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TO: Associations

I am pleased to inform you that Version 2 of the Good Manufacturing Practices (GMP) Guidelines 2002 Edition is now available on the Health Products and Food Branch Inspectorate website at:

www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate

This document replaces Version 1 of the GMP Guidelines 2002 Edition issued on December 1st, 2002, and the modification related to personnel published on May 23, 2002. This version also reflects changes made to Regulations as a result of the publication of Schedule 1247 on October 23, 2002.

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GOOD MANUFACTURING PRACTICES GUIDELINES

2002 EDITION

Version 2

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Canada

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INTRODUCTION

These guidelines on Good Manufacturing Practices (GMP) refer to Division 2, Part C of the *Food and Drug Regulations*. The guidelines apply to pharmaceutical, radiopharmaceutical, biological, and veterinary drugs and were developed by Health Canada in consultation with their stakeholders. These guidelines are designed to facilitate compliance by the regulated industry and to enhance consistency in the application of the regulatory requirements.

Division 1A, Part C of the *Food and Drug Regulations* defines activities for which GMP compliance is to be demonstrated prior to the issuance of an establishment licence. In addition to these guidelines, further guidance in specific areas is provided in the annexes to this document or in separate documents.

The content of this document should not be regarded as the only interpretation of the GMP Regulations, nor does it intend to cover every conceivable case. Alternative means of complying with these Regulations can be considered with the appropriate scientific justification. Different approaches may be called for as new technologies emerge.

The guidance given in this document has been written with a view to harmonization with GMP standards from other countries and with those of the World Health Organization (WHO), the Pharmaceutical Inspection Cooperation/Scheme (PIC/S) and the International Conference on Harmonization (ICH).

The present edition of this document reflects the results of regulatory revisions due to the implementation of the Mutual Recognition Agreements (MRA) Framework. The MRA establishes mutual recognition of GMP compliance certification and assessment methods by regulatory authorities of countries designated as equivalent.

ACRONYMS

API:	Active Pharmaceutical Ingredient
DIN:	Drug Identification Number
GMP:	Good Manufacturing Practices
ICH:	International Conference on Harmonization
HPFBI:	Health Products and Food Branch Inspectorate
NOC:	Notice of Compliance
MRA:	Mutual Recognition Agreement
PIC/S:	Pharmaceutical Inspection Cooperation/Scheme
WHO:	World Health Organization

GMP Sections applying to the establishment activity

Section	Regulation	F	P/L	I (non-MRA)	I (MRA)	D	W	T
1. Premises	C.02.004	X	X					
2. Equipment	C.02.005	X	X					X
3. Personnel	C.02.006	X	X	X	X	X	X	X
4. Sanitation	C.02.007	X	X					
	C.02.008	X	X					
5. Raw Material Testing	C.02.009	X						X
	C.02.010	X						
6. Manufacturing Control	C.02.011	X	X	X	X	X		
	C.02.012	X	X	X	X	X	X	
7. Quality Control	C.02.013	X	X	X	X	X		
	C.02.014	X	X	X	X	X		
	C.02.015	X	X	X	X	X	X	X
8. Packaging Material Testing	C.02.016	X	X					
	C.02.017	X	X					
9. Finished Product Testing	C.02.018	X	X	X	X	X		X
	C.02.019		X	X				
10. Records	C.02.020	X	X	X	X	X		X
	C.02.021	X	X	X	X	X		X
	C.02.022			X	X	X	X	
	C.02.023			X	X	X		
	C.02.024	X	X	X	X	X	X	
11. Samples	C.02.025	X		X	X	X		
	C.02.026	X		X	X	X		
12. Stability	C.02.027			X	X	X		
	C.02.028			X	X	X		
13. Sterile Products	C.02.029	X						

F =Fabricator P/L=Packager/Labeller I=Importer D=Distributor W=Wholesaler T=Tester

QUALITY MANAGEMENT

PRINCIPLE

The holder of an establishment licence, or any operation to which the requirements of Division 2 are applicable, must ensure that the fabrication, packaging, labelling, distribution, testing, and wholesaling of drugs comply with the requirements of the marketing authorization and do not place consumers at risk due to inadequate safety and quality. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of personnel in many different departments and at all levels within the establishment and its suppliers. To achieve the objective reliably, there must be a comprehensively designed and correctly implemented system of quality assurance that incorporates Good Manufacturing Practices and thus quality control. The system should be fully documented and its effectiveness monitored. All parts of the quality assurance systems should be adequately resourced with qualified personnel, suitable premises, equipment, and facilities. There are additional legislative responsibilities for the holder of the establishment licence and for the person(s) authorized to market drug products.

The basic concepts of quality assurance, Good Manufacturing Practices and quality control are inter-related. They are described here in order to emphasize their relationships and their fundamental importance to the production and control of drugs.

QUALITY ASSURANCE

Quality assurance is a wide-ranging concept that covers all matters that individually or collectively influence the quality of a drug. It is the total of the organized arrangements made with the objective of ensuring that drugs are of the quality required for their intended use. Quality assurance therefore incorporates Good Manufacturing Practices, along with other factors that are outside the scope of these guidelines.

A system of quality assurance appropriate for the manufacture of drugs should ensure that:

1. Drugs are designed and developed in a way that takes into account the GMP requirements;

2. Managerial responsibilities are clearly specified;

3. Systems, facilities and procedures are adequate;

4. Production and control operations are clearly specified, and GMP are adopted;

5. Arrangements are made for the supply and use of the correct raw and packaging materials;

6. Control on intermediates, in-process monitoring, and validation activities are carried out;

7. The finished product is processed, packaged/labelled, verified, and tested according to defined procedures;

8. Drugs are not sold or supplied before the quality control department has indicated that each batch has been produced and controlled in accordance with the requirements of the marketing authorization and of any other regulations relevant to the production, control and release of drugs;

9. Satisfactory arrangements exist for ensuring that the drugs are stored, distributed, and subsequently handled in such a way that quality is maintained throughout their shelf life;

10. There is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system;

GOOD MANUFACTURING PRACTICES (GMP) FOR DRUGS

Good Manufacturing Practices (GMP) are the part of quality assurance that ensures that drugs are consistently produced and controlled in such a way to meet the quality standards appropriate to their intended use, as required by the marketing authorization.

GMP are concerned with both production and quality control. Their basic requirements are as follows:

1. Manufacturing processes are clearly defined and controlled. All critical processes are validated to ensure consistency and compliance with specifications.

2. Manufacturing processes are controlled, and any changes to the process are evaluated. Changes that have an impact on the quality of the drug are validated as necessary.

3. All necessary key elements for GMP are provided, including the following:

    - qualified and trained personnel
    - adequate premises and space
    - suitable equipment and services
    - correct materials, containers and labels
    - approved procedures and instructions
    - suitable storage and transport

4. Instructions and procedures are written in clear and unambiguous language;

5. Operators are trained to carry out and document procedures;

6. Records are made, manually or by instruments, during manufacture that demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the drug was as expected. Deviations are investigated and documented;

7. Records of manufacture (including distribution) that enable the complete history of a batch to be traced are retained in a comprehensible and accessible form;

8. The distribution of the drugs minimizes any risk to their quality;

9. A system is available for recalling any batch of drug from sale or supply;

10. Complaints about marketed drugs are examined, the causes of quality defects are investigated, and appropriate measures are taken with respect to the defective drugs and to prevent recurrence.

QUALITY CONTROL

Quality control is the part of GMP that is concerned with sampling, specifications, testing, documentation and release procedures. This approach ensures that materials are not released for use, and that drugs released for sale or supply, until their quality has been deemed satisfactory.

The basic requirements of quality control are as follows:

1. Adequate facilities, trained personnel, and approved procedures are available for sampling, inspecting and testing of raw materials, packaging materials, intermediate bulk and finished products, and, where appropriate monitoring environmental conditions for GMP purposes;

    1.1 Samples of raw materials, packaging materials, and intermediate, bulk, and finished products are taken according to procedures approved by the quality control department;

    1.2 Test methods are validated;

    1.3 Records are made that demonstrate that all the required sampling, inspecting, and testing procedures were actually carried out, and any deviations are recorded and investigated;

    1.4 The finished products contain active ingredients that comply with the qualitative and quantitative composition requirements of the marketing authorization, have the purity required, are enclosed within their proper container and are correctly labelled;

    1.5 Records are made of the results of inspection, and to show that testing of materials, and of intermediate, bulk, and finished products is formally assessed against specification;

    1.6 Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;

    1.7 No batch of drug is released for sale or supply prior to approval by the quality control department, in accordance with the requirements of the marketing authorization (Notice of Compliance (NOC), Drug Identification Number (DIN));

1.8 Sufficient reference samples of raw materials and drugs are retained to permit future examination of the drug if necessary, and the drug is retained in its final pack unless exceptionally large packs are produced.

GLOSSARY OF TERMS

The definitions given below apply to the terms used in these guidelines, they also apply to the terms used in the annexes unless otherwise specified therein. Definitions quoted from other documents are identified in brackets at the end of the definition.

ACTIVE PHARMACEUTICAL INGREDIENT (ingrédient pharmaceutique actif) - Any substance or mixture of substances that is intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body. (ICH, Q7A, step 5)

AIRLOCK (sas) - An enclosed space with two or more doors, that is interposed between two or more rooms, usually of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when either people or goods need to enter or leave them.

ASEPTIC AREA (aire aseptique) - A zone or zones within a clean area where Grade A or B (see table in Section C.02.029 of these guidelines) conditions are maintained.

ASEPTIC PROCESS (procédé aseptique) - A method of producing a sterile product in which sterile bulk drug or sterile raw materials are compounded and assembled with sterile packaging components under Grade A or B conditions (see table in Section C.02.029 of these guidelines).

BATCH (lot de fabrication) - A quantity of drug in dosage form, a raw material, or a packaging material, homogeneous within specified limits, produced according to a single production order and as attested by the signatories to the order. In the case of continuous manufacture, a batch corresponds to a defined fraction of the production, that is characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

BATCH CERTIFICATE (certificat de lot) – A certificate issued by the fabricator of a lot or batch of a drug that is exported within the framework of a mutual recognition agreement and in which the fabricator

(a) identifies the master production document for the drug and certifies that the lot or batch has been fabricated, packaged/labelled and tested in accordance with the procedures described in that document;

(b) provides a detailed description of the drug, including

(i) a statement of all properties and qualities of the drug, including the identity, potency and purity of the drug, and

(ii) a statement of tolerances for the properties and qualities of the drug;

(c) identifies the analytical methods used in testing the lot or batch and provides details of the analytical results obtained;

(d) sets out the addresses of the buildings at which the lot or batch was fabricated, packaged/labelled and tested; and

(e) certifies that the lot or batch was fabricated, packaged/labelled and tested in accordance with the good manufacturing practices of the regulatory authority that has recognized those buildings as meeting its good manufacturing practices standard. (C.01A.001)

BATCH NUMBER (numéro de lot de fabrication) - A distinctive combination of numbers and/or letters that specifically identifies a batch. The batch number appears on the batch records, certificates of analysis, etc.

BRACKETING (méthode des extrêmes) - The design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, package size) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different sized capsule shells). Bracketing can be applied to different container sizes or to different fills in the same container closure system. (ICH, Q1A(R))

BULK DRUG (drogue en vrac) - Unpackaged dosage form, usually in quantities larger than the largest commercially available package size.

CERTIFICATE OF MANUFACTURE (certificat de fabrication) - A document issued by a vendor to a distributor or importer that attests that a specific lot or batch of drug has been produced in accordance with its master production document. Such certificates include a detailed summary of current batch documentation, with reference to respective dates of revision, manufacture, and packaging, and are signed and dated by the vendor's quality control department.

CHANGE CONTROL (contrôle des changements) - A written procedure that describes the action to be taken if a change is proposed (a) to facilities, materials, equipment, and/or processes used in the fabrication, packaging, and testing of drugs, or (b) that may affect the operation of the quality or support system.

CHANGEOVER PROCEDURE (procédure de conversion) - A logical series of validated

steps that ensures the proper cleaning of suites and equipment before the processing of a different product begins.

CLEAN AREA (aire propre) - A room or suite of rooms where Grade C or D conditions (see table in Section C.02.029 of these guidelines) are required. The rooms have a defined environmental control of particulate and microbial contamination and are constructed, maintained, and used in such a way as to minimize the introduction, generation, and retention of contaminants.

CRITICAL PROCESS (procédé critique) - A process that may cause significant variation in the quality of the finished product.

DATE OF FABRICATION (date de fabrication) - Unless otherwise defined in the *Food and Drug Regulations*, this is the date when any active ingredient, anti-oxidant, preservative, or air/oxygen scavenger is first added to the lot being processed.

DIRECTOR (directeur) - The Assistant Deputy Minister, Health Products and Food Branch, of the Department of Health. (A.01.010)

DISTRIBUTOR (distributeur) - A person, including an association or partnership, who under their own name, or under a trade, design or word mark, trade name or other name, word, or mark controlled by them, sells a food or drug. (A.01.010)

Divisions 1A and 2 to 4 apply to the following distributors (C.01A.003):

(a) a distributor of a drug listed in Schedule C or D to the *Act* or in Schedule F to these *Regulations,* a controlled drug as defined in subsection G.01.001 (1) or a narcotic as defined in the *Narcotic Control Regulations* who does not hold the drug identification number for the drug or narcotic; and

(b) a distributor of a drug for which that distributor holds the drug identification number.

DOSAGE FORM (forme posologique) - A drug product that has been processed to the point where it is now in a form in which it may be administered in individual doses.

DRUG (drogue) - Any substance or mixture of substances manufactured, sold, or represented for use in (a) the diagnosis, treatment, mitigation, or prevention of a disease, a disorder, an abnormal physical state, or the symptoms thereof, in humans or animals, (b) restoring, correcting, or modifying organic functions in humans or animals, or ©) "disinfection" in premises in which food is manufactured, prepared, or kept. (Section 2 of the Act)

In Division 1A and Division 2 of the *Food and Drug Regulations*, "drug" means a drug in dosage form, or a drug that is a bulk process intermediate that can be used in the preparation of a drug listed in Schedule C to the Act or in Schedule D to the Act that is of biological

origin. It does not include a dilute drug premix, a medicated feed as defined in Section 2 of the Feeds Regulations, 1983, a drug that is used only for the purposes of an experimental study in accordance with a certificate issued under Section C.08.015 or a drug listed in Schedule H to the Act. (C.01A.001(2))

FABRICATE (manufacturer) - To prepare and preserve a drug for the purpose of sale. (C.01A.001)

FABRICATOR'S BATCH CERTIFICATE (Certificat de fabrication d'un lot) - A certificate delivered under the scope of a mutual recognition agreement for a lot or batch of a drug. (The certificate's content is described in Annex A). Please refer to regulation C.01A.001 (1) for a complete definition of "batch certificate".

FILLING (remplissage) - Transferring a bulk drug into its final container and enclosing it in the container.

FINISHED PRODUCT (produit fini) - A product that has undergone all stages of production, including packaging in its final container and labelling.

FORMULATING (transformation) - Preparing components and combining raw materials into a bulk drug. For sterile products, this includes such steps as cleaning, rinsing, sterilizing, aerating, flushing, and filtering.

GROUP 2 PRODUCTS (produits du groupe 2) - Drugs listed in Schedule D to the *Act* and subject to Health Canada's lot release programme which require the highest level assessment after the notice of compliance (NOC) has been issued. This assessment includes targeted testing, protocol review, and written approval for sale of each lot in Canada in the form of a release letter.

IMPORTER (importateur) - A person who imports into Canada a drug for the purpose of sale.

IN-PROCESS CONTROL (contrôle en cours de fabrication) - Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the finished product conforms to its specifications. The control of the production environment or equipment may also be regarded as a part of in-process control.

IN-PROCESS DRUG (drogue semi-finie) - Any material or mixture of materials that must, to become a drug in dosage form, undergo further processing.

IN-PROCESS TESTING (analyse en cours de fabrication) - The examination or testing of any material or mixture of materials during the manufacturing process.

INSTALLATION QUALIFICATION (qualification d'installation) - The documented act of demonstrating that process equipment and ancillary systems are appropriately selected and correctly installed.

LABEL (étiquette) - Any legend, word, or mark attached to, included in, belonging to, or accompanying any food, drug, cosmetic, device, or package. (Section 2 of the Act)

LONG TERM TESTING (analyses à long terme) - Stability studies under the recommended storage condition, for the re-test period or shelf life proposed (or approved) for labelling. (ICH, Q1A(R))

LOT (lot) - A quantity of any drug in dosage form, a raw material, or a packaging material, homogeneous within specified limits, constituting all or part of a single batch and identified by a distinctive lot number that appears on the label of the finished product.

LOT FAILURE (lot défectueux) - A lot or batch that has been rejected due to failure to meet in
process or final product release specifications.

LOT NUMBER (numéro de lot) - Any combination of letters, figures, or both, by which any food or drug can be traced in manufacture and identified in distribution. (A.01.010)

MANUFACTURING BATCH DOCUMENT (fiche de lot de fabrication) - Instructions that outline in detail the materials and procedures required to fabricate, prepare, and preserve a single lot or batch of a drug in dosage form.

MARKETING AUTHORIZATION (autorisation de mise en marché) - A legal document issued by Health Canada, authorizing the sale of a drug product in Canada; it includes a Notice of Compliance (NOC) or a Drug Identification Number (DIN).

MASS BALANCE (somme des masses) - The process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error. (ICH, Q1A(R))

MASTER FORMULA (formule-type) - A document or set of documents specifying the raw materials with their quantities and the packaging materials, together with a detailed description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

MASTER PRODUCTION DOCUMENT (document-type de production) - a document that includes specifications for raw material, for packaging material and for packaged dosage form, master formula, sampling procedures, and critical processing related SOPs, whether or not these SOPs are specifically referenced in the master formula.

MATRIXING (méthode de la matrice) - The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches,

different strengths, different sizes of the same container closure system, and possibly in some cases, different container closure systems. (ICH, Q1A(R))

MRA COUNTRY (pays participant) - A country that is a participant in a mutual recognition agreement with Canada.(C.01A.001)

MUTUAL RECOGNITION AGREEMENT (accord de reconnaissance mutuelle) – An international agreement that provides for the mutual recognition of compliance certification for Good Manufacturing Practices for drugs. (C.01A.001)

OPERATIONAL QUALIFICATION (qualification opérationelle) - The documented action of demonstrating that process equipment and ancillary systems work correctly and operate consistently in accordance with established specifications.

PACKAGE/LABEL (emballer/étiqueter) - To put a drug in its immediate container or to affix the inner or outer label to the drug. (C.01A.001)

PACKAGING (emballage) - Operations required to package and label a single lot or batch of a drug in dosage form.

PACKAGING MATERIAL (matériel d'emballage) - Labels, printed packaging materials and those components in direct contact with the dosage form. (refer to C.02.002)

PACKAGING BATCH DOCUMENT (fiche d'emballage de lot de fabrication) - Instructions that outline in detail the materials and special procedures required to package and label a single lot or batch of a drug in dosage form.

