STATUTORY INSTRUMENTS

1966 No. 505

THERAPEUTIC SUBSTANCES

The Therapeutic Substances (Manufacture of Antibiotics) Regulations 1966

Made - - - -	*27th April* 1966
Laid before Parliament	*5th May* 1966
Coming into Operation	*1st June* 1966

The Joint Committee constituted by section 4(1) 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 section 4(2) of the said Act, hereby make the following regulations:—

PART I

PRELIMINARY

Citation, Commencement and Interpretation

1.—(1) These regulations may be cited as the Therapeutic Substances (Manufacture of Antibiotics) Regulations 1966, and shall come into operation on 1st June 1966.

(2) In these regulations, unless the context otherwise requires—

"the Act" means the Therapeutic Substances Act 1956;

"antibiotic" means any antimicrobial substance synthesized by bacteria, fungi or protozoa, any derivative of any such substance, and any substance the chemical properties of which are identical with or similar to any such antimicrobial substance but which is not produced by living organisms, being in any case a substance which is used in the specific treatment of human infections;

"the general regulations" means the Therapeutic Substances (Manufacture and Importation) General Regulations 1963, as amended(b);

"the licensing authority" has the same meaning as in the general regulations;

"parenteral injection" in relation to any substance includes any administration of the substance by insertion into the body by any route other than that of the gastro-intestinal tract but does not include any application of the substance to the skin.

(3) Any reference in these regulations to any provision of the general regulations shall be construed as a reference to that provision as amended, extended or re-enacted by any subsequent regulations made under Part I of the Act.

(4) In these regulations, wherever any provision specifies a minimum potency for a substance in solid form (being a substance other than erythromycin) such potency shall be calculated with reference to the dried substance.

(a) 4 & 5 Eliz.2. c. 25. (b) S.I.1963/1450, 1964/1076 (1963 II, p. 2483; 1964 II, p. 2380).

(5) In these regulations, wherever any provision requires the minimum potency of a substance to be specified by the licensing authority, that authority shall have regard to the molecular structure of the substance compared with that of any related substance for which a minimum potency is prescribed by these regulations and to such other information as may be relevant.

(6) For the purposes of these regulations the cubic centimetre may be used wherever the millilitre is indicated.

(7) The Interpretation Act 1889(a) shall apply to the interpretation of these regulations as it applies to the interpretation of an Act of Parliament.

Revocation of existing regulations

2. The Therapeutic Substances (Manufacture of Antibiotics) Regulations 1963(b) and the Therapeutic Substances (Manufacture of Antibiotics) Amendment Regulations 1964(c) are hereby revoked.

Inclusion of substances in schedule to Act

3.—(1) Notwithstanding the revocation by these regulations of the Therapeutic Substances (Manufacture of Antibiotics) Regulations 1963 and the Therapeutic Substances (Manufacture of Antibiotics) Amendment Regulations 1964, the following substances shall continue to be included in schedule 1 to the Act, namely, penicillin, streptomycin, chlortetracycline, oxytetracycline, tetracycline, polymyxin B, colistin, bacitracin, erythromycin, kanamycin and viomycin, in each case if intended for parenteral injection, derivatives of any such substance which are intended for such injection, and preparations intended for such injection which contain any of the said substances or derivatives.

(2) Amphotericin B, the lincomycins, neomycin, vancomycin and any of the tetracyclines other than those mentioned in paragraph (1) of this regulation and derivatives thereof which are intended for parenteral injection and preparations intended for such injection which contain any of the said substances or derivatives are hereby added to schedule 1 to the Act as being substances the purity or potency of which cannot be adequately tested by chemical means.

(3) References in this regulation to any substance or group of substances are references to that substance or group of substances as defined in the part of these regulations specifically applicable to it.

PART II

GENERAL PROVISIONS RELATING TO ANTIBIOTICS

Proper names

4. The proper name of an antibiotic is the name by reference to which it is defined in the part of these regulations 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.

Standard preparation

5. The standard preparation of an antibiotic is one in such form as may be prescribed by the part of these regulations specifically relating to it, which is kept at the National Institute for Medical Research, London :

(a) 52 & 53 Vict. c. 63. (b) S.I. 1963/1451 (1963 II, p. 2500).
(c) S.I. 1964/1430 (1964 III, p. 3304).

Provided that, in the case of a derivative of an antibiotic for which biological assay in the terms of the said standard preparation is invalid, the standard preparation shall be such preparation of the antibiotic as may be approved by the licensing authority as suitable for the assay of that derivative.

Unit of standardisation

6. The unit of an antibiotic 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 licensing authority after consultation with the Medical Research Council:

Provided that, in the case of an antibiotic of which there is a unit accepted for international use, the amount of the standard preparation so indicated shall be exactly equivalent to that unit.

