# THERAPEUTIC SUBSTANCES

## 1952 No. 1937

## The Therapeutic Substances Regulations, 1952

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| *Made* - - - - | *7th November*, 1952 |
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| *Coming into Operation* | *1st January*, 1953 |

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The Joint Committee constituted by subsection (1) of section 4 of the Therapeutic Substances Act, 1925(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 subsection (2) of section 4 aforesaid, hereby make the following regulations:—

## PART I

## GENERAL

*Citation*

**1.** These regulations may be cited as the Therapeutic Substances Regulations, 1952, and shall come into operation on the first day of January, 1953.

*Interpretation*

**2.**—(1) In these regulations, unless the context otherwise requires,—

"the Act" means the Therapeutic Substances Act, 1925;

"the existing regulations" means the regulations specified in the first schedule to these regulations;

"import licence" means a licence to import a therapeutic substance for purposes other than those of scientific research;

"licence" means a licence under the Act;

"the licensing authority" means the Minister of Health in the application of the regulations to England and Wales, the Secretary of State for Scotland in the application of the regulations to Scotland and the Minister of Health and Local Government for Northern Ireland in the application of the regulations to Northern Ireland;

"manufacturing licence" means a licence to manufacture a therapeutic substance for sale;

"proper name", in relation to a therapeutic substance, means the name prescribed in or approved in accordance with the relative schedule as the proper name of the substance;

"relative schedule", in relation to a therapeutic substance, means such of the provisions of any of the schedules to these regulations as are applicable to that substance;

"research licence" means a licence to import a therapeutic substance for the purpose of scientific research;

"therapeutic substance" or "substance" means one of the therapeutic substances specified in the Schedule to the Act or added to that Schedule by these regulations or by any regulations revoked by these regulations.

(2) References in these regulations to a substance of which there is a definition in the relative schedule shall be construed as references to the substance so defined.

(3) For the purposes of these regulations the cubic centimetre may be used wherever the millilitre is indicated.

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

*Licences and Applications for Licences*

**3.**—(1) The form of application to the licensing authority for a licence or the renewal of a licence under these regulations, and the form of licence to be granted by the licensing authority, shall be the appropriate form set out in the second schedule hereto or a form substantially to the like effect.

(2) Licences granted under these regulations shall, unless sooner suspended or revoked, continue in force for a period of two years.

(a) 15 & 16 Geo. 5. c. 60. (b) 52 & 53 Vict. c. 63.

## PART II

### LICENCES FOR MANUFACTURE OF THERAPEUTIC SUBSTANCES

*Licensing authority to be satisfied that conditions will be observed*

**4.** Before a manufacturing licence is issued or renewed, the applicant shall satisfy the licensing authority that upon the issue or renewal of the licence the conditions set out in regulation 5 of these regulations will be observed.

*Conditions*

**5.** Every manufacturing licence shall be subject to the following conditions:—

(*a*) the licensee shall provide and maintain an adequate staff and adequate premises and plant for the proper manufacture of the substance in respect of which the licence is issued;

(*b*) without prejudice to the generality of the foregoing requirement, the licensee, if he for any purpose engages in the culture or manipulation of pathogenic spore-bearing micro-organisms, shall provide to the satisfaction of the licensing authority separate laboratories, utensils and apparatus required for the culture or manipulation of such micro-organisms; and the separate laboratories, utensils and apparatus so provided shall not be used for the manufacture of any other therapeutic substance;

(*c*) the licensee shall either—

(i) provide and maintain an adequate staff and adequate premises and plant for carrying out such tests of the strength, quality and purity of the substance as, pursuant to part IV of these regulations, he may be required to carry out; and where animals are used for such tests they shall be suitably housed; or

(ii) make arrangements with some institution approved by the licensing authority for such tests to be regularly carried out on his behalf by that institution;

(*d*) the licensee shall keep readily available for inspection durable records (which shall not be destroyed without the permission of the licensing authority) of the details of manufacture of each batch of the substance and the tests carried out thereon in such a form that the records will be easily identifiable with the substance issued for sale by reference to the number of the batch as shown on the label of each container under the provisions of sub-paragraph (*c*) of paragraph (1) of regulation 7 of these regulations;

(*e*) the licensee shall allow an inspector authorised by the licensing authority in that behalf to enter, with or without prior notice, any premises where the manufacture is carried on and to inspect the premises and plant, the process of manufacture and the means employed for standardising and testing the substance and to take samples thereof;

(*f*) the licensee shall forthwith report to the licensing authority any changes in the expert staff responsible for the manufacture or testing of the substance and any material alterations in the premises or plant used for that purpose;

(*g*) the licensee shall on request furnish to the licensing authority from every batch of the substance, or from such batch or batches as the licensing authority may from time to time specify, a sample of such amount as the authority may consider adequate for any examination required to be made; and the licensee shall, if required by the licensing authority, furnish full protocols of the tests which have been applied;

PART II.—*cont.*

(*h*) if the licensing authority so direct, the licensee shall not sell or offer for sale any batch in respect of which a sample is or protocols are furnished under the last preceding sub-paragraph until a certificate authorizing the sale of the batch has been issued to him by the licensing authority;

(*i*) the licensee shall, on being informed by the licensing authority that any part of any batch of the substance has been found by the licensing authority not to conform with the standards of strength, quality or purity specified in these regulations and on being directed so to do, withdraw the remainder of that batch from sale and, so far as may be practicable, recall all issues already made from that batch;

(*j*) the licensee shall comply with the provisions of parts III and IV of these regulations, and, as respects each therapeutic substance which he is licensed to manufacture, with the requirements of the relative schedule, and with such further requirements, if any, as may be specified in any regulations which may be made under the Act, and of which the licensing authority has given the licensee not less than one month's notice.

## PART III

### PROVISIONS WITH REGARD TO CONTAINERS, LABELLING AND SALE OF THERAPEUTIC SUBSTANCES

*Containers*

**6.**—(1) No therapeutic substance shall be sold or offered for sale unless it has been sealed, in such manner as will in the opinion of the licensing authority suffice to preclude the access of micro-organisms, in a previously sterilised container of a material inert towards the substance:

Provided that in the case of a preparation of a vaccine intended for administration by any means other than injection into the tissues which is in a solid form or is to be administered in a solid vehicle, the container in which it is packed need not be sterile but the ordinary standards of pharmaceutical cleanliness shall be observed in the packing of the preparation.

(2) When any therapeutic substance is issued in liquid form in containers which are sealed in such a manner that portions of the contents can be withdrawn for use on different occasions, the liquid shall contain a sufficient proportion of some bacteriostatic to prevent the growth of any organism which may be introduced in the process of removing a portion of the contents of the container.

(3) The licensing authority may in the case of any particular preparation of any therapeutic substance dispense with any of the requirements of this regulation or any requirement of the relative schedule relating to containers, and may impose such additional requirements as, having regard to the nature of the preparation, they may deem necessary.