PARENTERAL USE (usage parentéral) - Administration of a drug by means of hypodermic syringe, needle or other instrument through or into the skin or mucous membrane. (C.01.001)

PHARMACEUTICAL (produit pharmaceutique) - A drug other than a drug listed in Schedule C or D to the *Act*. (C.01A.001)

POTENCY (teneur) - The activity or amount of active moiety, or any form thereof, indicated by l abel claim to be present.

PROCESS QUALIFICATION (qualification de procédé) - The phase of validation dealing with sampling and testing at various stages of the manufacturing process to ensure that product specifications are met.

PRODUCTION (production) - All operations involved in the preparation of a finished product, from receipt of materials, through processing and packaging, to completion of the finished product, including storage.

PURIFIED WATER (eau purifiée) - As defined in any standard listed in Schedule B to the

Food and Drugs Act.

PURITY (pureté) - The extent to which a raw material or a drug in dosage form is free from undesirable or adulterating chemical, biological, or physical entities as defined by specification.

QUALIFIED PERSONNEL (personnel qualifié) - Individuals who have the appropriate education, training and experience to perform their duties.

QUALIFIED AUTHORITY (autorité qualifiée) - An authority member of the Pharmaceutical Inspection Cooperation/Scheme (PIC/S) or the United States Food and Drug Administration (USFDA).

QUALITY CONTROL DEPARTMENT (service du contrôle de la qualité) - A separate and distinct operation, maintained by a manufacturer or an importer, that is responsible only to management, and that monitors the quality of production operations and exercises control over the quality of materials required for and resulting from those operations.

QUARANTINE (quarantaine) - Effective restriction of the availability of material or product for use (physically or by system), until released by the quality control department.

RAW MATERIAL (matière première) - Any substance, other than in-process drug or packaging material, intended to be used in the manufacture of drugs, including those that appear in the master formula but that do not appear in the drug such as solvents and processing aids.

RECOGNIZED BUILDING (bâtiment reconnu) - In respect of the fabrication, packaging/labelling or testing of a drug, a building that a regulatory authority that is designated under subsection C.01A.019(1) in respect of that activity has recognized as meeting its Good Manufacturing Practices standards in respect of that activity for that drug.(C.01A.001)

RECONCILIATION (bilan comparatif) - A comparison, making due allowance for normal variation, between the amount of product or materials theoretically produced or used and the amount actually produced or used.

RECOVERY (récupération) - The introduction of all or part of previous batches of the required quality into another batch at a defined stage of manufacture.

REGULATORY AUTHORITY (autorité réglementaire) - A government agency or other entity in an MRA country that has a legal right to control the use or sale of drugs within that country and that may take enforcement action to ensure that drugs marketed within its jurisdiction comply with legal requirements.

REPROCESSING (retraitement) - Subjecting all or part of a batch or lot of an in-process drug, a bulk process intermediate (final biological bulk intermediate) or a bulk drug of a

single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary and are validated and pre-approved by the quality control department or as part of the marketing authorization.

RE-TEST DATE (date de ré-analyse) - The date when samples of a drug substance are re-examined to ensure that the material is still suitable for use.

RE-TEST PERIOD (période de ré-analyse) - The period of time during which a drug substance can be considered to remain within the specifications and therefore acceptable for use in the fabrication of a given drug product, provided that it has been stored under defined conditions; after this period, the batch is re-tested for compliance with specifications and then used immediately. (ICH, Q1A(R))

RETURNED PRODUCT (produit retourné) - Bulk drug or finished product sent back to the manufacturer or importer.

REWORKING (reprise) - Subjecting an in-process drug, a bulk process intermediate (final biological bulk intermediate), or final product of a single batch/lot to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization. (WHO GMP)

SELF-CONTAINED FACILITY - (installation confinée) - means premises that provide complete and total separation of all aspects of the operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers as well as separate air handling systems. Self-contained facilities does not necessarily imply two distinct and separate buildings.

SELL (vendre) - Offer for sale, expose for sale, have in possession for sale, and distribute, regardless of whether the distribution is made for consideration. (Section 2 of the *Act*)

SHELF LIFE / EXPIRATION DATING PERIOD - (durée de conservation/période de péremption) - The time interval during which a drug product is expected to remain within the approved specification provided that it is stored under the conditions defined on the label and in the proposed containers and closure.

STANDARD OPERATING PROCEDURE (SOP) - (procédure opératoire normalisée) - A written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g., equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documents.

STERILE (stérile) - Free from viable microorganisms.

SYSTEM (système) - A regulated pattern of interacting activities and techniques that are united to form an organized whole.

TERMINAL STERILIZATION (stérilisation en phase terminale) - Sterilizing a drug in its final closed container.

VALIDATION (validation) - The documented act of demonstrating that any procedure, process, and activity will consistently lead to the expected results. Includes the qualification of systems and equipment.

VENDOR (vendeur) - The fabricator of the item.

WHOLESALE (vendre en gros) - To sell any of the following drugs, other than at retail sale, where the seller's name does not appear on the label of the drugs:

(a) a drug listed in Schedule C or D to the *Act* or in Schedule F to these *Regulations* or a controlled drug as defined in subsection G.01.001 (1); or

(b) a narcotic as defined in the Narcotic Control Regulations. (C.01A.001)

REGULATION

C.02.002

In this Division,

- "medical gas" means any gas or mixture of gases manufactured, sold, or represented for use as a drug; (gaz médical)

- "packaging material" includes a label; (matériel d'emballage)

- "quality control department" means a quality control department referred to in section C.02.013; (service du contrôle de la qualité)

- "specifications" means a detailed description of a drug, the raw material used in a drug, or the packaging material for a drug and includes:

  (a) a statement of all properties and qualities of the drug, raw material or packaging material that are relevant to the manufacture, packaging, and use of the drug, including the identity, potency, and purity of the drug, raw material, or packaging material,

  (b) a detailed description of the methods used for testing and examining the drug, raw material, or packaging material, and

(c) a statement of tolerances for the properties and qualities of the drug, raw material, or packaging material. (spécifications)

SALE

C.02.003

No distributor referred to in paragraph C.01A.003(b) and no importer shall sell a drug unless it has been fabricated, packaged/labelled, tested, and stored in accordance with the requirements of this Division.

PREMISES

REGULATION

C.02.004

The premises in which a lot or batch of a drug is fabricated or packaged/labelled shall be designed, constructed and maintained in a manner that;

(a) permits the operations therein to be performed under clean, sanitary and orderly conditions;

(b) permits the effective cleaning of all surfaces therein; and

(c) prevents the contamination of the drug and the addition of extraneous material to the drug.

RATIONALE

The pharmaceutical establishment should be designed and constructed in a manner such that it permits cleanliness and orderliness while preventing contamination. Regular maintenance is required to prevent deterioration of the premises. The ultimate objective of all endeavours is product quality.

INTERPRETATION

1. Buildings are located in an environment that, when considered together with measures being taken to protect the manufacturing processes, presents a minimum risk of causing any contamination of materials or drugs.

2. The premises are designed, constructed, and maintained such that they prevent the entry of insects and other animals into the building and also prevent the migration of extraneous material from the outside into the building and from one area to another.

2.1 Doors, windows, walls, ceilings, and floors are such that no holes or cracks are

evident (other than those intended by design).

2.2 Doors giving direct access to the exterior from manufacturing and packaging areas are used for emergency purposes only. These doors are adequately sealed. Receiving and shipping area(s) do not allow direct access to production areas.

2.3 Production areas are segregated from all non-production areas. Individual manufacturing, packaging, and testing areas are clearly defined and if necessary segregated. Areas where biological, microbiological or radioisotope testing is carried out require special design and containment considerations.

2.4 Laboratory animals' quarters are segregated.

2.5 Engineering, boiler rooms, generators, etc. are isolated from production areas.

3. In all areas where raw materials, in-process drugs, or drugs are exposed, the following considerations apply to the extent necessary to prevent contamination. In laboratories these considerations apply only to the extent necessary to ensure the validity of test results.

3.1 Floors, walls, and ceilings permit cleaning. Brick, cement blocks, and other porous materials are sealed. Surface materials that shed particles are avoided.

3.2 Floors, walls, ceilings, and other surfaces are hard, smooth and free of sharp corners where extraneous material can collect.

3.3 Joints between walls, ceilings and floors are sealed.

3.4 Pipes, light fittings, ventilation points and other services do not create surfaces that cannot be cleaned.

3.5 Floor drains are screened and trapped.

3.6 Air quality is maintained through dust control, monitoring of pressure differentials between production areas and periodic verification and replacement of air filters. The air handling system is well defined, taking into consideration airflow volume, direction, and velocity. Air handling systems are subject to periodic verification to ensure compliance with their design specifications. Records are kept.

4. Temperature and humidity are controlled, where required, in order to safeguard sensitive materials (e.g. raw materials, drugs, samples, reference standards, etc.).

5. Rest, change, wash-up, and toilet facilities are well separated from production areas and are sufficiently spacious, well ventilated, and of a type that permits good sanitary practices.

6. Premises layout is designed to avoid mix-ups and generally optimize the flow of personnel and materials.

6.1 There is sufficient space for receiving and all production activities.

6.2 Working spaces allow the orderly and logical placement of equipment (including parts and tools) and materials.

6.3 Where physical quarantine areas are used, they are well marked, with access restricted to designated personnel. Where electronic quarantine is used, electronic access is restricted to designated personnel.

6.4 A separate sampling area is provided for raw materials. If sampling is performed in the storage area, it is conducted in such a way as to prevent contamination or cross-contamination.

6.5 Working areas are well lit.

7. Utilities and support systems (e.g., HVAC, dust collection, and supplies of purified water, steam, compressed air, nitrogen, etc.) are qualified and are subject to periodic verification.

8. Outlets for liquids and gases used in the production of drugs are clearly identified as to their content.

9. Premises are maintained in a good state of repair. Repair and maintenance operations do not affect drug quality.

10. Where necessary, separate rooms are provided and maintained to protect analytical instruments and associated control systems from vibration, electrical interference, and contact with excessive moisture or other external factors.

11. Prevention of cross-contamination during manufacturing is the responsibility of the fabricator and packager. They must demonstrate that the premises are designed in such a manner that the risk of cross-contamination between products is minimized.

11.1 In order to minimize the risk of a serious health hazard due to cross-contamination, additional controls, including the need for self-containment should be considered for particular drugs, such as the following:

-highly sensitizing drugs (e. g., penicillins)
-biologicals (e. g., live vaccines)
-certain hormones (e. g., estrogen)
-certain cytotoxic drugs
-other highly active drugs

Factors to consider are the manufacturing processes, the use of closed systems, dedication of product contact equipment parts, HVAC controls, and engineering controls (such as fail-safe systems), coupled with validation and ongoing monitoring using highly sensitive analytical methods.

11.2 Campaign production can be accepted where, on a product by product basis, proper justification is provided, validation is conducted and rigorous validated controls and monitoring are in place and demonstrate the minimization of any risk of cross-contamination.

11.3 No production activities of highly toxic non-pharmaceutical materials, such as pesticides and herbicides, are conducted in premises used for the production of drugs.

11.4 Once the products are enclosed in their immediate final containers, co- mingle storage in warehouses is allowed.

Self-contained facility means premises that provide complete and total separation of all aspects of the operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers as well as separate air handling systems. Self-contained facilities does not necessarily imply two distinct and separate buildings.

EQUIPMENT

REGULATION

C.02.005

The equipment with which a lot or batch of a drug is fabricated, packaged/labelled, or tested shall be designed, constructed, maintained, operated, and arranged in a manner that:

(a) permits the effective cleaning of its surfaces;

(b) prevents the contamination of the drug and the addition of extraneous material to the drug; and

(c) permits it to function in accordance with its intended use.

RATIONALE

The purpose of these requirements is to prevent the contamination of drugs by other drugs, by dust, and by foreign materials such as rust, lubricant and particles coming from the equipment. Contamination problems may arise from poor maintenance, the misuse of equipment, exceeding the capacity of the equipment and the use of worn-out equipment. Equipment arranged in an orderly manner permits cleaning of adjacent areas and does not interfere with other processing operations. It also minimizes the circulation of personnel and optimizes the flow of materials. The fabrication of drugs of consistent quality requires that equipment perform in accordance with its intended use.

INTERPRETATION

1. The design, construction and location of equipment permit cleaning, sanitizing, and inspection of the equipment.

    1.1 Equipment parts that come in contact with raw materials, in-process drugs or drugs are accessible to cleaning or are removable.

    1.2 Tanks used in processing liquids and ointments are equipped with fittings that can be dismantled and cleaned. Validated Clean-In-Place (CIP) equipment can be dismantled for periodic verification.

    1.3 Filter assemblies are designed for easy dismantling.

    1.4 Equipment is located at a sufficient distance from other equipment and walls to permit cleaning of the equipment and adjacent area.

    1.5 The base of immovable equipment is adequately sealed along points of contact with the floor.

    1.6 Equipment is kept clean, dry and protected from contamination when stored.

2. Equipment does not add extraneous material to the drug.

    2.1 Surfaces that come in contact with raw materials, in-process drugs or drugs are smooth and are made of material that is non-toxic, corrosion resistant, non-reactive to the drug being fabricated or packaged and capable of withstanding repeated cleaning or sanitizing.

    2.2 The design is such that the possibility of a lubricant or other maintenance material contaminating the drug is minimized.

    2.3 Equipment made of material that is prone to shed particles or to harbour microorganisms does not come in contact with or contaminate raw materials, in-process drugs or drugs.

    2.4 Chain drives and transmission gears are enclosed or properly covered.

    2.5 Tanks, hoppers and other similar fabricating equipment are equipped with covers.

3. Equipment is operated in a manner that prevents contamination.

    3.1 Ovens, autoclaves and similar equipment contain only one raw material, in-process drug or drug at a time, unless precautions are taken to prevent contamination and mix-ups.

    3.2 Equipment is not operated where contaminants may fall into the material.

3.3 Equipment is placed in such a way to optimize the flow of material and to minimize the circulation of personnel.

3.4 Equipment is located so that production operations undertaken in a common area are compatible and so that prevent cross contamination between such operations is prevented.

3.5 Fixed pipework is clearly labelled to indicate the contents and, where applicable, the direction of flow.

3.6 Dedicated production equipment is provided where appropriate.

3.7 Water purification, storage, and distribution equipment is operated in such a manner so as to ensure a reliable source of water of the appropriate chemical and microbial purity.

4. Equipment is maintained in a good state of repair when in use.

4.1 Where a potential for the contamination of the drug being fabricated or packaged exists, surfaces are free from cracks, peeling paint and other defects.

4.2 Gaskets are functional.

4.3 The use of temporary devices such as tape is avoided.

4.4 Equipment parts that come in contact with drugs are maintained in such a manner that drugs are fabricated or packaged within specifications.

5. Production equipment is designed, located, and maintained to serve its intended purpose.

5.1 Scales and other measuring equipment of an appropriate range and precision are available for production and control operations. Such equipment is calibrated on a scheduled basis, and corresponding records are kept.

5.2 Defective and unused equipment is removed from production and quality control areas or is at least clearly labelled as such.

5.3 Equipment intended to be used during the critical steps of fabrication, packaging/labelling, and testing is subject to installation and operational qualification. Equipment qualification is documented.

5.4 Automatic, mechanical, electronic, or other types of equipment including computerized systems that are used in the fabrication, packaging/labelling, and storing of a drug is routinely calibrated, inspected or checked according to a written program designed to assure proper performance. Written records of these calibration checks and inspections are maintained.

5.5 Equipment usage logs are maintained.

PERSONNEL

REGULATION

C.02.006

Every lot or batch of a drug shall be fabricated, packaged/labelled, tested, and stored under the supervision of personnel who, having regard to the duties and responsibilities involved have had such technical, academic, and other training as the Director considers satisfactory in the interests of the health of the consumer or purchaser.

RATIONALE

People are the most important element in any pharmaceutical operation, without the proper personnel with the right attitude and the right training, it is almost impossible to fabricate, package/label, test, or store good quality drugs.

It is essential that qualified personnel be employed to supervise the fabrication of drugs. The operations involved in the fabrication of drugs are highly technical in nature and require constant vigilance, attention to details and a high degree of competence on the part of employees. Inadequate training of personnel or the absence of an appreciation of the importance of production control, often accounts for the failure of a product to meet the required standards.

INTERPRETATION

1. For fabricators, packagers/labellers and testers, individuals in charge of the manufacturing department and the quality control department;

    1.1 hold a university degree or equivalent in a science related to the work being carried out;

    1.2 have practical experience in their responsibility area;

    1.3 directly control and personally supervise on site, activities under their control; and

    1.4 can delegate their duties and responsibility to a person in possession of a diploma, certificate or other evidence of formal qualifications awarded on completion of a course of study at a university, college or technical institute in a science related to the

work being carried out combined with at least two years' relevant practical experience, while remaining accountable for those duties and responsibility.

2. Individuals responsible for packaging operations, including control over printed packaging materials and withdrawal of bulk drugs;

   2.1 are qualified by training and experience; and

   2.2 are directly responsible to the person in charge of the manufacturing department or a person having the same qualifications.

3. For distributors, importers, and wholesalers, individuals in charge of the quality control department;

   3.1 are qualified by pertinent academic training and experience; and

   3.2 can delegate their duties and responsibilities to a person who meets the requirements defined under Regulation C.02.006 Interpretation 3.1.

4. An adequate number of personnel with the necessary qualifications and practical experience appropriate to their responsibilities are available on site.

   4.1 The responsibilities placed on any one individual are not so extensive as to present any risk to quality.

   4.2 All responsible personnel have their specific duties recorded in a written description and have adequate authority to carry out their responsibilities.

   4.3 When key personnel are absent, qualified personnel are appointed to carry out their duties and functions.

5. All personnel are aware of the principles of GMP that affect them, and all personnel receive initial and continuing training relevant to their job responsibilities.

   5.1 Training is provided by qualified personnel having regard to the function and in accordance with a written program for all personnel involved in the fabrication of a drug, including technical, maintenance, and cleaning personnel.

   5.2 The effectiveness of continuing training is periodically assessed.

   5.3 Training is provided prior to implementation of new or revised SOPs.

   5.4 Records of training are maintained.

   5.5 Personnel working in areas where highly active, toxic, infectious, or sensitizing materials are handled are given specific training.

5.6 The performance of all personnel is periodically reviewed.

6. Consultants and contractors have the necessary qualifications, training, and experience to advise on the subjects for which they are retained.

SANITATION

REGULATION

C.02.007

(1) Every person who fabricates or packages/labels a drug shall have a written sanitation program that shall be implemented under the supervision of qualified personnel.

(2) The sanitation program referred to in subsection (1) shall include:

(a) cleaning procedures for the premises where the drug is fabricated or packaged/labelled and for the equipment used in the fabrication or packaging/labelling of the drug; and

(b) instructions on the sanitary fabrication and packaging/labelling of drugs and the handling of materials used in the fabrication and packaging/labelling of drugs.

RATIONALE

Sanitation in a pharmaceutical plant influences the quality of drug products as well as employee attitude. The quality requirement for drug products demand that such products be fabricated and packaged in areas that are free from environmental contamination and free from contamination by another drug.

A written sanitation program provides some assurance that levels of cleanliness in the plant are maintained and that the provisions of Sections 8 and 11 of the *Food and Drugs Act* are satisfied.

