European Journal of Anaesthesiology 1997, **14**, 231–235

EDITORIAL

'Off-label' use of prescription drugs: Legal, clinical and policy considerations

In this issue of the *European Journal of Anaesthesiology*, Foster and Williams [1], who practise in the United Kingdom, report intra-operative bradycardia immediately following intravenous (i.v.) administration of ketorolac to two healthy 7-year-old girls during surgical insertion of grommets and adenoidectomy. In the United States, Buck [2] published a retrospective review of the use of i.v. ketorolac in 110 patients, almost all of whom were under 16 years of age. Notwithstanding its clinical use in a paediatric population, ketorolac has *not* been approved for i.v. administration to children in either country. In the United States, the current package insert, with wording mandated by the Food and Drug Administration (FDA), states: 'Safety and efficacy [of ketorolac] in children (less than 16 years of age) have not been established. Therefore, use of [ketorolac] in children is not recommended.'

Administration or prescription of medications for purposes or by routes other than those approved by the FDA is termed 'off-label use'. Anaesthetic practice furnishes numerous examples of off-label use resulting from perceptive, innovative basic and clinical research. The transition from basic science observations to clinical application is well illustrated by our current use of opioids. Morphine's ability to block nociceptive impulses at a spinal cord level was demonstrated in the rat two decades ago [3,4]. Just a few years later, opioids were administered to humans by the subarachnoid [5–7] and epidural [8,5] routes. Yet, the FDA did not approve these techniques of morphine administration for treating *acute* pain until September 18, 1984. Approval of epidural and subarachnoid morphine to treat *chronic intractable* pain was not forthcoming until July 19, 1990 (Elkins-Sinn Pharmaceuticals, personal communication). Subarachnoid and epidural administration of fentanyl for surgical and post-operative analgesia is an accepted modality in today's anaesthetic practice [9] although these routes have never been approved by the FDA (Janssen Pharmaceuticals, personal communication).

Intravenous lignocaine administered to treat certain ventricular arrhythmias was approved by the FDA on October 6, 1969 (Astra Pharmaceuticals, personal communication). Yet, my colleagues and I were taught this use of lignocaine during our training as registrars which began more than 8 years prior to FDA approval.

In view of widespread off-label use of prescription drugs, let us consider the legal and ethical status of this medical practice, which I will do from the perspective of United States jurisprudence. I will first review the historic and statutory basis under which the FDA operates; this will clarify the legal status of off-label use. I will then briefly examine the policy considerations which not only support, but actually mandate, off-label use. Finally, I will focus on what the FDA can do when off-label use poses a threat to the public welfare.

The Federal Food, Drug and Cosmetic Act of 1938 (United States Code, Title 21, 'the Act') mandates that drugs introduced into interstate commerce be safe and effective. A public outcry resulting from the Elixir of Sulfanilamide tragedy of 1937 was a major precipitating factor for its passage. The original legislation addressed only safety – once a pharmaceutical company submitted data relating to safety, the drug could be marketed *unless* the FDA objected. Following the thalidomide disaster, the Act was amended in 1962 in a way that 'fundamentally restructured the way in which FDA regulated new medicines ... [requiring] individual premarket approval of the safety and effectiveness of every new drug' [10]. In other words,

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https://doi.org/10.1046/j.1365-2346.1997.00112.x Published online by Cambridge University Press

drugs *could not* be marketed or advertised until the FDA *affirmatively agreed* that they were both safe and effective.

With this brief history in mind, let us examine the statutory basis under which the FDA exerts its regulatory function. Fundamental to an understanding of the Act is that it governs the pharmaceutical industry, *not* the practice of medicine. The Act provides that drugs shipped in interstate commerce must have prior approval in the form of a New Drug Application (NDA). Section 505 of the Act mandates that:

> No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application . . . is effective with respect to such drug.

The Act defines 'new drugs' in section 201 (p) as:

> Any drug . . . the composition of which is such that such drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof . . .

An approved NDA requires that the drug be accurately labelled and not misbranded. Section 201 (m) defines labelling as:

> all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.

