Special Article

The introduction of new drugs into anaesthetic practice: a perspective in pharmaceutical development and regulation

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This article reviews the process by which new drugs are introduced into anaesthetic practice with particular emphasis on pharmaceutical development and government regulation. After a brief overview of the drug development process, new trends in drug development are discussed including implementation of pharmacokinetic, pharmacodynamic and toxicokinetic studies in both preclinical and human phases of drug evaluation. A synopsis of the drug regulatory process is provided and, in particular, the problem of unapproved drug use in anaesthesia is discussed. Ethical issues regarding physician-industry interactions are highlighted by examples of conflict of interest in anaesthesia. The processes of drug development and regulation require much effort and cooperation between clinicians, pharmaceutical manufacturers and government regulators to achieve a common goal; the development and utilization of safe and effective drugs. A fundamental understanding of these processes may further facilitate optimal drug utilization and the active involvement of anaesthetists in the drug development process.

Cet article passe en revue les mécanismes qui précèdent l'introduction de nouveaux produits pharmaceutiques en anesthésie, et plus particulièrement, sur leur développement et la réglementation gouvernementale qui s'y applique. Après un bref survol des mécanismes engagés dan l'élaboration d'un produit, les nouvelles directives qui régissent le développement des nouveaux agents sont discutées dont l'implémentation d'études pharmacocinétiques, pharmacodynamiques et toxicocinétiques pendant les phases précliniques et humaines de l'évaluation. Un résumé des mécanismes de la réglementation est présenté et, en particulier, les problèmes entraînés par l'utilisation de drogues non approuvées pour l'anesthésie. Les problèmes d'éthique propre aux interelations médecin-industrie sont aussi discutés avec des exemples de conflits d'intérêt s'appliquant à l'anesthésie. Les processus de développement et de réglementation des drogues requièrent beaucoup d'efforts et de collaboration entre cliniciens, manufacturiers et intermédiaires gouvernementaux pour atteindre un objectif commun: le développement et l'utilisation de produits efficaces et ne présentant que peu de risques. Une compréhension de ces processus peut favoriser l'utilisation optimale des drogues et la participation active des anesthésistes à leur développement.

Key words
Drug regulation, Drug industry, Anaesthetics, Clinical pharmacology.

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The ongoing search for safer, more effective drugs with minimal adverse effects is one way in which, together with the pharmaceutical industry, anaesthetists strive to improve patient care.[1] The involvement of anaesthetists in drug research and development originates, in part, from a longstanding association with the field of clinical pharmacology.[2,3] As well, continued research with already marketed drugs is important for providing ongoing safety surveillance[4] and for finding new applications for "old" drugs.[5] The importance of governmental drug regulation to the practice of medicine has been emphasized over the past decade by issues surrounding the acquired immune deficiency syndrome (AIDS) epidemic.[6] More recently, issues of drug safety regulation[7] and government approved indications for drug use[8] have received attention

in the anaesthesia literature. Such issues have highlighted the need for understanding the processes of drug development and regulation in anaesthesia practice. Thus, the purpose of this paper is to review the process by which new drugs are introduced into anaesthetic practice with particular emphasis on pharmaceutical development and government regulation.

New drug development

"It is estimated that for each useful and marketable drug, over 10,000 new chemical entities are discovered and discarded."[9] On average, ten to twelve years elapse from the onset of discovery to marketing approval of a new drug and this process can cost more than $200 million.[4] Figure 1 illustrates an overview of the drug development process.

Drug sourcing provides the drug developer with new substances possessing desired pharmacological characteristics. New drug sources may include naturally occurring compounds (e.g., d-tubocurarine from the Amazonian vine Chondodendron tomentosum),[10] synthetic compounds (e.g., alfentanil synthesized in 1976 by Janssen Pharmaceutical Ltd.)[11] or the licensing of partially developed compounds from other institutions.