Tests for sterility

7. Antibiotics and preparations containing antibiotics shall be tested for sterility in accordance with the general regulations, with such modifications (if any) as the licensing authority consider appropriate in the case of any particular antibiotic or preparation.

Tests for potency

8.—(1) Subject to the provisions of paragraph (2) of this regulation, an antibiotic shall be tested for potency by comparative tests in relation to the standard preparation by a method approved by the licensing authority, and the potency and the fiducial limits of error ($P = 0{\cdot}95$) of the potency shall be calculable from the result of the test.

(2) An antibiotic whose potency can be adequately tested by chemical or physical means may be tested by those means instead of by the tests mentioned in the foregoing paragraph:

Provided that a licensee shall not use any chemical or physical means for testing the potency of an antibiotic unless he is satisfied that, if the antibiotic when tested by those means will satisfy the relevant requirements as to potency of these regulations, it will also satisfy those requirements if tested in accordance with the foregoing paragraph.

(3) The potency shall be expressed in units per milligram in the case of an antibiotic in solid form and in units per millilitre in the case of solutions or suspensions:

Provided that, if the licensing authority approves the expression of the potency in any other manner, the potency may be expressed in that other manner.

(4) Where the part of these regulations containing provisions specifically relating to any antibiotic provides a minimum potency for that antibiotic—

(*a*) the lower fiducial limit of error ($P = 0{\cdot}95$) calculated in accordance with paragraph (1) of this regulation shall be greater than such minimum; and

(*b*) the licensing authority may authorise, with or without conditions, the issue for specified purposes of such an antibiotic which does not satisfy the said minimum potency.

Freedom from abnormal toxicity

9.—(1) An antibiotic shall be free from abnormal toxicity and, if the licensing authority so require, shall be tested for freedom from such toxicity in accordance with this regulation.

(2) A quantity of the antibiotic containing such number of units as is specified by the part of these regulations specifically relating to it, dissolved or suspended, if the antibiotic is in solid form, in a volume not exceeding 0·5 millilitre of purified water, or such other solvent as may be specified in relation to the antibiotic in the part of these regulations specifically relating to it, shall be injected intravenously over a period of time not exceeding one minute into each of 5 healthy mice each weighing between 17 and 22 grams. The sample shall be regarded as free from abnormal toxicity if either:—

(*a*) the injection does not cause death in any of the mice within 24 hours; or

(*b*) the injection having caused death in one only of the mice within that period, further such injections in 5 other such mice do not cause the death of any of those mice within 24 hours.

(3) Where, by reason of the physical properties of any antibiotic, intravenous injection as prescribed in paragraph (2) of this regulation is likely to produce death in any of the mice from causes other than that of abnormal toxicity, then the test shall be carried out by intraperitoneal injection and the other requirements of the said paragraph (2), with the exception of the limitation as to the volume of the solvent, shall apply.

(4) In its application to polymyxin B and colistin, paragraph (2) and paragraph (3) of this regulation shall have effect as if references in paragraph (2) to 24 hours were references to 48 hours.

(5) Where a manufacturer satisfies the licensing authority that he has in use tests for determining the freedom of an antibiotic from abnormal toxicity and that those tests, as applied by him, will be not less effective in determining such freedom than the test prescribed in paragraph (2) of this regulation, the licensing authority may approve the use of such tests in the place of the prescribed test, but the authority may at any time withdraw such approval and require the manufacturer to carry out the prescribed test.

(6) Where any antibiotic is comprised in a mixture, the quantity of the mixture to be used for the purpose of the test for freedom from abnormal toxicity shall be such as the licensing authority may require, having regard to the inherent toxicity of any other component of the mixture.

Freedom from pyrogenic substances

10.—(1) An antibiotic shall, if the licensing authority so require, be tested for freedom from pyrogenic substances in accordance with the general regulations, and in any event shall be free from such substances to such an extent that, if so tested, it would pass the test.

(2) Where any antibiotic is comprised in a mixture, the quantity of the mixture to be used for the purpose of the test for freedom from pyrogenic substances shall be such as the licensing authority may require, having regard to the inherent toxicity of any other component of the mixture.

Tests for freedom from histamine-like substances

11.—(1) Where the part of these regulations specifically relating to any antibiotic provides that the antibiotic shall be free from histamine-like substances the antibiotic shall, if the licensing authority so require, be tested for freedom from such substances in accordance with this regulation.

(2) An antibiotic shall be tested for freedom from histamine-like substances as follows:—

(*a*) A solution of the antibiotic, containing such quantity of the substance under examination as is specified in the part of these regulations specifically relating to it, shall be injected intravenously into a cat anaesthetised with chloralose or a suitable barbiturate. The volume of the solution shall correspond to 1 millilitre per kilogram of the cat's weight.

