STATUTORY INSTRUMENTS

1963 No. 1453

THERAPEUTIC SUBSTANCES

The Therapeutic Substances (Manufacture of Dextran Solution) 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 Dextran Solution) 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 dextran solution in schedule to Act

3. Dextran solution is hereby added to schedule 1 to the Act as being a substance the purity or potency of which cannot be adequately tested by chemical means.

PART II
PROVISIONS RELATING TO DEXTRAN SOLUTION

Definition and proper name

4.—(1) Dextran solution is a solution in physiological saline, or other vehicle suitable for intravenous injection, of degraded dextrans derived from the dextrans produced by the fermentation of sucrose by means of a

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

certain strain of *Leuconostoc mesenteroides* (National Collection of Industrial Bacteria, No. 8710), or, if the licensing authority so approve, by means of certain other Leuconostoc species, or by means of purified enzymes derived from such strain or other species. The degraded dextrans are polymers of glucose in which the linkages between the glucose units are almost entirely of the α–1 : 6 type.

(2) The proper name of the solution in physiological saline is "dextran injection" and the proper name of the solution in any other vehicle is "dextran injection" qualified by a word or words approved by the licensing authority as indicating the nature of the preparation.

Method of preparation

5. Dextran solution shall be prepared by a method approved by the licensing authority. The species and strain of Leuconostoc used during such preparation shall be ones which have been approved by the licensing authority.

Strength

6. Dextran solution shall contain either (*a*) not more than 6·5 grammes nor less than 5·5 grammes of dextran in a quantity of 100 millilitres or (*b*) not more than 10·5 grammes nor less than 9·5 grammes in a quantity of 100 millilitres such proportions to be determined by a method approved by the licensing authority.

Quality

7.—(1) Dextran solution shall: —

(*a*) be clear and colourless, or very slightly straw-coloured;

(*b*) have a pH value lying between 5·0 and 7·0 if physiological saline is the vehicle, between 3·5 and 6·5 if dextrose solution is the vehicle and between such limits as the licensing authority may approve if any other vehicle is used;

(*c*) if physiological saline is used as the vehicle, contain not more than 0·95 grammes nor less than 0·85 grammes of sodium chloride in a quantity of 100 millilitres or, if glucose is used as the vehicle, contain not more than 5·25 grammes nor less than 4·75 grammes of glucose in a quantity of 100 millilitres.

(2) Dextran solution shall not contain any bacteriostatic, and shall not contain in a quantity of 100 millilitres:—

(*a*) more than 50 milligrams of sulphated ash, exclusive of that due to added sodium chloride;

(*b*) more than 0·5 milligram of heavy metals, calculated as lead;

(*c*) more than 100 milligrams of reducing sugars, exclusive of sugars added in the vehicle, except when glucose solution is the vehicle;

(*d*) more than 1·0 milligram of total nitrogen;

(*e*) more than 0·02 millilitre of acetone;

(*f*) more than 0·06 millilitre of alcohols.

Test for Sterility

8. Dextran solution shall be tested for sterility in accordance with the general regulations.

Test for freedom from pyrogenic substances and for abnormal toxicity

9.—(1) Dextran solution shall be tested for freedom from pyrogenic substances in accordance with the general regulations, and the test shall be used also as a test for abnormal toxicity.

(2) The quantity of dextran solution for the purpose of the said test shall be not less than 10 millilitres per kilogram of the rabbit's weight.

(3) The substance shall be regarded as free from toxicity if none of the animals exhibits signs of distress during the period of the said test.

Test for freedom from abnormal antigenicity

10.—(1) Dextran solution shall be tested for abnormal antigenicity in accordance with this regulation.

(2) Into the peritoneal cavity of each of 6 healthy adult guinea pigs, each of which weighs not less than 250 grammes and has not previously been treated with any material which will interfere with the test, 0·5 millilitre of dextran solution shall be injected on 3 occasions at intervals of 2 days. A further 0·2 millilitre shall be injected intravenously into each of 3 of the guinea pigs 14 days after the first intraperitoneal injection, and into each of the other 3 guinea pigs 21 days after the first intraperitoneal injection. The guinea pigs shall be observed for 30 minutes after each intravenous injection and 24 hours later. The sample shall pass the test if the guinea pigs show no signs of anaphylaxis such as coughing, bristling or respiratory distress.

Molecular size of dextrans

11. The range of molecular size of the dextrans used to prepare dextran solution shall be such that, when tested by methods approved by the licensing authority, the following requirements are satisfied :—

(*a*) the intrinsic viscosity of the dextrans shall not be more than 0·35 or less than 0·29, or within a range approved by the licensing authority ;

(*b*) the intrinsic viscosity of a fraction which contains as nearly as possible 10 per cent. of the dextrans, but not more than that quantity, and which has been prepared in such a way that it contains the largest molecules shall be not more than 0·50, or a value approved by the licensing authority ;

(*c*) the mean dextran content of all the urine samples collected within 48 hours after the intravenous injection into each of 2 rabbits of 20 millilitres of the solution per kilogram of the rabbit's weight shall not exceed 25 per cent. of the dextrans injected, or a value approved by the licensing authority.

Relative viscosity

12. Relative viscosities for the purposes of regulation 11(*a*) and (*b*) of these regulations shall be calculated by relating the flow times of solutions of dextrans in water or physiological saline, determined at 37°C. in a viscometer (British Standard 188: 1957), to those of water or saline respectively. In the case of solutions of dextran in glucose, the relative viscosities shall be determined before the addition of the glucose.

Labelling

13.—(1) The particulars specified in regulation 6(1)(*g*) of the general regulations shall be borne both by the container of dextran solution 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 dextran solution.

(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 dextran solution or by the package in which it is offered for sale.

(4) The following further particulars shall be borne by the container of dextran solution :—

(*a*) the volume of the contents ;

(*b*) the percentage concentration w/v of the dextrans and the nature of the vehicle ;

(*c*) a statement that the contents should not be used if they are cloudy or if there is a deposit ;

(*d*) the identity of the strain of Leuconostoc species used during the preparation of the substance.

(5) Neither the container of dextran solution nor the package in which it is offered for sale shall state that dextran solution is a substitute for whole human blood.

(6) For the purposes of sub-paragraph (*f*) of the said regulation 6(1) the date on which the manufacture of a container of dextran solution is completed shall be such date as the licensing authority may approve.

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 relate to dextran solution, and provide for :—

(*a*) standards of strength and quality ;

(*b*) tests for sterility and for freedom from pyrogenic substances, abnormal toxicity and abnormal antigenicity ; and

(*c*) requirements as to labelling.

Dextran solution is added to the substances listed in schedule 1 to the 1956 Act.