Drug screening evaluates drug profiles in order to identify compounds with appropriate pharmacological activity. Such testing is performed using molecular (e.g., receptor/enzyme studies), cellular (e.g., receptor activity and vascular tone) and physiological (e.g., CNS, cardiorespiratory, renal and endocrine) models to examine variables specific to each drug and its intended action.[12] These screens are performed with *in vitro* (molecular and cellular) or *in vivo* (two to four animal species) studies.[12] For example, a study which evaluates the binding of synthetic opioids to μ opiate receptors is an *in vitro* drug screen[13] while the rat tail withdrawal test (withdrawal reaction time from a thermal stimulus) is an *in vivo* drug screen used to measure the analgesic effect of opioids.[11] Patent development generally begins upon identification of a lead compound and is completed by the time clinical research begins.[9]

The preclinical workup is necessary in order to obtain regulatory approval for testing in humans. From this preclinical evaluation, chemical, biochemical and animal data submitted in the form of an Investigational New Drug Application (IND) include studies of dosage formulation, metabolism, pharmacokinetics/dynamics and most importantly preclinical toxicology (safety testing).[9] Safety testing includes the assessment of acute, subacute and chronic toxicities.[12] Acute toxicity testing includes determination of the lethal dose or LD_{50} in animals. Subacute testing generally evaluates three drug doses in two species with a length of exposure proportional to the expected duration of clinical use.[12] Finally, chronic toxicity testing often takes one to two years and is conducted concurrently with clinical trials.[12] Toxicity is measured in the live animal by observing clinical chemistry, haematology and physiologic signs and after autopsy by examining histology and electron microscopy of specific organs (e.g., CNS, kidney, liver).[12] Other aspects of safety testing include reproductive effects (e.g., teratogenicity) and both carcinogenic and mutagenic potential.[12]

Once the IND has been approved, the drug may then enter the stage of clinical development. This stage involves the first three phases of clinical trials (Table I).[14] Drugs are first administered to humans during phase I trials which are conducted in healthy volunteers in order to study clinical dosage ranges, predictable toxicities and various pharmacokinetic/dynamic measures.[14] In phase II, the drug is tested in patients with the target disease in order to evaluate safety and efficacy and to detect a broader range of toxicities.[12] Although drugs in anaesthetic practice may not have a "target disease" *per se*, they may be studied in special populations (e.g., patients with renal or hepatic disease).[15] Phase III studies are pre-

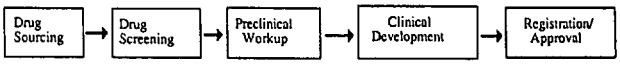

FIGURE 1 An overview of the drug development process (Adapted from: *Knoop SJ and Worden DE.* The Pharmaceutical Drug Development Process: An Overview. Drug Inf J 22: 259, 1988.)

TABLE I The four phases of clinical drug trials. (Adapted from Clinical Pharmacology, Laurence DR and Bennett PN, 6th ed, Churchill Livingstone, 1987, p 46)

Phase 1
Clinical Pharmacology (~20–50 subjects)
– healthy volunteers/patients
– pharmacokinetic/dynamic studies
Phase 2
Clinical Investigation (~50–300 subjects)
– carefully controlled dose ranging studies in patients to assess safety and efficacy (S & E)
Phase 3
Formal Therapeutic Trials (~250–1000)
– randomized and controlled
– comparison with other drugs (S & E)
Phase 4
Post-Marketing (2000–10,000)
– Further formal therapeutic trials
– S & E surveillance

marketing trials performed on a large population to examine safety and efficacy in comparison with comparable marketed drugs.[14] Drug registration and marketing approval requires the submission of safety and efficacy data from clinical trials in the form of a New Drug Application (NDA).[12] This application is reviewed by the regulatory agency which upon ascertainment of acceptable safety and efficacy may grant marketing approval. Subsequent to approval, postregistration activity such as phase IV postmarketing studies provide safety surveillance on an even larger scale than in phase III trials.[12] These postmarketing studies, although conducted by the pharmaceutical firm, sometimes receive input and analysis by independent clinicians as observed with the Diprivan Clinical Experience Program.[16] Given the practical limitations of premarketing clinical trials, postmarketing surveillance is a vital way in which physicians contribute to drug safety regulation so as to ensure that newly marketed drugs are being used appropriately.[4]

