



July 30, 2004

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

Dear Lisa Rovin:

As President of the National Osteoporosis Foundation (NOF), we are responding to the Food and Drug Administration's (FDA) request for comments regarding its Critical Path Initiative, Docket Number 2004-N-0181.

Osteoporosis and low bone density pose a major public health risk for an estimated 44 million Americans. In the US today, 10 million individuals are estimated to already have the disease and almost 34 million more are estimated to have low bone mass, placing them at increased risk for osteoporosis. NOF is the leading national voluntary health organization solely dedicated to promoting lifelong bone health and improving the lives of those affected by osteoporosis and related fractures while working to find a cure for the disease through programs of awareness, public and professional education, advocacy, and research.

The following responds to the questions posed in the above-referenced notice.

1. The hurdle we would like to address is the long and costly process of demonstrating the medical effectiveness of drugs to prevent and treat osteoporosis. The original Guidance document from 1994 provided the critical requirement that agents proposed for the treatment of osteoporosis show reductions in fracture risk. Clinical trials with several anti-resorptive agents, and more recently with anabolic agents, have been conducted using randomized, placebo-controlled designs that were powered to show fracture risk reductions. Since 1995, physicians who treat patients with osteoporosis and the patients themselves have been fortunate to have these new, safe and effective therapies made available to them. Clearly, however, the search for effective and safe treatments is far from over. We can now reduce the risk for low trauma fractures in a clinically meaningful way, but we have neither eliminated the risk of fragility fractures nor have we cured the disease. Continuing research in bone biology will lead to the development of new compounds and devices to be tested, and there are compelling social and economic factors that will require the evolution of newer and better approaches to managing this major public health problem.

The central issue is to identify acceptable alternatives to placebo-controlled trials. This is necessary because of:

- a) ethics concerns associated with placing patients in a placebo group and
- b) the magnitude of studies required (sample size and duration) for non-inferiority and active comparator studies will stifle further drug development.

2. The hurdle addressed in Number 1 above is the central hurdle.

3. This hurdle applies to drugs being developed for osteoporosis, a long-latency disease that results in fractures. Fractures are devastating to the individual and constitute a major public health burden, but the fracture rates and expected efficacy of drugs are such that large numbers of subjects must be studied over long periods in order to establish efficacy, under current regulations.

4. The solution posed would facilitate the development of new drugs to prevent and treat osteoporosis.

5. The issue of whether the fracture end point should be essential is a very complicated one. It requires a careful evaluation of the current evidence and the validity of using pre-clinical data and novel methods for assessing bone quality and quantity in the clinical trial subjects in order to be addressed.

All of us, together with the FDA, are struggling with this difficult dilemma. A previous meeting, "Osteoporosis Trials: Ethical Considerations in Study Design Meeting," which was sponsored by the American Society for Bone and Mineral Research (ASBMR) and held June 14-15, 2002 in Bethesda, MD, delineated the arguments but did not result in revision of the FDA Guidance. We believe that a revision of the guidance is needed in order to take advantage of new science to develop new agents, to protect the rights of subjects, to make it possible for pharmaceutical companies to engage in the process without massive costs that ultimately would be passed on to consumers, and to result in medications that are clearly safe and effective.

Therefore, NOF wishes to encourage the FDA to convene a two-day meeting to debate the issues before an FDA Advisory Panel and representatives from the FDA. After the relevant issues derived from your two questions (listed in the background information for Docket No. 2004D-0035) are presented and reviewed, you could pose additional questions to the panel, seeking guidance on how to proceed. This meeting would need to end with specific recommendations on how to proceed with altering or maintaining the current guidance. The objective of the proposed conference would be to serve as the basis for the development of a new FDA Guidance for an industry standard.

6. The proposed solution could be accomplished in less than two years.

7. It is essential that the FDA play the convening role, bringing the relevant parties together to discuss the issue and advise the FDA. As indicated above, the ASBMR provided a forum for many individual points of view, but additional input at the

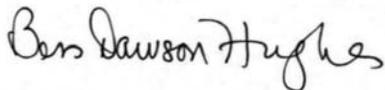
organizational level should be useful. Participants for the proposed meeting should include representatives of: scientific societies (i.e. ASBMR, Federation of American Societies for Experimental Biology), patient advocacy groups (i.e. NOF), the IRB , National Institutes of Health, and Department of Health and Human Services, and industry as well as FDA scientists.

8. Priorities need to be set, taking into account the:

- a) number of people affected by the problem and
- b) time line and cost required to implement the solution.

In closing, the hurdle described herein meets the criteria for a high priority. The information base upon which a solution can be derived is presently in place. Weighting and prioritizing this information wisely is the challenge. NOF would be glad to work with you to assist in the development of the topics and the identification of possible speakers, in an effort to help you reach the best possible solution to this critical problem. The design of clinical trials for testing promising new therapies for osteoporosis is one of the most important issues facing all of us who work each day in so many different ways to help patients who are at risk for osteoporotic fractures. We commend you for the serious effort you are making to resolve the dilemma we face, and offer you our support and help as we address these challenging questions.

Sincerely,



Bess Dawson-Hughes, MD
President NOF

CC: Lester Crawford, DVM, PhD
Acting Commissioner

Janet Woodcock, MD
Acting Deputy Commissioner for Operations