GUIDE FOR DRUG MANUFACTURERS

UBLICATION OF THE DEPARTMENT OF NATIONAL HEALTH AND WELFARE, CANADA

GUIDE FOR

DRUG MANUFACTURERS

The Food and Drug Directorate

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Preface

The Directorate has often been asked for its point of view in interpreting and administering those parts of the Food and Drugs Act and Regulations which relate to drug manufacturing.

Neither the Act nor the Regulations specify in detail what may or may not be done under the law, however through the years the Directorate has accumulated a body of administrative interpretations based upon the intent of the Act and Regulations, and this Guide attempts to set these forth. It should be noted that these interpretations are not the law. Should differences of interpretation of the provisions of the Act and Regulations arise which cannot be settled, the final decision must be sought in the courts.

This GUIDE cannot be comprehensive, and it is not intended to cover every conceivable case. While it is unlikely that there will be many changes, this GUIDE must not be regarded as a static document. It will be supplemented or amended from time to time as occasion arises and will also reflect the changing pattern of the legislation.

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SECTION 1

Introduction

"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 as provided in Section C.01.052".

This statement is a direct quotation from that part of the Food and Drug Regulations known as the Manufacturing Facilities and Controls section which outlines in general terms the conditions under which drugs shall be manufactured. The object of this guide is to interpret what is required under the Manufacturing Facilities and Controls Regulations (MFC Regulations).

An understanding of the three terms, "Drug", "Manufacturer" and "Sell" is essential since these form the basis of the MFC Regulations. These are defined in the Food and Drugs Act and Regulations as follows:

Drug -- *(Section 2(f) of the Act.)*

> *'"Drug" includes any substance or mixture of substances manufactured, sold, or represented for use in (i) the diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical state, or the symptoms thereof, in man or animal, (ii) restoring, correcting or modifying organic functions in man or animal, or (iii) disinfection in premises in which food is manufactured, prepared or kept, or for the control of vermin in such premises.'*

Manufacturer -- *(Section A.01.010 (g) of the Regulations)*

'"Manufacturer" except in Division (3) and Division (4) of Part C, (Food and Drug Regulations) means a person who under his own name, or under a trade, design or word mark, trade name or other name, word or mark controlled by him sells a food, drug, cosmetic or device, and includes a firm, partnership, or corporation.'

It should be noted that the definition of "manufacturer" in Division 3 and Division 4 of the Regulations reads as follows:

C.03.001. (c) "manufacturer" means a person to whom a licence has been issued as provided in this DIVISION.

C.04.001. (d) "manufacturer" means a person to whom a licence has been issued as provided in this DIVISION.

Sell -- *(Section 2(m) of the Act)*

'"Sell" includes sell, offer for sale, expose for sale, have in possession for sale, and distribute.'

Plant Inspection

Anyone who sells a drug as defined in the Act and who puts his name and address on the label is subject to the requirements of the MFC Regulations and a plant inspection.

Section 21 of the Act permits an inspector, at any reasonable time, to enter any place where a drug is manufactured for the purpose of examining the premises, and the product produced therein. He may take samples of the product for subsequent examination and inspect anything that he reasonably believes is used or is capable of being used for the manufacture, preparation, preservation, packaging or storing of drug products. This section also permits the inspector to open and examine any receptacle or package containing an article to which the Act or Regulations apply. He may examine any relevant books, documents or records found on the premises, and make copies thereof or extracts therefrom. The manufacturer is required to give the inspector all reasonable assistance and to furnish him with any information that he may reasonably require.

Normally, the inspector who visits a drug plant to conduct a plant inspection will have been employed by the Food and Drug Directorate for a number of years. He will be a university graduate, either in pharmacy or chemistry, and trained in drug plant inspection techniques.

The inspector, upon arrival at a drug plant to carry out an inspection, will introduce himself to management and explain the purpose of his visit. Many firms find it advantageous to assign one of their personnel to accompany the inspector throughout the inspection to see that he gets as much information as possible and to answer any questions that may arise. It is of mutual benefit to have a person familiar with plant operations accompany the inspector.

No set pattern for an inspection is followed, however, the prime consideration is to determine that the firm is complying with the MFC Regulations. While it may not be possible to review every product that is manufactured, a number will be selected for study.

Photographic records which may be made during the inspection are strictly confidential and serve the sole purpose of recording situations which the inspector feels might be described as unsanitary conditions. Authority for the taking of such photographs is given under Section A.01.026 of the Regulations and reads as follows: "An inspector may take photographs of premises and articles to which the Act or Regulations apply as defined in Section 21 of the Act as may be relevant to the administration of the Act or the Regulations insofar as they apply to unsanitary conditions."