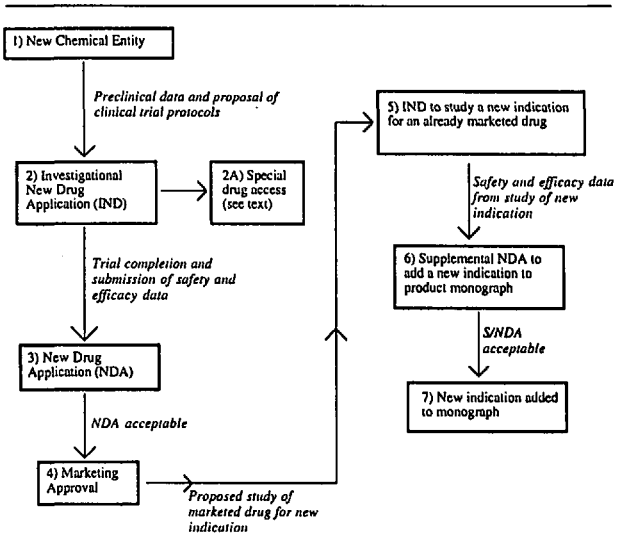

FIGURE 2 General overview of the drug regulatory process.

New trends in drug development

In 1991, a conference involving drug developers and regulators was held in the United States on "The Integration of Pharmacokinetic (PK), Pharmacodynamic (PD) and Toxicokinetic (TK) Principles in Rational Drug Development" from which a conference report was published in several pharmacology journals.[3] This report described strategies by which PK, PD and TK studies could be applied to both preclinical and clinical phases of drug development so as to develop new drugs more effectively and expediently. One strategy is to study the relationship between systemic drug concentrations and pharmacodynamic end points during preclinical animal studies. Such studies could correlate systemic drug concentrations with both pharmacologic and toxicologic drug effects and may help in developing appropriate dosing regimens for use in Phase I dose-response studies in humans. Another concept emphasized in this report is the importance of Phase I implementation of PK/PD studies in "the very first dose-tolerance studies in humans since this offers a unique (possibly one-time only) opportunity to evaluate drug concentration-acute toxic effect relationships of poorly tolerated doses which will be avoided in subsequent studies."[3]

The drug regulatory process

In 1938, sulphanilimide was marketed in a sweet-tasting formulation of the untested solvent diethylene glycol and resulted in 108 deaths.[17] In 1962, the administration of thalidomide to pregnant women produced the disfiguring results of fetal phocomelia and gave rise in the United States to the Kefauver-Harris drug regulation amendments.[4] These tragic historical milestones serve to highlight the importance of drug safety regulation.[17]

The Food and Drug Administration (FDA) in the United States and the Health Protection Branch (HPB) in Canada each fulfill the public mandate of regulating the development and marketing of pharmaceutical products.[18-20] These agencies are also responsible for medical devices regulation including that of anaesthesia equipment.[21,22] The legislation of drug and device regulation is covered by the Food, Drug and Cosmetic Act in the United States and the Food and Drugs Act in Canada.[18,20] An important difference between HPB and the FDA is that drug approval by HPB often occurs later than that by the FDA.[23] This difference can, to some degree, be explained by the fact that both countries have the same number of drugs to approve with resources which are roughly proportional to each country's population. Future HPB initiatives to increase the timeliness of drug approval in Canada include North American harmonization of drug regulation as initiated by recent joint drug reviews involving the collaboration of HPB and the FDA.[23]

Figure 2 illustrates an overview of the drug regulatory process. Before testing of any new chemical entity in humans, a pharmaceutical firm must first submit to the regulatory agency an Investigational New Drug Application (IND). As previously described, the IND includes data describing dosage formulation, metabolism, pharmacokinetics/dynamics and preclinical toxicology. As well, the IND must describe the proposed clinical trial protocols in order "to ensure that the properties and uses of a new drug are elucidated in a meaningful, scientific and ethical manner at minimal acceptable risk to those subjects."[20] Provided that the content of the IND is acceptable to the regulatory agency, the company/investi-

gator may then conduct the clinical trials as described. Data from phase I–III clinical trials which evaluate the safety and efficacy of a new drug are submitted in the New Drug Application (NDA). Review of the NDA, if found to be acceptable, will then result in marketing approval by the regulatory agency. Once the drug is approved, the company may then proceed with labeling, marketing and sale of the drug.[18]

In special circumstances where a physician or investigator submits that an investigational drug (as yet unmarketed) may have a favourable risk/benefit profile in an individual case (e.g., for last resort treatment of terminal AIDS or cancer patients), special administrative procedures exist for the regulatory agency to authorize release of an unmarketed drug by the manufacturer for this exceptional use (see Figure 2 item 2A).[6,24]

