STATUTORY INSTRUMENTS

1963 No. 1454

THERAPEUTIC SUBSTANCES

The Therapeutic Substances (Manufacture of Enzymes and Enzyme Inhibitors) 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 Enzymes and Enzyme Inhibitors) 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;

"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.

Inclusion of substances in schedule to Act

3. Notwithstanding the revocation by the general regulations of the Therapeutic Substances Amendment Regulations 1957(d), the enzymes and enzyme inhibitors to which parts III to VII of these regulations relate, and preparations of any of them, other than heparin which is not intended for parenteral injection and preparations thereof, shall continue to be included in schedule 1 to the Act.

(a) 4 & 5 Eliz. 2. c. 25. (b) S.I. 1963/1450 (1963 II, p. 2483).
(c) 52 & 53 Vict. c. 63. (d) S.I. 1957/550 (1957 II, p. 2553).

PART II

GENERAL PROVISIONS RELATING TO ENZYMES AND ENZYME INHIBITORS AND TO PREPARATIONS THEREOF

Tests for sterility

4. Enzymes and enzyme inhibitors to which the succeeding parts of these regulations apply, and preparations of any of them, shall be tested for sterility in accordance with the general regulations.

Labelling

5.—(1) The particulars specified in regulation 6(1)(*g*) of the general regulations shall be borne both by the container of any such enzyme or enzyme inhibitor or preparation as aforesaid and by the package in which it 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 any such enzyme or enzyme inhibitor or preparation.

(3) The particulars specified in sub-paragraphs (*e*), (*f*), (*h*) and (*i*) of the said regulation 6(1) shall be borne either by the container of any such enzyme or enzyme inhibitor or preparation or by the package in which it is offered for sale.

PART III

SPECIAL PROVISIONS RELATING TO HYALURONIDASE

Definition and proper name

6. Hyaluronidase is a preparation, or derivative, 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".

Standard preparation

7. The standard preparation is one of dried hyaluronidase kept at the National Institute for Medical Research, London.

Unit of standardisation

8. The unit of hyaluronidase for the purpose of these regulations is the 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.

Test for potency

9.—(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 300 units per milligram shall not be issued.

Test for abnormal toxicity

10.—(1) Hyaluronidase shall be tested for abnormal toxicity in accordance with this regulation.

(2) A quantity of hyalurodinase containing not less than 2,500 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 pass 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

11.—(1) Hyaluronidase shall be free from pyrogenic substances to such an extent that, if tested for freedom from any such substances in accordance with the general regulations, it would pass the test.

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

Quality

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

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

(*b*) the solution shall have a pH value between 4·5 and 7·5.

Method of issue

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

Labelling

14.—(1) In addition to the particulars required by regulation 5(2) of these regulations the following particulars shall be borne by a container of hyaluronidase:—

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

(*b*) in the case of a solution, the number of international units per millilitre of the solution;

(*c*) in either case;

(i) a statement that the preparation is not intended for intravenous injection; and

(ii) a statement of the species of animal from which the substance is derived.

(2) In the case of a preparation of hyaluronidase in solution, in addition to the particulars required by regulation 5(3) of these regulations, particulars of the nature of the solvent and of any stabilising agent shall be borne either by the container of the solution or by the package in which the solution is offered for sale.

PART IV

SPECIAL PROVISIONS RELATING TO STREPTOKINASE

Definition and proper name

15. 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

16. 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

17. The standard preparation in relation to streptokinase is one of streptokinase-streptodornase kept at the National Institute for Medical Research, London.

Unit of standardisation

18. 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

19.—(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 HD50 of streptolysin for each 100,000 units of streptokinase. For this purpose an HD50 of streptolysin is that amount of streptolysin in the reduced form which will cause 50 per cent. haemolysis of 5·0 millilitres of a 0·7 per cent. suspension of fresh washed red cells of a rabbit at 37°C. in 30 minutes.

Test for potency

20. 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

21.—(1) Streptokinase shall be tested for freedom from abnormal toxicity in accordance with this regulation.

(2) 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 which have not been previously treated with any material which will interfere with the test; 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

22. In addition to the particulars required by regulation 5(1) and (2) of these regulations, the following further particulars shall be borne by the container of streptokinase:—

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

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

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

PART V

SPECIAL PROVISIONS RELATING TO STREPTODORNASE

Definition and proper name

23. 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 IV

24. Regulations 16 to 22 of these regulations shall apply to streptodornase with the substitution for references to streptokinase (except in the expression " streptokinase-streptodornase ") of references to streptodornase.

PART VI

SPECIAL PROVISIONS RELATING TO STREPTOKINASE-STREPTODORNASE

Definition and proper names

25. 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 IV

26. Regulations 16 to 18 and regulation 19(1) of these regulations shall apply to streptokinase-streptodornase with the substitution for references to streptokinase of references to streptokinase-streptodornase.

Quality

27. Streptokinase-streptodornase shall not contain more than 100 HD50 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 an HD50 of streptolysin is that amount of streptolysin in the reduced form which will cause 50 per cent. haemolysis of 5·0 millilitres of a 0·7 per cent. suspension of fresh washed red cells of a rabbit at 37°C. in 30 minutes.

Test for potency

28. 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

29.—(1) Streptokinase-streptodornase shall be tested for freedom from abnormal toxicity in accordance with this regulation.

(2) 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 which have not been previously treated with any material which will interfere with the test; 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

30. In addition to the particulars required by regulation 5(1) and (2) of these regulations the following further particulars shall be borne by the container of streptokinase-streptodornase:—

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

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

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

PART VII

SPECIAL PROVISIONS RELATING TO HEPARIN AND PREPARATIONS THEREOF

Definitions and proper names

31.—(1) For the purposes of these regulations, heparin is a substance containing 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 preparations

32. The standard preparation of heparin is one kept at the National Institute for Medical Research, London.

Unit of standardisation

33. 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

34. Heparin shall have the following characteristics:—

(*a*) it shall be in the form of a white or creamy-white 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 shall have a pH value being between 6·0 and 8·0;

(*c*) it shall have a specific optical rotation of +35° to +55° when determined on a 4 per cent. w/v watery solution at 20° C.;

(*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*) in the case of a solid preparation it shall contain not less than 110 units per milligram, calculated with reference to the material dried to constant weight at 60° C. at a pressure not exceeding 5 millimetres of mercury.

Test for potency

35. 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 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

36.—(1) Heparin shall, if so required by the licensing authority, be tested for freedom from pyrogenic substances, and in any event shall be free from such substances to such an extent that, if tested for freedom from such substances in accordance with the general regulations, 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

37. In addition to the particulars required by regulation 5(1) and (2) of these regulations, the following further particulars shall be borne by a container of heparin or of any preparation of heparin:—

(*a*) the number of units of heparin or of the preparation contained in the container;

(*b*) in the case of a solid preparation, the number of international units per milligram of the contents;

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

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 enzymes and enzyme inhibitors, namely, hyaluronidase, streptokinase, streptodornase, streptokinase-streptodornase, and heparin and preparations thereof, and in particular provide for:—

(*a*) standards of quality;

(*b*) tests for sterility, potency and freedom from abnormal toxicity; and

(*c*) requirements as to labelling.