(*b*) Where, by reason of the physical properties of the antibiotic, intravenous injection of such a solution as is mentioned in sub-paragraph (*a*) of this paragraph is likely to affect the cat's circulatory system for reasons other than the presence of histamine-like substances, then the injection shall be of an extract prepared from twice such quantity of the substance under examination as is specified in the part of these regulations specifically relating to it and the volume of the extract shall correspond to 1 millilitre per kilogram of the cat's weight.

The antibiotic shall be regarded as free from histamine-like substances if the injection produces a smaller fall of arterial blood pressure than is produced by the injection into the same cat of an equal volume of a solution of a histamine salt containing 0·1 microgram of histamine base per millilitre.

(3) Where a manufacturer satisfies the licensing authority that he has in use tests for determining the freedom of an antibiotic from histamine-like substances and that those tests, as applied by him, will be not less effective in determining such freedom than the test prescribed in paragraph (2) of this regulation, the licensing authority may approve the use of such tests in the place of the prescribed test, but the authority may at any time withdraw such approval and require the manufacturer to carry out the prescribed test.

Labelling

12.—(1) The particulars specified in regulation 6(1)(*g*) of the general regulations shall be borne both by the container of an antibiotic and by the package in which the container is offered for sale.

(2) The particulars specified in sub-paragraphs (*a*), (*b*) and (*c*) of the said regulation 6(1) shall be borne by the container of an antibiotic or of a preparation containing an antibiotic.

(3) Subject to the provisions of paragraph (5) of this regulation, the following further particulars shall be borne by the container of a single antibiotic, or of a preparation of a single antibiotic:—

(*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 in the container, except in the case of a bulk container when the minimum number of units of the antibiotic per milligram of the contents of the container shall be stated;

(*c*) in either case the nature of any substance which has been mixed with the antibiotic.

(4) Subject as aforesaid, the following further particulars shall be borne by the container of a mixture of 2 or more antibiotics:—

(*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;

(*c*) in either case, the nature of any substance which has been mixed with the antibiotics.

(5) Where, in pursuance of paragraph (3) or paragraph (4) of this regulation, the number of units is stated on the container, it shall, in the case of an antibiotic of which there is a unit accepted for international use, be stated as the number of international units.

(6) The particulars with respect to the matters mentioned in paragraph (3) of this regulation which are to be borne by the container of a single antibiotic, or of a preparation of a single antibiotic, in relation to which the licensing authority, in accordance with regulation 8(3) of these regulations, has approved the expression of the potency in some other manner than units per millilitre or units per milligram, and the particulars with respect to the matters mentioned in paragraph (4) of this regulation which are to be borne by the container of a mixture of 2 or more antibiotics in relation to one or more of which the said authority has approved the expression of the potency in some such other manner, shall be 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.

(7) The particulars specified in regulation 6(1)(*e*), (*f*), (*h*) and (*i*) of the general regulations shall be borne either by the container of an antibiotic or of a preparation containing an antibiotic or by the package in which the antibiotic or the preparation is offered for sale.

PART III

SPECIAL PROVISIONS RELATING TO PENICILLIN

Definition

13. Penicillin is any antimicrobial acid, any salt thereof, or any derivative which is obtained therefrom, which may be shown on chemical and physical examination to contain in its structure a fused thiazolidine β-lactam nucleus.

Standard preparations

14. The standard preparation is—

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

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

Strength

15.—(1) Penicillin in the form of a salt with an inorganic base shall not be issued in solid form—

(*a*) in the case of sodium benzylpenicillin, with a potency of less than 1,570 units per milligram;

(*b*) in the case of any other salt of benzylpenicillin, with a potency less than that which may be specified by the licensing authority in relation to the particular salt.

(2) In any other case the minimum permitted potency of a preparation of penicillin shall be such as shall be specified by the licensing authority in relation to the particular preparation.

Number of units for purpose of tests

16.—(1) The number of units of benzylpenicillin for the purpose of the test for freedom from abnormal toxicity shall be not less than 1,000.

(2) The number of units of benzylpenicillin for the purpose of the test for freedom from pyrogenic substances shall be not less than 2,000 per kilogram of the weight of each rabbit used in the test.

(3) The number of units of any other preparation of penicillin for the purpose of the tests for freedom from abnormal toxicity or freedom from pyrogenic substances shall be such as shall be specified by the licensing authority in relation to the particular preparation.

