

The Food and Drug Administration's Osteoporosis Guidance Document: Past, Present, and Future

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ABSTRACT

In December 1979, the Food and Drug Administration's (FDA) Division of Metabolic and Endocrine Drug Products issued its *Guidelines for the Clinical Evaluation of Drugs Used in the Treatment of Osteoporosis*. The Guidance Document recommended study designs, patient populations for study, and techniques for evaluating skeletal mass and fracture frequency that were considered central to showing the efficacy and safety of drugs used to treat and prevent postmenopausal osteoporosis (PMO). In this paper, I discuss the evolution of the Osteoporosis Guidance as it relates to the pharmaceutical industry's efforts to develop effective and safe anti-osteoporosis drugs. Current regulatory policy on osteoporosis drugs and thoughts on the future direction of the Osteoporosis Guidance are also provided. (J Bone Miner Res 2003;18:1125–1128)

THE ORIGINAL GUIDANCE

RESPONDING TO THE NEED for effective and safe drugs to treat osteoporosis, the FDA's Division of Metabolic and Endocrine Drug Products, with input from an ad hoc workshop and an Advisory Committee, published the first issue of its Osteoporosis Guidance in December 1979. This document, entitled, *Guidelines for the Clinical Evaluation of Drugs Used in the Treatment of Osteoporosis*, began with the acknowledgment that evaluating the clinical effectiveness of osteoporosis drugs posed special challenges because of the "difficulties in assessing the state of skeletal bone quantitatively in vivo, the relatively small changes that are usually encountered, and the duration of studies necessary to show significant effects."⁽¹⁾

These limitations in mind, the Guidance recommended that phase II studies of osteoporosis drugs be randomized, double-blind, placebo-controlled, and at least 24 months in duration. Phase III studies were expected to be continuations of the phase II trials—no minimal duration of study was suggested, however. Appropriate criteria for patient inclusion in the studies included objective evidence of disease (history of an osteoporosis-related fracture) and/or the somewhat subjective criterion (evidence of a decrease in bone mass as measured by any of a number of techniques).

The views expressed in this paper are those of the author and should not be construed as representing the official position of the FDA.

The author has no conflict of interest.

Six methods to measure skeletal mass—all with noted disadvantages—were provided in the Guidance, with single photon absorptiometry, radiogammetry, and total body neutron activation analysis considered the most applicable to drug development. It was expected that skeletal mass would be measured at baseline and every 6 months during the first 2 years of the trials, and annually thereafter.

In an attempt to balance the desire for definitive evidence of efficacy (i.e., fracture reduction) with the realities of conducting a large clinical trial, the first issue of the Osteoporosis Guidance left ample room for interpretation regarding the most appropriate primary efficacy variable for osteoporosis trials: skeletal mass or fracture. On the one hand, the Guidance said that the assessment of a drug's effect on the frequency of fracture was "highly desirable," yet on the other hand, the document conceded that fracture trials would "require a relatively large numbers of patients to provide statistically significant results." As a compromise the Guidance offered "where there is evidence that bone formed during therapy is normal, adequate and well-controlled studies showing a favorable effect on bone mass [will] provide reasonable evidence of effectiveness of the drug in the management of osteoporosis." This approach was not without risk, however, as the Guidance made clear that in the event that bone formed was not normal, a fracture study would be required in addition to studies on bone mass.

In 1984, injectable salmon calcitonin (Calcimar), which had been approved by the FDA in the late 1970s for the treatment of Paget's disease and hypercalcemia, won approval for the treatment of patients with osteoporosis.⁽²⁾

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Market licensure was based primarily on the results from two 24-month studies of about 100 men and women, with total body calcium (TBC) measured by neutron activation analysis as the primary efficacy end-point. While there was little question of Calcimar's favorable effect on TBC (at least over a 1-year period), and hence skeletal mass, and no evidence that the drug adversely affected bone quality, some Advisory Committee members were hesitant to recommend approving a drug to treat osteoporosis in the absence of definitive fracture data. Nonetheless, because the minimum criteria for determining efficacy as set out in the Osteoporosis Guidance were satisfied by the Calcimar clinical data (i.e., increase or maintenance in bone mass and normal bone histology), and three of the five members of the Advisory Committee believed the data presented demonstrated adequate efficacy, the drug was approved.

