THERAPEUTIC SUBSTANCES

1957 No. 550

The Therapeutic Substances Amendment Regulations, 1957

Made - - - -	*28th March*, 1957
Laid before Parliament	*4th April*, 1957
Coming into Operation	*1st May*, 1957

The Joint Committee constituted by subsection (1) of section 4 of the Therapeutic Substances Act, 1956(**a**), in exercise of the powers conferred on them by sections 1 and 5 of the said Act, after consultation with the Advisory Committee constituted under subsection (2) of the said section 4, hereby make the following regulations:—

1.—(1) These regulations may be cited as the Therapeutic Substances Amendment Regulations, 1957, and shall come into operation on the first day of May, 1957.

(2) The principal regulations and these regulations shall be read together as one, and these regulations and the Therapeutic Substances Regulations, 1952 to 1956, may be cited together as the Therapeutic Substances Regulations, 1952 to 1957.

2. In these regulations the expression "the principal regulations" means the Therapeutic Substances Regulations, 1952(**b**), as amended by the Therapeutic Substances Amendment Regulations, 1953(**c**), the Therapeutic Substances Amendment Regulations, 1954(**d**) and the Therapeutic Substances Amendment Regulations, 1956(**e**).

3. The following therapeutic substances are hereby added to the First Schedule to the Therapeutic Substances Act, 1956, as being substances the purity or potency of which cannot be adequately tested by chemical means, namely:—

(*a*) any absorbent or protective material capable of being absorbed by the body tissues which is offered or intended to be offered for sale for use in surgical operations upon the human body;

(*b*) tetracycline, polymyxin B and viomycin which are intended for parenteral injection, and preparations containing any of the said substances which are intended for such injection;

(*c*) hyaluronidase, streptokinase, streptodornase, and streptokinase-streptodornase which are intended for parenteral injection, and preparations containing any of the said substances which are intended for such injection;

(*d*) heparin and preparations thereof;

(*e*) corticotrophin and preparations thereof.

(**a**) 4 & 5 Eliz. 2. c. 25.
(**b**) S.I. 1952/1937 (1952 III, p. 3420).
(**c**) S.I. 1953/1172 (1953 II, p. 2289).
(**d**) S.I. 1954/1645 (1954 II, p. 2384).
(**e**) S.I. 1956/1131 (1956 II, p. 2364).

4.—(1) In paragraph (1) of regulation 7 of the principal regulations (which relates to labelling) after the words " manufacturer of the substance " there shall be inserted the words " or by such other person as the licensing authority may in any particular case approve ".

(2) The following proviso shall be inserted at the end of the proviso to the said paragraph (1):—

" (iii) sub-paragraph (*d*) of this paragraph shall not apply in relation to an antibiotic or to a preparation containing an antibiotic ".

(3) The following provision shall be inserted at the end of the said regulation 7:—

" (4) For the purposes of sub-paragraphs (*b*) and (*c*) of paragraph (2) of this regulation, it shall be sufficient if the label or wrapper, instead of stating the dates therein mentioned, states the month and year which includes the date on which the manufacture of a batch was completed or, as the case may be, the month and year up to the end of which the substance may be expected to retain a stated potency or not to acquire excessive toxicity, and references to a date in—

(*a*) sub-paragraph (*e*) of the said paragraph (2);

(*b*) the next following regulation;

(*c*) sub-paragraph (3) of paragraph 10 of part II of the third schedule to these regulations, as it applies to dried B.C.G. vaccine; and

(*d*) paragraph 3 of part I of the eighth schedule to these regulations;

shall be construed accordingly:

Provided that this paragraph shall not apply to B.C.G. vaccine (other than dried B.C.G. vaccine), to smallpox vaccine (other than dried smallpox vaccine) or to whole human blood."

5.—(1) In regulation 12 of the principal regulations (which specifies the therapeutic substances to which the sterility tests contained in regulations 13 and 14 thereof are to be applied) in paragraph (*d*) (which relates to arsphenamine, its derivatives and analogous substances) at the end there shall be inserted the words " other than oxophenarsine hydrochloride and oxophenarsine tartrate ".

(2) In the said regulation 12 after paragraph (*i*) the following paragraphs shall be inserted:—

" (*j*) hyaluronidase, streptokinase, streptodornase and streptokinase-streptodornase, and preparations of any of the said substances;

(*k*) heparin and preparations thereof;

(*l*) corticotrophin and preparations thereof."

6.—(1) Where a therapeutic substance is required by the relative schedule to be subjected to a test for freedom from pyrogenic substances it shall be tested in the manner described in the first schedule to these regulations.

(2) In paragraph 6 of part I of the ninth schedule to the principal regulations (which requires an antibiotic to be subjected to the test for freedom from pyrogenic substances therein contained) for the words from " the following test " to the end of the paragraph there shall be substituted the words " a test for freedom from pyrogenic substances ".

7.—(1) The following paragraph shall be substituted for paragraph 1 of part II of the third schedule to the principal regulations:—

"1. Bacillus Calmette-Guérin vaccine is a preparation of the bacteria in a living pure culture of a strain of the bacillus of Calmette and Guérin, which bacillus is in this schedule referred to by the initials B.C.G. The proper name of the vaccine when prepared in a moist form is "B.C.G. vaccine", and the proper name of the vaccine when prepared in a dried form is "dried B.C.G. vaccine"."