Following the inspection, the inspector will discuss with management any deficiencies which may have been shown to exist in the operation. It is important that this discussion be as open and frank as possible so that no misconceptions exist on either side.

Following the inspection, the inspector evaluates the operation, prepares a report and assigns a rating. Essentially, this rating compares the operation of the plant to the minimum requirements of the Regulations. The rating scheme enables the Directorate to focus its attention on those plants requiring it. The inspector then prepares a letter to the firm, pointing out those aspects of the operation considered to be in violation, or likely to result in violation of the Regulations.

It is stressed that all material made available during a plant inspection is held in confidence within the Food and Drug Directorate.

SECTION 2

Premises and Equipment

The design and construction of a building for pharmaceutical production and the equipment used therein should incorporate features which eliminate hazards that might detract from the quality of the finished product.

The basic structure, consisting of floors, of an adequate area for the intended use, walls and ceilings, should be designed in such a way as to permit adequate cleaning. Surfaces should be hard, smooth and free of any cracks or sharp corners where extraneous material can collect. Such things as unsealed block or brick walls, acoustic tiling, floors and walls that present hard-to-clean corners, should be avoided.

Steps should be taken to prevent the migration of extraneous material from the outside and from one area to another within the building. Insects, rodents and filth can be prevented from entering the building by well-fitting windows and doors and properly sealed walls, ceilings and floors. Floor drains should be adequately screened and trapped. Inside the building, doors separating various areas should shut tightly, holes in walls to permit the passage of essential services should be sealed with collars. Beams and trusses in the ceiling should be concealed or properly sealed with a protective coating.

Cross-contamination between drug products is a definite hazard. Prevention is often difficult because of the minute quantities of material involved and the ease with which it can be transported by air currents. The use of adequate exhaust equipment, the isolation of dusty operations and the thorough cleaning of equipment all play an important part in preventing cross-contamination.

The lighting should be of sufficient intensity so that employees can adequately carry out their duties. All lighting fixtures should have their exposed surfaces cleaned at periodic intervals. The ventilation system should be designed to protect against the movement of extraneous material from one area to another. Open windows are not a satisfactory form of ventilation. A forced air system with adequate filters readily removable for cleaning and replacement is almost essential. Adequate separation should exist between inlet and exhaust ports.

Plant equipment should be designed with smooth surfaces to eliminate the entrapment of any contaminant and be of a non-reactive durable material. The design should be such that no possibility exists of a lubricant contaminating the product.

The equipment and the adjacent areas should be readily cleanable. Regular maintenance programmes should be carried out to ensure that the equipment performs in a satisfactory manner.

Normally, equipment should be cleaned following use according to a written procedure to ensure that when used again, subsequent lots will not be contaminated. All equipment not in use should be adequately covered. In all cases, the objective is to start manufacturing with clean equipment.

SECTION 3

Sanitation

A written sanitation programme is essential, and should outline the procedures to be employed, specify the personnel responsible for the programme, the areas to be cleaned, what materials are to be used in the cleaning process, and the frequency of the operation.

The premises should be clean, sanitary and orderly. Accumulated waste or debris and discarded obsolete equipment should be removed therefrom.

The presence of animals of any kind must not be tolerated, unless they are to be used for test purposes, and are suitably separated from the processing areas. The presence of any insect or rodent indicates that the sanitation programme is inadequate or not being followed correctly.

Working areas should be kept free of all unnecessary tools, lubricants, unused equipment and spare parts. Raw materials unrelated to the immediate production of a batch of a drug should not be in the processing area. Bulk dosage forms or labelling material should not be in evidence in the packaging area, unless associated with the finishing orders in progress.

Wash-up and toilet facilities should be of adequate size and of such design that they are easily cleaned on a regular basis. Adequate light and ventilation as well as suitable sanitary supplies should be available. Separate wash-up facilities should be available at strategic locations throughout the plant, where processes are such as to demand frequent hand-washing. Hands should be washed in hot water using soap, preferably from a dispenser, and dried with single service towelling or air dryers.

Eating and smoking should be confined to specific dining or rest room areas.

Clean uniforms and smocks, as well as suitable head covering should be available to and used by all employees in the production, packaging and testing areas. Consideration should be given to the use of a separate pair of shoes in the plant, since street shoes have been found to be a frequent source of contamination. Personnel should be circumspect in the use of cosmetics to preclude the possibility of product contamination from this source.

SECTION 4

Personnel

People are the most important element of any pharmaceutical operation, for without the proper staff with the right attitude and the right training, it will be almost impossible to produce good quality drug products. It has been demonstrated that inadequate training of personnel, or the absence of an appreciation of the importance of Quality Control, often accounts for the failure of a product to meet the required standards.