*Labelling*

**7.**—(1) Every phial, ampoule or other sealed container in which a therapeutic substance is sold or offered for sale shall bear a label affixed by the manufacturer of the substance on which is printed or written in indelible

PART III.—*cont.*

ink, or shall have indelibly marked in the body thereof, the following particulars and such further particulars, if any, as may be specified in the relative schedule :—

(*a*) the proper name of the substance in letters not less conspicuous than those in which the proprietary name, if any, is printed, written or marked, and following immediately after or under such proprietary name ;

(*b*) the number of every licence under which the substance or any of its constituents is manufactured or imported, preceded in the case of import licences by the words " Import Licence " ;

(*c*) a distinctive batch number, that is to say, the number by reference to which the prescribed tests and details of manufacture of the particular batch from which the substance in the container is taken are recorded and available for inspection under the provisions of paragraph (*d*) of regulation 5 of these regulations ;

(*d*) where a test for potency in units is required by these regulations, a statement of the potency in units defined in terms of relation to the standard preparation specified in the relative schedule:

Provided that—

(i) in the case of surgical ligature or suture the particulars required by sub-paragraphs (*a*) (*b*) and (*c*) of this paragraph shall either be indelibly marked on the body of the container or be indelibly marked or perforated on a label enclosed in the container and readily legible without opening the container ;

(ii) in the case of smallpox vaccine the particulars required as aforesaid may, instead of being printed, written or marked as aforesaid, be printed or written in indelible ink on a label or wrapper affixed to any package in which the container is offered for sale.

(2) The following particulars and such further particulars, if any, as may be specified in the relative schedule shall be printed or written in indelible ink either on the label borne by the container of any therapeutic substance or on a label or wrapper affixed to any package in which any such container is issued for sale :—

(*a*) the name and address of the manufacturer of the final product ;

(*b*) the date on which the manufacture of the particular batch from which the substance in the container is taken was completed, as defined in the relative schedule, or, if there is no definition in the relative schedule, as hereafter defined in this regulation ;

(*c*) where a test for potency or maximum toxicity is so required, the date up to which the substance, if kept under suitable conditions, may be expected to retain a potency not less than that stated on the label of the container or stated in the relative schedule, or not to acquire a toxicity greater than that permitted by the test, as the case may be ;

(*d*) where a bacteriostatic has been added, the nature and the percentage proportion of the bacteriostatic in the material as prepared for use ;

(*e*) the precautions necessary for preserving the properties of the contents to the date indicated in accordance with the provisions of sub-paragraph (*c*) of this paragraph ;

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

PART III.—*cont.*

(3) For the purposes of sub-paragraph (*b*) of the last preceding paragraph the date on which the manufacture of a batch is completed shall be—

(*a*) in cases where a test for potency or toxicity is required by these regulations, or where such a test is not required but is accepted by the licensing authority as sufficient for the purpose of fixing the date of completion of manufacture, the date on which the test was completed, or, if the substance has been kept continuously in cold storage at a temperature not exceeding 5° C. from the time when the last test was completed, the date (not being later than two years from the date on which the last test was completed) on which the substance was removed from cold storage;

(*b*) in cases where no such test is required or accepted—

(i) if the substance is a serum obtained from living animals, the earliest date on which any material contributing to the batch was removed from the animal;

(ii) if the substance was obtained by the growth of organisms on artificial media, the earliest date on which growth was terminated in any of the material contributing to the batch:

Provided that in such cases if a batch of the substance (including all materials contributing to the batch) has been kept continuously in cold storage at a temperature not exceeding 5° C. from the earliest practicable date after that on which the material was removed from the animal or on which growth was terminated in the material, as the case may be, the date (not being more than three years after the last-mentioned date) on which it is removed from cold storage shall be treated as the date on which the manufacture of the batch was completed.

*Prohibition of sale of substance after prescribed date*

**8.** No person shall sell any therapeutic substance after the date recorded on the container, label or wrapper as the date up to which the substance may be expected to retain a potency not less than, or not to acquire a toxicity greater than, that required or permitted by the test, as the case may be:

Provided that a person may at the request of a registered medical practitioner sell after the date aforesaid any therapeutic substance (except one that is required to be tested for maximum toxicity) if he has previously drawn the practitioner's attention to the dates recorded on the container, label or wrapper, and the practitioner is satisfied that the sale is required by the urgency of the case.

## PART IV

### STANDARDS OF STRENGTH, QUALITY AND PURITY AND TESTS FOR DETERMINING WHETHER THOSE STANDARDS HAVE BEEN ATTAINED

*Standards*

**9.** Every therapeutic substance intended for sale shall conform with the standards of strength, quality and purity specified in these regulations, and the tests for determining conformity therewith shall, except in the case of smallpox vaccine, be applied to samples taken from the final product after every manufacturing process has been completed:

Provided that—

(*a*) in the case of any preparation containing an antibiotic such of the tests may be applied at such earlier stage in the manufacture as may be approved by the licensing authority in respect of preparations of that kind;

PART IV.—*cont.*

(*b*) in the case of a preparation of a vaccine intended for administration by any means other than injection into the tissues, the tests may be applied to the vaccine from which the preparation is made instead of being applied to the preparation itself but the ordinary standards of pharmaceutical cleanliness shall be observed in the manufacture of the preparation.

*Tests for strength and quality*

**10.** The tests, if any, required for determining the strength and quality of a therapeutic substance shall be those set out in the relative schedule.

*Test for sterility in the case of surgical ligature or suture*

**11.** The test for sterility in the case of surgical ligature or suture shall be that prescribed in the eighth schedule to these regulations.

*Tests for sterility in other cases*

**12.** Tests for the presence of living aerobic or anaerobic micro-organisms shall be made in accordance with the two next following regulations in the case of the following substances, when intended for parenteral injection:—

(*a*) the microbial and viral vaccines to which part I of the third schedule to these regulations applies;

(*b*) toxins, antigens and mixtures of toxins or antigens with serum which are intended to be used in medical practice for immunising treatment or for diagnosis by inoculation of the patient;

(*c*) sera and solutions of serum proteins;

(*d*) arsphenamine, its derivatives and analogous substances;

(*e*) insulin and preparations of insulin;

(*f*) preparations of the posterior lobe of the pituitary body;

(*g*) antibiotics and preparations containing antibiotics;

(*h*) organic substances having the specific biological action of curare on neuro-muscular transmission, and preparations thereof, to which the Act applies; and

(*i*) dimercaprol and its derivatives, and preparations thereof:

Provided that—

(i) in the case of dry preparations of insulin, in the case of antibiotics and preparations containing antibiotics and in the case of preparations of a vaccine intended for administration by any means other than injection into the tissues, the tests shall be applied with such modifications as the licensing authority consider appropriate;

(ii) if a manufacturer satisfies the licensing authority that he has already in use tests for the presence of living aerobic or anaerobic micro-organisms in any of the above-named substances, and that those tests, as applied by him, will detect the presence of such micro-organisms in the substance as ready for issue with a certainty at least equal to that afforded by the tests prescribed by this part of these regulations, the licensing authority may approve the use of such tests in the place of the prescribed tests, but in such a case the authority may at any time withdraw such approval and require the manufacturer to carry out the prescribed tests:

PART IV.—*cont.*

(iii) the tests shall not apply to any preparation of human blood, or to any preparation as respects which the licensing authority is satisfied that it can be effectively sterilised by heat after being sealed in the container and which has been so sterilised in a manner satisfactory to the licensing authority.

*Application of tests for sterility*

**13.**—(1) The tests referred to in the last foregoing regulation shall be applied to a sample from each batch of the substance, consisting of such number of filled containers as is specified in the next following paragraph.

(2) The number of containers taken for test from every batch shall be 2 per cent. of the containers in the batch or 20 containers whichever is the less, taken at random from the batch, and, if so required by the licensing authority, an additional two containers from each thousand or part of a thousand after the first.

