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To the Editor. -- The recent editorial by Dr Archer [n1] is a useful addition to the literature exploring the nature and significance of official Food and Drug Administration (FDA) drug labeling and the role of such information in drug selection and use by physicians. The editorial correctly notes that the FDA cannot approve or disapprove of how a physician uses lawfully marketed drugs. The FDA can and does, however, approve indications for a drug's use and approves what a drug manufacturer may say in labeling, advertising, or publications intended to acquaint physicians with a drug's properties and uses. Although FDA officials [n2,n3] have over the years sought to clarify the status and role of approved drug labeling, we felt that a wider audience needed to have an authoritative policy statement on this issue. We chose the FDA Drug Bulletin, [n4] as Archer notes, as the most appropriate vehicle since it is sent to more than 1 million health professionals.

I believe it is helpful for the readers of JAMA to be reminded by Archer that the FDA does not approve or disapprove of how physicians use drugs. The agency's function in this area is, rather, to make certain that drug information provided to physicians by manufacturers conforms with the scientific data presented to the agency, including the results of controlled clinical trials, on which drug approval is based.

As I sought to clarify in an article [n5] on this issue in 1983, unlabeled uses range from unstudied to carefully investigated -- some salutary, others hazardous, some occurring very infrequently, others so common and so widespread as to constitute usual medical practice. The use of a drug for an unlabeled indication may be anything from appropriate to very unsound, even hazardous, medical practice. The latter occurs when a drug is found either ineffective or unsafe for a particular indication -- for example, the use of digitalis or drugs with thyroid hormone activity for weight control. In such cases, the official labeling may include a prominently displayed "box warning" advising physicians that such use of the drug

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is hazardous and in effect "disapproved." Such warnings are relatively rare and should be a deterrent to inappropriate prescribing.

Soffer [n6] examines the unlabeled use issue with respect to edetate disodium (EDTA), a drug widely promoted by its proponents in "chelation therapy" for cardiac and peripheral vascular disease. He states that such use cannot be recommended because there are no data from controlled trials that demonstrate efficacy and there is great potential danger in such treatment. In fact, he states that physicians who recommend such use are abusing a precious freedom, the flexibility to prescribe for unlabeled indications. Edetate disodium is officially labeled for the emergency treatment of hypercalcemia and for the control of ventricular arrhythmia associated with digitalis toxicity. It is not labeled, and indeed has never been adequately studied, for the treatment of atherosclerosis. While the promoted but unlabeled use is not referred to in the "Indications" or "Warning" section of the official labeling, under "Contraindications" the labeling states: "It is not indicated for the treatment of generalized arteriosclerosis associated with advancing age."

Thus, while physicians are not prevented from using edetate disodium to treat patients for atherosclerosis simply because that indication is not included in the FDA-approved labeling, the labeling does warn against it. We believe that the absence of the atherosclerosis indication and the presence of the contraindication of this use in the FDA official labeling serve as a very important alert to the physician. Thus, as Archer correctly points out, physicians are not legally bound to abide by FDA official drug labeling, nor do the dictates of sound medical practice require that they invariably do so. But, we would emphasize, it behooves them to be familiar with it.

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- [n2.] Crout JR: In praise of the lowly package insert. Food Drug Cosmetic Law J 1974; 29. 139-145.
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In Reply. -- I appreciate Dr Nightingale's letter and agree with everything he has stated. The letter does much to clarify and expand on what I said in my editorial. Although I was thinking in a somewhat different context about FDA disapproval of uses of drugs, Dr Nightingale's explanation of how the agency does sometimes validly express disapproval of some uses of some drugs should prove valuable to readers. As noted in the editorial, however, on some occasions labeling has, in a sense, expressed "disapproval" of valid uses of drugs as I specified. JOHN ARCHER, MD

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