INTERPRETATION

1. A written sanitation program is available on the premises of every person who fabricates, packages/labels, a drug.

2. The sanitation program contains procedures that outline the following:

2.1 cleaning requirements applicable to all production areas of the plant with emphasis on manufacturing areas that require special attention;

2.2 cleaning requirements applicable to processing equipment;

2.3 cleaning intervals;

2.4 products for cleaning and disinfection, along with their dilution and the equipment to be used;

2.5 the responsibilities of any outside contractor;

2.6 disposal procedures for waste material and debris;

2.7 pest control measures;

2.8 precautions required to prevent contamination of a drug when rodenticides, insecticides, and fumigation agents are used;

2.9 microbial and environmental monitoring procedures with alert and action limits in areas where susceptible products are fabricated or packaged; and

2.10 the personnel responsible for carrying out cleaning procedures.

3. The sanitation program is implemented and is effective in preventing unsanitary conditions.

3.1 Cleaning procedures for manufacturing equipment are validated based on the Cleaning Validation Guidelines.

3.2 Residues from the cleaning process itself (e.g., detergents, solvents, etc.) are also removed from equipment;

3.3 Evidence is available demonstrating that routine cleaning and storage does not allow microbial proliferation;

3.4 Analytical methods used to detect residues or contaminants are validated.

3.5 A cleaning procedure requiring complete product removal may not be necessary between batches of the same drug.

4. Individuals who supervise the implementation of the sanitation program;

4.1 are qualified by training or experience; and

4.2 are directly responsible to a person who has the qualifications described under Regulation C.02.006.

5. Dusty operations are contained. The use of unit or portable dust collectors is avoided in fabrication areas especially in dispensing, unless the effectiveness of their exhaust filtration is demonstrated and the units are regularly maintained in accordance with written approved procedures.

REGULATION

C.02.008

(1) Every person who fabricates or packages/labels a drug shall have in writing, minimum requirements for the health and the hygienic behaviour and clothing of personnel to ensure the clean and sanitary fabrication and packaging/labelling of the drug.

(2) No person shall have access to any area where a drug is exposed during its fabrication or packaging/labelling if the person

(a) is affected with or is a carrier of a disease in a communicable form, or

(b) has an open lesion on any exposed surface of the body

RATIONALE

Employee's health, behaviour, and clothing may contribute to the contamination of the product. Poor personal hygiene will nullify the best sanitation program and greatly increase the risk of product contamination.

INTERPRETATION

1. Minimum health requirements are available in writing and provide for the following:

1.1 Personnel who have access to any area where a drug is exposed during its fabrication or packaging/labelling must undergo health examinations prior to employment. Medical re-examinations, based on job requirements take place periodically.

1.2 Periodic eye examinations are required for personnel who conduct visual inspections.

1.3 When an employee has been absent from the workplace due to an illness that may adversely affect the quality of products, that employee's health is assessed before he or she is allowed to return to the workplace.

1.4 Actions to be taken in the event of a positive diagnosis or a case suspected of being hazardous to consumers of the products are specified.

1.5 Supervisory checks are conducted to prevent any person who has an apparent illness or open lesions that may adversely affect the quality of drugs from handling exposed raw materials, packaging materials, in-process drugs or finished products until the condition is no longer judged to be a risk.

1.6 Employees are instructed to report to their supervisor any health conditions they have that could adversely affect drug products.

2. The hygiene program clearly defines clothing requirements and hygiene procedures for personnel and visitors.

2.1 Where a potential for the contamination of a raw material, in-process material or drug exists, individuals wear clean clothing and protective covering.

2.2 Direct skin contact is avoided between the operator's hands and raw materials, primary packaging materials and intermediate or bulk drug.

2.3 Unsanitary practices such as smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material and personal medicines are not permitted in fabrication, packaging/labelling, and storage areas or in any other areas where they might adversely influence product quality.

2.4 Requirements concerning personal hygiene, with an emphasis on hand hygiene, are outlined and are followed by employees.

2.5 Requirements concerning cosmetics and jewelry worn by employees are outlined and are observed by employees.

2.6 Soiled protective garments, if reusable, are stored in separate containers until properly laundered and, if necessary, disinfected or sterilized.

2.7 Personal hygiene procedures including the use of protective clothing, apply to all persons entering production areas.

RAW MATERIAL TESTING

REGULATION

C.02.009

(1) Each lot or batch of raw material shall be tested against the specifications for the raw material prior to its use in the production of a drug.

(2) No lot or batch of raw material shall be used in the production of a drug unless that lot or batch of raw material complies with the specifications for that raw material.

(3) Notwithstanding subsection (1), water may, prior to the completion of its tests under that subsection, be used in the production of a drug.

(4) Where any property of a raw material is subject to change on storage, no lot or batch of that raw material shall be used in the production of a drug after its storage unless the raw material is retested after an appropriate interval and complies with its specifications for that property.

(5) Where the specifications referred to in subsections (1), (2) and (4) are not prescribed, they shall

(a) be in writing;

(b) be acceptable to the Director, who shall take into account the specifications contained in any publication mentioned in Schedule B to the *Act*; and

(c) be approved by the person in charge of the quality control department.

RATIONALE

The testing of raw materials before their use has three objectives: to confirm the **identity** of the raw materials, to provide assurance that the **quality** of the drug in dosage form will not be altered by raw material defects, and to obtain assurance that the raw materials have the characteristics that will provide the desired **quantity** or yield in a given manufacturing process.

INTERPRETATION

1. Each raw material used in the production of a drug is covered by specifications (see regulation C.02.002) that are approved and dated by the person in charge of the quality control department or by a designated alternate who meets the requirements described under Regulation C.02.006, Interpretation 1.4.

2. Specifications are of pharmacopoeial or equivalent status and are in compliance with the current marketing authorization. Where appropriate, additional properties or qualities not addressed by the pharmacopoeia (e.g., particle size, etc.) are included in the specifications.

3. Where a recognized pharmacopoeia (Schedule B of the *Food and Drugs Act*) contains a specification for microbial content, that requirement is included.

4. Purified water that meets any standard listed in Schedule B of the *Food and Drugs Act* is used in the formulation of a drug product, unless otherwise required in one of these standards or as stated in the marketing authorization.

5. Test methods are validated, and the results of such validation studies are documented. Full validation is not required for methods included in any standard listed in Schedule B to the *Food and Drugs Act,* but the user of such a method establishes its suitability under actual conditions of use.

   Note: Guidance for the validation of particular types of methods can be obtained in publications such as the International Conference on Harmonization (ICH) guidelines titled “Validation of Analytical Procedures: Methodology” or in any standard listed in Schedule B to the *Food and Drugs Act*.

6. A sample of each lot of raw material is fully tested against specifications. Sampling is conducted according to a statistically valid plan.

    6.1 In addition, each container of a lot of an active pharmaceutical ingredient (API) is tested for the identity of its contents using a specifically discriminating identity test.

    In lieu of testing each container for identity, testing a composite sample is acceptable, as long as the following conditions are met:

    6.1.1 the number of individual containers for each composite sample does not exceed 10; and

    6.1.2 a potency test is performed on each composite sample to establish the mass balance of the composite sample.

    6.2 APIs originating from a dedicated facility that fabricates only one ingredient are exempted from the requirements outlined under Interpretation 6.1, provided that no re-packaging or re-labelling has taken place.

7. Only raw materials that have been released by the quality control department and that are not past their established re-test date are used in fabrication.

8. If any API is held in storage after the established re-test date, that API is quarantined, evaluated, and tested prior to use. The re-test date is based on acceptable stability data developed under predefined conditions or on any other acceptable evidence. A batch of raw material can be re-tested and used immediately (i.e., within 30 days) after the re-test as long as it continues to comply with the specifications.

9. Any inactive raw material that is subject to chemical, microbiological, or physical changes is quarantined, evaluated and tested prior to use if the material has passed the expiration date as determined by the stability data or by any other documented evidence.

10. For most biotechnological/biological substances and certain antibiotics known to be labile, a shelf life is established rather than a re-test date.

REGULATION

C.02.010

(1) The testing referred to in section C.02.009 shall be performed on a sample taken

    (a) after receipt of each lot or batch of raw material on the premises of the fabricator; or

    (b) subject to subsection (2), before receipt of each lot or batch of raw material on the premises of the fabricator, if

        (i) the fabricator

(A) has evidence satisfactory to the Director to demonstrate that raw materials sold to him by the vendor of that lot or batch of raw material are consistently manufactured in accordance with and consistently comply with the specifications for those raw materials, and

(B) undertakes periodic complete confirmatory testing with a frequency satisfactory to the Director and

(ii) the raw material has not been transported or stored under conditions that may affect its compliance with the specifications for that raw material.

(2) After a lot or batch of raw material is received on the premises of the fabricator, the lot or batch of raw material shall be tested for identity.

RATIONALE

Section C.02.010 outlines options as to when the testing prescribed by Section C.02.009 is carried out. The purchase of raw materials is an important operation that requires a particular and thorough knowledge of the raw materials and their fabricator. To maintain consistency in the fabrication of drug products, raw materials should originate from reliable fabricators.

INTERPRETATION

1. Testing other than identity testing:

The testing is performed on a sample taken after receipt of the raw material on the premises of the person who formulates the raw material into dosage form, unless the vendor is certified. A raw material vendor certification program, if employed, is documented in a standard operating procedure. At a minimum, such a program includes the following:

1.1 A written contract outlining the specific responsibilities of each party involved. The contract specifies:

1.1.1 the content and the format of the certificate of analysis, which exhibits actual numerical results and makes reference to the raw material specifications and validated test methods used;

1.1.2 that the raw material vendor must inform the drug fabricator of any changes in the processing or specifications of the raw material and;

1.1.3 that the raw material vendor must inform the drug fabricator in case of any critical deviation during the manufacturing of a particular batch of a raw material.

1.2 An audit report is issued by a qualified regulatory authority demonstrating that the API fabricator complies with the ICH Good Manufacturing Practice guide for API

or with any standard or system of equivalent quality. This report should be less than 3 years old, but is valid for 4 years from the date of the inspection. If such an audit report is unavailable or is more than 4 years old, an on-site audit of the API fabricator, against the same standard or its equivalent, by a person who meets the requirements of Interpretation 1 under Section C.02.006, is acceptable.

1.3 Complete confirmatory testing is performed on the first lot of any raw material received from a new vendor. For API's, a copy of the results of the impurity and residual solvent profile is also obtained.

1.3.1 Where the manufacturing process for an API has been modified, a new profile for impurity and residual solvents is obtained from the vendor.

1.4 Identification of how re-testing failures and any subsequent re-qualification of the vendor are to be addressed.

1.5 The list of raw materials not subject to the reduced testing program (e.g. reprocessed lots).

1.6 Complete confirmatory testing is conducted on a minimum of one lot per year of any raw material received from each vendor, with the raw material being selected on a rotational basis.

1.7 A document is issued for each vendor verifying that the vendor meets the criteria for certification. The document is approved by the quality control department and is updated at an appropriate frequency.

2. Identity testing:

Specific identity testing is conducted on all lots of any raw material received on the premises of the person who formulates the raw material into dosage forms. This identity testing is performed in accordance with Regulation C.02.009, Interpretation 6.

3. Generally, due to the nature of its operations, a broker or wholesaler of raw materials cannot be directly certified. However, when the broker or wholesaler supplies materials received from the original vendor without changing the existing labels, packaging, certificate of analysis, and general information, then certification of the original source is still acceptable.

4. Provided that the identity test referred to in Interpretation 2 is performed, a lot or batch of raw material selected for confirmatory testing may be used in fabrication prior to completion of all tests with the approval of the quality control department.

5. Conditions of transportation and storage are such that they prevent alterations to the potency, purity, or physical characteristics of the raw material. In order to demonstrate that these conditions have been met, standard operating procedures and records for shipping and receiving are available and contain

    5.1 the type of immediate contact and protective packaging for the raw material;

    5.2 the labelling requirements including storage conditions and special precautions or warnings, for the packaged raw material;

    5.3 the mode(s) of transportation approved for shipping the packaged raw material;

    5.4 a description of how the packaged raw material is sealed;

    5.5 the verification required to ensure that each package has not been tampered with and that there are no damaged containers; and

    5.6 evidence that special shipping requirements (e.g., refrigeration) have been met if required.

6. Where a batch of any raw material, after leaving the site of its fabrication is handled in any substantial way (e.g., repackaged by a third party) prior to its receipt on the premises of the person who formulates the raw material into dosage forms, each container in that batch is sampled and its contents positively identified.

7. If a delivery or shipment of raw material is made up of different batches, each batch is considered as separate for the purposes of sampling, testing, and release.

8. If the same batch of raw material is subsequently received, this batch is also considered as separate for the purpose of sampling, testing, and release.

    However, full testing to specifications may not be necessary on such a batch provided that all the following conditions are met:

    8.1 a specifically discriminating identity test is conducted;

    8.2 the raw material has not been repackaged or re-labelled;

    8.3 the raw material is within the re-test date assigned by its vendor; and

    8.4 evidence is available to demonstrate that all pre-established transportation and storage conditions have been maintained.

MANUFACTURING CONTROL

REGULATION

C.02.011

(1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer of a drug shall have written procedures, prepared by qualified personnel, in respect of the drug to ensure that the drug meets the specifications for use of that drug.

(2) Every person required to have written procedures referred to in subsection (1) shall ensure that each lot or batch of the drug is fabricated, packaged/labelled and tested in compliance with those procedures.

RATIONALE

This Regulation requires that a number of measures be taken to maintain the integrity of a drug product from the moment the various raw materials enter the plant to the time the finished dosage form is released for sale. These measures seek to ensure that all manufacturing processes are clearly defined, systematically reviewed in light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their established specifications.

INTERPRETATION

1. All handling of materials and products, such as receipt, quarantine, sampling, storage, tracking, labelling, dispensing, processing, packaging and distribution is done in accordance with approved written procedures or instructions and recorded.

2. All critical production processes are validated. Detailed information is provided in Health Canada's Validation Guidelines for pharmaceutical dosage forms.

3. Validation studies are conducted in accordance with predefined protocols. A written report summarizing recorded results and conclusions is prepared, evaluated, approved, and maintained.

4. Changes to production processes, equipment, or materials that may affect product quality and/or process reproducibility are validated prior to implementation.

5. Any deviation from instructions or procedures is avoided. If deviations occur, qualified personnel write a report that describes the deviation, the investigation, the rationale for disposition, and any follow-up activities required. The report is approved by the quality control department.

6. Checks on yields and reconciliation of quantities are carried out at appropriate stages of the process to ensure that yields are within acceptable limits.

7. Deviations from the expected yield are recorded and investigated.

8. Access to production premises is restricted to designated personnel.

9. Provided that changeover procedures are validated and implemented, non-medicinal products may be fabricated or packaged/labelled in areas or with equipment that is also used for the production of pharmaceutical products.

10. Before any processing operation is started, steps are taken and documented to ensure that the work area and equipment are clean and free from any raw materials, products, product residues, labels, or documents not required for the current operation.

11. In-process control activities that are performed within the production areas do not pose any risk to the quality of the product.

12. Measuring devices are regularly checked for accuracy and precision, and records of such checks are maintained.

13. At all times during processing, all materials, bulk containers, major items of equipment and the rooms used are labelled or otherwise identified with an indication of the product or material being processed, its strength, and the batch number.

14. Rejected materials and products are clearly marked as such and are either stored separately in restricted areas or controlled by a system that ensures that they are either returned to their vendors or, where appropriate, reprocessed or destroyed. Actions taken are recorded.

15. Equipment is located so that production operations undertaken in a common area are compatible.

16. Upon receipt, bulk drugs, in-process (intermediate) drugs, raw materials, and packaging materials are accounted for and held in quarantine until released by the quality control department.

17. Procedures are in place to ensure the identity of the contents of each container. Containers from which samples have been drawn are identified.

18. For each consignment, all containers are checked for integrity of package and seal and to verify that the information on the order, the delivery note and the vendor's labels is in agreement.

19. Damage to containers, along with any other problem that might adversely affect the quality of a material, is recorded, reported to the quality control department, and investigated.

20. Upon receipt, containers are cleaned where necessary and labelled with the prescribed data.

21. Labels for bulk drugs, in-process drugs, raw materials, and packaging materials bear the following information:

    21.1 the designated name of the material and a code reference where applicable;

    21.2 the specific batch number(s) given by the vendor and on receipt by the fabricator or packager/labeller;

    21.3 the status of the contents (e.g., in quarantine, on test, released, rejected, to be returned or recalled) appears on the label when a manual system is used;

    21.4 an expiry date or a date beyond which re-testing is necessary.

    Note: When fully computerized storage systems are used, backup systems are available in case of system failure to satisfy the requirements of Interpretation 21.

22. Raw materials are dispensed and verified by qualified personnel, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labelled containers.

MANUFACTURING MASTER FORMULA

23. Processing operations are covered by master formulae, that are prepared by, and are subject to independent checks by, persons who have the qualifications described under Regulation C.02.006 Interpretation 1.

24. Master formulae are written to provide not less than 100% of label claim and include the following:

    24.1 the name of the product, with a reference code relating to its specifications;

    24.2 a description of the dosage form, strength of the product, and batch size;

    24.3 a list of all raw materials to be used, along with the amount of each, described using the designated name and a reference that is unique to that material (mention is made of any processing aids that may not be present in the final product);

    24.4 a statement of the expected final yield, along with the acceptable limits, and of relevant intermediate yields, where applicable;

    24.5 a statement of the principal equipment to be used;

24.6 the procedures, or reference to the procedures, to be used for preparing the critical equipment, e.g., cleaning (especially after a change in product), assembling, calibrating, sterilizing, etc.;

24.7 detailed stepwise processing instructions (e.g., checks on materials, pretreatment, sequence for adding materials, mixing times or temperatures, etc.);

24.8 the instructions for any in-process controls, along with their limits;

24.9 where necessary, the requirements for storage of the products, including the container, the labelling and any special storage conditions; and

24.10 any special precautions to be observed.

PACKAGING MASTER FORMULA

25. In the case of a packaged product, the master formula also includes for each product, package size and type, the following:

25.1 the package size, expressed in terms of the number, weight, or volume of the product in the final container;

25.2 a complete list of all the packaging materials required for a standard batch size, including quantities, sizes and types with the code or reference number relating to the specifications for each packaging material;

25.3 an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product are to be positioned;

25.4 special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before operations begin;

25.5 a description of the packaging operations, including any significant subsidiary operations and the equipment to be used; and

25.6 details of in-process controls, with instructions for sampling and acceptance limits.

MANUFACTURING BATCH DOCUMENT

26. Each batch processed is effectively governed by an individually numbered manufacturing order prepared by qualified personnel from the master formula by such means as to prevent errors in copying or calculation and verified by qualified personnel.

