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Quality Control of Pharmaceuticals

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ABSTRACT

Quality control is an essential operation of the pharmaceutical industry. Drugs must be marketed as safe and therapeutically active formulations whose performance is consistent and predictable. New and better medicinal agents are being produced at an accelerated rate. At the same time more exacting and sophisticated analytical methods are being developed for their evaluation. Requirements governing the quality control of pharmaceuticals in accordance with the Canadian Food and Drugs Act are cited and discussed.

SOMMAIRE

Le contrôle de la qualité est une phase essentielle de la préparation des produits pharmaceutiques. Quand les médicaments sont mis sur le marché, ils doivent avoir une activité thérapeutique qui soit uniforme et prévisible. Des médicaments, nouveaux et meilleurs, voient le jour à un rythme accéléré. En même temps, on met au point des méthodes analytiques plus précises et compliquées pour en permettre l'évaluation. Les auteurs citent et etudient les exigences posées par la Loi canadienne des aliments et des drogues concernant le contrôle des produits pharmaceutiques.

BY DICTIONARY definition "quality control" means checking and directing the degree or grade of excellence of processes and products. To the ethical pharmaceutical manufacturer it implies a detailed system of inspection and control covering the production, evaluation and distribution of every drug bearing his company's label. It is the purpose of these operations to produce medications of superior efficacy, safety and elegance, and to provide assurance to the physician, the pharmacist and the consumer that a given product performs uniformly and in a manner satisfactory for the purpose for which it is recommended.

Modern methods of marketing pharmaceuticals are in many respects unique when compared with those applying to most consumer products. While drugs for use in self-medication are sold freely over the counter at the corner drug store, most therapeutic agents are available only on prescription from a physician. The personal and professional role played by the pharmacist for many years in preparing and compounding drugs of all types has gradually been taken over by the pharmaceutical industry, which now provides an impressive array of drugs in finished dosage form. No longer does the pharmacist spend half or more of his time compounding medications in his apothecary. Eighty per cent or more of all the prescriptions he fills are preparations compounded and packaged for him by the industry.

With this development a good deal of the responsibility for the control of the quality of drugs has shifted from a recognized profession, subject to restrictions as to conduct and actions and well-defined codes of performance, to a competitive free-enterprise industry whose business it is to supply medicinals to the pharmacist as finished dosage forms. Although groups within the pharmaceutical industry organized themselves into trade associations governed by professional codes including requirements for quality control of products manufactured and marketed, member-

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ship in such associations has remained voluntary. Thus requirements for conducting a pharmaceutical enterprise are not restricted to any professional group as is the case in the practice of medicine and pharmacy. Legally, an individual or individuals without relevant professional background may engage in and carry on a pharmaceutical business in our free enterprise economy.

MANUFACTURING CONTROL OF PHARMACEUTICALS

Requirements pertaining to the control of the quality of pharmaceuticals must be examined in the light of the importance of the industry to the health and welfare of the nation. Many of its products are life-saving and essential for the well-being of both animal and man. Such far-reaching social responsibility imposes equally important moral obligations on the manufacturer to market drugs of continuing uniformity and safety. His reputation is indeed heavily vested in the controls he exercises over the merchandise he distributes. In many respects the advertising and sales organizations of a firm echo the claims for the standards of quality of the company's products. The government, protecting the consuming public against health hazards and fraud, also plays an important role in this area, and it is the object of this communication to outline some of the requirements set forth in the Food and Drugs Act and Regulations for the manufacture and quality control of drugs distributed in Canada.

BIOLOGICALS

The need for the protection of the public through the introduction of special legislation controlling the quality of a class of drugs often referred to as biologicals (e.g. drugs prepared from micro-organisms, toxoids, vaccines, sera, insulin, and others) was recognized a number of years ago. Authority to permit the sale of such preparations by licensed manufacturers only was provided through the Food and Drugs Act of 1928. Specific regulations were promulgated requiring inspection of the manufacturer's premises to determine whether adequate production facilities, technical staff and control systems were available and in operation. Authority was also obtained requiring the manufacturer to submit samples and protocols of tests, where applicable, on each lot of such drugs to the laboratories of the Department of National Health and Welfare for examination and to withhold such lots from distribution until a notice of release was issued by the Food and Drug Directorate.

