STATUTORY INSTRUMENTS

1977 No. 675

MEDICINES

The Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1977

Made - - - -	6*th April* 1977
Laid before Parliament	21*st April* 1977
Coming into Operation	12*th May* 1977

The Secretaries of State respectively concerned with health in England and in Wales, the Secretary of State concerned with health and with agriculture in Scotland, the Minister of Agriculture, Fisheries and Food, the Department of Health and Social Services for Northern Ireland and the Department of Agriculture for Northern Ireland, acting jointly, in exercise of powers conferred by section 47(1) of the Medicines Act 1968**(a)** and now vested in them **(b)** and of all other powers enabling them in that behalf, after consulting such organisations as appear to them to be representative of interests likely to be substantially affected by the following regulations, hereby make the following regulations:—

Citation, interpretation and commencement

1. These regulations, which may be cited as the Medicines (Standard Provisions for Licences and Certificates) Amendment Regulations 1977, shall be read as one with the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971**(c)** as amended **(d)** (hereinafter referred to as "the principal regulations") and shall come into operation on 12th May 1977.

Amendment of regulation 2(1) *of the principal regulations*

2. Regulation 2(1) of the principal regulations (interpretation) shall be amended by adding—

(a) immediately after the definition of "advertisement" the following definitions:—

" "BCG" means the bacillus of Calmette and Guerin;

"BCG vaccine" means a vaccine that is a preparation of the bacteria in a living pure culture of a strain of the bacillus of Calmette and Guerin;";

(a) 1968 c. 67.

(b) In the case of the Secretaries of State concerned with health in England and in Wales by virtue of Article 2(2) of, and Schedule 1 to, the Transfer of Functions (Wales) Order 1969 (S.I. 1969/388 (1969 I, p. 1070)), and in the case of the Northern Ireland Departments by virtue of section 40 of, and Schedule 5 to, the Northern Ireland Constitution Act 1973 (c. 36), and paragraph 2(1)(*b*) of Schedule 1 to the Northern Ireland Act 1974 (c. 28).

(c) S.I. 1971/972 (1971 II, p. 2809).

(d) S.I. 1972/1226, 1974/1523 (1972 II, p. 3708; 1974 III, p. 5811).

(b) immediately after the definition of "medicinal product" the following definitions:—

" "parenteral administration" means administration by breach of the skin or mucous membrane;

"serum" means a fluid fraction of coagulated blood;

"smallpox vaccine" means a vaccine that is a preparation of an infective vaccinia virus;

"toxins" means substances used in the diagnosis, prevention or treatment of disease consisting wholly or partly of poisonous substances derived from specific micro-organisms, plants or animals;

"vaccines" means antigenic substances which consist wholly or partly of—

(i) any micro-organisms, viruses or other organisms in any state,

(ii) any toxins of microbial origin which have been detoxified (toxoids), or

(iii) any extracts or derivatives of any micro-organisms or of any viruses,

being substances which, when administered to human beings or animals, are used for the prevention or treatment of specific diseases;".

Additional regulations

3. The principal regulations shall be amended by adding after Regulation 3 the following regulations:—

"*Standard provisions for manufacturer's licences and manufacturer's licences of right for vaccines, toxins and sera*

4.—(1) In addition to the standard provisions for manufacturer's licences set out in Schedule 2 to these regulations, the standard provisions for manufacturer's licences, including manufacturer's licences of right, relating to vaccines for human use shall be the following—

(*a*) for all vaccines, including smallpox vaccine and BCG vaccine, those provisions set out in Part I of Schedule 4 to these regulations,

(*b*) for smallpox vaccine, those provisions set out in Part II of Schedule 4 to these regulations, and

(*c*) for BCG vaccine, those provisions set out in Part III of Schedule 4 to these regulations.

(2) In addition to the standard provisions for manufacturer's licences set out in Schedule 2 to these regulations, the standard provisions for manufacturer's licences, including manufacturer's licences of right, relating to toxins and sera for human use shall be the following—

(*a*) for toxins, those provisions set out in Part IV of Schedule 4 to these regulations, and

(*b*) for sera, those provisions set out in Part V of Schedule 4 to these regulations.

Standard provisions for product licences including product licences of right for certain medicinal products

5.—(1) In addition to the standard provisions for product licences set out in Part I of Schedule 1 to these regulations, the standard provisions for product licences, including product licences of right, relating to medicinal products

to which this regulation applies shall be those provisions set out in Schedule 5 to these regulations.