After receiving marketing approval, every drug is distributed with a package insert (or product monograph) which is published by the manufacturer and approved by the drug regulatory agency.[18] This document contains, in addition to basic pharmacology and dosage information, the indications, contraindications and patient populations for which the drug was approved.[18] Should any research or clinical experience suggest that a marketed drug has another useful indication, the manufacturer or an investigator (with the manufacturer's approval) may submit a new IND to propose further study of this marketed drug for the new indication. Data from these studies are submitted in the form of a supplemental NDA which if approved would result in the addition of the new indication on to the drug's package insert.[19]

Once marketed, the manufacturer of a drug is responsible for collecting data of adverse drug events through adverse reaction reporting systems and phase IV postmarketing trials and this information must be shared with the drug regulatory agency.[18,19] Severe adverse drug reactions may result in modifications to product labelling to include new contraindications/warnings and if necessary withdrawal of the drug from the market.[4] This aspect of drug regulation is illustrated by issues regarding succinylcholine, as recently described by Bevan,[25] in a most interesting interaction between anaesthetists, government drug regulators and the pharmaceutical industry. Incited by recent reports of intractable cardiac arrest in children given succinylcholine,[26] the pharmaceutical firm Burroughs Wellcome issued in October 1993 (in both Canada and the United States) public notification of the new contraindication of succinylcholine in chilren and adolescent patients for routine tracheal intubation. This decision met with considerable protest from the paediatric anaesthesia community[27] claiming that this contraindication was not justified by an extremely low incidence occurrence (possibly as low as one in 500,000 or 100,000,000 in the world)[28] in light of the drug's tremendous clinical value and a 40-yr track record. In response to these concerns the Canadian subsidiary of Burroughs Wellcome, with the approval of HPB, eliminated this contraindication in Canada.[25] In 1995, succinylcholine remains contraindicated in the United States for routine use in children and adolescents.[29] In reply to recent letters to the editor of *Anesthesiology*, the Pilot Drug Evaluation Staff of the FDA invited the authors of those letters to attend the next FDA Anesthetic and Life Support Drugs Advisory Committee (ALSAC) meeting to voice their concerns regarding this contraindication.[30] Whether this invitation results in any amendments to the succinylcholine product monograph in the United States remains to be seen.

TABLE II Examples of unlabeled drug use in anaesthesia

- Intrathecal fentanyl/sufentanil
- Intravenous ketorolac
- Midazolam by continuous infusion
- Oral midazolam
- Paediatric use of fentanyl, bupivacaine and propofol

Unapproved drug use in anaesthesia

A practicing physician may freely prescribe or administer any marketed drug within the realm of accepted medical practice. However, drug use which exceeds the approved recommendations does place the physician in a medicolegally tenuous position.[31] This medicolegal risk does not prevent a physician from using his or her best clinical judgement with the patient's best interest in mind.[32] In fact, in two medical malpractice cases in the United States, the court upheld the physicians' rights to prescribe marketed drugs for unapproved uses given that judicious clinical judgement was being exercised.[32]

There are a number of clinically accepted practices in anaesthesia which exceed the approved guidelines of the package insert (Table II).[8] Such unapproved drug uses often become the mainstay of clinical practice without being legally approved. The issue of unapproved uses of approved drugs raises concerns about drug safety regulation, manufacturer and medicolegal liability, and professional freedom for physicians.

From the industry's viewpoint, support for INDs and supplemental NDAs to add new indications to already marketed drugs would entail additional manpower and expense. Sponsorship of supplemental NDAs to add a seldom used indication – for example *iv* guanethidine block for reflex sympathetic dystrophy[33] – is unlikely to be in the manufacturer's interest. Submission of an independent investigator-sponsored IND for a new indication requires manufacturer approval in order for the regulatory agency to access and cross-reference previously

submitted preclinical data legally.[19] Thus, clinical data supporting a new indication does not translate into regulatory approval without industry involvement.

