



**BlueCross BlueShield  
Association**

An Association of Independent  
Blue Cross and Blue Shield Plans

1310 G Street, N.W.  
Washington, D.C. 20005  
202.626.4780  
Fax 202.626.4833

March 14, 2007

Andrew C. von Eschenbach, M.D.  
Commissioner  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

Re: Notice of Proposed Rule Making Addressing Expanded Access to Investigational  
Drugs for Treatment Use (71 *Fed. Reg.* 75147)  
Docket No. 2006N-0062/RIN 0910-AF14

Notice of Proposed Rule Making Regarding Charging for Investigational Drugs  
(71 *Fed. Reg.* 75168)  
Docket No. 2006N-0061/RIN 0910-AF13

Dear Commissioner von Eschenbach:

On behalf of the Blue Cross and Blue Shield Association (BCBSA) – made up of 39 independent, locally operated Blue Cross and Blue Shield companies that collectively provide healthcare coverage for more than 98 million Americans – I am pleased to offer the following comments to the Notices of Proposed Rulemaking (NPRMs) for “Expanded Access to Investigational Drugs for Treatment Use, Proposed Rule” (71 *Fed. Reg.* 75147) and “Charging for Investigational Drugs, Proposed Rule” (71 *Fed. Reg.* 75168).

BCBSA has a particular interest in these NPRMs because of our long-standing commitment to clinical trials support. Blue Cross and Blue Shield Plans began supporting clinical trials nationally in 1991 with the establishment of the Demonstration Project on Breast Cancer Treatment to help resolve the clinical questions around high dose chemotherapy with autologous bone marrow transplantation (HDC-ABMT).<sup>1</sup>

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<sup>1</sup> The results of these trials – no survival advantage to HDC-ABMT relative to standard-dose chemotherapy – serve as a cautionary lesson about expanding access to investigational drugs outside of a clinical trial.

Since then BCBSA has identified and prioritized high quality clinical trials appropriate for Blue Plan support with the help of the National Institutes of Health, National Cancer Institute, and other research organizations.

While we commend the FDA for clarifying the criteria, submission requirements, and safeguards for different types of expanded access for treatment uses, we are concerned that in places the rule may inadvertently go too far in expanding access to investigational drugs, thus raising the risk of reducing participation in clinical trials, exposing patients to significant and unacceptable risks – and ultimately slowing the advance of evidence-based medicine. The rule also misses an opportunity to improve the process for informed consent. What follows are specific comments addressing these concerns.

### **Defining Serious Disease**

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The proposed rule would expand access to investigational drugs for patients with “immediately life-threatening diseases/conditions” – which the rule adequately defines – and for patients with “serious diseases/conditions” – which the rule expressly does not define.

In the report accompanying the Food and Drug Administration Modernization Act of 1997 (FDAMA), conferees wrote: [we] purposely used broad language in this section relating to “serious” conditions, without attempting to define them, in order to permit wide flexibility in implementation. Illnesses that do not cause death, or imminent death, can nonetheless destroy the lives of both patients and their families. The conferees therefore intend that the seriousness of an illness be given broad consideration, to take into account all of the circumstances involved.

The FDA has an opportunity to bring clarity to the conferees’ objective of flexibility in implementing expanded access. Specifically describing the criteria that characterize a serious disease/condition may be difficult, but failing to include such criteria will promote inconsistency in the rule’s application – and may lead to relatively unfettered access that would compromise clinical trials and expose patients to unacceptable risks.

In a 1999 report, *Definition of Serious and Complex Medical Conditions*, the Institute of Medicine (IOM) gave the following examples of descriptive criteria for serious and complex medical conditions that the FDA could consider in defining “serious” for the proposed rule:

- Conditions that cause serious disability such as stroke or closed head or spinal cord injuries.
- Conditions that cause significant pain or discomfort that can cause serious interruptions to life activities such as arthritis and sickle cell disease.
- Conditions that may require frequent monitoring such as schizophrenia and other psychotic illnesses.

- Conditions whose treatment carries the risk of serious complications such as most cancers or conditions requiring complex surgery.

Conditions such as these tend to be persistent, substantially disabling, and progressively (as opposed to imminently or immediately) life threatening.

- ***Therefore, BCBSA recommends amending §312.300 to add a new subsection (c) that defines serious diseases/conditions, based on the criteria discussed above.***

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### **Weighing Risks and Benefits**

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For individual patients' access to investigational drugs, the FDAMA requires that the licensed physician determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition. The proposed rule simply repeats this criterion, which is unfortunate because early pipeline products will likely not have appeared in any literature that is accessible to practicing physicians, leaving physicians no reasonable basis for assessing risk.

If this statutory criterion is to be applied sensibly, the FDA should inform the medical profession and such groups as voluntary health associations not only about the availability of investigational drugs – as is allowed under the law – but also about the available scientific evidence for the specific investigational drug that the physician is considering.

