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**VIA HAND DELIVERY**

Dockets Management Branch  
Food and Drug Administration  
Department of Health and Human Services  
Room 1061, HFA-305  
5630 Fishers Lane  
Rockville, MD 20857

**CITIZEN PETITION**

The National Coalition for Cancer Survivorship (NCCS) and the American Society of Clinical Oncology (ASCO) submit this petition under section 505 of the Food Drug and Cosmetic Act and implementing regulations at 21 C.F.R. § 312.34 to request the Commissioner of Food and Drugs to issue Guidance to Industry outlining procedures and standards for initiating an "expanded access program" for unapproved drugs.

***A. Action Requested***

While the regulations provide ample authority for the conduct of expanded access programs, giving patients access to unapproved drugs outside the context of clinical trials, there is uncertainty about the procedures and standards applicable to such programs. NCCS and ASCO request the agency to issue Guidance that will clarify the circumstances under which expanded access programs may be initiated for the benefit of patients lacking other acceptable treatment options.

***B. Statement of Grounds***

NCCS has been the voice of advocacy for cancer survivors for the past 20 years. ASCO is the world's largest medical society for physicians involved in cancer treatment and research. Together, NCCS and ASCO have taken a strong interest in the efficiency of the drug approval process at the Food and Drug Administration (FDA) in order to ensure that cancer patients have access to potentially life-extending therapies at the earliest possible time.

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NCCS and ASCO commend FDA, and especially the new Office of Oncology Drug Products, for their enhanced dialogue with the cancer community on issues related to endpoints and other criteria for approval of new products. Moreover, during the past few years, there has been a greater willingness by FDA to apply innovative approaches to review and approval of new drugs for cancer. The Subpart H regulation allowing for "accelerated approval" has been utilized frequently to approve drugs for marketing on the basis of phase II data reflecting success in surrogate endpoints that are reasonably likely to predict clinical benefit.<sup>1</sup> Thus, cancer patients are able to access new drugs much more rapidly than in the past, thanks in significant part to FDA's recent efforts.

Despite the greater rapidity with which many cancer drugs now receive marketing approval, there is nevertheless a continuing demand for access to new drugs prior to marketing approval and outside the context of clinical trials. Interest in investigational drugs is stimulated more than ever by information obtained through the internet or from the many highly motivated patient advocacy groups. It is understandable that patients without other treatment options would seek access to promising therapies even if they are unproven. NCCS and ASCO endorse expanded access to investigational drugs for patients who are not eligible to participate in clinical trials, but only so long as accrual to ongoing trials is not impaired and the marketing approval of the drug is not delayed. The best access for the greatest number of patients will inevitably flow from marketing approval, which should not be deterred by any expanded access program.

Industry sponsors seem to agree that expanded access is desirable. In fact, the drug development process increasingly involves expanded access in one form or another. There is, however, great variability, which creates uncertainty for patients and their physicians. Industry itself seems somewhat unclear about the opportunities and requirements related to expanded access, which likely leads to delays in the development and implementation of such programs. Therefore, NCCS and ASCO strongly urge the issuance of FDA Guidance to Industry regarding the appropriate circumstances and applicable standards for expanded access programs so that they may proceed efficiently and with a certain degree of uniformity, recognizing that some variability is unavoidable.

### **FDA Regulation of Expanded Access**

FDA regulations feature several different mechanisms for access to unapproved drugs outside of clinical trials. Individual patients may obtain access to unapproved drugs through a "special exception," also known as "compassionate use."<sup>2</sup> In an "emergency" setting, such access may be obtained even without filing an investigational new drug (IND) application

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<sup>1</sup> 21 C.F.R. § 314.500 et seq.

<sup>2</sup> Id. § 312.35.

beforehand.<sup>3</sup> Under certain circumstances, expanded access may be made available on a more systematic—i.e., beyond individual—basis through the “treatment IND” mechanism.<sup>4</sup>

### **Single-Patient Access**

The existing regulations envision that individual patients may obtain access to unapproved investigational drugs under defined conditions, including submission of a protocol, review by an institutional review board (IRB), and prior notification of FDA through a treatment IND request (except in cases of emergency, when the IND request may be submitted subsequently). Requests may be submitted either by the sponsor or by an individual physician. In either case, cooperation of the sponsor is necessary, and a licensed practitioner is required to receive and administer the investigational drug.

