Quality Assurance of Pharmaceuticals Manufactured in the Hospital

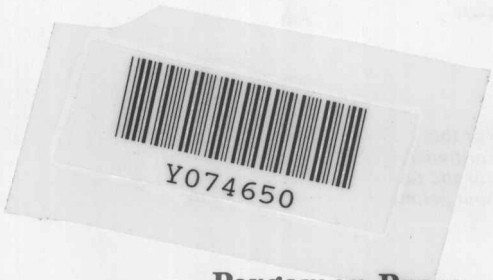
Ann Warbick-Cerone
Linda G. Johnston

PERGAMON PRESS

Quality Assurance of Pharmaceuticals Manufactured in the Hospital

Proceedings of the International Symposium on Drug Quality Assurance in the Hospital

Edited by
Ann Warbick-Cerone
Linda G. Johnston
Toronto General Hospital



Pergamon Press
New York • Oxford • Toronto • Sydney • Paris • Frankfurt

Pergamon Press Offices:

U.S.A.	Pergamon Press Inc., Maxwell House, Fairview Park, Elmsford, New York 10523, U.S.A.
U.K.	Pergamon Press Ltd., Headington Hill Hall, Oxford OX3 0BW, England
CANADA	Pergamon Press Canada Ltd., Suite 104, 150 Consumers Road, Willowdale, Ontario M2J 1P9, Canada
AUSTRALIA	Pergamon Press (Aust.) Pty. Ltd., P.O. Box 544, Potts Point, NSW 2011, Australia
FRANCE	Pergamon Press SARL, 24 rue des Ecoles, 75240 Paris, Cedex 05, France
FEDERAL REPUBLIC OF GERMANY	Pergamon Press GmbH, Hammerweg 6, D-6242 Kronberg-Taunus, Federal Republic of Germany

Library of Congress Cataloging in Publication Data

International Symposium on Drug Quality Assurance in the Hospital (1984 : Toronto, Ont.)
Quality assurance of pharmaceuticals manufactured in the hospital.

1. Hospital pharmacies--Quality control--Congresses. 2. Drugs--Standards--Congresses. I. Warbick-Cerone, Ann. II. Johnston, Linda G. III. Title. [DNLM: 1. Drugs--standards--congresses. 2. Pharmacy Service, Hospital--standards--congresses. 3. Quality Control--congresses. WX 179 I61q 1984]
RA975.5.P5I54 1984 362.1'782 85-3404
ISBN 0-08-025414-4

Printed in the United States of America

PREFACE

The concept of quality assurance is not new. The hospital pharmacist has a professional responsibility and a moral obligation to ensure that pharmaceuticals and radiopharmaceuticals manufactured in the hospital setting are of the highest possible quality. To achieve this, hospital manufacturing practices and standards must reflect good manufacturing practices. The development of a quality assurance manual and a quality assurance program is one of the first steps in this process.

The idea of a symposium was conceived to provide a forum for the discussion of topics relevant to the development of the drug quality assurance program specifically designed for hospitals and incorporating all those features which are essential in good manufacturing practice. This textbook, which is a compilation of manuscripts by experts in their specific fields is intended to serve as a reference to aid in the preparation of a quality assurance manual and as a basis to justify the financial commitment which a hospital administration must make to establish a facility designed to prepare and evaluate pharmaceuticals of the highest quality for patient use.

Ann Warbick Cerone

Linda G. Johnston

TABLE OF CONTENTS

HOSPITAL PHARMACY PRACTICE

NUCLEAR PHARMACY PRACTICE

INTRODUCTION

QUALITY ASSURANCE: IN SEARCH OF EXCELLENCE

Morrison, A.B., Ph.D.
Assistant Deputy Minister, Health Protection Branch
Health and Welfare Canada

ABSTRACT

Quality Assurance is a multitude of systems that are co-ordinated to assure the delivery of a defined product. Modern day practices in quality control date from the nineteenth century and are continually being improved as technological advancement arise.

Research, product development, production, control and distribution must be recognized as significant contributors to quality assurance. Good manufacturing practices are also readily identified as a key element of quality assurance.

