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IN PROCESS QUALITY CONTROL IN THE MANUFACTURE OF ESSENTIAL DRUGS

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ABSTRACT

During the Thirty First World Health Assembly of the World Health Organization, Resolution WMA 31.32 on the Action Programme on Essential Drugs which recognized the importance of an adequate supply of essential drugs and vaccines to meet the real health needs of people living in developing countries was passed. The resolution also recognized the legitimate aspiration of developing countries to establish local production of those essential drugs wherever feasible.

In implementing the resolution, the WHO has called a meeting of its Expert Committee on the Selection of Essential Drugs in October 1977. The report of that

Meeting resulted in a model list of essential drugs which appeared in the WHO Technical Report Series 615.

Continuing its efforts to fully implement WHA 31.32, the WHO has called the Meeting on Drug Policies: formulation and dosage forms and in-process quality control of essential drugs in developing countries in April 1979. The meeting discussed recommendations on criteria for the development of formulation, packaging and in-process quality control for the local manufacture of essential drugs including problems which may be encountered in local conditions.

The present paper which was presented at the Arpil 1979 meeting, discusses the importance of and recommends guidelines for in-process quality control, discusses problems which are anticipated and suggests solutions in the manufacture of drug products in small and medium scale formulation plants.

The paper cites the potential of drugs to cause serious injury/death, the inadequacy of sampling plans, the need for and an explanation of validation of critical steps in the manufacturing process and methods for assurance of quality. The paper classifies the list of essential drugs into seven categories based on complexity of manufacturing and discusses suggestions on how to initiate and maintain cost effective indigenous pharmaceutical manufacturing

including a scheme of complementary/cooperative activities within and among nations in a region, "turn key" type contracts for facilities, personnel training, and the acquisition of manufacturing and control of manufacturing technology through purchase/licensing.

I. INTRODUCTION

On October 17-21, 1977, a WHO Expert Committee on the Selection of Essential Drugs met in Geneva for the purpose of developing, among other objectives, a model list of essential and complementary drugs which is intended to meet the needs for the prevention and treatment of the most prevalent diseases in member nations. The report of the meeting was reflected in the Technical Report Series 615[1] which included a list of 209 drugs.

The objectives of this paper are: (1) to develop arguments to demonstrate the importance of in-process control in the manufacture of those essential drug products in small or medium scale formulation plants; (2) to develop guidelines which will enable formulation plants in developing nations to organize for in-process quality control activities; (3) to discuss problems which may be encountered in the development of these activities as well as suggestions on how to overcome those problems.

II. THE IMPORTANCE OF IN-PROCESS QUALITY CONTROL IN THE MANUFACTURE OF DRUG PRODUCTS IN SMALL OR MEDIUM SCALE FORMULATION PLANTS

A. The Uniqueness of Drug Products as a Consumer Commodity

Drug products, whether it be analgesic tablets, antibiotic injections, anesthetic gases, intravenous fluids, and the like, often contain potent ingredients so that errors due to over-potency or misapplication, or a mix-up in labeling or formulation, can lead to serious injury or death. Errors due to potency loss resulting from lack of stability may result in the disease state prevailing on the patient. The failure of the container/closure system to continuedly provide sterility and/or freedom from pyrogens in injections, may result in grave consequences to the patient. Yet, in the greatest number of these circumstances, the patient as a consumer, is totally incapable of being able to discern that the product is defective--he is incapable of even determining its identity. He has, in each of these instances, to rely absolutely on the credibility and integrity of the manufacturer; to place implicit trust and faith on the label statements of the product he has to take.

B. The State of the Pharmaceutical Manufacturing Art

The objective in the manufacture of a drug product is to reproduce in every dose or unit manufactured, all

the specifications of the original drug product which was developed through research, so that the manufactured drug product possesses all the attributes of efficacy, safety and stability of the investigated formulation. These attributes have to be maintained throughout the shelf life of the manufactured product until it is administered to a patient. In order to attain this objective, the manufacturing process has to be as accurate and as reproducible as possible.

In the past, the accuracy and reproducibility of a manufacturing process was determined through the performance of tests on samples at various points of manufacturing, specially in the completed product. The collective acts of sampling and testing were generally defined as the quality control function.

