



**STATEMENT**

**of the  
National Organization for Rare Disorders  
(NORD)**

**at the  
U.S. Food and Drug Administration Part 15 Public Hearing**

**"Considerations regarding FDA review and regulation  
of articles for the treatment of rare disease"**

**June 29, 2010**

Good morning. The National Organization for Rare Disorders (NORD) welcomes this opportunity to be the initial presenter at the FDA's first public hearing on rare disorder therapies. I am Frank Sasinowski, Chair of the Board of NORD, and we want to share our views on the FDA's exercise of its responsibilities for regulating therapies for Americans with rare disorders.

NORD is the leading advocate for the 30 million Americans with rare disorders. NORD is justifiably proud of our history as the principal force behind the effort that culminated in the 1983 Orphan Drug Act. And, NORD is just as equally proud of our current activities to advance the interests of Americans who have one of 6,000 rare disorders. I only have time to merely list some of NORD's major initiatives over the past 13 months.

1. NORD organized a full-day Summit on orphan disorders at the Willard Hotel in May 2009, which was chaired by former FDA Commissioner Kessler and key participants included Dr. Janet Woodcock and Dr. Francis Collins. A summary of this Summit is available on the NORD website.
2. NORD, with the assistance of John Crowley, CEO of Amicus, one of NORD's Corporate Council members, was responsible for organizing a Congressional Caucus on Rare and Neglected Diseases this year.
3. NORD was a key player involved in Section 740 of the FY 2010 Appropriations Act (the so-called Brownback/Brown amendment), which is the impetus for this hearing.
4. NORD suggested and supported that the FDA and the Center for Drug Evaluation and Research (CDER) establish its first position dedicated to issues related to the regulation of medicines for those with rare disorders, and in February FDA created the post of CDER Associate Director for Rare Diseases.
5. NORD worked for the passage of comprehensive health care reform, and in particular, those two provisions of vital interest to those with rare disorders: eliminating pre-existing conditions and eliminating lifetime and annual insurance caps. To see that what was gained in Congress is not lost in the courts, NORD is currently participating in an amicus brief to defend the constitutionality of the health care reform law.
6. NORD, with the involvement of FDA Commissioner Hamburg and NIH Director Collins, set up a Task Force on rare disorders in January. In several meetings at which senior FDA and NIH officials participated, NORD has explored ways to facilitate the development of therapies for rare disorders, including holding a series of 4 focus groups, each separately meeting with representatives of patient organizations, the medical and scientific research community, the pharmaceutical industry and the financial investment community.
7. And, finally, on the seventh day, NORD rested.

Both at the NORD Summit last May and at the NORD Task Force meetings, including focus groups, NORD has learned much and we want to share some of those key findings with FDA today.

First, over the 27 years since its enactment the *Orphan Drug Act* has proven a resounding success. This is best seen in the over 350 new medicines for more than 200 different rare disorders approved by FDA over the first quarter of a century of the law's existence. However, what NORD learned at its Summit and in its Task Force proceedings is that there are still about 5,800 disorders for which there are no FDA-approved therapies. Perhaps most discouraging is that many affected with these rare disorders do not even see any research being conducted in their conditions. To NORD, this seems as though the proverbial low hanging fruit has already been harvested in the first quarter of a century of the law's existence, while the vast majority of therapies are currently out of reach of those in need of an FDA-approved medicine. In sum, much has been accomplished by FDA, by NIH, by medical and scientific researchers, by the pharmaceutical industry, by the financial community and by patient advocates in these first 27 years, but much, much, much more beckons each of us to respond to the needs of those with rare disorders.

Second, how best can each of us respond to those in need of therapies? As part of the NORD Task Force, NORD – with senior FDA and NIH officials – in April held a series of four focus groups to listen and learn what are the barriers slowing or barring the development of new therapies for rare diseases, especially the 5,800 rare disorders for which there are no FDA-approved medicines. We had a separate focus group with each of the four major stakeholders involved in developing new therapies – the patient community, the academic research community, the pharmaceutical industry and the financial investment community. In those Task Force proceedings and at the NORD Summit, we heard many ideas. Several of those ideas would require new legislation and so those are beyond the scope of today's hearing.