PART IV

SPECIAL PROVISIONS RELATING TO STREPTOMYCIN

Definition

17. In this part of these regulations "streptomycin" means any antimicrobial complex organic base or mixture of such bases produced by *Streptomyces griseus* or other living organism which—

(*a*) yields on hydrolysis with mineral acids the base streptidine (*meso*-1 : 3-diguanido-2 : 4 : 5 : 6-tetrahydroxycyclohexane); and

(*b*) yields on hydrolysis by a 4 per cent. solution of sodium hydroxide the substance maltol (3-hydroxy-2-methyl-γ-pyrone);

and includes any salt or derivative, or salt of a derivative, of any such base, any mixture of any of the substances aforesaid, 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 preparations

18. The standard preparation in relation to a preparation of streptomycin other than dihydrostreptomycin is one of streptomycin sulphate, and the standard preparation in relation to dihydrostreptomycin is one of dihydrostreptomycin sulphate.

Strength

19.—(1) Streptomycin in the form of a salt with an inorganic acid shall not be issued in solid form with a potency of less than 700 units per milligram.

(2) The minimum potency of streptomycin in any other form or of a preparation of streptomycin shall be such as shall be specified by the licensing authority in relation to the particular form or preparation.

Quality

20. Streptomycin in the form of a salt shall produce a clear solution with a pH value lying between 4·5 and 7·0 when the dried substance is reconstituted with purified water in a concentration of 200,000 units per millilitre.

Number of units for purpose of tests

21.—(1) The number of units of streptomycin in the form of a salt with an inorganic acid for the purpose of the test for freedom from abnormal toxicity shall be not less than 750.

(2) The number of units of streptomycin in the form of a salt with an inorganic acid for the purpose of the test for freedom from pyrogenic substances shall be not less than 5,000 units per kilogram of the weight of each rabbit used in the test.

(3) The number of units of any other preparation of streptomycin for the purpose of the tests for freedom from abnormal toxicity or freedom from pyrogenic substances shall be such as shall be specified by the licensing authority in relation to the particular preparation.

Freedom from histamine-like substances

22. Streptomycin shall be free from histamine-like substances. The number of units for the purpose of the test shall be not less than 3,000 units per millilitre of the solution.

PART V

SPECIAL PROVISIONS RELATING TO THE TETRACYCLINES

Definitions

23.—(1) The substances collectively referred to in these regulations as the tetracyclines are the antimicrobial bases which contain the chemical structure naphthacene-2-carboxyamide, hydrogenated to any extent, and having each of the positions 1, 3, 10, 11 and 12 substituted by an hydroxyl or an oxo group. The expression includes the substances described in paragraphs (2), (3) and (4) of this regulation.

(2) Chlortetracycline is an antimicrobial organic base produced by *Streptomyces aureofaciens* and has the chemical structure 7-chloro-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 contains chlorine in the 7-position and any substance the chemical and biological properties of which are identical with or similar to those of any such substance but which is produced by other means.

(3) Tetracycline is an antimicrobial base produced by dechlorination of chlortetracycline 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 an hydroxyl group in the 5-position, and any substance the chemical and biological properties of which are identical with or similar to those of any such substance but which is produced by other means.

(4) Oxytetracycline is an antimicrobial organic base produced by *Streptomyces rimosus* and has the chemical structure 4-dimethylamino-1 : 4 : 4a : 5 : 5a : 6 : 11 : 12a-octahydro-3 : 5 : 6 : 10 : 12 : 12a-hexahydroxy-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 and any substance the chemical and biological properties of which are identical with or similar to those of any such substance but which is produced by other means.

Standard preparations

24. The standard preparation is—

(*a*) in relation to chlortetracycline, one of dry chlortetracycline hydrochloride ;

(*b*) in relation to tetracycline, one of dry tetracycline hydrochloride;

(*c*) in relation to oxytetracycline, one of dry oxytetracycline dihydrate;

(*d*) in relation to any other of the tetracyclines, one of such substance as may be indicated with respect thereto by the licensing authority.

Strength

25. The tetracyclines shall not be issued in solid form—

(*a*) in the case of tetracycline hydrochloride with a potency of less than 930 units per milligram;

(*b*) in the case of tetracycline in any other form, or in the case of any other of the tetracyclines, with a potency less than that which may be indicated by the licensing authority with respect to the particular substance.

Quality

26.—(1) The pH value of a solution of tetracycline in the form of a salt in purified water at a concentration of 10,000 units per millilitre shall lie between 1·8 and 2·8.

(2) The pH value of a solution of any other of the tetracyclines in the form of a salt in purified water at a concentration to be specified by the licensing authority, shall lie between such limits as shall be determined by that authority.

Number of units for purposes of tests

27.—(1) The number of units of chlortetracycline, tetracycline or oxytetracycline for the purpose of the test for freedom from abnormal toxicity shall be not less than 1,000.

(2) The number of units of chlortetracycline, tetracycline or oxytetracycline for the purpose of the test for freedom from pyrogenic substances shall be not less than 5,000 units per kilogram of the weight of each rabbit used in the test.