Finally, section 201 (n) of the Act states that an article may be misbranded "because the labeling or advertising is misleading'.

In summary, a manufacturer can advertise or otherwise promote medications *only* for indications approved by the FDA. Furthermore, all advertising must be based on data that were approved by the FDA for inclusion in the labelling of the drug. Thus, the Act requires both proved safety and efficacy *and* accurate labelling and advertising of the vast majority of drugs used by our specialty. Note that morphine and diethyl ether, antedating the 1938 Act, are exempted, unless promoted for new indications or routes.

In order to secure approval for a new drug's labelling and advertising, 'substantial evidence' of safety and efficacy must be demonstrated through accurate and meticulous clinical research. Section 505 (d) defines 'substantial evidence' as:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have . .

During the time that an unapproved drug is being evaluated in humans, an approved Investigational New Drug (IND) application allows the medication to be shipped in interstate commerce for the specific circumstances defined by the clinical studies. The data from such investigations are evaluated by the FDA; if they demonstrate safety and efficacy, the NDA is approved after which the drug may be marketed, advertised and promoted.

Approval of an NDA is not immutable. The pharmaceutical company is held to the *same standards for retaining* an NDA as was required to obtain it in the first place. Post-approval surveillance is mandated, and section 505 (e) allows the FDA to revoke its approval if:

> (1) clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available . . . until after such application was approved, or tests by new methods . . . [demonstrate that the drug is not] safe for use under the conditions of use upon the basis of which the application was approved; or (3) . . . that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use . . . suggested in the labeling thereof.

In summary, the Food, Drug and Cosmetic Act protects patients by mandating that the manufacturers prove safety and efficacy *before* any drug may be introduced into interstate commerce and advertised. However, at the same time the law *does not* regulate the practice of medicine – once the drug enters the stream of interstate commerce, physicians are free to prescribe an approved drug for any purpose they deem appropriate. While a *pharmaceutical manufacturer* may not promote or advertise any use not approved by the FDA, the *physician* may use the medication for objectives outside those approved by the FDA, or to patient groups never studied as part of the IND process. Such off-label use is an accepted

https://doi.org/10.1046/j.1365-2346.1997.00112.x Published online by Cambridge University Press

part of sound medical practice. The American Medical Association's Council on Drugs has taken the position 'that it is within the physician's sole discretion to choose and prescribe a drug for his [sic] own patient' (hearing before the House of Representatives Subcommittee on Government Operations, 1971).

The statutory basis of off-label use is clearly supported by regulations; 37 Federal Register 16503 (August 15, 1972) states:

> If an approved new drug is shipped in interstate commerce with the approved package insert, and neither the shipper nor the recipient intends that it be used for an unapproved purpose, the requirements of ... the Act are satisfied. Once the new drug is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration.

Federal case law also supports off-label use; in *United States* vs. *Evers* [11], a Federal District court supported the claim that

> [L]icensed physicians have a right and a duty to use drugs in prescribing for their patients' usage in accordance with their best judgment as physicians ... Congress did not intend the Food and Drug Administration to interfere with medical practice as between the physician and the patient ... It is well recognized that a package insert may not contain the most up to date information about a drug and the physician must be free to use the drug for an indication not in the package insert when such usage is part of the practice of medicine and for the benefit of the patient ... [T]he physician can ascertain from medical literature and from medical meetings new and interesting proposed uses for drugs marketed under package inserts not including the proposed usages.

While physicians may prescribe medications for off-label use, the manufacturer may *not* market, promote or advertise them for anything other than approved indications. On August 1, 1996, the FDA's Division of Drug Marketing, Advertising and Communications issued a *Warning Letter* to a pharmaceutical company for promoting an antidepressant, approved only for treating 'major depressive disorders', for off-label therapy of premenstrual dysphoric disorders, postpartum disorders and obsessive-compulsive disorders. Warning letters are the principal means of giving industry prior notice of violations requiring prompt voluntary correction. Failure to comply with a Warning Letter may result in enforcement including seizure or withdrawal of the NDA, without further notice.

