STATUTORY INSTRUMENTS

1966 No. 503

THERAPEUTIC SUBSTANCES

The Therapeutic Substances (Manufacture of Preparations of Human Blood) Amendment Regulations 1966

Made - - - -	*27th April* 1966
Laid before Parliament	*5th May* 1966
Coming into Operation	*1st June* 1966

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, Commencement and Interpretation

1.—(1) These regulations may be cited as the Therapeutic Substances (Manufacture of Preparations of Human Blood) Amendment Regulations 1966 and shall come into operation on 1st June 1966.

(2) The Therapeutic Substances (Manufacture of Preparation of Human Blood) Regulations 1963(b) (hereinafter referred to as "the principal regulations") and these regulations may be cited together as the Therapeutic Substances (Manufacture of Preparations of Human Blood) Regulations 1963 and 1966.

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

Amendment of the Therapeutic Substances (Manufacture of Preparations of Human Blood) Regulations 1963

2. The Therapeutic Substances (Manufacture of Preparations of Human Blood) Regulations 1963 shall be amended as follows:—

(*a*) in regulation 5 (which relates to the withdrawal of blood) the present regulation shall be numbered paragraph (1), and there shall be added the following paragraph—

> "(2) Where blood intended for the manufacture of a preparation of human blood is obtained by any method other than a method involving a withdrawal operation, the conditions under which such blood is obtained, transported, stored and processed shall be approved by the licensing authority.";

(a) 4 & 5 Eliz. 2. c. 25. (b) S.I. 1963/1456 (1963 II, p. 2539). (c) 52 & 53 Vict. c. 63.

(*b*) for the heading to part VII there shall be substituted—

"SPECIAL PROVISIONS RELATING TO HUMAN FIBRIN AND HUMAN THROMBIN";

(*c*) in regulation 28 (which relates to definitions and proper names) paragraphs (2) and (4) shall be omitted and paragraph (3) shall be renumbered paragraph (2);

(*d*) in regulation 29 (which relates to quality, storage and labelling) for the words "Human fibrin, fibrinogen, thrombin and gamma globulin," there shall be substituted the words "Human fibrin and human thrombin,";

(*e*) parts VIII and IX and regulations 30 to 38 (which relate to human serum albumin and 131-radioiodinated human serum albumin) shall be renumbered parts XI and XII and regulations 45 to 53 respectively;

(*f*) after regulation 29 there shall be inserted the following regulations—

"PART VIII

SPECIAL PROVISIONS RELATING TO HUMAN FIBRINOGEN

Definition and proper name

30.—(1) Human fibrinogen is the soluble protein constituent of liquid human plasma which, on the addition of human thrombin, is transformed into human fibrin. Its proper name is "human fibrinogen".

(2) Human fibrinogen has a molecular weight of 330,000 to 350,000.

Preparation

31. Human fibrinogen shall be prepared from liquid human plasma by a method approved by the licensing authority.

Quality

32.—(1) Human fibrinogen shall be a white powder or friable solid, soluble in water, and when dried for a period of 24 hours at a temperature of 20°C. to 25°C. over phosphorus pentoxide at a pressure not exceeding 0·02 millimetres of mercury, shall not lose more than 0·5 per cent. in weight.

(2) Human fibrinogen shall—

(*a*) when tested by precipitation tests with specific antisera be shown to contain only human plasma proteins;

(*b*) contain not less than 65 per cent. of protein material which coagulates when thrombin is added;

(*c*) when tested by moving boundary electrophoresis in a solution of phosphate buffer at pH 8·6 and of ionic strength 0·2, show the characteristic mobility of human fibrinogen;

(*d*) when in solution made according to the instructions issued by the manufacturer, have a pH value lying between 6·5 and 7·5.

Test for freedom from pyrogenic substances

33.—(1) Human fibrinogen shall, if the licensing authority so require, be tested for freedom from pyrogenic substances in accordance with this regulation and 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.

