To the Editor—The guiding principles of sound drug formulary system decisions, as endorsed by the Academy of Managed Care Pharmacy, the American Medical Association, the US Pharmacopeia, and other professional organizations are based “on scientific and economic considerations that achieve appropriate, safe, and cost-effective drug therapy” [1]. There is a natural hierarchy to the judgments that must be made. First, what are the magnitude and balance of clinical benefits and risks for a new drug? Second, what are the relative clinical benefits and risks of a new therapy compared to existing treatments? Third, what is the estimated economic impact of the new versus existing therapies? The first two questions should be made within the context of an evidence-based medicine framework. The third question is made within a financial and economic framework.

Recently, the Academy of Managed Care Pharmacy (AMCP) has promulgated a format for formulary submissions, one of whose goals is to make transparent the assumptions and evidence that are critical to decisions. The format also standardizes information requirements and provides a template for formalizing analyses that estimate the potential impact on both a health plan and its enrolled patient population. “AMCP’s format has the potential to move managed care away from the pharmacy silo-budgeting approach typically utilized for formulary decisions to a total cost and health-impact approach to health care delivery” [2]. While one might expect that support for this format would be similar to that for “mom and apple pie,” this has not, as yet, been the case [3].

However, as it gains greater acceptance, those who attempt to rigorously use the AMCP dossier approach will encounter additional challenges. This arises from the uncertainty inherent in the questions that formulary committees must answer, particularly if they adhere to the principles of evidence-based medicine. Formulary committees must make recommendations when there is incomplete information available to answer the three questions stated above. To deal with this inherent uncertainty, formularies follow a decision logic that attempts to limit uncertainty through simplifying assumptions.

Commonly, formulary committees start by asking the question—does the new therapy represent a new “class” of drugs or is it a member of an existing therapeutic class? If the drugs are in the same class, they are presumed to be interchangeable since they have closely related pharmacology, therapeutic activity, and adverse reactions—that is, there is a presumption of comparability of risk-benefit profiles. This presumption allows rational formulary designs that employ “preferred agents” or “tiered copays” since—all other things being equal—selection of a less expensive therapeutic agent for preferred status enhances the ability of a managed care organization to maximize the provision of health services to its members. In pharmacoeconomic terms, it facilitates a cost-minimization approach to drugs within a therapeutic class; a cost-effectiveness analysis may be utilized when drugs within a class exhibit different profiles with respect to biomarkers or surrogate end points with the assumption that these are the only important differences in their risk-benefit profiles—that is, they are otherwise interchangeable. Here we use the terms biomarkers and surrogate end points as defined by the Biomarkers Working Group: biomarkers are objectively measured indicators of biologic processes, pathogenetic processes, or pharmacologic responses to therapeutic interventions (e.g., blood cholesterol, CEA levels); surrogate end points are biomarkers that are expected to predict clinical benefit or harms based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence (e.g., blood pressure, LDL cholesterol) [4].

Drugs from different therapeutic classes are presumed not to be interchangeable. Thus separate attention must be paid to the individual profile of benefits, risks, and costs for drugs being compared. In this situation, the comparison often rapidly focuses on relative effectiveness. If the first drug in a new class provides significantly greater benefit in comparison to existing therapy, it will be added to the formulary. This is generally followed by a more
extended discussion to determine whether and to what extent access should be limited—either because of perceived financial impact or because the new drug has a significantly different balance of benefits and risks for specific subpopulations of patients.

However, as Furberg et al. and others [5–7] have argued, there is no established clinical or scientific definition of a therapeutic drug class. While the grouping of drugs into a class is generally based on a common mechanism of action (reflected by their impact on specific biomarkers or surrogate end points), all drugs exhibit multiple effects determined by their unique chemical structures. There are important differences in clinical benefits and risks within a drug class and one can be led astray by too great a reliance on surrogate end points [8–10]. DeMets and Califf [9] have reviewed the dramatic failure of the surrogate endpoint of suppression of premature ventricular contractions as a predictor of survival in the Cardiac Arrhythmia Suppression Trial (CAST). They elegantly describe the limits to the validity of other surrogate end points such as blood pressure and LDL cholesterol levels based upon the results of various of recent large randomized controlled clinical trials including the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). They also note that the product recall of cerivastatin occurred within a context of a known risk of rhabdomyolysis in the absence of quantification of clinical benefit.

We should strongly reconsider the blanket use of the concept of therapeutic class as a simplifying assumption by formulary committees. Perhaps greater consideration should be given to drugs with end point outcome data and/or extensive drug experience. Certainly, that was the recent recommendation from Oregon Health and Science University’s Evidence-Based Practice Center in their review of HMGs for Oregon Medicaid [11]. Formulary committees should also require stronger information regarding effectiveness and/or safety from new entrants into an established class, especially if the class has been available for a substantial length of time.

There has been much concern among payers and managed care organizations that “me-too” drugs are not valuable—because in their opinion they neither provide substantial efficacy advantages as measured by biomarkers or surrogate end points, nor do they provide substantial decreases in drug acquisition costs. This view not only discounts the value that new entrants may bring in terms of convenience and adherence as a result of new dosing regimens or formulations, but also reinforces the current dynamics of the marketplace for pharmaceutical research and development. A policy of preference for drugs with proven outcomes and established tolerability would be a powerful incentive for manufacturers to develop and provide end point outcomes data as part of the launching a third or fourth entrant in an established drug class. While such a preference would neither be desirable or feasible with respect to the launch of the first entrant in a new class, a general preference for drugs with proven outcomes would also serve as a powerful incentive for manufacturers to expeditiously complete endpoint clinical trials—lest that subsequent class entrants supply end point data, reaping the preference benefit. If our recent experience means anything, we need much more data from end point clinical trials for providers to have the information necessary to truly practice evidence-based medicine. Shouldn’t it be worth it?—Marc L. Berger, M.D., Vice President, USHH Outcomes Research & Management, Merck & Co., Inc.

References