A quality product can be produced only by well qualified personnel. Quality Control is more than just the sampling and testing of products after the manufacturing operation is completed.

Health

A medical examination of all new employees is in the interest of management. Management should take precautions to ensure that on-the-job employees who become ill do not contaminate products in process. This is particularly applicable to the parenteral manufacturing area.

Maintenance Personnel

Duties assigned to the maintenance unit may differ from plant to plant, but regardless of the scope of their duties, such personnel should have some interest in maintaining the plant in a clean and sanitary condition. It is expected that they will have had some on-the-job or academic training in this field and be granted sufficient authority to ensure that the standards for which they are responsible are enforced.

Technical Personnel

Experienced university graduates are required for most senior positions in a pharmaceutical firm. They should hold a degree in a science related to the work being carried out and in addition should have some practical experience in their responsibility area. It is expected that most firms would employ at least two such people: one in charge of the Production Department, and the other in charge of the Quality Control Department.

Personnel with these qualifications are expected to prepare and check all Master Formula Cards, supervise the formulation, processing and testing operations, or directly supervise the personnel responsible for these operations.

Technically competent personnel are also required in many other critical areas. They should have some working experience in their responsibility areas and management should supplement this with further training to suit their particular requirements.

Competency

An individual may have sufficient academic qualifications but lack the experience necessary to put his knowledge into practice. Management should always be watchful to ensure that employees are competent to carry out the tasks required of them.

SECTION 5

Quality Control

Quality Control may be defined as the sum of those duties which must be carried out to ensure that the quality objectives of the company are met. At present a universally applicable quality control system does not exist since the tremendous number and variety of substances used in the industry, the many types and sizes of company organizations and the complexity and diversity of products are such that some of the elements of quality control can only be generalized. Nevertheless, there are certain minimum functions that should be carried out.

The Quality Control Department and the Quality Control exercised over the products will be only as good as Management demands. Unless Management has a good understanding of Quality Control, determines what the quality objectives are and defines the responsibility for action, the overall system is liable to be less than adequate.

Too often, the Quality Control Department is thought of as the Analytical Laboratory where chemical assays are carried out and not as the group of people who ensure that the final product possesses all the desired characteristics of identity, purity, potency, safety, uniformity, efficacy, and stability within established levels that meet all legal, professional, and company standards.

Raw Material Control

Raw Material is defined as any material entering the plant for use in any stage of production of the final dosage form. This includes items such as active ingredients, excipients and solvents.

Packaging Material Control

Packaging material includes all material used in packaging the final dosage form, such as containers, caps, labels and desiccants.

Purchase Order

All raw materials, including packaging materials should be ordered according to established specifications, whether these be official standards or house standards. Although emphasis is placed on specifications for active ingredients and excipients to ensure that a pharmaceutical grade is received, all materials used in production are important. These standards should form part of a permanent record and be checked from time to time by the Control Department.

Receiving Number

Receipt of all raw materials and packaging materials should be recorded and a lot number, receiving number or laboratory control number assigned. The material should be clearly labelled as to identity, and the assigned numbers should be included in whatever records are maintained in the Control Laboratory. This number should appear on the raw material container and the name and number on the release tags and manufacturing orders.

Quarantine Area

Upon receipt, all raw and packaging materials should be quarantined in a designated area, until the Control Department has carried out the necessary inspections and tests on representative samples to ensure that the materials comply with the purchase specifications. Materials awaiting approval should be differentiated from those which have been released. Preferably, the quarantine area

should be under lock and key and be accessible only to specified personnel. However, where space is limited, the quarantine area may be indicated by painting the floor a distinctive colour, and by the use of signs indicating that this is a quarantine area and is therefore restricted to designated personnel. Released material should be relocated under proper inventory control in the appropriate storage area.

Storage Area for Raw and Packaging Materials

Released materials should be stored away from the immediate manufacturing and packaging area. This is essential in order to reduce the danger that the wrong material may be used in the processing and packaging of a drug product and to effect proper inventory control. Released raw and packaging materials should be stored in an organized fashion, properly identified by labels on which all pertinent information appears and kept under strict inventory control with access limited to designated personnel. These materials should only be released on receipt of a written order.

It is recommended that labels for different potency preparations of the same product be stored in a separate box clearly marked. All labels should be kept under lock and key, and made accessible only to designated personnel.

Storage Conditions for Raw Materials

Conditions of temperature and humidity in all storage areas should be such as not to affect adversely the raw materials therein stored. The Control Department should establish appropriate storage conditions for all raw materials.