(2) The standard provisions contained in this regulation shall only apply to medicinal products which include a substance or substances specified in paragraphs 1 to 35 in column 1 of Schedule 1 to the Medicines (Control of Substances for Manufacture) Order 1971**(a)** in the circumstances set out in column 2 of the said Schedule other than medicinal products as aforesaid manufactured, assembled, sold, supplied, imported or exported for use as veterinary drugs.".

Additional schedules

4. After Schedule 3 to the principal regulations, there shall be added as Schedules 4 and 5, the Schedules set out in the Schedule to these regulations.

David Ennals,
Secretary of State for Social Services.

4th March 1977.

John Morris,
Secretary of State for Wales.

25th March 1977.

Bruce Millan,
Secretary of State for Scotland.

31st March 1977.

(a) S.I. 1971/1200 (1971 II, p. 3506).

In witness whereof the official seal of the Minister of Agriculture, Fisheries and Food is hereunto affixed on 4th April 1977.

(L.S.) *John Silkin,*
Minister of Agriculture, Fisheries and Food.

Sealed with the official seal of the Department of Health and Social Services for Northern Ireland this 5th day of April 1977.

(L.S.) *N. Dugdale,*
Permanent Secretary.

Sealed with the official seal of the Department of Agriculture for Northern Ireland this 6th day of April 1977.

(L.S.) *J. A. Young,*
Permanent Secretary.

SCHEDULE *Regulation* 4

Schedules added to the principal regulations

SCHEDULE 4

PART I *Regulation* 4(1)(*a*)

Standard provisions for manufacturer's licences and manufacturer's licences of right relating to vaccines

1. The licence holder shall ensure that the premises on which vaccines are produced and tested shall be under the complete direction and control of a suitably qualified person approved by the licensing authority for the purpose.

2. The licence holder shall provide separate premises or separate parts of premises for the activities specified in the following sub-paragraphs, namely—

(*a*) the production and the testing involved in the production of cell cultures for use in the production of vaccine,

(*b*) the production and the testing involved in the production of vaccine prepared from viruses, and

(*c*) the production and the testing involved in the production of vaccine prepared from micro-organisms or detoxified microbial toxins,

and shall ensure that only persons necessary to each activity as aforesaid shall have access to the separate premises or separate parts of premises provided for that activity.

3. The licence holder shall ensure that any procedure which, in the course of any of the activities specified in the preceding paragraph, involves or might involve—

(*a*) the presence of transmissible agents, or

(*b*) the use of cell cultures, animal tissues or micro-organisms,

other than those from which the vaccine is produced, shall not be carried out in the separate premises or separate parts of premises as aforesaid.

4. The licence holder shall ensure that no person who has been in contact with transmissible agents or experimental animals other than those connected with the vaccine being produced in the separate premises or separate parts of premises as aforesaid shall enter those premises or separate parts of premises on the same day that the contact as aforesaid has been made.

5. Before an animal is used in the production of vaccine the licence holder shall take all reasonable steps to ensure that it is free from disease and to this end shall keep the animal in quarantine and under observation for such period as the licensing authority may direct.

6.—(1) The licence holder shall ensure that animals used in the production of vaccine are isolated and shall provide separate premises (not being the premises or parts of premises referred to in paragraph 2 above) for this purpose.

(2) The licence holder shall ensure that only persons engaged in the production and testing of vaccine or in the maintenance of animals or premises shall have access to the separate premises in which the animals are isolated.

7. The licence holder shall provide a special room capable of being washed and disinfected in the separate premises referred to in paragraph 6 above for the purpose of—

(*a*) the inoculation of animals, and

(*b*) the collection of material to be used in the preparation of vaccine.

8. Without prejudice to any other requirements to keep records, where vaccines contain or might contain micro-organisms or microbial toxins the licence holder shall keep a durable record, readily available for inspection by a person authorised by the licensing authority, of the origin, properties and characteristics of the cell cultures used in the production of those vaccines and shall ensure that the said record is not destroyed for a period of five years from the date when the relevant production occurred.

Regulation 4(1)(*b*) PART II

Standard provisions for manufacturer's licences and manufacturer's licences of right relating to smallpox vaccine

1.—(1) The licence holder shall ensure that animals used in the production of smallpox vaccine—

(*a*) shall only be inoculated on a part of the skin that has been depilated and cleansed and which cannot be soiled by urine or faeces, and

(*b*) are kept under observation for 28 days after the collection of the vaccinal material.

(2) Should any animal during the 28 days as aforesaid be found to be suffering from any infection other than vaccinia or show serious or persistent signs of ill health, vaccinal material obtained from that animal shall not be used in the production of smallpox vaccine.