More recently, during the last decade, a growing awareness of the risk factors attendant to sampling plans[2], has led to the pharmaceutical industry's evolving a distinct function of quality assurance. This latter term is defined by Juran[3] as the àctivity of providing to all concerned, the evidence needed to establish confidence that the quality function is being performed adequately. Some specific activities of quality assurance are the following:

a. Development of a sampling plan with known levels of confidence;

b. Validation of critical steps in the manufacturing process;

c. Assurance of compatibility and stability in the market container;

d. Assurance of sterility and freedom from pyrogen in injections and other sterile products which require them.

In general, as it was so aptly put by Lintner[4], the main purpose of a quality assurance program "is to devise and implement systems and procedures that provide a high probability that each dose or package of a pharmaceutical product, will have homogeneous characteristics and properties (within reasonably acceptable limits) to insure both safety and efficacy of the formulation," or in contemporary phraseology, to assure that the firm is in compliance with current good manufacturing practices.

The homogeneity of characteristics and properties of each dose or package is dependent on what Shrock[5] identifies as assignable causes of error, or viewing it positively, the elements of quality. In effect, the failure of one or more of the following elements will result in a defective product:

1. Men
2. Materials

3. Machinery

4. Methods

In the context of this paper, the "men" refers to all persons that contribute toward the manufacturing process; the "materials" are components, containers/closures, labels, in-process materials, finished drug products, supplies, etc.; the "machinery" refers to buildings, facilities, equipment, instruments, tools, support systems, etc.; and "methods" refer to manufacturing and control of manufacturing procedures, records, etc.

Moreoever, the homogeneity of characteristics and properties of the product depend on the reliability of critical manufacturing steps. The greater the knowledge of these critical steps, the more reliable the step. This knowledge is developed through assiduous validation.

This reporter suggests the validation procedure to consist of the following phases[6]:

A. Qualification

B. Challenge

C. Monitor

D. Requalification

"Qualification" is the performance of tests to determine if an element of quality possesses the

attributes it is purported to possess. "Challenge" is the performance of tests to determine if an element of quality can accomplish its intended function, and the limits of that capability, i.e., the conditions at which the element starts to fail. "Monitor" is the recording of conditions at events during the employment of the element. "Requalification" is the performance of tests at finite intervals to reestablish the capability of an element to accomplish its intended function.

Combining these concepts of factors which affect the production of homogeneously acceptable product, the following grid is proposed in the validation of each critical step in the manufacturing procedure.

Once a critical step is validated, the reproducibility of the manufacturing process is assured through

VALIDATION PHASE	QUALITY ELEMENTS			
	1 MEN	2 MATERIALS	3 MACHINERY	4 METHOD
A. QUALIFICATION				
B. CHALLENGE				
C. MONITOR				
D. REQUALIFICATION				

the performance of monitor tests which would effectively confirm that the process was in fact accurately reproduced.

This monitor function is currently viewed as one of the functions of Quality Control and the philosophy manifested differs greatly from the past concept of the function of Quality Control which was stated in an earlier section as the performance of tests to determine if a process was being reproduced.

C. In-Process Quality Control

Another basic concept in the production of homogeneously acceptable drug products is the theory of confinement of error. This concept may be stated simply as the development of activities that would prevent defectives from being proliferated.

For example, errors by manufacturers of components, closures/components and other materials, may be prevented from affecting manufacturing in the firm through a system of quarantining of all in-coming shipments, sampling and testing them before using in production[7]. Similarly, errors committed within the firm, are prevented from affecting consumers (patients) by the quarantine of manufactured lots, sampling and testing them before releasing for distribution. This concept is illustrated in Figure 2.

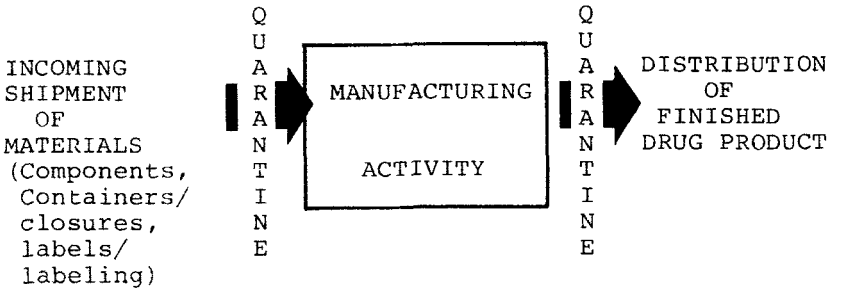

Figure 2
Confinement of

Error In Pharmaceutical Manufacturing

An expansion of the manufacturing activity will disclose the following general sub-processes:

1. Receiving
2. Storing (Released Materials)
3. Batching
4. Processing (e.g. Tablets from directly compressible formulation of granulation)
    a. Drug mixing of components
    b. Compression
5. Packaging
6. Storing (Finished Drug Products)
7. Distribution

Within the manufacturing activity, there are specific critical points wherein controls need to be applied in addition to the screening of in-coming shipments of components, containers/closures, labels/

labeling, and the outgoing lots of manufactured products. E.g. immediately after the dry mixing of the batch, samples of granulation may be taken and tested to confirm such specifications as homogeneity, moisture content, particle size distribution and color. After compression, samples of tablets may be taken and tested to confirm such specifications as tablet hardness, average weight variation, content uniformity, dissolution rate, tablet thickness, diameter, etc.

Depending on the product category, the check points and tests performed will vary.

The total quality control activity shown above from the screening of possible defectives produced by suppliers, through the certification of finished lots for distribution, may be referred to as In-Process Quality Control. It can therefore be seen that In-Process Quality Control is the cutting edge of Quality Assurance in drug product manufacturing. It is a principal deterrent to the manufacture of defective drug product. It represents a major justification for the credibility of a firm. In-Process Quality Control as a unit, is the screen between a consuming public that is powerless in determining quality and any defective drug product that may be provided to it for consumption.

III. GUIDELINES

The principal objective of In-Process Quality Control is to assist the Manufacturing unit in the production of universally competetive drug products through: (1) confirmation of expected specifications, (2) the detection of and the prevention of proliferation of defectives through confinement and/or recall of such defective material. To accomplish this objective throughout the spectrum of activities in the manufacture of essential and complementary drugs, the following guidelines are recommended:

A. The creation of a Pharmaceutical Coordinating Committee for each participating member nation or for each region of participating nations which will operate in a cooperative relationship consisting of representatives of the potential industry, namely, the private sector, the government laboratories, the regulatory agency, and academia.

B. The re-classification of the list of essential and complementary drugs into categories of increasing complexity of manufacturing processes involved such as is shown in Table I.

C. The synthesis of a phased development plan, based on complementary/cooperative activities among elements of a participating member nation or among participating member nations within a cooperative

TABLE I

CATEGORIES OF ESSENTIAL AND COMPLEMENTARY DRUGS AS A FUNCTION OF COMPLEXITY OF MANUFACTURING

Category I - Oral and Topical dosage forms of less potent drugs.
(E.g. Acetylsalicylic acid tablets, vitamins, antacid tablets, benzoic acid + salicylic acid ointments)

Category II- Oral & Topical dosage forms of more potent drugs. (E.g. Digoxin tablets, betamethazone ointment)

Category III-Oral & Topical dosage forms of antibiotics. (E.g. Ampicillin capsules, neomycin + bacitracin ointment)

Category IV - Sterile dosage forms - parenterals (small volume), ophthalmics.
(E.g. Diazoxide injection, pilocarpine ophthalmic solution)

Category V - Sterile dosage forms - large volume parenterals.
(E.g. Glucose injection 5%) irrigation solutions.

Category VI - Biologicals
(E.g. Snake antivenom)

Category VII - Specialties
(E.g. Ether, anesthetic)

region, for the orderly initiation and growth of the indigenous pharmaceutical industry, including the decision to delay the manufacture of certain categories until the capabilities have been developed while emphasizing motivational factors for effecting the full development plan in the most expeditious way.

D. Grouping of participating member nations or regions consisting of contiguous participating member nations according to capability to produce different categories of drugs.

E. Within each participating member nation or region of participating member nations, the identification of the specific private and government entities which will be responsible for the manufacture and control of manufacture of specific drug categories.

F. Identification of the funding source and assistance in the obtention of the fund.

G. Acquisition of manufacturing and control of manufacturing facilities including buildings, equipment, instruments and tools.

H. Organization, in cooperation with participating developed member nations, of cost effective programs for the training of operating and supervisory personnel in manufacturing and control of manufacturing.

I. Acquisition of pre-validated master production records and quality control measures required for the manufacture of the above-listed essential and complementary drug products.

J. Creation of instruments of agreement among participating member nations for drug quality standardization and mutual inspection for compliance to good manufacturing practice guidelines.