(3) The number of units of any other of the tetracyclines or any preparation thereof for the purpose of the tests for freedom from abnormal toxicity or freedom from pyrogenic substances shall be such as may be specified by the licensing authority in relation to the particular tetracycline or preparation.

Solvent for oxytetracycline for purposes of tests

28.—(1) For the purpose of testing oxytetracycline for freedom from abnormal toxicity the substance shall be dissolved in any solvent specifically recommended by the licensee for the reconstitution of oxytetracycline or, if no solvent is so recommended, in a buffer solution containing 3·75 grams of glycine and 2·1 grams of sodium hydroxide in 1 litre.

(2) In its application to oxytetracycline, paragraph 6 of schedule 3 to the general regulations shall have effect as if for the reference to pyrogen-free water or physiological saline there were substituted a reference to the solvents described in the preceding paragraph.

Freedom from histamine-like substances

29. The tetracyclines shall be free from histamine-like substances. The number of units for the purpose of the test shall be, in the case of chlortetracycline, tetracycline or oxytetracycline, not less than 3,000 units per millilitre of the solution, and in the case of any other of the tetracyclines or any preparation thereof, such number as may be specified by the licensing authority in relation to the particular tetracycline or preparation.

PART VI

SPECIAL PROVISIONS RELATING TO THE ANTIMICROBIAL PEPTIDES POLYMYXIN B AND COLISTIN AND PREPARATIONS THEREOF

Definitions

30.—(1) Polymyxin B is a mixture of antimicrobial peptides produced by strains of *Bacillus polymyxa* and it yields on hydrolysis with mineral acids only the amino-acids leucine, phenylalanine, threonine and $\alpha : \gamma$ diaminobutyric acid together with 6-methylheptanoic acid and 6-methyloctan-1-oic acid. Polymyxin B includes any salt thereof with an inorganic acid, any derivative thereof and any substance the chemical or biological properties of which are identical with or similar to those of any of the substances aforesaid but which is produced by other means.

(2) Colistin is a mixture of antimicrobial peptides produced by strains of *Bacillus polymyxa* (var. *colistinus*) and it yields on hydrolysis with mineral acids only the amino-acids leucine, threonine and $\alpha : \gamma$ diaminobutyric acid together with 6-methylheptanoic acid and 6-methyloctan-1-oic acid. Colistin includes any salt thereof with an inorganic acid, any derivative thereof and any substance the chemical or 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 preparations

31.—(1) The standard preparation of polymyxin B is one of polymyxin B sulphate.

(2) The standard preparation of colistin is one of colistin sulphate.

(3) The standard preparation of any derivative of polymyxin B or of colistin shall be one of a substance designated by the licensing authority as appropriate to that derivative.

Strength

32.—(1) Polymyxin B sulphate shall not be issued in solid form with a potency of less than 6,400 units per milligram.

(2) Colistin sulphate shall not be issued in solid form with a potency of less than 14,700 units per milligram.

(3) Salts or derivatives of polymyxin B or of colistin, other than those mentioned in paragraphs (1) and (2) of this regulation, shall not be issued in solid form with a potency less than that specified by the licensing authority in relation to the particular salt or derivative.

Quality

33. Salts of polymyxin B or of colistin shall form a clear solution with a pH value lying between 5·0 and 7·0 when the dried substance is reconstituted with purified water at a concentration of 100,000 units per millilitre in the case of polymyxin B or 300,000 units per millilitre in the case of colistin.

Number of units for purposes of tests

34.—(1) For the purpose of the test for freedom from abnormal toxicity the number of units shall be—

(*a*) for polymyxin B or salts or derivatives thereof whose potency is expressed in terms of the standard preparation referred to in regulation 31(1) of these regulations, not less than 600 ;

(*b*) for colistin or salts or derivatives thereof whose potency is expressed in terms of the standard preparation referred to in regulation 31(2) of these regulations, not less than 2,000 ;

(*c*) for salts or derivatives of polymyxin B or of colistin other than those mentioned in sub-paragraphs (*a*) and (*b*) of this paragraph, a number specified by the licensing authority in relation to the salt or derivative.

(2) For the purpose of the test for freedom from pyrogenic substances the number of units per kilogram of the weight of each rabbit used in the test shall be—

(*a*) for polymyxin B or salts or derivatives thereof whose potency is expressed in terms of the standard preparation referred to in regulation 31(1) of these regulations, not less than 10,000 ;

(*b*) for colistin or salts or derivatives thereof whose potency is expressed in terms of the standard preparation referred to in regulation 31(2) of these regulations, not less than 30,000 ;

(*c*) for salts or derivatives of polymyxin B or of colistin other than those mentioned in sub-paragraphs (*a*) and (*b*) of this paragraph, a number specified by the licensing authority in relation to the salt or derivative.