Single-patient access imposes substantial burdens on both sponsors and physicians, particularly in light of the fact that each application must be processed individually. Sponsors can facilitate the necessary paperwork somewhat by having standard protocols and model consent forms available, but the facts of each case will offer sufficient variation so that economies of scale are difficult to achieve. Even if sponsors can smooth the process in this fashion, the burden on individual physicians remains significant, particularly for those in community practice without the supportive infrastructure associated with clinical research. Also, because third-party payers do not generally cover the cost of investigational therapy outside the clinical trial setting, reimbursement for the resources necessary to administer the drug may not be forthcoming.

### **Treatment INDs**

More systematic access to unapproved drugs for numerous individuals rather than single patients can be provided under the treatment IND mechanism.<sup>5</sup> Treatment INDs are applicable only to drugs for serious or life-threatening diseases. The regulation provides:

“In the case of a serious disease, a drug ordinarily may be made available . . . during Phase 3 investigations or after all clinical trials have been completed; however, in appropriate circumstances, a drug may be made available for treatment use during Phase 2. In the case of an immediately life-threatening disease, a drug may be made available for treatment use . . . earlier than Phase 3, but ordinarily not earlier than Phase 2.”

In order to justify access to multiple persons under a treatment IND, the drug must not only be intended to treat a serious or immediately life-threatening disease, but there must also be a showing that:

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<sup>3</sup> Id. § 312.36.

<sup>4</sup> Id. § 312.34.

<sup>5</sup> Id.

- There is no comparable or satisfactory alternative drug or other therapy available to treat that stage of the disease in the intended patient population;
- The drug is under investigation in a controlled clinical trial under an IND in effect for the trial, or all clinical trials have been completed; and
- The sponsor of the controlled clinical trial is actively pursuing marketing approval of the investigational drug with due diligence.

For serious diseases, a treatment IND may be denied “if there is insufficient evidence of safety and effectiveness to support [the] use.” For immediately life-threatening diseases, a treatment IND may be denied “if the available scientific evidence, taken as a whole, fails to provide a reasonable basis for concluding that the drug “[m]ay be effective for its intended use in its intended population” and “[w]ould not expose the patients to whom the drug is to be administered to an unreasonable and significant additional risk of illness or injury.”

### **Expanded Access Program Standards**

While FDA may reasonably react to single-patient or emergency requests according to a case-by-case standard, demand for new agents—outside the context of clinical trials and before approval for marketing—is frequently such that a more systematic approach is required. FDA has rightly identified the treatment IND regulation as the best, and perhaps the only, regulatory authority for widespread distribution of unapproved drugs to patients in need.

It is important to note that the treatment IND regulation was promulgated more than a decade ago, well before the current era when drugs for life-threatening diseases like cancer are routinely approved on an accelerated basis. The treatment IND rules should perhaps be read more liberally than in the past to account for modern accelerated approval standards. Liberally interpreted, those rules provide sufficient flexibility for broad-based expanded access programs.

### **Stage of Development**

The treatment IND regulation expresses a preference that the drug in question be either in Phase 3 or in a situation where all clinical trials have been concluded. However, the regulation also recognizes that a treatment IND may be appropriate during the conduct of Phase 2 trials or even earlier in extraordinary circumstances. Those circumstances that might justify very early access are discussed below.

The decision on the appropriate stage of development when an expanded access program might be launched will depend to some degree on the strength of the safety and efficacy data being submitted to FDA. A very strong registration package should encourage both the sponsor and the agency to make potentially life-saving drugs available on an expanded and systematic

basis to patients who could be expected to benefit from them during the period prior to marketing approval.