Drug regulatory bodies recognize that physicians may prescribe unapproved uses for marketed drugs within the realm of accepted medical practice.[31] However, without the presentation of formally conducted trials, these agencies can carry no official position on an indication for which they have received no data. One of the concerns of drug regulators is that without official labeling such as the package insert, public safety may be jeopardized without uniformly accepted guidelines regarding these unapproved indications.[31]

Clinicians, through research or clinical experience, often discover and develop new techniques which may entail unapproved drug use. Despite evidence suggesting that patients may benefit substantially from such unauthorized use, physicians may be reluctant to provide this treatment if, medicolegally, they "stand alone."[8] As expressed by White and Watcha, the regulatory process which has evolved in order to protect the public in this case can work against it.[8]

The issue of unapproved uses of marketed drugs is complex. Potential solutions suggested by Nightingale, the associate commissioner of the FDA include: (1) more frequent supplemental NDA submissions for new indications by pharmaceutical companies, (2) modified procedures by drug regulatory agencies to facilitate further the addition of new indications to the package insert and (3) modification of postmarketing/phase IV studies by industry to expedite the addition of new indications.[31] Some tangible efforts observed in this area include recent initiatives by the FDA to compile lists of, and evaluate frequently employed "off label drug uses" which are supported by scientific evidence[34] as well as new labeling regulations that encourage more extensive paediatric clinical drug trials.[35]

Physician interaction with the pharmaceutical industry

The association of physicians with the pharmaceutical industry has raised several ethical concerns. This is most notable in the areas of industry-sponsored research and pharmaceutical representative-physician interactions and these have received much attention in the medical literature.[36-41]

Issues such as excessive incentives to physicians from pharmaceutical representatives, advertising and commercially sponsored supplements in journals and industry biasing in continuing medical education have been discussed in the anaesthesia literature.[42-45] In particular, a recent editorial by Saidman, the editor-in-chief of *Anesthesiology*, discusses issues of conflict of interest which relate to the peer review and industry support of research in anaesthesia.[46] This editorial accompanied two articles describing the toxicity of compound A, an olefin formed by the reaction between soda lime or Baralyme and sevoflurane, a volatile anaesthetic under investigation by Abbott Laboratories in the United States.[47,48] The alleged conflict of interest lay in the fact that one of their senior authors was a paid consultant to Ohmeda, the manufacturer of desflurane a competitor to sevoflurane.[46] Saidman discussed the link between financial sources of conflict of interest and the potential for loss of scientific objectivity. Despite open disclosure of possible conflicts of interest regarding industry-sponsored research, this issue remains a concern.[46] In the end, he supports the decision to publish these reports with the merit of their scientific quality which the reviewing editors unanimously agreed was of principal importance.[46]

Although communication and cooperation between physicians and the pharmaceutical industry may lead to well-directed research, up-to-date medical education, and appropriate drug development and utilization, the possibility of conflict of interest is an area of concern which requires ongoing attention and scrutiny by all involved parties.

Principles and guidelines for the ethical association of physicians with the pharmaceutical industry have been put forth by organizations such as the Canadian and American Medical Associations and the American College of Physicians.[49-51] Such guidelines include (1) ethical and scientifically valid industry-sponsored research, (2) the involvement of institutionally based review boards in industry related research, (3) physician-organizer control of continuing medical education activities and (4) the maintenance of professional autonomy and commitment to the scientific method when interacting with the pharmaceutical industry.[49-51] The setting of these guidelines are examples of physician-directed initiatives to protect the responsibility for patient care from external conflicts of interest.

Conclusion

In the 31st Rovenstine lecture, Greene proclaimed that: "Any consideration of the broadening of our horizons in anaesthesia deserves inclusion of the radical changes in and the complexity of, the pharmacologic basis of modern operative anaesthesia."[52] The current diversity of pharmacological development and utilization contributes largely to our clinical capabilities in anaesthetic practice. Some future goals for anaesthesia's pharmacopoeia as suggested by Scheller in 1992 include: (1) inhalational anaesthetics with very low blood/gas solubility ratios that might replace nitrous oxide, (2) extremely short-acting non-depolarizing muscle relaxants that might replace succinylcholine, (3) very short-acting potent opioids without

such side effects as muscle rigidity, nausea, hypotension or pruritis and (4) future possible forms of gene therapy that might control for proteins such as β-endorphin or even hibernation factors.[53] The recent marketing of desflurane (in the United States) and mivacurium (in the United States and Canada), as partial fulfillment of these goals illustrates the success of drug development in anaesthesia.