Strong policy arguments support off-label use. Of importance is that acquisition of information concerning drug action does not stop at the time of FDA approval. Invaluable information, not available during the limited phase of clinical investigation, is gleaned only through post-marketing surveillance. Newly approved drugs are administered to patients with a variety of diseases, and who may be taking a panoply of other medications. Adverse effects occurring with extremely low frequency, unlikely to have been noted during the phase of clinical investigation, may only become manifest after approval. Often, clinical studies designed to gather data to support the NDA do not include members of every group who will eventually receive the medication. Indeed, exclusion of large portions of the population have been routine until recently. Three quarters of prescription drugs marketed in the United States are not approved for use in children [12]. Fentanyl is used in children 'despite the knowledge that [its pharmacokinetics are] significantly altered by age-specific activity of enzymatic metabolism and neonatal hepatic blood flow' [13]. Exclusion on the basis of gender has been common until recently. Levine [14] states:

> It is a custom in the United States to develop new drugs based upon testing for their safety and efficacy almost exclusively in adults who are incapable of becoming pregnant. As a consequence, administration of drugs approved for use in non-pregnant adults to pregnant women and children is conducted according to usual standards of medical practice without rigorous testing of safety and/or efficacy.

As a result of these factors, newly approved drugs entering the stage of post-marketing surveillance are often *guaranteed to undergo off-label use*. This applies not only to women of 'child-bearing potential' and children, but is also true, to some extent, of ethnic minority groups. In addition, off-label use will be inevitable, even if the drug is administered for an *approved* purpose, if a specific patient's medical status diverges from that of the clinical subjects evaluated in support of the NDA.

https://doi.org/10.1046/j.1365-2346.1997.00112.x Published online by Cambridge University Press

Significant ethical problems might arise if drugs approved for one specific use were mandated to undergo separate randomized controlled trials and be approved for *every new use*. This is especially true if the drug had already demonstrated safety and efficacy for the proposed off-label use. The US AIDS Clinical Trials Group insisted on a *placebo* controlled study on the ability of trimethoprim-sulfamethoxazole to prevent superinfection with Pneumocystis carinii pneumonia (PCP) [15]. These requirements were imposed even though community doctors had used PCP prophylaxis successfully for several years in patients with AIDS and in the face of the knowledge that trimethoprim-sulfamethoxazole had been used successfully for 20 years in patients whose immune systems had been compromised by carcinoma.

Our own specialty has derived great benefit from off-label use. New applications for approved drugs, or even for their 'adverse effects', often result from experience gained only after approval. For example, the sole indication for halothane (1996 package insert) is 'the induction and maintenance of general anesthesia'. Furthermore, 'the patient should be closely observed for signs of overdosage, i.e. depression of blood pressure'. Deliberate hypotension [16] produced by inhalation of halothane is a clear example of off-label use. Intrathecal or epidural administration of morphine for pain-relief and i.v. lignocaine to treat ventricular arrhythmias have already been cited as examples of what once were off-label use. Fentanyl *remains unapproved* for administration by the subarachnoid or epidural route, while sufentanyl is approved only for epidural administration during labour and delivery (Janssen Pharmaceuticals, personal communication).

Are there reasons that a manufacturer might not seek approval for new indications or modes of administration? For one thing, the pharmaceutical industry may not be prepared to sustain a major expense simply to allow advertising and promotion of an already approved drug. This is especially true if the market for a new use is not large, or if the knowledge of such new use has already been adequately promulgated. Furthermore, legal liability may be minimized if an NDA is not sought for new indications; if there is no advertising or promotion, a manufacturer could claim that it had never encouraged or supported the new use.