Licensed drugs are identified in the trade by their Canadian licence number, which must be shown on each label. At the present time such licences are held for approximately 700 biological preparations, marketed by some 60 pharmaceutical manufacturers. Schedules C and D of the Food and Drugs Act list the types of products involved.

Regulatory requirements cover preparations manufactured in foreign countries and imported into Canada as well as preparations manufactured in Canada. The licences are subject to renewal each year and annual inspections of the premises of the manufacturer are made to ensure compliance with the law. Authority is provided to cancel or suspend the licence of any manufacturer failing to maintain satisfactory control over the biological products that he markets. Thus, relatively stringent regulations govern the production, quality control and distribution of these medicinals.

Authority for a licensing system on a lot release basis has not been established to date for drugs other than the biologicals. Enforcement of such a program would prove a tremendous task. It is estimated that in the vicinity of 25,000 different drugs— distributed by some 1200 to 1500 manufacturers in a variety of dosage forms—are currently on the Canadian market. No pertinent data are available regarding the number of lots of these drugs produced annually by any firm.

PHARMACEUTICALS

Reflecting the awareness of the importance of good manufacturing practices by the government, Section 11 of the Food and Drugs Act as revised in 1952 states that "No person shall manufacture, prepare, preserve, package or store for sale any drug under unsanitary conditions," i.e. under "such conditions or circumstances that might contaminate a drug with dirt or filth or render the same injurious to health". Following its promulgation a drug plant inspection program was initiated to improve the sanitary aspects of pharmaceutical manufacture. Adopting an educational approach, especially in the case of medications for parenteral administration, efforts were made to ensure that premises were kept clean and chances of drug contamination by filth and dirt were eliminated. It was found during the course of these inspections that the quality controls exercised by some manufacturers over their products were below recognized standards. Authority to correct such transgressions, except by official analyses of finished dosage forms to determine compliance with label claims for active ingredients was, however, not provided by law.

At the time these inspections were undertaken, a number of government departments procuring large quantities of drugs for their hospitals *via* the tender system expressed concern over product quality and requested the Canadian Government Specifications Board—an agency of the government preparing commodity specifications for government purchasing—to establish standards as a guide to ethical pharmaceutical manufacturers and distributors. A committee of representatives of the Canadian Pharmaceutical Association, the Canadian Pharmaceutical Manufacturers Association, the Proprietary Association of Canada, the Departments of National Defence, Defence Produc-

tion, Veterans Affairs, National Health and Welfare, and the Canadian Government Specifications Board was accordingly set up to prepare such standards. Detailed recommendations were made by this committee to the Board regarding minimum facilities and controls for the manufacture, evaluation and distribution of drugs. These were accepted as commodity standard 74-GP-1 for use by any drug manufacturer or distributor wishing to supply any agency of the Government of Canada. Continued inspections following issuance of this standard in 1961 showed that some revisions would have to be made to ensure the success of this endeavour. Accordingly, the document was reissued as standard 74-GP-1a in February 1964. It consists of detailed requirements which a primary manufacturer, distributor, importer and commercial testing laboratory must meet with regard to plant sanitation, personnel, operations, equipment, processing, packaging, finishing, laboratory control, labelling and storage of drugs destined for use by any agency of the Government of Canada. Copies of the document may be obtained at a cost of 25 cents each from the Office of the Secretary of the Canadian Government Specifications Board, Ottawa, Ontario.

