THERAPEUTIC SUBSTANCES

The Therapeutic Substances Amendment Regulations, 1948

1948 No. 2418

Made - - - -	*4th November*, 1948
Laid before Parliament	*8th November*, 1948
Coming into Operation	*1st December*, 1948

M.H. 107267.

The Joint Committee constituted under subsection (1) of section 4 of the Therapeutic Substances Act, 1925 (in these regulations called " the Act "), in exercise of the powers conferred on them by sections 1 and 5 of the Act, after consultation with the Advisory Committee constituted under subsection (2) of section 4 of the Act, hereby make the following regulations:— 15 & 16 Geo. 5. c. 60.

PART I

Preliminary

1.—(1) These regulations may be cited as the Therapeutic Substances Amendment Regulations, 1948, and the Therapeutic Substances Regulations, 1931 to 1946, and these regulations shall be read as one and may be cited together as the Therapeutic Substances Regulations, 1931 to 1948.

(2) These regulations shall come into operation on the first day of December, 1948.

2.—(1) In these regulations—

" the principal regulations " means the Therapeutic Substances Regulations, 1931(**a**), as amended by the Therapeutic Substances Amendment Regulations, 1935(**b**), the Therapeutic Substances (Amendment) Regulations, 1937(**c**), the Therapeutic Substances Amendment Regulations, 1939(**d**), the Therapeutic Substances Amendment Regulations, 1944(**e**), and the Therapeutic Substances Amendment Regulations, 1946(**f**);

" the regulations of 1946 " means the Therapeutic Substances Amendment Regulations, 1946.

(2) The Interpretation Act, 1889(**g**), applies to the interpretation of these regulations as it applies to the interpretation of an Act of Parliament.

3. For a period of nine months after these regulations come into operation the requirements of these regulations in regard to the proper name and labelling of any therapeutic substance shall be deemed to be complied with if the corresponding provisions hereby revoked are complied with.

(**a**) S.R. & O. 1931 (No. 633) p. 1311. (**b**) S.R. & O. 1935 (No. 580) p. 1668.
(**c**) S.R. & O. 1937 (No. 767) p. 2294. (**d**) S.R. & O. 1939 (No. 1395) II, p. 3172.
(**e**) S.R. & O. 1944 (No. 370) I, p. 1009. (**f**) S.R. & O. 1946 (No. 467) I, p. 1590.
(**g**) 52 & 53 Vict. c. 63.

PART II

Miscellaneous amendments of principal regulations

4.—(1) In paragraph (1) of regulation 2 of the principal regulations (which contains definitions) the following definition of penicillin shall be inserted in place of the definition thereof inserted by regulation 3 of the Therapeutic Substances Amendment Regulations, 1947(a):—

" ' penicillin ' means any antimicrobial acid which—

(*a*) may be shown on chemical and physical examination to contain in its structure a fused thiazolidine beta-lactam nucleus; or

(*b*) loses its antimicrobial activity on hydrolysis by the penicillinases which destroy the antimicrobial activity of the substance known as ' International Standard penicillin ', and accordingly may, without chemical and physical examination, be presumed to contain in its structure such a nucleus as aforesaid;

and includes any salt or derivative obtained from any such acid, and any solution containing any such acid or salt or derivative."

(2) The following definition shall be inserted at the end of paragraph (1) of the said regulation 2:—

" ' preparations of human blood ' includes any serum or plasma made from human blood, any protein or other substance separated from human blood and any dried product prepared from any such serum, plasma, protein or other substance ".

5. In paragraph (1) of regulation 10 of the principal regulations (which provides as to the labelling of the container of a therapeutic substance) for the words " of a therapeutic substance shall bear a label " there shall be substituted the words " in which a therapeutic substance is sold or offered for sale shall bear a label affixed by the manufacturer of the substance ", and after the word " ink " there shall be inserted the words " or shall have indelibly marked in the body thereof ".

6. The provisions of Division (B) of Part II of the Second Schedule to the principal regulations (which relates to diphtheria prophylactic) are hereby revoked, without prejudice to anything duly done or suffered thereunder, and the provisions set forth in Part I of the schedule to these regulations shall be inserted in the said Second Schedule in the place thereof.

7.—(1) In Division (A) of Part IV of the Second Schedule to the principal regulations—

(*a*) in sub-paragraph (1) of paragraph 2 (which provides that a serum for which no potency test is prescribed may be issued only in certain forms, including that of a solution of the purified serum proteins containing the specific antibodies) there shall be inserted after the word " proteins " the words " or derivatives thereof ";

(*b*) at the end of the said sub-paragraph there shall be added the following provision:—

" or (*c*) a dry substance prepared from a preparation in either of the above-mentioned forms ".

(2) The provisions of Divisions (B) to (K) of Part IV of the said Second Schedule (which contain provisions relating to various antitoxins and antisera) are hereby revoked, without prejudice to anything duly done or suffered thereunder, and the provisions set forth in Part II of the schedule to these regulations shall be inserted in the said Second Schedule in the place thereof.

(a) S.R. & O. 1947 (No. 1821) I, p. 2102.

8.—(1) The following provision shall be substituted for head (*a*) of sub-paragraph (3) of paragraph 2 of Part I of the Third Schedule to the principal regulations:—

" (*a*) *Tests for maximum toxicity.*—Several separate containers from each finished batch shall be tested for toxicity by a method approved by the licensing authority, and no batch shall be issued which shows a toxicity greater than that of the standard preparation."

(2) Paragraph 3 of Part IV of the said Schedule (which provides as to the carrying out of the tests for maximum toxicity and therapeutic potency) is hereby revoked.

