STATUTORY INSTRUMENTS

1963 No. 1457

THERAPEUTIC SUBSTANCES

The Therapeutic Substances (Manufacture of Sera and Antitoxins) Regulations 1963

Made - - - -	*23rd August* 1963
Laid before Parliament	*2nd September* 1963
Coming into Operation	*16th 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 section 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 Sera and Antitoxins) 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 purpose 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.

PART II

PROVISIONS RELATING TO THE PRODUCTION OF ALL SERA FROM LIVING ANIMALS

Staff of establishment

3. The establishment in which the sera are prepared shall be under the complete direction and control of an expert approved by the licensing authority.

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

Buildings and equipment

4.—(1) Laboratories where sera are exposed to the air in the course of the process of preparation shall be separated from buildings housing animals so as to avoid the risk of airborne and flyborne contamination from animal excreta. Such laboratories shall have impervious walls and floors and shall be capable of being readily disinfected when necessary.

(2) A special room with impervious walls and floor which can be washed and chemically disinfected shall be provided for the collection of blood from the living animal.

(3) An adequate number of efficient sterilizers shall be provided for the sterilization of all glass-ware or other apparatus with which the serum may come into contact in the course of its preparation.

Condition of animals

5.—(1) Only healthy animals shall be used in the preparation of sera, and in particular the presence of glanders in horses or other equidae and of tuberculosis in cattle shall be excluded by testing with mallein and tuberculin respectively, as required by the licensing authority.

(2) Every new animal intended to be used as a source of serum shall be subjected to a period of observation in quarantine for at least 7 days before being admitted to the stables in which the serum-yielding animals are housed.

(3) Every animal used as a source of serum shall either be actively immunized against tetanus toxin or be passively immunized against that toxin by injections of tetanus antitoxin in such doses as to ensure the constant presence of that antitoxin in its blood while it is being so used.

(4) If an animal used in the production of sera is found to be suffering from an infection, except one produced by living organisms against which it is being immunized, or shows signs of serious or persistent ill-health not reasonably attributable to the process of immunization, the licensee shall immediately report the matter to the licensing authority and shall, if the authority orders an inspection and the inspector so directs, cause such animal to be killed and a post-mortem examination of it to be made, and take steps to prevent any serum obtained from the animal being sold or offered for sale until permission is given by the authority. If the result of the post-mortem examination casts suspicion on the health of any other animals used for the production of sera, the licensing authority may prohibit the use of those animals for the production of sera or take such other steps as may be necessary to prevent the issue of sera which may be dangerous to human health:

Provided that in a case of emergency the person in charge of the establishment may order the destruction of an animal used in the production of sera and suspected of infection, and shall in that case give notice forthwith to the licensing authority and permit an inspector to be present at the post-mortem examination.

Precautions to be observed in preparation

6.—(1) An efficient system of manure removal shall be used which will prevent its accumulation near any room where blood or serum is collected or handled.

(2) All processes to which the serum is subjected during and after its collection from the animal shall be designed to preserve its sterility but, in

the case of artificially concentrated sera, it shall suffice that the process of concentration is conducted with scrupulous cleanliness and in such a manner as to avoid unnecessary or dangerous contamination.

PART III

GENERAL PROVISIONS RELATING TO SERA AND ANTITOXINS

Tests for sterility

7. The substances to which these regulations relate shall be tested for sterility in accordance with the general regulations.

Labelling

8.—(1) The particulars specified in regulation 6(1)(*g*) of the general regulations shall be borne both by the container of any substance to which these regulations relate and by the package in which the substance 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 substance.

(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 substance or by the package in which the substance is offered for sale.

(4) In addition to the particulars required by paragraphs (1) and (2) of this regulation, a statement of the species of animals from which the substance is derived shall be borne by the container of any such substance.