STATUTORY REQUIREMENTS FOR PHARMACEUTICAL MANUFACTURERS

Following completion of standard 74-GP-1 regulating the purchasing of drugs by government agencies it was considered expedient to recommend that regulatory requirements under the Food and Drugs Act be enacted to cover likewise the manufacture and control of drugs sold to other than government agencies. Discussions were accordingly initiated with the pharmaceutical industry using the existing standard as a general guide. Tentative specifications were drawn up after a series of meetings with all interested parties and presented to the Minister of the Department of National Health and Welfare for consideration as regulations under the Food and Drugs Act. They were passed by Order-in-Council under PC-1963-449, March 19, 1963, and are recorded in the Office Consolidation of the Food and Drugs Act and Regulations under Sections C.01.051 and C.01.052, respectively. The amendments specify that "No manufacturer shall sell a drug in dosage form unless the drug has been prepared, manufactured, preserved, packaged, processed, stored, labelled *and tested* under suitable conditions." These conditions call for all areas of the building where drugs are handled to be of such material and finish as to permit ready and efficient cleaning of all surfaces, prevent the introduction of extraneous materials at any stage during processing and eliminate the migration of dust, having regard to the nature of the operation. All premises and auxiliary facilities are to be kept clean, sanitary and in orderly condition, free from vermin, infestation, accumulated waste and debris. If parenteral drugs are being processed, all filling and aseptic operations are to be carried out in separate and specially designed areas to prevent contamination.

It is essential that technically qualified personnel be employed to supervise formulation, processing, testing, packaging and labelling of the drug and that competent staff be placed in charge of the maintenance of machinery, equipment and sanitation. Each lot of raw material must be tested to ensure its identity and purity, and each batch of drug in dosage form must be examined for identity, composition and potency. A system for checking both identity and amount of ingredients used in a given formulation as well as a system for auditing weights of raw materials *versus* product yields must be followed. A system of records defining all manufacturing, finishing and testing operations is to be adopted to ensure that errors in the identification and proper labelling of all raw materials and final products do not occur. An effective system for the complete and rapid recall of any lot or batch of drug from the market if this should become necessary must also be available.

Additional requirements include the keeping of samples and records of each lot of the drug for a period of five years or until its expiration date. For drugs imported into Canada such information should be supplied before their admittance into the country. Such drugs may, furthermore, be refused entry or their release may be withheld if it is considered necessary that they be first tested in this country by acceptable methods and in the form in which they are to be marketed.

Since the issuance of standard 74-GP-1 by the Canadian Government Specifications Board detailing requirements for the control of drugs purchased by government agencies and the enactment of legislation embodied in the Food and Drugs Act, a number of Canadian manufacturers have remodelled their plants, revised quality control systems and engaged competent personnel in order to comply with the law. There is every indication that the enforcement of the regulations provided has had a salutary effect in improving the quality and safety of drugs distributed in Canada.

Statutory requirements for manufacturing facilities and controls do not by themselves, however, impart high quality to any drug, since quality is a property made up of many elements built subtly into the product—knowledge, integrity and motivation to compound a drug of excellence and choice. Systems of inspection, checking and testing are merely tools to eliminate mishaps as far as is humanly and practically possible. They may be looked upon as a form of insurance provided by law for the benefit of the physician who prescribes, the pharmacist who dispenses, and the consumer who purchases drugs for the alleviation of his suffering and pain.

INVESTIGATIONAL NEW DRUGS

An important amendment to the Food and Drugs Act promulgated in October 1963 concerns the

development, quality control and distribution of new drugs. It requires the manufacturer to file a preclinical submission "in a form and content satisfactory to the Director of the Food and Drug Directorate" before distributing his product to qualified investigators willing to evaluate its therapeutic efficacy. It is the purpose of such submissions to ensure that the manufacturer has complied with certain basic requirements before approaching clinicians to administer the medication to any patient. The requirements to be met include a statement of the objective of the proposed clinical trials and submission of the results of all animal studies made to support the clinical use of the drug, along with dosage directions, descriptions of possible side effects, precautions and contraindications. Qualified investigators appraising the biological response of the drug must also be provided with this information.

In addition it is mandatory for the manufacturer to submit relevant data and procedures pertaining to the preparation and quality control of the product. These include:

1. *The identifying name or mark of the new drug,* along with its accepted chemical name, as well as any code names, synonyms, non-proprietary and brand names which may be known.

2. *The chemical structure or other specific identification of the composition of the new drug,* such as its molecular formula and molecular weight.

3. *The source of the new drug,* along with information concerning the role of the manufacturer in its production, packaging and distribution, relevant data showing whether the drug is of domestic or foreign origin, and whether or not it is a product of private formula or custom manufacture.