(3) In the case of every substance which is itself bactericidal or bacteriostatic, and of every preparation to which a bactericide or bacteriostatic has been added, there shall be added to the sample before it is tested—

(*a*) such a volume of medium as will dilute the bactericide or bacteriostatic so as to render it ineffective, or

(*b*) such a substance in such concentration as will neutralise the bactericidal or bacteriostatic activity of the substance or preparation being tested without inhibiting the growth of micro-organisms.

*Method of testing for sterility*

**14.**—(1) The tests referred to in the last foregoing regulation shall be made on a fluid medium which, as sterilised for use, shall be capable of promoting the vigorous growth of small numbers of the commoner contaminating micro-organisms, both aerobic and anaerobic:

Provided that if the licensing authority so require tests specified by the licensing authority shall also be made on animals or on special media.

(2) When the medium used for test is equally capable of detecting aerobic and anaerobic micro-organisms, 2 millilitres, or in the case of a solid substance 100 milligrams, of the substance in each container included in the sample or the whole content of the container if the substance in it is 2 millilitres or less or 100 milligrams or less, as the case may be, shall be inoculated into a tube or other vessel containing the medium.

(3) When two media are used for test, one to detect aerobic and one to detect anaerobic micro-organisms, 1 millilitre or 50 milligrams from each sample container, or where the substance in the container is 2 millilitres or less or 100 milligrams or less, approximately half its contents, shall be inoculated into each of two tubes or vessels each containing one of the media.

(4) The inoculated tubes or vessels shall be incubated at 37° C. for 5 days and examined during and after incubation, and durable records shall be kept of the results of the examination of each tube.

(5) If at this examination no growth of micro-organisms is found in any tube, the sample may be regarded as having passed the test.

PART IV.—*cont.*

(6) If at the examination a growth of micro-organisms is found in any tube, a further sample may be taken from the batch in the quantity specified in paragraph (2) of the last foregoing regulation, and the tests may be repeated on the further sample so taken. If on examination of the further sample no micro-organism is found, the sample shall be regarded as having passed the test; but if the same organism is found as was found in the first sample tested the batch shall be treated as not sterile and the material contained in the batch shall not be issued or used as part of a further batch.

(7) If on such examination a micro-organism is found, but the same micro-organism as was found in the sample first tested is not found, the test may be repeated on a third sample taken from the batch in the quantity aforesaid. If on examination of this sample no micro-organism is found the batch shall be regarded as having passed the test; but if any micro-organism is found the batch shall be treated as not sterile and the material contained in the batch shall not be issued or used as part of a further batch.

(8) No container shall be issued before a sample from the batch of which it forms part is regarded as having passed the test in accordance with the foregoing provisions of this regulation.

*Testing in emergency and testing of unstable substances*

**15.** Notwithstanding anything contained in the last foregoing regulation, in any case where—

(*a*) a substance is required in an emergency by a registered medical practitioner, but the licensee has no filled containers in stock; or

(*b*) a substance, in the opinion of the licensing authority, is so unstable that the delay occasioned by the completion of the sterility test on filled containers would render its issue in active form impossible;

the licensee may issue the substance from a batch without completing the sterility test on the filled containers in accordance with the provisions of that regulation, provided that he complies with the following conditions:—

(i) in a case to which paragraph (*a*) of this regulation applies, the licensee shall not issue the substance unless, before the batch from which it was taken was filled into containers, a sample of the batch consisting of not less than 0.1 per cent. of the total volume of the batch if the volume was less than 10 litres and not less than 10 millilitres if the volume was 10 litres or more, but not in any case less than 1 millilitre, was tested for sterility in the manner, so far as may be, required by the said regulation and passed the test;

(ii) the licensee shall before the issue take samples in the required proportions from the containers into which the batch is filled, and shall after the required inoculation and incubation examine the tubes every day for five days;

(iii) if at any examination any growth is visible in any of the tubes, he shall immediately notify the licensing authority and the person supplied;

(iv) he shall keep available for inspection a record of all issues made under this regulation containing such particulars of the circumstances in which the issue is made as the licensing authority may require.

## PART V

### LICENCES FOR IMPORT OF THERAPEUTIC SUBSTANCES

*Undertaking by applicant*

**16.** Every applicant for an import licence shall furnish to the licensing authority a written undertaking in a form approved by the licensing authority, signed by or on behalf of the person who manufactures the therapeutic substance to which the application relates (in this part of these regulations referred to as the " manufacturer "), that for the duration of the licence—

(*a*) the applicant shall be the sole accredited agent of the manufacturer for the import of the substance ;

(*b*) the manufacturer will comply with the conditions imposed on a licensee by paragraphs (*a*) to (*e*) inclusive of regulation 5 of these regulations ;

(*c*) the manufacturer will forthwith report to the licensing authority any proposal to carry on the manufacture of the therapeutic substance in premises other than those in which it was carried on when the licence was issued, and any such change of premises if and when effected, and, in a case in which the manufacture is carried on in more than one factory, any proposal for redistributing functions between factories and any such redistribution if and when effected ;

(*d*) the manufacturer will comply with the provisions of part III of these regulations ;

(*e*) every substance manufactured by the manufacturer for import under licence will as regards strength, quality and purity conform with the provisions of part IV of these regulations and the relative schedule, or, if the substance is one the manufacture of which is not carried on in the United Kingdom, with such standards of strength, quality and purity as may be prescribed for that substance by any regulations made under the Act and for the time being in force, or, if no such standards are so prescribed, with such standards of strength, quality and purity as are prescribed in the case of therapeutic substances of a similar class ;

(*f*) the manufacturer will comply with such further requirements, if any, applicable to manufacturers of therapeutic substances as may be specified in any regulations which may be made under the Act and of which the licensing authority has given to the licensee not less than one month's notice.

*Conditions*

**17.**—(1) Every import licence shall be subject to the observance by the manufacturer of the undertaking furnished by him as aforesaid, and for the purpose of the suspension or revocation of the licence any breach of the undertaking on the part of the manufacturer shall be deemed to be a non-compliance on the part of the licensee with the conditions of the licence.

(2) Every import licence shall, in addition, be subject to the conditions specified in sub-paragraphs (*g*) (*h*) and (*i*) of regulation 5 and to the following further conditions:—

(*a*) the licensee shall allow any inspector authorised in that behalf by the licensing authority to enter with or without prior notice any premises where the imported substance is stocked, to inspect the premises and the means, if any, employed for testing the substance and to take samples ;

(*b*) the licensee shall comply with such further requirements, if any, applicable to the holders of import licences, as may be specified in any regulations which may be made under the Act and of which the licensing authority has given to him not less than one month's notice.

## PART VI

### RESEARCH LICENCES

*Conditions*

**18.** Every research licence shall be subject to the following conditions:—

(*a*) the licensee shall use the substances imported under the licence exclusively for purposes of scientific research, and shall not carry on such research elsewhere than in the place specified in the licence or such other place as the licensing authority may from time to time authorise;

(*b*) the licensee shall allow any inspector authorised in that behalf by the licensing authority to enter with or without prior notice the premises where the substances are kept, to inspect the premises and investigate the manner in which the substances are being used, and to take samples thereof;

(*c*) the licensee shall keep a record of the substances imported under the licence, together with the quantities imported, the date of importation and the name of the manufacturer;

(*d*) the licensee shall comply with such further requirements, if any, applicable to the holders of research licences, as may be specified in any regulations which may be made under the Act and of which the licensing authority has given to the licensee not less than one month's notice.