27. As it becomes available during the process, the following information is included on or with the manufacturing order:

27.1 the name of the product;

27.2 the number of the batch being manufactured;

27.3 dates and times of commencement and completion of significant intermediate stages, such as blending, heating, etc., and of production;

27.4 the batch number and/or analytical control number, as well as the quantity of each raw material actually weighed and dispensed (for active raw material, the quantity is to be adjusted if the assay value is less than 98% calculated on "as is" basis and on which the master formula was based);

27.5 confirmation by qualified personnel of each ingredient added to a batch;

27.6 the identification of personnel performing each step of the process; and of the person who checked each of these steps;

27.7 the actual results of the in-process quality checks performed at appropriate stages of the process and the identification of the person carrying them out;

27.8 the actual yield of the batch at appropriate stages of processing and the actual final yields, together with explanations for any deviations from the expected yield;

27.9 detailed notes on special problems with written approval for any deviation from the master formula; and

27.10 after completion, the signature of the person responsible for the processing operations.

28. Batches are combined only with the approval of the quality control department and according to pre-established written procedures.

28.1 The introduction of part of a previous batch, conforming to the required quality, into the next batch of the same product at a defined stage of fabrication is approved beforehand. This recovery is carried out in accordance with a validated procedure and is recorded.

PACKAGING BATCH DOCUMENT

29. Packaging operations are performed according to comprehensive and detailed written operating procedures or specifications, which include the identification of equipment and packaging lines used to package the drug, the adequate separation and if necessary, the dedication of packaging lines that are packaging different drugs and disposal procedures for unused printed packaging materials. Packaging orders are individually numbered.

30. The method of preparing packaging orders is designed to avoid transcription errors.

31. Before any packaging operation begins, checks are made that the equipment and work station are clear of previous products, documents, and materials that are not required for the planned packaging operations and that equipment is clean and suitable for use. These checks are recorded.

32. All products and packaging materials to be used are checked on receipt by the packaging department for quantity, identity and conformity with the packaging instructions.

33. Precautions are taken to ensure that containers to be filled are free from contamination with extraneous material.

34. The name and batch number of the product being handled is displayed at each packaging station or line.

35. Packaging orders include the following information (recorded at the time each action is taken):

    35.1 the date(s) and time(s) of the packaging operations;

    35.2 the name of the product, the batch number, and the quantity of bulk product to be packaged, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained and the reconciliation;

    35.3 the identification of the personnel who are supervising packaging operations and the withdrawal of bulks;

    35.4 the identification of the operators of the different significant steps;

    35.5 the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;

    35.6 the general appearance of the packages;

    35.7 whether the packages are complete;

    35.8 whether the correct products and packaging materials are used;

    35.9 whether any on-line printing is correct;

    35.10 the correct functioning of line monitors;

    35.11 handling precautions applied to a partly packaged product;

    35.12 notes on any special problems, including details of any deviation from the packaging instructions with written approval by qualified personnel;

    35.13 the quantity, lot number, and/or analytical control number of each packaging material

and bulk drug issued for use; and

35.14 a reconciliation of the quantity of printed packaging material and bulk drug used, destroyed or returned to stock.

36. To prevent mix-ups, samples taken away from the packaging line are not returned.

37. Whenever possible, samples of the printed packaging materials used, including specimens bearing the batch number, expiry date, and any additional overprinting, are attached to packaging orders.

38. Filling and sealing are followed as quickly as possible by labelling. If labelling is delayed, procedures are applied to ensure that no mix-ups or mislabelling can occur.

39. Upon completion of the packaging operation, any unused batch-coded packaging materials are destroyed, and their destruction is recorded. A procedure is followed if non-coded printed materials are returned to stock.

40. Outdated or obsolete packaging materials are destroyed and their disposal is recorded.

41. Products that have been involved in non-standard occurrences during packaging are subject to inspection and investigation by qualified personnel. A detailed record is kept of this operation.

42. Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units packaged is investigated and satisfactorily accounted for before release. Validated electronic verification of all printed packaging materials on the packaging line may obviate the need for their full reconciliation.

43. Printed packaging materials are

43.1 stored in an area to which access is restricted to designated personnel who are supervised by persons who have the qualifications outlined under Regulation C.02.006 Interpretation 2;

43.2 withdrawn against a packaging order;

43.3 issued and checked by persons who have the qualifications outlined under Regulation C.02.006 Interpretation 2; and

43.4 identified in such a way as to be distinguishable during the packaging operations.

44. To prevent mix-ups, roll-fed labels are preferred to cut labels. Gang printing is avoided.

45. Cut labels, cartons, and other loose printed materials are stored and transported in separate closed containers.

46. Special care is taken when cut labels are used, when overprinting is carried out off-line and in hand-packaging operations. On line verification of all labels by automated electronic means can be helpful in preventing mix-ups. Checks are made to ensure that any electronic code readers, label counters or similar devices are operating correctly.

47. The correct performance of any printing (e.g., of code numbers or expiry dates) done separately or in the course of the packaging is checked and recorded.

48. Raw materials, packaging materials, intermediates, bulk drugs and finished products are (a) stored in locations that are separate and removed from immediate manufacturing areas, and (b) transported under conditions designated by the quality control department to preserve their quality and safety.

49. All intermediate and finished products are held in quarantine and are so identified in accordance with Interpretation 21, until released by the quality control department.

50. Every package of a drug is identified by a lot number.

REGULATION

C.02.012

(1) Every fabricator, packager/labeller or distributor referred to in section C.01A.003, importer, and wholesaler of a drug shall maintain

(a) a system of control that permits complete and rapid recall of any lot or batch of the drug that is on the market; and

(b) a program of self-inspection.

(2) Every fabricator and packager/labeller and subject to subsections (3) and (4), every distributor referred to in section C.01A.003(b) and importer of a drug shall maintain a system designed to ensure that any lot or batch of the drug fabricated and packaged/labelled on premises other than their own is fabricated and packaged/labelled in accordance with the requirements of this Division.

(3) The distributor referred to in paragraph C.01A.003(b) of a drug that is fabricated, packaged/labelled, and tested in Canada by a person who holds an establishment licence that authorizes those activities is not required to comply with the requirements of subsection (2) in respect of that drug.

(4) If a drug is fabricated or packaged/labelled in an MRA country at a recognized building, the distributor referred to in paragraph C.01A.003(b) or importer of the drug is not required to comply with the requirements of subsection (2) in respect of that activity for that drug if

(a) the address of the building is set out in that person's establishment licence; and

(b) that person retains a copy of the batch certificate for each lot or batch of the drug received by that person.

RATIONALE

The purpose of a recall is to remove from the market, a drug that represents an undue health risk.

Drugs that have left the premises of a fabricator, packager/labeller, distributor, wholesaler and importer can be found in a variety of locations. Depending on the severity of the health risk, it may be necessary to recall a product to one level or another. Fabricators, packagers/labellers, distributors, wholesalers, and importers are expected to be able to recall to the consumer level if necessary. Additional guidance on recalls can be found in the Heath Canada document titled "Product Recall Procedures".

This *Regulation* also requires fabricators, packagers/labellers, distributors, wholesalers, and importers to maintain a program of self-inspection. The purpose of self-inspection is to evaluate the compliance with GMP in all aspects of production and quality control. The self-inspection program is designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions.

Drugs offered for sale in Canada, regardless of whether they are domestically produced or are imported, must meet the requirements of the GMP Division of the *Food and Drug Regulations*. Contract production and analysis must be correctly defined, agreed on, and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality. Normally, a contract or other written agreement exists between the parties involved, and that document clearly establishes the duties of each party.

INTERPRETATION

1. A written recall system is in place to ensure compliance with Section C.01.051 of the *Food and Drug Regulations* and requires the following:

    1.1 Health Canada is to be notified of the recall.

    1.2 Action that is taken to recall a product suspected or known to be in violation is prompt and in accordance with a pre-determined plan; the procedures to be followed are in writing and are known to all concerned.

    1.3 The person(s) responsible for initiating and co-ordinating all recall activities are identified.

1.4 The recall procedure is capable of being put into operation at any time, during and outside normal working hours.

1.5 The recall procedure outlines the means of notifying and implementing a recall and of deciding its extent.

1.6 Distribution records enable tracing of each drug product, and account is taken of any products that are in transit, any samples that have been removed by the quality control department, and any professional samples that have been distributed.

1.7 Recalled products are identified and are stored separately in a secure area until their disposition is determined.

1.8 The progress and efficacy of the recall is assessed and recorded at intervals, and a final report is issued (including a final reconciliation).

1.9 All Canadian and foreign establishments involved in the fabrication, distribution, or importation of the recalled product are notified.

2. A self-inspection program appropriate to the type of operations of the company, in respect to drugs, ensures compliance with Division 2, Part C of the *Food and Drug Regulations*.

2.1 A comprehensive written procedure that describes the functions of the self-inspection program is available.

2.2 The program of a fabricator engaged in processing a drug from raw material through to the drug in dosage form addresses itself to all aspects of the operation. For packagers/labellers, distributors, importers, and wholesalers engaged only in packaging and/or distributing drugs fabricated by another fabricator, the written program covers only those aspects of the operations over which they exercise control on their premises.

2.3 The self-inspection team includes personnel who are suitably trained and qualified in GMP.

2.4 Periodic self-inspections are carried out.

2.5 Reports on the findings of the inspections and on corrective actions are reviewed by appropriate senior company management. Corrective actions are implemented in a timely manner.

3. To ensure compliance of contract fabricators and packagers/labellers:

3.1 All arrangements for contract fabrication or packaging/labelling and testing are in accordance with the marketing authorization for the drug product concerned.

3.2 There is a written contract or other agreement covering the fabrication or

packaging/labelling and/or analysis arranged among the parties involved. The contract or agreement specifies their respective responsibilities relating to the fabrication or packaging/labelling and control of the product.

3.2.1 Technical aspects of the contract or agreement are drawn up by qualified personnel suitably knowledgeable in pharmaceutical technology, analysis, and GMP.

3.2.2 The contract or agreement permits the distributor or importer to audit the facilities of the contractor.

3.2.3 The contract or agreement clearly describes who is responsible for:

- purchasing, sampling, testing, and releasing materials
- undertaking production, quality, and in-process controls
- process validation
- test method validation

3.2.4 The contract specifies the way in which the quality control department of the distributor or importer releasing the lot or batch for sale, ensures that each lot or batch has been fabricated and packaged/labelled in compliance with the requirements of the marketing authorization.

3.2.5 The contract describes the handling of raw materials, packaging materials, in-process drug, bulk drug and finished products if they are rejected.

3.3 The contractor's complaint/recall procedures specify that any records relevant to assessing the quality of a drug product in the event of complaints or a suspected defect are accessible to the distributor or importer.

3.4 The fabricator, packager/labeller, distributor, or importer provides the contractor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The fabricator, packager/labeller, distributor, or importer ensures that the contractor is fully aware of any problems associated with the product, work or tests that might pose a hazard to premises, equipment, personnel, other materials or other products.

3.5 The fabricator, packager/labeller, distributor, or importer is responsible for assessing the contractor's continuing competence to carry out the work or tests required in accordance with the principles of GMP described in these guidelines.

3.5.1 Distributors of drugs fabricated, packaged/labelled and tested at Canadian sites are required only to have a copy of the relevant valid Canadian establishment licence held by the Canadian fabricator or packager/labeller or tester.

3.5.2 Importers of drugs fabricated, packaged/labelled, or tested at a foreign

site must meet the requirements described in the policy titled *Conditions for Acceptance for Foreign Inspection Reports*.

QUALITY CONTROL DEPARTMENT

REGULATION

C.02.013

(1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer shall have on their premises in Canada a quality control department that is supervised by personnel described in section C.02.006.

(2) The quality control department referred to in subsection (1) shall be a distinct organizational unit that functions and reports to management independently of any other functional units including the manufacturing, processing, packaging or sales unit.

RATIONALE

Quality control is the part of GMP concerned with sampling, specifications, and testing and with the organization, documentation, and release procedures. This Regulation ensures that the necessary and relevant tests are actually carried out and that raw materials and packaging materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be incorporated into all activities and decisions concerning the quality of the product.

Although manufacturing and quality control personnel share the common goal of assuring that high-quality drugs are fabricated, their interests may sometimes conflict in the short run as decisions are made that will affect a company's output. For this reason, an objective and accountable quality control process can be achieved most effectively by establishing an independent quality control department. The independence of quality control from manufacturing is considered fundamental. The rationale for the requirement that the quality control department be supervised by qualified personnel is outlined under Regulation C.02.006.

INTERPRETATION

1. A person responsible for making decisions concerning quality control requirements of the fabricator, packager/labeller, distributor, and importer, is on site or fully accessible to the quality control department and has adequate knowledge of on-site operations to fulfill the responsibilities of the position.

2. The quality control department has access to adequate facilities, trained personnel, and equipment in order to fulfill its duties and responsibilities.

3. Approved written procedures are available for sampling, inspecting, and testing raw

materials, packaging materials, in-process drugs, bulk drugs, and finished products.

4. Quality control personnel have access to production areas for sampling and investigations as appropriate.

REGULATION

C.02.014

(1) No lot or batch of drug shall be made available for sale unless the sale of that lot or batch is approved by the person in charge of the quality control department.

(2) A drug that is returned to the fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) or importer thereof shall not be made available for further sale unless the sale of that drug is approved by the person in charge of the quality control department.

(3) No lot or batch of raw material or of packaging/labelling material shall be used in the fabrication or packaging/labelling of a drug, unless that material is approved for that use by the person in charge of the quality control department.

(4) No lot or batch of a drug shall be reprocessed without the approval of the person in charge of the quality control department.

RATIONALE

The responsibility for the approval of all raw materials, packaging materials and finished products is vested in the 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.

To maintain this level of quality, it is also important to examine all returned drugs and to give special attention to reprocessed drugs.

INTERPRETATION

1. All decisions made by the quality control department pursuant to Regulation C.02.014 are signed and dated by the person in charge of the quality control department or by a designated alternate meeting the requirements described under Section C.02.006, Interpretation 1.4 or Interpretation 3.1 as applicable to the activity.

2. The assessment for the release of finished products embraces all relevant factors, including the production conditions, the results of in-process testing, the fabrication and packaging documentation, compliance with the finished product specifications, an examination of the finished package, and if applicable, a review of the transportation conditions.

2.1 Deviations and borderline conformances are evaluated in accordance with a written procedure. The decision and rationale are documented. Where appropriate, batch deviations are subject to trend analysis.

3. The quality control department ensures that raw materials and packaging materials are quarantined, sampled, tested, and released prior to their use in the fabrication or packaging/labelling of a drug.

4. Finished products returned from the market are destroyed unless it has been ascertained that their quality is satisfactory. Returned goods may be considered for resale only after they have been assessed in accordance with a written procedure. The reason for the return, the nature of the product, the storage conditions, the product's condition and history, and the time elapsed since it was originally sold are to be taken into consideration in this assessment. Records of any action taken are maintained.

5. Rejected materials and products are identified as such and quarantined. They are either returned to the vendors, reprocessed, or destroyed. Actions taken are recorded.

6. The reworking of any lot or batch of drug is given prior approval by the quality control department. Approval of a reworked lot or batch of a drug by the quality control department is based on documented scientific data, which may include validation. The reworking of products that fail to meet their specifications is undertaken only in exceptional cases. Reworking is permitted only when the following conditions are met:

- The quality of the finished product is not affected;
- The reworked lot meets specifications;
- If it is done in accordance with a defined procedure approved by the quality control department;
- All risks have been evaluated;
- Complete records of the reworking are kept;
- A new batch number is assigned; and
- The reworked lot is included in the ongoing stability program.

7. The reprocessing of any lot or batch of drug is given prior approval by the quality control department. Approval of a reprocessed lot or batch of a drug by the quality control department is based on documented scientific data, which may include validation. The reprocessing of products that fail to meet their specifications is undertaken only in exceptional cases. Reprocessing is permitted only when the following conditions are met:

- The quality of the finished product is not affected;
- The reprocessed lot meets specifications;
- The reprocessing is done in accordance with a defined procedure approved by the quality control department;
- All risks have been evaluated;
- Complete records of the reprocessing are kept;
- A new batch number is assigned; and
- Validation demonstrates that the quality of the finished product is not affected.

8. Recovery is not considered to be either a reprocessing or a reworking operation. Guidance regarding recovery is found under Regulation C.02.011, Interpretation 28.1.

9. The need for additional testing of any finished product that has been reprocessed, or reworked, or into which a recovered product has been incorporated, is evaluated and acted on by the quality control department. A record is maintained.

REGULATION

C.02.015

(1) All fabrication, packaging/labelling, testing, storage, and transportation methods and procedures that may affect the quality of a drug shall be examined and approved by the person in charge of the quality control department before their implementation.

(2) The person in charge of the quality control department shall cause to be investigated every complaint on quality that is received and cause corrective action to be taken where necessary.

(3) The person in charge of the quality control department shall cause all tests or examinations required pursuant to this Division to be performed by a competent laboratory.

RATIONALE

Pharmaceutical processes and products must be designed and developed taking GMP requirements into account. Production procedures and other control operations are independently examined by the quality control department. Proper storage, transportation, and distribution of materials and products minimize any risk to their quality. Complaints may indicate problems related to quality. By tracing their causes, one can determine which corrective measures should be taken to prevent recurrence. Having tests carried out by a competent laboratory provides assurance that test results are genuine and accurate.

Written contracts for consultants and contract laboratories describe the education, training, and experience of their personnel and the type of services provided and are available for examination and inspection. Records of the activities contracted are maintained.

INTERPRETATION

The quality control department is responsible for the following:

1. All decisions made pursuant to Regulation C.02.015. These decisions are signed and dated by the person in charge of the quality control department or by a designated alternate who meets the requirements described under Regulation C.02.006, Interpretation 1.4 or Interpretation 3.1 as applicable to the activity.

2. Ensuring that guidelines and procedures are in place and implemented for storage and transportation conditions, such as: temperature, humidity, lighting controls, stock rotation,

sanitation, and any other precautions necessary to maintain the quality and safe distribution of the drug.

3. The sampling of raw materials, packaging materials, in-process drugs, bulk drugs, and finished products is carried out in accordance with detailed written procedures. Samples are representative of the batches of material from which they are taken.

4. All complaints and other information concerning potentially defective products are reviewed according to written procedures. The complaint is recorded with all the original details and thoroughly investigated. Appropriate follow-up action is taken after investigation and evaluation of the complaint. All decisions and measures taken as a result of a complaint are recorded and referenced to the corresponding batch records. Complaint records are regularly reviewed for any indication of specific or recurring problems that require attention. The same procedures are applied to recalls.

5. Establishing a change control system to provide the mechanisms for ongoing process optimization and for assuring a continuing state of control. All changes are properly documented, evaluated, and approved by the quality control department and are identified with the appropriate effective date. Any significant change may necessitate re-validation.

6. The tests are performed by a laboratory that meets all relevant GMP requirements.

    6.1 Laboratory facilities are designed, equipped, and maintained to conduct the required testing.

    6.2 The individual in charge of the laboratory either (a) is an experienced university graduate who holds a degree in a science related to the work being carried out and has practical experience in his or her responsibility area or (b) reports to a person who has these qualifications (C.02.006, Interpretation 1).

    6.3 Laboratory personnel are sufficient in number and are qualified to carry out the work they undertake.

    6.4 Laboratory control equipment and instruments are suited to the testing procedures undertaken. Equipment is serviced and calibrated at suitable intervals according to an approved procedure, and records are maintained.

