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TO: ALL INTERESTED PARTIES

I am pleased to inform you that Health Canada has adopted the revised PIC/S guidance document entitled "Guide to Good Manufacturing Practice for Medicinal Products Annexes-Annexe 17, Parametric Release", which is now available on Health Canada's Compliance and Enforcement website at:

http://www.hc-sc.gc.ca/dhp-mps/compli-conform/index_e.html

This guideline, which replaces the previous 2001 version, addresses both the elimination of the sterility testing and other finished product testing based on parametric release. At this time, the Food and Drug Regulations (C.01.065 (b) (ii)) only allows for the elimination of the sterility testing based on parametric release. Therefore, the part of this document addressing the elimination of the other finished product testing will not be considered, since full testing of a drug in its final dosage form, against its specifications and prior to it being released for sale, remains a Canadian regulatory requirement.

This guidance document should be used when seeking authorization to eliminate the sterility testing based on parametric release. Please note that the elimination of the sterility testing will only be considered for terminally sterilized drugs in their immediate containers and following the submission and approval of acceptable evidence as per this guideline.

As a member of PIC/S, the Health Products and Food Branch Inspectorate (HPFBI) may adopt and implement PIC/S guidance documents. This is done in order to work towards the global harmonization of technical standards and procedures related to Good Manufacturing Practices (GMP). This document does not constitute part of the Food and Drugs Act (Act) or the Food and Drugs Regulations (Regulations) and in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or the Regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the Regulations and the applicable administrative policies.

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This document is not intended to provide legal advice regarding the interpretation of the Act or Regulations. If a regulated party has questions about their legal obligations or responsibilities under the Act or Regulations, they should seek the advice of legal counsel.

Inquiries about this guidance document can be submitted in writing by mail to the Manager, Drug GMP Inspection Unit, HPFB Inspectorate, Graham Spry Building, A.L. #2002B, 250 Lanark Avenue, Ottawa, Ontario, K1A 0K9, by telephone at (613) 957-1492, by fax at 613-957-6709, or by e-mail at GMP_questions_BPF@hc-sc.gc.ca .

Original signed by

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Director General

PHARMACEUTICAL INSPECTION CONVENTION

PHARMACEUTICAL INSPECTION CO-OPERATION SCHEME

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GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS ANNEXES

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ANNEXE 17

PARAMETRIC RELEASE

1. PRINCIPLE

1.1 The definition of Parametric Release used in this Annex is based on that proposed by the European Organization for Quality: “A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to Parametric Release.”

1.2 Parametric release should comply with the basic requirements of GMP, with applicable annexes and the following guidelines.

2. PARAMETRIC RELEASE

2.1 It is recognised that a comprehensive set of in-process tests and controls may provide greater assurance of the finished product meeting specification than finished product testing.

2.2 Parametric release may be authorised for certain specific parameters as an alternative to routine testing of finished products. Authorisation for parametric release should be given, refused or withdrawn jointly by those responsible for assessing products together with the GMP inspectors.

3. PARAMETRIC RELEASE FOR STERILE PRODUCTS

3.1 This section is only concerned with that part of Parametric Release which deals with the routine release of finished products without carrying out a sterility test. Elimination of the sterility test is only valid on the basis of successful demonstration that predetermined, validated sterilising conditions have been achieved.

3.2 A sterility test only provides an opportunity to detect a major failure of the sterility assurance system due to statistical limitations of the method.

3.3 Parametric release can be authorised if the data demonstrating correct processing of the batch provides sufficient assurance, on its own, that the process designed and validated to ensure the sterility of the product has been delivered.

3.4 At present Parametric release can only be approved for products terminally sterilized in their final container.

3.5 Sterilization methods according to European Pharmacopoeia requirements using steam, dry heat and ionising radiation may be considered for parametric release.

3.6 It is unlikely that a completely new product would be considered as suitable for Parametric Release because a period of satisfactory sterility test results will form part of the acceptance criteria. There may be cases when a new product is only a minor variation, form the sterility assurance point of view, and existing sterility test data from other products could be considered as relevant.

3.7 A risk analysis of the sterility assurance system focussed on an evaluation of releasing non-sterilised products should be performed.

3.8 The manufacturer should have a history of good compliance with GMP.

3.9 The history of non sterility of products and of results of sterility tests carried out on the product in question together with products processed through the same or a similar sterility assurance system should be taken into consideration when evaluating GMP compliance.

3.10 A qualified experienced sterility assurance engineer and a qualified microbiologist should normally be present on the site of production and sterilization.

3.11 The design and original validation of the product should ensure that integrity can be maintained under all relevant conditions.

3.12 The change control system should require review of change by sterility assurance personnel.

3.13 There should be a system to control microbiological contamination in the product before sterilisation.

3.14 There should be no possibility for mix ups between sterilised and non sterilised products. Physical barriers or validated electronic systems may provide such assurance.

3.15 The sterilization records should be checked for compliance to specification by at least two independent systems. These systems may consist of two people or a validated computer system plus a person.

3.16 The following additional items should be confirmed prior to release of each batch of product.

- ➢ All planned maintenance and routine checks have been completed in the sterilizer used.

- ➢ All repairs and modification have been approved by the sterility assurance engineer and microbiologist.

- ➢ All instrumentation was in calibration.

- ➢ The sterilizer had a current validation for the product load processed.

3.17 Once parametric release has been granted, decisions for release or rejection of a batch should be based on the approved specifications. Non-compliance with the specification for parametric release cannot be overruled by a pass of a sterility test.

4. GLOSSARY

Parametric Release
A system of release that gives the assurance that the product is of the intended quality based on information collected during the manufacturing process and on the compliance with specific GMP requirements related to Parametric Release.

Sterility Assurance System
The sum total of the arrangements made to assure the sterility of products. For terminally sterilized products these typically include the following stages:

a) Product design.

b) Knowledge of and, if possible, control of the microbiological condition of starting materials and process aids (e.g. gases and lubricants).

c) Control of the contamination of the process of manufacture to avoid the ingress of microorganisms and their multiplication in the product. This is usually accomplished by cleaning and sanitization of product contact surfaces, prevention of aerial contamination by handling in clean rooms, use of process control time limits and , if applicable, filtration stages.

d) Prevention of mix up between sterile and non sterile product streams.

e) Maintenance of product integrity.

f) The sterilization process.

g) The totality of the Quality System that contains the Sterility Assurance System e.g. change control, training, written procedures, release checks, planned preventative maintenance, failure mode analysis, prevention of human error, validation calibration, etc.