Master Formula

A master formula should exist for each product manufactured. These formulae should be maintained in an organized manner and in such a form as to facilitate photocopying or duplication. The preparation of the master formulae should be the responsibility of academically qualified personnel and each master formula should be checked independently by a similarly qualified person, and dated and initialled or signed by both. When alterations or changes are required, a complete new master formula should be prepared by qualified personnel and checked again. The old master formulae should then be maintained in a separate file designated as out-of-date so that there is no possibility of confusion with the current master formulae. Master formulae are prepared for a standard batch size. It is, therefore, necessary that separate master formulae should contain all information pertinent to the manufacturing of the drug. This information should include at least:

(1) Specifications for and a quantitative list of ingredients.
(2) A detailed description of the manufacturing procedure.
(3) Notation of any special precautions to be observed.

Manufacturing Order or Work Order

The manufacturing order, which normally is a copy of the master formula, should be issued on the instructions of a qualified person. Where the manufacturing order is not a photocopy of the master formula, particular care should be taken in transcription and in either case the manufacturing order should be checked independently by a qualified person.

In addition to a complete listing of the ingredients by name or code and a description of manufacturing procedures, the manufacturing order should include space for the lot number, the size of the particular batch, spaces for the receiving number for each raw material and space for the initials of the weigher and checker, and the person responsible for each step in the manufacturing process. The order should also include the date of issue, the name of the person issuing it, and the actual and theoretical yield.

The use of initials has a good psychological effect as it impresses upon the individual the responsibility undertaken in performing or checking the work, and also supplies accurate information as to personnel involved in the production of a specific lot or batch. The manufacturing order should carry a precise description of all raw materials to be used indicating the particular grade of raw material required. Every step in the manufacturing operation should be explained in sufficient detail to prevent misinterpretations. Any special precautions to be observed, the equipment to be used and any quality control checks required to be carried out, should be described and explained on the manufacturing order.

General Manufacturing Procedures

When the manufacture of a batch of a drug is to be effected, the manufacturing order should be prepared as already described and a copy forwarded to those departments and personnel directly concerned. The supervisor of the chemical raw material stock, upon receipt of an order, should have each ingredient dispensed and weighed

according to the instructions on the manufacturing order. The raw materials gathered for dispensing should be independently checked for identity and appearance. As each ingredient is weighed, the container in which it is placed should be clearly labelled as to identity and weight, together with the batch number from which it was dispensed. When all the ingredients have been procured, they should be grouped together for removal to the appropriate production area, and the dispenser and his checker should both initial the order. As each ingredient called for on the manufacturing order is used, it should be visually checked for identity and weight by two qualified persons. The initials of each person should appear opposite the name of the ingredient in the space provided. The name or the identification number and the receiving number for each ingredient on the manufacturing order should agree with those on the original ingredient container. The manufacturing order should remain with the drug throughout the manufacturing process and should either be attached to or be placed as near as possible to the machinery being used. It is mandatory that equipment, and containers, in which the drug may be placed during and after processing are labelled properly as to identity and lot number. As each step in the manufacturing process is performed, the person doing the work should initial the manufacturing order in the appropriate place.

Quarantine and Storage of Bulk Dosage Form

When manufacture is complete, the bulk dosage form should be held in quarantine, pending examination and release by the Control Department. The testing at this stage may or may not be comprehensive, depending on company policy. If the

bulk dosage form is to be stored for any period of time before packaging, the control department should specify conditions of storage and areas should be developed incorporating these requirements. The containers used to store the bulk dosage form during these waiting periods should be adequate to preserve potency and quality, and should be clearly labelled as to identity.

Packaging Control

Master packaging specifications should exist for each package size of each product, and should be prepared and independently checked by competent and responsible individuals. The master packaging specification should indicate

(1) the name of the drug for which the packaging materials are intended
(2) the size, type and a description of the container, cap and all other related packaging material
(3) pertinent information relating to labels, cartons, inserts and all other printed packaging materials
(4) any special precautions or requirements, e.g. desiccant
(5) the type of equipment and procedures required for the operation.

Copies of all printed material normally accompanying the product should be attached to the master packaging order.

Master Packaging Order

The packaging order may be prepared by either photocopying the master packaging specifications or by manual transcription. In the latter case, it should be prepared and independently checked by competent and responsible personnel. In addition to the information contained in the master

packaging specification, the packaging order should specify the lot number which is to appear on the label of the packaged dosage form, the quantity of each of the components, such as labels, containers and caps, as well as the identification and quantity of the bulk dosage form to be packaged. It is important that there is adequate information on the packaging order to relate it to the particular batch of bulk dosage form to be packaged. To facilitate issuing of printed packaging materials, it is advisable to have a specimen of the materials to be used attached to the packaging order. Spaces should be provided on the packaging order for the initials of the supervisor. The information contained on the packaging order should be in sufficient detail to prevent errors during the packaging operation.