2. Where it is necessary for an animal which has been inoculated as aforesaid to be killed, the licence holder shall ensure that—

(*a*) the vaccinal material is collected immediately after the animal has been killed,

(*b*) if the licensing authority so direct, a post-mortem examination of the carcass of the animal is made by a person with experience of the diseases of the particular animal so killed,

(*c*) a durable record of the examination is kept readily available for inspection by a person authorised by the licensing authority,

(*d*) the said record is not destroyed for a period of five years from the date when the animal was killed, and

(*e*) where the examination indicates that the animal was suffering from diseases other than vaccinia, no vaccinal material obtained from that animal shall be used in the production of smallpox vaccine.

Regulation 4(1)(*c*) PART III

Standard provisions for manufacturer's licences and manufacturer's licences of right relating to BCG vaccine

1. The licence holder shall provide separate premises or separate parts of premises for the production of BCG vaccine and shall ensure that only persons necessary to the production and testing of that vaccine shall have access to those separate premises or separate parts of premises.

2. The licence holder shall ensure that any procedure which involves or might involve—

(*a*) the presence of transmissible agents other than BCG, or

(*b*) the use of microbial cultures other than BCG,

shall not be carried out in the separate premises or separate parts of premises referred to in paragraph 1 of this Part of this Schedule.

3. The licence holder shall ensure that all media, glassware and other apparatus issued in the production of BCG vaccine shall be kept and prepared for use in the separate premises or separate parts of premises referred to in paragraph 1 of this Part of this Schedule.

4. The licence holder shall not permit animals to be in the separate premises or separate parts of premises referred to in paragraph 1 of this Part of this Schedule and where it is necessary to use animals for testing BCG vaccine, the tests shall not be carried out in those separate premises or separate parts of premises.

5.—(1) The licence holder shall arrange for all persons engaged in the production of BCG vaccine to be examined clinically by a doctor and where appropriate, radiologically and bacteriologically, at least every twelve months and whenever such a person shows signs of ill health.

(2) The licence holder shall ensure (as far as sub-paragraph (*c*) below is concerned, in so far as is reasonably practicable), that persons falling within the following descriptions shall not engage in the production of BCG vaccine, that is to say—

(*a*) persons examined as aforesaid who are found to be suffering from active or potentially active tuberculous lesions,

(*b*) persons who show a negative reaction when tested with tuberculin, or

(*c*) persons who are in close contact with a person who is suffering from any active form of tuberculosis.

(3) If on examination as aforesaid a person engaged in the production of BCG vaccine is found to be suffering from active or potentially active tuberculous lesions, then, after that person has been removed from the separate premises or separate parts of premises referred to in paragraph 1 of this Part of this Schedule, the licence holder shall make arrangements for those separate premises or separate parts of premises and all equipment used in the production of BCG vaccine to be treated in such a manner as to remove the risk of contamination of the vaccine and shall cease to use any unsealed cultures of BCG and all current preparations of BCG vaccine which may have become contaminated with other Mycobacterium tuberculosis organisms.

6. The licence holder shall ensure that no person who has been in contact with transmissible agents other than BCG vaccine shall enter the separate premises or separate parts of premises referred to in paragraph 1 of this Part of this Schedule on the same day that the contact as aforesaid has been made.

PART IV *Regulation* 4(2)(*a*)

Standard provisions for manufacturer's licenses and manufacturer's licences of right relating to toxins

1. The licence holder shall ensure that the premises on which toxins are produced and tested shall be under the complete direction and control of a suitably qualified person approved by the licensing authority for the purpose.

2. The licence holder shall provide separate premises or separate parts of premises for the production and the testing involved in the production of toxins and shall ensure that only persons necessary to the production and testing of toxins (or related toxoids) shall have access to the separate premises or separate parts of premises as aforesaid.

3. The licence holder shall ensure that any procedure which in the course of the production and testing referred to in the previous paragraph involves or might involve the presence of micro-organisms, plants or animals other than those from which the toxins are to be produced, shall not be carried out in the separate premises or separate parts of premises as aforesaid.

PART V *Regulation* 4(2)(*b*)

Standard provisions for manufacturer's licences and manufacturer's licences of right relating to sera

1. The licence holder shall ensure that premises on which any serum is produced and tested shall be under the complete direction and control of a suitably qualified person approved by the licensing authority for the purpose.

2. The licence holder shall ensure that blood used in the production of any serum shall only be collected from living animals in separate premises which—

(*a*) are used for no other purpose,

(*b*) have impervious walls and floors, and

(*c*) are capable of being washed and chemically disinfected.