(2) Sub-paragraph (*d*) of paragraph (2) of the said part shall have effect as if for the expression "5 milligrams" there were substituted the expression "0·5 milligram".

(3) The following provision shall be inserted after paragraph 5 of the said part:—

"Test for potency

5A. B.C.G. vaccine shall be tested for potency by a method approved by the licensing authority".

(4) The following paragraph shall be substituted for paragraph 6 of the said part:—

"6. Each batch of vaccine shall be tested for virulence by intramuscular injection of 5 milligrams moist weight of the constituent organisms into each of 6 healthy guinea-pigs each weighing not more than 250 grammes. The batch shall be deemed to have passed the test if none of the animals dies within 42 days after the injection or if one only of the animals dies within that period and a post-mortem examination establishes that the animal is free from tuberculosis. If 2, but not more, of the animals die within the said period and a post-mortem examination establishes that both of them are free from tuberculosis, 6 further such guinea-pigs may be similarly injected, and the batch shall be deemed to have passed the test if none of these animals dies within 42 days after injection or if one only of the animals dies within that period and a post-mortem examination establishes that the animal is free from tuberculosis".

(5) In sub-paragraph (1) of paragraph 10 of the said part, for the words from "the prophylactic dose" to the end of the sub-paragraph there shall be substituted the words "the moist weight of organisms in the container".

(6) The following paragraph shall be inserted at the end of the said part:—

"Dried B.C.G. vaccine.

11.—(1) Dried B.C.G. vaccine shall be dried by a method approved by the licensing authority, and shall be tested in the manner set out in regulations 13 and 14 of these regulations.

(2) In their application to dried B.C.G. vaccine, paragraphs 2 to 10 of this part of this schedule shall have effect with the following modifications:—

(*a*) paragraph 5 and sub-paragraph (1) of paragraph 9 shall not apply;

(*b*) sub-paragraph (2) of paragraph 9 shall have effect as if the reference to paragraph 5 (2) were omitted;

(*c*) sub-paragraph (1) of paragraph 10 shall have effect as if the reference to the moist weight of organisms in the container were a reference to the moist weight of organisms in the material from which the dried vaccine was prepared;

(*d*) sub-paragraph (3) of paragraph 10 shall have effect as if the reference to 14 days were a reference to 12 months".

8.—(1) In paragraph 1 of part IV of the third schedule to the principal regulations (which relates to smallpox vaccine) for the words "or in the membranes of the chick embryo" there shall be substituted the words "or on other tissue of a kind approved by the licensing authority".

(2) The following paragraph shall be substituted for paragraph 7 of the said part IV:—

"7.—(1) After the process of purification has been completed each batch of smallpox vaccine shall be tested for potency so as to ensure its activity at the time of issue. These tests shall be applied not more than 12 months before a batch of vaccine is finally issued.

(2) The vaccine shall be tested—

(*a*) on the skin of a rabbit, or of an animal of some other species approved by the licensing authority, in the manner described in sub-paragraph (4) of this paragraph, or in that manner with such modifications as may be approved by the licensing authority; or

(*b*) on the chorio-allantoic membrane of the chick embryo in the manner described in sub-paragraph (5) of this paragraph, or in that manner with such modifications as aforesaid; or

(*c*) on material of such other kind, and in such manner, as may be approved by the licensing authority.

(3) For the purpose of the tests progressive dilutions of the vaccine shall be made in physiological saline or other suitable diluent. The dilutions shall be used for the test without filtration.

(4) If the test on the skin of a rabbit or other animal is used, the vaccine shall be tested by the application of the dilutions to the suitably prepared skin of the animal, in direct comparison with similar dilutions of a control vaccine of established potency approved by the licensing authority; and the vaccine shall pass the test if both the vaccine under test and the control vaccine—

(*a*) in a dilution of 1 in 1,000 produce confluent lesions characteristic of vaccinia;

(*b*) in a dilution of 1 in 10,000 produce not less than 10 characteristic discrete vesicles.

(5) If the test on the membrane of the chick embryo is used, the vaccine shall be tested by preparing inocula of 0·1 millilitre of at least two suitable dilutions of the vaccine at not more than tenfold differences, applying inocula of each dilution to the chorio-allantoic membrane of separate groups of at least 5 embryos, each of 11 to 13 days incubation and enumerating the specific vaccinial lesions produced on the membranes after 48 hours further incubation. The vaccine shall pass the test if—

(*a*) one of the dilutions produces a mean count of not less than 20 and not more than 100 discrete lesions on the membranes after 48 hours further incubation; and

(*b*) the mean count produced by one of the dilutions shows that the undiluted vaccine contains not less than 10^8 infective units of virus per millilitre."

9. Part VI of the fifth schedule to the principal regulations (which relates to oxophenarsine hydrochloride and oxophenarsine tartrate) shall cease to have effect.

10. The provisions contained in the second schedule to these regulations (which relate to surgical materials for use in operations upon the human body) shall be substituted for the provisions contained in the eighth schedule to the principal regulations.

11.—(1) The following paragraph shall be inserted in part I of the ninth schedule to the principal regulations (which relates to antibiotics) after paragraph 1 thereof:—

"Proper names

1A. The proper name of an antibiotic is the name by reference to which it is defined in the part of this schedule specifically relating to it, and the proper name of a derivative of an antibiotic, or of a preparation containing an antibiotic, is such name as may be approved by the licensing authority as indicating the nature of the derivative or the preparation."