The Advisory Committee's concerns about fracture efficacy did not fall on deaf ears, however, as the company agreed to conduct a 3-year, 300 patient, phase IV study to examine the effect of Calcimar on fracture frequency. Unfortunately, after 4 years of enrollment, it was obvious that the trial had significant problems (e.g., 50% dropout rate) that would hinder successful completion. Indeed, the study was eventually considered unsalvageable and terminated. While FDA officials were eager for data verifying that an increase in TBC was a valid surrogate for reduced fracture risk, they did not believe that the unsuccessful fracture trial justified withdrawal of the drug's osteoporosis indication, as some had suggested. For those who read the drug's labeling, it was clear that the osteoporosis indication was based on TBC data and that the Calcimar studies were not designed to detect differences in fracture rates.⁽²⁾

THE 1984 GUIDANCE

In the same year that calcitonin received its osteoporosis indication, the Division of Metabolic and Endocrine Drugs updated its Osteoporosis Guidance.⁽³⁾ The changes of note included suggestions for studies designed to secure an indication for the prevention of PMO and an upgrading of dual-energy photon absorptiometry from an investigational to a valid and reliable method for measuring trabecular bone mass of the spine, a recommendation to supplement all trial participants with calcium and vitamin D, and inclusion of the option to use an active versus a placebo control in trials of women with established osteoporosis. All but the last of these updates were embraced by industry.

The years 1980–1990 were critical to the approach to development and regulation of osteoporosis drugs. In 1982, Riggs et al. published results of a study that indicated that the combination of calcium fluoride, a stimulator of bone formation, and estrogen, an antiresorptive agent, had favorable effects on vertebral fracture risk.⁽⁴⁾ Encouraged by these findings, a randomized, double-blind, placebo-controlled 4-year trial of sodium fluoride was conducted in 202 postmenopausal women with osteoporosis, the results of which were published in a 1990 issue of the *New England Journal of Medicine*.⁽⁵⁾ Despite a massive 35% placebo-subtracted median increase in bone mineral density (BMD) of the lumbar spine, the rates of new vertebral fracture were

similar for the fluoride and placebo groups. More worrisome was the statistically significant increase in nonvertebral fractures in the active versus control-treated women. *Journal Watch General Medicine* headlined the findings, *Fluoride not helpful, and possibly harmful, in osteoporosis*.⁽⁶⁾ The implication of the discrepancy between bone density and fracture frequency was obvious; a pharmacologically induced increase in bone mass did not necessarily equate with reduced fracture risk. This dictum would find tangential support when the results of studies with the bisphosphonate etidronate were reviewed by the FDA and its Advisory Committee.

The March 8, 1991 Advisory Committee meeting held to discuss etidronate's effects on PMO began with the traditional Open Public Hearing.⁽⁷⁾ The sole speaker in this hearing, the president of the National Osteoporosis Foundation (NOF) and co-investigator of the fluoride studies mentioned above, spoke of accumulating evidence that bone mass predicted osteoporotic fracture as accurately as cholesterol levels predicted coronary artery disease. He urged members of the FDA and its advisory panel to rely on bone mass, not fracture, as the primary indicator of drug efficacy and approval. "When fractures are used as an end-point," he remarked, "extremely large groups and a long follow-up are required to eliminate type II errors." Such requirements, he believed, "would lead to very high costs and to poor patient compliance, therefore, sharply reducing the likelihood of approval of the effective new drugs for the treatment of osteoporosis which we badly need."

To allay fears brought about by the fluoride experience, the same speaker pointed out that fluoride was known to cause abnormal mineralization and altered structure of bone. . . . "So, clearly bone mass can predict fractures only when the bone is structurally normal, and these results are not relevant to most agents used to treat osteoporosis." The take home message was "when bone biopsy examination reveals normal histology, a drug-induced increase in bone mass is an adequate biomarker on which to approve a drug for the treatment of osteoporosis." Thus, it was clear that although the 1979 and 1984 versions of Osteoporosis Guidance indicated that favorable effects on bone mass coupled with normal bone quality *could* form the basis of drug approval, some believed that the FDA was too narrowly equating drug efficacy with reduction in fractures, to the exclusion of data on bone mass. The stage was set for discussion of the etidronate clinical trials.