PART VII

SPECIAL PROVISIONS RELATING TO VIOMYCIN

Definition

35. Viomycin is any antimicrobial organic base produced by the growth of *Streptomyces griseus* (var. *purpureus*), which yields on hydrolysis with mineral acids urea, L-serine, $\alpha:\beta$ diaminopropionic acid and 3:6-diaminohexanoic acid, 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

36. The standard preparation of viomycin is one of viomycin sulphate.

Strength

37.—(1) Viomycin in the form of a salt with an inorganic acid shall not be issued in solid form with a potency of less than 685 units per milligram.

(2) The minimum permitted potency of viomycin in any other form or of a preparation of viomycin shall be such as shall be specified by the licensing authority in relation to the particular form or preparation.

Quality

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

Number of units for purposes of tests

39.—(1) The number of units of viomycin for the purpose of the test for freedom from abnormal toxicity shall be not less than 1,000.

(2) The number of units of viomycin for the purpose of the test for freedom from pyrogenic substances shall be not less than 5,000 units per kilogram of the weight of each rabbit used in the test.

Freedom from histamine-like substances

40. Viomycin shall be free from histamine-like substances. The number of units for the purpose of the test shall be not less than 3,000 units per millilitre of the solution.

PART VIII

SPECIAL PROVISIONS RELATING TO BACITRACIN

Definition

41. Bacitracin is any antimicrobial polypeptide produced by certain strains of *Bacillus licheniformis* and by *Bacillus subtilis* (var. *Tracey*), which yields on hydrolysis with mineral acids the amino acids L-cysteine, D-glutamic acid, L-histidine, L-isoleucine, L-leucine, L-lysine, D-ornithine, D-phenylalanine and DL-aspartic acid. The expression includes any salt or derivative of any such polypeptide 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

42. The standard preparation of bacitracin is one of zinc bacitracin.

Strength

43.—(1) Bacitracin shall not be issued in solid form with a potency of less than 54 units per milligram.

(2) The minimum permitted potency of salts or derivatives of bacitracin shall be such as shall be specified by the licensing authority in relation to the salt or derivative.

Quality

44. Bacitracin (other than salts or derivatives thereof) shall form a clear solution with a pH value lying between 5·5 and 7·5 when dissolved in purified water at a concentration of 10,000 units per millilitre.

Number of units for purposes of tests

45.—(1) The number of units of bacitracin for the purpose of the test for freedom from abnormal toxicity shall be not less than 100.

(2) The number of units of bacitracin for the purpose of the test for freedom from pyrogenic substances shall be not less than 300 units per kilogram of the weight of each rabbit used in the test.

(3) The number of units of any other preparation of bacitracin for the purpose of the tests for freedom from abnormal toxicity or freedom from pyrogenic substances shall be such as shall be specified by the licensing authority in relation to the particular preparation.

PART IX

SPECIAL PROVISIONS RELATING TO ERYTHROMYCIN

Definition

46. Erythromycin is any antimicrobial weakly basic substance or mixture of such substances produced by *Streptomyces erythreus* (Waksman) which has the following characteristics:—

(*a*) it forms a dihydrate which has a melting point of about 135°C.;

(*b*) on mild acid hydrolysis it yields the base erythralosamine with a melting point of about 206°C.

The expression includes any salt or derivative, or salt of a derivative, of any such basic substance and any substances the chemical and biological properties of which are identical with or similar to those of any of the said substances but which is produced by other means.

Standard preparation

47. The standard preparation of erythromycin is one of anhydrous erythromycin.

Strength

48.—(1) Erythromycin base shall not be issued in solid form with a potency of less than 880 units per milligram.

(2) The minimum permitted potency for salts, derivatives or salts of derivatives of erythromycin shall be such as shall be specified by the licensing authority in relation to the salt, derivative or salt of the derivative.

Quality

49.—(1) Erythromycin glucoheptonate and erythromycin lactobionate shall form a clear solution with a pH value lying between 6·0 and 7·5 when the dried substance is dissolved in purified water at a concentration of 20,000 units per millilitre.

(2) The quality of other salts, derivatives or salts of derivatives of erythromycin shall be such as shall be specified by the licensing authority in relation to the salt, derivative or salt of the derivative.

Number of units for purposes of tests

50.—(1) The number of units of erythromycin base for the purpose of the test for freedom from abnormal toxicity shall be not less than 2,000.

(2) The number of units of erythromycin base for the purpose of the test for freedom from pyrogenic substances shall be not less than 5,000 units per kilogram of the weight of each rabbit used in the test.