(2) Paragraph 2 of part II of the said schedule, paragraph 2 of part III thereof, paragraph 2 of part IV thereof and paragraph 2 of part V thereof are accordingly hereby revoked.

(3) The following paragraph shall be substituted for paragraph 7 of part I of the said schedule:—

"7.—(1) Subject to the provisions of sub-paragraph (3) of this paragraph, the label on the container of a single antibiotic, or of a preparation of a single antibiotic, shall state—

(*a*) in the case of a solution or a suspension, the minimum number of units of the antibiotic per millilitre of the solution or suspension and the minimum volume of the contents of the container;

(*b*) in the case of a solid preparation the minimum number of units of the antibiotic per milligram of the contents and the minimum total number of units of the antibiotic in the container;

and, in either case, the nature of any substance which has been mixed with the antibiotic:

Provided that the licensing authority may in the case of any solid preparation of an antibiotic dispense with the requirement that the minimum number of units of the antibiotic per milligram of the contents shall be stated.

(2) Subject as aforesaid, the label on the container of a mixture of two or more antibiotics shall state—

(*a*) in the case of a solution or suspension, the minimum number of units of each antibiotic per millilitre of the solution or suspension and the minimum volume of the contents of the container;

(*b*) in the case of a solid preparation, the minimum total number of units of each antibiotic in the container;

and, in either case, the nature of any substance which has been mixed with the antibiotics.

(3) The label on the container of a single antibiotic, or of a preparation of a single antibiotic, with respect to which the licensing authority has approved the expression of the potency in some other manner than units per millilitre or units per milligram, and the container of a mixture of two or more antibiotics with respect to one or more of which the said authority has approved the expression of the potency in some such other manner, shall bear such particulars with respect to each antibiotic in

the container, and with respect to the nature of any substance other than an antibiotic contained therein, as the licensing authority may require".

(4) The following provision shall be substituted for paragraph 3 of part II of the said ninth schedule:—

"3. The standard preparation is—

(*a*) in relation to benzylpenicillin, a quantity of dry sodium salt of benzylpenicillin;

(*b*) in relation to phenoxymethylpenicillin, a quantity of dry phenoxymethylpenicillin;

(*c*) in relation to any other preparation of penicillin, a quantity of such substance as may be indicated with respect thereto by the licensing authority".

(5) The following provision shall be substituted for sub-paragraph (1) of paragraph 4 of the said part II:—

"4.—(1) Salts of penicillin with inorganic bases, if in solid form, shall not be issued—

(*a*) in the case of benzylpenicillin, with a potency of less than 1,100 units per milligram;

(*b*) in the case of any other preparation of penicillin, with a potency less than that which may be indicated with respect to that preparation by the licensing authority".

(6) In sub-paragraph (1) of paragraph 4 of part III of the said ninth schedule (which provides that salts of streptomycin with inorganic acids, if in solid form, shall not be issued with a potency of less than 600 units per milligram) for the expression "600 units" there shall be substituted the expression "700 units".

(7) In paragraph 6 of part III of the said ninth schedule (which specifies the number of units of streptomycin for the purposes of the test for freedom of abnormal toxicity) for the figure "1,000" there shall be substituted the figure "750".

(8) In paragraph 8 of part III of the said ninth schedule (which contains details of the test for freedom from histamine-like substances) for the expression "3,000 units per millilitre" there shall be substituted the expression "30,000 units per millilitre".

(9) The provisions contained in the third schedule to these regulations (which relate to tetracycline, polymyxin B and viomycin and to preparations containing any of the said substances) shall be inserted at the end of the said ninth schedule as parts VI, VII and VIII thereof.

12. The provisions contained in the fourth schedule to these regulations (which relate to human serum albumin and 131-radioiodinated human serum albumin) shall be inserted at the end of the tenth schedule to the principal regulations as parts VII and VIII thereof.

13. In part III of the eleventh schedule to the principal regulations at the end of paragraph 3 (which requires tests for potency and undue toxicity to be applied to substances having the specific biological action of curare on neuromuscular transmission whose action thereon is not due to tubocurarine) there shall be inserted the following proviso:—

"Provided that this paragraph, so far as it relates to undue toxicity, shall not apply to dimethyltubocurarine or to any salt thereof."

14. In sub-paragraph (*c*) of paragraph 5 of part II of the twelfth schedule to the principal regulations (which requires the label on a container of oily injection of dimercaprol to state that the solution is intended for subcutaneous or intramuscular injection only) the words "subcutaneous or" shall be omitted.

15. The provisions contained in the fifth schedule to these regulations (which relate to hyaluronidase, streptokinase, streptodornase, and streptokinase-streptodornase; heparin and preparations thereof; and corticotrophin and preparations thereof) shall be inserted in the principal regulations after the twelfth schedule as the thirteenth, fourteenth and fifteenth schedules thereto.

16. For sub-paragraph (4) of paragraph 6 of part XVII of the third schedule to the principal regulations(a) (which provides that the total volume of a poliomyelitis virus suspension shall not exceed 50 litres) there shall be substituted the following sub-paragraph:—

"(4) The total volume of the virus suspension shall not exceed such volume as may for the time being be approved by the licensing authority."