## PART VII

### THERAPEUTIC SUBSTANCES MANUFACTURED OR IMPORTED FOR EXPORT ONLY

*Dispensation with requirements of regulations*

**19.** The licensing authority may in the case of any particular substance dispense with any of the requirements of these regulations if satisfied that the substance is being manufactured exclusively for sale outside the United Kingdom or is being imported exclusively for re-export, and that such dispensation is desirable, having regard to the nature of any arrangements for regulating the manufacture and sale of the substance in force in the country to which the substance is to be exported.

## PART VIII

### THERAPEUTIC SUBSTANCES INTENDED FOR VETERINARY PURPOSES ONLY

*Act and regulations not to apply to substances intended for veterinary use*

**20.**—(1) Every container of a therapeutic substance intended to be used solely for veterinary purposes shall bear a label on which are printed or written in indelible ink the words "to be used for animal treatment only".

(2) Save as aforesaid, neither the Act nor any regulations made thereunder shall apply to any therapeutic substance which is so labelled and is intended to be used solely for veterinary purposes.

## PART IX

### NON-STERILE SURGICAL LIGATURE AND SUTURE

*Act and regulations to apply only to ligature and suture used on the human body*

**21.**—(1) Every container of and wrapper enclosing surgical ligature or suture, other than a ligature or suture offered or intended to be offered for sale as sterile, shall bear a label on which are printed or written in a

PART IX.—*cont.*

conspicuous manner in indelible red ink the words "non-sterile surgical ligature (suture)—not to be used for operations upon the human body unless efficiently sterilized".

(2) Surgical ligature or suture to which the provisions of the preceding paragraph apply shall not, except for the purposes of that paragraph, be deemed to be added to the Schedule to the Act.

## PART X

### ADDITION OF SUBSTANCES TO SCHEDULE TO ACT

**22.** Dimercaprol and its derivatives, and preparations thereof, and preparations of streptomycin which are intended for parenteral injection, are hereby added to the Schedule to the Act as being substances the purity or potency of which cannot be adequately tested by chemical means.

## PART XI

### SUPPLEMENTARY

*Schedules*

**23.** The provisions of the third and subsequent schedules to these regulations shall have effect with respect to the therapeutic substances to which they respectively relate.

*Revocation*

**24.** The existing regulations are hereby revoked, without prejudice to anything duly done or suffered or to any right, privilege, obligation or liability acquired, incurred or accrued thereunder:

Provided that—

(*a*) the substances added by the said regulations to the Schedule to the Act (that is to say, 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; penicillin which is intended for parenteral injection and preparations containing penicillin which are intended for such injection; preparations of human blood; surgical ligature and surgical suture; and streptomycin), other than streptomycin which is not intended for parenteral injection, shall continue to be included in the Schedule to the Act;

(*b*) any approval or licence granted under the said regulations shall not cease to have effect by reason of the revocation of the said regulations but shall continue in force and have effect as if it had been granted under these regulations.

## FIRST SCHEDULE

### REGULATIONS REVOKED

Therapeutic Substances Regulations, 1931(a).
Therapeutic Substances Amendment Regulations, 1935(b).
Therapeutic Substances (Amendment) Regulations, 1937(c).
Therapeutic Substances Amendment Regulations, 1939(d).
Therapeutic Substances Amendment Regulations, 1944(e).
Therapeutic Substances Amendment Regulations, 1946(f).
Therapeutic Substances Amendment Regulations, 1948(g).
Therapeutic Substances Amendment Regulations, 1949(h).
Therapeutic Substances Amendment Regulations, 1950(i).

## SECOND SCHEDULE

### FORM 1

*Form of Application for *a Licence for Manufacture of Therapeutic Substances for Sale*

*Therapeutic Substances Act.* 1925

To †the Licensing Authority for England and Wales
[*or* Scotland *or* Northern Ireland].

I, / We, , of ,

hereby apply for *a licence to manufacture for sale at the undermentioned therapeutic substances:—

and I / we undertake to allow any inspector authorised by the licensing authority to enter any premises where the manufacture of any of the above-mentioned substances is or is intended to be carried on and to inspect the premises and plant and process of manufacture for the purpose of enabling the authority to be satisfied that the conditions upon which the licence may be issued are or will be complied with, and for the same purpose to take samples.

The names and qualifications of the expert staff responsible for the manufacture or testing of the above-mentioned substances are as follows:—

| *Names.* | *Qualifications.* |
|---|---|
| | Signature |
| | Date |

* In the case of an application for renewal insert after "for" the words "the renewal of".

† The application should be sent, in the case of England and Wales, to the Licensing Authority (Therapeutic Substances), Ministry of Health, Savile Row, London, W.1.; in the case of Scotland to the Licensing Authority (Therapeutic Substances), Department of Health for Scotland, St. Andrew's House, Edinburgh; and in the case of Northern Ireland to the Licensing Authority (Therapeutic Substances), Ministry of Health and Local Government for Northern Ireland, Stormont, Belfast.

(a) S.R. & O. 1931/633; Rev XXII, p. 535; 1931, p. 1311.
(b) S.R. & O. 1935/580; Rev. XXII, p. 535; 1935, p. 1668.
(c) S.R. & O. 1937/767; Rev. XXII, p. 535; 1937, p. 2294.
(d) S.R. & O. 1939/1395; Rev. XXII, p. 535; 1939 II, p. 3172.
(e) S.R. & O. 1944/370; Rev. XXII, p. 535; 1944 I, p. 1009.
(f) S.R. & O. 1946/467; Rev. XXII, p. 589; 1946 I, p. 1590.
(g) S.I. 1948/2418; Rev. XXII, p. 591; 1948 I, p. 4067.
(h) S.I. 1949/1846; 1949 I, p. 4020.
(i) S.I. 1950/1865; 1950 II, p. 1035.

2ND SCH.—*cont.*

FORM 2

*Form of Manufacturing Licence*

*Therapeutic Substances Act,* 1925

The Minister of Health [*or* the Secretary of State for Scotland *or* the Minister of Health and Local Government for Northern Ireland], being the licensing authority under the above-named Act for England and Wales [*or* Scotland *or* Northern Ireland], hereby licenses of , to manufacture for sale at the undermentioned therapeutic substances :—

This licence is granted subject to the conditions contained in any regulations made under the said Act and for the time being in force, and to any requirements thereof relating to the above-named substances, and may be suspended or revoked if the licensee contravenes or fails to comply with any of those conditions and requirements. The licence will, unless previously suspended or revoked, continue in force until the day of

Given under the official seal of the this day of , nineteen hundred and

FORM 3

*Form of Application for *a licence to import a Therapeutic Substance*

*Therapeutic Substances Act,* 1925

To †the Licensing Authority for England and Wales [*or* Scotland *or* Northern Ireland].

I, / We, , of

hereby apply for a *licence to import from of the undermentioned therapeutic substance.

I / We enclose with this application an undertaking signed by or on behalf of the said as required by regulation 16 of the Therapeutic Substances Regulations, 1952.