3. The licence holder shall ensure that an adequate system of manure removal is in operation in the separate premises referred to in paragraph 2 of this Part of this Schedule.

4. Before an animal is used in the production of any serum, the licence holder shall take all reasonable steps to ensure that it is free from disease and to this end shall

keep the animal in quarantine and under observation for such period as the licensing authority may direct.

5. The licence holder shall notify the licensing authority if any animal which has been used in the production of any serum is found to be suffering from an infection other than an infection produced by living organisms against which it is being immunised or shows serious or persistent signs of illhealth not attributable to the process of immunisation and shall withhold any serum obtained from that animal from sale, supply or exportation until he has obtained the consent of the licensing authority in writing to its release.

6. The licence holder shall notify the licensing authority if any post-mortem examination on any animal indicates that any other animals used in the production of any serum are or are likely to be unhealthy, and the licence holder shall not use those animals for the production of any serum until either he has obtained the consent of the licensing authority in writing or has complied with any requirements the licensing authority may consider necessary in the interest of safety.

7. The licence holder shall ensure that laboratories in which any serum is processed are separate from premises in which animals are housed.

8. The licence holder shall provide such number of sterilizers as are necessary for the sterilization of all glassware and other apparatus used in the production of sera as aforesaid.

9. Without prejudice to any other requirements to keep records, the licence holder shall keep the following durable records relating to the production of sera readily available for inspection by a person authorised by the licensing authority and shall ensure that the said record is not destroyed for a period of five years from the date when the relevant production occurred:—

(*a*) as to the cultures used—

(i) the source from which the culture was obtained,

(ii) the nature of the material from which the culture was isolated,

(iii) the date of the isolation, and

(iv) evidence of the identity and specificity of the culture;

(*b*) as to the procedure used in the immunizing of animals—

(i) the method of preparing the culture or antigen used for immunization,

(ii) the dosage and methods employed in administering the culture or antigen, and

(iii) the time in the course of immunization at which blood is withdrawn for preparation of the serum;

(*c*) the results of any tests which may have been applied to the serum to determine its content of specific antibodies or its specific therapeutic potency.

Regulation 5(1)

SCHEDULE 5

PART I

Standard provisions for product licences including product licences of right relating to medicinal products to which regulation 5 of these regulations applies

1. In this Part of this Schedule "expiry date" means the date after which, or the month and year after the end of which, the medicinal product should not be used, or the date before which, or the month and year before the beginning of which, the medicinal product should be used.

2. The licence holder shall, within 28 days of any request made by the licensing authority, supply to the licensing authority a sample of the standard preparation with which each batch of the medicinal product to which the licence relates is or is to be compared, being a sample of such amount as the licensing authority may reasonably require for any examination to be made.

3. Until the expiry date and for six months thereafter the licence holder shall on request supply to the licensing authority in respect of any batch of the medicinal product to which that request applies a sample from the said batch of such amount as the licensing authority may reasonably require for any examination and, if so requested, detailed protocols of the tests which have been applied to the said batch.

4. Where the licence holder has supplied the licensing authority with a sample or protocols or both a sample and protocols in accordance with the preceding paragraph, if the licensing authority so direct, the licence holder shall not sell, supply or export any batch or any part of any batch referred to in the preceding paragraph until he has obtained the consent of the licensing authority in writing to such sale, supply or exportation.

5. Where the licence holder has been informed by the licensing authority that any batch as aforesaid has been found not to conform as regards strength, quality or purity to the specification of that product or with the provisions of the Act or of any regulations made under the Act that are applicable to the medicinal product, he shall, if so directed and so far as may be reasonably practicable, recall all medicinal products already sold or supplied from that batch.

6. Unless and to the extent that the licensing authority otherwise direct in writing, the licence holder shall ensure that a medicinal product to which the licence relates complies with any requirements applicable to it specified in the Compendium of Licensing Requirements for the Manufacture of Biological Medicinal Products prepared and published under section 99 of the Act **(a)**.

7.—(1) Unless the licensing authority otherwise direct in writing, the licence holder shall ensure that any medicinal product which is for parenteral administration satisfies the following tests—

(*a*) sterility,

(*b*) abnormal toxicity, and

(*c*) pyrogens (except in the case of vaccines and preparations of insulin).

(2) Where the licensing authority has directed that the provisions of the preceding sub-paragraph need not apply, the licence holder shall either—

(*a*) ensure that the medicinal product as aforesaid has satisfied the said tests, or

(*b*) satisfy himself, taking into consideration—

(i) the in-process controls carried out during the manufacture of the medicinal product as aforesaid, and

(ii) the results obtained from testing in accordance with sub-paragraph (1) above other batches of medicinal products of the same description,

that if tested in accordance with sub-paragraph (1) above, the medicinal product as aforesaid would satisfy the said tests.