What we at NORD heard which can be addressed by FDA is the benefit that would be gained from FDA action on the following two NORD recommendations:

- I. For a clearer, more granular expression of FDA's historic commitment to exercise flexibility in its review of therapies for rare disorders; and
- II. For an FDA expression of ways to reduce regulatory uncertainty in the development and review of orphan disorder therapies.

Let's explore each of those.

### **NORD Recommendation I: For an FDA Statement of Policy on FDA's Historic Flexibility in Regulating Orphan Drugs.**

NORD heard, especially from the investment community and the pharmaceutical industry, that FDA delivers a consistent, repeated message that the statutory standards for safety and efficacy are the same for both rare disorders and prevalent diseases. What is not often heard is

the companion portion that completes that statement which is that, while the statutory standards are the same, the FDA interpretation and application of those same standards have historically been tailored by FDA to the unique facts of each particular medicine under FDA review. Moreover, there are FDA regulations and guidances that express this flexibility. In addition, FDA actions on marketing applications eloquently embrace and express this concept of flexibility. This exercise of FDA scientific judgment in applying these statutory standards flexibly to various situations apparently is not being heard by some of the key stakeholders in this system.

So, today NORD is asking the FDA to develop and issue a specific Statement of Policy on FDA's role in regulating therapies for rare disorders, which includes an explanation and affirmation of the FDA's historic position that FDA flexibly applies the standards of safety and effectiveness with respect to therapies for those with rare disorders. What we, NORD, have heard is that the investment community and pharmaceutical industry may benefit from such a formal, explicit statement of policy that will encourage investment in, research of and development of medicines for those with rare disorders, especially for those 20 million Americans with one of the 5,800 rare disorders for which there still is not a single FDA-approved therapy.

## 1. FDA regulations and guidances

- A. In responding to the AIDS crisis that was becoming apparent around the same time that FDA was implementing the *Orphan Drug Act* in the mid-1980's, FDA promulgated Subpart E of the IND regulations for "drugs intended to treat life-threatening and severely-debilitating illnesses." FDA stated that the purpose of Subpart E is "to establish procedures designed to expedite the development, evaluation, and marketing of new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists. As stated [in section] 314.105(c) of this chapter, while the statutory standards of safety and effectiveness apply to all drugs, the many kinds of drugs that are subject to them, and the wide range of uses for those drugs, demand *FLEXIBILITY* in applying the standards. The FDA has determined that it is appropriate to exercise the broadest *FLEXIBILITY* in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness. *These procedures reflect the recognition that physicians and patients are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses, than they would accept from products that treat less serious illnesses. These procedures also reflect the recognition that the benefits of the drug need to be evaluated in light of the severity of the disease being treated.*" (Emphasis added.)
- B. The regulation that was referenced in the Subpart E regulation is section 314.105(c), which even predates the Subpart E regulation and illustrates again FDA's historic position on applying the same statutory standards in a flexible way depending upon the circumstances. Section 314.105(c) states that: "FDA will approve an application after it determines that the drug meets the statutory standards for safety and effectiveness, manufacturing and controls, and labeling. While the statutory standards apply to all drugs, the many kinds of drugs that are subject to them and the wide range of uses for

those drugs demand *FLEXIBILITY* in applying the standards. Thus FDA is required to exercise its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet them. FDA makes its views on drugs products and classes of drugs available through guidelines, recommendations and *statements of policy*" (emphasis added).