Signature

Date

FORM 4

*Form of Import Licence*

*Therapeutic Substances Act,* 1925

The Minister of Health [*or* the Department of Health for Scotland *or* the Minister of Health and Local Government for Northern Ireland] being the licensing authority under the above-named Act for England and Wales [*or* Scotland *or* Northern Ireland], hereby licenses of , to import from the under-mentioned therapeutic substance. This licence is granted subject to the conditions pertaining to the importation of the above-named substance set out in any regulations made under the said Act and for the time being in force and may be suspended or revoked if the licensee contravenes or fails to comply with any of those conditions. The licence will, unless previously suspended or revoked, continue in force until the day of

Given under the official seal of the this day of , nineteen hundred and

* In the case of an application for renewal insert after " for " the words " the renewal of ".

† The application should be sent, in the case of England and Wales, to the Licensing Authority (Therapeutic Substances), Ministry of Health, Savile Row, London, W.1 ; in the case of Scotland to the Licensing Authority (Therapeutic Substances), Department of Health for Scotland, St. Andrew's House, Edinburgh ; and in the case of Northern Ireland to the Licensing Authority (Therapeutic Substances), Ministry of Health and Local Government for Northern Ireland, Stormont, Belfast.

2ND SCH.—*cont.*

FORM 5

*Form of application for a *licence to import therapeutic substances for the purpose of scientific research*

*Therapeutic Substances Act*, 1925

To †the Licensing Authority for England and Wales
[or Scotland or Northern Ireland].

I of
hereby apply for a *licence to import therapeutic substances for the purpose of scientific research at and I undertake to comply with the conditions applicable to this licence.

This application is supported by the recommendations appearing below.

Signature

Date

$\frac{\text{I}}{\text{We}}$ ‡recommend that the above application be granted.

1
of
President [Chairman, Principal or Vice-Chancellor] of

2
of
Professor of

---

* In the case of an application for renewal insert after "for" the words "the renewal of".

† The application should be signed by the individual person desiring to import or continue to import the substance and be sent, in the case of England and Wales, to the Licensing Authority (Therapeutic Substances), Ministry of Health, Savile Row, London, W.1; in the case of Scotland to the Licensing Authority (Therapeutic Substances), Department of Health for Scotland, St. Andrew's House, Edinburgh; and in the case of Northern Ireland to the Licensing Authority (Therapeutic Substances), Ministry of Health and Local Government for Northern Ireland, Stormont, Belfast.

‡ The recommendation must be signed by one of the persons named at (*a*) below and also (unless the applicant be such a person) by a person holding one of the offices named at (*b*) below:—

(*a*) The Chairman of the Medical Research Council;
The President of the Royal Society;
The President of the Royal Society, Edinburgh;
The President of the Royal Irish Academy;
The President of the Royal Colleges of Physicians in London, Edinburgh or Dublin;
The President of the Royal Colleges of Surgeons in London, Edinburgh or Dublin;
The President of the Royal College of Obstetricians and Gynaecologists;
The President of the General Medical Council;
The President of the Royal Faculty of Physicians and Surgeons of Glasgow;
The Vice-Chancellor of Queen's University, Belfast;
The President of the Royal College of Veterinary Surgeons;
The Principal of the Royal Veterinary College, London;
The President of the Royal Institute of Chemistry;
The President of the Pharmaceutical Society of Great Britain; or
The President of the Pharmaceutical Society of Northern Ireland.

(*b*) A professor of physiology, medicine, anatomy, medical jurisprudence, materia medica, surgery, pathology, bacteriology, pharmacology, therapeutics or biochemistry in a university in Great Britain or Ireland or in a college in Great Britain or Ireland which is incorporated by royal charter.

2ND SCH.—*cont.*

FORM 6

*Form of Research Licence*

*Therapeutic Substances Act,* 1925

The Minister of Health [*or* the Secretary of State for Scotland *or* the Minister of Health and Local Government for Northern Ireland], being the licensing authority under the above-named Act for England and Wales [*or* Scotland *or* Northern Ireland], hereby licenses of to import therapeutic substances for the purpose of scientific research at or in such other place as the licensing authority may from time to time authorise. This licence is granted subject to the conditions pertaining to the importation of the therapeutic substances for the purpose of scientific research set out in any regulations made under the said Act and for the time being in force and may be suspended or revoked if the licensee contravenes or fails to comply with any of those conditions. The licence will, unless previously suspended or revoked, continue in force until the day of

Given under the official seal of the this day of in the year nineteen hundred and

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## THIRD SCHEDULE

### VACCINES, TOXINS AND ANTIGENS

### PART I

### PROVISIONS APPLICABLE TO MICROBIAL AND VIRAL VACCINES

#### Definition

1.—(1) This part of this schedule applies to vaccines made from any micro-organism or virus pathogenic to man or other animal and to vaccines made from other micro-organisms or viruses having antigenic value.

(2) For the purposes of this part of this schedule a vaccine means a sterile suspension of a killed culture of the micro-organism or virus from which the vaccine derives its name or a sterile extract or derivative of a micro-organism or virus which has been prepared from a genuine culture of the micro-organism or virus.

#### Proper name

2.—(1) The proper name of any vaccine is the name of the micro-organism or virus from which it is made, followed by the word " vaccine ", or such other alternative name as the licensing authority may approve.

(2) The proper name of a combination of vaccines is such name as the licensing authority may approve.

#### Staff of establishment

3. The establishment in which vaccines are prepared shall be under the complete direction and control of an expert in bacteriology.

#### Identity of cultures

4. Cultures used in the preparation of vaccines shall, before being manipulated into a vaccine, be thoroughly tested for identity by the generally accepted tests applicable to the particular micro-organism or virus. The records which the licensee is required to keep shall include a record of the origin, properties and characters of the cultures.

3RD SCH.—*cont.*

Method of preparation of oral vaccines in non-liquid form

5. In the case of a preparation of a vaccine intended for administration by any means other than injection into the tissues—

(*a*) any preparatory process of drying or concentration shall be performed with such precautions as are necessary to secure that the vaccine does not lose its sterility in the process ;

(*b*) the method of preparation shall be such as to secure that there shall be no bacterial growth arising from inside the preparation.

Tests

6. In the case of any vaccine prepared from a micro-organism or virus which does not grow readily in ordinary culture media, each batch of the vaccine shall, in addition to being submitted to the general tests for sterility prescribed in part IV of these regulations, be tested for the presence of living micro-organisms either in a similar manner on media which are specially favourable to the growth of the particular micro-organism or virus from which the vaccine was prepared or by injection into an animal of a species known to be susceptible to infection by the particular micro-organism or virus, and no material from any batch shall be issued unless the batch has passed one of these tests.

Labelling

7.—(1) The label on the container shall indicate the composition of the vaccine by reference either—

(*a*) to the number of micro-organisms per millilitre ; or

(*b*) to the weight of dried substance of micro-organisms per millilitre ; or

(*c*) to the number of micro-organisms or weight of dried substance of micro-organisms used in preparing 1 millilitre of the finished product ; or

(*d*) to the immunising power of the vaccine in relation to a standard vaccine approved by the licensing authority ; or

(*e*) to any other criteria approved by the licensing authority.

In the case of a combined vaccine the reference to the number of micro-organisms per millilitre or to the weight of dried substance of micro-organisms shall distinguish between the several kinds of contributing micro-organisms.

(2) If the vaccine as issued for sale is combined with any substance other than a simple diluent, the exact nature and strength of that substance shall be stated on the label.

Method of issue

8. Vaccines may be issued either singly or combined in any proportion in the same container.

PART II

PROVISIONS APPLICABLE TO BACILLUS CALMETTE-GUÉRIN VACCINE

Definition and proper name

1. Bacillus Calmette-Guérin vaccine is a suspension of the bacteria in a living pure culture of a strain of the bacillus of Calmette and Guérin, which bacillus is in this schedule referred to by the initials B.C.G. The proper name of the vaccine is " B.C.G. vaccine ".