PART IV

PROVISIONS RELATING TO ANTIBACTERIAL SERA AND ANTITOXIC SERA FOR WHICH NO POTENCY TEST IS PRESCRIBED

Definition

9. This part of these regulations relates to the sera, or solutions of the purified proteins of sera, separated from the blood of animals which have been artificially immunised against cultures of one or more organisms or against a soluble toxin or toxins produced by the organism or organisms or against antigenic substances prepared from the organism or organisms.

Proper names

10. The proper name of any antibacterial serum to which this part of these regulations applies is the recognised scientific name of the organism or some generally recognised abbreviation thereof, either preceded by the prefix "anti", and followed by the word "serum", as, for example, "anti-meningococcus serum", or followed by the word "antiserum", as, for example, "meningococcus antiserum". The proper name of any antitoxic serum may be formed from the word "antitoxin", preceded by the name of the disease against which the antitoxin is intended for use, and followed, if necessary, by a term indicating the source or the strain of the organism used.

Cultures

11. The cultures used in immunizing the animals shall be at all times open to inspection, and specimens shall be furnished for examination at the request of the licensing authority.

Freedom from abnormal toxicity

12.—(1) A serum to which this part of these regulations relates shall be free from abnormal toxicity and shall be tested in accordance with this regulation.

(2) A dose of 0·5 millilitre of the serum shall be injected subcutaneously into a healthy mouse weighing not more than 30 grammes and the serum may be regarded as free from abnormal toxicity if the injection does not produce any serious effects within 4 days.

(3) A dose of not less than 5 millilitres of the serum shall be injected subcutaneously or intraperitoneally into a healthy guinea pig weighing 250 to 350 grammes and not previously treated with any material which will interfere with the test and the serum may be regarded as free from abnormal toxicity if the injection does not produce any serious effects within 4 days.

Quality

13.—(1) A serum to which this part of these regulations relates shall be issued for therapeutic use in the form of either—

(*a*) native serum, i.e., the liquid from coagulated blood or plasma without any addition, other than a bacteriostatic; or

(*b*) a solution of the purified serum proteins or derivatives thereof containing the specific antibodies; or

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

(2) At the time of issue, the liquid shall be clear or show at most a slight opalescence or precipitate. Preparations of the native serum shall not contain more than 10 per cent., and a solution of the serum protein shall not contain more than 20 per cent., of solid matter.

Records

14.—(1) The records which the licensee is required to keep shall include the following particulars:—

(*a*) as to the cultures—

(i) the source from which the culture was obtained;

(ii) the nature of the material from which the culture was isolated, and the date of its isolation; and

(iii) evidence of the identity and specificity of the culture;

(*b*) as to the procedure used in immunizing the animals—

(i) the method of preparing the culture or antigen used for immunization;

(ii) the dosage and methods employed in administering the culture or antigen;

(iii) the period in the course of immunization at which blood is withdrawn for preparation of the serum;

(*c*) any tests which may have been applied to the serum to determine its content of specific antibodies or its specific therapeutic potency.

(2) If the licensee desires to have the performance of any test recorded under paragraph (1)(*c*) of this regulation accepted by the licensing authority as sufficient for the purpose of fixing the date of completion of manufacture for the purposes of regulation 6(1)(*f*) of the general regulations, he shall submit full particulars of the proposed test to the licensing authority and obtain their approval.

Labelling

15.—(1) In addition to the particulars required by regulation 8(1) and (2) of these regulations, particulars shall be borne by the container of the total number of millilitres therein.

(2) In addition to the particulars required by paragraph (3) of the said regulation 8, particulars of the nature of the particular product (that is to say, whether native serum or purified serum proteins) shall be borne either by the container of the product or by the package in which the product is offered for sale.

PART V

GENERAL PROVISIONS APPLICABLE TO THE SUBSTANCES TO WHICH THE SUCCEEDING PARTS OF THESE REGULATIONS RELATE

Proper names

16. Where an antitoxin or antiserum to which any of the succeeding parts of these regulations relates is obtained from animals other than horses or other equidae, the proper name of the antitoxin is its proper name as defined therein followed by the common name of the animal from which it is prepared.

