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Investigational Drugs and the Law

George F. Archambault*

THE SUBJECT OF investigational drugs is one of the most talked about issues of this day in law, medicine, pharmacy, the drug industry and hospital worlds. To illustrate this point one need only look at the headlines in the press. For example:

MEDICARE RESEARCH ON HUMANS IS SPARKING BEHIND THE SCENES ROW OVER ETHICAL CODE.¹

William Carley² stated in the *Wall Street Journal*, "At the convention, the AMA may adopt the Declaration of Helsinki, a set of general ethical principles created by an international medical group in 1964. It leaves doctors wide areas of discretion in matters of ethics in research with humans."³ Carley went on to state, ". . . whether the Helsinki principles are adopted or rejected by AMA, a subsequent drive for the adoption of another and controversial set of guidelines seems probable. This set, which isn't scheduled for consideration at the AMA convention this week, is a 14-page document written by AMA lawyers and is far more specific and detailed than the one page Helsinki Declaration."

Also, Dr. Henry Beecher's article that appeared in the *New England Journal of Medicine*⁴ created news in many of the leading newspapers. Among other points the press reported were: "Beecher's statement listed 22 projects involving what he termed questionable practices," and "Medical testing without consent involves 1000 humans, doctor says."⁵

American Druggist carried a news item, "Clinical investigators are now being sued."⁶ The article stated in part, ". . . several suits already have been filed against drug investigators by persons allegedly harmed by experimental drugs, a Cleveland attorney⁷ told a recent meeting of the Drug Chemical and Allied Trade Association."

In June last year some 100 attorneys representing hospitals met for the American Hospital Association's Annual Institute on Hospital Law.

* Dean of the College of Pharmacy, University of Florida, formerly Pharmacy Liaison Officer, Office of the Surgeon General, U. S. Public Health Service, Washington, D. C. [This is a paper presented at the 1966 Annual Meeting of the American College of Legal Medicine.]

¹ *Wall Street Journal*, p. 5 (June 24, 1966).

² Carley is the same writer who handled the January 21, 1966, article on the lung cancer cell study patient consent controversy involving the Jewish Chronic Disease Hospital and the Sloan Kettering Institute.

³ *Supra* n. 1.

⁴ 274 *New Engl. J. of Med.* (24) 1354 (June 16, 1966).

⁵ *Washington Post*, p. A2 (June 17, 1966).

⁶ April 12, 1965.

⁷ R. Crawford Morris, of Arter, Hadden, Wykoff and Van Duzer.

Two days were spent in workshops studying new case law and statutes. Titles VI, XVIII, and XIX of the 1965 S. S. Amendments; H. R. 2, and the *Darling* case⁸ were key topics as were medication error law suits, adverse drug reaction suits, and the "law" of investigational drugs.

At the Drug Information Association meeting recently⁹ many M.D.'s, directors of research for pharmaceutical firms, conducting tests at prisons, mental institutions, and hospitals, spoke on the consent issue and on "proper control" for drug investigational studies.

Moving directly to the subject "Investigational Drugs and the Law" and being concerned primarily with preventative law, a topic not unlike preventative medicine, what is it that must be known as a lawyer in this specialty field in order to aid physicians and pharmacists involved in clinical research, in clinical pharmacology research, in hospital administration, and in nursing and pharmacy practices to keep them from legal pitfalls? It is necessary to tackle the subject in a two-pronged manner: (1) the federal and state statutes, and (2) case law.

Federal and State Statutes

As we are mainly concerned with the Food and Drug Act, a short historical resume might well be in order before examining the statutes. Around 1900, several children were killed in the St. Louis area as a result of the administration of a diphtheria anti-toxin produced from the serum of a horse ill with tetanus. The result was a federal law creating what is today the Division of Biologics Standards of the U. S. Public Health Service. For some 34 years now this nation has had a splendid record of safety in this area of drugs. Only one failure in the search for a polio vaccine: the standards were not as they should have been and the tragic Cutter polio cases resulted. You will recall these cases were settled in the framework, not of tort negligence, but contract law, the law of sales, on the ground of an implied warranty of fitness for use as applied to items "inherently dangerous."