PART III

Addition of substances to Schedule to Act

9.—(1) Penicillin which is intended for parenteral injection, preparations containing penicillin which are intended for such injection, and preparations of human blood shall be added to the Schedule to the Act as being substances the purity or potency of which cannot be adequately tested by chemical means.

(2) Organic substances having the specific biological action of curare on neuro-muscular transmission, and preparations thereof, being substances or preparations the purity or potency of which cannot be adequately tested by chemical means, shall be added to the Schedule to the Act.

PART IV

Penicillin

10. In the proviso to paragraph (1) of regulation 9 of the principal regulations(a) (under which a container of penicillin need not be of glass) after the word " penicillin " there shall be inserted the words " or of any preparation containing penicillin ".

11. At the end of regulation 7 of the regulations of 1946 (which exempts penicillin from the requirement that the label shall contain a statement that the substance has passed a test for maximum toxicity) there shall be added the words " or to any preparation containing penicillin ".

12. In the proviso to regulation 12 of the principal regulations(b) (which enables the tests applicable to penicillin to be applied before all manufacturing processes are completed) for the words " penicillin in any form " there shall be substituted the words " any preparation containing penicillin ", and for the words " penicillin in that form " there shall be substituted the words " preparations of that kind ".

13.—(1) At the end of paragraph (*g*) of regulation 15 of the principal regulations(c) (which makes tests of sterility applicable to penicillin) there shall be inserted the words " and preparations containing penicillin ".

(2) In paragraph (i) of the proviso to the said regulation(c) (which provides for the application of the said tests, in certain cases, with modifications), for the words " and penicillin " there shall be substituted the words " penicillin and preparations containing penicillin ".

(a) *See* S.R. & O. 1946 (No. 467) I, p. 1590, reg. 6.
(b) *See* S.R. & O. 1946 (No. 467) I, p. 1590, reg. 8.
(c) *See* S.R. & O. 1946 (No. 467) I, p. 1590, reg. 9.

14. The Seventh Schedule to the principal regulations(**a**) shall have effect with the following amendments:—

(*a*) in paragraph 1 (which prescribes the proper name of penicillin) there shall be inserted after the word " penicillin " where it first occurs the words " or a preparation containing penicillin ", for the words " followed by " there shall be substituted the words " together with ", and at the end there shall be inserted the words " or " penicillin (oil-wax) suspension " ";

(*b*) at the end of sub-paragraph (1) of paragraph 4 (which requires the potency of penicillin to be expressed in units per c.c. in the case of solutions) there shall be added the words " or suspensions ";

(*c*) in sub-paragraph (2) of paragraph 4 (which requires that penicillin with a potency, in the case of a solid, of less than 300 units per milligramme, or, in the case of a solution, of less than 2,000 units per c.c., shall not be issued) for the words " 300 units per milligramme " there shall be substituted the words " 900 units per milligramme " and the words " or, in the case of a solution, of less than 2,000 units per c.c." shall be omitted;

(*d*) in paragraph 7 (which provides as to the materials of which a container of penicillin is to be made) after the word " penicillin " where it first occurs there shall be inserted the words " or of a preparation containing penicillin ";

(*e*) in paragraph 8 (which requires in the case of mixtures containing penicillin that the label on the container shall state the minimum number of units of penicillin per gramme of the mixture in the case of penicillin in solid form or per c.c. thereof in the case of a solution) for the word " penicillin " where it last occurs there shall be substituted the words " a substance ", and at the end there shall be inserted the words " or a suspension ".

PART V

Preparations of human blood

15. At the end of paragraph (3) of regulation 10 of the principal regulations (which by sub-paragraph (*b*) requires the date of manufacture to be stated on the label or wrapper of the container of a therapeutic substance) there shall be added the following proviso:—

" Provided that sub-paragraph (*b*) of this paragraph shall not apply to preparations of human blood other than whole human blood ".

16. Paragraph (iii) of the proviso to regulation 15 of the principal regulations(**b**) (which paragraph excepts certain substances from the sterility tests required by that regulation) shall have effect as if after the word " lymph " there were inserted the words " or to any preparation of human blood ".

17. The provisions set forth in Part III of the Schedule to these regulations, being provisions relating to preparations of human blood, shall be inserted in the principal regulations after the Seventh Schedule thereto.

(**a**) *See* S.R. & O. 1946 (No. 467) I, p. 1590, **reg. 10.**
(**b**) *See* S.R. & O. 1944 (No. 370) p. 1009, reg. 3.

PART VI

Tubocurarine, etc.

18.—(1) In regulation 15 of the principal regulations (which requires sterility tests to be made in the case of the substances therein mentioned) after paragraph (*g*) there shall be inserted the following paragraph:—

" (*h*) organic substances having the specific biological action of curare on neuro-muscular transmission, and preparations thereof."

(2) The following proviso shall be inserted at the end of regulation 16 of the principal regulations:—

" Provided that paragraph (*a*) of this article shall not apply to *d*-tubocurarine chloride."

19. The provisions set forth in Part IV of the Schedule to these regulations, being provisions relating to substances having the specific biological activity of curare on neuro-muscular transmission, shall be inserted in the principal regulations after the Eighth Schedule thereto.

PART VII

Revocation

20. Regulation 4, and paragraph (2) of regulation 5, of the regulations of 1946(**a**), and the Therapeutic Substances Amendment Regulations, 1947(**b**), are hereby revoked, without prejudice to anything duly done or suffered or any right, privilege, obligation or liability acquired, accrued or incurred thereunder.

SCHEDULE

PART I

Provisions substituted for Division (B) of Part II of the Second Schedule to the Principal Regulations.