Armed with the largest osteoporosis clinical trial program to date and one specifically designed to satisfy the efficacy and safety criteria of the Osteoporosis Guidance, the sponsoring company, Norwich-Eaton, and their clinical investigators, were confident that "etidronate [was] of definite benefit in treating osteoporosis—a public health problem of near epidemic proportions."⁽⁷⁾ The primary efficacy data came from one foreign 3-year study and two U.S. 2-year randomized, double-blind studies comparing intermittent cyclical etidronate to placebo. Although vertebral fracture data were collected, the change in lumbar spine bone mass, measured by dual photon absorptiometry, was, according to the company, the primary efficacy variable for the three trials. Compared with placebo, 3 years of intermittent treat-

ment with etidronate increased spinal bone mass by 8% and significantly reduced the vertebral deformity index, but not the rate of new vertebral fractures. Pooled data from the U.S. studies supported the findings from the 3-year trial, with one critical exception. At the end of the 2 years, patients were given the option of continuing for an additional year of double-blind treatment or changing to open-label calcium. Eighty-four percent of the subjects elected to receive an additional year of blinded treatment. The significant increase in vertebral bone mass was maintained during the third year; however, compared with placebo, there was an increase in new vertebral fractures during year 3 in patients who received etidronate—a complete reversal of the 2-year data. The company and its clinical investigators had a host of explanations for the unexpected third year fracture data, including small sample size, a short period of observation, and a belief that new vertebral fractures was a “relatively insensitive” method compared with the vertebral deformity index.

Cautiously optimistic that their explanations for the puzzling third-year fracture findings eased the committee's concern, the company turned the lectern over to the FDA medical officer responsible for review of the etidronate application. The Agency reviewer spoke for about 20 minutes, but it only took 60 s for him to deliver his opening and closing remarks, which were probably sufficient to end any hope the company had for their drug's approval.⁽⁷⁾ He began his presentation by pointing out to the committee that in preclinical testing, relatively low doses of etidronate caused osteomalacia, hyperosteoidosis, and increased the potential for fracture. He closed his talk with reference to the increased fracture rate noted in the third year of the U.S. studies and asked, rhetorically: “[Does] prolonged cyclical etidronate therapy have any deleterious effects on bone architecture that lead to an increased incidence of fracture?” Because there were no bone biopsy data from the third year of the studies in question, the company and its investigators could only sit in silence. With preclinical evidence of osteomalacia and clinical concerns about etidronate's long-term effect on fractures, favorable data on bone mass, the primary efficacy variable, were insufficient for drug approval.

THE 1994 GUIDANCE

Unlike the 1979 and 1984 versions of the Osteoporosis Guidance, which had little practical experience to draw from and hence were vague on the regulatory requirements for drug approval, the 1994 issue of the Guidance incorporated lessons learned from the fluoride and etidronate experiences and left no question as to what was required for licensure of a non-estrogenic drug indicated to treat PMO.⁽⁸⁾ These requirements included (1) normal bone quality in preclinical studies of two animal species, (2) normal bone quality in a subset of clinical trial participants, (3) a statistically and clinically significant increase in BMD, and (4) most importantly, at least a positive trend (i.e., $p < 0.2$) in 3-year fracture data.

The first non-estrogenic drug evaluated within the regulatory paradigm of the 1994 Guidance was the oral bisphos-

phonate, alendronate. Approved by the FDA in 1995 for the treatment of PMO, Merck and its clinical investigators provided phase III data from more than 900 women that left little doubt of alendronate's efficacy.⁽⁹⁾ Preclinical and clinical studies indicated that the drug increased bone mass by a statistically and clinically significant amount, maintained normal bone quality, and significantly reduced the risk for vertebral fracture over a 3-year treatment period. With normal bone quality and positive long-term fracture data in hand, as per the 1994 Guidance, alendronate secured an indication for the prevention of PMO based on 2-year BMD data. Using a very similar development program, risedronate was approved for the prevention and treatment of PMO in 1999.⁽¹⁰⁾

ESTROGENS AND SELECTIVE ESTROGEN RECEPTOR MODULATORS

Estrogen's regulatory history dates to 1942 when the FDA approved conjugated estrogens for menopausal symptoms. Three decades later, the National Academy of Sciences and the National Research Council took part in the Drug Evaluation study Implementation (DESI) process, whereby an assessment was made of estrogen's role in the treatment of osteoporosis. After reviewing the limited available data, the DESI panel half-heartedly endorsed estrogen's use, concluding that it was “probably effective” in select cases of osteoporosis.⁽¹¹⁾ This language formed the basis for estrogen's osteoporosis indication from about 1974 until 1986, when additional research was believed to support strengthening the osteoporosis indication to read “estrogen effective in the treatment of osteoporosis.”