FIRST SCHEDULE

Test for Freedom from Pyrogenic Substances

1. In this schedule—

"maximum temperature", in relation to a rabbit which has been injected as mentioned in paragraph 6 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 such a rabbit, means the average of the temperature readings recorded for the rabbit in the 40 minutes immediately before the injection;

"response", in relation to such a rabbit, means the difference between its mean initial temperature and its maximum temperature.

2. A test for freedom from pyrogenic substances (in this schedule called "a pyrogen test") shall be made with a group of 3 healthy rabbits of either sex, each weighing not less than 1·5 kilograms and having immediately before the test a rectal temperature not exceeding 39·8°C.

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

(*a*) if it has been used in a pyrogen test in the preceding 3 days; or

(*b*) if it has been used in the preceding 3 weeks in a pyrogen test in which the substance under examination failed to pass the test; or

(*c*) 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

(*d*) unless within 3 days before the test it has been intravenously injected with 10 millilitres per kilogram of its body weight of pyrogen-free water or pyrogen-free physiological saline and has shown no undue rise or fall in temperature.

4. 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 : 1953 (Clinical Maximum Thermometers) or by any other suitable instrument of at least equal precision, inserted in the rectum to a depth of not less than 6 centimetres and not more than 9 centimetres, the depth of insertion being constant for any one rabbit in any one test. If the instrument 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. The rabbits used

(a) see S.I. 1956/1131 (1956 II, p. 2364).

in the 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.

6. A pyrogen test shall be made by injecting intravenously into each of the 3 rabbits in the group such quantity of the substance under examination as is specified in the relevant schedule, dissolved in not more than 5 millilitres of water or physiological saline, and 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.

7. The test may be repeated on a substance so often as the aggregate of the responses of the rabbits used in the test or tests so far made exceeds the amount shown in the second column of the table at the end of this schedule in relation to the number of rabbits so far used but does not exceed the amount shown in the third column thereof in relation thereto :

Provided that not more than 4 tests in all may be made.

8. The substance shall be deemed to be free from pyrogenic substances if after the first test, or after any subsequent test permitted by the last 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 so used.

TABLE

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°	—

SECOND SCHEDULE

SURGICAL MATERIALS

PART I

GENERAL PROVISIONS APPLICABLE TO SURGICAL MATERIALS

Scope of schedule

1. This schedule relates to—

(*a*) surgical ligature and surgical suture ; and

(*b*) any absorbent or protective material capable of being absorbed by the body tissues ;

which are offered or intended to be offered for sale for use in surgical operations upon the human body.

Test for sterility

2.—(1) The provisions of regulations 13 and 14 of these regulations, except paragraphs (6) and (7) of regulation 14, shall apply to the substances to which this schedule relates, with the modification that in paragraph (4) of regulation 14 the expression " 12 days " shall be substituted for the expression " 5 days ".

(2) The tests required by those provisions as so applied shall be applied to the whole of the material in the containers :

Provided that in the case of the materials to which parts III to V of this schedule relate the tests may be applied to a portion of the material in the container if the licensing authority approves a method of so applying them.

(3) In the case of surgical ligature and surgical suture, if any growth of micro-organisms is found during the period of the test the batch from which the sample was taken shall not be issued.

(4) In the case of the materials to which parts III to V of this schedule relate, if any growth of micro-organisms is found during the period of the test, a further sample may be taken from the batch in the proportions specified in paragraph (2) of the said regulation 13, and the tests may be repeated on the sample so taken. If on examination of the further sample no micro-organism is found, the sample shall be regarded as having passed the test; but if on such further examination any growth of micro-organisms is found the batch from which the sample was taken shall not be issued.

Labelling

3. For the purpose of sub-paragraph (*b*) of paragraph (2) of regulation 7 of these regulations, the date on which the manufacture of the batch is completed shall be the date on which the test for sterility was completed.

PART II

SPECIAL PROVISIONS APPLICABLE TO SURGICAL LIGATURE AND SURGICAL SUTURE

Definition and proper name

1. Surgical ligature or suture is any ligature or form of binding material prepared from the gut or any tissue of an animal. When such ligature or suture is offered or intended to be offered for sale as sterile and ready for use, the proper name of the substance shall be "sterilised surgical ligature" or "sterilised surgical suture" followed, in brackets, by the accepted scientific name or a title descriptive of the true nature and origin of the substance as, for example, "sterilised surgical ligature (catgut)" or "sterilised surgical suture (horsehair)".

Quality

2. Every batch of sterilised surgical ligature or suture shall consist entirely of material which has been simultaneously subjected to the same process or series of processes for rendering it sterile.

PART III

SPECIAL PROVISIONS APPLICABLE TO ABSORBABLE GELATIN

Definition and proper names

1. Absorbable gelatin is gelatin prepared in the form of a finely porous sponge-like material or of a film. Its proper name is "absorbable gelatin sponge" or "absorbable gelatin film", as the case may be.

PART IV

SPECIAL PROVISIONS APPLICABLE TO OXIDISED CELLULOSE

Definition and proper name

1. Oxidised cellulose is a polyanhydroglucuronic acid obtainable by the nitrogen dioxide oxidation of surgical gauze or cotton. Its proper name is "oxidised cellulose", followed by a word or words approved by the licensing authority as descriptive of the form of the material.

PART V

SPECIAL PROVISIONS APPLICABLE TO CALCIUM ALGINATE

Definition and proper name

1. Calcium alginate consists of the calcium salt or the mixed calcium and sodium salt of alginic acid (which is a polyuronic acid composed of residues of D-mannuronic acid) and is prepared in the form of gauze or wool. Its proper name is "calcium alginate" followed by a word or words approved by the licensing authority as descriptive of the form of the material.