Cost effectiveness is extremely important and the contribution which participating member nations and regions can make in attaining this goal can not be overemphasized.

IV. PROBLEMS ANTICIPATED AND SUGGESTED SOLUTIONS

The more outstanding problems which are anticipated may be classified into Technical and Non-Technical types.

A. Technical Problems

1. The identification and training of personnel in manufacturing and control of manufacturing.

When the key personnel for the industry in a participating member nation have been selected, their training can be undertaken through the assistance of developed member nations. Short but concentrated programs can be organized so that trainees can have

adequate "hands on" type of learning experiences. All trainees should go through the manufacturing and control of manufacturing courses.

Consideration of baccalaureate in pharmacy or related biological or health science degrees as a minimum background for key personnel in manufacturing and a baccalaureate in chemistry, chemical engineering or related field for key personnel in control of manufacturing operations is recommended.

Consideration should be given to sequential, multiple level training programs in manufacturing and control of manufacturing, including the following topics:

Dosage Forms

Dosage Forms manufacturing

- Non-sterile products
- Sterile products
- Specialties

Statistical methods including sampling theory

Chemical Testing

Physical Testing

Microbiological Testing

Validation Procedures

Operating personnel will be trained by the key personnel in the manufacturing site.

2. Planning, design and construction of buildings and facilities and installation of processing and support equipment and instruments.

This problem may be resolved through the assistance of firms specializing in pharmaceutical construction in the developed countries. Consideration should be given to "turn key" operations where the scope of the work can be adequately defined.

3. Acquisition of manufacturing and control of manufacturing technology.

The expense of investigative activity in research and development of original dosage forms including quality control procedures is known to be substantial. Even of more serious concern is the length of time that is involved. To be sure this problem can only be compounded when the personnel involved in the study have yet to be trained. The recommendation of this reporter is to acquire the knowledge which is restricted to generic medication through purchase. The strategy should be to acquire through purchase or licensing, pre-validated master production records and quality control procedures for the particular drug products for which a participating member nation may be responsible.

4. Consultants

In general, the resolution of the technical problems should consider the assistance of consultants from developed member nations.

a. General consultants with broad pharmaceutical manufacturing experience should be considered to assist the Pharmaceutical Coordinating Committees.

b. Project consultants to assist in specific problems, e.g. water purity, analytical methods, should also be considered.

Subsequently, when the indigenous industry has developed the potential capability, studies should be conducted to determine whether in-house investigative activity or purchased technology is more cost effective. It is only when originally developed drug products are programmed when intensive indigenous investigative capability is recommended.

B. Non-Technical Problems

1. Authority of the Pharmaceutical Coordinating Committee

The Pharmaceutical Coordinating Committee should have the full support of the government of the participating member nation and the respect of the professional, academic and business community in order for it to be able to act expenditiously.

2. Financing

The funding of activities from the organization of the Pharmaceutical Coordinating Committees, training of personnel, acquisition of facilities and technology will be substantial. The funding source(s) has to be identified and be accurately informed of the time frames of the different phases. Participants have to be assisted in the obtention of funds.

3. Overt and Covert Rivalry

Rivalry among elements within a participating member nation and among nations in a region may produce obstacles in the realization of the scheme to develop the indigenous pharmaceutical industry.

Pride of accomplishment and economic gains are identified as the rewards of success in this venture and is seen as both reasons for rivalry as well as for cooperation and complementation. Excessive competition will surely defeat the venture in a technological as well as in an economic sense.

4. Converting participating member nations from consumer to producing nation.

Elements in nations which were traditionally economically dependent may opt to continue a policy of purchasing drug products as opposed to manufacturing because of the tempting ease by which financial

profits may be made. But as has been pointed out earlier, if the indigenous pharmaceutical industry is properly nurtured, there is a great wealth of pride, new high levels of economic gains and national self sufficiency in essential drugs which can be attained.

5. How far to industrialize?

Consideration should be given to the opportunity of the new indigenous pharmaceutical industry to contribute to the employment needs of the participating member nation. In mechanizing pharmaceutical manufacturing activity, thought should be given to the level and extent of industrialization so that a balance is attained between assurance of drug product quality through homogeneity of manufactured batches attainable only through mechanization and certain labor intensive activities such as packaging in which there is minimal impact on the quality of the product. Thus, the new indigenous industry is able to contribute maximally to the economic amelioration of the participating member nation.

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