    6.5 Sensitive apparatus are protected against conditions (e.g., humidity, temperature, vibration, etc.) that may affect their functioning.

    6.6 All reagents and culture media are recorded upon receipt or preparation. Reagents made up in the laboratory are prepared according to written procedures and are labelled. Both positive and negative controls are applied to verify the suitability of

culture media. The size of the inoculums used in positive controls relates to the required sensitivity. Records are maintained.

6.7 Reference standards are available in the form of the current reference standards listed in Schedule B to the *Food and Drugs Act*. When such standards have not been established or are unavailable, primary standards can be used. Secondary standards are verified against a Schedule B reference standard or against the primary standard and are subject to complete confirmatory testing at predetermined intervals. All reference standards are stored and used in a manner that will not adversely affect their quality. Records relating to their testing, storage, and use are maintained.

PACKAGING MATERIAL TESTING

REGULATION

C.02.016

(1) Each lot or batch of packaging material shall, prior to its use in the packaging of a drug, be examined or tested against the specifications for that packaging material.

(2) No lot or batch of packaging material shall be used in the packaging of a drug unless the lot or batch of packaging material complies with the specifications for that packaging material.

(3) The specifications referred to in subsections (1) and (2) shall

(a) be in writing;

(b) be acceptable to the Director who shall take into account the specifications contained in any publication mentioned in Schedule B to the Act; and

(c) be approved by the person in charge of the quality control department.

RATIONALE

Where a drug product is presented in an inadequate package, the entire effort put into the initial research, product development and manufacturing control is wasted. Drug quality is directly dependent on packaging quality. In many cases (e.g., metered-dose aerosols), packaging quality is critical to the overall performance and effectiveness of the drug product. Faults in the packaging and labelling of a drug product continue to be a major cause of drug recalls. Packaging materials are required to be tested or examined prior to their use in a packaging operation to ensure that materials of acceptable quality are used in the packaging of drugs.

INTERPRETATION

1. Each packaging material used in the packaging/labelling of a drug is covered by specifications (as defined under C.02.002) that are approved and dated by the person in charge of the quality control department or by a designated alternate who meets the requirements described under Regulation C.02.006, Interpretation 1.4. The use of recycled or reprocessed primary packaging components is permitted only after a full evaluation of the risks involved, including any possible deleterious effects on product integrity. Specific provision is made for such a situation in the specifications.

2. Where applicable, specifications are of pharmacopoeial or equivalent status and are in compliance with the marketing authorization.

3. The adequacy of test or examination methods that are not of pharmacopoeial or equivalent status is established and documented.

4. Only packaging materials released by the quality control department are used in packaging/labelling.

5. Outdated or obsolete packaging material is adequately segregated until its disposition.

REGULATION

C.02.017

(1) The examination or testing referred to in section C.02.016 shall be performed on a sample taken

(a) after receipt of each lot or batch of packaging material on the premises of the person who packages a drug; or

(b) subject to subsection (2), before receipt of each lot or batch of packaging material on the premises of the person who packages a drug, if

(i) that person

(A) has evidence satisfactory to the Director to demonstrate that packaging materials sold to him by the vendor of that lot or batch of packaging material are consistently manufactured in accordance with and consistently comply with the specifications for those packaging materials; and

(B) undertakes periodic complete confirmatory examination or testing with a frequency satisfactory to the Director,

(ii) the packaging material has not been transported or stored under conditions that may affect its compliance with the specifications for that packaging material.

(2) After a lot or batch of packaging material is received on the premises of the person who packages a drug,

(a) the lot or batch of the packaging material shall be examined or tested for identity; and

(b) the labels shall be examined or tested in order to ensure that they comply with the specifications for those labels.

RATIONALE

Regulation C.02.017 outlines options as to when the testing or examination prescribed by Regulation C.02.016 is carried out. As with raw materials, the purchase of packaging materials is an important operation that involves personnel who have a particular and thorough knowledge of the packaging materials and vendor.

Packaging materials originate only from vendors named in the relevant specifications. It is of benefit that all aspects of the production and control of packaging materials be discussed between the manufacturer and the vendor. Particular attention is paid to printed packaging materials; labels are examined or tested after receipt on the premises of the person who packages a drug.

INTERPRETATION

1. The testing or examination of the packaging material is performed on a sample taken after their receipt on the premises of the person that packages the drug unless the vendor is certified. A packaging material vendor certification program, if employed, is documented in a standard operating procedure. The following approaches may be used for vendor certification:

1.1 A written contract outlines the specific responsibilities of each party involved. As a minimum, that contract specifies the following:

1.1.1 all the tests to be performed by the vendor, along with the content and format of the certificate of analysis, which exhibits actual numerical results, if applicable, and makes reference to product specifications.

1.1.2 that the vendor must inform the drug packager/labeller of any changes in the processing or specifications of the packaging material; and

1.1.3 that the vendor must inform the drug packager/labeller of any critical deviations during the manufacturing of a particular batch of a packaging material.

1.2 In lieu of a contract, an on-site audit of the vendor's facilities and controls by qualified personnel is acceptable. The audit ensures that all criteria described under Interpretation 1.1 are verified. These audits are performed at an appropriate frequency, and the results are documented.

2. The certification procedure also outlines how re-testing failures and any subsequent re-qualification is to be addressed.

3. A document is issued for each vendor verifying that the certification criteria have been met. The document is approved by the quality control department and is updated at an appropriate frequency.

4. When a certification program is implemented, complete confirmatory examination or testing of a minimum of one lot per year per vendor is required for non-printed packaging material.

5. Generally, due to the nature of its operations, a broker or wholesaler of packaging materials cannot be directly certified. However, when evidence is available that all original labels, certificate of analysis, general information, and package supplied by the original vendor of the packaging material has not been altered in any way during the distribution sequence, certification of the original source is still acceptable.

6. Provided that the material is properly identified, a lot or batch of packaging material selected for confirmatory testing may, with the approval of the quality control department, be used in packaging prior to completion of that testing.

7. Conditions of transportation and storage are such that they prevent alterations of the characteristics of the packaging material. In order to demonstrate that these conditions have been met, standard operating procedures and records are available and contain the following:

   7.1 the type of packaging to be employed;

   7.2 labelling requirements;

   7.3 mode of transportation;

   7.4 the type of seal used on the package; and

   7.5 the verification required to ensure that the package has not been tampered with and that there are no damaged containers.

8. Positive identification on all packaging materials, along with examination of all labels and other printed packaging materials, is conducted following their receipt on the premises of the person who packages the drug.

9. If a delivery or shipment of packaging material is made up of different batches, each batch is considered as separate for the purposes of sampling, testing, and release.

FINISHED PRODUCT TESTING

REGULATION

C.02.018

(1) Each lot or batch of a drug shall, prior to its availability for sale, be tested against the specifications for that drug.

(2) No lot or batch of a drug shall be available for sale unless it complies with the specifications for that drug.

(3) The specifications referred to in subsections (1) and (2) shall

(a) be in writing;

(b) be approved by the person in charge of the quality control department; and

(c) comply with the *Act* and these *Regulations*.

RATIONALE

Finished product tests complement the controls employed during the manufacturing process. It is at this stage that drugs are either accepted or rejected. For these reasons, it is the responsibility of each fabricator, packager/labeller, distributor, and importer to use adequate specifications and test methods that will ensure that each drug sold is safe and meets the standard under which it is represented.

INTERPRETATION

1. The written specifications contain a description of the drug in dosage form. This description includes all properties and qualities, including physical characteristics, identity, purity, and potency. Specifications also include tolerances and describe of all tests used to determine those properties and qualities, in sufficient detail to permit performance by qualified personnel. When a unique identifier is used, it is described in the specifications. These specifications are approved by the person in charge of the quality control department or by a designated alternate who meets the requirements described under Regulation C.02.006, Interpretation 1.4 or Interpretation 3.1 as applicable to the activity.

2. Specifications are equal to or exceed a recognized standard as listed in Schedule B to the *Food and Drugs Act* and are in compliance with the marketing authorization.

3. Where a recognized pharmacopoeia (Schedule B to the *Food and Drugs Act*) contains a specification for microbial content, that requirement is included.

4. Test methods are validated, and the results of such validation studies are documented.

Note: Guidance for the validation of particular types of methods can be obtained in publications such as the ICH guidelines titled "Validation of Analytical procedures: Methodology" or any standard listed in Schedule B to the *Food and Drugs Act*.

5. All tests are performed according to the approved specifications. These tests may be carried out by the distributor or by their contracted testing laboratory when a written contract specifically excludes the fabricator from this obligation.

REGULATION

C.02.019

(1) Subject to subsections (3) and (4), in the case of a packager/labeller, distributor referred to in paragraph C.01A.003(b) or importer, the testing referred to in section C.02.018 shall be performed on a sample taken

(a) after receipt of each lot or batch of the drug on the premises in Canada of the packager/labeller, distributor referred to in paragraph C.01A.003(b) or importer of the drug; or

(b) subject to subsection (2), before receipt of each lot or batch of the drug on the premises described in paragraph (a), if;

(i) the packager/labeller, distributor referred to in paragraph C.01A.003(b) or importer

(A) has evidence satisfactory to the Director to demonstrate that drugs sold to him by the vendor of that lot or batch of the drug are consistently manufactured in accordance with and consistently comply with the specifications for those drugs; and

(B) undertakes periodic complete confirmatory testing with a frequency satisfactory to the Director; and

(ii) the drug has not been transported or stored under conditions that may affect its compliance with the specifications for that drug.

(2) Where the packager/labeller, distributor referred to in paragraph C.01A.003(b) or importer of a drug receives a lot or batch of a drug on the premises in Canada, and the useful life of the drug is more than 30 days, the lot or batch of the drug shall be tested for identity, and the packager/labeller shall confirm the identity after the lot or batch is packaged/labelled.

(3) The distributor referred to in paragraph C.01A.003(b) of a drug that is fabricated, packaged/labelled and tested in Canada by a person who holds an establishment licence that

authorizes those activities is not required to comply with the requirements of subsections (1) and (2) in respect of that drug.

(4) If a drug is fabricated, packaged/labelled and tested in an MRA country at a recognized building, the distributor referred to in paragraph C.01A.003(b) or importer of that drug is not required to comply with the requirements of subsections (1) and (2) in respect of that drug if

(a) the address of the building is set out in that person's establishment licence; and

(b) that person retains a copy of the batch certificate for each lot or batch of the drug received by that person.

RATIONALE

Paragraph C.02.019(1)(b) outlines requirements that are to be met if the finished product testing is done before receipt on the premises of the packager/labeller, distributor, or importer of the drug. Paragraphs C.02.019(3) and C.02.019(4) outline exemptions to this requirement.

INTERPRETATION

1. Identity is confirmed by the packager/labeller after the lot or batch is packaged.

TRANSPORTATION AND STORAGE

2. Conditions of transportation and storage prevent any changes to the potency, purity, and physical characteristics of the drug. Standard operating procedures and records for shipping and receiving are available and contain the following:

2.1 a description of the shipping configuration and the type of protective packaging to be employed for shipping the finished product;

2.2 the labelling requirements, including storage conditions and special precautions or warnings, for shipments of the finished product;

2.3 mode(s) of transportation approved for shipping the finished product;

2.4 a description of how shipments of the finished product are to be sealed;

2.5 the verifications required to ensure that no finished product in the shipment has been tampered with and that there are no damaged containers; and

2.6 evidence that shipping requirements (e.g., temperature control) have been met if required.

SITES HOLDING A CANADIAN ESTABLISHMENT LICENCE

3. To demonstrate compliance with finished product specifications, distributors of drugs fabricated, packaged/labelled and tested at Canadian sites are required only to have a copy of the authentic certificate of analysis from the licensed Canadian fabricator. This certificate shows actual numerical results and refers to the product specifications and validated test methods used. Re-testing, including identity testing, is not required.

RECOGNIZED BUILDINGS BY A REGULATORY AUTHORITY IN A MRA COUNTRY

4. To demonstrate compliance with finished product specifications, importers of drugs fabricated, packaged/labelled, and tested at recognized buildings authorized by a Regulatory Authority as listed by virtue of Regulation C.01A.019 are required only to have a fabricator's batch certificate from the foreign fabricator in the format agreed on by the MRA partners. Re-testing, including identity testing, is not required when the drug is fabricated, packaged/labelled, and tested in an MRA country.

SITES IN NON-MRA COUNTRIES

5. For testing other than identity testing, the following conditions are to be met if the packager/labeller or importer chooses to rely on the test results provided by a fabricator located in a non-MRA country:

    5.1 Evidence of ongoing GMP compliance is provided according to a system described in the interpretation of Regulation C.02.012.

    5.2 Each lot is accompanied by an authentic certificate of analysis or by a copy thereof (an electronic copy with an electronic signature is acceptable). The certificate of analysis exhibits actual numerical results and makes reference to the product specifications and validated test methods used.

        5.2.1 For terminally sterilized products, documented evidence is available from the fabricator to demonstrate that each sterilizer load was individually tested.

        5.2.2 For aseptically filled products, evidence demonstrates that samples include the first container filled, the last container filled, and those filled after any significant interruption of work.

    5.3 Periodic complete confirmatory testing is performed on at least one lot per year per dosage form per fabricator. For each dosage form, products are selected on a rotational basis. Re-testing by the original laboratory is acceptable; however, it is recommended that re-testing be performed by an alternate laboratory. No confirmatory testing for sterility, pyrogen, bacterial endotoxin, particulate matter, or general safety is required.

5.4 Provided that a specific identity test is performed, a lot or batch of the finished product selected for periodic confirmatory testing may, with the approval of the quality control department, be released for sale prior to completion of all tests.

6. Should any failure to conform to finished product testing requirements be identified, an investigation of the extent of the non-compliance is to be conducted. This investigation may lead to reassessment and re-testing of all dosage forms from the fabricator. This procedure may include:

6.1 re-evaluation of GMP compliance; and

6.2 additional complete confirmatory testing, based on the risk associated with the non-compliance.

7. Positive identification of each lot or batch in a shipment of a drug is carried out on a sample taken after receipt on the premises of the packager/labeller or the importer. This identity testing requirement applies to lots received from any non-MRA site. Laboratory chemical/biological testing is required unless the dosage form has unique physical characteristics. Acceptable identity testing methods include the following:

7.1 chemical testing;

7.2 biological testing; and

7.3 physical verification in cases where the product has unique identifiers.

7.3.1 The unique identifier principle must be applied before the final chemical or biological identity testing is performed by the fabricator. Where only a portion of a lot is packaged/labelled for Canada, the identity testing must be performed after the unique identifier is applied on the Canadian labelled product.

7.3.2 For each product and each strength, uniqueness must be confirmed in writing by the fabricator to the importer at least once a year, as well as whenever a change occurs. When no such confirmation can be obtained, chemical or biological identity testing will be required from the importer.

7.3.3 The unique identifier must be confirmed on the certificate of analysis for each lot received from the fabricator.

Note: Label review or examination of the shape and size of the container is not generally considered adequate identity testing.

7.4 The following unique identifiers are considered acceptable:

7.4.1 Tablets and capsules that are engraved, embossed, or printed with a unique logo;

7.4.2 Permanent identification on the drug's closure system that indicates the name and strength of the contents. This marking must be applied as part of a continuous filling process and only where the closure cannot be removed without being destroyed.

7.4.3 Colour closure systems as part of a continuous filling process when the fabricator uses a uniquely coloured cap or closure for only one product and strength;

7.4.4 A coloured vial, sometimes used for light-sensitive drugs, if it is unique to one product, strength, and fabricator;

7.4.5 A dedicated facility fabricating only one product;

7.4.6 Labelling, where preprinted containers are issued to the filling line and where the lot number either is pre-printed or is printed or crimped onto the package in a continuous process; and

7.4.7. Group 2 products subject to Health Canada's lot release program.

RECORDS

REGULATION

C.02.020

(1) Every fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer shall maintain on their premises in Canada for each drug sold

(a) master production documents for the drug;

(b) evidence that each lot or batch of the drug has been fabricated, packaged/labelled, tested and stored in accordance with the procedures described in the master production documents;

(c) evidence that the conditions under which the drug was fabricated, packaged/labelled, tested and stored are in compliance with the requirements of this Division;

(d) evidence establishing the period of time during which the drug in the container in which it is sold will meet the specifications for that drug; and

(e) adequate evidence of the testing referred to in section C.02.018.

(2) Every distributor referred to in paragraph C.01A.003(b) and importer shall make available on request the results of testing performed on raw materials and packaging/labelling materials for each lot or batch of a drug sold.

(3) Every fabricator shall maintain on his premises

(a) the written specifications for the raw material; and

(b) adequate evidence of the raw materials testing referred to in section C.02.009.

(4) Every person who packages a drug shall maintain on his premises

(a) the written specifications for the packaging materials; and

(b) adequate evidence of the packaging material examination or testing referred to in section C.02.016.

(5) Every fabricator shall maintain on their premises in Canada:

(a) detailed plans and specifications of each building in Canada at which they fabricate, package/label or test; and

(b) a description of the design and construction of those buildings.

(6) Every fabricator, packager/labeller and tester shall maintain on their premises in Canada details of the personnel employed to supervise the fabrication, packaging/labelling and testing, including each person's title, responsibilities, qualifications, experience and training.

C.02.021

(1) Subject to subsection (2), all records and evidence on the fabrication, packaging/labelling, testing and storage of a drug that are required to be maintained under this Division shall be retained for a period of at least one year after the expiration date on the label of the drug, unless otherwise specified in the person's establishment licence.

(2) All records and evidence on the testing of raw materials and packaging/labelling materials that are required to be maintained under this Division shall be retained for a period of at least five years after the materials were last used in the fabrication or packaging/labelling of a drug unless otherwise specified in the person's establishment licence.

C.02.022

Every distributor referred to in section C.01A.003, wholesaler and importer of a drug shall retain records of the sale of each lot or batch of the drug, which enable them to recall the lot or batch from the market for a period of at least one year after the expiration date of the lot or batch unless otherwise specified in their establishment licence.

C.02.023

(1) On receipt of a complaint respecting the quality of a drug, every distributor referred to in paragraph C.01A.003(b), and importer of the drug shall make a record of the complaint and of its investigation and retain the record for a period of at least one year after the expiration date of the lot or batch of the drug, unless otherwise specified in their establishment licence.

(2) On receipt of any information respecting the quality or hazards of a drug, every distributor referred to in paragraph C.01A.003(b), and importer of the drug shall make a record of the information and retain it for a period of at least one year after the expiration date of the lot or batch of the drug unless otherwise specified in their establishment licence.

C.02.024

(1) Every fabricator, packager/labeller, distributor referred to in section C.01A.003 importer and wholesaler shall

(a) maintain records of the results of the self-inspection program required by section C.02.012 and of any action taken in connection with that program; and

(b) retain those records for a period of at least three years.

(2) Every person who fabricates or packages/labels a drug shall

(a) maintain records on the operation of the sanitation program required to be implemented under section C.02.007, and

(b) retain those records for a period of at least three years.

RATIONALE

Good documentation is an essential part of the quality assurance system and should therefore be related to all aspects of GMP. Its aims are to define the specifications for all materials and methods of fabrication, packaging/labelling, and control; to ensure that the quality control department has all the information necessary to decide whether or not to release a batch of a drug for sale; and to provide an audit trail that will permit investigation of the history of any batch that is suspected to be defective.