C. An example of a formal regulatory policy or guidance that expresses this concept of "flexibility" in FDA's application of the statutory standards of safety and efficacy is seen in the ICH E1A guidance. That FDA-adopted international guidance stipulates the minimum quantum of safety exposures necessary for FDA to even accept a marketing application for review when the medicine is intended for a chronic condition. Most rare disorders are chronic in nature and not acute, and so this guidance applies to most rare disorder therapies. The guidance states that the minimum number of safety exposures to meet the statutory standard for safety are 1500 persons exposed to the investigational therapy with 300 to 600 of those exposed for at least 6 months and with at least 100 exposed for one year. However, the guidance states that these minimum safety thresholds do not apply to therapies for rare disorders. Importantly, the guidance then does NOT state what is required in the alternative whereas it could have stated an algorithm such as at least 1% of the U.S. population with the rare disease must be exposed with half of them for at least one year. No, instead the guidance relies upon the exercise of FDA's scientific judgment to determine what is appropriate to meet the statutory standard for safety in each particular rare disorder therapy.

## 2. FDA actions on rare disorder therapy marketing applications

Instead of reviewing many such precedents, NORD refers to but one recent example as illustrative. In March of this year, FDA approved Carbaglu for NAGS deficiency, the rarest urea cycle disorder, with only 10 patients in the U.S. generally at any time. In the FDA briefing document for the January 13, 2010 Advisory Committee meeting, FDA explained that while Congress in 1962 added a new statutory standard requiring that a drug prove its effectiveness, "FDA has been *FLEXIBLE* within the limits imposed by the Congressional scheme, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug were convincing... Thus, evidence obtained from retrospectively reviewed case series could be considered as substantial evidence of effectiveness... The fact that the case series presented in this application is retrospective, un-blinded, and uncontrolled precludes any meaningful formal statistical analyses of the data. Under these conditions, any statistical inference from confidence intervals and/or p-values is uninterpretable and, consequently, should not be utilized to inform clinical decision making." (See pages 9 & 10 of the briefing document attached to Dr. Griebel's December 16, 2009 memo to the Advisory Committee, emphasis added.)

## 3. Dr. Goodman's June 23, 2010 Statement to Congress

Dr. Jesse Goodman, FDA Chief Scientist and Deputy Commissioner for Science and Public Health, testified last week before the Senate Appropriations Committee Agriculture Subcommittee on "FDA's efforts on rare and neglected diseases." In Dr. Goodman's commendable testimony he cites to the Carbaglu example as well as several others to

illustrate that “FDA is fully committed to applying the requisite *FLEXIBILITY* in the development and review of products for rare diseases, while fulfilling its important responsibility to assure that the products are safe and effective for these highly vulnerable populations. There are numerous examples of drugs approved for treating rare diseases where FDA’s *FLEXIBILITY* and sensitivity to the obstacles of drug development for rare diseases has brought forth a successful treatment” (emphasis added).

4. Personal example from meeting this month with FDA.

In a meeting I had this month the FDA told the sponsor at an End of Phase 2 meeting for a therapy to treat a very troublesome symptom of a very serious and common (that is, prevalent) disease that the sponsor had not only to prove the effectiveness of the drug to treat the symptom but also had to rule out that the drug did not increase unacceptably the risk of death in that patient population with this serious disease. FDA stated that the sponsor would have to show what increase in the risk of death could be excluded by reference to the upper 95% confidence interval. While we did not at that meeting arrive at an agreement on the size of the magnitude of risk that had to be excluded, even ruling out only a doubling of the risk of death would likely require a study of thousands of subjects for a long period of time. While I have been involved in scores, maybe hundreds, of therapies for rare disorders, I have never heard FDA express a similar requirement for a therapy for a rare disease. Why? This is likely because FDA is being flexible in interpreting and applying the statutory standards for safety and efficacy in that FDA knows that to require a similar type of showing for a therapy for a rare disorder would be impossible for almost all orphan drugs given the limited pool of potential subjects for clinical trials. The statutory standards are the same both for the prevalent disease and the orphan condition, but FDA rightly interprets and applies the standards in light of the disease and investigational therapy.