About 1910, a Federal Food and Drug Act, pushed for by the women of the country through *Good Housekeeping*, came into being. Two decades later the Elixir of Sulfanilamide tragedy occurred. A drug firm used as a sulfanilamide vehicle the solvent diethylene glycol, not poisonous in 1 or 2 ml. doses but lethal in large doses. The result was that the FDA laws and regulations were again tightened, this time to require "safety" of the product. Even then there was no strong requirement as to the efficacy of the medication. A few years ago the thalidomide disaster and the phocomelias brought about the Harris-

⁸ *Darling v. Charleston Community Memorial Hospital*, 33 Ill.2d 326, 211 N.E.2d 253, cert. den. 383 U.S. 946 (1965).

⁹ Chicago, Ill., June 25, 1966.

Kefauver FDA Amendments of 1962 requiring not only drug safety but also efficacy for our drugs.

Incidentally, the writer has in his possession what Dr. Letourneau calls a "collector's item," the preliminary medical brochure placed in the hands of physicians at the time the drug thalidomide went into clinical trials in the United States. It reads in part, "A very safe and effective new drug prepared for the treatment of nervous tension and insomnia as well as potentiation of analgesics."

Who among us had given thought to the teratogenic effects of medications prior to 1962? Perhaps some as to German measles but few as to drugs. Yet, the observant, like Flemming and his penicillin discovery, if he had thumbed through the annual publications in the veterinary field, would have spotted a notation around 1959-1960 that pregnant sheep pastured during the early fall on certain meadow ranges in Idaho gave birth to deformed lambs. Why? A plant, a species of veratrum (*veratrum californicum*) carried an offending glycoside or alkaloid and this is a drug used in eclampsia. The signs were there but not recognized.

The net results of the work of Senator Kefauver and his committee and others who subsequently carried on that work are good. The legitimate drug industry, medicine, pharmacy, and the public will benefit greatly because of the new legislation that requires not only proof of safety but of efficacy as well.

Medication, today, to move in the market place must be efficacious for the purposes intended and reasonably safe. Obviously absolute safety can never be guaranteed.

F. D. A. and Investigation Drugs

Now, proceeding to the current FDA amendments as these relate to investigational drugs, these regulations can be summarized as follows:

1. The labels of containers holding drugs not cleared for interstate commerce must bear the statement "Caution—New Drug—Limited by Federal (or U. S.) law to investigational use." Note the language used is "investigational." The word "experimental" is taboo, it seems, in connection with human trials.
2. Three forms of statements must be filed with FDA:

Form FD 1571—Claims for exemptions—usually by a manufacturer, a university, or medical doctor. Some thirteen points of information are to be supplied. Here are but two: (1) the scientific training and experience considered appropriate to qualify the investigators as suitable experts to investigate the safety of the particular drug (item 8), (2) the names and a summary of the training and experience of each investigator and the same for the monitoring investigator (item 9).

Form FD 1572—filed by the clinical pharmacology investigator. Some six points of information are required, including such in-

formation as the qualifications of the investigator and the general outline of protocol study. Also, the clinical investigator certifies that *he will inform any patients* or any persons used as controls, or their representatives, that the drugs are *being used for investigational purposes* and will obtain the consent of the subjects, or their representatives, except when this is not feasible or, in the investigator's professional judgment, is contrary to the best interest of the subjects.

Form FD 1573—(a somewhat similar form to 1572) must be filed by the clinical (not pharmacological) investigators. Four points of information are requested, with some twelve subheadings. Items such as (1) the "consent statement" previously mentioned, (2) the investigator agrees to report to the sponsor, (3) the sponsor agrees to report to the FDA, at least once a year, and (4) any adverse reaction will be *promptly reported*. All records to be kept for two years and the drugs will be administered only to subjects under the personal supervision of other (state names) investigators responsible to him and that the *drug will not be supplied* to any other investigator (fellow physician) or to clinics for administration to a subject.