In the 20th century, the pharmaceutical industry has made considerable contributions to the field of medicine as observed, for example, by the profound impact of antibiotics and cardiovascular drugs on morbidity and mortality in modern society.[9] This industry's function and viability requires complex interactions with government, and with the medical, scientific and business communities. As anaesthetists, we should be aware of those aspects of the industry which directly affect clinical practice such as drug development and regulation. A basic understanding of these issues will allow us to utilize anaesthetic drugs optimally as well as to participate actively in the drug development process.

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References

1 *Anonymous.* The testing of new drugs (Editorial). Br J Anaesth 1970; 42: 911.
2 *Jellet LB, Oh TE.* Anaesthesia and clinical pharmacology: related disciplines. Anaesth Intensive Care 1975; 3: 327–30.
3 *Peck CC, Barr WH, Benet LZ, et al.* Opportunities for integration of pharmacokinetics, pharmacodynamics, and toxicokinetics in rational drug development. Clin Pharmacol Ther 1992; 51: 465–73.
4 *Grasela TH, Watkins WD, Hug CC Jr, et al.* The role of pharmacoepidemiology research in postmarketing surveillance and anesthesia practice/critical care medicine. Anesth Analg 1993; 77: S44–50.
5 *Eisenach JC.* Aspirin, the miracle drug: spinally, too? Anesthesiology 1993; 79: 211–3.
6 *Kessler DA.* The regulation of investigational drugs. N Engl J Med 1989; 320: 281–8.
7 *Hull CJ.* The safety of new drugs (Editorial). Br J Anaesth 1989; 62: 587–9.
8 *White PF, Watcha MF.* The practice of anesthesiology and the package insert: decision-making regarding drug use in anesthesiology (Editorial). Anesth Analg 1993; 76: 928–30.
9 *Knoop SJ, Worden DE.* The pharmaceutical drug development process: an overview. Drug Information Journal 1988; 22: 259–68.
10 *Bevan DR, Donati F.* Muscle relaxants. *In*: Barash PG (Ed.). Clinical Anesthesia, 2nd ed., Philadelphia: JB Lippincot, 1992: 481–508.
11 *Cookson RF, Niemegeers CJE, Vanden Bussche G.* The development of alfentanil. Br J Anaesth 1983; 55: 147S–55S.
12 *Berkowitz BA, Katzung BG.* Basic and clinical evaluation of new drugs. *In*: Katzung BG (Ed.). Basic and Clinical Pharmacology, 6th ed. East Norwalk: Appleton and Lange, 1995: 60–70.
13 *Leysen JE, Gommeren W, Niemegeers CJE.* [^{3}H]-sufentanil, a superior ligand for μ-opiate receptors: binding properties and regional distribution in rat brain and spinal cord. Eur J Pharmacol 1983; 7: 209–25.
14 *Laurence DR, Bennett PN.* Clinical Pharmacology, 6th ed. New York: Churchill Livingstone, 1987: 46–65.
15 *Cook DR, Freeman JA, Lai AA, et al.* Pharmacokinetics of mivacurium in normal patients and in those with hepatic or renal failure. Br J Anaesth 1992; 69: 580–5.
16 *Nahrwold ML, Roizen MF, Stanley TH, et al.* Phase IV study of propofol: validation of the data set. Anesth Analg 1993; 77: S34–43.
17 *Pugsley LI.* The administration of federal statutes on foods and drugs in Canada. Medical Services Journal 1967; 387–449.
18 An Introduction to FDA Regulation. Washington, DC: Department of Health and Human Services Public Health Service, Food and Drug Administration, 1990.
19 *Mailhot R.* The Canadian drug regulatory process. J Clin Pharmacol 1986; 26: 232–9.
20 *Somers E, Kasparek MC, Pound J.* Drug regulation – the Canadian approach. Reg Toxicol Pharmacol 1990; 12: 214–23.
21 *Schneider AJL.* Regulation of anesthesia devices in the United States, *In*: Dinnick OP, Thompson PW (Guest Eds.). Baillières Clinical Anaesthesiology, Vol. 2, No. 2, London: Baillière Tindall, June 1988: 353–78.
22 *Gilron I.* Anaesthesia equipment safety in Canada: the role of government regulation. Can J Anaesth 1993; 40: 987–92.
23 *Gagnon D, Swierenga SHH, Beaulieu H.* Working in Partnerships – Drug Review for the Future, report prepared for the Health Protection Branch, Department of National Health and Welfare, Canada, July 1992; 27–35.
24 *Gilron I.* The Emergency Drug Release Program: regulatory aspects of new drug access in Canada. Can Med Assoc J 1993; 148: 1151–3.
25 *Bevan DR.* Succinylcholine (Editorial). Can J Anaesth 1994; 41: 465–8.
26 *Rosenberg H, Gronert GA.* Intractable cardiac arrrest in children given succinylcholine (Letter). Anesthesiology 1992; 77: 1054.
27 *Lerman J, Berdock SE, Bissonnette B, et al.* Succinylcholine (Letter). Can J Anaesth 1994; 41: 165.

