

Attachment A

Comments in Response to the Food and Drug Administration Notices of Proposed Rulemaking Response of America's Health Insurance Plans

AHIP offers the following comments and recommendations in response to the Notices of Proposed Rule Making (NPRMs) that were issued by the Food and Drug Administration (FDA) in the *Federal Register* on December 14, 2006. One NPRM addressed Expanded Access to Investigational Drugs for Treatment Use (71 Fed. Reg. 75147) and the second NPRM addressed Charging for Investigational Drugs (71 Fed. Reg. 75168). The issues highlighted below correspond with those noted in the NPRMs.

Improving Patient Information and Consent

Issue: FDA regulatory requirements should ensure that patients are well-informed about the risks and benefits of experimental and investigational drugs and therapies before patients can consent to receive them.

Discussion: Patients with immediately life-threatening conditions are extremely vulnerable. In these circumstances, information from health care practitioners may not be well communicated or understood. As a result, patients may not comprehend the complex medical information or appreciate the very real risks and potential benefits of experimental and investigational drugs.

One example illustrates the harm that can result when a careful scientific approach to investigational therapies is undermined by the pressure to offer treatment. Several years ago, autologous bone marrow transplants were performed on approximately 30,000 women with advanced breast cancer. At that time, the procedure was considered experimental because the bone marrow transplants were not scientifically proven as an effective treatment for advanced stage breast cancer. Instead of providing a greater chance of survival, some of the women who received the treatment had increased suffering and shortened lives.

As the FDA seeks to expand access to investigational drugs, we recommend that new measures be developed to improve the patient informed consent process. The new measures can help ensure that patients and their families are informed about and fully comprehend the attendant risks and possible benefits of using experimental or investigational drugs or therapies.

Recommendation: Before granting approval of a request for expanded access to an experimental or investigational drug, the FDA should require that Institutional Review Boards (IRBs) establish special criteria to ensure that clinicians have discussed the full range of treatment options with patients as part of the informed consent process. In addition, IRBs should be required to develop special criteria which demonstrate that patients and their families fully understand: (1) the experimental and investigational nature of a drug or other therapy; (2) the types and degrees of unknown risks; and (3) the potential positive and negative health outcomes.

Defining What Constitutes a “Serious Disease or Condition”

Issue: The final regulations should include definitions that delineate the types of diseases and conditions that the regulations intend to cover.

Discussion: AHIP supports the FDA’s proposed definition of the term “immediately life-threatening disease.” The definition will help patients, clinicians, and policymakers understand the objective and the applications of the proposed regulations and help ensure consistency in their administration. We encourage the FDA to include this definition in the final regulations.

In addition, we believe that it is equally important to clearly define the term “serious disease or condition.” Some patients may have “serious diseases or conditions” that cause disabling health effects and suffering for a period of time without death occurring prematurely or in a matter of months. As the preamble to the NPRM recognizes, such conditions can include schizophrenia, rheumatoid arthritis, chronic depression, and seizures. (71 Fed. Reg. 75151) However, the preamble also recognizes that the term “serious disease or condition” was meant “to exclude expanded access to investigational drugs for conditions that are clearly not serious.” (71 Fed. Reg. 75151)

Since most diseases or conditions can affect functioning or other aspects of quality of life, the occurrence of chronic (but not life-threatening) symptoms may prompt some individuals to pursue experimental and investigational alternatives. Without a regulatory definition that specifies the types and categories of “serious diseases or conditions,” the population of individuals who could benefit from investigational drugs will be uncertain and possibly expanded to include populations and conditions that the regulations did not intend to cover.

Recommendation: We recommend that the final regulations include a definition of “serious disease or condition.” We suggest that the FDA adopt the following definition¹:

“A serious disease or condition is one which is persistent, substantially disabling, progressive, and likely to result in death within 6 – 12 months.”

Weighing Reasonable Risks vs. Possible Benefits

Issue: The final regulations should specify specific criteria for health care professionals to use in various situations before experimental or investigational drugs or therapies are offered or administered.

Discussion: A patient should have some assurance that using an experimental or investigational treatment or therapy for his or her immediately life-threatening disease or condition can result in a positive outcome (i.e., life-saving treatment) which outweighs any potentially negative risks associated with the treatment or therapy. A potential benefit, however, should not be based solely on pre-clinical data. The benefits and risks should be evaluated in each individual’s situation after considering factors such as: an individual’s physical and mental state; the type of

¹ In 1999, a special committee from the Institute of Medicine (IOM) developed a definition for “serious diseases and complex medical conditions.” The definition recommended above is substantially similar to the IOM definition.

disease or condition and its progression; whether all other medically-accepted treatment options have been exhausted; and the evidence upon which the health care professional is relying in recommending an experimental or investigational treatment option.