(B)

Provisions Applicable to Diphtheria Prophylactic

(1)

General Provisions Applicable to Diphtheria Prophylactic

Definitions and Proper Names

1. Diphtheria Prophylactic is diphtheria toxin (that is to say, the sterile filtrate from a culture on or in a suitable culture medium of *Corynebacterium diphtheriae*), or material derived therefrom, of which either—

(*a*) the specific toxicity has been completely removed by the action of chemical substances; or

(*b*) the specific toxicity has been reduced to a low level by the action of chemical substances and the remaining toxicity has been completely removed by the addition of an appropriate quantity of diphtheria antitoxin.

The proper name of a preparation in relation to which no special provisions are hereinafter made applicable, or of a mixture of diphtheria prophylactic with another therapeutic substance, is " Diphtheria Prophylactic " together with such other words or abbreviations as may be approved by the licensing authority as descriptive of that preparation.

(**a**) S.R. & O. 1946 (No. 467) I, p. 1590.
(**b**) S.R. & O. 1947 (No. 1821) I, p. 2102.

Quality

2. No batch of Diphtheria Prophylactic shall be issued until it is an efficient immunising antigen.

Tests for toxicity

3. 5 c.c. of the preparation, or, if a different volume is specified in this Division or approved by the licensing authority in relation to any preparation, the volume so specified or approved, shall be injected subcutaneously, or intraperitoneally into each of not less than five normal guinea-pigs, each weighing from 250 to 350 grammes. The injection must not cause the death from specific intoxication of any of the guinea-pigs within thirty days following the injection.

Definition of Schick test dose and flocculation equivalent

4.—(1) For the purpose of testing Diphtheria Prophylactic for minimum potency as an immunising antigen, a Schick test dose is a quantity of diphtheria toxin which contains the one-thousandth part of a specific flocculation equivalent (0.001 Lf) and such an amount of free toxin, that, when one-twentieth of this quantity (0.00005 Lf) or less is injected intracutaneously into normal guinea-pigs, they will, when examined 48 hours after injection, regularly exhibit local reactions of the Schick positive type.

(2) For the purpose of a test of Diphtheria Prophylactic involving the determination of a specific flocculation equivalent, the diphtheria antitoxin used shall be a suitable sample which has been standardised, by comparative tests, in terms of the Preparation of Diphtheria Antitoxin (Reagent for the Flocculation Test) supplied by the National Institute for Medical Research, London.

(2)

Special Provisions Applicable to Diphtheria Prophylactic (Formol Toxoid)

Definition and Proper Name

1. Diphtheria Prophylactic (Formol Toxoid) is diphtheria toxin, or material derived therefrom, the specific toxicity of which has been completely removed by the action of formaldehyde. The proper name of the substance is " Diphtheria Prophylactic F.T."

Tests for minimum potency as an immunising antigen

2. 0.05 c.c. of the Diphtheria Prophylactic F.T. diluted with physiological salt solution to a volume of 1 c.c. shall be injected into each of ten normal guinea-pigs on each of two occasions separated by an interval of not more than four weeks. The guinea-pigs shall be tested for immunity to diphtheria toxin at a date not later than three weeks after the second injection. The test for immunity shall be made by the intracutaneous injection into each guinea-pig of 0.2 c.c. of a dilution of diphtheria toxin containing the equivalent of 5 Schick test doses (0.005 Lf). If, when examined 48 hours after injection, more than two of the ten guinea-pigs exhibit a positive Schick reaction, the batch shall be treated as insufficiently potent and shall not be issued.

(3)

Special Provisions Applicable to Diphtheria Prophylactic (Alum Precipitated Toxoid)

Definition and Proper Name

1. Diphtheria Prophylactic (Alum Precipitated Toxoid) is a preparation made by adding a solution of alum in suitable quantity to Diphtheria Prophylactic F.T., and collecting, adequately washing and resuspending the resulting precipitate in physiological salt solution. The proper name of the substance is " Diphtheria Prophylactic A.P.T."

Tests for specific combining power with diphtheria antitoxin

2. Diphtheria Prophylactic A.P.T. shall be tested for its specific combining power with diphtheria antitoxin by dissolving the suspended precipitate of alum toxoid by the addition of sodium citrate or other suitable salt. 1 c.c. of the final preparation must represent not less than 50 specific flocculation equivalents (50 Lf) of the toxoid used in its preparation.

Tests for minimum potency as an immunising antigen

3. A quantity of Diphtheria Prophylactic A.P.T. corresponding to one flocculation equivalent (1 Lf) and diluted with physiological salt solution to 1 c.c. shall be injected into each of ten normal guinea-pigs on each of two occasions separated by an interval of not more than four weeks. The guinea-pigs shall be tested for immunity at a date not later than three weeks after the second injection, by determining the diphtheria antitoxin content of the serum of each guinea-pig separately. If the geometric mean of the antitoxin contents so determined is less than 2 units the batch of Diphtheria Prophylactic A.P.T. shall be treated as insufficiently potent and shall not be issued.

Test for toxicity

4. The volume of Diphtheria Prophylactic A.P.T. to be used for the purpose of the tests for toxicity shall be 1 c.c.

(4)

Special Provisions Applicable to Diphtheria Prophylactic (Toxoid-Antitoxin Mixture)

Definition and Proper Name

1. Diphtheria Prophylactic (Toxoid-Antitoxin Mixture) is a preparation made from diphtheria toxin, the specific toxicity of which has been either completely removed by the action of formaldehyde or has been so reduced by the action of formaldehyde that the content of unaltered toxin is not greater than 5 Schick test doses (0.005 Lf) per c.c., and to which diphtheria antitoxin has been added in an amount sufficient to neutralise completely the remainder, if any, of unaltered toxin but insufficient to satisfy completely the combining power of the toxoid. The proper name of the substance is " Diphtheria Prophylactic T.A.M."