Evidence that drugs have been fabricated and packaged/labelled under prescribed conditions can be maintained only after developing adequate record systems. The information and evidence should provide assurance that imported drugs are fabricated and packaged/labelled in a like manner to those produced in Canada.

INTERPRETATION

For all sections of Good Manufacturing Practices guidelines, standard operating procedures (SOPs) are retained for reference and inspection. These SOPs are regularly reviewed and kept up

to date by qualified personnel. The reasons for any revisions are documented. A system is in place to ensure that only current SOPs are in use. Records of SOPs for all computer and automated systems are retained where appropriate.

All relevant GMP documents (such as associated records of actions taken or conclusions reached) and SOPs are approved, signed, and dated by the quality control department. Documents are not altered without the approval of the quality control department. Any alteration made to a document is signed and dated; the alteration permits the reading of the original information. Where appropriate, the reason for the change is recorded.

Records may be maintained in electronic format provided that backup copies are also maintained. Electronic data must be readily retrievable in a printed format. During the retention period, such records must be secured and accessible within 48 hours to the fabricator, packager/labeller, distributor, or importer.

An electronic signature is an acceptable alternative to a handwritten signature. When used, such a system must be evaluated and tested for security, validity, and reliability, and records of those evaluations and tests must be maintained. The validation of electronic signature identification systems is documented.

Any documentation requested for evaluation by Health Canada is provided in one of the official languages.

1. The following documents are maintained by the fabricator, packager/labeller, distributor referred to in paragraph C.01A.003(b) and importer of a drug:

    1.1 Master production documents as defined in the Glossary of Terms.

        1.1.1 When the fabricator is located in Canada, specific parts of a master production document considered to be a trade secret or confidential may be held by the fabricator rather than the distributor. When the fabricator is located outside Canada, specific parts of a master production document considered to be a trade secret or confidential may be held on behalf of the distributor or importer by an independent party in Canada. In either case, the distributor or importer must ensure that Health Canada has access to the data in a timely manner.

        1.1.2 Regardless of whether the fabricator is Canadian or foreign, the master production document retained by the distributor or importer describes in general terms whatever information has been deleted as a trade secret or confidential.

    1.2 Evidence that each lot or batch of the drug has been fabricated, packaged/labelled, tested and stored in accordance with the procedures described in the master production documents.

        1.2.1 This evidence includes manufacturing orders, packaging orders, and test

results for raw materials, packaging materials, and drugs in dosage form. However, when the drug is fabricated or packaged outside the premises of the distributor or importer, test results for raw materials and packaging materials need only be made available on request in a timely manner.

1.2.2 A certificate of manufacture is considered an acceptable alternative to complete batch documentation, provided that complete documentation is made available on request in a timely manner.

1.2.3. Where an importer of drugs from non-MRA countries employs a system involving a "certificate of manufacture", complete batch documentation is obtained at least once per year per drug.

1.2.4. A certificate of manufacture alone cannot be employed where reworking has taken place. Should there be changes to the production documents, the complete documentation is provided to the importer or distributor, and any changes that have been made are indicated.

1.3 Evidence that the conditions under which the drug was fabricated, packaged/labelled, tested, and stored are in compliance with requirements of this Division.

1.3.1 This evidence includes records generated under subsection C.02.012(2) and evidence of validation. For additional guidance, refer to the "Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers/Labellers, Distributors and Importers."

1.3.2 Records include the name, address, and qualifications/experience of any consultant employed for GMP purposes, along with the services that each consultant provides. Records of consultants' activities (contracts) are maintained.

1.4 Evidence establishing the period of time during which the drug in the container in which it is sold will meet the specifications for that drug.

1.4.1 The documentation to be maintained includes the written stability program, the data generated in accordance with that program, and the conclusions leading to the establishment of the period of time during which each drug in the package in which it is sold complies with the specifications for that drug. Also included are data generated as part of the continuing stability program.

1.5 For each lot of drug in dosage form, adequate evidence of compliance with finished product specifications.

2. The following documents are maintained by the fabricator, packager/labeller, distributor, wholesaler, and importer of a drug as they relate to all operations in Canada:

2.1 Distribution records of all sales of drugs, including those of professional samples.

2.1.1 Records of all sales are retained or are kept readily accessible in a manner that will permit a complete and rapid recall of any lot or batch of a drug. This requirement need not necessarily involve tracking by lot number.

2.1.2 Records to indicate that all customers who have received a recalled drug have been notified.

2.2 Records of the results of the self-inspection program, evaluation, and conclusions, and corrective measures implemented.

3. The following documents are maintained by every fabricator, packager/labeller, distributor, and importer of a drug:

3.1 Records of complaints relating to quality and of subsequent investigations of complaints, including corrective actions taken.

3.2 Records concerning information received respecting the quality or hazards of a drug.

4. The following documents are maintained by the fabricator:

4.1 the written specifications for the raw materials;

4.2 the results of the raw material testing;

4.3 the sources of the raw materials supplied;

4.4 records on the operation of the sanitation program required by Regulation C.02.007; and

4.5 detailed plans and specifications of each building where fabrication occurs, including a description of the design and construction.

5. The following documents are maintained by the person who packages or labels a drug:

5.1 the written specifications for the packaging materials;

5.2 the results of the packaging material examinations or testing;

5.3 the sources of the packaging materials supplied; and

5.4 records on the operation of the sanitation program required by Regulation C.02.007.

6. Every fabricator, packager/labeller, and tester maintains

6.1 Details of the personnel employed to supervise the fabrication, packaging/labelling, and testing, including organization charts; each person's title, job description, responsibilities, qualifications, experience, and training; and the name(s) of each person's designated alternate(s).

7. Records required under Regulations C.02.021(1), C.02.022, and C.02.023 are retained for a period of at least one year past the expiration date of the drug to which the records apply.

7.1 For medical gases, which do not require an expiration date, records required under Regulations C.02.021(1), C.02.022, and C.02.023 are retained for a period of at least five years from the date of fabrication of the drug.

SAMPLES

REGULATION

C.02.025

(1) Every distributor referred to in paragraph C.01A.003(b) and importer of a drug shall retain in Canada a sample of each lot or batch of the packaged/labelled drug for a period of at least one year after the expiration date on the label of the drug unless otherwise specified in the distributor's or importer's establishment licence.

(2) The fabricator shall retain a sample of each lot or batch of raw materials used in the fabrication of a drug for a period of at least two years after the materials were last used in the fabrication of the drug unless otherwise specified in the fabricator's establishment licence.

C.02.026

The samples referred to in section C.02.025 shall be in an amount that is sufficient to determine whether the drug or raw material complies with the specifications for that drug or raw material.

RATIONALE

These requirements help ensure that responsible officials at fabricating, distributing, or importing establishments and at Health Canada have ready access to those samples that are essential for re-examination should a product quality concern arise.

INTERPRETATION

1. A sample of each lot or batch of a packaged drug is retained in Canada by the distributor referred to in paragraph C.01A.003(b) or by the importer of the drug.

    1.1 The sample is retained in its trade package or in a container of the same material and construction. In the case of large containers, a smaller representative sample may be substituted. This allowance does not apply to hermetically sealed containers.

    1.2 The sample is stored under the conditions indicated on the label.

    1.3 Retention samples are maintained in accordance with a written procedure.

2. A sample of each lot or batch of a raw material (including both active and inactive ingredients), is retained by the fabricator of the drug.

    2.1 The sample is stored in the same packaging system in which the raw material is stored or in one that is equivalent to or more protective than the marketed packaging system of the raw material.

    2.2 The sample is stored under the conditions indicated in the specifications.

    2.3 Retention samples are maintained in accordance with a written procedure.

3. In determining the size of sample to be maintained, it is to be kept in mind that Health Canada needs at least enough of the material to carry out tests to determine whether the drug or the raw material complies with its specifications. The fabricator, distributor, or importer may also wish to test the material in the event of a complaint; the sample should therefore be at least double the amount needed to complete all required tests.

4. This requirement is not considered to be applicable to the number of units normally required for sterility and pyrogen testing, or to water, solvents, and medical gases.

5. Health Canada will consider alternate sample retention for distributors and importers as referred to in sub-section C.02.025(1) if a product specific request is submitted as outlined in Annex B to these guidelines. This request can be submitted with an establishment licence application, amendment, or notification. The establishment licence for the distributor or the importer may be modified with respect to sample retention of specific products where

    - the fabricator of the product has committed to retaining the sample using the same container-closure system as the one marketed in Canada; or
    - the information supplied by the applicant supports a shorter retention period than that required under Regulation C.02.025.

    5.1 The application demonstrates that the product meets one or more of the following criteria:

        5.1.1. Testing of the drug requires specialized product-specific methodology that is not available in Canada

5.1.2. The drug is subject to Health Canada's lot release program.

5.1.3. There is a limited volume of the drug sold in Canada due to the indications for use (e.g, orphan-like drugs)

5.1.4. There is a limited quantity of the drug available to the Canadian market (e.g., small portions of many batches)

5.1.5. Individual samples of the drug are very expensive. The number of samples to be retained (e.g., high volume) is not an acceptable factor.

5.1.6. Perishable drugs that have expiration dates based solely on the shelf life of the food ingredients, not on the stability of the active drug ingredient (e.g., juices with added calcium or vitamins).

5.1.7. Radiopharmaceuticals.

5.1.8. The following non-prescription drugs (see Category IV product monographs):

- Acne therapies (topical)
- Anticaries products containing fluoride
- Antidandruff products
- Antiperspirants
- Antiseptic skin cleansers
- Athletes foot treatments
- Medicated skin-care products
- Sunburn protectants

5.1.9 Hard-surface disinfectants

5.2. An alternate sample retention request or notification provides the following:

5.2.1. evidence that sufficient numbers of samples of lots sold in Canada will be maintained to allow access to those samples by all pertinent regulatory authorities, including Health Canada; and

5.2.2. a commitment to provided samples within 48 hours of receiving a request from Health Canada.

5.3. Should circumstances change regarding any of the above criteria, the applicant must inform Health Canada so that the alternate means may be reassessed.

STABILITY

REGULATION

C.02.027

Every distributor referred to in paragraph C.01A.003(b) and importer shall establish the period of time during which each drug in the package in which it is sold comply with the specifications.

RATIONALE

The purpose of the written stability program is to ascertain the normal shelf life of the products that is to determine how long the products can be expected to remain within specifications under recommended storage conditions. The requirements for the formal stability studies (primary and commitment batches) are outlined in the various Health Canada and ICH Guidelines. Each packaged dosage form must be covered by a sufficient amount of data to support its asserted shelf life in its trade package.

INTERPRETATION

1. The stability of the drug is determined prior to marketing and prior to adoption of significant changes in formulation, fabrication procedures, or packaging materials that may affect the shelf life of the drug.

    1.1 Accelerated stability data are considered to be preliminary information only. The accelerated data are supported by long term testing. The assignment of the expiry date is based on the long-term testing.

    1.2 Stability studies are carried out on the drug in each package type in which it is to be sold in Canada.

    1.3 For new chemical entities, at least three lots of each strength are sampled for the development of shelf life data, unless such data are submitted as a part of the application for marketing approval. For existing chemical entities (e.g., generic drugs), two lots of each strength are sampled. The principle of bracketing and matrixing designs may be applied if justified.

    1.4 Stability data originating from foreign fabricators are acceptable provided that the data meet the requirements of the various Health Canada and ICH guidelines regarding stability. The data provide evidence that the drug product is not affected by transportation.

    1.5 The shelf life is established from the date of fabrication.

    1.6 Stability data are available for drugs that are to be reconstituted or further diluted.

1.7 Analytical test procedures used in stability evaluation are validated in accordance with the ICH guidelines titled "Validation of Analytical Procedures: Methodology". Assays are to be stability-indicating, (i.e., sufficiently specific to detect breakdown products and to distinguish between degraded and non-degraded materials). Limits for individual unidentified, individual identified and total degradation products are included.

REGULATION

C.02.028

Every distributor referred to in paragraph C.01A.003(b) and importer shall monitor, by means of a continuing program, the stability of the drug in the package in which it is sold.

RATIONALE

The purpose of the written continuing stability program is to monitor the shelf life of the product. It also serves to determine how long the product can be expected to remain within specifications under recommended storage conditions. Each packaged dosage form must be covered by a sufficient amount of data to support its labelled expiry date in its trade package. Any significant change that may have an impact on the quality of the product should be assessed and may require further stability studies.

INTERPRETATION

1. A continuing stability program is implemented to ensure compliance with the approved shelf life specifications. A protocol is available and is implemented for each drug marketed in Canada. A summary of all the data generated, including the evaluation and the conclusions of the study, is prepared. This program includes but is not limited to the following parameters:

    - number of batch(es) per strength and batch sizes,
    - tests and acceptance criteria,
    - container closure system(s),
    - testing frequency,
    - storage conditions (and tolerances) of samples, and
    - other applicable parameters specific to the drug.

    1.1 A minimum of one batch of every strength of the drug is enrolled into the continuing stability program each year. The principle of bracketing and matrixing designs may be applied if justified in accordance with ICH guideline Q1A(R).

    1.2 Any differences in the protocol for the continuing stability program and the protocol for the formal stability studies are scientifically justified.

1.3 Stability data originating from foreign fabricators are acceptable, provided that the data meet the requirements of the various Health Canada and ICH guidelines regarding stability. The data provide evidence that the drug product is not affected by transportation.

2. Minor changes (e.g., addition, deletion, or substitution of a fragrance, flavour, or colour) to the formulations of certain designated non-prescription drugs may be acceptable without new stability data, provided that the following conditions are met:

2.1 Ongoing stability studies are conducted on the revised formulation to demonstrate that the proposed change does not affect the quality of the drug product.

2.2 A continuing stability program of stability is conducted concurrently with the marketing of the modified product throughout the shelf life of the product.

2.3 Minor changes are acceptable for the following non-prescription products (see Category IV product monographs):

- Acne therapies (topical)
- Anti-caries products containing fluoride
- Antidandruff products
- Antiperspirants
- Antiseptic skin cleansers
- Athletes foot treatments
- Medicated skin-care products
- Secondary sunburn protectants (e.g., lipstick with SPF)

Note: The chart shown on the next page is a guide for selecting parameters to be studied in the stability program. Each product must be examined separately.

a) The inclusion of a sterility test in the stability study of a sterile drug may not be necessary if the container closure system has been proven to be hermetic.

b) In addition to preservative content testing, a single regular production batch of the drug is to be tested for antimicrobial preservative effectiveness at the end of the proposed shelf life.

Note: For further information on the requirements of the formal stability studies, see references listed in Annex C of these guidelines.

STABILITY
(Chart to be used as a guide only)

	TABLETS	CAPSULES	LIQUIDS AND GELS	OINTMENTS AND CREAMS	POWDERS	INJECTABLES	SUPPOSITORIES	AEROSOLS
POTENCY	Assay all active ingredients as well as other "elements" outlined below		Plus: preservatives, antioxidants, and bacteriostats if effectiveness not checked under Purity section	Plus: preservatives, antioxidants, and bacteriostats if effectiveness not checked under Purity section	Plus: complete testing data on reconstituted forms	Plus: preservatives, antioxidants, and bacteriostats if effectiveness not checked under Purity section		Quantity delivered per spray for metered dose products
Physical Characteristics	Containers: (1) Appearance of inner walls and cap interiors colour (2) Integrity of seals (3) Appearance and adhesion of label							
	-dissolution -disintegration -odour -hardness	-dissolution -disintegration -condition of shells	-odour -viscosity -specific gravity -pH -clarity of solution -precipitation of ingredients -non-homogeneity of suspensions -homogeneity (gels)	-odour -texture -pH -homogeneity -precipitation of ingredients	-odour -texture -clarity of solution -homogeneity - pH (after reconstitution) -particle size -flow characteristics (inhalation powders)	-clarity -particulate matter -pH -precipitation of ingredients -optical rotation -multiple dose vials: product integrity after initial use	-melting point -homogeneity	-net weight -delivery weight -delivery pressure -pH -delivery effectiveness (e.g. spray pattern and droplet size) -number of doses or sprays per package
PURITY	Containers: (1) Migration of drug into plastic (2) Migration of plasticisers into drug (3) Corrosion							
	-moisture content	-moisture content	-sterility for ophthalmics -particulate matter for ophthalmics	-sterility for ophthalmics -particulate matter for ophthalmics	-moisture content	-sterility		
	Microbial Test							
	Degradation products							

STERILE PRODUCTS

REGULATION

C.02.029

In addition to the other requirements of this Division, a drug that is intended to be sterile shall be fabricated and packaged/labelled

(a) in separate and enclosed areas;

(b) under the supervision of personnel trained in microbiology; and

(c) by a method scientifically proven to ensure sterility.

RATIONALE

Sterile drugs are susceptible to particulate, pyrogenic and microbiological contamination. Due to the health hazard associated with the use of contaminated sterile products, special precautions are required in the production of these products. The skill, training, and competency of all personnel involved are critical. Quality assurance is important and the production must follow carefully established and validated methods of preparation and sterilization.

INTERPRETATION

GENERAL

1. Separate packaging and labelling operations of hermetically sealed containers are not subject to Regulation C.02.029 but are covered under Regulation C.02.011.

2. When designing procedures for achieving sterility, a number of factors must be considered, particularly airborne microorganisms, particulate matter, the size of the opening of the container, the length of time contents are exposed, and assurance that all the material is exposed to the sterilization condition or process.

3. All aqueous-based sterile products are subjected to terminal steam sterilization, with the following exceptions:

   3.1 Instances where terminal steam sterilization is not practicable (e.g., where the sterilization process would cause product or packaging degradation). Such instances are fully evaluated and documented.

   3.2 Aseptic processes that exclude human intervention (e.g., robotics, form-fill-seal, and barrier systems) may be employed in lieu of terminal sterilization, provided that the data developed demonstrate equivalent sterility assurance. Any such methods

introduced are fully validated, taking into account all critical factors of the technology used as well as the routine monitoring to be carried out.

4. Environmental grade requirements

Drugs subject to terminal sterilization:

4.1 Formulation takes place in an environmental where a minimum of Grade C conditions is maintained, provided that the formulated bulk is immediately subjected to its subsequent processing step, (e.g., filtration, sterilization), in order to minimize bio-burden and particulates.

4.2 Formulation may take place in a Grade D environment if additional measures (e.g., the use of closed systems of manufacture) are taken to minimize contamination.

4.3 Parenterals are filled in an aseptic area with at least a Grade B environment or in a Grade A zone with at least a Grade C background, before terminal sterilization.

4.3.1 Parenterals that are to be terminally sterilized may be filled in a Grade C area if the process or product does not pose a high-risk of microbial contamination. Examples of high-risk situations include slow filling operations, the use of wide-necked containers, or the exposure of filled containers to the environment for more than a few seconds before sealing.

4.4 Non-parenterals may be filled in a Grade C environment before terminal sterilization.

Drugs not subject to terminal sterilization:

4.5 Parenterals sterilized by filtration, are formulated in an environment where a minimum of a Grade C conditions is maintained.