(2) Where human fibrinogen is required in accordance with this regulation to be tested for freedom from pyrogenic substances, the test prescribed by schedule 3 to the general regulations shall be modified by substituting for paragraph 6(*a*) of the said schedule the following:—

"(*a*) injecting intravenously into each of the 3 rabbits in the group 10 millilitres per kilogram of the rabbit's weight of a solution prepared by dissolving fibrinogen in a volume of pyrogen-free water equal to the original volume of the fibrinogen solution before drying;".

Labelling

34.—(1) In addition to the particulars required by regulation 9(1) and (2) of these regulations, the following further particulars shall be borne by the container of human fibrinogen:—

(*a*) the particulars specified in regulation 6(1)(*g*) of the general regulations;

(*b*) the amount of human fibrinogen in the container and the nature and volume of solvent necessary to reconstitute the material to its original volume;

(*c*) the content of sodium chloride and other salts in the material;

(*d*) a statement to the effect that the solution must be used immediately following reconstitution and filtered when intended for intravascular use.

(2) In addition to the particulars required by regulation 9(2) of these regulations, the particulars specified in regulation 6(1)(*h*) of the general regulations shall be borne either by the container of human fibrinogen or by the package in which it is offered for sale.

PART IX

SPECIAL PROVISIONS RELATING TO PLASMA PROTEIN FRACTION

Definition and proper name

35. Plasma protein fraction is a preparation of the proteins of liquid human plasma containing albumin and other heat stable proteins which, when in the form of a solution, exerts a colloid osmotic pressure equivalent to that of pooled liquid human plasma of protein concentration 5·2 per cent. w/v. Its proper name is "plasma protein fraction".

Preparation

36. During preparation plasma protein fraction shall be heated to and kept at a temperature of 60°C. ± 0·5°C. for not less than 10 hours. Any stabilising agent added shall be approved by the licensing authority.

Quality

37. Plasma protein fraction shall—

(*a*) when tested by precipitation with specific antisera, be shown to contain only human plasma proteins;

(*b*) when tested by moving boundary electrophoresis in diethyl barbituric acid and its sodium salt at pH 8·6 and of ionic strength 0·1, contain not less than 85 per cent. of protein having the mobility characteristic of human serum albumin;

(*c*) have a total protein concentration of not less than 4·3 grams per 100 millilitres and comply with such test for denatured protein as the licensing authority may approve;

(*d*) have a total sodium concentration lying between 140 and 160 milli-equivalents per litre, a total potassium concentration not exceeding 2 milli-equivalents per litre, and a citrate ion concentration (expressed as citric acid) not exeeeding 2·5 grams per litre;

(*e*) in the case of a liquid preparation and in the case of a reconstituted solid preparation, have a pH value lying between 6·7 and 7·3;

(*f*) in the case of a solid preparation—

(i) not lose more than 0·5 per cent. in weight when dried for a period of 24 hours at a temperature of 20°C. to 25°C. over phophorus pentoxide at a pressure not exceeding 0·02 millimetres of mercury; and

(ii) dissolve completely in not more than 10 minutes when reconstituted to its original volume.

Storage

38. Plasma protein fraction shall be stored at a temperature lying between 5°C. and 20°C. and during storage shall be protected from light.

Labelling

39.—(1) In addition to the particulars required by regulation 9(1) and (2) of these regulations, the following further particulars shall be borne by the container of plasma protein fraction:—

(*a*) the particulars specified in regulation 6(1)(*g*) of the general regulations;

(*b*) the volume or weight of material in the container;

(*c*) the concentration of protein expressed in grams per litre (g/l), the concentrations of sodium and potassium expressed as milli-equivalents per litre (m. eq/l) and the concentration of citrate ions expressed as citric acid in grams per litre (g/l);

(*d*) the nature and concentration of any other substance in the container;

(*e*) in the case of a solid preparation the nature and volume of solvent necessary to reconstitute the material to its original volume;

(*f*) a statement to the effect that the contents should not be used if the solution is turbid or contains a deposit.