(3) The number of units of any other preparation of erythromycin for the purpose of the tests for freedom from abnormal toxicity or freedom from pyrogenic substances shall be such as shall be specified by the licensing authority in relation to the particular preparation.

Freedom from histamine-like substances

51. Erythromycin shall be free from histamine-like substances. The number of units for the purpose of the test shall be—

(*a*) in the case of erythromycin base, not less than 3,000 units per millilitre of the solution;

(*b*) in the case of any other preparation of erythromycin, such number as may be specified by the licensing authority in relation to the particular preparation.

PART X

SPECIAL PROVISIONS RELATING TO KANAMYCIN

Definition

52. Kanamycin is any antimicrobial substance or mixture of such substances produced by *Streptomyces kanamyceticus*. The expression includes any salt or derivative, or salt of a derivative, of kanamycin and any substance the chemical and biological properties of which are identical with or similar to those of the said substance but which is produced by other means.

Standard preparation

53. The standard preparation of kanamycin is one of kanamycin sulphate.

Strength

54.—(1) Kanamycin monosulphate in solid form shall not be issued with a potency of less than 735 units per milligram.

(2) Any salt or derivative of kanamycin other than that mentioned in paragraph (1) of this regulation shall not be issued in solid form with a potency less than that specified by the licensing authority in relation to the salt or derivative.

Quality

55.—(1) Kanamycin shall not be issued containing more than 5 per cent. of kanamycin B.

(2) Kanamycin shall form a clear solution with a pH value lying between 6·0 and 8·5 when the dried substance is dissolved in purified water at a concentration of 10,000 units per millilitre.

Number of units for purposes of tests

56.—(1) The number of units of kanamycin for the purpose of the test for freedom from abnormal toxicity shall be not less than 1,000.

(2) The number of units of kanamycin for the purpose of the test for freedom from pyrogenic substances shall be not less than 10,000 units per kilogram of the weight of each rabbit used in the test.

Freedom from histamine-like substances

57. Kanamycin shall be free from histamine-like substances. The number of units for the purpose of the test shall be not less than 3,000 units per millilitre of the solution.

PART XI

SPECIAL PROVISIONS RELATING TO VANCOMYCIN

Definition

58. Vancomycin is any mixture of antimicrobial substances produced by *Streptomyces orientalis*. The expression includes any salt or derivative, or salt of a derivative, of vancomycin and any substance the chemical and biological properties of which are identical with or similar to those of the said substance but which is produced by other means.

Standard preparation

59. The standard preparation of vancomycin is one of vancomycin sulphate.

Strength

60.—(1) Vancomycin in the form of a salt with an inorganic acid shall not be issued in solid form with a potency of less than 880 units per milligram.

(2) The minimum permitted potency of vancomycin in any other form or of a preparation of vancomycin shall be such as shall be specified by the licensing authority in relation to the particular form or preparation.

Quality

61. Vancomycin in the form of a salt with an inorganic acid shall form a clear solution with a pH value lying between 2·5 and 4·5 when the dried substance is dissolved in purified water at a concentration of 50,000 units per millilitre.

Number of units for purposes of tests

62.—(1) The number of units of vancomycin for the purpose of the test for freedom from abnormal toxicity shall be not less than 2,000.

(2) The number of units of vancomycin for the purpose of the test for freedom from pyrogenic substances shall be not less than 5,000 units per kilogram of the weight of each rabbit used in the test.

PART XII

SPECIAL PROVISIONS RELATING TO AMPHOTERICIN B

Definition

63. Amphotericin B is any antimicrobial substance or mixture of such substances produced by *Streptomyces nodosus*. The expression includes any derivative, or salt of a derivative, of amphotericin B and any substance the chemical and biological properties of which are identical with or similar to those of the said substance but which is produced by other means.

Standard preparation

64. The standard preparation of amphotericin B is one of amphotericin B.

Strength

65. Amphotericin B shall not be issued with a potency of less than 735 units per milligram.

Quality

66.—(1) Amphotericin B shall not be issued containing more than 5 per cent. of amphotericin A.

(2) Amphotericin B for intravenous use shall be mixed with suitable buffering agents and agents for aiding solubility, and shall have a pH value lying between 7·0 and 8·0 when the mixture is dissolved in purified water at a concentration of 10,000 units per millilitre.

Number of units for purposes of tests

67.—(1) The number of units of amphotericin B for intravenous use for the purpose of the test for freedom from abnormal toxicity shall be not less than 16.

(2) The number of units of amphotericin B for intravenous use for the purpose of the test for freedom from pyrogenic substances shall be not less than 1,000 units per kilogram of the weight of each rabbit used in the test.