Standard preparation

17. The standard preparation of an antitoxin to which any of the said parts relates is one of the dried antitoxin kept in the National Institute for Medical Research, London.

Unit of standardisation

18. The unit for the purpose of these regulations of an antitoxin to which any of the said parts 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:

Provided that in the case of an antitoxin of which there is a unit accepted for international use, the amount of the standard preparation so indicated shall be exactly equivalent to that unit.

Tests for potency

19. The potency in units of an antitoxin to which any of the said parts relates shall be determined in accordance with methods approved by the licensing authority by comparative tests in relation to the standard preparation.

Freedom from abnormal toxicity

20. An antitoxin to which any of the said parts relates shall be free from abnormal toxicity and shall be tested in accordance with regulation 12(2) and (3) of these regulations.

Quality

21.—(1) An antitoxin to which any of the said parts relates other than diphtheria antitoxin shall be issued for therapeutic and prophylactic use in the form of—

(*a*) the serum separated from the blood or plasma of the immunized 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 in either of the above-mentioned forms.

(2) Where such an antitoxin 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 sub-paragraph (*a*) of the preceding paragraph, it shall not contain more than 10 per cent. of solid matter.

Strength

22. Each container of antitoxin to which any of the said parts 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 regulation 6(1)(*h*) of the general regulations as the date up to which the preparation may be expected to retain its potency.

Labelling

23.—(1) In addition to the particulars required by regulation 8(1) and (2) of these regulations, the following further particulars shall be borne by the container of an antitoxin to which any of the said parts relates:—

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

(*b*) the minimum total number of units in the container;

(*c*) either—

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

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

(2) In addition to the particulars required by paragraph (3) of the said regulation 8, particulars of 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) shall be borne either by the container of the product or by the package in which the product is offered for sale.

(3) Where, in pursuance of paragraph (1) of this regulation the number of units is stated on the container, it shall, in the case of an antitoxin of which there is a unit accepted for international use, be stated as the number of international units.

PART VI

SPECIAL PROVISIONS RELATING TO DIPHTHERIA ANTITOXIN

Definition and proper name

24. Diphtheria antitoxin is a preparation from native serum containing the antitoxic globulins or derivatives that have the specific power of neutralising the toxin formed by *Corynebacterium diphtheriae*. Its proper name is "diphtheria antitoxin".

Strength

25. Diphtheria antitoxin which has a potency of less than 1,000 units per millilitre in the case of liquid preparations, or less than 10,000 units per gramme in the case of dried preparations, shall not be issued.

Quality

26. Diphtheria antitoxin shall not contain more than 0·1 gramme of solid matter for each 500 units.

PART VII

SPECIAL PROVISIONS RELATING TO TETANUS ANTITOXIN

Definition and proper name

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

Strength

28.—(1) Tetanus antitoxin in the form of serum which has a potency of less than 500 units per millilitre, or a dried preparation of such substance, which has a potency of less than 5,000 units per gramme, shall not be issued for prophylactic use.

(2) Tetanus antitoxin in the form of a solution of the antitoxin globulins, or derivatives thereof which has a potency of less than 1,000 units per millilitre, or a dried preparation of such substance which has a potency of less than 7,500 units per gramme, shall not be issued for prophylactic use.

(3) Tetanus antitoxin in the form of a solution of the antitoxic globulins, or of derivatives thereof which has a potency of less than 3,000 units per millilitre, or a dried preparation of such substance which has a potency of less than 15,000 units per gramme, shall not be issued for the treatment of tetanus.

Quality

29. 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 if the antitoxin is issued for prophylactic use or for each 1,500 units if it is issued for the treatment of tetanus.