4. *The tests applied to control the potency, purity and safety of the new drug,* and

5. *The methods, equipment, plant and controls used in the manufacture, processing and packaging of the new drug.*

Such documentation applies both to bulk drugs and to pharmaceutical dosage forms. If the new drug is a synthetic product, the sequence of reactions by which it is obtained should be shown and the formation of intermediates be indicated to illustrate the occurrence of contaminants and to account for possible undesirable side reactions that might be observed. Purification procedures to accomplish the efficient removal of such contamination or admixture from the bulk drug should be described, and specifications for solvents used in this process should also be given.

If the new drug is a natural product, the sequence of steps followed for its isolation, concentration and purification should be defined and references to data published in the scientific or patent literature should also be cited. Related information to be supplied includes a description of pertinent physicochemical methods of analysis and specifications, such as appearance, physical form and colour, melting point, solubility and pH characteristics, optical crystallographic properties, stability at normal and elevated temperature, typical colour reactions, paper, gas-liquid and thin-layer chromatograms, infrared and ultraviolet absorption spectra, polarograms and x-ray diffraction patterns, along with characteristic constants displayed by suitable derivatives. Identification tests for specific impurities are also to be given.

If the drug is to be marketed as a pharmaceutical dosage form, its quantitative composition must be stated. Both active ingredients as well as excipients, including bulking agents, binders, disintegrators, lubricants, colours, coatings and flavourings are to be listed and their purities specified. Sensitive reactions permitting the detection of active ingredients present in the formulation should be indicated, and these tests, in turn, must be supplemented by one or more selective quantitative assays directly applicable to the pharmaceutical dosage form.

It is essential that a preclinical submission should also contain relevant physical criteria reflecting the *in vitro* performance of the new drug. Results of tests concerning the disintegration time and dissolution rate of tablets, the weight variation of solid dosage forms, the viscosity of liquid and semi-liquid preparations should be ascertained to illustrate that adequate control for ensuring uniform drug potency from batch to batch is maintained at all stages of production.

Although full knowledge of the pharmacology of a new drug derived from controlled experiments using several animal species is a prerequisite for clinical evaluation, it is equally important to have available detailed laboratory data concerning its manufacture and quality control, for only thus will it be possible to ensure that risks in administration are kept to a minimum.

Modifications in formulation made following acceptance of a new drug for clinical trials should be duly reported, for it is essential that therapeutic efficacy determined by clinical investigations be equated to precise pharmaceutical dosage forms. It is likewise imperative that all quality control data submitted for the product be critically appraised and revised if necessary in accordance with any subsequent formulation change. Similarly, modifications of the synthesis of the new drug should also be supplied.

In the evidence submitted by the Canadian Pharmaceutical Manufacturers Association before the Special Committee on Food and Drugs (Minutes of Proceedings and Evidence No. 7, June 19, 1964), Dr. A. D. Grieve reported on Analytical Development and End Product Control. He stated, "Before these dosage forms can be prepared and released for clinical trial it is necessary to establish specifications and analytical methods by which these specifications can be enforced for the New Drug substance and the dosage forms which are to be tried. For this purpose use is made of the physical,

chemical and physiological properties of the New Drug substance." Again in respect of dosage forms, Dr. Grieve stated, "The dosage forms made from such a New Drug substance must also be controlled for identity, potency, purity and safety. The same physical, chemical and biological properties can be used as were used in controlling the New Drug substance itself."

The importance and necessity for the control of pharmaceutical formulations of drugs was stressed in a brief presented by Cyanamid of Canada, Ltd. before the Special Committee on Food and Drugs (Minutes of Proceedings and Evidence No. 11, July 9, 1964). This brief states, in part, "Frequently entirely new tests have to be developed for each drug. A detailed knowledge of the interactions of the bulk chemical and the vast number of ingredients employed in formulations must be known under a variety of changing physical conditions. Improper particle size, poor selection of vehicles, inattention to stability and compatibility under a wide variety of changing circumstances, and lack of knowledge about disintegration times and degradation products are just some of the factors that have rendered drugs inactive or frankly dangerous."

