STATUTORY INSTRUMENTS

1964 No. 1431

THERAPEUTIC SUBSTANCES

The Therapeutic Substances (Manufacture of Enzymes and Enzyme Inhibitors) 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, Commencement and Interpretation

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

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

(3) 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.

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

Hyaluronidase

2. For paragraph (3) of regulation 9 of the principal regulations there shall be substituted the following paragraph:—

"(3) Hyaluronidase in the solid form with a potency of less than 300 units per milligram calculated with reference to the dried substance shall not be issued."

Streptokinase and Streptokinase-Streptodornase

3. In paragraphs 22(*c*) and 30(*c*) of the principal regulations (which relate to the labelling of containers of streptokinase and streptokinase-streptodornase respectively) for the word "intravenous" there shall be substituted the word "intravascular".

(a) 4 & 5 Eliz. 2. c. 25. (b) S.I. 1963/1454 (1963 II, p. 2521). (c) 52 & 53 Vict. c. 63.

Preparations of Streptokinase intended for intravascular administration

4. After Part IV of the principal regulations there shall be inserted the following part:—

"PART V

SPECIAL PROVISIONS RELATING TO PREPARATIONS OF STREPTOKINASE INTENDED FOR INTRAVASCULAR ADMINISTRATION

Method of preparation

23. Preparations of streptokinase intended for intravascular administration shall be prepared from streptokinase complying with Part IV of these regulations.

Quality

24. Preparations of streptokinase intended for intravascular administration—

(*a*) when dissolved according to the manufacturer's directions, or, if there are no such directions, in physiological saline, shall have a pH value lying between 7·0 and 7·5;

(*b*) shall not contain more than 5 HD 50 of streptolysin for each 100,000 units of streptokinase, and for this purpose an HD 50 of streptolysin shall be the amount specified in regulation 19(2) of these regulations;

(*c*) shall not contain more than 5 units of streptodornase for each 100,000 units of streptokinase when estimated by a method approved by the licensing authority.

Potency

25. Preparations of streptokinase intended for intravascular administration—

(*a*) shall be tested for potency in their final form by measurement of their ability to lyse a preformed clot of fibrinogen containing human plasminogen, by comparison against the standard preparation mentioned in regulation 17 of these regulations, and such potency shall be expressed in terms of the unit of standardisation as defined in regulation 18 of these regulations;

(*b*) shall have a potency of not less than 300 units per microgram of protein nitrogen contained in each preparation.

Test for freedom from pyrogenic substances and for abnormal toxicity

26.—(1) Preparations of streptokinase intended for intravascular administration shall be tested for freedom from pyrogenic substances in accordance with regulation 10 and schedule 3 of the general regulations, and the same test shall be used as a test for freedom from abnormal toxicity.

(2) The quantity of any such preparation for the purpose of any such test shall be 20,000 units per kilogram of the weight of each rabbit used in the test.

(3) The preparation shall be regarded as free from abnormal toxicity if all the rabbits used in the test survive for 7 days without showing significant signs referable to the injected substance.

Labelling

27.—(1) 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 a preparation of streptokinase intended for intravascular administration—

(*a*) in the case of a solid preparation, the minimum number of units per milligram, and the total number of units of streptokinase in the container;

(*b*) in the case of a solution, the number of units per millilitre, and the total number of units of streptokinase in the container;

(*c*) the nature of the buffer and the diluent (if any) in the container;

(*d*) the nature of the vehicle recommended by the manufacturer for dissolving or diluting the preparation;

(*e*) a statement that the preparation is intended for intravascular administration;

(*f*) the maximum period of time after dissolving the preparation after which the solution must not be administered intravascularly.

(2) In addition to the particulars required by regulation 5(3) of these regulations, the following further particulars shall be borne either by the container of a preparation of streptokinase intended for intravascular administration or by the package in which it is offered for sale—

(*a*) the method of administration recommended and any particular precautionary measures;

(*b*) a statement that the material is antigenic.".

5.—(1) Parts V, VI and VII of the principal regulations shall be renumbered Parts VI, VII and VIII respectively.

(2) Regulations 23 to 35 of the said regulations shall be renumbered regulations 28 to 40 respectively.

Heparin

6. For paragraph 39(*b*) (as renumbered) of the principal regulations (which relates to the quality of heparin) there shall be substituted the following paragraph:—

"(*b*) it shall be soluble, at 20°C., in not more than 2·5 parts of water, and in a 1 per cent. w/v solution in water shall have a pH value lying between 6·0 and 8·0;".

7.—(1) After regulation 40 (as renumbered) of the principal regulations there shall be inserted the following regulation:—

"*Freedom from depressor substances*

41.—(1) Heparin shall, if so required by the licensing authority, be tested for freedom from depressor 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 this regulation, it would pass the test.

(2) A quantity of heparin containing not less than 1,000 units of heparin dissolved in one millilitre of water or physiological saline shall be injected intravenously into a cat anaesthetised with chloralose or a suitable barbiturate. The sample shall pass the test if the injection causes a smaller fall of arterial blood pressure than that produced by the injection into the same

cat of a solution of histamine salt containing 0·3 microgram of histamine base in one millilitre of water or physiological saline.".

(2) Regulations 36 and 37 of the principal regulations shall be renumbered regulations 42 and 43 respectively.

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 amend the provisions of the Therapeutic Substances (Manufacture of Enzymes and Enzyme Inhibitors) Regulations 1963 in respect of hyaluronidase and heparin.

They also add to the said 1963 regulations provisions with regard to the strength, quality and purity of preparations of streptokinase intended for intravascular administration.