In other areas FDA can exercise similar flexibility. For instance, where the potential number of subjects is limited, the degree to which FDA demands dose selection be optimized in pre-approval studies may be reduced as can be FDA’s requirements for validation of a patient reported outcome instrument in a rare disorder population or proof of the sensitivity, specificity and clinical meaningfulness of a primary endpoint. Given that each investigational therapy for a rare disorder will present unique features, NORD understands that the granularity of the requested statement of policy on rare disorder therapies may necessarily be limited. However, even cataloging the nature and scope of the orphan product precedents that illustrate FDA’s flexibility may enable key stakeholders to better understand FDA’s position. That is, even while FDA states correctly that the statutory standards are the same for prevalent and rare conditions, FDA will have a formal companion statement of the equally important and consistent FDA historic position that FDA will exercise its scientific judgment to interpret and apply those statutory standards in a flexible manner, tailored to each rare disorder therapy.

NORD looks forward to the FDA issuance of an FDA Statement of Policy on FDA’s regulation of therapies for rare disorders and to the day when every FDA official who speaks to patients or to other stakeholders, including researchers and sponsors, about the FDA policies on

regulating therapies for rare disorders does so in the complete and balanced way that Dr. Goodman did last week when he testified both that as to the identical statutory standards that rare disorder therapies must meet as well as to the historic FDA flexibility in interpreting and applying those standards, exercising FDA's scientific judgment in light of the particular circumstances of that unique rare disorder and specific investigational therapy.

## **NORD Recommendation II: Reducing Regulatory Uncertainty in the Development of Medicines for Rare Disorders.**

In addition to the willingness of persons with rare, serious diseases to accept more safety risks and less rigorous evidence of effectiveness than for a prevalent disease or for a less serious disease or for one with some already approved therapy, and in addition to learning that some key stakeholders would benefit from a formal FDA statement of policy on FDA's exercise of its flexibility, the other consistent message we at NORD learned from our research and interactions since the NORD Summit in May 2009 is that the development of therapies for rare disorders could additionally benefit from a reduction in regulatory uncertainty.

It is axiomatic that the perfect is the enemy of the good. In the world of rare disorders, there is much that is often not known or not known well, starting with the etiology and pathophysiology of the condition, including its natural history, and ranging to a lack of agreement among even a small handful of world experts on the most common clinical manifestations of some conditions. Against this backdrop, it is entirely understandable that FDA on occasion will find it difficult to concur in advance with a development program, even the design of a registrational trial under a special protocol assessment. However, researchers, industry and FDA, as well as most importantly, persons with the condition, may find that sometimes a study needs to proceed because patients are suffering and can not wait for the perfect trial design with the ideal primary endpoint to be eventually determined or developed and consensually accepted.

Research resources in the universe of rare disorders are precious, with the most precious being the persons with the rare disorders who are heroically volunteering to participate in a trial, usually under conditions where there is less known than in trials of therapies for prevalent diseases about the safety and potential effectiveness of the investigational therapy from animal models, animal toxicology and early human trials. So, when these trials are conducted, sometimes with designs with which all parties may not be in full concurrence, including the FDA, great deference should be afforded the design of these trials and flexibility applied in the interpretation of their results. If such a principle were to be addressed and accepted by the FDA, much good would come of it.

## **CLOSING**

On behalf of all those with rare disorders, NORD commends the FDA on its stellar, worldwide leadership role on orphan product issues for the past 27 years, and NORD exhorts FDA to continue to embrace even more fully the historic flexibility FDA has long noted and exercised in FDA's regulation of medicines for those Americans with rare disorders and to grapple with ways that can be managed by FDA to reduce the regulatory uncertainty in the development and review process.

NORD commits to do all it can to continue to provide input to FDA on matters related to FDA's vital responsibilities for the regulation of investigational therapies for each of the 30 million Americans with rare disorders, but especially for those more than 20 million who have the 5,800 rare disorders for which there are no current FDA-approved therapies.

Finally, NORD would like to publicly and formally express NORD's deep appreciation to the FDA for holding this hearing today on these critically important issues to so many Americans.

Thank you.