Quality

2. 1 c.c. of the final preparation must represent not less than 3 specific flocculation equivalents (3 Lf) of the toxoid used in its preparation.

Test for minimum potency as an immunising antigen

3. 0.1 c.c. of Diphtheria Prophylactic T.A.M. diluted with physiological salt solution to 1 c.c. shall be injected into each of ten normal guinea-pigs on each of two occasions separated by an interval of not more than four weeks. The guinea-pigs shall be tested for immunity to diphtheria toxin at a date not later than three weeks after the second injection. The test for immunity shall be made by the intracutaneous injection into each guinea-pig of 0.2 c.c. of a dilution of diphtheria toxin containing the equivalent of 1 Schick test dose (0.001 Lf). If, when examined 48 hours after injection, more than two of the ten guinea-pigs exhibit a positive Schick reaction, the batch of Diphtheria Prophylactic T.A.M. shall be treated as insufficiently potent and shall not be issued.

(5)

Special Provisions Applicable to Diphtheria Prophylactic (Toxoid-Antitoxin Floccules)

Definition and Proper Name

1. Diphtheria Prophylactic (Toxoid-Antitoxin Floccules) is a preparation made by adding to diphtheria toxin, the specific toxicity of which has been either completely removed by the action of formaldehyde or has been so reduced by the action of formaldehyde that the content of unaltered toxin is not greater

than 5 Schick test doses (0.005 Lf) per c.c., an amount of diphtheria antitoxin equivalent to about 80 per cent. of the toxoid so produced, and collecting and adequately washing the resultant specific precipitate and resuspending it in physiological salt solution. The proper name of the substance is " Diphtheria Prophylactic T.A.F."

Method of Preparation

2. No procedure shall be used at any stage of the preparation which leads to the liberation of toxoid from its combination.

Quality

3. 1 c.c. of the final suspension must represent not less than 100 specific flocculation equivalents (100 Lf) of the original toxoid used in its preparation.

Tests for minimum potency as an immunising antigen

4. 0.1 c.c. of the Diphtheria Prophylactic T.A.F. diluted with physiological salt solution to 1 c.c. shall be injected into each of at least nine normal guinea-pigs on each of two occasions separated by an interval of not more than four weeks. Tests for immunity to diphtheria toxin shall be made at a date not later than three weeks after the second injection by the separate but simultaneous intracutaneous injection, into each of not less than nine of the guinea-pigs, of 0.2 c.c. of dilutions of diphtheria toxin containing respectively the equivalent of 1 Schick test dose (0.001 Lf) and 2 Schick test doses (0.002 Lf) of diphtheria toxin. If, when examined 48 hours after injection, more than one third of the guinea-pigs tested exhibit a positive reaction to the equivalent of one Schick test dose of diphtheria toxin, or, alternatively, more than two thirds of the guinea-pigs tested exhibit a positive reaction to the equivalent of two Schick test doses of diphtheria toxin, the batch shall be treated as insufficiently potent and shall not be issued.

PART II

Provisions substituted for Divisions (B) to (K) of Part IV of the Second Schedule to the Principal Regulations.

(B)

General Provisions Applicable to the substances to which Division (C) of this Part relates

Proper Names

1. Where an antitoxin or antiserum to which Division (C) of this Part of this Schedule relates is obtained from animals other than horses or other Equidae, the proper name of the antitoxin or antiserum is its proper name as defined in the said Division (C) followed by the common name of the animal from which it is prepared.

Tests for Potency

2. The potency in units of an antitoxin or antiserum to which the said Division (C) relates shall be determined, in accordance with methods approved by the licensing authority, by comparative tests in relation to the standard preparation.

Standard Preparation

3. The standard preparation of an antitoxin or antiserum to which the said Division (C) relates is a quantity of the dried antitoxin or antiserum kept in the National Institute for Medical Research, London.

Unit of Standardisation

4. The unit for the purpose of these regulations of an antitoxin or antiserum to which the said Division (C) relates is the specific biological activity contained in such an amount of the standard preparation as the Medical Research Council may from time to time indicate.

Quality

5.—(1) Antitoxins and antisera to which the said Division (C) relates shall be issued for therapeutic and prophylactic use in the form of—

(*a*) the serum separated from the blood or plasma of the immunised animal; or

(*b*) a solution of the globulins, or derivatives thereof, containing the specific antitoxin or specific immune substance; or

(*c*) a dry substance prepared from the antitoxin or antiserum in either of the above-mentioned forms.

(2) Where such an antitoxin or antiserum is issued in liquid form, the liquid at the time of issue shall be clear or shall show at most a slight turbidity after shaking. Where the preparation is issued in the form specified in head (*a*) of the preceding sub-paragraph, it shall not contain more than 10 per cent. of solid matter.

Strength

6. Each container of antitoxin or antiserum to which the said Division (C) relates shall contain a sufficient number of units in excess of the minimum total number of units indicated on the label to ensure that the said minimum total number of units will still be present in the container at the date appearing on the label, pursuant to article 10 (3) of these regulations, as the date up to which the preparation may be expected to retain its potency.

Labelling

7.—(1) The label on the container shall indicate—

(*a*) the minimum total number of units in the container, and

(*b*) either—

(i) the potency of the preparation expressed as the minimum number of units of antitoxin or antiserum per c.c. in the case of liquid products, or as the minimum number of units of antitoxin or antiserum per gramme in the case of solid products; or

(ii) the total number of c.c. in the container.

(2) The label on the container, or the label or wrapper on the package, shall indicate the nature of the particular product, that is to say, whether it is serum, or a solution of antibody globulins or derivatives thereof, or dried serum, or dried antibody globulins or dried derivatives of antibody globulins.