Characters of the strain of B.C.G.

2. The strain of B.C.G. employed in the preparation of vaccine shall be approved by the licensing authority and, if tested, shall have the following properties :—

(*a*) it shall be a non-pigmented acid-fast bacillus having the morphological and antigenic characters of the bovine variety of *Mycobacterium tuberculosis ;*

3RD SCH.—*cont.*

(*b*) it shall not grow on any medium in a temperature of 22° C., or within 7 days on ox-heart extract peptone agar in a temperature of 37° C., but it shall grow profusely within 7 to 10 days at a temperature of 37° C. on a solid medium containing lemco extract, peptone, glycerol and egg yolk;

(*c*) if injected intramuscularly in a quantity of 5 milligrams moist weight into each of at least 10 healthy guinea-pigs, each weighing not more than 250 grammes, it shall produce no sign of progressive tuberculosis within a year of the injection in any of the animals. The test shall be held to be invalid if more than 5 of the guinea-pigs die within 12 months after the injection;

(*d*) if injected subcutaneously or intramuscularly in a quantity of 5 milligrams moist weight into each of 10 healthy guinea-pigs, each weighing not more than 250 grammes, it shall within 4 weeks of the injection induce in at least 9 of the guinea-pigs sensitivity to the intracutaneous injection of 10 international units of old tuberculin in a volume of 0.1 millilitre, of a degree which shall cause an area of induration and oedema not less than 5 millimetres in diameter, irrespective of the area of erythema;

(*e*) if injected intracutaneously in doses of 0.1, 0.01, 0.001 and 0.0001 milligram moist weight, into each of 9 healthy guinea-pigs, each weighing from 300 to 500 grammes, it shall produce within 2 to 3 weeks after the injection definite non-suppurating nodules from the doses of 0.1 and 0.01 milligram, slight nodules from the dose of 0.001 milligram and none from the dose of 0.0001 milligram.

Staff of establishment

3.—(1) The establishment in which B.C.G. vaccine is prepared shall be under the complete direction and control of an expert.

(2) No worker shall be employed in the preparation of the vaccine unless, after full clinical, radiological and bacteriological examinations carried out by specialists approved by the licensing authority and repeated not less often than at three-monthly intervals and whenever there is cause to suspect ill health, he is shown to be free from signs of active or potentially active tuberculosis lesions. If an examination reveals signs of active or potentially active tuberculosis the worker shall be removed from the establishment, all strains of B.C.G. shall be re-examined and the unit thoroughly sterilized. The licensee shall take all reasonably practicable precautions to secure that no person is employed in the establishment who is in close contact with a sufferer from any form of open tuberculosis.

Precautions to be observed in preparation and testing

4.—(1) The preparation of B.C.G. vaccine shall be carried out in a special room or in special rooms forming a topographically separate unit, to which only members of the staff authorised by the licensing authority shall have access. All media, glassware and other apparatus required for the preparation and testing of the vaccine shall be prepared and kept in these rooms. Effective precautions shall be taken to prevent the introduction of microbial contamination through the agency of air, water, equipment, material or personnel. No microbial culture other than that of B.C.G. shall be introduced into the unit without the consent of the licensing authority.

(2) No animals shall be permitted in the unit; the inoculations necessary for the testing of the parent strain of B.C.G. and the batches of vaccine shall be given to the animals in premises topographically and functionally separate from the unit in which the vaccine is prepared.

(3) The parent strain of B.C.G. shall be maintained under conditions which will preserve the properties defined in paragraph 2 of this part of this schedule.

(4) The growth from which the vaccine is made shall not be more than 14 days old, and shall be such that, when harvested, one milligram of moist weight of the growth shall give rise to not less than 20 million colonies when plated on a suitable solid medium.

3RD SCH.—*cont.*

Tests for sterility

5.—(1) Regulation 15 of these regulations shall apply to B.C.G. vaccine as being a substance so unstable that the delay occasioned by the completion of the sterility test on filled containers prescribed by part IV of these regulations would render its issue in active form impossible.

(2) In addition to the test prescribed by the said regulation 15, the licensee shall carry out a test for the presence of organisms other than B.C.G. by inoculation of an animal by a method approved by the licensing authority.

(3) The licensee shall not issue the vaccine if there is within 48 hours evidence from any test of contamination by any such organism.

Test for virulence

6. Each batch of vaccine shall be tested for virulence by the intramuscular injection of 5 milligrams moist weight of the constituent organisms into each of 2 healthy guinea-pigs each weighing not more than 250 grammes. The batch shall not be deemed to have passed the test if either animal dies within 3 months or both animals die within 6 months of the injection, or either of the animals shows any sign of progressive tuberculosis during those 6 months.

Test for toxicity

7. Each batch of vaccine shall be tested for toxicity by its intracutaneous injection in doses of 0.1, 0.01, 0.001, and 0.0001 milligram moist weight into each of 2 healthy guinea-pigs, each weighing from 300 grammes to 500 grammes. 2 to 3 weeks after the injection the doses of 0.1 and 0.01 milligram shall produce definite non-suppurating nodules and the dose of 0.001 milligram slight nodules in both animals, and the dose of 0.0001 milligram no nodules in either animal.

Test for skin-sensitizing potency

8. Each batch of vaccine shall be tested for skin-sensitizing potency by its injection into 2 healthy guinea-pigs by the method outlined in sub-paragraph (*d*) of paragraph 2 of this part of this schedule. It shall pass the test if the sensitivity therein described is produced in both guinea-pigs.

Condition of issue

9.—(1) No batch of vaccine shall be issued until it has passed the 48-hour sterility test defined above.

(2) If the result of any of the tests required by paragraphs 5 (2), 6, 7 and 8 of this part of this schedule should after the issue of the vaccine indicate that a particular batch does not fulfil the requirements of these regulations, the licensee shall immediately inform the licensing authority.

Labelling

10.—(1) The label on the container or the label on the wrapper affixed to the packet in which the container is issued for sale shall indicate the prophylactic dose appropriate for the age of the patient and the route of inoculation.

(2) For the purposes of sub-paragraph (*b*) of paragraph (2) of regulation 7 of these regulations, the date on which the manufacture of a batch was completed shall be the date on which the B.C.G. culture was harvested for making the batch.

(3) For the purposes of sub-paragraph (*c*) of paragraph (2) of the said regulation the date to be specified shall be 14 days from the date of manufacture, or such other date as the licensing authority may approve.

PART III

PROVISIONS APPLICABLE TO TUBERCULOSIS VACCINES CONTAINING LIVING BACTERIA, OTHER THAN B.C.G. VACCINE

1. The definitions and proper names of tuberculosis vaccines containing living bacteria other than B.C.G. vaccine, the characters of the strain of bacteria from which any such vaccine is made, the conditions under which the strain must

3RD SCH.—*cont.*

be maintained in order to preserve these characters, the conditions under which the strain is to be harvested for the preparation of the vaccine, the tests for sterility, virulence, toxicity and immunizing or sensitizing potency, the conditions of issue, the contents of the label and the dates of manufacture and expiry of the vaccine, shall be such as shall be approved by the licensing authority.