### **Quantity and Quality of Evidence And Other Considerations**

A decision to provide expanded access earlier than Phase 3 or at the completion of clinical trials—or in unusual circumstances, even prior to Phase 2—should depend on a number of different variables, such as:

- Nature and strength of the evidence: If the endpoint being measured is response rates, for example, it is important to consider the quality of the responses. Is there a high rate of complete response or substantial tumor regression? Are responses markedly durable, at least in some patients? Are the responses accompanied by relief of cancer-related symptoms in the majority of patients? If so, FDA should feel more comfortable allowing an expanded access program to proceed. In general, the more compelling the data, the more favorably FDA should regard a request for approval of an expanded access program.
- Unmet patient need: To the extent that patients with cancer or other life-threatening disease have no treatment alternative using an approved agent or commonly accepted standard therapy, expanded access should be an option more readily pursued.
- Likelihood and imminence of marketing approval: As approval seems more certain and more immediate, expanded access programs offer greater hope to patient in need and less risk of disappointing outcomes. In such settings, FDA should facilitate expanded access programs that are sought by sponsors.
- Drug availability: The feasibility of expanded access programs is greatly dependent upon the capacity of the sponsor to supply drugs to patients outside the clinical trial setting. Experience has demonstrated that sponsors are better able to deliver significant quantity of drug outside of trials if the agent in question is a small molecule with a relatively straightforward manufacturing process and cost, in contrast to more complex biological products, where supply may pose greater challenges and uncertainty.

### **Program Design**

Although expanded access programs are not the same as clinical trials, they should be reviewed and approved by an FDA that is mindful of the clinical program supporting the drug's application and should be structured to be consistent with that program.

### **Comprehensive Development Plan**

Expanded access programs should be regarded as part of an overall clinical development plan. Accordingly, an expanded access program would normally not be considered appropriate

for an indication not being evaluated in clinical trials by the sponsor. An exception to this general rule might be in rare instances where there is strong pre-clinical or clinical evidence that the drug could be efficacious in a population with virtually no therapeutic option.

### **Defined Eligibility Criteria**

Expanded access programs can pose a risk to clinical trial accrual, which could jeopardize timely approval of the drug for marketing and ultimately hinder access for broader populations of patients who could benefit from the therapy. Therefore, patients participating in expanded access programs should generally be those who are clearly not eligible for trial participation. As noted above, the eligibility criteria for expanded access programs should also be based on disease indications that are consistent with the overall development plan for the drug—i.e., mirroring indications that are being pursued in ongoing or pending clinical trials.

### **Data Requirements**

Expanded access programs offer the opportunity to expand the safety data base for drugs moving through the approval process, which could be particularly important in the “accelerated approval” context, where the total number of patients supporting registration could be relatively small. FDA has repeatedly taken the position that collection of such safety information should not be viewed as a threat to approval, as there is no historical precedent for that concern. Careful collection of designated data sets may also provide insights into the effects of the drug in different populations beyond those enrolled in clinical trials, for example those with more extensive prior therapy or with significant co-morbidities. It is therefore important that expanded access programs provide a framework for data collection and reporting and that sponsors comply carefully with all data collection and reporting requirements.

### **Process Issues**

As expanded access programs differ in many respects from clinical trials, there are certain procedural steps that sponsors should take that are specific to the expanded access setting.

### **Expanded Access Team**

Expanded access programs generally require a distinct infrastructure to address the issues confronted by sponsors and patients in a somewhat less structured environment than clinical trials. It is advisable, at the earliest possible time when an expanded access program is under consideration, for the sponsor to assemble an expanded access team with the expertise necessary to advise on the legal, ethical and clinical ramifications of expanded access. Sponsors should schedule a meeting with FDA reviewers to initiate discussions about expanded access when the available data indicate that it might be appropriate for a given unapproved drug or indication.

### **Informed Consent**

Expanded access programs operate under an IND granted by FDA. Among the requirements for an IND is informed consent by the patient. In the expanded access setting, informed consent will be constructed differently from that in a clinical trial, but it is no less important. Informed consent documents for expanded access programs should carefully convey to patients the risks, potential benefits, alternatives and uncertainties involved in their access to unapproved agents.

### **Equitable Access**

Patients with no standard treatment options may be desperate to obtain access to unapproved drugs through expanded access programs. At the same time, depending on the resources of the sponsor and other variables, drug supply may be limited. Where rationing of access is required in expanded access programs, there should be fair and equitable mechanisms for determining which patients get access and which are denied. Evenhanded lotteries, with complete transparency, would appear to be the best approach. Sponsors should absolutely resist the efforts of influential or high-profile individuals—including government officials and celebrities—to obtain preferential treatment for themselves or their friends or families.