THIRD SCHEDULE

PART VI

SPECIAL PROVISIONS APPLICABLE TO TETRACYCLINE

Definition

1. Tetracycline is an antimicrobial base produced by dechlorination of aureomycin and has the chemical structure 4-dimethylamino-1:4:4a:5:5a:6:11:12a octahydro-3:6:10:12:12a-pentahydroxy-6-methyl-1:11-dioxonaphthacene - 2 - carboxyamide. The expression includes any salt or derivative of the said base which does not contain organically bound chlorine in the 7- position or a hydroxyl group in the 5- position, and any substance the chemical and biological properties of which are identical with, or similar to, those of the said substances but which is produced by other means.

Standard preparation

2. The standard preparation is a quantity of tetracycline hydrochloride.

Strength

3.—(1) Salts of tetracycline with inorganic acids, if in solid form, shall not be issued with a potency of less than 900 units per milligram.

(2) In the case of other salts or derivatives of tetracycline or preparations thereof the minimum permitted potency shall be such as shall be determined by the licensing authority.

Quality

4.—(1) A salt of tetracycline shall form a clear solution when the dried substance is dissolved in distilled water in a concentration of 10,000 units per millilitre.

(2) The pH value of a saturated watery solution of a salt of tetracycline with an inorganic acid shall lie between 2·0 and 3·0.

Test for freedom from abnormal toxicity

5. The number of units of tetracycline for the purpose of the test for freedom from abnormal toxicity shall be not less than 1,000.

Test for freedom from pyrogenic substances

6. The number of units of tetracycline for the purpose of the test for freedom from pyrogenic substances shall be not less than 5,000 units per kilogram of the rabbit's weight.

Test for freedom from histamine-like substances

7. Paragraph 8 of part III of this schedule shall apply to tetracycline as if for references to streptomycin there were substituted references to tetracycline.

PART VII

SPECIAL PROVISIONS APPLICABLE TO POLYMYXIN B AND PREPARATIONS THEREOF

Definition

1. Polymyxin B is an antimicrobial peptide produced by strains of *Bacillus polymyxa,* which yields on hydrolysis with acid the amino-acids leucine, phenylalanine, threonine and α : γ-diaminobutyric acid, but no other amino-acids, together with d-6-methyloctan-1-oic acid, and includes any salt thereof with an inorganic acid, any derivative thereof and any substance the chemical and biological properties of which are identical with or similar to those of any of the substances aforesaid but which is produced by other means.

Standard preparation

2. The standard preparation is a quantity of polymyxin B sulphate.

Strength

3.—(1) Salts of polymyxin B with inorganic acids, if in solid form, shall not be issued with a potency of less than 6,000 units per milligram.

(2) In the case of other salts or derivatives of polymyxin B, the minimum permitted potency shall be such as shall be determined by the licensing authority.

Quality

4. A salt of polymyxin B shall form a clear solution with a pH value lying between 5·0 and 7·0 when the dried substance is reconstituted with distilled water in a concentration of 100,000 units per millilitre.

Test for freedom from abnormal toxicity

5. The number of units of polymyxin B for the purpose of the test for freedom from abnormal toxicity shall be not less than 1,000, and in its application to polymyxin B paragraph 5 of part 1 of this schedule shall have effect as if references to 24 hours were references to 48 hours.

Test for freedom from pyrogenic substances

6. The number of units of polymyxin B for the purpose of the test for freedom from pyrogenic substances shall be not less than 10,000 units per kilogram of the rabbit's weight.

PART VIII

SPECIAL PROVISIONS APPLICABLE TO VIOMYCIN

Definition

1. Viomycin is any antimicrobial organic base produced by the growth of *Streptomyces griseus*, var. *purpureus* which yields on hydrolysis by mineral acids urea, L-serine, α: β diaminopropionic acid and β-lysine, and includes any salt or derivative, or salt of a derivative, of any such base and any substance the chemical and biological properties of which are identical with or similar to those of any of the substances aforesaid but which is produced by other means.

Standard preparation

2. The standard preparation is a preparation of viomycin sulphate.

Strength

3.—(1) Salts of viomycin with inorganic acids, if in solid form, shall not be issued with a potency of less than 700 units per milligram.

(2) In the case of other salts or derivatives of viomycin, the minimum permitted potency shall be determined by the licensing authority.

Quality

4. A salt of viomycin shall form a clear solution with a pH value lying between 4·5 and 7·0 when the dried substance is dissolved in distilled water at a concentration of 100,000 units per millilitre.

Test for freedom from abnormal toxicity

5. The number of units of viomycin for the purposes of the test for freedom from abnormal toxicity shall be not less than 1,000.

Test for freedom from pyrogenic substances

6. The number of units of viomycin for the purpose of the test for freedom from pyrogenic substances shall be not less than 2,000 units per kilogram of the rabbit's weight.

Test for freedom from histamine-like substances

7. Paragraph 8 of part III of this schedule shall apply to viomycin as if for references to streptomycin there were substituted references to viomycin.

FOURTH SCHEDULE

PART VII

SPECIAL PROVISIONS APPLICABLE TO HUMAN SERUM ALBUMIN AND PREPARATIONS THEREOF

Definition and proper name

1. Human serum albumin is that fraction of the water soluble protein derived from human plasma or serum of which the mean molecular weight is 70,000. Its proper name is " human serum albumin ".

