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**Richard A. Justman, MD**  
National Medical Director  
Mail Route MN12-S117  
5901 Lincoln Drive  
Edina, Minnesota 55436

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Dockets Management Branch (HFA-305)  
United States Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville MD 20852

Re: Docket No. 2006N-0061  
RIN 0910-AF13 and  
Docket No. 2006N-0062  
RIN 0910-AF14

To whom it may concern:

Thank you for allowing UnitedHealth Group to comment on two proposed rule changes put forth by the US Food and Drug Administration (FDA), Expanded Access to Investigational Drugs for Treatment Use and Charging for Investigational Drugs.

We greatly appreciate that the intent of the FDA's proposed rule change is to make investigational medications more available to very sick persons who may have few, if any, treatment options. However, UnitedHealth Group has serious concerns that these rule changes will create significant difficulties while offering minimal, if any, benefit to the persons they are intended to help.

### **About UnitedHealth Group**

UnitedHealth Group is a diversified health services delivery company offering products and services impacting the lives of approximately 70 million Americans through its six constituent companies. UnitedHealthcare and Uniprise are the UnitedHealth Group companies that offer and administer health care benefit coverage to approximately 22 million Americans. We are committed to improving the health and well-being of all of our enrollees and plan participants, including those affected by serious and life-threatening illnesses.

### **Impact on evidence-based medicine and the national clinical research enterprise**

While clearly not the intent of the proposed rule change, we believe that the nation's clinical research enterprise, particularly the development and completion of clinical trials, will be seriously impeded by the proposed rules that offer access to investigational drugs outside of clinical trials. Our own experience offering benefit coverage for participation in clinical trials demonstrates that seriously ill persons are frequently reluctant to be randomized to an

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investigational treatment. Patient access to investigational drugs outside of a trial will make it that much more difficult to find out which investigational drugs really work and which ones do not. The impact will slow the development of clinical evidence necessary to support broader access to these drugs.

### **Patient Safety Issues**

We also believe the rules as outlined have the potential to increase risk to patients without offering the possibility of commensurate benefit. For example, treating physicians are likely to request access to investigational drugs not based upon likelihood of clinical benefit but because they believe they do not have other treatment options to offer.

Moreover, seriously ill patients will be exposed to patient safety issues that are much better addressed within the context of clinical trials. For example, had Herceptin® (trastuzumab) been made available to seriously ill breast cancer patients outside of a clinical trial and before the issue of HER2 overexpression had been addressed, many women would likely have been exposed to significant cardiotoxicity without clinical advantage over other available treatments.

We believe one approach that would more appropriately balance the benefits and risks of expanded access would be to require that all investigational drugs should be given under the umbrella of a defined protocol as outlined by a qualified clinical investigator. Investigational drugs need rigorous outlines for administration in their early development in order to prevent unnecessary misadventures by inexperienced physicians. These protocols would define the dosage range, monitoring for side effects and specified time intervals for assessing responses. The protocols need not be limited to certain age groups or diseases and could be as simple as a descriptive registry.

A protocol could also define the data elements to be documented in connection with the treatment, to capture additional evidence regarding the effectiveness of the investigational drug. To the extent possible, these data elements should attempt to replicate the evidence captured in a clinical trial. If paired with reporting requirements, this data capture could mitigate some of the concerns associated with expanded access outside a clinical trial.

### **Benefit Design Issues**

UnitedHealthcare benefit design already recognizes that some patients should receive benefit coverage for treatments that are not yet supported by clinical evidence. To that end, we cover enrollee participation in clinical trials when certain conditions are met. In addition, we cover treatment for promising but unproven treatments for life-threatening illnesses outside of clinical trials. Finally, we have a Cancer Resource Service, a network of centers of excellence available nationally that provide treatment for our enrollees with rare, complex or difficult to treat cancers.

The proposed rule changes need to clarify that any expanded access to investigational therapies relate specifically to compassionate use access policies of FDA, and such therapies shall continue to be considered as unapproved and experimental. Further, patient access under this program does not constitute or provide evidence that such treatments are "reasonable," "necessary" or "medically necessary," as defined in benefit documents.

Payers will cover the medical expenses associated with protocols and trials. We believe that clinical trials offer treatment based upon best practice, evidence based medicine. Payers would welcome a more standardized approach to treatment of diseases without established therapies, particularly as these rules raise questions about responsibility for routine costs associated with otherwise excluded care.

### **Charging for Investigational Drugs**

Neither patients nor payers should be required to pay for investigational drugs or treatments; the manufacturer should provide the drug at no cost. Manufacturers will profit from the drug sale if it is eventually proven to be effective. Access to and affordability of health care are already significant problems in America. These problems would be significantly exacerbated under the FDA's proposed expansion of rules governing access to and charging for investigational drugs. We believe that states will create mandated coverage to mirror the proposed FDA rule expansion. If payers are required to cover the cost of these drugs they will have to increase their premiums. We know that increased premium costs are causing more and more people to be uninsured. It is particularly unjust to require coverage for non-evidence based care for small numbers of persons when the consequence will be loss of coverage and access to proven care for large numbers of other persons.

### **Data-driven assumptions about the cost consequences of the proposed rule change**

UnitedHealth Group has asked its affiliate company, Ingenix, to review claims data surrounding the treatment of illnesses and conditions likely to fall under the FDA's proposed rule changes, and to make reasonable assumptions about the cost impact of these changes. The information provided below is our assumption of the additive cost of these changes as they will apply to enrollees in commercial/private health plans, including our own. For the various disease categories, we have assumed that only the very sickest persons would request access to investigational drugs. Specifically, physicians would request access to investigational drugs only when available therapies have failed or when conventional therapies do not exist. We also believe that depending upon the circumstances, investigational drugs will be used as first-line therapy, second-line therapy, monotherapy and combined therapy with FDA-approved medications.

- Aggregate additive cost, per year, to all US private sector payers: \$273,600,000
  - Annual cost for cancer treatment: \$190,800,000
  - Annual cost for HIV/AIDS treatment: \$6,100,000
  - Annual cost for hepatitis treatment: \$1,200,000
  - Annual cost for metabolic disease treatment: \$3,400,000
  - Annual cost for neurological disease treatment: \$32,600,000
  - Annual cost for collagen-vascular disease treatment: \$39,600,000

We believe these estimates actual understate the burden to private sector payers, because it excludes potential annual costs to Medicare Advantage plans. We acknowledge that our

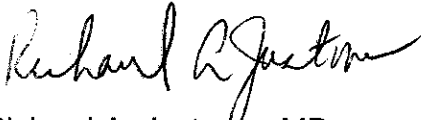
calculations are much larger than those anticipated by the FDA, and we would be happy to share additional detail with you upon request.

**Conclusion and recommendations**

UnitedHealth Group recognizes the need of seriously ill persons to access drugs likely to help them. We believe that facilitating clinical trials and offering investigational drugs within established protocols is the best way to achieve this goal. We also believe that payers should cover the cost of having their enrollees participate in such trials. For seriously ill persons not eligible for participation in clinical trials, other vehicles to access investigational drugs must be developed. Investigational drugs, whether given within or outside the context of a clinical trial, should be provided free of charge. However, expansion of access and the capability to charge for investigational drugs as currently proposed will be counter-productive to the achievement of better health outcomes for persons with rare, complex and otherwise difficult to treat diseases. We hope that the FDA will consider these comments and then rescind the proposed rule changes.

We would be happy to visit you in your offices to discuss this more directly if that would be helpful to you.

Sincerely,



Richard A. Justman, MD  
National Medical Director