2. The provisions of paragraph 3 and sub-paragraphs (1) and (2) of paragraph 4 of part II of this schedule shall apply to any such vaccine with any necessary modifications.

## PART IV

## PROVISIONS APPLICABLE TO SMALLPOX VACCINE (VACCINIA VACCINE)

### Definition and proper name

1. Smallpox vaccine is a preparation of the vaccinal material obtained from the lesions produced on the skin of healthy animals or in the membranes of the chick embryo by inoculation of vaccinia virus. Its proper name is " smallpox vaccine ", or alternatively, where obtained from the skin of animals, " vaccine lymph ".

### Staff of establishment

2. The establishment in which smallpox vaccine is prepared shall be under the complete direction and control of an expert.

### Buildings

3.—(1) The animals used in the production of vaccine lymph shall be housed under hygienic conditions in premises satisfactory for this purpose.

(2) A special room, with impervious walls and floor, which can be washed and, when necessary, chemically disinfected, shall be provided for the inoculation of the animals and the collection of the vaccinal material.

(3) Laboratories in which vaccinal material, after harvesting, is being manufactured into vaccine shall be in a building separated by a reasonable distance from stables or buildings housing animals. Such laboratories shall have impervious walls and floors and shall be capable of being readily disinfected.

### Condition of animals

4. Only healthy animals or embryos shall be used in the production of smallpox vaccine. Each animal intended to be used as a source of smallpox vaccine shall, before being passed for the production of smallpox vaccine, be subjected to a period of observation in quarantine for at least 5 days. During the period of quarantine the animal shall remain free from any sign of disease and shall be thoroughly cleaned and groomed.

### Precautions to be observed in preparation

5.—(1) The inoculation shall be made on such parts of the animal as are not liable to be soiled by the passage of faeces. The surface used for inoculation shall be shaved and so cleaned as to procure the nearest possible approach to asepsis. Prior to the collection of vaccinal material the inoculated area of the skin shall be cleaned in a similar fashion.

(2) The vaccinal material shall be collected immediately after the animal has been killed and a thorough *post-mortem* examination of the carcase shall be made by an expert. A complete record of the examination shall be kept, and shall be open to inspection by or on behalf of the licensing authority at any time. If the examination reveals any condition which indicates or suggests that the animal was suffering from any communicable disease (other than vaccinia) the lymph obtained from that animal shall not be issued.

(3) All instruments and appliances used in the production of smallpox vaccine shall be previously sterilized.

3RD SCH.—*cont.*

(4) All processes concerned with the manufacture of smallpox vaccine shall be carried out with thorough aseptic precautions.

(5) All vaccinal material shall be subjected, after collection, to such treatment with glycerol, with or without some other disinfectant, as will bring the content of extraneous micro-organisms of the vaccine within the limit prescribed in paragraph 6 of this part of this schedule.

(6) When such treatment has been completed, the vaccine shall be kept continuously in cold storage, at a temperature below 0° C., but not below −20° C., until it is withdrawn to be filled into containers for issue, after which process the filled containers shall immediately be returned to cold storage and kept continuously at a temperature within the said limits until required for issue:

Provided that the vaccine may be removed from one such cold store to another, if adequate precautions are taken during removal to guard against deterioration.

Tests for purity

6.—(1) The vaccinal material shall be exposed to the action of glycerol, with or without some other disinfectant, under suitable conditions of temperature until tests made by means of plate cultures have shown that the total number of living extraneous micro-organisms has been reduced to not more than 1 in 1 milligram, or 1,000 in 1 millilitre, of the vaccine. The results of these tests shall be recorded and the records kept for inspection. The determination of the content of the living micro-organisms in the vaccine shall be made in a manner approved by the licensing authority, and the enumeration of colonies shall be made after incubation for 2 days at approximately 37° C., and then for at least 3 days at approximately 20° C.

(2) If *Bacillus anthracis* is found to be present the batch of vaccine shall be rejected forthwith, and if *Bacterium coli* or any other pathogen is found which may prove harmful if introduced into the body by the process of vaccination the vaccine shall be kept in cold storage until an examination of at least 10 milligrams or 0.01 millilitre of the vaccine fails to reveal its presence.

(3) When the prescribed reduction in the number of living micro-organisms has been effected, the batch of vaccine may be issued if—

(*a*) tests carried out in a manner approved by the licensing authority on a sample of not less than 0.1 per cent. of the batch have failed to reveal the presence of *Clostridium tetani*; and

(*b*) tests carried out after the process of purification has been completed on a sample of not less than 10 milligrams or 0.01 millilitre have failed to reveal the presence of streptococci pathogenic to man.

Tests for potency

7.—(1) After the process of purification has been completed each batch of smallpox vaccine shall be tested for potency so as to ensure its activity at the time of issue. These tests shall be applied not more than 12 months before the batch of vaccine is finally issued.

(2) For the purpose of the tests progressive dilutions of the vaccine shall be made in physiological saline solution, or other suitable diluent. The dilutions shall be used for the test without filtration.

(3) The vaccine shall be tested by the application of the dilutions to the suitably prepared skin of a rabbit or an animal of such other species as the licensing authority may approve, in direct comparison with similar dilutions of a control vaccine of established potency approved by the licensing authority; and the test shall not be deemed to be satisfied unless both the vaccine under test and the control vaccine—

(*a*) in a dilution of 1 in 1,000 produce in the animal confluent lesions characteristic of vaccinia; and

3RD SCH.—*cont.*

(*b*) in a dilution of 1 in 10,000 produce in the animal not less than 10 characteristic discrete vesicles:

Provided that the licensing authority may approve any other form of test for potency which may be submitted to the licensing authority for approval.

Labelling

8.—(1) The label on the container or a label or wrapper affixed to the package in which the container is issued for sale shall bear a statement that the potency of the vaccine cannot be assured for more than 7 days from the date of completion of manufacture, unless—

(*a*) the vaccine is kept continuously at a temperature below 10° C., in which case its potency is assured for 14 days, or

(*b*) it is kept continuously at a temperature below 0° C., but not below −20° C., in which case its potency is assured for 12 months.

(2) For the purposes of sub-paragraph (*b*) of paragraph (2) of regulation 7 of these regulations, the date on which the manufacture of the batch is completed shall be the date on which it is removed from cold storage for issue.

Application of this part of this schedule to dried smallpox vaccine

9.—(1) Sub-paragraphs (5) and (6) of paragraph 5 and sub-paragraph (2) of paragraph 8 of this part of this schedule shall not apply to smallpox vaccine prepared in a dry form (in this paragraph called "dried smallpox vaccine").

(2) The tests specified in paragraph 6 of this part of this schedule shall in the case of dried smallpox vaccine be applied to the vaccine as reconstituted, and sub-paragraph (1) of that paragraph shall have effect in that case as if for the words from the beginning to "inspection" there were substituted the words "Dried smallpox vaccine as reconstituted shall not have more than 1,000 living extraneous micro-organisms in 1 millilitre. Tests shall be made for this purpose and the results of the tests shall be recorded and the records kept for inspection".

(3) Paragraph 7 of this part of this schedule shall have effect in relation to dried smallpox vaccine as if in sub-paragraph (1) thereof for the words from the beginning to "issue" the following words were substituted:—

"(1) Samples of each batch of dried smallpox vaccine shall be reconstituted in the form in which they are to be inoculated and tested for potency so as to ensure their activity at the time of issue."