Canadian drug legislation applies to all persons who are involved with the manufacture, control and distribution of drugs in Canada. The Health Protection Branch consults with affected parties to ensure that regulatory requirements are effective, practical and reasonable. Through the QUAD Program information on drug quality is made available to provincial health authorities and hospitals involved in drug purchasing programs.

KEYWORDS

Quality assurance; good manufacturing practices; Canadian drug legislation; surveillance activities.

I wish to begin my address today with a quote from Aldous Huxley. I quote; "Every man who knows how to read has it in his power to magnify himself, to multiply the ways in which he exists, to make his life full, significant and interesting". In examining that quote I don't believe that Huxley intended a narrow interpretation of the verb "read" but rather used it to exemplify the ability and enthusiasm to learn. The program that will be presented over the next four days should stimulate and provoke your further exploration of the many aspects of quality assurance. Quality assurance demands a continuing effort to achieve excellence. I think the program certainly exhibits a broad perspective

of quality control and particularly as it applies to the manufacture of drugs and radiopharmaceuticals in hospitals. The challenge will be yours to participate in this symposium to its fullest and to glean as much knowledge from it as you possibly can.

Quality control or quality assurance is a topic that has received a fair amount of attention over the past 20 or 30 years. The volume of reference materials is enormous. There are numerous books and journals dedicated to this subject. There are books that range from those directed toward the more technical aspects of quality control to those which give the broad principles and those which deal with management. However, it is the practical application of quality assurance procedures that really counts. This symposium will give us the opportunity to share some experiences.

The principles of quality control are generic. They are not limited to the manufacture of pharmaceutical products but to a whole host of goods and services. The Quality Assurance program developed and implemented for your particular practice carries your trademark. It will identify your particular concerns for the safety and protection of your patients. Therefore the more you put into it, the more you will gain in return. A good quality assurance program will not only ensure that a good quality product is delivered but should also give you information for management purposes. Your quality assurance program can give you data that will enable you to make your operation more efficient and effective. Therefore it can be a cost saving tool. Quality Assurance is a very comprehensive subject and requires much ability to apply the various aspects to your particular situation.

Let me go back now and just give a bit of historical perspective to quality control or quality assurance. Many authors have considered that quality control began as a result of industrialisation and particularly relating to the manufacture of military goods. Governments, in particular, have been on the leading edge of setting specifications and various parameters for the production and purchase of goods for their purposes. Military supplies have usually been the stimulus for government use of quality control. Let me take a moment to portray one of the many stories that are related to quality control.

About the year 1800 the United States Army determined that it needed 10,000 muskets. Since guns were made by hand in those days there were no manufacturers who could supply that quantity.

The manufacture of guns was still very much a cottage industry. Each gun was manufactured by an individual craftsman so that no two were alike. Each part was individually crafted to fit with its mate. Therefore, the product was identified by the craftsman and by his ability to make the parts fit accurately. Obviously this meant that parts could not be interchanged. It also meant that manufacturers could not produce large quantities of goods, particularly 10,000 muskets. Contracts of that size were usually spread amongst many small firms.

An enterprising businessman approached the government proposing to make the entire quantity for the government. Obviously this was a surprise to the purchasing agents, and they were curious how he could handle the order. He explained that he would buy the best hand-made musket available. He would take it apart piece by piece, and he would then proceed to make 10,000 exact copies of each individual part. His skilled mechanics would be controlled so that they

would produce exact copies. These parts could then be assembled, "et voilà", 10,000 muskets. In fact, he proposed that extra parts could be produced, and therefore replacements for broken or worn-out parts would be available for the army.

Unfortunately the businessman did not define the word "exactly" nor did the U.S. Army think to ask him to define it in the contract. In giving instructions to his workers he had not adequately prescribed the specifications or tolerances that would be allowed for each part. In other words each craftsman was able to produce what he thought was an exact copy. When inspectors checked samples there were acceptable variances since they also were able to interpret the meaning of exact.