(3) The tests referred to in sub-paragraph (1)(*a*), (*b*) and (*c*) above shall be—

(*a*) the tests set out in Parts II, III and IV respectively of this Schedule, or

(*b*) where the medicinal product as aforesaid is one in respect of which there is a monograph in the European Pharmacopoeia, the tests specified in the European Pharmacopoeia, or

(*c*) such other tests as the licensing authority may in any particular case approve.

(4) The said tests shall be made after every manufacturing process has been completed unless the licence holder has obtained the consent of the licensing authority in writing to testing at an earlier stage in the manufacture.

(5) The licence holder shall keep readily available for inspection by a person authorised by the licensing authority durable records of all the relevant details of the said tests including records of the examination of each tube, vessel or animal as the case may be and shall ensure that the said records are not destroyed for a period ending six months after the expiry date has passed.

(a) The current edition is Issue I: 1977 taking effect on 1st May 1977.

8. The licence holder shall not sell, supply, import or export any medicinal product for parenteral administration unless it has been sealed in a previously sterilised container of a material inert towards that product in such a manner as will preclude the access of micro-organisms.

9. The provisions of this Schedule shall not have effect until 1st September 1977 in relation to a product licence being a licence of right where, immediately before the first appointed day **(a)** the manufacture or importation of substances or articles to which the licence relates was authorised by a licence issued under Part I of the Therapeutic Substances Act 1956**(b)** or under Part II of the Diseases of Animals Act 1950**(c)**, or of the Diseases of Animals Act (Northern Ireland) 1958**(d)**.

PART II

Tests for sterility

1. In this Part of this Schedule—

"batch" means a homogeneous collection of sealed containers prepared in such a manner that the risk of contamination is the same for each of the units in the collection;

"the tests for sterility" means a test for bacterial sterility and a test for fungal sterility and "sterility" has a corresponding meaning.

2.—(1) The test for bacterial sterility shall be applied to the quantity of the medicinal product specified in paragraph 3 of this Part of this Schedule taken from the number of filled containers specified in paragraph 4 of the said Part (hereinafter referred to as "the sample").

(2) The test for fungal sterility shall be applied to a sample of the medicinal product obtained in accordance with the provisions of the preceding sub-paragraph, save that the quantity of medicinal product as aforesaid may be taken from the same containers as were used in the test for bacterial sterility wherever this is possible.

(3) Where the quantity of the medicinal product specified in paragraph 3 of this Part of this Schedule exceeds 10 per cent of the quantity of medium to be used in the tests for sterility, then the said tests shall be either by use of a membrane filter or by use of a concentrated culture medium which has been prepared in a manner that takes account of the subsequent dilution.

3.—(1) The quantity of the medicinal product required for the tests for sterility shall be determined in accordance with the following provisions of this paragraph.

(2) Where the medium used for the said tests is equally capable of detecting aerobic and anaerobic micro-organisms, then—

(*a*) if the medicinal product is in liquid form the following minimum quantities shall be used in each of the said tests—

(i) the whole of the contents of each container included in the sample (hereinafter referred to as "each container") if the total volume in each container is less than 1 millilitre,

(ii) half of the contents of each container if the total volume in each container is 1 millilitre or more but less than 4 millilitres,

(iii) 2 millilitres if the total volume in each container is 4 millilitres or more but less than 20 millilitres,

(iv) 10 per cent of the contents of each container if the total volume in each container is 20 millilitres or more;

(*b*) if the medicinal product is in solid form, the following minimum quantities shall be used in each of the said tests—

(i) the whole of the contents of each container if the total contents in each container are less than 50 milligrammes,

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(a) 1st September. See S.I. 1971/1153 (1971 II, p. 3393).
(b) 1956 c. 25. **(c)** 1950 c. 36.
(d) 1958 c. 13 (N.I.)

(ii) half of the contents of each container if the total contents in each container are 50 milligrammes or more but less than 200 milligrammes,

(iii) 100 milligrammes if the total contents in each container are 200 milligrammes or more.

(3) Where two media are used for the said tests, one to detect aerobic and one to detect anaerobic micro-organisms, then

(*a*) if the total contents of each container are less than 1 millilitre or 50 milligrammes as the case may be—

(i) twice the number of containers specified in paragraph 4 of this Part of this Schedule shall be included in each of the said tests,

(ii) half that number shall be appropriated for testing in one medium and the remaining half in the other medium, and

(iii) the whole contents of each container shall be used in every case;

(*b*) if the total contents of each container are 1 millilitre or more or 50 milligrames or more, as the case may be, half the quantities specified in sub-paragraph (2) of this paragraph shall be used for testing with each of the two media.