The phase of the clinical trial (i.e., phase 1, 2, or 3) will determine size of the group being evaluated, the type of information expected to be derived from the trial, and the successfulness of the clinical tests results as the trial progresses in the staged process. After reviewing the individual facts and circumstances, the experimental or investigational treatment or therapy should be offered if the benefits and risks are reasonable to assume. To help foster consistent decision-making processes and evaluation criteria across various practice settings, we encourage the FDA to expand the criteria listed in the proposed regulations.

Recommendation: The final regulations should include the following additional criteria for making recommendations about the use of experimental or investigational treatments or therapies:

- **In individual situations that are immediately life threatening.** We recommend that phase 1 safety testing in humans be completed at doses similar to those used in treatment. Preliminary evidence suggesting possible effectiveness can also be used to evaluate possible benefits and risks.
- **In individual situations that involve serious diseases or conditions.** We believe that evidence of safety and effectiveness from phase 3 clinical trials is needed, although in some circumstances compelling data (i.e., data gathered from a clinical trial that is currently in progress but not yet completed or verified) from phase 2 trials may be sufficient.
- **In intermediate-size patient populations for situations that are immediately-life threatening.** At this stage some preliminary clinical evidence of the effectiveness of a drug or therapy should be evident for its use to be considered a reasonable therapeutic option in the anticipated patient population.
- **In intermediate-size patient populations that involve serious diseases or conditions.** Evidence of safety and effectiveness from phase 3 clinical trials should be required, although compelling data from phase 2 trials may be sufficient for the treatment or therapy options in this patient population.
- **In situations involving an Investigational New Drug (IND) application or treatment protocol for immediately life-threatening diseases or conditions.** In this scenario, only clinical data (i.e., data gathered and learned from a clinical trial that has been completed and verified) from phase 3 clinical trials or compelling data from phase 2 trials should be evaluated and considered.
- **In situations involving an IND application or treatment protocol for serious diseases or conditions.** Evidence used in assessing the potential benefits and risks should consist of data from phase 3 clinical trials.

Expanding Patient Access While Developing Evidence

Issue: Expanded access to experimental and investigational treatments and therapies should not hamper the initiation, enrollment, conduct, or completion of clinical trials.

Discussion: We believe that patients who receive access to experimental and investigational drugs (whether through individual treatment situations, intermediate-size patient populations, or IND applications) should participate in activities which promote some form of evidence development to aid in the evaluation of the risks and benefits of these drugs. This evidence could be used by the FDA to better manage the IND application process. In addition, the FDA should consider compiling a database of evidence for use by patients, clinicians, manufacturers, and researchers to guide decision-making about currently used investigational drugs to help identify areas that researchers might pursue for new treatments and therapies.

Recommendation: We recommend that the final regulations require all categories of patients to receive access to treatments and therapies under a clearly defined research protocol. The final regulations should also require that: (1) an appropriate sponsor be responsible for collecting patient outcomes data; (2) reports be submitted in a timely fashion to the FDA; and (3) patients should be required by the FDA to participate in official data gathering processes within a formal cohort study or patient registry.

Charging for Investigational Drugs

Issue: The proposed regulations establish an inequitable system for paying for experimental and investigational drugs.

Discussion: We acknowledge the importance of the FDA's attempt to clarify the conditions under which sponsors should be allowed to charge for drugs used in clinical trials and within the various patient groups and settings. While this practice may be appropriate once a drug is approved by the FDA, we are concerned that allowing sponsors to charge for investigational drugs can inhibit recruitment into clinical trials. This practice may also have a perverse effect on attempts to bring new drugs to the market.

When a health plan or contract defines what benefits are covered, individuals are assured of accessing appropriate health care services for their individual situations. Experimental or investigational treatments or therapies are often not covered as part of an employer's health benefits plan or contract because their safety and effectiveness is not proven as effective in treating or curing a disease or condition. In addition, patients risk substantial harm from adverse effects.

A more equitable and fair proposition is for the FDA to consider working with pharmaceutical manufacturers to develop better ways of funding clinical trials of experimental and investigational drugs.

Recommendation: We recommend that the FDA evaluate practical ways that the pharmaceutical industry can fund patient expenses for experimental and investigational drugs used in clinical trials. One option is for the FDA to evaluate the viability of establishing a common patient pool that would be funded by pharmaceutical companies on a voluntary or required basis.