In the end many of the muskets were of poor quality and would not function. The slight variation in the parts would not allow some of the assembled parts to perform properly. Most of the muskets worked, but some didn't. This, unfortunately, is an example of the poor quality control that was exercised back in the 1800's. However it does show us that there is a need for proper specifications of products for the quality control activities to be performed adequately. We must also recognize that this businessman had the foresight to have samples of his production checked by inspectors rather than each individual part. Thus he initiated cost reduction due to quality assurance measures.

I know that there are many pharmacists present today, and I am sure you are going to tell me that pharmacists employed quality control procedures long before 1800. Although not as refined as today there are records of documents on materia medica that existed 4,000 years ago. Their intent was to insure replication of formulae and some adherence to consistency. Again, it was the pharmacist's attempt to produce a quality product and maintain his reputation. Down through the ages pharmacopoeias have been developed to control the preparation and testing of drugs. Standards in today's pharmacopoeias are written to define the levels of potency and purity that are acceptable to insure safety and accuracy. As our technical capabilities to produce and test drugs improve the compendia are revised to reflect these advancements. Presently we are reaching a point where our in vitro analytical capabilities enable us to detect drugs and their impurities to levels measured in parts per billion and even parts per trillion. However our ability to measure biologically is far less advanced. Whether we are attempting to measure a pharmacological effect or a toxicological effect, we can not conclusively determine the biological response at these levels. One of science's frontiers lies in developing techniques that will give us better information to predict more accurately the beneficial and hazardous aspects of chemicals.

We must maintain a rational approach to standard setting and make sure that the safety of the patient is protected at a reasonable cost. The challenge is also yours to make sure that you have adequately established the specifications for your products and that your test methods will reproducably give accurate results.

The terms "Quality Control" and "Quality Assurance" are often used interchangeably. However there is a definable difference. Quality control involves the sampling, testing, inspecting and approving products for release.

The basis for the quality control of medicines has many aspects. There are the fundamental chemical and physical examinations to determine identity and chemical

structure; homogeneity and purity; quantitative determinations; and characterization of the solid state. Increasingly, health professionals are placing greater emphasis on the biological aspects. Studies in bioequivalence or bioavailability are now considered essential as part of the control of drugs. Pharmacokinetic considerations play a major role in the clinical measurement and application of drugs.

Beyond the processing operations, stability studies ensure that appropriate packaging and storage conditions are prescribed to maintain the integrity of the product during its shelf-life.

The quality control department must have authority to take samples, not only of the finished product, but throughout the entire operation.

Many people think of the quality control department as the police force of the manufacturing system. I prefer to view the quality control unit as an information system. This unit gathers information and reports that all procedures have been well controlled and that a good quality product is ready for the consumer. Quality control has a stabilizing effect to ensure consistent adherence to defined standards. It provides the necessary information to prevent fluctuations in production.

Quality assurance has a broader quality connotation. Quality assurance is associated with activities needed to assure that the systems of design, formulation, manufacture, control and distribution are adequately prescribed and adhered to. GMP, i.e. Good Manufacturing Practices is a major component of quality assurance. The Health Protection Branch has published an interpretative document entitled "Good Manufacturing Practices for Drug Manufacturers and Importers". This document applies to all those involved in the manufacture, control and distribution of drugs for sale in Canada. Mr. Rowsell will be discussing GMP in his presentation, but let me just highlight what we consider to be the pertinent aspects of GMP. They are as follows:

a) Premises

The design and construction of a building for pharmaceutical production must incorporate features which prevent hazards that might adversely affect the quality of the drug;

b) Equipment

Machinery and utensils must be arranged and maintained appropriately for the processing operations;

c) Personnel

Staff must have adequate education and training for their responsibilities;

d) Sanitation

The quality of a drug product demands that it be produced in an area

that is free from environmental contamination and free from contamination with another drug or chemical;

e) Raw Material Testing

This is the initial assurance that acceptable quality of the finished product may be achieved;

f) Manufacturing Control

The measures taken to eliminate as many sources of error as possible so that only those drugs which have met established specifications are distributed;

g) Quality Control Department

It is very important that adequate controls be exercised by this department in order to guarantee the quality of the end product;

h) Packaging Material Testing

Only packaging materials of acceptable quality are to be used in the packaging of drugs;

i) Finished Product Testing

Due to the limitations of sampling methodology, finished product tests complement the controls employed during the manufacturing process. It is the responsibility of each manufacturer to use adequate specifications and test methods that will assure that each drug sold is safe and meets the standard under which it is represented;

j) Records

Evidence that drugs have been produced under prescribed conditions can be maintained only after developing adequate records;

k) Samples

Samples must be retained in the event that re-examination is necessary;

l) Stability

Each packaged dosage form must be covered by sufficient amount of data to support its asserted shelf-life in its trade package;

m) Sterile Products

Sterile products must be prepared under well controlled conditions.