As stated in the 1994 Osteoporosis Guidance, manufacturers of estrogens were not required to provide evidence of fracture efficacy to gain a treatment of PMO indication because “epidemiological studies have demonstrated that estrogen therapy reduces the risk of vertebral and nonvertebral fractures. Therefore, fracture evaluation for estrogen preparations is not required for the treatment study.”⁽⁸⁾ BMD was considered sufficient for both prevention and treatment of PMO indications.

The selective estrogen receptor modulator (SERM) raloxifene was approved for the prevention of PMO in 1997.⁽¹²⁾ Considered an estrogen from a regulatory perspective, raloxifene's initial approval was based on BMD data alone. While U.S. approval of raloxifene for the treatment of PMO would at that time have been possible based on BMD data, because of European regulatory requirements, a fracture trial of nearly 8000 women was conducted and provided the basis for raloxifene's approval for the treatment of PMO in 1999.

Since raloxifene's approval, and in contrast to the position articulated in the 1994 Guidance, it has been regulatory policy to require evidence of fracture efficacy from adequately powered prospective trials before approving an estrogen (ERT), an estrogen plus progestin (HRT), or a SERM for the treatment of PMO. Such evidence from the Women's Health Initiative has just been published, but the reduction in risk for osteoporotic fractures associated with the use of HRT came at the price of an increased risk for breast cancer

and cardiovascular disease, tipping the scale of risk–benefit in the wrong direction.⁽¹³⁾ It is unclear how these results will affect the regulatory status of HRT and ERT as therapeutic options for osteoporosis.

THE FUTURE OF THE GUIDANCE

While some have criticized the requirement to show fracture efficacy of an osteoporosis drug before approval as too stringent, this approach has provided drug regulators, pharmaceutical manufacturers, physicians, and patients with definitive evidence of drug efficacy, and in turn, permitted a more reliable benefit–risk assessment. The requirement for fracture data has also created a dilemma, however: with the availability of drugs that have been shown to reduce the risk for vertebral, and in some cases, nonvertebral fractures, is it appropriate to continue to conduct placebo-controlled fracture trials? This is, I believe, the most important question that regulators, companies, investigators, institutional review boards, and patients must now address as the field of clinical osteoporosis research moves forward.

Opponents to the continued use of placebos cite the Declaration of Helsinki, which states that it is unethical to use a placebo control if effective therapy exists and if the use of placebo will increase a patient's risk for serious or irreversible harm.⁽¹⁴⁾ There is no evidence that the drugs approved for the treatment of osteoporosis reduce mortality, but there is unquestionable evidence that alendronate, risedronate, and raloxifene reduce the risk for morphometric vertebral fracture, and in the case of the bisphosphonates, nonvertebral fractures. Do these events represent irreversible harm?

Proponents of the continued use of placebo-controlled fracture trials consider the frequently discussed alternative, active-control trials, to be at best, unfeasible, and at worst, unethical.⁽¹⁵⁾ Resurrecting the decade-old rationale used to argue against the regulatory requirement for fracture trials, today's placebo advocates believe that the sample sizes required to show fracture equivalence or non-inferiority would be prohibitively large. In this scenario, research and development of new osteoporosis drugs would decline, to the detriment of patients. Furthermore, some placebo advocates believe that because equivalence or non-inferiority trials, by definition, lack internal validity (i.e., there is no assurance that the reference treatment was actually effective relative to placebo), a new drug could be deemed equivalent or non-inferior to an approved drug, when in fact, the new drug is no better than placebo. In this case, an ineffective osteoporosis drug would be approved for widespread use, itself an unethical proposition. Since its inception, the Osteoporosis Guidance has reflected a joint effort among FDA,

industry, and academia. To be sure, continued collaboration will bring changes to the Guidance, and patients with osteoporosis should be assured that these changes will not forsake their needs.

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