Quality

2.—(1) Human serum albumin, when buffered with M/15 sodium phosphate to a pH value of 8·0 and at an ionic strength of 0·2, shall not contain more than 5 per cent of globulins, as determined by electrophoretic analysis.

(2) In the case of a liquid preparation the pH value of the liquid shall lie between 6·5 and 7·0 and the albumin shall be dissolved in a solvent approved by the licensing authority.

(3) Human serum albumin in the dry form—

(*a*) shall not lose more than 1·0 per cent by weight after exposure for 24 hours to phosphorus pentoxide at a pressure not exceeding 1·0 millimetre of mercury;

(*b*) shall, when distilled water is added to give a concentration of 6 grammes per 100 millilitres, dissolve completely in not more than 10 minutes.

Storage and labelling

3.—(1) Human serum albumin and preparations thereof shall be stored in a manner approved by the licensing authority.

(2) The container shall state the total amount of human serum albumin in the container and the nature of any other substances which may have been added, and in particular, in the case of a liquid preparation, the nature and volume of the solvent and the nature of the buffer.

PART VIII

SPECIAL PROVISIONS APPLICABLE TO 131-RADIOIODINATED HUMAN SERUM ALBUMIN

Definition and proper name

1. 131–Radioiodinated human serum albumin is a watery solution of the organic compound formed by the union of radioactive iodine (^{131}I) with human serum albumin. Its proper name is " 131–radioiodinated human serum albumin ".

Test for absence of denatured albumin

2. 131–Radioiodinated human serum albumin shall be tested for the absence of denatured albumin by a method approved by the licensing authority.

Test for free iodide

3. 131–Radioiodinated human serum albumin shall not contain more than 2 per cent of its total iodine as free iodide as determined by a method approved by the licensing authority.

Freedom from pyrogenic substances

4.—(1) 131–Radioiodinated human serum albumin shall, if so required by the licensing authority, be subjected to a test for freedom from pyrogenic substances, and shall in any event be free from such substances to such an extent that, if tested in the manner applicable where a substance is required to be subjected to a test for freedom from such substances, it would pass the test.

(2) The quantity of 131–radioiodinated human serum albumin for the purpose of the said test shall be such a quantity thereof as to contain a total radioactivity of not less than 10 microcuries per kilogram of the rabbit's weight.

Labelling

5. The container shall state—

(*a*) the nature and volume of the contents ;

(*b*) the total radioactivity in microcuries or millicuries of the contents, and the date on which it was measured ;

(*c*) the total weight of 131–radioiodinated human serum albumin in the container ;

(*d*) the nature and concentration of the salts present ; and

(*e*) the date after which the contents should not be used.

FIFTH SCHEDULE

"THIRTEENTH SCHEDULE

ENZYMES

PART I

HYALURONIDASE

Definition and proper name

1. Hyaluronidase is a preparation, prepared from mammalian testicles or sperm or from other sources approved by the licensing authority, of the enzymes which diminish the viscosity of the hyaluronic acid present in mammalian tissues. Its proper name is " hyaluronidase ", qualified by a word or words describing its source (for example, " hyaluronidase, bovine ").

Standard preparation

2. The standard preparation is a quantity of dry hyaluronidase kept at the National Institute for Medical Research, London.

Unit of standardisation

3. The unit of hyaluronidase for the purpose of these regulations is the activity contained in such an amount of the standard preparation as may be indicated from time to time by the Medical Research Council.

Test for potency

4.—(1) Hyaluronidase shall be tested for potency by comparative tests in relation to the standard preparation by a method approved by the licensing authority.

(2) The potency so determined shall be expressed in units per milligram of the solid form, and in units per millilitre of solutions.

(3) Hyaluronidase in the solid form with a potency of less than 250 units per milligram shall not be issued.

Test for abnormal toxicity

5. Hyaluronidase shall be subjected to the following test for abnormal toxicity :—

A quantity of hyaluronidase containing not less than 2500 units shall be made up in a volume of physiological saline not exceeding 0·25 millilitre and shall be injected subcutaneously into each of 5 healthy mice weighing between 17 and 22 grammes. The sample shall be treated as having passed the test if either—

(*a*) the injection does not cause death or necrosis of the skin in any of the mice within 48 hours ; or

(*b*) the injection having caused death or necrosis of the skin in one only of the mice within that period, similar injections in 5 other such mice do not cause the death or necrosis of the skin of any of those mice within 48 hours.

Freedom from pyrogenic substances

6.—(1) Hyaluronidase shall be free from pyrogenic substances to such an extent that, if tested in the manner applicable where a substance is required to be subjected to a test for freedom from such substances, it would pass the test.

(2) The number of units of hyaluronidase for the purpose of the said test shall be not less than 250 units per kilogram of the rabbit's weight.

Quality

7. Hyaluronidase in solution, and the dry solid when reconstituted with freshly boiled and cooled water so as to give a concentration of 3 milligrams per millilitre, shall have the following characteristics:—

(*a*) the solution shall be a clear colourless or faintly yellow liquid;

(*b*) the solution shall have a pH value lying between 6·5 and 8·0.