If you read any texts on the management of quality control you will often find the definition of GMP as Good Management Practices. Whether we refer to good management or good manufacturing we are saying that systems must be validated and documented as being in control. Validation is a subject that has received considerable attention in the past few years. Basically it is the evaluation and documentation of evidence to demonstrate that the conditions and methods employed as defined can be relied upon to produce the intended result.

Due to the deficiencies of sterility testing, namely sample size and reliability, validation of the sterilization process is highly recommended. In fact, I shall go so far to say that it is required.

Total reliance on sterility testing of final products to give assurance of sterility could lead to serious problems. Audit of the various functions of manufacture is a role of quality assurance and is independent of quality control.

Whether we are talking about quality assurance or quality control there is one indispensable ingredient. That is people. Many of you will be familiar with the advertising slogan of one of our steel manufacturers. I quote: "Our product is steel, our strength is people". In the manufacture and control of pharmaceutical preparations we rely upon the knowledge and integrity of qualified people to deliver a safe and efficacious product. There must be an understanding of the total operations as well as the rationale behind those operations. There must be an emphasis on the development and education of the persons who are involved in the operations. Training programs and cultivation of attitudes committed to quality performance are essential. Remember that you cannot test quality into a product, people must ensure that the product is built with quality. I cannot emphasize enough that the selection, development and training of people is a critical element of any quality assurance program.

As head of a regulatory agency I would be remiss if I did not refer to the legislative requirements. The Canadian drug legislation, both the Food and Drugs Act and the Narcotic Control Act, is criminal law coming within the regulatory power of the Federal Government. It is not necessary to prove interprovincial trade in order to invoke federal control. The Food and Drugs Act applies to <u>any</u> food or <u>any</u> drug or <u>any</u> medical device sold <u>anywhere</u> at <u>anytime</u> in Canada. You will recognize that those are broad powers. Even the interpretation of sell is extensive. Let me quote from the Act: "Sell includes sell, offer for sale, expose for sale, have in possession for sale and distribute". Therefore, sale is not necessarily dependent upon a financial transaction. I have raised this point to clarify for you that the Health Protection Branch does have the authority to insure that drugs are manufactured, packaged, controlled and distributed in hospitals according to regulatory requirements of the Food and Drugs Act.

I should also like to point out that regulatory requirements are not limited to the GMP Regulations. Hospitals that are involved in manufacturing, packaging or distribution must comply with requirements for New Drugs, labelling, drug notification etc. In fact we consider the entire Part C, where applicable, applies to hospitals in the same manner as to any drug manufacturer in Canada.

Now that I have your attention, let me hasten to add that reason must prevail. For a number of years I have addressed various sectors of the pharmaceutical

industry with the theme "Come let us reason together". We must not lose sight of the fact that our ultimate goal is the benefit to the patient. It is my deeply held belief about the philosophy of a regulatory agency that our relationship with those being regulated must be carried out in an atmosphere of frankness; that we must deal with each other openly, candidly and honestly. I hope that the rules of the game can be understood by all and not only agreed to but adhered to, so that dialogue and discussion will prevail over legal actions. We prefer to work cooperatively with responsible profesionnals and to encourage voluntary compliance for the provision of safe and efficacious medications of acceptable quality.

