STATUTORY INSTRUMENTS

1964 No. 1430

THERAPEUTIC SUBSTANCES

The Therapeutic Substances (Manufacture of Antibiotics) Amendment Regulations 1964

Made - - - -	*7th September* 1964
Laid before Parliament	*15th September* 1964
Coming into Operation	*16th September* 1964

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:—

Citation and Commencement

1.—(1) These regulations may be cited as the Therapeutic Substances (Manufacture of Antibiotics) Amendment Regulations 1964 and shall come into operation on 16th September 1964.

(2) The Therapeutic Substances (Manufacture of Antibiotics) Regulations 1963(b) (hereinafter referred to as "the principal regulations") and these regulations may be cited together as the Therapeutic Substances (Manufacture of Antibiotics) Regulations 1963 and 1964.

Interpretation

2.—(1) In these regulations and in the principal regulations the expression "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; and the categories of substances included in schedule 1 to the Therapeutic Substances Act 1956 by regulation 3 of the principal regulations shall be extended accordingly.

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

(3) The Interpretation Act 1889(c) applies to the interpretation of these regulations as it applies to the interpretation of an Act of Parliament.

Inclusion of substances in schedule 1 to the Therapeutic Substances Act 1956

3.—(1) In paragraph (2) of regulation 3 of the principal regulations for the words "Bacitracin and erythromycin" there shall be substituted the words "Bacitracin, erythromycin and kanamycin", and for the word "either" there shall be substituted the word "any".

(2) Paragraph (3) of regulation 3 of the principal regulations shall be renumbered as paragraph (4) and after paragraph (2) of the said regulation 3 there shall be inserted the following paragraph:—

(a) 4 & 5 Eliz. 2. c. 25. (b) S.I. 1963/1451 (1963 II, p. 2500). (c) 52 & 53 Vict. c. 63.

" (3) Colistin and derivatives thereof which are intended for parenteral injection, any substance intended for such injection the chemical or biological properties of which are identical with or similar to those of colistin or any derivatives thereof, and preparations intended for such injection which contain colistin or derivatives thereof or any such substance 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.".

Freedom from abnormal toxicity

4. The following paragraphs shall be substituted for paragraph (2) of regulation 9 of the principal regulations (which prescribes the test for ensuring that an antibiotic is free from abnormal toxicity):—

" (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 grammes. 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.".

Freedom from histamine-like substances

5. The following paragraph shall be substituted for paragraph (2) of regulation 11 of the principal regulations (which prescribes tests for freedom from histamine-like substances):—

" (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 subparagraph (*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.".

Penicillin

6. In regulation 15(1)(*a*) of the principal regulations (which relates to the strength of penicillin) for the word " benzylpenicillin " there shall be substituted the words " sodium benzylpenicillin " and for the expression " 1,100 units " there shall be substituted the expression " 1,600 units ".

Tetracycline

7. For paragraph (1) of regulation 25 of the principal regulations there shall be substituted the following paragraph:—

" (1) Where any of the tetracyclines is in the form of a salt with an inorganic acid, it shall not be issued in solid form with a potency of less than 880 units per milligram in the case of oxytetracycline or 900 units per milligram in the case of chlortetracycline or 950 units per milligram in the case of tetracycline.".

Antimicrobial peptides

8. For part VI of the principal regulations there shall be substituted the following:—

" 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 acid only the amino-acids leucine, phenylalanine, threonine and $\alpha:\gamma$ diaminobutyric acid together with d-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 acid only the amino-acids leucine, threonine and $\alpha:\gamma$ diaminobutyric acid together with d-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 appropriate to that derivative.

Strength

32.—(1) Polymyxin B sulphate shall not be issued in solid form with a potency of less than 6,500 units per milligram.

(2) Colistin sulphate shall not be issued in solid form with a potency of less than 18,000 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 determined by the licensing authority with reference to the molecular structure of the salt or derivative compared with that of polymyxin B sulphate or colistin sulphate as the case may be, or with reference to such other information as may be relevant.

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 determined by the licensing authority.

(2) For the purpose of the test for freedom from pyrogenic substances the number of units per kilogram of the weight of the 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 determined by the licensing authority.".

Viomycin

9. In regulation 39(2) of the principal regulations (which relates to the testing of viomycin) for the expression "2,000 units" there shall be substituted the expression "5,000 units".

Bacitracin

10. In regulation 43(1) of the principal regulations (which relates to the strength of bacitracin) for the expression "50 units" there shall be substituted the expression "55 units".

Kanamycin

11. After regulation 51 of the principal regulations there shall be added the following:—

"PART X

SPECIAL PROVISIONS RELATING TO KANAMYCIN

Definition

52. Kanamycin is the antimicrobial substance 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 is one of kanamycin sulphate.

Strength

54.—(1) Kanamycin monosulphate in solid form shall not be issued with a potency of less than 750 units per milligram.

(2) Salts or derivatives 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 determined by the licensing authority with reference to the molecular structure of the salt or derivative compared with that of kanamycin monosulphate or with reference to such other information as may be relevant.

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 purpose 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 the 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.".

These regulations were made by the aforesaid Joint Committee on 7th September 1964.

Anthony Barber,
Wm. Craig,
Michael Noble,
Members of the Joint Committee.

W. Turner,
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 add colistin and derivatives thereof and kanamycin to the substances listed in schedule 1 to the Therapeutic Substances Act 1956 and amend the Therapeutic Substances (Manufacture of Antibiotics) Regulations 1963—

(*a*) by adding special provisions with regard to colistin and derivatives thereof and kanamycin;

(*b*) by modifying certain testing requirements to bring them into line with recent advances in manufacturing practice; and

(*c*) by introducing a time element for certain test injections made intravenously.