Method of issue

8. Hyaluronidase shall be issued either in a watery solution or as a dry solid for reconstitution with a watery solvent.

Labelling

9.—(1) The container shall state—

(*a*) that the preparation is not intended for intravenous injection;

(*b*) in the case of a solid preparation, the total number of units in the container;

(*c*) in the case of a solution, the number of units per millilitre of the solution.

(2) The label on the package shall state, in the case of a solution, the nature of the solvent and of any stabilising agent.

PART II

STREPTOKINASE

Definition and proper name

1. Streptokinase is the substance produced by certain strains of streptococcus which activates an inactive precursor of a fibrinolytic enzyme present in human plasma. Its proper name is "streptokinase".

Method of preparation

2. Streptokinase shall be prepared, by methods approved by the licensing authority, from strains of streptococci other than those belonging to Lancefield's Group A.

Standard preparation

3. The standard preparation of streptokinase is a preparation of streptokinase-streptodornase kept at the National Institute for Medical Research, London.

Unit of standardisation

4. The unit of streptokinase is the specific activity contained in such amount of the standard preparation of streptokinase-streptodornase as may from time to time be indicated by the Medical Research Council in relation to streptokinase.

Quality

5.—(1) Streptokinase, when dissolved according to the manufacturer's directions, or, if there are no directions, in physiological saline, shall have a pH value lying between 6·0 and 8·5.

(2) Streptokinase shall not contain more than 100 units of streptolysin for each 100,000 units of streptokinase. For this purpose a unit of streptolysin is that amount of streptolysin in the reduced form which will cause 50 per cent. haemolysis of 5·0 millilitres of an 0·7 per cent suspension of fresh washed rabbit red cells at 37°C in 30 minutes.

Tests for potency

6. Streptokinase shall be tested for potency by comparative tests in relation to the standard preparation by methods approved by the licensing authority.

Test for abnormal toxicity

7. Streptokinase shall be subjected to the following test for freedom from abnormal toxicity:—

A quantity of streptokinase containing 10,000 units of streptokinase, in a volume not exceeding 5·0 millilitres of a watery solution, shall be injected intravenously into a healthy rabbit weighing between 2 and 2·5 kilograms and subcutaneously into each of 3 healthy guinea-pigs weighing between 250 and 350 grammes; and a quantity thereof containing 1,000 units of streptokinase, in a volume not exceeding 0·5 millilitre of a watery solution, shall be injected intra-peritoneally into each of 3 healthy mice. The sample shall pass the test if all the animals survive for 7 days without showing significant signs referable to the injected substance.

Labelling

8. The container shall state—

(*a*) the number of units of streptokinase contained in the container;

(*b*) the nature of the buffer, if any, contained in the preparation;

(*c*) that the preparation is not intended for intravenous injection.

PART III

STREPTODORNASE

Definition and proper name

1. Streptodornase is the substance produced by certain strains of streptococcus which catalyzes the depolymerisation of deoxyribonucleic acid. Its proper name is "streptodornase".

Application of part II

2. Paragraphs 2 to 8 of part II of this schedule shall apply to streptodornase with the substitution for references to streptokinase (except in the expression "streptokinase-streptodornase") of references to streptodornase.

PART IV

STREPTOKINASE-STREPTODORNASE

Definition and proper name

1. Streptokinase-streptodornase is a combination of streptokinase and streptodornase prepared by the growth of streptococci in a suitable liquid medium and subsequently purified therefrom. Its proper name is "streptokinase-streptodornase".

Application of part II

2. Paragraphs 2 to 4 and sub-paragraph (1) of paragraph 5 of part II of this schedule shall apply to streptokinase-streptodornase with the substitution for references to streptokinase of references to streptokinase-streptodornase.

Quality

3. Streptokinase-streptodornase shall not contain more than 100 units of streptolysin for each 100,000 units of streptokinase or for each 100,000 units of streptodornase, whichever has the greater number of units in the preparation being tested. For this purpose a unit of streptolysin is that amount of streptolysin in the reduced form which will cause 50 per cent. haemolysis of 5·0 millilitres of an 0·7 per cent suspension of fresh washed rabbit red cells at 37°C in 30 minutes.

Test for potency

4. Streptokinase-streptodornase shall be tested for potency of both constituents by comparative tests in relation to the standard preparation by methods approved by the licensing authority.

Test for abnormal toxicity

5. Streptokinase-streptodornase shall be subjected to the following test for freedom from abnormal toxicity:—

A quantity of streptokinase-streptodornase containing 10,000 units of streptokinase or 10,000 units of streptodornase, in a volume not exceeding 5·0 millilitres of a watery solution, shall be injected intravenously into a healthy rabbit weighing between 2 and 2·5 kilograms and subcutaneously into each of 3 healthy guinea pigs weighing between 250 and 350 grammes; and a quantity thereof containing 1,000 units of streptokinase or 1,000 units of streptodornase in a volume not exceeding 0·5 millilitre of a watery solution, shall be injected intra-peritoneally into each of 3 healthy mice. The sample shall pass the test if all the animals survive for 7 days without showing significant signs referable to the injected substances.

Labelling

6. The container shall state—

(*a*) the number of units of streptokinase and the number of units of streptodornase contained in the container;

(*b*) the nature of the buffer, if any, contained in the preparation;

(*c*) that the preparation is not intended for intravenous injection.

FOURTEENTH SCHEDULE

HEPARIN AND PREPARATIONS THEREOF

Definitions and proper names

1.—(1) Heparin is the sodium salt of a complex organic acid, obtained from mammalian tissue, which has the property of prolonging the clotting-time of blood in man or other animals.