(3) In the case of a preparation in relation to which a unit has been accepted for international use, the units indicated on the label shall be international units.

(C)

Special Provisions applicable to particular Antitoxins and Antisera

(1)

Diphtheria Antitoxin

Definition and Proper Name

1. Diphtheria Antitoxin is the serum, or the antitoxic globulins or derivatives thereof, separated from the blood of animals which have been immunised against diphtheria toxin. Its proper name is " Diphtheria Antitoxin ".

Strength

2. Diphtheria Antitoxin having a potency of less than 500 units per c.c. in the case of liquid preparations, or less than 5,000 units per gramme in the case of dried preparations, shall not be issued.

Quality

3. A solution of the antitoxic globulins, or of derivatives thereof, shall not contain more than 0.1 gramme of solid matter for each 500 units.

(2)

Tetanus Antitoxin

Definition and Proper Name

1. Tetanus Antitoxin is the serum, or the antitoxic globulins or derivatives thereof, separated from the blood of animals which have been immunised against tetanus toxin. Its proper name is " Tetanus Antitoxin ".

Strength

2. Tetanus Antitoxin having a potency of less than 1,000 units per c.c. in the case of liquid preparations, or less than 10,000 units per gramme in the case of dried preparations, shall not be issued for prophylactic use.

3. Tetanus Antitoxin having a potency of less than 5,000 units per c.c. in the case of liquid preparations, or less than 50,000 units per gramme in the case of dried preparations, shall not be issued for the treatment of tetanus.

Quality

4. A solution of the antitoxic globulins, or of derivatives thereof, shall not contain more than 0.1 gramme of solid matter for each 2,000 units.

Labelling

5. The label on the container shall bear a statement that the number of international units indicated is equivalent to one-half of that number of American units.

(3)

Gas Gangrene Antitoxin
(perfringens)

Definition and Proper Name

1. Gas Gangrene Antitoxin (perfringens) is the serum, or the antitoxic globulins or derivatives thereof, separated from the blood of animals which have been immunised against the alpha-toxin (Glenny) prepared by the growth of *Clostridium perfringens* (commonly known as Welch's bacillus, Type A) in a liquid medium. Its proper name is " Gas Gangrene Antitoxin (perfringens) ".

Strength

2. Gas Gangrene Antitoxin (perfringens) having a potency of less than 250 units per c.c. in the case of liquid preparations, or less than 2,500 units per gramme in the case of dried preparations, shall not be issued.

Quality

3. A solution of the antitoxic globulins, or of derivatives thereof, shall not contain more than 0.1 gramme of solid matter for each 750 units.

Mixed Antitoxins

4. A mixed antitoxin containing antitoxins against other toxins than *Clostridium perfringens* shall, with respect to its content in units of Gas Gangrene Antitoxin (perfringens) conform with paragraphs 4 to 7 of Division (B) of this Part of this Schedule.

(4)

Gas Gangrene Antitoxin
(septicum)

Definition and Proper Name

1. Gas Gangrene Antitoxin (septicum) is the serum, or the antitoxic globulins or derivatives thereof, separated from the blood of animals which have been immunised against the specific toxin prepared by the growth of *Clostridium septicum*, commonly known as Vibrion Septique, in a liquid medium. Its proper name is " Gas Gangrene Antitoxin (septicum) ".

Strength

2. Gas Gangrene Antitoxin (septicum) having a potency of less than 500 units per c.c. in the case of liquid preparations, or less than 5,000 units per gramme in the case of dried preparations, shall not be issued.

Quality

3. A solution of the antitoxic globulins, or of derivatives thereof, shall not contain more than 0.1 gramme of solid matter for each 1,500 units.

Mixed Antitoxins

4. A mixed antitoxin containing antitoxins against other toxins than *Clostridium septicum* shall, with respect to its content in units of Gas Gangrene Antitoxin (septicum), conform with paragraphs 4 to 7 of Division (B) of this Part of this Schedule.

(5)

Gas Gangrene Antitoxin
(oedematiens)

Definition and Proper Name

1. Gas Gangrene Antitoxin (oedematiens) is the serum, or the antitoxic globulins or derivatives thereof, separated from the blood of animals which have been immunised against specific toxins prepared by the growth of *Clostridium oedematiens* in a liquid medium. Its proper name is " Gas Gangrene Antitoxin (oedematiens) ".

Strength

2. Gas Gangrene Antitoxin (oedematiens) having a potency of less than 1,500 units per c.c. in the case of liquid preparations, or less than 15,000 units per gramme in the case of dried preparations, shall not be issued.

Quality

3. A solution of the antitoxic globulins, or of derivatives thereof, shall not contain more than 0.1 gramme of solid matter for each 2,500 units.

Mixed Antitoxins

4. A mixed antitoxin containing antitoxins against other toxins than *Clostridium oedematiens* shall, with respect to its content in units of Gas Gangrene Antitoxin (oedematiens), conform with paragraphs 4 to 7 of Division (B) of this Part of this Schedule.

(6)

Staphylococcus Antitoxin

Definition and Proper Name

1. Staphylococcus Antitoxin is the serum, or the antitoxic globulins or derivatives thereof, separated from the blood of animals which have been immunised against the alpha-toxin prepared by the growth of *Staphylococcus aureus* in a liquid medium. Its proper name is " Staphylococcus Antitoxin ".

Quality

2. A solution of the separated antitoxic globulins, or of derivatives thereof, shall not contain more than 20 per cent. of solid matter.

PART III

Provisions inserted in the Principal Regulations after the Seventh Schedule.