State Regulations

A state may tighten a federal law by state statute or code; however a state does not have the power to loosen a federal code. Therefore lawyers know that the statutes of a state and political subdivisions thereof, such as cities, must be checked on this point of clinical investigations, or more precisely, the issue here, patient consent. New York City has special regulations on this point and probably Georgia does also as a result of the Milledgeville Mental Institution probe of several years ago.

The role of the New York Board of Regents is still another type of state jurisdiction that must be analyzed. The board of fifteen Regents, in a unanimous decision, ruled that the two doctors from Sloan Kettering who conducted the cancer cell studies at the Jewish Chronic Disease Hospital, had their medical licenses suspended (but stayed execution of the sentence, placing the physicians on probation for one year) for fraud and deceit in the practice of medicine. They were charged with *not informing the patients* of the true nature of the study and for *not obtaining the voluntary consent of the fully informed patient*. Administrative rulings on professional activities by such boards do carry, in effect, the force of law.

So much for a brief review of state statutes, codes, regulations, and jurisdiction, except to add the comment that Boards of Registration in Medicine and Pharmacy may well find themselves policing this area of human drug testing more actively than ever before in the last third of this twentieth century because of the potency of new drugs and devices.

Now to the practical application of present day regulations. Lawyers would be wise to inform their medical and pharmaceutical colleagues involved in Phase II (pharmacological testing), and Phase III (clinical testing) as to the following:

1. They should be guided by the drug firm's medical research director. He knows the law and will protect his company and the investigator.
2. If one is in a study under Phase III (clinical testing) and reporting to a principal investigator, one needs to know the principal investigator's reputation for quality controls. If other of his investigators (physicians) submit "graphite" reports on dead or long ago released patients, your physician client could be smirched should the names of all clinical investigators operating with the principal investigator be released.
3. Many drug firms, since the Boston exposé, have tightened up their quality controls on drug testing. Most drug firms can quickly spot situations where more patient reports are submitted than is possible with the number of doses distributed when used in accordance with the FDA filed protocol of study.
4. For the investigator's protection, he should obtain the written consent¹⁰ from the fully informed patient or explain on the patient's chart, at the time of the decision, why he did not elect to obtain the consent.
5. Concerning the consent issue—good causes for not disclosing to the patient that an investigational drug is being used might well be because: (a) the patient is an unconscious child and has no relatives, (b) the same, for an insane patient, (c) the patient is terminal.
6. Some researchers and hospitals have added a new document for additional protection, for want of a better name, the "Review Statement of Patient Consent." This document goes to a peer committee. If the committee is not satisfied with the information furnished to the patient, as related by the patient on the form, the investigator is asked to return to the patient and explain further the study.
7. Remember, "consent" is a matter of medical judgment. The Food and Drug Administration does not require the consent to be in writing,¹¹ and does not require consent where the professional judgment of the physician so indicates.
8. How does one handle the consent issue when double blind studies are used? Inasmuch as the patient might not receive the investigational drug but might receive the placebo, one can state ". . . we are asking you to participate in a course of treatment in which you *may* receive an investigational drug, or you *may* be one of the control patients" and then explain the study. This is an honest approach to the consent issue.

¹⁰ The AMA Medicolegal Forms with Legal Analysis Brochure has as Form Number 29 "Authorization for Treatment with Drug Under Clinical Investigation" (1961).

¹¹ The Federal Register, vol. 21, no. 168, carries the new regulation of the FDA requiring written consent except in certain instances (Aug. 30, 1966).