General Packaging Procedures

Packaging materials should only be issued against a written packaging order. As these materials are issued, ideally a complete identity check of each label should be made and the packaging order initialled by the checker. The approved bulk dosage drug should be issued only upon receipt of a written packaging order. This procedure should be checked carefully to ensure that the quantity and identity of the bulk dosage drug corresponds to the details given in the packaging order. The complete packaging and labelling procedure should be supervised by a qualified person who should be available at all times. As each operation is completed, it should be checked and initialled by the supervisor. Particular care should be taken to ensure that the right labels are used on the right containers. Written instructions concerning the disposal of unused labels should be available. Unused labels should be returned to the

supervisor who may return them to stock provided that no lot number has been stamped on them. It is good practice to destroy unused labels imprinted with a lot number.

Quarantine and Storage of Finished Dosage Form

When the packaging procedure is complete, the packaged drugs should be held in quarantine until released by the Control Department. It is essential, that the Control Department examine the product at this stage since it is the last check before the product is released for sale. After release, the packaged product should be stored under conditions designated by the Control Department.

SECTION 6

Control Department

Every drug firm should have a Control Department that is separate and distinct from the processing, packaging and sales department. This department should have full authority to carry out its responsibilities, with its decisions reviewed only by the highest level of management. If a laboratory is attached to the Control Department, it should be equipped to carry out adequate chemical, physical, biological and bacteriological testing, having regard to the nature of the products produced. It is not necessary that the Control Department have its own laboratory since it may be more convenient to use the facilities of outside laboratories. Nevertheless, full responsibility and control over the types of testing done is the responsibility of the Control Department, as is an assessment of the capabilities of the outside laboratory.

The Control Department should be staffed with well qualified personnel and be under the direct supervision of an academically qualified Control Manager. This department should maintain control records for a specified period of time. Where sampling is required, it is emphasized that the Control Department should obtain its own specimens rather than relying on other personnel to submit them. Only when the Control Department itself samples the product can it say with any degree of assurance that the sample that has been tested actually came from the lot in question. Sample size should be of such magnitude as to ensure that the quality control department can be confident that the test results accurately reflect the true character of the lot.

The Control Department is responsible for the approval of all raw materials and finished products and such in-process testing as is deemed necessary. It should also establish a definite policy for the handling of complaints dealing with the quality of the drug and be responsible for all returned drugs and their eventual disposal.

Raw Materials and Packaging Materials

The Control Department should ensure that raw and packaging materials of acceptable quality are used in the processing and packaging of drug products. It should establish specifications for each material and sample and test it adequately, to ensure that the company's specifications are met. These specifications are normally drawn up by the Control Department in conjunction with the Purchasing, Research and Development and Production departments in order that all may be aware of the exact requirements for each material.

When a raw material is analyzed, prior to receipt, by an outside laboratory, an identity test should be conducted on the firm's premises to ensure that the material received in the plant corresponds with the material previously analyzed. The analytical certificate should give specific details in the following areas:

(a) Physical characteristics including form, colour, melting point, solubility and so on.

(b) The chemical characteristics including identity and purity.

(c) The actual test results and analytical figures should be declared for each of the above factors.

Words such as "passes test" or "satisfactory" are unacceptable in instances where specific data is available.

The Control Department is responsible for releasing all approved materials from the quarantine area and may do this by placing an "approved" sticker on the body of each material container. The Control Department should also be responsible for the disposal of materials demonstrated not to meet specifications and a formalized procedure should be established to ensure proper disposal of rejected materials.

In-Process Control

Where in-process control is required as part of the manufacturing and packaging process, this control should be monitored by the Quality Control Department by personal inspection. The Control Department should also thoroughly review all completed manufacturing and packaging orders prior to release of the batch to ensure that:

(a) the actual yield compares with the theoretical yield, within the established limits, to show that no unspecified additions or deletions have been made.

(b) the production and packaging staff have carried out all steps and checks required of them.

(c) the completed manufacturing and packaging orders compare with the masters to insure that no unauthorized changes have been made.

Finished Products

As in the case of raw materials, all finished products should have individual detailed specifications which should

set forth in detail the physical characteristics of the product, the identity and potency tests that are carried out and the variation allowed from the specifications. The certificate of analysis resulting from these tests should report the results in detail. Phrases such as "passes test", or "satisfactory" should not be used in instances where specific detail is available. Until such time as the Control Department approves for sale a finished product, it should be held in quarantine in an area separate and distinct from the finished stock area. The Control Department must have some written direction outlining what is to be done with products failing to meet the company's specifications. Under no circumstances should these materials be marketed.

