STATUTORY INSTRUMENTS

1963 No. 1451

THERAPEUTIC SUBSTANCES

The Therapeutic Substances (Manufacture of Antibiotics) Regulations 1963

Made - - - -	23*rd August* 1963
Laid before Parliament	2*nd September* 1963
Coming into Operation	16*th September* 1963

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

1. These regulations may be cited as the Therapeutic Substances (Manufacture of Antibiotics) Regulations 1963 and shall come into operation on 16th September 1963.

Interpretation

2.—(1) 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(b) ;

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

(2) 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.

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

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

(a) 4 & 5 Eliz. 2. c. 25. (b) S.I. 1963/1450 (1963 II, p. 2483). (c) 52 & 53 Vict. c. 63.

Inclusion of substances in schedule to Act

3.—(1) Notwithstanding the revocation by the general regulations of the Therapeutic Substances Regulations 1952 and the regulations amending them(a), the following substances, namely, penicillin, streptomycin, chlortetracycline, oxytetracycline, tetracycline, polymyxin B and viomycin, 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, shall continue to be included in schedule 1 to the Act.

(2) Bacitracin and erythromycin which are intended for parenteral injection, and preparations of either of the said substances which are intended for such injection 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 substances are references to that substance 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:

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 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:

Provided that the tests for sterility shall be applied to any antibiotic and to any preparation containing an antibiotic with such modifications (if any)

(a) S.I. 1952/1937, 1953/1172, 1954/1645, 1956/1131, 1957/550 (1952 III, p. 3420; 1953 II, p. 2289; 1954 II, p. 2384; 1956 II, p. 2364; 1957 II, p. 2553).

as the licensing authority consider appropriate in the case of that 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.

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

Freedom from abnormal toxicity

9.—(1) An antibiotic shall be free from abnormal toxicity and if so required by the licensing authority 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 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.

Freedom from pyrogenic substances

10. An antibiotic shall, if so required by the licensing authority, 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.

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 so required by the licensing authority, be tested for freedom from such substances in accordance with this regulation.

(2) A solution of the antibiotic, containing the number of units 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 in a volume corresponding to 1 millilitre per kilogram of the cat's weight. The substance 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.

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 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;

(*c*) 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 particulars shall include the minimum number of units of the antibiotic per milligram of the contents.

(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 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 fuzed 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 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.

(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.

Number of units for purpose of tests

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

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

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 by 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 sulphate 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) In any other case the minimum permitted potency of a preparation of streptomycin shall be such as shall be specified by the licensing authority.

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 for the purpose of the test for freedom from abnormal toxicity shall be not less than 750.

(2) The number of units of streptomycin 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.

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) 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 same 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.

(2) 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 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 any such substance but which is produced by other means.

(3) 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 not produced by other means.

(4) Chlortetracycline, tetracycline and oxytetracycline are in this part of these regulations collectively referred to as the tetracyclines.

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.

Strength

25.—(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 900 units per milligram in the case of chlortetracycline and tetracycline or 870 units per milligram in the case of oxytetracycline.

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

Quality

26.—(1) The pH value of a saturated watery solution of chlortetracycline in the form of a salt with an inorganic acid shall lie between 2·3 and 3·3.

(2) 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.

(3) The pH value of a solution of oxytetracycline in the form of a salt in purified water in a concentration of 10,000 units per millilitre shall lie between 2·3 and 2·9.

Number of units for purposes of tests

27.—(1) The number of units of any of the tetracyclines for the purpose of the test for freedom from abnormal toxicity shall be not less than 1,000, or such number as may be specified by the licensing authority.

(2) The number of units of any of the tetracyclines 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, or such number as may be specified by the licensing authority.

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 grammes of glycine and 2·1 grammes 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 not less than 3,000 units per millilitre of the solution.

PART VI

SPECIAL PROVISIONS RELATING TO POLYMYXIN B

Definition

30. 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

31. The standard preparation is one of polymyxin B sulphate.

Strength

32.—(1) Polymyxin B in the form of a salt with an inorganic acid shall not be issued in a solid form with a potency of less than 6,000 units per milligram, calculated with reference to the substance dried at 60°C. at a pressure not exceeding 5 millimetres of mercury for 3 hours.

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

Quality

33. Polymyxin B in the form of a salt shall produce a clear solution with a pH value lying between 5·0 and 7·0 when the dried substance is dissolved in purified water in a concentration of 2 per cent.

Number of units for purposes of tests

34.—(1) 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 regulation 9(2)(*a*) and (*b*) of these regulations shall have effect as if reference to 24 hours were references to 48 hours.

(2) 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 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 by mineral acids urea, L-serine, $\alpha : \beta$ 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

36. The standard preparation 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 700 units per milligram of the dried substance.

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

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 purposes 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 2,000 units per kilogram of the rabbit's weight.

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 contains the amino acids L-cysteine, D-glutamic acid, L-histidine, L-*iso*leucine, 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 is one of bacitracin.

Strength

43.—(1) Bacitracin shall not be issued in solid form with a potency of less than 50 units per milligram.

(2) The minimum permitted potency for salts or derivatives of bacitracin shall be such as shall be determined by the licensing authority.

Quality

44. Bacitracin 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 rabbit's weight.

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 is one of anhydrous erythromycin.

Strength

48—(1) Erythromycin base shall not be issued in solid form with a potency of less than 900 units per milligram.

(2) The minimum permitted potency for salts, derivatives or salts of derivatives of erythromycin shall be such as shall be determined by the licensing authority.

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 determined by the licensing authority.

Number of units for purpose of tests

50.—(1) The number of units of erythromycin 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 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.

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 not less than 3,000 units per millilitre of the solution.

These regulations were made by the aforesaid Joint Committee on 23rd August 1963.

J. Enoch Powell,
Michael Noble,
Wm. J. Morgan,
Members of the Joint Committee.

B. H. Betts,
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, made under part I of the Therapeutic Substances Act 1956, form part of a comprehensive code relating to the manufacture and importation of therapeutic substances and are to be read in conjunction with the Therapeutic Substances (Manufacture and Importation) General Regulations 1963.

These regulations consolidate with minor amendments those requirements of the Therapeutic Substances Regulations 1952 to 1957 which apply to the following antibiotics, namely, penicillin, streptomycin, tetracyclines, polymyxin B and viomycin.

The regulations also contain provisions with regard to bacitracin and erythromycin which are intended for parenteral injection and preparations of either of the said substances which are intended for parenteral injection, which substances are included in schedule 1 to the 1956 Act.

In relation to these antibiotics, the regulations lay down—

(*a*) tests for sterility and potency ;

(*b*) tests for freedom from abnormal toxicity, pyrogenic substances and histamine-like substances, and

(*c*) requirements as to labelling.