9. The AMA law department, not the FDA, first suggested that a consent form be used.
10. Finally, do not forget the Nuremberg trials involving medical experimentation. Fifteen defendants were found guilty, seven were hanged and four of the seven were physicians.¹²

A discussion of investigational drugs would be incomplete if the Five Point Statement of Principles on the Use of Investigational Drugs in Hospitals, as approved by the Board of Trustees of the American Hospital Association and the American Society of Hospital Pharmacologists (1957), was not reviewed at this point. These elements are:

1. Investigational drugs should be used only under the direct supervision of the principal investigator, who should be a member of the medical staff and who should assume the burden of securing the necessary consent.
2. The hospital should do all in its power to foster research consistent with adequate safeguard for the patient.
3. When nurses are called upon to administer investigational drugs, they should have available to them basic information concerning such drugs; dosage forms, strengths available, actions and uses, side effects, and symptoms of toxicity, and so forth.
4. The hospital should establish, preferably through the pharmacy and drugs therapeutics committee, a central unit where essential information on investigational drugs is maintained and whence it may be made available to authorized personnel.
5. The pharmacy department is the appropriate area for the storage of investigational drugs, as it is for all other drugs. This will also provide for the proper labeling and dispensing in accord with the investigator's written orders.

Tort Negligence

At this point tort negligence law should be considered. Attorneys should advise their colleagues to:

1. Insist that the investigator and hospital officials make certain that the code used in double blind and other studies be capable of being broken at the hospital should a patient's life or health become jeopardized.¹³
2. Not permit a sponsor or chief investigator to interfere with legal responsibility as to "code breaking" as some may do to "protect the integrity of the research."

Parke Davis of Detroit has an excellent system for breaking the code when a patient's condition so warrants. The system was developed by Dr. Wheeler of Parke Davis' Research Division—a sealed envelope is used in which is placed an 8½ x 11 punch card, not unlike a "chance card." A typical case study might have the following caption:

¹² See, Hospital Management, "A Drug Moves Into Human Trials" (April 1963).

¹³ See Editorial, "Hospitals" 32 J. Amer. Hospital Assoc. 35 (Jan. 1, 1958).

- Group A—Drug A—10 mgm.
- Group B—Drug A—25 mgm.
- Group C—Drug B—50 mgm.
- Group D—Drug B—150 mgm.
- Group E—Placebo

The doctor knows he is using drugs A and B, each in two strengths, and a placebo. The card controls fifty patients. If "Patient No. 12" is in trouble, the M.D. pulls slot 12 on the card and may see "D," meaning the patient is on "B" drug with a 150 mgm. dose. The rest of the study is not imperiled as the investigator has the answer to the one case he has concern for. The card must be returned to Parke Davis at the end of the study in the same sealed envelope.

The following common law cases: *Darling v. Charleston Community Hospital*,¹⁴ *Sullivan v. Sister of St. Francis*,¹⁵ and *Norton v. Argonaut Insurance Co.*,¹⁶ on careful reading lead to these inescapable conclusions:

1. Hospitals, more and more, are being held liable for misfeasance and nonfeasance of employees.
2. Hospital administrators find themselves personally involved in not only malpractice tort litigation but also criminal negligence cases.
3. *Statement of Principles*, such as that on the *Use of Investigational Drugs in Hospitals* by the Board of Trustees of the American Hospital Association, plus the Joint Commission and Medicare Standards, are being increasingly used as "tools" by plaintiff attorneys to help prove alleged negligence.
4. Attorneys need to advise their medical colleagues to set up systems to periodically check the workers under their supervision, to make certain that subordinates (M.D.'s and others) are following the laws, rules, regulations, policies, and procedures set up for patient safety. Otherwise, the client may find himself trying to defend a most difficult legal position.
5. And last, but not least, the client and his institution should be covered with adequate malpractice insurance covering investigational drug study activities.

¹⁴ *Supra* n. 8.

¹⁵ 374 S.W.2d 294 (Tex. Civ. App. 1963).

¹⁶ 144 So.2d 249 (La., 1962).