Where the manufacturer has carried out the complete testing on the finished dosage form of the drug before packaging, it is his responsibility to perform at least an identity test on the finished packaged drug as well as the routine inspections of labelling and packaging. When products have been held in storage for a considerable length of time, the Control Department should re-test them to ensure that they still meet specifications particularly where stability may be a problem. Specifications detailing the condition of storage of finished products should also be the responsibility of the Control Department, and products which require specific storage conditions should bear appropriate storage instructions on the label. The Control Department should retain samples of all finished products, preferably in finished package form, in sufficient quantity to enable further tests to be run without difficulty.

When testing is done by an outside laboratory the Control Department is responsible for reviewing the results and checking against specifications.

Stability

The Control Department should have available data on the shelf-life and stability of each product marketed, as well as information concerning possible degradation products which may appear therein.

Storage Area

The Control Department, being responsible for specifying the storage conditions of all raw materials, in-process material and finished products, should check storage areas from time to time to ensure that these specifications are being met.

Complaints and Returned Drugs

The Control Department should be aware of all complaints with the exception of those dealing with price, delivery or other administrative details. A separate complaint file should be maintained for each product and should contain information as to the nature of the complaint, action taken, and conclusions reached.

A system should exist whereby continuing complaints concerning a particular product are automatically brought to the attention of the Control Department. The Control Department must have a definite procedure for dealing with returned drugs. There should exist a strict policy of quarantine of such material upon its entry into the plant followed by thorough examination before final disposal.

SECTION 7

Records and Samples

Records

Several sections of the MFC Regulations require that tests be conducted. Evidence that such tests have been done can only be indicated by maintaining adequate records. Such records should cover raw material and finished product testing, packaging material checks, quality control, information on complaints, stability test data, recall procedures and sanitation. The MFC Regulations require that records be kept for a period of five years or until the expiration date appearing on the label of the product has been exceeded. No record should be destroyed under any circumstances until this period has elapsed. Certified copies of records shall be sent to the Director-General of the Food and Drug Directorate on his request. Records are useless if they cannot be examined, hence care should be taken to see that they are properly organized, identified and readily available for examination upon request.

Samples

A sufficient sample of each lot of the finished drug in dosage form must be kept under suitable storage conditions for a period of five years from the date of testing, or until the expiration date appearing on the label of the drug has been exceeded. Adequate portions of these samples must be forwarded to the Director-General on request. In determining the size of sample to maintain, one should always keep in mind that the Directorate needs at least

enough of the product to carry out adequate tests, and it would be expected that the company would also wish to test the product, hence the sample should be at least double the amount necessary to complete all required tests.

Good manufacturing practice would indicate that adequate samples of all raw materials should be retained for an appropriate period after the lot of raw material from which the sample was withdrawn has been exhausted.

SECTION 8

Product Information Records

There should be available for each product, information relating to the quality and hazards of the drug as well as reports of suspected and known adverse reactions. Complaints or reports concerning changes in efficacy of a product should be included and accompanied by a summary of follow-up action. Details of suggested treatment in case of over-dosage should be included. Information relative to new uses or to hitherto unknown side-effects as may appear in medical and scientific journals should form a part of this file.

It is also useful to have on file, memoranda concerning labelling errors and apparatus breakdown, repair and change. It may be of interest to include information concerning batches produced before and after the breakdown.

The MFC Regulations should not be interpreted to mean that reports are made only on accepted or proven drug adverse reactions. Any reactions of an unexpected nature should be catalogued and the information passed on to the Directorate.

SECTION 9

Recall System

The object of any Recall System is to notify as rapidly as possible those persons who have in their possession the drug which is the object of the recall. While it is sometimes necessary to recall all stocks of the drug, the recall of one specific lot number is the most frequent occurrence. This requires an accurate knowledge of the distribution pattern by lot number.

When it has been decided that recall is necessary, a pre-determined plan of action should be put into operation. This differs from plant to plant and may vary according to the seriousness of the situation necessitating the recall. In some circumstances national radio and television coverage will have to be given if the problem is serious enough, however it may be sufficient to notify the purchasers of the lot number of the drug and request their cooperation in withholding it from further sale.

Experience has shown that the initial recall notice should be forthright, brief and to the point. It must demand the immediate attention of the consignees and impress upon them the urgency of the matter. To supplement this recall letter, the use of medical representatives, newspapers, telephone and telegrams is recommended.

The following are suggested steps:

(1) Notification of all interested government agencies.

(2) Distribution of a circular letter to all customers, doctors, hospitals and pharmacists.

(3) Notification of those members of the firm's staff involved in such procedures and an indication of the role each is to play in the recall.

(4) The establishment of a system to control the returned stock, the disposal procedures to be used, and an accounting of the returned stock versus the total which was sold.

(5) The setting-up of investigational procedures to determine the reason for the failure of the product to conform to standard.