(2) The proper name of heparin is "heparin", and the proper name of a preparation thereof is "heparin" qualified by such word or words as may be approved by the licensing authority as indicating the nature of the preparation.

Standard preparation

2. The standard preparation of heparin is a quantity thereof kept at the National Institute for Medical Research, London.

Unit of standardisation

3. The unit of heparin for the purpose of these regulations is the specific activity contained in such an amount of the standard preparation as the Medical Research Council may from time to time indicate as the quantity exactly equivalent to the unit accepted for international use.

Quality

4. Heparin shall have the following characteristics:—

(*a*) it shall be in the form of a white or greyish-brown amorphous powder which is odourless, or nearly so, and hygroscopic;

(*b*) it shall be completely soluble in water, and in a 1 per cent. w/v solution in water may have a pH value between 6·0 and 8·0;

(*c*) it shall have a specific optical rotation of less than +65°;

(*d*) on drying to constant weight over phosphorus pentoxide at 60°C. at a pressure not exceeding 5 millimetres of mercury it shall not lose more than 12 per cent of its weight;

(*e*) when so dried, it shall not contain more than 5·5 per cent nitrogen or less than 8 per cent sulphur;

(*f*) when 0·25 millilitre of a 5 per cent w/v solution of trichloroacetic acid is added to 1 millilitre of a 1 per cent watery solution of heparin no turbidity or precipitation shall occur;

(*g*) it shall contain not less than 100 units per milligram.

Test for potency

5. Heparin and preparations thereof shall be tested biologically for potency by a method approved by the licensing authority by comparison with the standard preparation and the potency and the fiducial limits of error (P = 0·95) of the potency shall be calculated from the results of the test.

The estimated potency of a preparation shall be not greater than 111 per cent nor less than 90 per cent of the stated potency. The percentage fiducial limits of error (P = 0·95) of the estimated potency shall lie between 80 per cent and 125 per cent of the stated potency.

Freedom from pyrogenic substances

6.—(1) Heparin shall, if so required by the licensing authority, be subjected to a test for freedom from pyrogenic substances, and in any event shall be free from such substances to such an extent that, if tested in the manner applicable where a substance is required to be subjected to a test for freedom from such substances, it would pass the test.

(2) The quantity of heparin for the purpose of the said test shall be 500 units per kilogram of the rabbit's weight.

Labelling

7. The container shall state the number of units per milligram in the case of a solid preparation or per millilitre in the case of a solution.

FIFTEENTH SCHEDULE

CORTICOTROPHIN AND PREPARATIONS THEREOF

PART I

GENERAL PROVISIONS

Definition and proper name

1.—(1) Corticotrophin is the hormone obtained from the anterior lobe of the pituitary gland which induces an immediate increase in the rate at which corticoid hormones are secreted by the cortex of the adrenal gland. Its proper name is "corticotrophin".

(2) The proper name of a preparation of corticotrophin, or of a mixture of corticotrophin with another therapeutic substance, is "corticotrophin" together with such words or abbreviations as may be approved by the licensing authority as a description of that preparation or mixture.

Labelling

2. The container shall state—

(*a*) the nature of the animal source of the corticotrophin;

(*b*) in the case of a liquid preparation, the nature of the vehicle.

PART II

SPECIAL PROVISIONS APPLICABLE TO LONG-ACTING CORTICOTROPHIN

Definition

1. Long-acting corticotrophin is a preparation of corticotrophin mixed or combined with a substance or substances which prolong the period of its activity in the body.

Nature of substance

2. The applicant for a manufacturing or import licence for long-acting corticotrophin shall submit to the licensing authority with his application a statement of the composition of the preparation to which the application relates, and a full and detailed account of the tests by which its composition is determined and by which the uniformity of successive batches is secured.

Test for prolongation of action

3. Long-acting corticotrophin shall be tested biologically, by a method approved by the licensing authority, for its power of prolonging the specific effects of the corticotrophin contained therein.

Labelling

4. The container of long-acting corticotrophin shall bear the words "not for intravenous use"."

These regulations were made by the aforesaid Joint Committee this twenty-eighth day of March, nineteen hundred and fifty-seven.

Dennis Vosper,
John S. Maclay,
J. L. O. Andrews,
Members of the Joint Committee.

W. G. Honnor,
Clerk to the Joint Committee.

EXPLANATORY NOTE

(This Note is not part of the Regulations but is intended to indicate their general purport.)

These regulations—

(*a*) add to the first schedule to the Therapeutic Substances Act, 1956, the substances specified in regulation 3;

(*b*) make a number of detailed amendments in the Therapeutic Substances Regulations, 1952, as amended by the regulations mentioned in regulation 2 (regulations 4, 7, 8, 11, 13, 14 and 16);

(*c*) substitute for the provisions of the Regulations of 1952 relating to surgical ligature and surgical suture more up-to-date and extended provisions relating to surgical materials (regulation 10 and second schedule);

(*d*) revoke the provisions of the Regulations of 1952 relating to oxophenarsine salts (regulations 5 (1) and 9);

(*e*) provide more up-to-date provisions relating to pyrogen tests (regulation 6 and first schedule);

(*f*) enact new schedules relating to the substances specified in regulation 3 (regulations 11 (9), 12 and 15, and third, fourth and fifth schedules).