- ***Therefore, BCBSA recommends amending §312.310(a)(1) to require that physicians receive a full accounting of the available scientific evidence – including access to a database of systematically collected evidence (as recommended below) – before making a determination about the probable risk to the patient from the investigational drug.***

The FDA proposes using a “sliding scale” of evidence that would allow individuals in immediately life-threatening situations to receive investigational drugs in the absence of any preliminary clinical evidence. The preamble notes that where there is no relevant clinical experience, “the case for the potential benefit may be based on *pre-clinical data or on the mechanism of action* [emphasis added].” However, in the absence of any safety testing, it may be impossible to make an informed determination about the relative benefits and risks of a particular drug.

- ***Therefore, BCBSA recommends that preliminary evidence (such as phase I safety testing) be available for any expanded use request regardless of the number of patients.***

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### **Promoting Evidence-based Medicine**

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The fundamental principle of evidence-based medicine is that clinical practice should rest on a sound scientific foundation established by clinical studies involving human

subjects.<sup>2</sup> If exceptional individual cases are to be given access to investigational drugs outside of clinical trials, there must still be a commitment to gather evidence on the individual's clinical situation and to use that evidence in a systematic way to help other clinicians and patients.

The proposed rule does require that, at the conclusion of treatment for an individual patient, "the licensed physician or sponsor must provide a written summary of the results of the expanded access use, including unexpected adverse effects." However, the rule is silent on how the FDA might use these written summaries in a systematic way to advance knowledge and the practice of evidence-based medicine.

- ***Therefore, BCBSA recommends amending §312.310(c)(2) to require the FDA to provide a template to standardize these written summaries, and then to compile these summaries into a systematic database of evidence that will be available to any patient or clinician interested in expanded access to investigational drugs, as well as to the research community.***
  - *Failure to provide a standardized written summary should preclude that licensed physician or sponsor from future participation in expanded access programs.*

### **Improving Informed Consent**

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The proposed rule requires that in all cases of expanded access, investigators ensure that the FDA's informed consent requirements are met. Yet the proposed rule offers no further guidance on informed consent, even though the rule will probably increase the number of patients who obtain access to investigational drugs on the basis of limited clinical information.

This is a serious missed opportunity because studies have shown that consent documents – the most common vehicle for providing information in clinical investigations – are often written at a level that makes them virtually unreadable by many patients. Although the problem has been identified and quantified many times over more than two decades, there is little evidence to indicate that there has been any meaningful improvement in the quality of informed consent documents.<sup>3</sup>

Evidently, FDA guidance to Institutional Review Boards (IRBs) – that the informed consent document properly translate complex scientific concepts into simple concepts that the typical subject can read and comprehend – is not improving communication with patients. Now that the FDA is proposing rules to expand access to investigational drugs, the time is right for the FDA to improve the quality of informed consent documents.

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<sup>2</sup> Hlatky, Mark. (2004). Evidence-based use of cardiac procedure and devices. *New England Journal of Medicine*, v.350, issue 21.

<sup>3</sup> Sharp, Michael. (2004). The problem of readability of informed consent documents for clinical trials of investigational drugs and devices. *Drug Information Journal*, v.38, n.4.

This issue is especially important for patients with immediately life-threatening conditions for whom clear information about palliative care – the relief of physical, emotional, and spiritual suffering for those affected by life-limiting or complex chronic illnesses – may be as important as information about the risks and benefits of the investigational drug.

- ***Therefore, BCBSA recommends amending §312.305(c) to require that Institutional Review Boards (IRBs) reduce readability difficulty levels by establishing and enforcing clear criteria for the length and readability of informed consent documents.***
  - *Especial attention should be give to vulnerable patients facing end-of-life care who face unique challenges understanding and appreciating their treatment options, which may include hospice or other palliative care.*

### **Charging for Investigational Drugs**

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Hoping to increase the availability of investigational drugs to patients with serious and life-threatening diseases, the proposed rule expands the circumstances in which sponsors would be allowed to charge for such drugs. A sponsor could recover only the direct costs of making an investigational drug available, such as cost per unit to manufacture the drug.

Yet charging for investigational drugs could have the opposite effect because few seriously ill patients, even those with health insurance, would have the means to pay: most health benefit plans exclude coverage for investigational or experimental drugs.

Moreover, the FDA would face a difficult challenge in overseeing manufacturers' costs, as the proposed rule implicitly acknowledges. Although sponsors must provide supporting documentation for their cost calculation, the preamble notes that "if such such documentation relies on financial information or accounting methods beyond the expertise of FDA reviewers, FDA may request that a sponsor provide independent certification."

- ***Therefore, BCBSA recommends that the FDA look to mechanisms other than expanding the charging of patients to increase the availability of investigational drugs when appropriate.***

Thank you for the opportunity to offer these comments.

Sincerely,



Allan M. Korn, MD, FACP  
Senior Vice President and Chief Medical Officer