(6) Steps to be taken to prevent a recurrence of the problem.

SECTION 10

Parenteral Drugs

The requirements for a parenteral manufacturing area may be broken down into three categories: (a) General requirements, (b) Aseptic fill preparations, (c) Terminally-sterilized preparations.

General Requirements

All parenteral products, other than live vaccines, must be sterile when they leave the premises of the manufacturer. One of the best ways to ensure sterility is to subject the finished product to pressurized steam sterilization. This is the method of choice, and dry heat sterilization, gas sterilization or filtration should only be considered when steam sterilization will harm the product. Sterilization which can be performed only on the components of the pharmaceutical, necessitates that all compounding and filling be carried out under aseptic conditions.

Normally, all sterility testing is carried out in a room physically separated from the processing area, to avoid the contamination of the production area should an accident occur.

A routine should be established to ensure that water used in the production of parenteral products is pyrogen-free. The containers used to collect pyrogen-free water should themselves be pyrogen-free and have adequate closures to ensure against recontamination. To understand the complexities of parenteral manufacturing requires a person of broad skill and knowledge and the production and testing of parenteral products should be under the close supervision of an adequately academically trained and experienced individual.

Sterile distilled water plays a very important part in the operation of a parenteral plant and proper procedures for the cleaning and operation of stills should be established. Stills should not be operated beyond their capacity since this is likely to lead to the production of contaminated water.

While sterile distilled water is normally used as soon as it is prepared, adequate storage and handling procedures should be established to prevent contamination if this is not the case.

Complete records of all steps taken in the processing, filling and sterilizing procedures should be kept for review, and should include specific information on the sterilizing procedure and, where applicable, records of time, temperature and pressure.

Aseptic fill preparations

An enclosed part of the plant should be provided for an aseptic filling operation. Openings into these areas should be limited, ledges should be eliminated, and ceilings, walls and floors sealed so that they may be washed and sprayed or wiped down with a germicide. A minimum of equipment should be kept within the area, and should be of such a design as to be easily dismantled for cleaning.

Ultraviolet lights should be checked for emission and cleaned routinely. To prevent cleaning compound build-up, a distilled water or alcohol rinse should be used. Those lights whose emission falls below 70% of their maximum rated output should be considered for replacement.

The air that enters the aseptic area is possibly one of the greatest sources of contamination. One of the many types of sterile air systems should be installed, and the air should be delivered under positive pressure to prevent contaminants entering through temporarily opened doors or other normal openings. The air flow should be properly graded so that the most critical area receives the sterile air first and this is then transmitted to less critical areas for exhaust.

The cleanliness achieved in this area is dependent upon the ability of the air-handling system to purge the room of contaminants. This depends not only on the effectiveness of the filters and the number of air changes per hour, but also on the distribution of the air within the room, so that all areas are washed with sterile air.

The aseptic area should be subject to regular disinfectant sprays or wipedowns to eliminate the presence of micro-organisms. Dense fogging of the area using a disinfectant spray and a fan is one of the most effective means. The most commonly used antibacterial agent is one of the quaternary ammonium compounds.

Only authorized personnel should be permitted to enter the area.

Despite all precautions to ensure freedom from bacteria, there is the possibility that some may remain and, therefore, it is recommended that companies be on constant guard against this possibility by continually monitoring the air. This can be accomplished by taking air samples or exposing plates at strategic locations. Normally, plate counts or air sampling should be conducted during each operation.

Personnel employed in this area should be highly skilled, and thoroughly familiar with the processes they are carrying out as well as the reason for their constant vigilance. Employees showing any signs of illness should be barred from the aseptic area until completely recovered.

Employees entering this area should first scrub their hands with a germicidal soap and then properly attire themselves in clean sterile uniforms. Headgear that completely covers the hair, face masks and shoe coverings or sterile shoes should be employed. Usually rubber gloves are prescribed.

It is recommended that procedures should be checked at routine intervals by running a filling operation with sterile fluid thioglycollate medium or trypticase soy broth. The production-run of the media should comprise an adequate number of containers to permit a proper evaluation of the sterile process. All containers should be incubated and examined for micro-organisms.

Terminally sterilized preparations

Physical facilities required for the production of large-volume solutions vary greatly from those required for the production of ampoules or vials. It is possible that a firm making only vials and ampoules may wish to use their aseptic area for the production of terminally sterilized products employing identical techniques. Solutions are usually manufactured in an area which while not aseptic is kept as clean as possible. However, many of the architectural criteria for an aseptic area should be observed in its design.

Production personnel should be of high competence. Procedures, while less stringent than those necessary in the aseptic area, are nonetheless important. It is not necessary to wear sterile clothing nor shoe covers, but special precautions should be taken to avoid any type of contamination.

