THERAPEUTIC GOODS ORDER NO 50

GENERAL STANDARD FOR PYROGEN AND ENDOTOXIN CONTENT OF THERAPEUTIC GOODS

(28 February 1995)

I, Derrick Roy Beech, delegate of the Minister of State for Family Services, for the purposes of the exercise of the Minister's powers under section 10 of the Therapeutic Goods Act 1989 and acting under subsection 10(1), hereby **DETERMINE** that, with respect to quality, the standard for pyrogen and endotoxin content of goods to which this Order applies, is the standard specified in this Order.

Application

1 .This Order applies to -

(1) parenteral products where the nature of the product makes testing practical and where-

(a) the volume to be injected in a single dose is 15mL or more, including those products requiring dilution, reconstitution or suspension before injection as appropriate; or
(b) the label on the container indicates that the product is pyrogen free;

(2) irrigation solutions, where the nature of the product makes testing practical;

(3) therapeutic devices included in the Schedule to this Order; and

(4) goods, where a test for pyrogen or endotoxin content is part of a statutory requirement.

Interpretation

2. In this Order -

'irrigation solutions' means sterile solutions intended to be used for the irrigation of body cavities, for the flushing of wounds or operation cavities or for the irrigation of the urogenital system;

'therapeutic devices' means all sterile therapeutic devices identified in the Schedule to this Order;

'parenteral products' means sterile preparations in the form of injections, intravenous infusions, concentrated solutions for injection or medicaments for injection; and

'United States Pharmacopeia' means the current edition of the book called the United States Pharmacopeia published by authority of the United States Pharmacopeial Convention Inc. or, if that edition has been added to or amended by additions or amendments, that edition as affected by such additions or amendments.

Goods to be tested

3. The pyrogen and endotoxin content of goods, to which this Order applies, shall be determined in accordance with the test methods for pyrogen or endotoxin content specified in this Order.

Standard for Pyrogen and Endotoxin Content

4. (1) Goods, other than therapeutic devices, shall comply with -

(a) the standard for pyrogen content if they pass the Test for Pyrogens specified in the British Pharmacopoeia (BP); or

(b) the standard for endotoxin content if they pass the Bacterial Endotoxins Test (BET) specified in the United States Pharmacopeia (USP) applying the limits specified in the USP or, where no limits exist in the USP, if they comply with the limits specified in the US Food and Drug Administration publication identified in paragraph 5(1)(b).

(2) Therapeutic devices to be tested for endotoxins or pyrogens shall be extracted or rinsed as described in monographs <85> and <161> of the current edition of the USP and the extract or rinse solution used in the test.

(3) Therapeutic devices, other than devices intended for cerebrospinal contact, shall comply with -

(a) the standard for pyrogen content if they pass the Test for Pyrogens specified in the BP using a test dose of 10mL of extractant or rinse volume per kilogram of body weight; or

(b) the standard for endotoxin content if they pass the Bacterial Endotoxins Test (BET) specified in the USP applying the limits

specified in the USP or, where no limits exist in the USP, if they comply with the limits specified in the US Food and Drug Administration publication identified in paragraph 5(1)(b).

(4) Therapeutic devices, intended for cerebrospinal contact, shall comply with the standard for endotoxin content if they pass the Bacterial Endotoxins Test (BET) specified in the USP and the limit of content of endotoxin shall be not more than 0.06 EU/mL.

Test Methods

5.(1) The test shall be carried out using either -

(a) the Test for Pyrogens specified in the BP, and, where the product is the subject of a monograph of the BP, using the test dose specified in the monograph; or

(b) the Bacterial Endotoxins Test specified in the USP and applying the limits specified in the USP or, if no limits are specified in the USP, applying the limits specified in the 1987 edition of the US Food and Drug Administration publication entitled -

'GUIDELINES ON VALIDATION OF THE LIMULUS AMEBOCYTE LYSATE TEST AS AN END-PRODUCT ENDOTOXIN TEST FOR HUMAN AND ANIMAL PARENTERAL DRUGS, BIOLOGICAL PRODUCTS, AND MEDICAL DEVICES'

or, if that edition has been amended by additions or amendments, that edition as affected by such additions or amendments;

unless the goods are a therapeutic device intended for cerebrospinal contact, in which case, the test shall only be carried out using the BET of the USP.