Freedom from pyrogenic substances

68.—(1) Where amphotericin B for intravenous use is required in accordance with regulation 10 of these regulations to be tested for freedom from pyrogenic substances, the test prescribed by that regulation and schedule 3 to the general regulations shall be modified by substituting for paragraphs 7 and 8 of the said schedule the following:—

"If no rabbit shows an individual rise in temperature of 1·1°C. or more above the mean value of its respective control temperatures and if the sum of individual rises in temperature of the 3 rabbits does not exceed 3°C. then the sample meets the requirements for freedom from pyrogenic substances. If one or two rabbits show a temperature rise of 1·1°C. or more, or if the sum of temperature rises of the 3 rabbits exceeds 3°C. then the test may be repeated on a further 5 rabbits. If not more than three of the eight rabbits show a temperature rise of 1·1°C. or more and if the sum of the temperature rises does not exceed 8°C. then the sample meets the requirements for freedom from pyrogenic substances.".

PART XIII

SPECIAL PROVISIONS RELATING TO NEOMYCIN

Definition

69. Neomycin is any antimicrobal substance or mixture of such substances produced by *Streptomyces fradiae* which are complex organic bases and which yield on hydrolysis with mineral acids the base neamine, and the expression includes any salt or derivative, or salt of a derivative, of neomycin and any substance the chemical and biological properties of which are identical with or similar to those of any of the said substances but which are produced by other means.

Standard preparation

70. The standard preparation of neomycin is one of neomycin sulphate.

Strength

71.—(1) Neomycin sulphate shall not be issued in solid form with a potency of less than 640 units per milligram.

(2) In any other case the minimum permitted potency of a preparation of neomycin shall be such as shall be determined by the licensing authority.

Number of units for purposes of tests

72.—(1) The number of units of neomycin for the purpose of the test for freedom from abnormal toxicity shall be not less than 100.

(2) The number of units of neomycin for the purpose of the test for freedom from pyrogenic substances shall be not less than 10,000 units per kilogram of the weight of each rabbit used in the test.

Freedom from histamine-like substances

73. Neomycin shall be free from histamine-like substances. The number of units for the purpose of the test shall be not less than 3,000 units per millilitre of the solution.

PART XIV

SPECIAL PROVISIONS RELATING TO THE LINCOMYCINS

Definitions and proper name

74.—(1) The substances collectively referred to in this part of these regulations as the lincomycins are the antimicrobal substances produced by *Streptomyces lincolnensis* (var. *lincolnensis*). These substances are basic amides of hygric acid or of a substituted hygric acid with 6-amino-6, 8-dideoxy-1-thiogalacto-octopyranose or with substituted 6-amino-6, 8-dideoxy-1-thiogalacto-octopyranose. The expression includes the substance described in paragraph (2) of this regulation, any salt or ester or salt of an ester of any lincomycin, 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.

(2) Lincomycin is that substance which incorporates *trans*-L-4-propylhygric acid and a methylthio group in the pyranose ring. Its proper name is " lincomycin ".

Standard preparation

75.—(1) The standard preparation in relation to lincomycin is one of lincomycin hydrochloride.

(2) The standard preparation of any other of the lincomycins is one of such substances as may be indicated with respect thereto by the licensing authority.

Strength

76.—(1) Lincomycin hydrochloride shall not be issued in solid form with a potency of less than 810 units per milligram.

(2) The minimum permitted potency of any other lincomycin or of a preparation of any of the lincomycins shall be such as shall be determined by the licensing authority.

Number of units for purposes of tests

77.—(1) The number of units of lincomycin for the purpose of the test for freedom from abnormal toxicity shall be not less than 2,000.

(2) The number of units of lincomycin for the purpose of the test for freedom from pyrogenic substances shall be not less than 500 units per kilogram of the weight of each rabbit used in the test.

(3) The number of units of any other of the lincomycins or any preparation thereof for the purpose of the test for freedom from abnormal toxicity or freedom from pyrogenic substances shall be such as may be specified by the licensing authority in relation to the particular lincomycin or preparation.

These regulations were made by the aforesaid Joint Committee on 27th April 1966.

Kenneth Robinson,
William Ross,
Wm. J. Morgan,
Members of the Joint Committee

Wilfred Turner,
Clerk to the Joint Committee

EXPLANATORY NOTE

(This Note is not part of the Regulations.)

These regulations, made under Part I of the Therapeutic Substances Act 1956—

(*a*) consolidate, with amendments, the Therapeutic Substances (Manufacture of Antibiotics) Regulations 1963 and 1964;

(*b*) add amphotericin B, the lincomycins, neomycin, vancomycin, certain tetracyclines and derivatives thereof which are intended for parenteral injection to the substances listed in Schedule 1 to the 1956 Act, and make special provisions relating to the added substances, including provisions as to:—

(i) standards of strength and purity; and

(ii) tests for freedom from pyrogenic substances, abnormal toxicity and histamine-like substances.