EIGHTH SCHEDULE

PREPARATIONS OF HUMAN BLOOD

PART I

General Provisions applicable to Preparations of Human Blood

Provisions as to donors of blood

1. Preparations of human blood shall not be prepared from blood taken from any person—

(*a*) who is known to be suffering or to have suffered from syphilis; or

(*b*) whose blood has not been tested, with negative results, by a method approved by the licensing authority for evidence of syphilitic infection; or

(*c*) the haemoglobin content of whose blood, as ascertained by a method approved by the licensing authority, is less than the equivalent of 85 per cent. as estimated against the National Physical Laboratory Haldane haemoglobinometer colour standard (B.S.S. No. 1079—1942); or

(*d*) who is not, so far as can be ascertained by a registered medical practitioner after inspection or simple clinical examination and consideration of his medical history, free from disease transmissible by blood transfusion.

Withdrawal of Blood

2. The operation of withdrawing blood intended for the manufacture of a preparation of human blood shall be performed—

(*a*) as respects the insertion of the needle, by a registered medical practitioner, and, as respects any other part of the operation, by or under the supervision of such a practitioner;

(*b*) by a method approved by the licensing authority and in conformity with the accepted standards of asepsis; and

(*c*) in premises suitable for the purpose approved by the licensing authority.

Method of Preparation

3.—(1) Preparations of human blood shall be prepared by methods approved by the licensing authority.

(2) All apparatus used for the manufacture of preparations of human blood shall be cleaned and sterilised by methods approved by the licensing authority.

Tests for Sterility

4. Preparations of human blood shall be tested for sterility by methods approved for the particular type of preparation by the licensing authority.

Records

5. A person licensed to manufacture preparations of human blood shall keep records, in such form and for such period as the licensing authority may require, of all information received by him, being information material for the purposes of paragraph 1 of this schedule, and of the distribution by him of every batch of any such preparation, and shall allow any inspector authorised by the licensing authority in that behalf to inspect any such records.

Part II

Special provisions applicable to particular preparations of human blood

(A)

Whole Human Blood

Definition and proper name

1. Whole human blood is blood withdrawn from a human being for the purpose of transfusion and mixed with an anti-coagulant. Its proper name is "whole human blood".

Method of Preparation

2. The quantity of blood drawn on one occasion shall not exceed 440 c.c.

3. The anti-coagulant used shall be made with materials of a quality approved by the licensing authority, and shall be inserted in the container before the container is sterilised.

Quality

4. No whole human blood shall be issued for the purpose of transfusion unless—

(*a*) there is a clear line of demarcation between sedimented cells and supernatant plasma, and the plasma is free from visible products of haemolysis; and

(*b*) the blood group into which it falls under the ABO system has been determined by the examination of both cells and serum; and

(*c*) the volume of the blood contained in it is not less than 75 per cent. of the total volume.

Storage

5. The container shall, immediately after the insertion of the whole blood, be sealed and cooled to a temperature of 6°C., and shall thereafter be maintained (except during such period not exceeding thirty minutes as may be necessary for examination or transfer) at a temperature not higher than 6° and not lower than 4°C.

Date of Manufacture

6. For the purposes of sub-paragraph (*b*) of paragraph (3) of article 10 of these regulations the date on which the manufacture of a container of whole human blood is completed shall be the date on which the operation of withdrawing the blood was performed.

Labelling

7. The label on the container shall state—

(*a*) the ABO group of the blood, as determined by a method approved by the licensing authority;

(*b*) either the Rhesus group of the blood, as determined by a method approved by the licensing authority, or that its Rhesus group has not been determined;

(*c*) the total volume of fluid, the proportion of blood and the nature and proportion of the anti-coagulant and of any other material introduced;

(*d*) the date, calculated by reference to the period approved by the licensing authority as being the period during which whole human blood is suitable for use for transfusion, after which the preparation is not suitable for use for that purpose;

(*e*) the conditions of storage under which the preparation may be expected to maintain its quality until the date specified under the last foregoing sub-paragraph;

(*f*) that the contents should not be used if there is any visible evidence of deterioration.

(B)

Liquid Human Plasma and Liquid Human Serum

Definitions and Proper Names

1.—(1) Liquid human plasma is the fluid which is separated, by centrifuging or by standing, from whole human blood. Its proper name is " liquid human plasma ".

(2) Liquid human serum is the fluid which is separated from whole human blood which has clotted. Its proper name is " liquid human serum ".

Quality

2. No liquid human plasma or liquid human serum shall be issued for purposes of transfusion unless—

(*a*) it contains in the case of plasma not less than 4.5 per cent., and in the case of serum not less than 6.5 per cent., of protein as determined by a method approved by the licensing authority; and

(*b*) on inspection by the naked eye it is free from red blood corpuscles and coloration from haemoglobin.

Storage

3. Liquid human plasma and liquid human serum shall be stored at an equable temperature not higher than 20° or lower than 10°C. in a place shaded from direct sunlight.

Labelling

4. The label on the container shall state—

(*a*) the protein content of the plasma or serum;

(*b*) in the case of plasma, the nature and proportion of the anti-coagulant and of any other material introduced;

(*c*) the date, calculated by reference to the period approved by the licensing authority as being the period during which liquid human plasma or liquid human serum is suitable for use for transfusion, after which the preparation is not suitable for use for that purpose;

(*d*) the conditions of storage under which the preparation may be expected to maintain its quality until the date specified under the last foregoing sub-paragraph;

(*e*) that the plasma or serum should not be used if it is cloudy or there is a deposit.

(C)

Dried Human Plasma and Dried Human Serum

Definitions and Proper Names

1.—(1) Dried human plasma is liquid human plasma which has been dried by a method approved by the licensing authority. Its proper name is " dried human plasma ".

(2) Dried human serum is liquid human serum which has been dried by a method approved by the licensing authority. Its proper name is " dried human serum ".