(2) If a therapeutic device fails to comply with the BET of the USP, the test can be repeated once using the same test method, and, if the device passes the second test, it complies with the standard for endotoxin content. If it can be clearly shown that failure to comply, when tested using the BET of the USP, is due to the presence of non endotoxin substances which interfere with the BET or due to the presence of substances such as cellulose leachables which are Limulus Amebocyte Lysate -reactive, the device, other than a device intended for cerebrospinal contact, can be retested using the Test for Pyrogens specified in the BP. If the device then passes the Test for Pyrogens of the BP, the device complies with the standard for pyrogen content.

(3) If goods are tested using the BET of the USP and fail to pass the test, the goods shall not be retested and passed using the Test for Pyrogens of the BP, unless they are a therapeutic device which is not intended for cerebrospinal contact.

Dated this twenty eighth day of February 1995

Derrick Roy Beech
(Delegate of the Minister of State for Family Services)

THE SCHEDULE

THERAPEUTIC DEVICES TO WHICH THIS ORDER APPLIES

All sterile therapeutic devices which are intended for contact, directly or indirectly, with the cardiovascular system, the lymphatic system or the cerebrospinal fluid and nervous system, including -

1. Containers used to store, administer or treat -

    .blood or blood products;
    .any parenteral products in volumes greater than 15 mL;
    .irrigation solutions;
    .haemodialysis solutions;
    .peritoneal dialysis solutions; and
    .any injectables that contact cerebrospinal fluid;

2. transfusion and infusion assemblies:

3. extension sets, transfer sets, accessories or closures which connect to the fluid path of those containers or assemblies included in 1. or 2. above;

4. intravenous catheters;

5. other drug delivery catheters;

6. implants, with the exception of orthopaedic and dental products which are exempt from the requirements of this Order.

SUPPLEMENTARY NOTES FOR THE GENERAL STANDARD FOR PYROGEN AND ENDOTOXIN CONTENT OF THERAPEUTIC GOODS

1. The pyrogenic contamination of some products can only be reliably detected by the rabbit pyrogen test; in other cases, the Limulus Amebocyte Lysate (LAL) test is more appropriate. The choice of test method must also consider that certain contaminants, materials or products can cause non-specific activation of the LAL or can inhibit or enhance the test results. It is the responsibility of the manufacturer to choose the method that is valid and appropriate for the product being tested. This may require preliminary comparative testing.

2. Where imported goods are fully manufactured overseas and comply with the Test for Bacterial Endotoxins of the British Pharmacopoeia or with the Test for Bacterial Endotoxins of the European Pharmacopoeia or with the BET of the USP, this shall be regarded as sufficient for compliance with the Order, provided that evidence can be supplied to the regulatory authority in Australia -

   (a) that testing has been carried out by an overseas laboratory which complies with an acceptable Code of Good Manufacturing Practice; or
   (b) that testing has been carried out by an overseas laboratory certified by a national accreditation body for the performance of the test.

   If the importer is unable to provide such evidence, on request, the goods will require to be retested in Australia to show compliance with the BET of the USP.

3. The therapeutic devices included in the Schedule to this Order correspond with current international opinion and requirements. The Schedule is subject to ongoing review and the devices included there may change in the future as more information is accumulated.

4. It is strongly recommended that wound or burn dressings intended for major body trauma should also be tested for compliance with the requirements in this Order although they have not been included in the Schedule at present.

   The intent of this recommendation is to ensure that dressings that are used for third degree burns, for areas of extensive skin loss or that contact internal tissues as a result of surgery are not contaminated with endotoxins. It has been shown that endotoxins can have potentially serious local as well as systemic effects (other than temperature elevation) if introduced intramuscularly, into body wounds during surgery, or into epithelial burns and wounds. They affect a whole range of tissue cytokines and have been shown to cause inflammation, damage to microcirculation and an enhanced immune response. This can lead to impaired healing and an overgrowth of scar tissue.