4.—(1) Subject to the provisions of sub-paragraph (2) below, the number of containers taken for each of the tests for sterility shall be—

(*a*) 2 per cent of the batch or 20 containers whichever is the less where the batch consists of 500 or more containers,

(*b*) 10 containers where the batch consists of more than 100 but less than 500 containers, or

(*c*) 10 per cent of the batch or 4 containers whichever is the greater where the batch consists of not more than 100 containers.

(2) Where the medicinal product has been sterilised in an autoclave by steam under pressure, then, notwithstanding the number of containers in the batch, the number to be tested may be reduced to not less than 10 for each of the said tests or such lower number as the licensing authority in any particular case direct.

(3) The containers to be tested shall be taken at random from each batch.

5. In the case of a medicinal product which is itself bactericidal or bacteriostatic or to which a bactericide or bacteriostat has been added, then before a sample of such product is tested for sterility either—

(*a*) there shall be added to the sample either—

(i) such a volume of medium as will dilute the sample so as to render ineffective the bactericidal or bacteriostatic activity, or

(ii) such a substance in such concentration as will neutralise the bactericidal or bacteriostatic activity of the sample without inhibiting the growth of micro-organisms; or

(*b*) a solution of the sample shall be made and passed through a membrane filter with an average pore diameter not greater than 0·47 micrometres. The membrane filter may be pretreated by passing through it a sterile washing fluid. After the sample has been passed through the membrane filter, the filter shall be washed with sterile washing fluid in such a manner as will remove bactericidal or bacteriostatic activity. The membrane filter shall then be tested for sterility in accordance with paragraphs 8(2)(*b*), 9 and 10 of this Part of this Schedule.

6. Where more than one test is to be performed on the medicinal product and a membrane filter is to be used in more than one of the tests, the membrane filter may be divided and different parts used for the different tests if (and only if) the quantity of the medicinal product passed through the membrane filter is the amount required for each of such tests by paragraph 3 of this Part of this Schedule.

7.—(1) The tests for sterility shall be made on a medium capable of detecting or revealing the presence of viable common contaminating micro-organisms.

(2) Each batch of medium shall be tested for its capability to initiate and maintain the growth of viable micro-organisms as aforesaid and, if the licensing authority so direct, the said test shall be by a method approved by the licensing authority.

(3) Where there is reason to expect that the tests for sterility may be influenced by the nature of the sample, tests shall be carried out which ensure that the tests for sterility are effective and, if the licensing authority so direct, the said tests shall be by a method approved by the licensing authority.

(4) The filled containers used in the tests referred to in paragraph 3 above shall be in addition to the containers used in the tests for sterility.

8.—(1) The sample shall be applied to the media selected for each of the tests for sterility in accordance with the following provisions of this paragraph.

(2) Where the sample is in liquid form, the media shall be inoculated with either—

(*a*) the sample, or

(*b*) the membrane filter if this method of testing has been employed.

(3) Where the sample is in solid form, the sample shall either—

(*a*) be dissolved or suspended in a suitable sterile liquid and applied to the media in accordance with sub-paragraph (2) of this paragraph, or

(*b*) be distributed evenly into the media.

(4) Where the sample is of an oily consistency either—

(*a*) the sample shall be distributed throughout the media by either—

(i) gentle agitation at regular intervals if easily emulsified, or

(ii) by adding an emulsifying agent, or

(*b*) the sample shall be dissolved in a solvent suitable for the tests for sterility and applied to the media in accordance with sub-paragraph (2)(*b*) of this paragraph.

(5) Where the sample is distributed in the media by adding an emulsifying agent, the final concentration of that agent shall be less than its bacteriostatic or fungistatic concentration.

9. The tubes or vessels of media to which the sample has been applied in accordance with the preceding paragraph shall be incubated for a period of not less than 7 days at between 30°C and 32°C in the test for bacterial sterility and at between 22°C and 25°C in the test for fungal sterility and examined during and after incubation.

10.—(1) If at the examination at the end of the incubation period referred to in the preceding paragraph no growth of micro-organisms is found in the media to which the sample has been applied, the medicinal product shall be regarded as having satisfied the test.

(2) If at any examination a growth of micro-organisms is found in the media to which the sample has been applied, a further sample may be taken from the batch and tested in accordance with the foregoing provisions of this Part of this Schedule.