4.6 Non-parenteral products may be formulated in a Grade D environment if additional measures are taken to minimize contamination, such as the use of closed systems.

4.7 Sterile filtration requires a minimum filter rating of 0.22 µm. The integrity of the filter is verified before and after use by an appropriate method such as a bubble point, diffusion or pressure hold tests.

4.8 Filling operations are performed under local Grade A conditions within a Grade B background environment. However a lower-grade background environment may be acceptable if specialized automated or barrier techniques are employed and if those techniques are validated to demonstrate that their use has no negative impact on the quality of the drug.

Drugs not subject to filtration or terminal sterilization:

4.9 Sterile products subject to neither filtration nor terminal sterilization, are produced from sterile raw materials and packaging components in an aseptic area.

5. The air standards described in the following tables are to be achieved throughout the area when it is occupied and in operation. In the operational condition for Grade A, the air standards apply in the zone immediately surrounding the drug whenever it is exposed. It may not always be possible to demonstrate conformity with air standards for non-viable particulates at the point of fill when filling is in progress, owing to the generation of particles or droplets by the product itself.

5.1 The "at rest" state is the condition where the installation is complete, including fabrication equipment installed and present in an operational condition but not in use and with operating personnel absent. The "in operation" state is the condition where equipment and personnel are in place and ready for production.

6. The classification of aseptic and clean areas is based on environmental results obtained using acceptable standardized air sampling methods. Such methods take into account the volume and number of samples taken at each location and the total number of sampling locations. The number of sampling locations is based on room volume and on the nature of the operations being undertaken. Sampling methods used during the operational state do not interfere with zone protection.

7. Radiation sterilization is used mainly for heat-sensitive materials. Since drugs and packaging materials are radiation-sensitive, this method is permissible only when, prior to use, evidence has confirmed the absence of any damaging effects on the material.

8. Ethylene Oxide sterilization is used only when other methods are not practicable. Evidence must be available to show the absence of any damaging effect on the drug when this method is used. The conditions and time allowed for degassing the drug are such that residual gas and reaction products are reduced to clearly defined acceptable limits.

9. Ultraviolet irradiation is not an acceptable method of sterilization.

BASIC ENVIRONMENTAL STANDARDS FOR THE MANUFACTURE OF STERILE PRODUCTS

	at rest (5)		in operation	
Grade	Maximum permitted number of particles / m3 equal to or above (3)			
	0,5 µm	5 µm	0,5 µm	5 µm
A (1)	3 500	1 (6)	3 500	1 (6)
B (2)	3 500	1 (6)	350 000	2 000
C (2)	350 000	2 000	3 500 000	20 000
D (2)	3 500 000	20 000	not defined (4)	not defined (4)

Notes:

1. Unidirectional (laminar) airflow systems provide a homogeneous air speed of 0.45 m/s +/- 20% (guidance value) at the working position. Precise air speeds will depend on the type of equipment.

2. In order to attain air Grades B, C, and D, the number of air changes will be related to the size of the area and to the equipment and personnel present in the area.

3. Low values for contaminants are reliable only when a large number of air samples are taken.

4. The requirement and limits for this area will depend on the nature of the operations carried out.

5. The particulate conditions given in the "at rest" column are to be achieved after a short clean-up period (20 minutes) after the operation has been completed.

6. It is expected to get these areas completely free from particles sized equal or greater than 5 µm. As it is impossible to demonstrate absence of particles with any statistical significance the limits are set to 1 particle / m^3. During the qualification of classified rooms it should be shown that the areas could be maintained within the defined limits.

Recommended limits for microbial contamination (a) (e)				
GRADE	air sample cfu/m3	settle plates (diameter 90mm), cfu/4 hours (b)	contact plates (diameter 55 mm), cfu/plate ©)	glove print (5 fingers) cfu/glove (d)
A	< 1	< 1	< 1	< 1
B	10	5	5	5
C	100	50	25	-
D	200	100	50	-

Notes:

(a) These are average values. For a Grade A area, no individual result should exceed 3 without investigation.
(b) Individual settle plates may be exposed for less than 4 hours.
©) The surface sampled with a contact plate is subject to appropriate cleaning immediately after use.
(d) Monitoring is conducted after critical operations are complete.
(e) All indicated sampling methods are required unless alternative methods demonstrate equivalency.

PREMISES

1. To the extent possible, premises are designed to avoid the unnecessary entry of supervisory or control personnel. Grade B areas are designed so that all critical operations can be observed from outside.

2. To prevent the shedding or accumulation of dust and other particulate matter, ceilings, floors, and walls in aseptic areas, and floors and walls in clean areas, have smooth impervious surfaces that permit the repeated application of cleaning and disinfecting agents.

3. To reduce the accumulation of dust and to facilitate cleaning, projecting ledges or shelves and electrical and mechanical equipment are kept to a minimum. Covings are required where walls meet floors or ceilings. Walls, floors, and ceilings form an effective seal around any traversing pipe or duct.

4. False ceilings are sealed to prevent contamination from the space above them.

5. Uncleanable devices, such as certain sliding-door rails, are avoided.

6. Where required, sinks and drains are designed, located, and maintained so as to minimize risks of microbial contamination. Sinks and drains are excluded from areas where aseptic operations are carried out.

7. Hand-washing facilities are provided only in changing rooms.

8. Changing rooms are designed as airlocks and are used to separate the different stages of changing, thus minimizing microbial and particulate contamination of protective clothing. They are effectively flushed with filtered air. In the final stage, they are, at rest, the same grade as the area into which they lead.

9. Access to the aseptic areas is provided only through air-locks. Doors to air locks are arranged so that, either by design or by procedure, only one side or door may be opened at one time (except for emergencies).

10. The air for clean and aseptic areas is supplied through filters of suitable efficiency. Laminar air flow systems are of appropriate design.

11. The filtered air supply for clean and aseptic areas is designed to provide a fabrication environment that meets the required grade classifications. Under all operational conditions, a positive pressure of filtered airflow is maintained in relation to surrounding areas of a lower grade. Particular attention is paid to protecting the zone of greatest risk, that is, the immediate environment to which the product and the treated components are exposed.

12. Warning systems alert personnel when air pressure or airflow falls below established limits. Pressure differentials between areas are monitored and recorded where such differences are of importance.

13. Airflow patterns do not present a contamination risk. For example, care is taken to ensure

that airflows do not distribute particles from a particle-generating person, operation, or machine to a zone of higher product risk.

14. All work with microorganisms and other infectious agents known to require special precautions in manipulation is safely segregated.

EQUIPMENT

1. Equipment designed in such a way as to facilitate cleaning, disinfection, or sterilization. Electronic accessories and those parts of large equipment that are not readily amenable to such treatment are appropriately and adequately sealed or effectively isolated.

2. To the extent possible, equipment fittings and services are designed and installed so that operations, maintenance, and repairs can take place outside clean or aseptic areas.

3. When equipment maintenance is carried out within clean or aseptic area, clean instruments and tools are used. If the required standards of cleanliness and/or asepsis are not maintained during the maintenance work, the area is cleaned and disinfected before processing recommences.

4. All equipment, including sterilizers, air-filtration systems, and water-treatment systems, are subject to planned maintenance, validation, and monitoring. Following maintenance/validation, the approval for use of the equipment is documented.

5. For aseptically filled products, conveyor belts do not pass through a partition from a Grade A or grade B area to an area of lower cleanliness unless the belts are continuously sterilized (e.g., they pass through a sterilizing tunnel).

WATER TREATMENT SYSTEMS

1. Water treatment facilities are designed, constructed, and maintained so as to ensure the reliable production of water of an appropriate quality. They are not operated beyond their designed capacity. Water is produced, stored, and distributed in a manner that minimizes microbial growth and prevents other types of contamination.

2. The quality of the raw feed water is established by specification and is periodically monitored for compliance. The sampling plan takes seasonal variations into account. Records are maintained.

3. Purified water is used as feed water for Water for Injection (WFI) systems and for clean steam generators. WFI is produced either by distillation or by reverse osmosis.

4. WFI is used in the formulation of parenteral, irrigation, and intra-ocular products.

5. Purified water and WFI systems are validated that is, the ability of the systems and its procedures to maintain the appropriate level of chemical and microbial control, taking seasonal variations into account, is demonstrated and documented.

6. The bacterial endotoxins limit for WFI and the microbial action limit are set. These limits meet any standard listed under Schedule B to the *Food and Drugs Act*.

7. WFI storage tanks are equipped with hydrophobic bacterial-retentive vent filters.

8. Sanitization or regeneration of water systems is carried out according to a predetermined schedule and also whenever established microbial counts are exceeded within any of the system's components.

9. The WFI system is maintained at an elevated temperature and kept in continuous movement. Water velocity through pipes is sufficient to prevent microbial attachment.

10. Piping is sloped to provide for complete drainage of the system. The system is free of dead legs.

11. All metal surfaces in contact with WFI are, as a minimum, 316 stainless steel.

12. While in use (during processing), WFI is sampled daily from at least two points of use on a rotating basis so as to cover all outlets.

13. Revalidation of water systems is required if any of the following situations arise:

    13.1 Unscheduled or extensive maintenance is performed on the system.

    13.2 New or revised sections or components are added to or removed from the system.

    13.3 The system exhibits an out-of-control trend in either chemical or microbiological parameters.

14. The extent of the re-validation work necessary is determined jointly by the personnel from the quality control, engineering, production, and any other appropriate departments. A pre-approved protocol is signed and dated by the parties involved.

Note: Refer to Interpretations 11 and 12 under "Manufacturing Control" in the "Sterile Products" section for further requirements regarding water to be used in fabrication.

PERSONNEL

1. In addition to the requirements outlined under Regulation C.02.006, the personnel responsible for the fabrication and testing of sterile products have had training in microbiology.

2. High standards of personal hygiene and cleanliness are maintained. Personnel involved in

the fabrication of sterile preparations are instructed to report any condition that may cause the shedding of abnormal numbers or types of contaminants. Periodic health checks for such conditions are conducted, and appropriate action (e.g., deciding whether to allow an individual to be involved in a particular operation) is taken by designated qualified personnel when necessary.

3. All personnel (including those whose duties involve cleaning and maintenance) employed in such areas receive regular training in disciplines relevant to the correct fabrication of sterile products, including reference to hygiene and to the basic elements of microbiology. When outside personnel who have not received such training (e.g., building or maintenance contractors) need to be brought in, particular care is taken with regard to their supervision.

4. Personnel who have been engaged in the processing of animal-tissue materials or of cultures of microorganisms other than those used in the current fabrication process do not enter areas where sterile products are fabricated unless rigorous and clearly defined decontamination procedures have been followed.

5. Only the minimum number of personnel required are present in areas where sterile products are fabricated; this is particularly important during aseptic processes. Inspections and controls are conducted from outside such areas to the extent that such an approach is possible.

6. Outdoor clothing is not brought into these areas. Personnel entering the changing rooms are already clad in standard protective garments designed for factory facilities. Changing and washing follow written procedures.

7. The clothing worn by personnel and its quality are adapted to the particular process and workplace, and the clothing is worn in such a way as to protect the product from contamination.

8. Clothing is appropriate to the air grade of the area where the personnel will be working. Descriptions of the clothing required for each grade are given below.

   For Grade D areas: The person's hair, as well as any beard or mustache, is covered. Protective clothing and appropriate shoes or overshoes are worn.

   For Grade C areas: The person's hair, as well as any beard or mustache, is covered. A one- or two-piece trouser suit, gathered at the wrists and with a high neck, and appropriate shoes or overshoes are worn. The protective clothing sheds virtually no fibres or particulate matter.

   For Grade A and B areas: Headgear totally encloses the person's hair, as well as any beard or mustache, the headgear is tucked into the neck of the suit; a face mask is worn to prevent the shedding of droplets; sterilized non-powdered rubber or plastic gloves and sterilized or disinfected footwear are worn; trouser-bottoms are tucked inside the footwear and garment sleeves are tucked

into the gloves. The protective clothing sheds virtually no fibres or particulate matter and retains particles shed by the body.

9. For every worker in a Grade B area, clean sterilized protective garments are provided at each re-entry and or at least once a day if monitoring results justify it. Gloves are regularly disinfected during operations. Masks and gloves are changed prior to every new working session.

10. Clothing used in clean and aseptic areas is laundered or cleaned in such a way that it does not gather additional particulate contaminants that can later be shed. Separate laundry facilities for such clothing are desirable. If fibres are damaged by inappropriate cleaning or sterilization, there may be an increased risk of shedding particles. Washing and sterilization operations follow standard operating procedures. Repair of clothing is carried out using appropriate materials (e.g., non-shedding thread).

SANITATION

1. Walls, floors, ceilings, and equipment in clean areas are cleaned and, when required, disinfected in accordance with a written procedure. This procedure differentiates between procedures that are followed daily and those that are undertaken whenever fabrication of a different drug is about to begin.

2. Walls, floors, ceilings, and equipment in aseptic areas are cleaned and, when required disinfected in accordance with a written procedure. This procedure differentiates between the cleaning and disinfection procedures that are followed daily and those that are undertaken whenever fabrication of a different drug is about to begin.

3. Where disinfectants are used, it is recommended that more than one type be employed.

4. Disinfectants and detergents are monitored for microbial contamination and are sterile when used in Grade A or grade B areas. Dilutions are kept in previously cleaned containers and are not stored for long periods unless sterilized. Partly emptied containers are not topped up.

5. Fumigation of clean and aseptic areas may be useful for reducing microbiological contamination in inaccessible places.

6. During operations, clean and aseptic areas, are monitored at planned intervals for particulate and microbial counts of air and surfaces. Where aseptic operations are performed, monitoring is conducted frequently to ensure that environmental specifications are met. The results of such monitoring are considered when batches are assessed for approval. Additional monitoring is desirable even when no production operations are taking place (e.g., after validation of systems, cleaning, and fumigation).

7. The cleaning procedures are validated, and the disinfection procedures are monitored.

MANUFACTURING CONTROL

1. During all processing stages, precautions are taken to minimize contamination.

2. Preparations containing live microorganisms are neither made nor transferred into containers in areas used for the processing of other pharmaceutical products. Preparations containing only dead organisms or bacterial extracts may be dispensed into containers, in the same premises as other sterile pharmaceutical products, provided that validated inactivation procedures and validated cleaning procedures are followed.

3. Activities in these areas are kept to a minimum, especially when aseptic operations are performed. The movement of personnel is controlled and methodical in order to avoid excessive shedding of particles and organisms. The ambient temperature and humidity are controlled and monitored to ensure the comfort of personnel.

4. Prior to sterilization, possibilities for microbiological contamination of raw materials and packaging materials are kept to a minimum. Specifications include requirements for microbiological quality when monitoring has indicated the need for such requirements.

5. Articles are sterilized and passed into the aseptic areas by the use of doubled-ended sterilizers equipped with interlocking doors or by another validated method.

6. Written standards are available specifying the air quality, including microbiological and particulate matter counts, to be maintained in clean and aseptic areas. Microbiological counts are taken at least once a day in aseptic areas, while aseptic filling and aseptic fabrication operations are carried out, and at appropriate intervals in areas where other fabrication takes place.

7. The presence of containers and materials liable to generate fibres is minimized in clean and aseptic areas.

8. Following cleaning and sterilization, components, bulk-product containers, and equipment are handled in such a way that they are not re-contaminated. The stage of processing of components, bulk-product containers, and equipment is properly identified.

9. The interval between cleaning and sterilization of components, bulk-product containers, and equipment, as well as between their sterilization and use, is as short as possible and subject to a time-limit appropriate to the validated storage conditions.

10. The time between the start of the preparation of a solution and its sterilization or filtration through a bacteria-retentive filter is as short as possible. A maximum permissible time is validated for each product, taking into account its composition and the prescribed method of storage.

11. Water used in the preparation of parenterals is tested for endotoxins and complies with its approved specifications.

12. Water used for the final rinsing of container components that are used for parenteral drugs is tested for endotoxins unless such components are depyrogenated subsequently.

13. Any gas that is used to purge a solution or to blanket a product passes through a sterilizing filter.

14. The microbiological contamination of products (bioburden) is minimal prior to sterilization. There is a working limit on contamination immediately before sterilization, that limit is related to the efficiency of the method to be used and to the risk of pyrogens. All solutions, particularly large-volume parenterals, are passed through a bacteria-retentive filter; if possible, this filtering occurs immediately before the filling process. Where aqueous solutions are held in sealed vessels, any pressure-release outlets are protected (e.g., by hydrophobic microbial air filters).

15. Documented evidence that establishes the validation and validity of each sterilization process is available. The validation and validity of the process are verified at scheduled intervals, at least annually, and also whenever significant modifications or changes are made to the equipment. Loading patterns for all sterilization processes are established and validated.

    15.1 Sterilization by heat

    Chemicals or biological indicators may also be used, but should not take the place of physical measurements.

        15.1.1 Sufficient time is allowed for the whole load to reach the required temperature before measurement of the sterilizing time-period begins. This time is determined for each type of load to be processed.

        15.1.2 After the high-temperature phase of a heat sterilization cycle, precautions are taken to prevent contamination of a sterilized load during cooling.

    15.2 Sterilization by moist heat:

        15.2.1 Both temperature and pressure controls are used to monitor the process. Control instrumentation is independent from both monitoring instrumentation and recording charts. Where automated controls and monitoring systems are used for these applications, they are fully validated to ensure that the critical process requirements are met. System and cycle faults are registered by the system and observed by the operator. The reading of the independent temperature indicator is periodically monitored. For sterilizers fitted with a drain at the bottom of the chamber, it may also be necessary to record the

temperature at this position throughout the sterilization period. There are frequent leak tests on the chamber when a vacuum phase is part of the cycle.

15.2.2 The items to be sterilized, other than products in sealed containers, are wrapped, if necessary, in a material that allows the removal of air and the penetration of steam but that prevents re-contamination after sterilization. All parts of the load are in contact with the sterilizing agent at the required temperature and pressure for the required time.

15.2.3 Clean steam is used for sterilization and does not contain additives at a level that could cause contamination of product or equipment.

15.3 Sterilization by dry heat:

15.3.1 The process used includes air circulation within the chamber and the maintenance of a positive pressure to prevent the entry of non-sterile air. Any air admitted passes through a HEPA filter.

15.4 Sterilization by radiation:

15.4.1 The radiation dose is measured during the sterilization procedure. For this purpose, dosimetry indicators that are independent of dose rate are to be used, giving a quantitative measurement of the dose received by the product itself. Dosimeters are inserted into the load in sufficient number and close enough together to ensure that there is always a dosimeter in the irradiator. Where plastic dosimeters are used, they are within the time limit of their calibration. Dosimeter absorbencies are read within a specified time period after exposure to radiation.

15.4.2 Biological indicators may be used as an additional control.

15.4.3 Materials handling procedures are designed so as to prevent mix-up between irradiated and non-irradiated materials. Radiation-sensitive colour disks are used on each package to differentiate between packages that have been subjected to irradiation and those that have not.

15.4.4 The total radiation dose is administered within a predetermined time span.

15.5 Sterilization with ethylene oxide:

15.5.1 Direct contact between gas and microbial cells is essential; precautions are taken to avoid the presence of organisms likely to be enclosed in such material as crystals or dried protein. The nature and quality of packaging materials can significantly affect the process.

