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A National Network for Healthcare Reform

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Doris Simonson

March 14, 2007

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

**Re: Docket No. 2006N-0061/RIN 0910-AF13 (Charging for Investigational Drugs)
Docket No. 2006N-0062/RIN 0910-AF14 (Expanded Access to Investigational
Drugs for Treatment Use)**

Dear Sir or Madam:

The National Patient Advocate Foundation (“NPAF”) thanks you for the opportunity to submit comments on the Agency’s plans to provide expanded access to investigational drugs and to allow sponsors of investigational new drug applications (“INDs”) to charge patients for such access. The Proposed Rule on Charging for Investigational Drugs (“Charging Proposed Rule”) and the Proposed Rule on Expanded Access to Investigational Drugs for Treatment Use (“Expanded Access Proposed Rule”) represent a significant step forward in opening a dialogue with stakeholders on this very important topic.

NPAF is a non-profit organization dedicated to improving access to health care services through policy reform. The advocacy activities of NPAF are informed and influenced by the experiences of patients who receive counseling and case management services from our companion organization, the Patient Advocate Foundation (“PAF”), which specializes in mediation for access to care, job retention, and relief from debt crisis resulting from the diagnosis with a chronic, debilitating or life-threatening disease. From July 1, 2005 – June 30, 2006, PAF was contacted by more than 6 million patients requesting information and/or direct professional intervention in the resolution of access disputes. In 2006, PAF helped enroll 1,778 patients in clinical trials as reported in the Patient Data Analysis Report of 2006.

NPAF believes any efforts to expand access to investigational drugs to individuals outside of clinical trials must take into account the principles set forth in the five “Pillars of Safety,” which have been developed and recommended by NPAF and have been the subject of testimony before the Senate Committee on Health, Education, Labor and Pensions by Nancy Davenport-Ennis, the Chief Executive Officer of NPAF. The five “Pillars of Safety” are as follows:

- Safety and efficacy must continue to be the foundational elements of the FDA regulatory process. Safety cannot exist in a vacuum apart from efficacy;
- Mechanisms to enhance existing structures and processes for post-market safety monitoring and adverse event reporting must be explored;
- Efforts to bring even greater efficiency and scientific expertise to the FDA’s review and monitoring processes must continue; such efforts must be done in a

manner that empowers the Agency to keep pace with the rapid advancements now occurring in areas such as genomics, proteomics, and nanotechnology;

- FDA must continue to work with industry, patient groups, physicians, hospitals, academia, and other government agencies to enhance the critical path;
- The FDA must be sufficiently resourced in order to insure more effective pursuit of its existing mandates. Additional resources are even more essential if FDA is to successfully implement a comprehensive suite of reforms.

We applaud FDA's efforts to provide expanded access to drugs under development for patients with serious and life-threatening diseases, such as cancer, HIV/AIDS, and diabetes. In the past, FDA has demonstrated its commitment to helping patients with these diseases, particularly through the efforts of its Office of Special Health Issues, Cancer Liaison Program and the hard work of individuals at the Agency such as Patty Delaney and Joanne Minor who should be commended. NPAF appreciates the Agency's efforts to set forth a uniform framework for expanded access to investigational drugs for individuals, intermediate populations, and larger populations under treatment INDs (collectively referred to herein as "treatment use"); however, we respectfully submit that there are some concepts embodied in the proposed rules that NPAF urges the FDA to reconsider.

I. Expanded Access to Investigational Drugs Must Be Balanced Against Protecting the Integrity of FDA's Approval Process and Patient Safety

NPAF appreciates the challenge faced by the Agency in balancing the need for expanded access to investigational drugs by patients with serious or terminal illnesses with the need to protect the integrity of FDA's drug approval process. As recognized in NPAF's Five Pillars of Safety, safety and efficacy are the foundation of FDA's regulatory process. Any steps taken by the Agency to expand access to investigational drugs for treatment use cannot undermine FDA's ability to evaluate the safety and efficacy of drugs as part of the drug approval process. Expanded access cannot, and should not, be used to bypass the traditional means of obtaining approval for drugs. Nor can it be implemented in such a manner that it delays enrollment in clinical trials and, thus, the approval of new drugs to treat life-altering and/or life-threatening conditions like cancer, AIDS, or diabetes.

NPAF believes it is appropriate, then, for individuals and larger groups to obtain access to investigational drugs outside of the clinical trial process based on less evidence than would be required for the approval of the drug, as provided in the Expanded Access Proposed Rule. As NPAF has advocated with regard to FDA's drug approval process, FDA should be flexible in the amount of data required to justify access, based on the condition being treated, the size of the patient population being treated, the risks faced by the individual patient or group of patients, and the strength of existing data.

However, NPAF shares the concerns of others in the medical advocacy community that allowing access to investigational drugs based on limited clinical data, such as the results from Phase I trials or, in some cases, the results of animal studies, as suggested in the Expanded Access Proposed Rule, seriously compromises the safety of patients. As a preliminary matter, neither promising animal studies nor early Phase I studies necessarily guarantee that the drug will be safe or effective for the proposed treatment use. Furthermore, even if the drug is ultimately shown to be safe, but not effective, a patient's safety is compromised any time he or

she forgoes treatment with an approved drug that has been reviewed for its safety and effectiveness for treatment with an ineffective drug.