The sterilizing procedure should also be checked routinely for effectiveness by processing tubes similar to the normal sterilizer load, and known to be contaminated. If contamination can be demonstrated after the sterilization procedure has been carried out, suitable steps should be taken to improve the procedure.

There is also some merit to the practice of checking filled vials and ampoules prior to sterilization to determine levels of bacteriological contamination. If too-high levels are found, steps may be taken to improve the production and filling operations.

SECTION 11

Miscellaneous

Manufacturing Facilities and Controls Regulations

C.01.051. 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, as provided in section C.01.052.

C.01.052. For the purpose of section C.01.051, suitable conditions in respect of a drug require

(a) that the construction, fittings and furnishings of the area in a building where the drug is processed and packaged shall be of such material and finish as

(i) will permit the ready and efficient cleaning of all surfaces,

(ii) will prevent the introduction of extraneous materials into drugs during their processing and testing, and

(iii) will prevent the migration of dust,

in accordance with good pharmaceutical practices;

(b) that the premises used for the processing, testing, finishing, distribution and storage of the drug and all auxiliary facilities shall be maintained in a clean, sanitary and orderly condition free from vermin, infestation, accumulated waste or debris;

(c) in the event parenteral drugs are processed, that all fillings and aseptic processes shall be carried out in a separate and enclosed area designed for the processing and filling of such drugs and operated in a manner that will prevent contamination of the drug compounded and filled;

(d) that qualified personnel shall be used as supervisors in the formulation, processing, testing, packaging and labelling of the drug, who shall have such technical training as is deemed necessary by the Director, having reasonable regard for performance of the duties and the responsibilities involved;

(e) that qualified personnel shall be responsible for the maintenance of machinery, equipment and sanitation;

(f) that each lot or batch of raw or bulk material used in the processing of the drug in dosage form shall be tested to ensure identity and purity of such raw or bulk materials;

(g) that each lot or batch of drug in dosage form shall be tested to ensure identity, potency and purity for its recommended use;

(h) that quality controls shall be used that are adequate having regard to the nature of the drug;

(i) that a system of control shall be used permitting a complete and rapid recall of any lot or batch of the drug from the market; and

(j) that records shall be maintained relating to the drug in a form, manner and content satisfactory to the Director showing

(i) the tests of each lot or batch of raw or bulk materials used in the processing of the drugs,

(ii) the tests of each lot or batch of drugs in the dosage form,

(iii) the quality controls,

(iv) all information received pertaining to the quality or hazards of any drug,

(v) the results of tests to determine the stability of drugs, and

(vi) the measures taken to ensure the recall of lots or batches of drugs from the market.

C.01.053. The records required to be maintained by paragraph (j) of section C.01.052 in respect of a drug shall be kept

(a) until the expiration of five years from the date of the testing of the drug; or

(b) until the expiration date of the drug,

whichever first occurs, and certified copies of any of the records shall be sent to the Director on his request.

C.01.054. A sufficient sample of each lot of the finished drug in dosage form shall be kept by the manufacturer under suitable conditions of storage

(a) until the expiration of five years from the date of the testing of the drug, or

(b) until the expiration date of the drug,

whichever first occurs, and an adequate portion thereof for analyses and examination shall be submitted to the Director on his request.

C.01.055. No person shall import into Canada for sale a drug in dosage form unless the person seeking to import the drug has available in Canada information and evidence that the conditions prescribed in section C.01.052 have been met in respect of that drug and at the Director's request furnishes to him such information and evidence.

C.01.056. No person who imports a drug in dosage form into Canada shall sell any lot or batch of that drug unless

(a) each lot or batch of the drug in dosage form has been tested in Canada by an acceptable method to ensure identity, potency and purity for its recommended use; or

(b) evidence is available in Canada, satisfactory to the Director, that each lot or batch of the drug in dosage form has been adequately tested in the country of origin.

Trade Information Letters

In order to advise manufacturers of changes in the Act and Regulations as well as other pertinent information, the Directorate publishes periodically Trade Information Letters. Any manufacturer may have his name placed on the mailing list by addressing his request to: Technical Secretariat, Food and Drug Directorate, Tunney's Pasture, Ottawa 3, Canada.

Office Consolidation of the Food and Drugs Act and Regulations

The texts of the Food and Drugs Act and the Regulations thereunder are published in loose leaf form. This Consolidation may be ordered from the Queen's Printer by any interested person. The Queen's Printer also publishes from time to time, revised sheets designed to replace those sheets in the Consolidation made obsolete by changes in the Act or the Regulations. A subscription service is offered at nominal cost whereby revised sheets are made available as they appear. All manufacturers are urged to use this service to ensure that they are aware of such new legislation as may from time to time be enacted.

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