the false-positive rate (139). In other words, the greater the number of subgroups that are defined by the Clinical Study Protocol, the greater the probability that the study data will provide a false positive. It is this type of false positive that FDA seeks to prevent. Another regulatory body, the European Medicines Agency (EMA), has also cautioned about the over-use of subgroup analysis, writing that, "[a] common misuse of subgroup analysis is to rescue a trial which, formally fails based on the pre-specified primary analysis in the full analysis set" (140). Patsopoulos et al. (141) provide a thorough account of misleading subgroup analyses, involving the subgroups of male versus female, that were based on insufficient and spurious documentation. Examples of subgroups are shown below.

b. Subgroup of Non-Elderly Subjects and Subgroup of Elderly Subjects

In a study of breast cancer, Roché et al. (142) included subgroups of women under 50 years old, and greater or equal to 50 years old. The authors discovered that, "[w]omen age 50 years or older derived significant benefit in DFS from treatment with FEC-D ($P = 0.001$), but this advantage was not found in younger women ($P = 0.65$)." DFS refers to the endpoint of disease-free survival. FEC-D refers to a combination of drugs, namely, fluorouracil, epirubicin, and cyclophosphamide (FEC) followed by docetaxel (D).

This type of discovery, that is, the discovery by Roche et al. (143) that women of age 50 or older derived benefit, is concrete and easy to put into practice in the context of routine patient care. In other words, in treating breast cancer patients, it is easy to determine the patient's age, and it is easy to make a go/no-go decision to administer a particular drug. Both things are easy to do.

The following more broadly concerns the subgroup of elderly subjects and geriatric subjects. In a review of the influence of old age on risk for adverse drug reactions, Shah (144) disclosed that old age, that is, age of 70 years or older, increases the risk for adverse reactions to benoxaprofen. Benoxaprofen is an anti-inflammatory drug with the adverse drug reactions of photosensitivity and hepatotoxicity. Halsey and Cardoe (145) report that benoxaprofen's adverse effects increase greatly in persons over 70 years of age. Shah (146) also documents a few differences in the pharmacokinetics of

[139]Rubinstein L. E-mail of October 12, 2010.

[140]European Medicines Agency. Concept paper on the need for a guideline on the use of subgroup analyses in randomised controlled trials. April 22, 2010.

[141]Patsopoulos NA, et al. Claims of sex differences: an empirical assessment in genetic associations. J. Am. Med. Assoc. 2007;298:880–93.

[142]Roché H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 trial. J. Clin. Oncol. 2006;24:5664–71.

[143]Roché H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 trial. J. Clin. Oncol. 2006;24:5664–71.

[144]Shah RR. Drug development and use in the elderly: search for the right dose and dosing regimen (Parts I and II). Br. J. Clin. Pharmacol. 2004;58:452–69.

[145]Halsey JP, Cardoe N. Benoxaprofen: side-effect profile in 300 patients. Br. Med. J. (Clin. Res. Ed.). 1982;284:1365–8.

[146]Shah RR. Drug development and use in the elderly: search for the right dose and dosing regimen (Parts I and II). Br. J. Clin. Pharmacol. 2004;58:452–69.