With this in mind, NPAF urges the Agency to make clear in the final rule that reliance solely upon the results of Phase I trials or animal studies to justify expanded access for treatment use would only be appropriate in very rare circumstances and based on very compelling results. Sole reliance upon animal studies to justify expanded access for treatment use should almost never occur. As a general matter, access should only be based on data from Phase II trials or later.

The individual's need for access to investigational drugs prior to marketing must be balanced against the needs of the wider patient populations. Even when individual access is permitted based on minimal data, approval of the drug could not be based on such evidence; further clinical trials are generally required to obtain approval. However, if expanded access for treatment use, either for individuals or for larger groups, undermines a sponsor's ability to enroll subjects in a clinical trial or otherwise delays the development of a drug for marketing, the community as a whole suffers because the drug will not be widely available to others who need it, many of whom face the same life-threatening diseases as those who obtained access for treatment use. Correspondingly, the development of post-marketing safety databases, which are critical to the safe use of the drugs, is delayed. Thus, in finalizing and implementing the Expanded Access Proposed Rule, NPAF urges FDA to be vigilant in enforcing the provisions requiring sponsors to demonstrate that the use of their investigational drugs for treatment use is not interfering with the conduct of clinical trials and the development of the products for market.

II. Sponsors Should Not Be Allowed to Charge for Investigational Drugs

A. Sponsors Should Not Be Allowed to Charge for Investigational Drugs for Treatment Use

Allowing pharmaceutical companies and other IND sponsors to charge for investigational drugs for treatment use, as the Agency has proposed, may very well undermine FDA's goal of improving access to investigational drugs for patients with serious or life-threatening diseases. Indeed, while the Expanded Access Proposed Rule may result in more patients *theoretically* being able to obtain access to investigational drugs for treatment use, these same patients may *in actuality* not be able to afford the life-saving medicines once they become available.¹ Essentially, the finalization of the Charging Proposed Rule likely will deny access to investigational drugs for treatment use for many of the very patients who may obtain access to the drugs under its companion rule. If the FDA could gain a collaborative commitment from CMS to provide reimbursement for their beneficiaries seeking this expanded access, that model would likely be embraced by the private sector. With these assurances, NPAF could have a more moderate position.

Further, NPAF is concerned that any FDA policy that allows pharmaceutical companies to charge for investigational drugs for treatment use will unnecessarily create a dichotomy between rich and poor. As you know, while expanded access for treatment use provides all patients with an investigational drug, in most clinical trials, patients are randomized to receive

¹ This problem is particularly acute in the case of many new oncology drugs, which often contain large molecules and may cost upwards of several thousand dollars per month for treatment.

either the investigational drug or a control, which is generally either a placebo or standard therapy. Except in the rare case of open-label clinical trials, subjects in clinical trials cannot be sure whether they are receiving the drug being tested, standard treatment, or a placebo. Under the Charging Proposed Rule, those patients who are able to afford to pay for investigational drugs can be guaranteed access to them under treatment use protocols, while those without such resources will be forced to enroll in clinical trials with only a chance that they will receive the investigational drug in question. If the goal of FDA's rulemaking is to ensure that expanded access to investigational drugs is uniform for all of those who need them, regardless of their financial means, personal connections, familiarity with FDA's regulatory processes, and proximity to academic centers, it will not be accomplished by retaining this provision. NPAF urges FDA to revoke this provision from the Charging Proposed Rule.

B. IND Sponsors Should Not Be Allowed to Charge for Investigational Drugs during Clinical Trials

NPAF respectfully submits that FDA's policy of permitting IND sponsors to charge patients for the costs of investigational drugs, embodied in the current regulations at 21 C.F.R. § 312.7 and in the Charging Proposed Rule at 21 C.F.R. § 312.8, is misplaced. Simply put, the financial burden for conducting clinical trials, including supplying the investigational drug, should be carried by the sponsors, who stand to profit from the drug if commercialized. The patients cannot, and should not, be required to bear the burden of cost here, when they are providing the service of exposing themselves to unknown health risks by participating in the trial. Furthermore, this policy does not take into account the disparate impact that allowing pharmaceutical companies to charge for investigational drugs will have on seniors and other groups that typically do not participate in clinical research, often because of financial constraints.

For example, due in large part to the costs associated with participation in clinical research, seniors are significantly underrepresented in clinical trials, particularly trials of therapies for cancer.² In an attempt to encourage participation by seniors in clinical research, the Center for Medicare and Medicaid Services (CMS) has allowed reimbursement for routine patient care costs associated with clinical trials since 2000.³ CMS is currently in the process of updating and expanding its National Coverage Decision on Clinical Trials and issuance of a revamped Clinical Research Policy should occur shortly. Even with the routine costs of care covered by Medicare and investigational drugs provided free of charge by sponsors, seniors still face non-medical barriers to their participation in clinical trials, including the logistical challenges associated with getting to clinical or academic centers. The proposed rule allowing sponsors to charge for investigational simply presents another barrier and may effectively exclude this group from enrolling in clinical trials.