(3) If on examination during or after the incubation of the further sample no growth of micro-organisms is found, the medicinal product shall be regarded as having satisfied the test, but if growth of the same organism is found as was found in the first sample tested, the medicinal product shall be regarded as having failed to satisfy the test.

(4) If on any examination of the further sample a micro-organism is found, but the same micro-organism as was found in the sample first tested is not found, a third sample may be taken from the batch and tested in accordance with the foregoing provisions of this Part of this Schedule.

(5) If on any examination during or after the incubation of the third sample no micro-organism is found the medicinal product shall be regarded as having satisfied the test, but if any micro-organism is found the medicinal product shall be regarded as having failed to satisfy the test.

(6) If the nature of the sample or any other factor makes the result of the test uncertain, then subculture shall be carried out and the subcultures shall be incubated and examined in accordance with the provisions of paragraph 9 above and the provisions of this paragraph.

11.—(1) Notwithstanding the provisions of paragraph 10 above, where the medicinal product is—

(*a*) required in an emergency and the licence holder has no filled containers in stock,

(*b*) so unstable that the delay occasioned by the completion of the tests for sterility on filled containers would render its sale, supply or exportation in active form impossible, or

(*c*) declared by the relevant product licence to be a product to which this paragraph applies,

and, in the case of sub-paragraphs (*a*) and (*b*) above, the licensing authority has directed that the provisions of this paragraph shall apply to the medicinal product, the medicinal product may be regarded as having satisfied the tests for sterility if and so long as the conditions specified in the following sub-paragraph are satisfied.

(2) The conditions referred to in the preceding sub-paragraph are—

(i) in a case to which sub-paragraph (1)(*a*) of this paragraph applies, the medicinal product is not sold, supplied or exported unless, before it is filled into containers, the following amounts of the medicinal product are tested for sterility in accordance with the foregoing provisions of this Part of this Schedule—

(*a*) where the medicinal product is in liquid form, not less than 10 millilitres if the contents of the batch are over 10 litres, not less than 0·1 per cent of the batch if the contents of the batch are between 1 and 10 litres and not less than 1 millilitre if the contents of the batch are less than 1 litre,

(*b*) where the medicinal product is in solid form, 1 gramme if the weight of the batch is over 1 kilogramme, 0·1 per cent of the contents of the batch if the weight of the batch is between 1 kilogramme and 100 grammes and not less than 100 milligrammes if the weight of the batch is less than 100 grammes;

(ii) in a case to which sub-paragraphs (1)(*b*) or (1)(*c*) of this paragraph applies, the medicinal product is not sold, supplied or exported before a sample is taken and after the sale, supply or exportation the sample is tested in accordance with the foregoing provisions of this Part of this Schedule;

(iii) if at any examination made during the testing of a sample taken in accordance with the foregoing provisions of this paragraph any growth of micro-organisms is found, the licensing authority and any person to whom the medicinal product was sold, supplied or exported shall be notified forthwith.

PART III

Test for abnormal toxicity

1.—(1) The amount of medicinal product as is specified in the relevant product licence shall be dissolved or suspended in a volume not exceeding 0·5 millilitres of purified water or such other solvent as may be specified in the relevant product licence and injected intravenously into each of 5 healthy mice each weighing between 17 and 22 grammes over a period of time for each injection not exceeding 30 seconds per mouse or as specified in the relevant product licence.

(2) Subject to sub-paragraph (3) below, the medicinal product shall be regarded as having satisfied the test for abnormal toxicity if no mouse injected as aforesaid

dies in the 24 hours following the injection (or in such other period as may be specified in the relevant product licence).

(3) Where only one of the 5 mice injected as aforesaid dies within the said period the test may be repeated on another 5 mice and the medicinal product may be regarded as having satisfied the test for abnormal toxicity if no mouse dies in the 24 hours following the second series of injections.

2. Where, by virtue of the nature of any substance used in the test, the intravenous injection is likely to produce the death of any of the mice from causes other than abnormal toxicity, then—

(*a*) the amount of solvent used in the test shall not be limited as aforesaid, and

(*b*) the injection shall be intraperitoneal.

PART IV

Test for pyrogens

1. In this Part of this Schedule—

"maximum temperature", in relation to a rabbit which has been injected in accordance with paragraph 7 of this Part of this Schedule means the highest temperature reading recorded for the rabbit in the 3 hours after the injection;

"mean initial temperature", in relation to a rabbit as aforesaid, means the average of two temperature readings recorded for that rabbit with an interval of 30 minutes between the two readings in the 40 minutes immediately before the injection;

"response", in relation to a rabbit as aforesaid, means the difference between its mean initial temperature and its maximum temperature, a mean initial temperature higher than a maximum temperature being regarded as no response.