Finally, what if off-label use proves to be harmful? I have already noted the requirement for post-approval surveillance and the FDA's statutory authorization to withdraw approval of drugs which prove to be unsafe or ineffective after the NDA has been granted. If data demonstrate that an approved drug is being used frequently in a way that threatens the public health, the FDA can issue a warning, issue a contraindication, or recall the drug by rescinding the NDA. In such an eventuality, the FDA will attempt to work with the sponsor rather than acting unilaterally. As an example germane to this editorial, ketorolac's original approval was as a short-term analgesic. It was then approved for brief oral use (5 days) after surgery. However, as numerous physicians began to use it orally for long periods, concomitant development of duodenal ulcers became obvious. This was felt to be 'unacceptable harm' both in Europe and the United States. Some European nations have removed the drug, while in the United States the FDA is working with the manufacturer to solve the problem (C. Wright [FDA], personal communication).

In summary, off-label drug use allows a flexible public policy. It represents a compromise between a bureaucratic rigidity which would demand that every possible eventuality be subject to clinical testing and a laissez-faire approach which would allow new, untested and potent medications to enter the market with no proof of safety and efficacy. The FDA regulates only the industry; while the company may promote its products only for approved use, dissemination of new knowledge through peer reviewed publication is not only permitted but encouraged [17].

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Acknowledgment

I wish to express my appreciation to Curtis Wright, MD, Center for Drug Evaluation and Research, United States Food and Drug Administration, for his helpful thoughts concerning his long experience in the drug evaluation and approval process.

References

1 Foster PN, Williams JG. Bradycardia following intravenous ketorolac in children. *Eur J Anaesthesiol* 1997; **14**: 307–309.

2 Buck ML. Clinical experience with ketorolac in children. *Ann Pharmacother* 1994; **28**: 1009–1013.

3 Yaksh TL, Rudy, TA. Analgesia mediated by a direct spinal action of narcotics. *Science* 1976; **192**: 1357–1358.

4 Yaksh TL, Rudy, TA. Studies on the direct spatial action of narcotics in the production of analgesia in the rat. *J Pharmacol Exp Ther* 1977; **202**: 411–428.

5 Cousins MJ, Mather LE, Glynn CJ, Wilson PR, Graham JR. Selective spinal analgesia. *Lancet* 1979; **1**: 1141–1142.

6 Samii K, Feret J, Harari A, Viars P. Selective spinal analgesia. *Lancet* 1979; **1**: 1142.

7 Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally appplied morphine in man. *Anesthesiology* 1979; **50**: 149–151.

8 Behar M, Olshwang D, Magora F, Davidson JT. Epidural morphine in treatment of pain. *Lancet* 1979; **1**: 527–592.

9 Chaney MA, Smith TC. Effects on respiratory control of anaesthetic agents and adjuvants. In: Healy TEJ, Cohen PJ, eds. *Wylie and Churchill-Davidson's A Practice of Anaesthesia*, 6th edn. Edward Arnold, London, 1995.

10 Hutt PB, Merrill RA. *Food and Drug Law, Cases and Materials*, 2nd edn. Foundation Press, Westbury, New York, 1991.

11 *United States v. Evers*, 453 F. Supp. 1141, 1143, 1149 (M.D. Ala. 1978).

12 Committee on Drugs. Unapproved uses of approved drugs: the physician, the package insert, and the Food and Drug Administration: Subject Review. *Pediatrics* 1996; **98**: 143–145.

13 Coté CJ, Kauffman RE, Troendle GJ, Lambert GH. Is the 'therapeutic orphan' about to be adopted? *Pediatrics* 1996; **98**: 118–123.

14 Levine RJ. Appropriate guidelines for the selection of human subjects for participation in biomedical and behavioral research. In: The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, DHEW Publications (OS) 78-003. Washington, DC: Department of Health, Education, and Welfare, 1978: Appendix 1.

15 Schüklenk U, Hogan C. Patient access to experimental drugs and AIDS clinical designs: ethical issues. *Camb Q Healthc Ethics* 1996; **5**: 400–409.

16 Thompson GE, Miller RD, Stevens WC, Murray WR. Hypotensive anesthesia for total hip arthroplasty: a study of blood loss and organ function (brain, heart, liver, and kidney). *Anesthesiology* 1978; **48**: 91–96.

17 Winker MA. The FDA's decisions regarding new indications for approved drugs. Where's the evidence? *J Amer Med Assoc* 1996; **276**: 1342–1343.

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