## **Economic Issues**

### **Charging for Drugs**

The treatment IND regulation permits charging for unapproved drugs on a “cost recovery” basis. The custom among sponsors has been to provide drug free of charge, and this would appear to be the preferable practice by far. FDA should urge sponsors to forgo cost recovery and provide drugs without charge to patients in expanded access programs.

### **Physician Reimbursement**

As part of a comprehensive expanded access program—indeed, as part of the general development plan for a new drug—sponsors need to consider how to compensate physicians for the time and other resources involved in administering unapproved drugs outside the clinical trial context and for collecting and reporting clinical outcome data. Third-party payers will often pay for routine patient care costs incurred in a clinical trial, but not for those patients accessing investigational agents outside a trial. Shortfalls in reimbursement to already challenged providers may substantially deter participation in expanded access programs. Sponsors should consider innovative approaches to this problem in order to secure the widest possible access to patients in need.

### **Transition Issues Upon Approval**

Patients enrolled in clinical trials receive investigational drugs free of charge, and the protocol generally specifies the degree to which the practice will continue beyond marketing approval. To the extent that patients enrolled in expanded access programs receive free drug—and that certainly should be the industry standard—informed consent should make clear how patients will transition from receiving free investigational drug to self-sufficiency, hopefully with insurance coverage. Sponsors have no ethical obligation to continue provision of free drug to expanded access patients after marketing approval for their specific disease indication. Patients receiving expanded access drugs for an indication other than that for which marketing approval is obtained should continue to receive drugs free of charge, at least until reimbursement becomes available, either through approval for that indication or through compendia listing.

### **Status of Single-Patient Use**

Although single-patient access remains an option under the regulations, it poses problems for the efficient operation of the system of pre-approval access. Some steps could be taken to increase efficiency, such as development of standard consent forms and protocols. Single-patient access, however, is inherently more resource intensive on a per patient basis and imposes significant burdens on individual physicians, who may for that reason discourage their patients from seeking an unapproved drug on a single-use basis. More widespread and regular use of the expanded access mechanism should obviate the need for single-patient requests and perhaps make the overall system of pre-approval access more user-friendly and efficient.

### **Role of FDA**

Aside from development of Guidance for Industry outlining the appropriate standards and procedures for expanded access programs, FDA could facilitate the process in several significant ways. First, FDA should create on its web site a comprehensive list of expanded access programs, together with details of each program, so that patients may have a reliable resource for such information. While FDA has an obligation to maintain the confidentiality of INDs, that confidentiality may be waived by sponsors, who would likely welcome FDA's help in disseminating information about their expanded access programs. Second, FDA should serve as a meaningful gatekeeper to expanded access, ensuring that expanded access programs meet the specified criteria and relate to drugs that are proceeding toward full marketing approval.

## **CONCLUSION**

Pharmaceutical sponsors develop new products with substantial support from the public, sometimes in the form of research investment from public sources like the National Institutes of Health (NIH) but always with the necessary engagement of patients who willingly participate in

clinical trials. Given the supportive involvement of patients and the general public, sponsors should feel a moral obligation to make potentially life-extending drugs available at the earliest possible time, consistent with FDA guidance. Expanded access programs providing unapproved agents outside of clinical trials are always voluntary on the part of sponsors, but responsible sponsors will consider them essential elements of the drug development process. Correspondingly, FDA must recognize the legitimate role of expanded access programs in giving patients with life-threatening diseases access to critical products as early in the development process as possible.

***C. Environmental Impact***

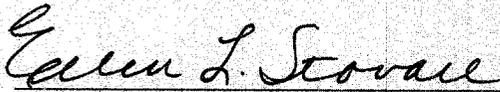
The action requested is subject to a categorical exemption from environmental assessment under 21 C.F.R. §§ 25.22 and 25.31.

***D. Economic Impact***

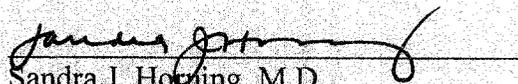
Pursuant to 21 C.F.R. § 10.30(b), NCCS and ASCO will provide data concerning the economic impact of the requested action should such information be sought by the Commissioner.

***E. Certification***

The undersigned certify that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



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