2. A test for pyrogenic substances (hereinafter referred to as a "pyrogen test") shall be made on a group of 3 healthy rabbits of either sex, each weighing not less than 1,500 grammes and having immediately before the test a rectal temperature of not less than 38°C and not more than 39·8°C.

3. A rabbit shall not be used in a pyrogen test—

(*a*) if, in the 40 minute period before the injection, two temperature readings, taken with an interval of 30 minutes between each reading, show a difference in that rabbit's temperature of more than 0·2°C,

(*b*) if its mean initial temperature is more than 1°C higher or lower than the mean initial temperature of the other two rabbits in the test,

(*c*) if it has been used in the preceding 3 days in a pyrogen test in which the medicinal product under examination satisfied the conditions for the test,

(*d*) if it has been used in the preceding 3 weeks in a pyrogen test in which the medicinal product under examination failed to satisfy the test,

(*e*) if it has been used at any time in a pyrogen test in which the average responses of the rabbits in the group exceeded 1·2°C, or

(*f*) if it is a rabbit which has not been used for a pyrogen test within the preceding 2 weeks, unless within 3 days before the proposed test it has been injected intravenously with 10 millilitres per kilogramme of its body weight of a pyrogen free solution containing 9 grammes of sodium chloride per litre and has shown a temperature variation not exceeding 0·6°C.

4.—(1) The measurement of the temperatures of the rabbits in a pyrogen test shall be by a clinical thermometer complying with the requirements of British Standard 691: 1966 (Clinical Maximum Thermometers) or by any other suitable instrument having a precision of at least ± 0·1°C, inserted in the rectum to a depth of not less than 5 centimetres and not more than 9 centimetres, the depth of insertion being constant for any one rabbit in the test.

(2) Where the thermometer is left in the rectum throughout the test, the rabbit may be restrained only with a loosely fitting neck-stock, so designed that the rabbit sits in a normal posture.

5. A pyrogen test shall be conducted in a quiet room which has a temperature within 3°C of that of the rabbits' living quarters or a temperature at which the rabbits have been kept for at least 18 hours before the test.

6. The rabbits used in the pyrogen test shall not be fed during the period beginning with the night before the test and ending with the completion of the test and shall be given no water during the test.

7.—(1) A pyrogen test shall be made by—

(*a*) injecting into the marginal vein of the ear of each of the 3 rabbits in the group, in each case over a period not exceeding 4 minutes or for such period as may be specified in the relevant product licence, the quantity of the medicinal product as is specified in the relevant product licence dissolved or suspended in or diluted with such volume of pyrogen free water or physiological saline as will result in a final preparation for injection of not less than 0·5 millilitres or more than 10 millilitres per kilogramme of the body weight of the rabbit which may be warmed to not more than 38·5°C prior to injection;

(*b*) taking the temperature of each of the rabbits at regular intervals of not more than 30 minutes over a period beginning at least 90 minutes before the injection and ending 3 hours after the injection.

(2) Four pyrogen tests may be made on a medicinal product if and so long as the aggregate of the responses of the rabbits used in the test or tests made exceeds the amount shown in the second column of the table at the end of this paragraph in relation to the number of rabbits used but does not exceed the amount shown in the third column of that table in relation to the number of rabbits used.

Number of rabbits used	Aggregate of responses	
	Pass if not exceeding	Limit for further test
3	1·15°	2·65°
6	2·80°	4·30°
9	4·45°	5·95°
12	6·60°	

8. The medicinal product shall be regarded as having satisfied the pyrogen test if after the first test, or after any subsequent test permitted by the foregoing paragraph, the aggregate of the responses of the rabbits used in the test or tests does not exceed the amount shown in the second column of the said table in relation to the number of rabbits used.

EXPLANATORY NOTE

(*This Note is not part of the Regulations.*)

These Regulations amend the Medicines (Standard Provisions for Licences and Certificates) Regulations 1971 by adding two new Schedules containing further standard provisions which may be incorporated in licences, namely—

(*a*) standard provisions for manufacturer's licences relating to all vaccines, smallpox vaccine, BCG vaccine, toxins and sera, and

(*b*) standard provisions for product licences relating to medicinal products which contain the substances listed in paragraphs 1 to 35 of Schedule 1 to the Medicines (Control of Substances for Manufacture) Order 1971, being substances the purity and potency of which cannot be tested by chemical means.

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