15.5.2 Before exposure to gas, materials are brought into equilibrium with the humidity and temperature required by the process. The time required for this is balanced against the opposing need to minimize the time before sterilization.

15.5.3 Each sterilization cycle is monitored with suitable biological indicators, using the appropriate number of test pieces distributed throughout the load. The information so obtained is part of the batch record.

15.5.4 For each sterilization cycle, records are made of the time taken to complete the cycle, the pressure, the temperature and the humidity within the chamber during the process, the gas concentration, and total amount of gas used. The pressure and temperature are recorded throughout the cycle on a chart. The readings are part of the batch record.

15.5.5 After sterilization, the load is stored in a controlled manner under ventilated conditions to allow residual gas and reaction products to reduce to the defined level. This process is validated.

Note: Refer to Health Canada's "Process Validation Guidelines" for further guidance on these processes.

16. A written standard designed to test the efficiency of the overall aseptic filling operation is maintained. This standard includes a requirement to perform normal aseptic filling operations using sterile media.

16.1 The use of nutrient media that support microbial growth in trials to simulate aseptic operations (i.e., sterile media fills, "broth fills") is a valuable part of the overall validation of an aseptic process. Such trials have the following characteristics:

16.1.1 The trials simulate actual operations as closely as possible and also take into consideration worst case conditions.

16.1.2 The medium or media selected are capable of growing a wide spectrum of microorganisms, including those that would be expected to be found in the filling environment.

16.1.3 The trials include a sufficient number of units of production to give a high degree of assurance that low levels of contamination, if present, would be detected.

16.2 A statistically valid number of containers is filled during each broth-fill trial. The target is zero growth but a contamination rate of less than 0.1% with a 95% confidence limit is acceptable. Any contamination is investigated, and records of such investigations are maintained. Broth fills are repeated at regular intervals, as

well as whenever a significant alteration in the product, premises, equipment, or process warrants re-validation.

Observed number of failures	0	1	2	3	4	5	6	7	8	9	10
Upper 95% confidence limit	3.0	4.74	6.3	7.75	9.15	10.51	11.84	13.15	14.43	15.71	16.96

$$\text{Contamination Rate} = \frac{\text{Upper 95\% Confidence Limit}}{\text{Number of Filled Units}} \times 100\%$$

If batches smaller than 3,000 units are produced, the minimum number of containers used for process simulation with sterile nutrient media should be equal to the commercial batch size and no contaminated unit should be found after the incubation period.

17. Biological indicators are considered only as an additional method for monitoring the sterilization, except in the case of ethylene oxide sterilization, where they are a normal part of the monitoring criteria. If they are used, strict precautions are taken to avoid transferring microbial contamination from them.

18. Records are available indicating that the requirements for each sterilization cycle have been met. These records include all recording charts (e.g., time/temperature).

19. A clear means is used for differentiating products that have not been sterilized from those that have. Each basket, tray, or other carrier of products or components is clearly labelled with the name of the material, its batch number, and an indication of whether or not it has been sterilized. Such indicators as autoclave tape or radiation sensitive colour disks may be used, where appropriate, to indicate whether or not a batch (or sub-batch) has passed through a sterilization process, but they do not give a reliable indication that the lot is in fact sterile.

20. Filled containers of parenteral products are inspected individually for the presence of particulates and other defects. When inspection is done visually, it takes place under suitable and controlled conditions of illumination and background. Operators doing the inspection pass regular eyesight checks, while wearing corrective lenses if such lenses are normally worn, and are allowed frequent breaks from inspection. Where other methods of inspection are used, the process is validated and the performance of the equipment is checked at intervals.

21. Filled ampules are subjected to a leaker test (e.g. dye immersion test). Samples of other containers closed by appropriately validated methods are checked for integrity of seal and/or maintenance of vacuum where applicable after an appropriate predetermined period.

QUALITY CONTROL

1. Samples taken for sterility testing are representative of the whole of the batch, but in particular include samples taken from parts of the batch considered to be most at risk of contamination, for example:

    1.1 For products that have been filled aseptically, samples include the first container filled the last container filled, and those filled after any significant interruption of work.

    1.2 For products that have been heat-sterilized in their final containers, consideration is given to taking samples from the potentially coolest part of the load. Each sterilizer load is treated as a separate batch for sterility testing purposes.

2. The validated sterility test applied to the finished product is only one measure taken to assure sterility. It is to be interpreted in conjunction with the environmental and batch processing records.

3. Batches failing an initial sterility test are rejected unless a thorough investigation is carried out and the initial test is invalidated. The procedure for handling sterility test failures takes into account the guidance provided in official pharmacopeias (Schedule B to the *Food and Drugs Act*).

4. Where authorization for parametric release has been issued, after review of the submission which includes validation and monitoring of the process data pursuant to paragraph C.01.065(b)(ii), end product sterility testing is not required.

MEDICAL GASES

REGULATION

C.02.030

The provisions of sections C.02.025, C.02.027, and C.02.028 do not apply to medical gases.

ANNEX A

INTERNATIONALLY HARMONIZED REQUIREMENTS FOR BATCH CERTIFICATION

Content of the Fabricator's/Manufacturer's Batch Certificate
for Drug/Medicinal Products Exported to Countries
under the Scope of a Mutual Recognition Agreement (MRA)

Explanatory Note

In the framework of Mutual Recognition Agreements, the Sectoral Annex on Good Manufacturing Practices (GMP) requires a batch certification scheme for drug/medicinal products covered by the pharmaceutical Annex. The internationally harmonized requirements for the content of the batch certificate of a drug/medicinal product are attached. The importer of the batch is to receive and maintain the batch certificate issued by the fabricator/manufacturer. Upon request, the batch certificate has to be readily available to the regulatory authority of the importing country. This certification by the manufacturer regarding the conformity of each batch is essential to exempt the importer from re-control (re-analysis).

Each batch shipped between countries having an MRA in force must be accompanied by a batch certificate issued by the fabricator/manufacturer in the exporting country. This certificate will be issued after a full qualitative and quantitative analysis of all active and other relevant constituents to ensure that the quality of the products complies with the requirements of the marketing authorization of the importing country. The certificate will attest that the batch meets the specifications and has been manufactured in accordance with the marketing authorization of the importing country; will detail the specifications of the product, the analytical methods referenced, and the analytical results obtained; and will contain a statement that the batch processing and packaging quality control records were reviewed and found in conformity with GMP. The batch certificate will be signed by the person responsible for releasing the batch for sale or supply/export at the fabrication/manufacturing recognized building.

These harmonized requirements have been agreed on by the regulatory authorities of the following parties/countries: Australia, Canada, European Community, New Zealand, and Switzerland.

ANNEX A1

Designated regulatory authorities

	Regulatory authority	Drug or category of drugs	Activities
1	Swiss Agency for Therapeutic Products (Swissmedic), Bern, Switzerland	Pharmaceuticals for humans or veterinary use Drugs listed in Schedules C and D to the Act.	Fabricating, packaging/labelling, testing
2	Regional Medicines Inspectorate of Northwestern Switzerland (RFS-NW), Basel, Switzerland	Pharmaceuticals for human or veterinary use. Drugs listed in Schedules C and D to the Act.	Fabricating, packaging/labelling, testing
3	Regional Medicines Inspectorate of Eastern and Central Switzerland (RFS-OZ), Zurich, Switzerland	Pharmaceuticals for human or veterinary use. Drugs listed in Schedules C and D to the Act.	Fabricating, packaging/labelling, testing
4	Regional Medicines Inspectorate of Southern Switzerland (RFS-S), Ticino, Switzerland	Pharmaceuticals for human or veterinary use. Drugs listed in Schedules C and D to the Act.	Fabricating, packaging/labelling, testing
5	Regional Medicines Inspectorate of Western Switzerland (RFS-W), Lausanne, Switzerland	Pharmaceuticals for human or veterinary use. Drugs listed in Schedules C and D to the Act.	Fabricating, packaging/labelling, testing

Content of the Fabricator's/Manufacturer's Batch Certificate for Drug/Medicinal Products Exported to Countries under the Scope of a Mutual Recognition Agreement (MRA)

[LETTERHEAD OF EXPORTING MANUFACTURER]

1. **Name of product.**
   Proprietary, brand, or trade name in the importing country.

2. **Importing country.**

3. **Marketing authorization number.**
   The marketing authorization number of the product in the importing country should be provided.

4. **Strength/Potency.**
   Identity (name) and amount per unit dose are required for all active ingredients/constituents.

5. **Dosage form** (pharmaceutical form).

6. **Package size** (contents of container) and type (e.g., vials, bottles, blisters).

7. **Lot/batch number.**
   As related to the product.

8. **Date of fabrication/manufacture.**
   In accordance with national (local) requirements.

9. **Expiry date.**

10. **Name(s) of fabricator(s)/manufacturer(s) and address(es) of- manufacturing recognized building(s).**
    All recognized buildings involved in the manufacture of the batch including packaging and quality control of the batch, should be listed. The name(s) and address(es) given must correspond to the information provided on the manufacturing authorization/establishment licence.

11. **Number(s) of manufacturing authorization(s)/licence(s) or certificate(s) of GMP compliance held by fabricator(s)/manufacturer(s).**
    A number should be given for each recognized building listed under Item 10.

12. **Results of analysis.**
    Should include the approved specifications, describe all results obtained, and refer to the analytical methods used (May refer to a separate certificate of analysis, which must be dated, signed, and attached).

13. Comments/remarks.

Any additional information that might be of value to the importer and/or inspector who must verify the compliance of the batch certificate (e.g., specific storage or transportation conditions).

14. Certification statement.

Should cover the fabrication/manufacturing, including packaging and quality control. The following text should be used: "I hereby certify that the above information is authentic and accurate. This batch of product has been fabricated/manufactured, including packaging and quality control, at the above-mentioned recognized building(s) in full compliance with the GMP requirements of the local regulatory authority and with the specifications in the marketing authorization of the importing country. The batch processing, packaging, and analysis records were reviewed and found to be in compliance with GMP".

15. Name and position/title of person approving the batch release.

Must include the person's company/recognized building name and address, if more than one company is mentioned under Item 10.

16. Signature of person approving the batch release.

17. Date of signature.

Annex B

Alternate Sample Retention Site Application Form

Formulaire de demande de site alternatif pour la rétention d'échantillons

***Once completed, please fax this application form to the Health Products and Food Branch Inspectorate at (613) 952-9805 or e-mail it to GMP_Questions_BPF@hc-sc.gc.ca .**
Une fois complété, veuillez faire parvenir ce formulaire de demande à l'Inspectorat de la Direction générale des produits de santé et des aliments par télécopieur au (613) 952-9805 ou par courriel à l'adresse suivante GMP_Questions_BPF@hc-sc.gc.ca .

1. Importer or Distributor / *Importateur ou distributeur*
Name / *Nom* : **Address / *Adresse* :** **Telephone number / *Numéro de téléphone* :** **Fax number / *Numéro de télécopieur* :**
2. Product / *Produit*
Name / *Nom* : **DIN (if applicable) / *DIN (le cas échéant)* :**
3. Fabricator / *Manufacturier*
Name / *Nom* : **Address / *Adresse* :** **Telephone number / *Numéro de téléphone* :** **Fax number / *Numéro de télécopieur* :**
4. Site where samples are to be retained / *Établissement où les échantillons seront conservés*
Name / *Nom* : **Address / *Adresse* :** **Telephone number / *Numéro de téléphone* :** **Fax number / *Numéro de télécopieur* :** ***Please note that if the alternate site is located outside of Canada, it must be listed as a foreign site on a Canadian establishment's Drug Establishment Licence. If the alternate site is located in Canada, the Canadian establishment must hold a Drug Establishment Licence.** ***Veuillez prendre note que si le site alternatif est situé à l'extérieur du Canada, il doit être inscrit en tant que site étranger sur la licence d'établissement pharmaceutique d'un établissement canadien. Si le site alternatif est situé au Canada, l'établissement canadien doit détenir une licence d'établissement pharmaceutique.***
5. Criteria for assessment (complete as applicable) / *Critères d'évaluation (remplir selon le cas)*
a. The testing of this product requires specialized product-specific methodology that is not available in Canada: ***L'analyse de ce produit exige une méthode spécialisée, spécifique au produit, qui n'est pas disponible au Canada :*** **Yes/Oui ☐ No/Non ☐** **If yes, please specify (e.g. unique bioassay involving the use of cell lines or animals):** ***Dans l'affirmative, veuillez préciser (p. ex. dosage biologique particulier exigeant le recours à des lignées cellulaires ou à des animaux)* :**

Alternate Sample Retention Site Application Form (...continued)
Formulaire de demande de site alternatif pour la rétention d'échantillons (...suite)

b. This product is subject to Health Canada's lot release programme:
***Le produit est visé par le programme d'autorisation de mise en circulation des lots de Santé Canada* :**
Yes/Oui ☐ No/Non ☐

c. Estimated Canadian utilization:
***Consommation canadienne estimative* :**
i. Approximate number of lots sold annually in Canada:
***Nombre approximatif de lots vendus annuellement au Canada* :**
ii. Approximate number of units sold annually in Canada:
***Nombre approximatif d'unités vendues annuellement au Canada* :**

d. Average batch size imported to Canada / *Taille moyenne d'un lot de fabrication importé au Canada* :

e. Approximate unit cost/value per sample / *Coût/valeur unitaire approximatif par échantillon* :

f. Shelf life of perishable drug / *Durée de vie de la drogue périssable* :

g. Radiopharmaceuticals / *Produits radiopharmaceutiques* :
Yes/Oui ☐ No/Non ☐

h. Non-prescription drug (see Category IV product monographs):
***Drogues en vente libre (voir les monographies de produit de la catégorie IV)* :**
Yes/Oui ☐ (Specify below/*Spécifier ci-dessous)* No/Non ☐

- ☐ **Acne therapies / *produits contre l'acné (topique)***
- ☐ **Anti dandruff products / *produits antipelliculaires***
- ☐ **Antiperspirants / *produits antisudorifiques***
- ☐ **Antiseptic skin cleansers / *nettoyants antiseptiques pour la peau***
- ☐ **Athletes foot treatments / *traitements contre le pied d'athlète***
- ☐ **Fluoride-containing anti-caries products / *produits contre la carie dentaire contenant du fluorure***
- ☐ **Medicated skin care products / *produits médicamenteux pour le soin de la peau***
- ☐ **Sunburn protectants / *agents de protection solaire***

i. Hard surface disinfectants / *désinfectants pour surface dure* :
Yes/Oui ☐ No/Non ☐

j. The fabricator of the drug is located in Canada and is responsible for keeping the retained samples.
Le manufacturier du médicament est situé au Canada et est responsable de la rétention d'échantillons.
Yes/Oui ☐ (Complete section 4 / Remplir la section 4) No/Non ☐

Alternate Sample Retention Site Application Form (...continued)
Formulaire de demande de site alternatif pour la rétention d'échantillons (...suite)

6. Attestation / *Attestation*
We have formally arranged with the storage site to maintain sufficient numbers of samples of lots and retained as per storage conditions indicated on the label, with the same container-closure sold in Canada to allow access by all pertinent regulatory authorities including Health Canada. ***Nous avons pris des dispositions officielles avec l'établissement d'entreposage pour qu'il conserve, conformément aux conditions d'entreposage indiquées sur l'étiquette, des nombres suffisants d'échantillons de lots doté du même système contenant-fermeture vendus au Canada de manière à ce que toutes les autorités réglementaires concernées, y compris Santé Canada, puissent y avoir accès.*** **Yes/Oui ☐ No/Non ☐**
7. Commitment / *Engagement*
We have a written commitment with the responsible person at the storage site that samples will be provided within 48 hours of receiving a request from Health Canada. ***Nous avons un engagement écrit avec la personne responsable de l'établissement d'entreposage pour qu'il fournisse des échantillons dans les 48 heures qui suivent la réception d'une demande provenant de Santé Canada.*** **Signature, Responsible Officer / *Signature de l'agent responsable* :** **Title / *Titre* :** **Emergency Telephone Number / *Numéro de téléphone en cas d'urgence* :**

ANNEX C

REFERENCES

1. **Cleaning Validation Guidelines**
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/clean_val_gui_tc_e.html

2. **Controlled Drugs and Substances Act**
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/acts_regs_e.html

3. ***Food and Drugs Act***
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/acts_regs_e.html

4. ***Food and Drug Regulations***
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/acts_regs_e.html

5. **Good Manufacturing Practices for Medical Gases**
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/gmp_med_gases_tc_e.html

6. **Good Manufacturing Practices for Schedule C Drugs**
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/annex_sched_c_tc_e.html

7. **Good Manufacturing Practices for Schedule D Drugs, Part 1, Biological Drugs**
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/sched_d_part1_tc_e.html

8. **Good Manufacturing Practices for Schedule D Drugs, Part 2, Human Blood and Blood Components**
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/sched_d_part2_tc_e.html

9. **Good Manufacturing Practices Interpretation Decision Record Guide**
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/guide_21_tc_e.dpf

10. **International Conference on Harmonisation (ICH) Topics and Guidelines, Quality Topics**
http://www.ifpma.org/ich5q.html

11. **ICH Q1A(R): Stability Testing of New Drug Substances and Products**
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/q1a(r2)_e.html

12. **ICH Q1C: Stability Testing: Requirements for New Dosage Forms**
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/q1c_e.html

13. **ICH Q2A: Text on Validation of Analytical Procedures**
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/q2a_e.html

14. **ICH Q2B: Validation of Analytical Procedures: Methodology**
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/q2b_main_e.html

15. **ICH Q7A: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (draft)**
http://www.ich.org/MediaServer.jser?@_ID=433&@_TYPE=MULTIMEDIA&@_TEMPLATE=616&@_MODE=GLB

16. **Pharmaceutical Inspection Convention (PIC) and Pharmaceutical Inspection Cooperation Scheme (PIC/s)**
http://www.picscheme.org/index.htm

17. **Process Validation Guidelines:**

Moist Heat Sterilization for Pharmaceuticals
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/moist_heat_ster_pharm_tc_e.html

Irradiation Sterilization for Pharmaceuticals
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/irra_ster_pharm_tc_e.html

Gaseous Sterilization for Pharmaceuticals
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/gaseous_2001_tc_e.html

Form-Fill-Seal for Drugs
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/form_fill_seal_drugs_tc_e.html

Aseptic Processes for Pharmaceuticals
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/asep_proc_pharm_tc_e.html

18. **Product Recall Procedures**
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/recall_procedure_tc_e.html

19. **Risk classification of GMP observations**
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/risk_clas_gmp_obs_tc_e.html

20. **Stability Requirements for Changes to Marketed New Drugs**
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/mkndpsta_e.html

21. **Stability Testing of Existing Drug Substances and Products**
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/stability_testing_e.html

22. **Validation Documentation Requirements and Responsibilities for Drug Fabricators, Packagers/Labellers, Distributors and Importers**
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/validation_guide_tc_e.html

23. **Validation Guidelines for Pharmaceutical Dosage Forms**
http://www.hc-sc.gc.ca/hpfb-dgpsa/inspectorate/pharm_dos_form_tc_e.html

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