(2) In addition to the particulars required by regulation 9(2) of these regulations, the particulars specified in regulation 6(1)(*h*) of the general regulations shall be borne either by the container of plasma protein fraction or by the package in which it is offered for sale.

PART X

SPECIAL PROVISIONS RELATING TO HUMAN GAMMA G-IMMUNOGLOBULIN

Definition and proper name

40. Human gamma G-immunoglobulin is the soluble protein which is derived from human plasma or serum. It contains the gamma G globulins of normal human plasma or serum together with smaller amounts of other

plasma or serum proteins. Its proper name is " human gamma G-immunoglobulin ".

Preparation

41. Human gamma G-immunoglobulin shall be prepared from human plasma or human serum by methods approved by the licensing authority.

Quality

42. Human gamma G-immunoglobulin shall—

(*a*) when tested by precipitation tests with specific antisera, be shown to contain only human serum proteins;

(*b*) when tested by moving boundary electrophoresis in diethyl barbituric acid and its sodium salt at pH 8·6 and of ionic strength 0·1, contain not less than 90 per cent. of material moving as the slowest moving component of normal human plasma;

(*c*) when a 1 per cent. solution in phosphate buffer at a pH value lying between 6·0 and 8·0 and of ionic strength not less than 0·2, is examined in an ultracentrifuge, contain not less than 80 per cent. of protein having a sedimentation coefficient of approximately 7, not more than 15 per cent. having a sedimentation coefficient of approximately 10, not more than 5 per cent. having a sedimentation coefficient of between 3 and 5, and not more than traces having a sedimentation coefficient of approximately 19;

(*d*) in the case of a solid preparation—

(i) not lose more than 0·5 per cent. in weight when dried for a period of 24 hours at a temperature of 20°C. to 25°C. over phosphorous pentoxide at a pressure not exceeding 0·02 millimetres of mercury; and

(ii) dissolve completely in not more than 10 minutes when reconstituted to its original volume.

Stability

43. Human gamma G-immunoglobulin shall, if the licensing authority so require, be stored at a temperature of 37°C. for not less than 1 month and shall, at the end of that period, be subjected to the test prescribed by regulation 42(*c*) of these regulations. The material shall not show an increase in the proportion of protein content having a sedimentation coefficient of between 3 and 5.

Labelling

44.—(1) In addition to the particulars required by regulation 9(1) and (2) of these regulations, the following further particulars shall be borne by the container of human gamma G-immunoglobulin:—

(*a*) the particulars specified in regulation 6(1)(*g*) of the general regulations;

(*b*) the volume or weight of material in the container;

(*c*) the nature and concentration of any added substances in the container;

(*d*) in the case of a solid preparation the nature and volume of solvent necessary to reconstitute the material to its original volume;

(*e*) a statement to the effect that the material must not be given by intravascular injection.

(2) In addition to the particulars required by regulation 9(2) of these regulations, the following further particulars shall be borne either by the container of human gamma G-immunoglobulin or by the package in which it is offered for sale:—

(*a*) the particulars specified in regulation 6(1)(*h*) of the general regulations;

(*b*) details of any specific antibody concentrations claimed by the manufacturer, expressed in terms of international units per millilitre or international units per milligram.".

These regulations were made by the aforesaid joint Committee on 27th April 1966.

Kenneth Robinson,
William Ross,
Wm. J. Morgan,
Members of the Joint Committee.

Wilfred Turner,
Clerk to the Joint Committee.

EXPLANATORY NOTE

(*This Note is not part of the Regulations.*)

These regulations, made under Part I of the Therapeutic Substances Act 1956, amend the Therapeutic Substances (Manufacture of Preparations of Human Blood) Regulations 1963 by including a provision as to blood obtained otherwise than by withdrawal, and by adding special provisions relating to human fibrinogen, plasma protein fraction and human gamma G-immunoglobulin, including provisions as to quality, freedom from pyrogenic substances and labelling.