28 *Berry FA.* Succinylcholine: a premature death knell? (Editorial). Paediatric Anaesthesia 1994; 4: 205.
29 Physicians' Desk Reference, 49th Edition, 1995.
30 *Katz L, Wright C.* Revised label regarding use of succinylcholine in children and adolescents: II (Letter). Anesthesiology 1994; 80: 243–4.
31 *Nightingale SL.* Unlabeled uses of approved drugs. Drug Information Journal 1992; 26: 141–7.
32 *Torres A.* The use of Food and Drug Administration-approved medications for unlabelled (off-label) uses. Arch Dermatol 1994; 130: 32–6.
33 *Hannington-Kiff JG.* Intravenous regional sympathetic block with guanethidine. Lancet 1974; 1: 1019–20.
34 *Somberg JC.* New FDA intiatives. J Clin Pharmacol 1993; 33: 587.
35 *Wilson JT, Kearns GL, Murphy D, Yaffe SJ.* Paediatric labelling requirements: implications for pharmacokinetic studies. Clin Pharmacokinet 1994; 26: 308–25.
36 *Woollard RF.* Addressing the pharmaceutical industry's influence on professional behaviour (Editorial). Can Med Assoc J 1993; 149: 403–4.
37 *Lichstein PR, Turner RC, O'Brien K.* Impact of pharmaceutical company representatives on internal medicine residency programs. Arch Intern Med 1992; 152: 1009–13.
38 *Rosner F.* Ethical relationships between drug companies and the medical profession. Chest 1992; 102: 266–9.
39 *Girard DE.* The relationship between physicians in training and pharmaceutical companies (Editorial). Arch Intern Med 1992; 152: 920–1.
40 *Lexchin J.* Doctors and detailers: therapeutic education or pharmaceutical promotion? Int J Health Serv 1989; 19: 663–79.
41 *Rawlins MD.* Doctors and the drug makers. Lancet 1984; 2: 276–8.
42 *Morell RC, Foreman AS, Royster RL.* Is it really free? (Letter) Anesthesiology 1993; 78: 798–9.
43 *Johnstone RE.* Relationships with industry are OK if you follow the rules (Letter). Anesthesiology 1993; 79: 1143.
44 *Miller RD.* The publication of commercially sponsored supplements (Editorial). Anesth Analg 1993; 77: 651–2.
45 *Atkins RF.* Truth in advertising: the journal's responsibility (Letter). Anesthesiology 1991; 75: 547.
46 *Saidman LJ.* Unresolved issues relating to peer review, industry support of research, and conflict of interest. (Editorial). Anesthesiology 1994; 80: 491–2.
47 *Gonsowski CT, Laster MJ, Eger EI II, Ferrell LD, Kerschman RL.* Toxicity of compound A in rats: effect of a 3-hour administration. Anesthesiology 1994; 80: 556–65..
48 *Gonsowski CT, Laster MJ, Eger EI II, Ferrell LD, Kerschman RL.* Toxicity of compound A in rats: effect of increasing duration of administration. Anesthesiology 1994; 80: 566–73.
49 Guidelines for an ethical association with the pharmaceutical industry. From The Canadian Medical Association Ad Hoc Committee on Physician-Pharmaceutical Industry Guidelines. May 1991.
50 The American Medical Association's ethical guidelines for physicians. JAMA 265: 2304–2309, 1991.
51 American College of Physicians. Physicians and the pharmaceutical industry. Ann Intern Med 1990; 112: 624–6.
52 *Greene NM.* The 31st Rovenstine lecture. The changing horizons in anesthesiology. Anesthesiology 1993; 79: 164–70.
53 *Scheller MS.* The future of anesthesiology. *In*: Barash PG, (Ed.). Clinical Anesthesia, 2nd ed. Philadelphia: JB Lippincott, 1992: 30–3.