicare purposes, and are not eligible for reimbursement.20 The CTP permits reimbursement for unapproved products only if they are not the investigational product, a situation that rarely exists. Thus, unapproved drugs that are used in clinical trials will generally not qualify for Medicare reimbursement even if FDA’s charging regulations permit sponsors to charge for them. Similarly, unapproved drugs that are made available through FDA’s expanded access provisions, treatment INDs, or treatment protocols will typically not be covered by Medicare.

2. Approved Investigational Drugs

Even FDA-approved drugs may not qualify for Medicare reimbursement if they are the investigational item that is the subject of a trial. The CTP permits reimbursement for investigational drugs “to the extent that the item ... would be covered outside of a clinical trial.”21 Drugs are normally covered outside of a clinical trial for: (1) their labeled uses; (2) “medically accepted” off-label uses; and (3) in the case of anti-cancer drugs, off-label uses that are supported in certain compendia or the medical literature (and consistent with the compendia).22 In most cases, approved investigational drugs will not meet these criteria because the investigational use is off-label or not medically accepted. One example where Medicare coverage may apply is a clinical trial supporting a labeling change to add a new indication where the investigational use is already medically accepted.

Separate from the CTP, Medicare policies may permit reimbursement of investigational drugs through national coverage decisions, local coverage decisions (applicable within certain geographic regions), and case-by-case determinations (usually made by Medicare contractors). CMS has clarified that the CTP does not disturb coverage that has been

22 CMS, Medicare Benefit Policy Manual, ch. 15, §§ 50.4.1, 50.4.2, 50.4.5.
made available through these mechanisms. Therefore, Medicare reimbursement may be available in expanded access or clinical trial settings in some limited situations beyond those permitted by the CTP.

Where CMS does allow coverage of investigational items, it is important that sponsors and investigators are aware of the host of compliance and operational issues—from the application of Medicare Secondary Payer rules to the use of billing modifiers—that can arise in these circumstances.

3. **Approved Drugs—Non-Investigational Items**

Under the CTP, Medicare will reimburse non-investigational products that are otherwise generally available to Medicare beneficiaries. Thus, Medicare should reimburse sponsors who charge study subjects for such products under FDA’s final charging regulations. Medicare beneficiaries should be charged to the same extent as other study subjects are charged; Medicare will not pay for items or services that are offered free to other (non-indigent) study subjects.23

**B. ****OUTPATIENT PRESCRIPTION DRUGS AND MEDICARE**

Most self-administered drugs are reimbursed through Medicare’s outpatient prescription drug program, Medicare Part D. Part D products are not subject to the CTP. With a few rare exceptions, the Part D program is limited to FDA-approved drugs.24 Furthermore, to be a “covered part D drug,” a drug or biological must be used for a medically-accepted indication. For purposes of the Part D program, a use is “medically accepted” if the FDA has approved the drug for that use, if the use is supported by certain compendia, or, in the case of anti-cancer drugs, if the beneficiary’s Part D plan determines that the use is supported by peer-reviewed medical literature (and consistent with the compendia).25 As most investigational products are either not FDA-approved or not being used for medically accepted indications, they are unlikely to be “covered Part D drugs” and are consequently not covered by Medicare Part D.

An approved product that is being used for a medically-accepted indication (e.g., as a control or combination therapy in a clinical trial) may be eligible for Part D coverage. The Part D program operates through private prescription drug plans (PDPs). While the Medicare program requires that PDPs cover certain broad categories of drugs, PDPs are private plans and the precise formularies will vary from plan to plan. If a trial sponsor meets FDA’s new criteria for charging for a drug, and that drug is a “covered Part D drug,” Medicare coverage will depend on the formulary of the study participant’s PDP.

**C. ****MEDICARE ADVANTAGE PLANS**

Some Medicare beneficiaries elect to receive their benefits through private plans, which are known as Medicare Advantage (MA) plans, or, in the case of MA plans that also offer outpatient prescription drug coverage, as Medicare Advantage - Prescription Drug Plans (MA-PDPs). The CTP provides that MA plans must cover items or services covered under the CTP regardless of whether the items or services are available through in-network providers. Although MA plans may impose reporting requirements on enrollees who participate in clinical trials, MA plans cannot require prior authorization or approval. Thus, Medicare coverage will generally be available for participants in MA plans to the same extent it is available under the CTP. Where coverage is available, legal and operational

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24 SSA § 1860D-2(e), 42 U.S.C. § 1395w-102(e).
issues involving responsibility for co-payments and deductibles, submission of bills, and calculation of payments may arise.

On the other hand, MA-PDPs are generally treated like stand-alone PDPs.\(^\text{26}\) Thus, investigational drugs are unlikely to be covered, but coverage may be available for approved products that are being used for medically accepted indications, as long as the formulary for the study participant’s MA-PDP covers the drug at issue.

**D. Private Plans**

Many private plans tend to follow Medicare’s policies regarding coverage of medical services and items, including prescription drugs. There is nevertheless a great deal of variety among private plans with respect to coverage of clinical trials. More and more states are also passing laws requiring that health plans cover certain clinical trial costs. Many, but not all, of these laws relate specifically to trials for anti-cancer drugs. Therefore, it is important that sponsors or investigators planning to charge patients for clinical trial drugs comply not only with the relevant FDA and CMS rules, but take care to have a plan to deal with private payers.

If you have any questions concerning the material discussed in this client alert, please contact the following members of our food & drug practice group:

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\(^{26}\) 42 C.F.R. § 422.500(a).