# Comments by NPS Pharmaceuticals, Inc.
# to the
# Endocrinologic and Metabolic Drugs Advisory Committee
### September 25, 2002

Good afternoon and thank you for the opportunity to present these comments. My name is Tom Marriott and I am VP, Development Research at NPS Pharmaceuticals in Salt Lake City. This morning's speakers have outlined many of the points and much of the data that need to be considered regarding clinical trial design and the clinical evidence necessary for the approval of new osteoporotic agents. The summaries of the guidance documents also make it clear that there is an urgent need for an ICH-like harmonization of the meaning of the terms prevention and treatment as they relate to osteoporosis and of the regulatory requirements for the approval of new agents. At this point, NPS still believes that randomized, double blind, calcium and Vitamin D controlled trials are the best way to evaluate the safety and efficacy of new agents.

However, our recent experience suggests that it may become increasingly difficult to conduct calcium and Vitamin D controlled studies. We are currently conducting a 2600 patient randomized, calcium and Vitamin D controlled study in nine countries. In 2000, when we were initiating the study in the US and Canada, several IRBs refused to approve the study because we included women with severe osteoporosis, *i.e.* women with a BMD less than -2.5 and a prevalent fracture. In 2001, as we expanded the study worldwide, two Multiple Research Ethics Committees in the UK and the central ethics committee in Denmark would not approve the study because they considered it "placebo controlled" and requested that we add an approved agent to the calcium and Vitamin D control group.

Thus, if we are to continue to employ calcium and Vitamin D controlled studies, the scientific and regulatory communities must clearly describe why this study

design is appropriate and better than alternative study designs. We must also demonstrate that we have reduced the risk to our patients as much as possible. We suggest that there are several ways to minimize risk to patients:

**Reduce the Number of Clinical Studies.** Harmonization of the definitions of treatment and prevention may allow both indications to be investigated in a single trial. An obvious example would be in a study with a true anabolic agent where a reduction in fracture incidence is demonstrated and virtually all patients show an increase in BMD, beginning in the osteoporotic range and increasing through the osteopenic range. A second study to specifically investigate prevention defined by an increase in BMD should not be necessary.

**Reduce the Recommended Duration of Clinical Studies.** It is clear that it is possible to demonstrate statistically significant increases in BMD in short periods of time with many agents and statistically significant decreases in vertebral fracture incidence in less than 3 years. The recommended duration of efficacy studies required for approval should be reconsidered.

**Reduce the Number of Patients in Clinical Studies.** There are at least two ways to reduce the number of patients participating in clinical trials for new osteoporotic agents. The first is to use one-sided tests when determining efficacy. For example, if the control group is calcium and Vitamin D, it is obvious that a treatment would need to demonstrate better efficacy than the control group. Therefore, the null hypothesis is whether the incidence of fractures in patients receiving the experimental treatment is lower than the incidence of fractures in patients receiving calcium and vitamin D, not whether the incidence is different. This question can be answered using a one-sided test. Use of a one-sided test would reduce the number of patients by 15-20%.

The second way to reduce patient numbers is to accept a lower level of confidence, *e.g.* 80%, for the reduction in fracture incidence at a second fracture

site once reduction in the fracture incidence at a first site has been demonstrated. Since the significance level is the risk of concluding a difference exists when, in fact, there is no difference, the level of significance is chosen based on the consequences of this decision. Therefore, if a treatment has been demonstrated to reduce the incidence of vertebral fractures, for example, the question of whether it also reduces the incidence of fractures at another site, *e.g.* the hip, should be addressed using the one-sided test with a lower level of confidence. This does not substantially increase the risk of concluding that an agent with a deleterious effect at the second site is better than control, but will require fewer patients or fractures at the second site to reach an appropriate conclusion.

Thank you.