Quality

2. The dried human plasma or serum—

(*a*) shall not lose more than 1 per cent. by weight after exposure for 24 hours to phosphorus pentoxide at a pressure not exceeding 1 millimetre of mercury;

(*b*) shall dissolve completely in not more than 10 minutes when a volume of distilled water equal to the original volume of plasma or serum is added.

Storage

3. Dried human plasma and dried human serum shall be stored at an equable temperature not higher than 20° or lower than 10°C. in a place shaded from direct sunlight.

Labelling

4. The label on the container shall state—

(*a*) in the case of plasma, the nature and proportion of the anti-coagulant and of any other material introduced;

(*b*) the amount of diluent necessary to reconstitute the original volume of the plasma or serum;

(*c*) the protein content of the plasma or serum when reconstituted to the original volume of the plasma or serum;

(*d*) that the reconstituted plasma or serum must be used immediately after reconstitution;

(*e*) the date, calculated by reference to the period approved by the licensing authority as being the period during which dried human plasma or dried human serum is suitable for use for transfusion, after which the preparation is not suitable for use for that purpose;

(*f*) the conditions of storage under which the preparation may be expected to maintain its quality until the date specified under the last foregoing sub-paragraph.

(D)

Concentrated Human Red Blood Corpuscles

Definition and proper name

1. Concentrated human red blood corpuscles is the product resulting from the removal from whole human blood, not later than 7 days after the date of its manufacture, of a quantity of plasma and anti-coagulant solution amounting to not less than 40 per cent. by volume of the whole human blood. Its proper name is " concentrated human red blood corpuscles ".

Method of Preparation

2. Concentrated human red blood corpuscles shall be prepared by a method approved by the licensing authority.

Quality

3. Concentrated human red blood corpuscles shall contain not less than 5·5 million red blood cells per cubic millimetre.

Storage

4. Concentrated human red blood corpuscles shall be stored at a temperature not higher than 6° or lower than 4°C.

Labelling

5. The label on the container shall state—

(*a*) the reference numbers of the containers of the whole human blood from which the preparation is made;

(*b*) the ABO group, as determined by a method approved by the licensing authority, of the whole human blood from which the preparation is made;

(*c*) either the Rhesus group, as determined by a method approved by the licensing authority, of the whole human blood from which the preparation is made, or that its Rhesus group has not been determined;

(*d*) the time, being not more than 24 hours after the completion of the removal of the plasma and anti-coagulant solution or more than 8 days after the date of the manufacture of the whole human blood from which the preparation is made, up to which the preparation is suitable for use for transfusion;

(*e*) the conditions of storage under which the preparation may be expected to maintain its quality until the date specified under the last foregoing sub-paragraph;

(*f*) that the contents should not be used if there is any visible evidence of deterioration.

(E)

Human Fibrin, Fibrinogen, Thrombin and Immune Globulin

Definitions and proper names

1.—(1) Human fibrin is the insoluble protein which forms the matrix of a clot of human blood. Its proper name is " human fibrin ".

(2) 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 ".

(3) Human thrombin is the enzyme which transforms human fibrinogen into human fibrin. Its proper name is " human thrombin ".

(4) Human immune globulin is soluble protein which is derived from human plasma or serum and has specific anti-bacterial, anti-viral or anti-toxic activity. Its proper name is " human immune globulin ".

Quality, Storage and Labelling

2. Human fibrin, fibrinogen, thrombin and immune globulin, and preparations thereof, shall be of a quality, and shall be stored and labelled in a manner, approved by the licensing authority.

PART IV

Provisions inserted in the principal regulations after the Eighth Schedule.

NINTH SCHEDULE

PROVISIONS APPLICABLE TO ORGANIC SUBSTANCES HAVING THE SPECIFIC BIOLOGICAL ACTION OF CURARE ON NEURO-MUSCULAR TRANSMISSION, AND PREPARATIONS THEREOF

PART I

Provisions applicable to *dextro*-tubocurarine chloride and preparations thereof

Definitions and proper names

1.—(1) *Dextro*-tubocurarine chloride is the chloride which—

(*a*) is the salt of an alkaloid which can be extracted from the stems of plants of the genus *Chondrodendron,* and

(*b*) has the characteristics mentioned in sub-paragraph (2) of this paragraph.

d-tubocurarine chloride solution is a suitably stabilised solution of *dextro*-tubocurarine chloride.

(2) The characteristics referred to in the last foregoing sub-paragraph are as follows—

(*a*) the substance is a white, odourless, microcrystalline powder;

(*b*) the substance is soluble in water, especially in warm water, and in solutions of alkali hydroxides, but is precipitated from aqueous solution by sodium bicarbonate solution;

(*c*) when a few crystals of the substance are added to 0.5 c.c. of Millon's reagent at room temperature, a cherry-red colour slowly develops;

(*d*) the substance after drying at 100° C. melts with effervescence at 274-275° C.;

(*e*) the specific rotation of the anhydrous salt, in water at 20° C., with the mercury green wave-length 546.1 millimicrons is between + 260° and + 275°, and with the sodium wave-length 589.3 millimicrons is between + 210° and + 220°;

(*f*) the loss of weight on drying of the substance at 100° C. is not more than 12 per cent.;

(*g*) the methoxyl content of the substance after drying at 100° C. is not more than 9 per cent. by weight;

(*h*) the substance has the specific biological activity of curare on neuro-muscular transmission.

(3) The proper name of *dextro*-tubocurarine chloride is " *d*-tubocurarine chloride ", and the proper name of a preparation thereof is " *d*-tubocurarine chloride " together with a word or words indicating the nature of the preparation.

Test for potency

2. *d*-tubocurarine chloride and preparations thereof shall be tested for potency by comparative biological tests in relation to the standard preparation, by methods approved by the licensing authority. The potency so determined shall not differ from that of the standard preparation by more than 10 per cent.

