



March 24, 2005

**The Honorable Michael B. Enzi
Chairman, Health, Education, Labor & Pensions Committee
United States Senate
Washington, DC 20510
Attention : Ms. Amy Muhlberg (via email)**

Dear Mr. Chairman:

Thank you for the two questions regarding my testimony at the drug safety hearing of the HELP Committee. My answers are as follows:

1) As you know, there are things about rare disorders that make a different approval standard appropriate. Could you discuss whether rare disorders are the right model for approval for drugs to treat more common disorders, and if so, how that model would translate?

The *Orphan Drug Act of 1983* does not provide a different standard for orphan drug approvals. During three years of intense debate about the design of the law, consumers made it very clear that we wanted orphan drugs to comply with the same standards of safety and efficacy as other pharmaceuticals and biologics. We do not want treatments that are less safe, or less effective than other treatments. Rather, the law provides financial incentives to entice companies into developing drugs for small populations of patients (fewer than 200,000 patients in the United States), because the industry felt that such small populations represent a limited market that would not be profitable enough. However, the law does provide a mechanism for patients to have access to orphan drugs while they are still investigational if the patient is not eligible to participate in a controlled clinical trial. In this case the patient gives informed consent and the doctor provides the medicine under an IND.

At the beginning of the AIDS/HIV epidemic FDA was under pressure to speed the development of new AIDS drugs, but consumers representing other deadly diseases felt that the rules should not be changed for one disease. Rather, the new rules should allow an accelerated approval process for treatments applicable to any serious or life-threatening disease when other treatments were unavailable or unsatisfactory. Subsequently, then Commissioner Frank Young created an "accelerated approval" or a "fast-track" process allowing drugs for serious and/or life-threatening diseases to show less efficacy data than is required for drugs to treat less serious conditions, or serious conditions where there were already available therapies. However, the manufacturer had

to promise to conduct clinical trials (to confirm the efficacy or treatment benefit) after the drug was on the market.

Section 506 of the Food and Drug Modernization Act of 1997, which codifies the regulation instituted in the 1980s by Commissioner Young, defines fast-track as follows:

Designation of Drug as a Fast Track Product. - In general. The Secretary shall, at the request of the sponsor of a new drug, facilitate the development and expedite the review of such drug if it is intended for the treatment of a serious or life-threatening condition and it demonstrates the potential to address unmet medical needs for such a condition. (In this section, such a drug is referred to as a `fast track product'.)

Thus, since the mid-1980s until now, drugs for many diseases, both rare and common, were eligible to use this process if the drug fit within the serious or life-threatening parameters of the regulation. However, the drug had to have concrete clinical evidence that it was probably safe and effective before it could be approved for patients under the fast track system, and manufacturers had to promise they would conduct these confirmatory post-approval (Phase 4) trials if the FDA asked them to. As you know, not all of those Phase 4 trials have been done, and those that have been done may have taken longer than FDA required.

2) Ms. Meyers, you have testified previously that the primary purpose of the FDA Modernization Act "was to speed the approval of more new drugs and devices, even if those drugs and devices were relatively unimportant to the public health." But we know that no two drug compounds are exactly the same in terms of how they affect patients. Each patient has a unique genetic predisposition that affects how a drug affects him or her. Each patient has his or her related or unrelated medical complications that affect how a drug reacts. A drug that might be right for me, might not be right for you - so who decides which drugs are important or not important to the public health?

There has been much written about "personalized medicines", but they are not yet available for general use. This is primarily because science does not yet have the tools to understand the genetic differences between humans. The first DNA test to examine how a person's liver may metabolize certain drugs has very recently been approved by the FDA, and some cancer drugs can be aimed at certain types of tumors but not others. Everyone expects that science will evolve so that personalized medicines will eventually become available in the future, but it is not available now, and doctors generally cannot prescribe a treatment based on a person's genetic profile.

It is indeed true that a drug that works for me may not be good for you. Companies spend a lot of money developing "me-too" drugs for common diseases that are similar to other available therapies (e.g., many companies have or were recently developing Cox-2 inhibitors for the most common form of arthritis, osteoarthritis). There are minor differences between these drugs

in order not to violate a competitor's patent. But in terms of speeding approval of any new drug, FDA should recognize that arthritis is not life-threatening, there are dozens of available treatments already on the market for arthritis pain, and the people who take pain drugs are either healthy people who want minimal risk from any medication (e.g., for a sprained ankle or dental pain), or elderly people with other diagnoses who are taking other drugs. The risk of a dangerous interaction with other medicines, the difference of metabolism between young healthy patients and older people, and the problems of taking a medicine long-term for a chronic disease like arthritis, should raise significant safety questions before a new drug for arthritis pain enters the market.

The only way for a doctor to tell which drug will work better on a person with arthritis is to prescribe each one, one at a time. The manufacturers of Vioxx® and Celebrex® have never claimed that their products are more effective than other anti-inflammatories. In general they were marketed to be "as effective", but with greater safety on the stomach. However, there are other anti-inflammatories on the market that are manufactured to dissolve in the intestines rather than the stomach, for patients who have stomach problems. Additionally, long-term studies of the Cox-2 inhibitors have shown that people who took the drugs for more than one year had an equal incidence of stomach ulcers to those who took older anti-inflammatories.

So I agree with you, Senator Enzi, that "me-too" drugs that are similar to other medications, are good because they provide more choice for consumers, even though doctors are usually unable to determine which may be better for each patient. But these kinds of treatments for non-life threatening diseases, that will be taken chronically for a disorder such as arthritis, and used by a frail elderly population with other illnesses, should not be approved for marketing on a priority review. Instead such drugs should be studied longer on a population that reflects the "real world" market, not a pristine group of individuals who have no other complicating factors. Once these drugs reach our local pharmacies, people with heart conditions, diabetes, high cholesterol, etc., take them. Even if FDA thought that the first Cox-2 inhibitor was a break-through drug, then the second and third Cox-2 drugs should not have been reviewed on a shortened priority basis.

We believe that fast-track reviews of pharmaceuticals should revert to their original intent: They should be used as treatments for serious and life-threatening diseases that have no other satisfactory treatments available (an unmet medical need).

I hope this answers your questions.

Abbey S. Meyers
President
National Organization for Rare Disorders (NORD)
P.O. Box 1968
Danbury, CT 06813-1968
meyersa7@rarediseases.org

www.rarediseases.org

Phone: 203-744-0100 Fax: 203-798-2757