Re: Statement by Dr. Willard Dere, Eli Lilly and Company
Endocrinologic and Metabolic Drugs Advisory Committee Meeting on "Clinical Trials for New Osteoporosis Treatments"
September 25, 2002

Chairman Braunstein, Dr. Orloff and members of the Advisory Committee, Lilly commends the efforts of the Agency to provide a forum for discussion on this critical topic.

During the past years, the FDA has approved a number of new agents for the prevention and treatment of osteoporosis. These drugs were approved with heavy emphasis on the existing 1994 Draft FDA guidelines for the development of osteoporosis therapies. Those guidelines were developed when there were few options available to the medical community to treat this potentially debilitating disease. It is now time to develop new guidelines, which must take into consideration advances in medicine and science and the current climate of drug development. These guidelines must take into account workable strategies for testing and registering osteoporosis therapies for women and men with osteoporosis of various etiologies. We offer the following points for consideration as you continue your deliberations today.

1. There is a need to define a common standard for demonstration of efficacy that can be applied to drugs of different classes. Lilly believes that while BMD is a useful diagnostic to identify those at the risk of OP, we maintain that change in BMD, and in biochemical markers of bone are not suitable to replace fracture as an endpoint for evaluation of efficacy of a new chemical entity. The relationship between change in BMD to that of reduction in fracture risk is not the same for the different classes of therapy and accounts for only a small part of the observed fracture risk reduction.

   Lilly agrees with the current recommendation that reduction in vertebral fracture risk is necessary to prove efficacy for osteoporosis compounds in order to obtain a treatment indication. Using surrogates for vertebral fracture endpoints would make it difficult to establish the true anti-fracture efficacy of new drugs, and would result in a less informative and less competitive labeling for sponsors with new drug development programs.

   However, we agree that treatment-induced change in BMD remains an acceptable endpoint for new formulations and indications (such as glucocorticoid-induced osteoporosis and male osteoporosis) for compounds whose fracture efficacy has previously been established.

2. While we recognize that a number of osteoporosis therapies are now available, Lilly maintains that a randomized, controlled trial (using calcium and vitamin D for all patients) should remain the standard for establishing efficacy and safety. In the current environment there is a dilemma regarding the acceptability of these so-called

placebo-controlled studies for evaluation of compounds for treatment of a disease for which alternate treatments exist. However, a relatively small placebo-controlled study that clearly demonstrates superiority of a new drug over placebo may be more broadly useful and more ethical (with respect to number of patients exposed) than a much larger study against an active comparator.

The European CPMP guidance on osteoporosis drug development that was issued in 2001 states that although active-control trials are preferred, placebo-controlled trials are still acceptable. Placebo-controlled studies provide greater flexibility in study designs (e.g., use of escape clauses and stopping rules to maximize patient safety, use of add-on therapies) and should be considered for new drugs in development.

3. There are considerable challenges in conducting active comparator trials rather than placebo-controlled studies. For example,
   - Lack of access to data, other than that present in the public domain for the active comparator, may hamper elucidation of statistical and sample size estimations for hypothesis testing.
   - Non-inferiority trials would require exposing large numbers of patients in potentially longer clinical trials.
   - Trials designed to establish either non-inferiority or superiority of drug compared to an established therapy might be compromised due to difficulty in replicating the effectiveness of the comparator active therapy depending on population studied and conditions of the trial design. Without a placebo-treated control group, one could not know whether or not the active comparator had worked!
   - If an active comparator were required, how would a sponsor determine which therapy is best for comparison, given that different classes of osteoporosis therapies work via different mechanisms, have different PK profiles, and even have different target populations?
   - Finally, there may be a lack of understanding of the safety profile because the 'true' adverse event rate for a new drug is best derived from placebo-controlled studies.

4. As I stated, Lilly maintains that the most appropriate study endpoint is the reduction in the incidence of osteoporotic vertebral fracture. While demonstration of reduction of fractures at the hip is not required by current guidelines, guidance is needed for purpose of label language on ways to be able to describe the efficacy at the hip. It is not practical to limit studies specifically to hip fractures. For example, to demonstrate a 40% reduction in incidence of hip fracture assuming a 3% event rate, the number of patients required for a placebo-controlled study is 5000, and for an active controlled non-inferiority study with a 20% margin of non-inferiority, the number of patients required is 33,000 and for an active controlled superiority study, the number of patients required would be 40,000!

   Therefore, we propose that a reduction in combined nonvertebral osteoporotic fractures, an increase in hip BMD, and improvements in bone structural measurements such as those described by Thomas Beck and colleagues from dual

energy X-ray absorptiometry (DXA) scans, should be considered adequate to demonstrate substantial evidence for a hip fracture reduction claim.

5 Guidelines should provide for the acceptability of shorter duration clinical trials (12 month with vertebral fracture endpoint) for an antiresorptive, possibly shorter for anabolic agents provided preclinical studies clearly show no detrimental effect on bone quality and sufficient safety data will be accrued during follow-up, such as in a post-marketing surveillance program. While further guidance is needed on number of years of follow-up required to assess clinical safety and durability of effect, we believe that a total exposure of 3-4 years should be considered appropriate for safety evaluation.

6. Current guidelines do not consider histomorphometric parameters of bone biopsies as efficacy endpoints. Given the lack of treatment effect (i.e. fracture reduction) predicted by changes in BMD alone, the agency should consider accepting the use of advanced imaging and computer-based analytical techniques for demonstrating changes in bone microarchitecture and quality. For example, 3-D analysis of bone structure using micro-computerized tomography (uCT) may provide efficacy measures of bone quality and structure, and could be used to define and distinguish true anatomical effects of different classes of osteoporosis therapies. For the purpose of human studies, bone quality may be assessed by appropriate combinations of: bone mineral densitometry; specialized radiographic techniques *in vivo* and *in vitro* (e.g., microCT, spiral CT, and NMR) and histologic assessments of trabecular and cortical bone mass, cortical thickness, trabecular connectivity, and bone remodeling. Sponsors should be encouraged to consider new assessments for bone strength that could include bone quality and architecture during clinical development.

7. With the availability of a variety of therapeutic options, drugs are likely to be used for the treatment of osteoporosis in a number of ways, alone or in combinations. Guidance will be needed to support claims for sequential or combined use of osteoporosis agents with the same or different mechanisms of action

8. There will be a critical need for harmonization of guidelines between the various regulatory agencies to provide for similar registration requirements across countries. Divergent guidelines will make registration of new osteoporosis therapies needlessly expensive and difficult.

We believe that the points raised are critical; if they are not dealt with, patients needing advanced therapies may suffer as important advances are delayed or prevented from ever reaching them. We anticipate that the Division and the committee will continue to engage in constructive dialog with industry today and in the future. Additionally it will be important to keep communications open with the CPMP and with public health agencies such as the NIH to address these critical questions and provide recommendations for workable new guidelines for developing osteoporosis therapies.

Thank you