We recognize that the Branch does not have a monopoly on talent or integrity and that the regulatory process must of necessity and economy involve extensive discussion among the various groups (i.e., the regulators, the regulated and consumer representatives). Indeed the assistance of the regulated is required to make certain that proposed regulatory changes are theoretically sound and capable of practical applications. Hospital pharmacists have participated in the development of the document on Good Manufacturing Practices for Drug Manufacturers and Importers and the Guidelines for Radiopharmaceutical Quality Control in Hospitals. I encourage you to be active participants, particularly where the regulatory requirements will directly affect your operations.

What is the role of the Health Protection Branch in quality assurance? Believe me, it is very extensive. Almost every unit of the Branch is involved in quality assurance to some extent. Respecting drugs and radiopharmaceuticals we are involved with research, evaluation, monitoring, education, information and compliance or enforcement.

I should like to remark about two particular aspects. Prior to marketing a New Drug the regulatory requirements are very specific. These requirements cover specifications for raw materials, information on the pharmaceutical dosage form including specifications and stability data, manufacturing procedures used in the production of the drug, and the quality control program and procedures used during all phases of production. The pharmaceutical quality of a drug is a condition "sine qua non" of its safety and efficacy.

Under the Canadian Regulations, the new drug procedure tends to apply to all drugs that continue to require careful scrutiny in order to assure their safety, efficacy and pharmaceutical quality, as well as to maintain appropriate surveillance of their effects and an adequate description of their properties and conditions of use. However, since there is no justification on a scientific or cost/benefit basis for the requirement of large volumes of repetitive drug data, it is felt that after the period of true development of a new drug, a New Drug Submission can be of the abbreviated type and should contain only information that is reasonable to require in order to provide the necessary assurance of safety, efficacy and quality of the product in question. Contrary to what has been alleged with regard to regulatory authorities, the Drugs Directorate wishes to be proactive in not impeding original research through the requirement of clearly excessive data, or slowing the development and introduction of new useful drugs.

Our experience points to increasing numbers of sponsorless drugs that manufacturers are not willing to make available for clinical investigation in this country, despite our requirements for such drugs being pared down to information without which no drug should be used for the first time in humans.

In the case of drugs without a sponsor, a research institution or a qualified investigator may file with the Health Protection Branch his own IND Submission, provided he can supply satisfactory evidence to support the safety of the drug for the trials he proposes to conduct, including the manufacturing data necessary to assure the integrity of the product. In some instances, a manufacturer who does not market or intend to market his product in this country, may be willing to make available to an investigator, the safety and manufacturing data required for the filing of an individual IND (by providing it in confidence to the Health Protection Branch). Officers of the appropriate Division of the Bureau of Human Prescription Drugs, will be happy to assist a qualified investigator in filing this type of IND and will discuss with him the experimental data and protocol requirements for his submission.

In the event that a New Drug is not available on the Canadian market, the Health Protection Branch can authorize a drug manufacturer to sell a designated amount of that drug to a qualified practitioner for use under his professional responsibility in one or several patients, if the emergency or contingency in question, the information available, and other related circumstances, warrant the issuance of such an authorization. Requests for this type of release should be directed to one of the specialized Divisions of the Bureau of Human Prescription Drugs, depending on the pharmacological or therapeutic category of the drug.

Once the product is actually marketed, the Branch has several surveillance activities. Let me use the QUAD Program as an example.

The Department of National Health and Welfare implemented the QUAD Program (Quality Assessment of Drugs) in 1971, with the objective of providing health professionals with unbiased scientific and technical information on the quality of drugs. The intent of the Government of Canada was to demonstrate to Canadians that the level of quality of drugs is relatively high. Concentration was placed on multisource drugs so that quality and price would be considered during prescribing and dispensing. During the following years, the provincial Departments of Health, within the framework of their responsibility for health in Canada, developed their drug reimbursement plans. The need for information upon which the provinces could make rational decisions on the selection of drug firms and drug products was common to all.

The following basic principles were established to guide this surveillance program:

i) the manufacturer is responsible for the drug products that he manufactures and sells;

ii) the government monitors the capability of pharmaceutical manufacturers and their conformity with the legislation; and,

iii) the government provides unbiased objective data so that health professionals and provinces may make sound decisions on the prescribing and dispensing of drugs and on selection of drugs.

On-site inspection, laboratory analyses and provision of information are the three main features of QUAD.