Reduction of hazards and maintenance of the potency of new drugs developed continuously by an ever-expanding industry are the purpose of the drug-manufacturing requirements under the Food and Drugs Act. Sound scientific principles must be applied in the manufacture of products affecting the health of the nation, and in this context the law merely sanctions an obligation which every good pharmaceutical manufacturer undertakes when making available new drugs for evaluation.

The clinical investigator has also a key role to play in this endeavour. Just as a research chemist embarking on the synthesis of a new compound is elated when he has completed its characterization the clinical investigator undertakes an exciting venture when he administers and follows the mode of action of a new drug. He is indeed a vital link in the sequence of events which begins with the manufacture of a new drug in a pharmaceutical laboratory and ends with ultimate product acceptance. The introduction of a new drug is a team effort and joint responsibility of the pharmaceutical industry on the one hand and the medical profession on the other hand.

Compliance by the manufacturer with the requirements of the Food and Drugs Act will minimize hazards to patients through the administration of new potent therapeutic agents and contribute materially to providing the clinical investigator and physician with knowledge and background information needed in the proper use of drugs for the prevention and treatment of illness and disease—which is the objective of both the industry and the government.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

VASOSPASM REVISITED

Since the publication of Pal's monograph in 1905, the literature of angiospasm and the vascular crises has become considerable. It will be remembered how ably Dr. A. E. Russell in the Goulstonian Lectures, 1909, advocated the thesis that focal angiospasm (or combined spasm and dilatation) is the immediate underlying factor in the epileptic seizure. He also urged the same causation in the case of migraine; Pierce Clark (*Am. J. Obstetrics*, November, 1912) has written up the subject of vasomotor and trophoneuroses, naming amongst the clinical associations of angiospasm, neurasthenia, hysteria, traumatic neuroses, affections of special organs, angina pectoris (in its functional form), abdominal disturbances, nervous dyspepsia, and other conditions.

The cerebral crises have naturally attracted most attention. Sir William Osler and others have written on the grosser manifestations—the transient hemiplegias, monoplegias and aphasias. Whilst only the other day Professor William Russell, of Edinburgh, attributed to cerebral angiospasm the fleeting loss of memory, the attacks of mental obscuration and of inability to perform ordinary work, the recurring vertigo and other phenomena so often seen in elderly people with sclerosing vessels.

As regards that much debated point, the true cause of the pain phenomena in *angina pectoris*, one may merely refer to the widely held view that myocardial ischemia due to spasm of the more or less diseased coronary arteries is an essential factor in its production in some cases at least. An extensive network of nerve fibrillae has been demonstrated on these vessels (by Dehio, if I mistake not, in 1903). The wide extent of the referred pain areas in some cases of angina, involving spinal segments either above or below those in definite connexion with the heart and its immediate blood supply, has led many observers to the conclusion that the vascular crises *must* affect at times other visceral branches of the abdominal aorta. Thus Charles F. Hoover (Osler's "Modern Medicine", art. Angina Pectoris) thinks that the gastric symptoms described in some cases have been caused by disease of the arterial supply to the stomach, and not by referred pains from the heart, "so that the respiratory symptoms and nervous symptoms, and symptoms from the abdominal viscera, which have been so closely linked with attacks of angina pectoris, are merely concomitant symptoms, and do not sustain an essential relation to cardiac angina."

There can be little doubt that these visceral crises have been responsible for the occasional opening of the abdomen, with negative surgical findings.

The peripheral crises, "intermittent claudication", Raynaud's disease, and its allies, are too well known to detain us; but I may remind you that Déjérine long ago described for us (and has recently repeated the description with all the *verve* and clarity of the French school) intermittent claudication of the spinal cord. This writer lays stress on its commonly syphilitic origin, its differentiation from peripheral claudication, and its inevitable result (if unchecked by treatment) in chronic spastic paraplegia.

Finally, to emphasize the wide application being made to-day of the angiospasm and claudication idea, reference may be made to two interesting recent papers. In one of these Solis-Cohen describes the angioneurotic affections of joints (*Am. J. Med. Sciences*, July 1914), in the other J. Ramsay Hunt quotes cases to illustrate the condition he names "ischaemic lumbago", or the lumbar type of intermittent claudication.—A. Birt, *Canad. Med. Ass. J.*, 4: 855, 1914.