Standard preparation

3. The standard preparation of *d*-tubocurarine chloride is a quantity thereof kept in the National Institute for Medical Research, London.

Labelling

4.—(1) The label on a container of *d*-tubocurarine chloride or of a preparation thereof other than *d*-tubocurarine chloride solution shall state the total number of milligrammes of the solid preparation in the container.

(2) The label on a container of *d*-tubocurarine chloride solution shall state—

(*a*) the nature of the solvent;

(*b*) the number of milligrammes of *d*-tubocurarine chloride per c.c. of the solution.

(3) The label on a container of a solution other than an oily solution, or the label or wrapper on the package thereof, shall state that the dose of *d*-tubocurarine chloride for an adult human being should not ordinarily exceed 15 milligrammes.

(4) In the case of an oily solution the label on the container, or the label or wrapper on the package thereof, shall state that the solution is for subcutaneous or intramuscular injection only, and that the dosage should not ordinarily exceed 30 milligrammes.

PART II

Provisions applicable to preparations, other than *d*-tubocurarine chloride and preparations thereof, which owe their action on neuro-muscular transmission to *d*-tubocurarine.

Quality

1. Preparations, other than *d*-tubocurarine chloride and preparations thereof, which owe their action on neuro-muscular transmission to *d*-tubocurarine shall have a potency such that the equivalent of 1 unit of *d*-tubocurarine chloride is contained, if the preparation is a solid, in not more than 10 milligrammes thereof and, if the preparation is a liquid, in not more than 10 milligrammes of the solid content thereof (other than constituents of the solvent).

Tests for potency

2. Any such preparation as aforesaid shall be tested for potency by a method approved by the licensing authority. The potency shall be determined by comparison with the standard preparation of *d*-tubocurarine chloride.

Unit of Standardisation

3. The unit of *d*-tubocurarine chloride for the purposes of this Part of this Schedule is the specific activity contained in one milligramme of the standard preparation.

Test for undue toxicity

4. Any such preparation as aforesaid shall be tested for undue toxicity by biological methods approved by the licensing authority.

Labelling

5.—(1) The label on the container of such a preparation as aforesaid shall state—

(*a*) the number of units of *d*-tubocurarine chloride per milligramme in the case of a solid preparation or per c.c. in the case of a liquid, and

(*b*) that one unit of *d*-tubocurarine chloride is equivalent to one milligramme thereof.

(2) The label on the container of such a preparation as aforesaid or the label or wrapper on the package shall state that the dose of *d*-tubocurarine chloride for an adult human being should not ordinarily exceed 15 British units.

PART III

Provisions applicable to preparations whose action on neuro-muscular transmission is not due to *d*-tubocurarine

Extent of Part III

1. This Part of this Schedule applies to preparations added to the Schedule to the Act by paragraph (2) of regulation 9 of the Therapeutic Substances Amendment Regulations, 1948, to which the foregoing Parts of this Schedule do not apply.

Strength

2. Preparations to which this Part of this Schedule applies shall have such potency as may be required by the licensing authority.

Tests for potency and undue toxicity

3. Any such preparation as aforesaid shall be tested for potency and undue toxicity by methods approved by the licensing authority.

Labelling

4. Any such preparation as aforesaid shall be labelled in a manner approved by the licensing authority.

These regulations were made by the aforesaid Joint Committee this fourth day of November nineteen hundred and forty-eight.

Aneurin Bevan,
Arthur Woodburn,
William Grant,
Members of the Joint Committee.

F. F. Marchbank,
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 Therapeutic Substances Regulations, 1931, as amended by subsequent regulations, by—

(1) substituting a new definition of "penicillin" for that contained in regulation 4 of the Therapeutic Substances Amendment Regulations, 1946;

(2) substituting new provisions for Part II (B) of the Second Schedule to those regulations (which relates to Diphtheria Prophylactic);

(3) adding penicillin (as re-defined), preparations of human blood, and *dextro*-tubocurarine chloride and kindred substances, to the Schedule to the Therapeutic Substances Act, 1925, (thus rendering them subject to control under that Act), and inserting in those regulations new or modified schedules dealing with the preparation, testing, packing and labelling of the substances so added;

(4) making a number of consequential or minor amendments.

The Streptomycin Regulations, 1948

1948 No. 1735

Made - - - -	*23rd July*, 1948
Laid before Parliament	*27th July*, 1948
Coming into Operation	*1st August*, 1948

108115.

The Minister of Health, the Secretary of State for Scotland and the Minister of Health and Local Government for Northern Ireland, acting jointly, in exercise of their powers under section 2 of the Penicillin Act, 1947(**a**), after consultation with the Medical Research Council, hereby make the following regulations:—

1.—(1) These regulations may be cited as the Streptomycin Regulations, 1948, and shall come into operation on the first day of August, 1948.

(2) The Interpretation Act, 1889(**b**), applies to the interpretation of these regulations as it applies to the interpretation of an Act of Parliament.

2.—(1) Streptomycin shall be a substance to which the Penicillin Act, 1947, applies.

(2) In this regulation "streptomycin" means any antimicrobial complex organic base or mixture of such bases produced by *Streptomyces griseus* or other living organisms which—

(*a*) yields on hydrolysis by mineral acids the base streptidine (*ms*-2:4:5:6-tetrahydroxy-1:3-diguanidocyclohexane); and

(*b*) yields on hydrolysis by a 4% solution of sodium hydroxide the substance maltol (3-hydroxy-2-methyl-gamma-pyrone);

(**a**) 10 & 11 Geo. 6. c. 29. (**b**) 52 & 53 Vict. c. 63.