PART VIII

SPECIAL PROVISIONS RELATING TO GAS GANGRENE ANTITOXIN (WELCHII)

Definition and proper name

30. Gas gangrene antitoxin (Welchii) is the serum, or the antitoxic globulins or derivatives thereof, separated from the blood of animals which have been immunized against the α-toxin prepared by the growth of *Clostridium Welchii* type A in a liquid medium. Its proper name is "gas gangrene antitoxin (Welchii)".

Strength

31.—(1) Gas gangrene antitoxin (Welchii) in the form of serum which has a potency of less than 300 units per millilitre or a dried preparation of such substance which has a potency of less than 3,000 units per gramme shall not be issued.

(2) Gas gangrene antitoxin (Welchii A) in the form of a solution of the antitoxic globulins, or of derivatives thereof, which has a potency of less than 1,500 units per millilitre, or a dried preparation of such substance which has a potency of less than 6,000 units per gramme, shall not be issued.

Quality

32. 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

33. A mixed antitoxin containing antitoxins against other toxins than *Clostridium Welchii* type A shall, with respect to its content in units of gas gangrene antitoxin (Welchii), conform with regulations 18, 21, 22 and 23 of these regulations.

PART IX

SPECIAL PROVISIONS RELATING TO GAS GANGRENE ANTITOXIN (SEPTICUM)

34. Gas gangrene antitoxin (septicum) is the serum, or the antitoxic globulins or derivatives thereof, separated from the blood of animals which have been immunized against the specific toxin prepared by the growth of *Clostridium septicum* in a liquid medium. Its proper name is "gas gangrene antitoxin (septicum)".

Strength

35.—(1) Gas gangrene antitoxin (septicum) in the form of serum which has a potency of less than 300 units per millilitre, or a dried preparation of such substance which has a potency of less than 3,000 units per gramme, shall not be issued.

(2) Gas gangrene antitoxin (septicum) in the form of a solution of the antitoxic globulins, or of derivatives thereof, which has a potency of less than 1,500 units per millilitre, or a dried preparation of such substance which has a potency of less than 6,000 units per gramme in the case of dried preparations, shall not be issued.

Quality

36. 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

37. 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 regulations 18, 21, 22 and 23 of these regulations.

PART X

SPECIAL PROVISIONS RELATING TO GAS GANGRENE ANTITOXIN (OEDEMATIENS)

Definition and proper name

38. Gas gangrene antitoxin (oedematiens) is the serum, or the antitoxic globulins or derivatives thereof, separated from the blood of animals which have been immunized against the α-toxin prepared by the growth of *Clostridium oedematiens* in a liquid medium. Its proper name is "gas gangrene antitoxin (oedematiens)".

Strength

39.—(1) Gas gangrene antitoxin (oedematiens) in the form of serum which has a potency of less than 1,000 units per millilitre or a dried preparation of such substance which has a potency of less than 10,000 units per gramme, shall not be issued.

(2) Gas gangrene antitoxin (oedematiens) in the form of a solution of the antitoxic globulins, or of derivatives thereof, which has a potency of less than 3,750 units per millilitre, or a dried preparation of such substance which has a potency of less than 15,000 units per gramme, shall not be issued.

Quality

40. 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

41. 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 regulations 18, 21, 22 and 23 of these regulations.

PART XI

SPECIAL PROVISIONS RELATING TO STAPHYLOCOCCUS ANTITOXIN

Definition and proper name

42. Staphylococcus antitoxin is the serum, or the antitoxic globulins or derivatives thereof, separated from the blood of animals which have been immunized against the α-toxin prepared by the growth of *Staphylococcus aureus* in a liquid medium. Its proper name is " staphylococcus antitoxin ".

Quality

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

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 sera and antitoxins and in particular prescribe requirements as to:—

(*a*) staff, buildings and equipment used in the manufacture;
(*b*) the condition of animals used in the production of sera;
(*c*) tests for sterility, potency and freedom from abnormal toxicity;
(*d*) quality and strength;
(*e*) records; and
(*f*) labelling.