² In a study published in 2004 in the *Journal of Clinical Oncology*, FDA experts analyzed age-related enrollment of cancer patients into trials of drugs approved by the FDA from 1995 to 2002. The authors concluded that there was significant underrepresentation of older people in trials for all cancer treatments except for breast cancer hormonal therapies, and patients ages 70 and older were the most underrepresented group.

³ Reimbursement for the cost of investigational drug itself is not typically reimbursed by CMS and third-party insurance carriers.

Because seniors are more likely to suffer from diseases and may metabolize drugs differently, as a public policy matter, FDA should encourage the enrollment of seniors in clinical trials, particularly for treatments for cancer and other life-threatening conditions. Furthermore, the barriers to access to clinical trials faced by seniors are shared by individuals with limited income, individuals who live far from major medical or academic centers, or individuals who lack access to high-quality medical care. FDA should encourage sponsors to include these diverse populations in their clinical trials, in order to allow the Agency to fully evaluate the safety and effectiveness of a drug and predict its outcomes in the population at large. The Charging Proposed Rule works at a cross purpose to these goals. NPAF believes the Agency should revoke the Charging Proposed Rule provisions related to the ability of sponsors to charge for investigational drugs during clinical trials.

C. If FDA Allows IND Sponsors to Charge for Investigational Drugs, It Should Be Under More Limited Circumstances

If the Agency determines it would be beneficial, under some circumstances, to allow a company to charge subjects in its clinical trials and those receiving the investigational drug for treatment use for the drug, NPAF urges that the Agency should only do so under more limited conditions than set forth in the proposed rule. Under proposed Section 312.8(c), a sponsor who wishes to charge patients for an investigational drug provided for treatment use must furnish to FDA “reasonable assurance that charging will not interfere with developing the drug for marketing approval,” including evidence of sufficient enrollment in any ongoing clinical trial(s) and “evidence of adequate progress in the development.” This standard is far too vague and does not provide adequate safeguards against a sponsor’s ability to charge for an investigational drug interfering with that drug’s clinical development and marketing.

As explained above, anything that causes a delay in the completion of clinical trials, and a corresponding delay in the approval and marketing of a drug, ultimately denies access to the medication to thousands of patients suffering from life-threatening disorders for whom time is a precious commodity. NPAF recommends that, in its final rule, FDA set forth very specific requirements that a sponsor must meet in order to demonstrate that its authorization to charge for an investigational drug for treatment use is not interfering with its ability to enroll patients in its clinical trial.

The Charging Proposed Rule currently requires a sponsor seeking authorization to charge for its investigational drug for treatment use to submit information from its general investigational plan specifying the drug development milestones anticipated to be reached over the next year. This requirement should be expanded to require that a sponsor submit a copy of, or cross-reference to, its general investigational plan, including a development timeline and enrollment estimates. Further, upon a request for reauthorization, a sponsor should be required to show that its actual enrollment is no more than five percent less than its original estimates. If enrollment has dropped by more than five percent, the onus must be on the sponsor to explain why the enrollment drop has occurred (for example, a very limited patient population) and demonstrate why it should still be permitted to charge for its investigational drug. In addition, sponsors seeking authorization to charge should be required to register their trials on clinicaltrials.gov or a similar government trial registry such as CancerNet/PDQ. This requirement would achieve the dual purpose of promoting awareness of, and enrollment in, the clinical trial, as well as providing FDA with a means of enforcing the clinical trial registry requirements under the Food and Drug Administration Modernization Act of 1997.

With respect to charging for treatment use, the Charging Proposed Rule provides that FDA will ordinarily authorize charging for the drug for a period of one year, unless “there is a particular concern that charging would interfere with drug development.” 71 Fed. Reg. at 75172. However, all instances of charging for investigational drugs for treatment use present a high risk that enrollment in clinical trials will be compromised, because guaranteed access to a promising therapy, even at a price, will be preferred by many over being subject to randomization in a clinical trial. As a result, NPAF urges the Agency to consider reducing to six months the period during which a company may charge for an investigational drug for treatment use so that the Agency may more closely monitor the progress of clinical trials of the drugs for which it grants expanded access for treatment use.

Finally, if sponsors are permitted to charge for investigational drugs for treatment use, the final rule should cap these charges at the sponsor’s cost to produce the product. Otherwise, allowing sponsors to profit from such changes could further undermine clinical trial accrual efforts.

III. Conclusion

Again, NPAF thanks the Agency for this opportunity to participate in the creation of a new policy on expanded access to investigational drugs for treatment use. We are confident that the Agency will diligently consider all comments received and arrive at regulatory framework that allows access to patients outside of clinical trials while maintaining the integrity of FDA’s drug approval process.

Sincerely,

A handwritten signature in black ink, appearing to read "Nancy Davenport-Ennis". The signature is written in a cursive style and is positioned above the typed name.

Nancy Davenport-Ennis
Chief Executive Officer and President
National Patient Advocate Foundation