

editorials

The FDA Does Not Approve Uses of Drugs

As a reviewer of medical manuscripts and reader of published articles, I find it frustrating to continue to find reference to "Food and Drug Administration (FDA)-approved uses of drugs"-or worse, allegations that certain uses are "not approved." For nearly two decades, through published articles, speeches, and personal communications, I have cautioned the medical profession against such diction. Perhaps the most definitive article was "Instrument or Impediment? The Regulatory Monograph in Medical Communications." The FDA cannot approve or disapprove of how a legally marketed drug is used by a physician in his practice. The agency approves of what the manufacturer may recommend about uses in its labeling (package insert) and advertising.

Failure to recognize this distinction can have various harmful results. Many valid uses of drugs become recognized long before they are included in manufacturers' literature--provided they ever are. Such uses may range from the unstudied (but reasonable) to the thoroughly investigated. Yet, references to

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“approved uses” may lead physicians into the mistaken notion that they are somehow prohibited from medically sound prescribing merely because a manufacturer and the FDA, for whatever **reason**, have not concluded a transaction between themselves to include a use in the labeling.

A third-party provider may refuse to furnish or Pay for a drug based on the absence of some recommendation in the manufacturer’s FDA-approved literature. If that is the only reason for refusal, it is a deplorable administrative mistake. The FDA has no legal authority to impose **such** action.

If a malpractice suit should arise from real or alleged injury by a drug, the plaintiff’s lawyer would probably ‘attempt to strengthen his case **if** he could point to lack of recommendation in the manufacturer’s literature for the use involved. Injustice might result if the defense failed to point out that the FDA does not regulate the practice of medicine. The labeling might be given some consideration in how well it *reflects* proper practice, but it should not be allowed to establish what is proper. Other medical licitarrurc or expert testimony can quite validly support correct use of a drug.

The fact that, based on adequate clinical trials, **the** FDA often approves additions to labeling recommendations for uses **that have** been employed for years gives mute testimony that the uses were proper all along. Some examples among many are worth repeating’: propranolol for angina pectoris and hypertension, metronidazole for amebiasis, amantadine for parkinsonism, diazepam **for** status epilepticus, imipramine for childhood enuresis, **colestyminine resin** for hyperlipidemia, lidocaine for arrhythmias. Thus, physicians, not the FDA, still determine how drugs *are* used in the practice of medicine.

For **anyone** who might continue to consider package inserts as dogma, the preceding list involves *some* remarkable incongruities. Long before propranolol was labeled for angina pectoris, many cardiologists considered it a form of malpractice to perform a coronary bypass operation unless a patient had had a therapeutic trial with the drug.’

For years after injectable diazepam was recognized as the drug of choice for status epilepticus, its labeling bore warnings *against* its use in patients with epilepsy. After that absurdity was corrected regarding a largely pediatric disorder, the labeling long continued to advise that ‘The safety and efficacy of [the drug] in children under age 12 have not been established.’ (!)

For about a decade after imipramine was **used successfully** for childhood enuresis, the labeling contained warnings against giving the drug to children. Before labeling for amantadine disclosed that the drug could be useful in treatment of **early A**, influenza (as contrasted with mere ‘prophylaxis), it actually *denied*, contrary to fact, that such evidence existed. Almost amusing,’ for years after colestyramine resin was used successfully for hyperlipidemia, manufacturers listed this property of the drug as an “adverse reaction” or “side effect.”

Some other valid uses of marketed drugs may never reach the status of being an addition to the existing labeling. A manufacturer may **never see any financial incentive for pursuing the approval** to advertise a drug for an uncommon need.

Another negative motive could be even **more persuasive**. As

an example, certain urinary tract infections **may be** cured by a single dose of an **appropriate** drug.’ If a manufacturer’s approved labeling recommended, say, a ten-day regimen, that manufacturer might not choose to supplicate the government for the privilege of reducing sales.

Fortunately, the myth about the authoritarian scapus of the package **insert is disappearing**. An honorable and welcomed statement by the FDA’ has confirmed what I have said for two decades about “approved uses” of **drugs: there is no such thing**. The FDA statement even endorsed the same alternate and correct phrasing that I coined: An ****unapproved use**” should not connote a disapproved use, but merely an “unlabeled use.” Uses *in* the labeling are merely that: “labeled uses.”

The House of Delegates of the American Medical Association, at its 1982 Interim Meeting, adopted a **report** that quoted in full the FDA statement on **this** subject. The report called for the publisher of the *Physician’s Desk Reference* (PDR) (Medical Economics Company, Oradell, NJ) to include this statement in future editions. Accordingly, in the 1983 and 1984 editions of the *PDR*, a summary of the FDA statement regarding the use of approved drugs for purposes not in the labeling appears in the **FOREWORD**.

Yet, habit is tenacious. Every edition of the *AMA Drug Evaluations* (American Medical Association, Chicago), beginning in 1971, has contained a discussion noting that the FDA has no authority to approve (or disapprove) how a physician **may use** a marketed drug in his practice. Ironically, however, the fifth edition’ organizes its discussion **of** at least one drug **in terms of “approved”** and “unapproved uses.” (That will be avoided in future editions--John C. Ballin, PhD, oral communication, 1934.)

Perhaps the *year* 1984 will see one reversal of George **Orwell’s prediction**.’ I have often read well-meaning statements that something was the “drug of choice” **or** “well established” or “fully recognized” **for** treatment of a disease-combined with the caveat that **such use was “not approved.”** **Such reasoning is Orwellian doublethink**: the process of considering two opposite concepts at the **same** time and believing both.

The doublethink under discussion resulted in part from my own **naivete 22 years ago**, when I contributed **some** unfortunate language to a federal stature. That, however, is another matter: I apologized *to* the world as best I could **in a previous** publication.’

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1. Archer J: Instrument or impediment? The regulatory monograph in medical communications. *JAMA* 1972;220:1474-1477.
2. Archer JD: A guide into chaos: Resist it. *JAMA* 1974;227:1397-1398.
3. ~~Lesagna~~ Wardell WM: The FDA, politics, and the public. *JAMA* 1975;232:141-142.
4. Treatment of urinary tract infections. *Med L/r Drugs Ther* 1981;23:69-72.
5. Use of **approved** drugs for unlabeled indications. *FDA Drug Bull* 1982;12:4-5.
6. Archer J: Eternal vigilance-the price of liberty. *JAMA* 1972;222:1553-1555.
7. *AMA Oivirion of Drugs: AMA Drug Evaluations*, cd 5. Chicago, American Medical Association. 1983, pp. 1738-1739.
8. Orwell G: 1984. New York, Harcourt Brace Jovrnrvich Inc. 1946.
9. Archer JD: The confession of an erstwhile bureaucrat. *JAMA* 1978;239:1608.