(4) Sub-paragraph (1) of paragraph 8 of this part of this schedule, in its application to dried smallpox vaccine, shall have effect as if for the words from "date of completion of manufacture" to the end of the sub-paragraph there were substituted the words "date of reconstitution."

(5) Dried smallpox vaccine, when reconstituted for use, shall be kept continuously in cold storage, at a temperature below 0° C., but not below −20° C., until it is withdrawn for use.

PART V

PROVISIONS APPLICABLE TO VACCINES CONTAINING LIVING BACTERIA, VIRUSES, OR OTHER POTENTIALLY INFECTIVE AGENTS, OTHER THAN VACCINES TO WHICH PARTS II TO IV OF THIS SCHEDULE APPLY.

Extent of this part

1. This part of this schedule applies to every therapeutic substance, other than those to which parts II to IV of this schedule apply, containing, or stated to contain, bacteria, viruses or other potentially infective agents in the living condition.

Proper name

2. The proper name of such a substance is that which the licensing authority, in each particular case, shall approve.

3RD SCH.—*cont.*

Tests

3. Such a substance shall be tested in such manner as the licensing authority shall approve in each particular case for the purpose of determining—

(*a*) that it contains in living condition the bacteria, viruses or other potentially infective agents;

(*b*) that its administration is free from danger; and

(*c*) that it is free from living organisms other than those which it is stated to contain.

## PART VI

## PROVISIONS APPLICABLE TO THE REAGENTS USED IN THE SCHICK TEST FOR THE DIAGNOSIS OF SUSCEPTIBILITY TO DIPHTHERIA

Definitions and proper names

1.—(1) The reagents used in the Schick test are two, Schick toxin and Schick control. Their proper names respectively are "Schick test toxin" and "Schick control".

(2) Schick test toxin is a sterile filtrate from a culture on nutrient broth of the specific organism of diphtheria (*Corynebacterium diphtheriae*), diluted with an appropriate saline solution to the strength proper for use in the test.

(3) The dilution of Schick test toxin proper for the test is that in which 0.2 millilitre contains one test dose.

(4) A test dose for the purposes of the foregoing sub-paragraph is such an amount of Schick test toxin—

(*a*) as, if injected intracutaneously into a healthy guinea-pig, will cause no local reaction if mixed with 1/750th or more of a unit of diphtheria antitoxin, and will cause a definite local reaction of the type known as "the positive Schick test reaction" if mixed with 1/1250th or less of such a unit;

(*b*) as, if so injected in a dilution of 1 in 50, will not cause a local reaction; and

(*c*) as, if so injected in a dilution of 1 in 25, will cause a definite local reaction of the type known as the "positive Schick test reaction".

(5) Schick control is prepared from the same batch of Schick test toxin as that with which it is issued for sale, by destroying the specific toxicity. This is effected by heating the toxin at a temperature not lower than 70° C. for not less than 5 minutes. Schick control is issued in a dilution not weaker than that in which the corresponding toxin is used in the test.

## PART VII

## GENERAL PROVISIONS APPLICABLE TO DIPHTHERIA PROPHYLACTIC

Definitions and proper names

1.—(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.

(2) 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 or mixture.

3RD SCH.—*cont.*

Quality

2. No batch of diphtheria prophylactic shall be issued unless it is an efficient immunising antigen.

Test for toxicity

3. 5 millilitres of the preparation, or, if a different volume is specified in the next following five parts of this schedule 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 5 healthy guinea-pigs, each weighing from 250 to 350 grammes. The injection shall not cause the death of any of the guinea-pigs from specific intoxication within 30 days.

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 healthy guinea-pigs, they will 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.

## PART VIII

### 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 millilitre of the diphtheria prophylactic F.T. diluted with physiological saline solution to a volume of 1 millilitre shall be injected into each of 10 healthy guinea-pigs on each of 2 occasions separated by an interval of not more than 4 weeks. The guinea-pigs shall be tested for immunity to diphtheria toxin not later than 3 weeks after the second injection. The test for immunity shall be made by the intracutaneous injection into each guinea-pig of 0.2 millilitre of a dilution of diphtheria toxin containing the equivalent of 5 Schick test doses (0.005 Lf). If, 48 hours after injection, more than 2 of the 10 guinea-pigs exhibit a positive Schick reaction, the batch shall be treated as insufficiently potent and shall not be issued.

## PART IX

### 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 saline solution. The proper name of the substance is "diphtheria prophylactic A.P.T."

3RD SCH.—*cont.*

Test 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 millilitre of the final preparation shall represent not less than 50 specific flocculation equivalents (50 Lf) of the toxoid used in its preparation.

Test 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 saline solution to 1 millilitre shall be injected into each of 10 healthy guinea-pigs on each of two occasions separated by an interval of not more than 4 weeks. The guinea-pigs shall be tested for immunity not later than 3 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 test for toxicity shall be 1 millilitre.

## PART X

### SPECIAL PROVISIONS APPLICABLE TO DIPHTHERIA PROPHYLACTIC (PURIFIED TOXOID, ALUMINIUM PHOSPHATE PRECIPITATED)

Definition and proper name

1. Diphtheria prophylactic (purified toxoid, aluminium phosphate precipitated) is a preparation made by adding a suitable quantity of dissolved purified diphtheria toxoid to a suspension of hydrated aluminium phosphate in physiological saline, so adjusted that the required amount of the toxoid is adsorbed by the aluminium phosphate. The proper name of the substance is "diphtheria prophylactic P.T.A.P.".

Tests

2. The provisions of paragraphs 2, 3 and 4 of part IX of this schedule shall apply to diphtheria prophylactic P.T.A.P., with the substitution for references to diphtheria prophylactic A.P.T. of references to diphtheria prophylactic P.T.A.P.

## PART XI

### 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 millilitre, and to which diphtheria antitoxin has been added in an amount sufficient to neutralise completely any remaining 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 millilitre of the final preparation shall represent not less than 3 specific flocculation equivalents (3 Lf) of the toxoid used in its preparation.

3RD SCH.—*cont.*

Test for minimum potency as an immunising antigen

3. 0.1 millilitre of diphtheria prophylactic T.A.M. diluted with physiological saline solution to 1 millilitre shall be injected into each of 10 healthy guinea-pigs on each of two occasions separated by an interval of not more than 4 weeks. The guinea-pigs shall be tested for immunity to diphtheria toxin not later than 3 weeks after the second injection. The test for immunity shall be made by the intracutaneous injection into each guinea-pig of 0.2 millilitre of a dilution of diphtheria toxin containing the equivalent of 1 Schick test dose (0.001 Lf). If, 48 hours after injection, more than 2 of the 10 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.

## PART XII

## 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 millilitre, 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 saline 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 millilitre of the final suspension shall 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 millilitre of the diphtheria prophylactic T.A.F. diluted with physiological saline solution to 1 millilitre shall be injected into each of at least 9 healthy guinea-pigs on each of two occasions separated by an interval of not more than 4 weeks. Tests for immunity to diphtheria toxin shall be made not later than 3 weeks after the second injection by the separate but simultaneous intracutaneous injection, into each of not less than 9 of the guinea-pigs, of 0.2 millilitre 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, 48 hours after injection, not 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, not more than two-thirds of the guinea-pigs tested exhibit a positive reaction to the equivalent of 2 Schick test doses of diphtheria toxin, the batch shall be treated as sufficiently potent.

## PART XIII

## PROVISIONS APPLICABLE TO STAPHYLOCOCCUS TOXOID

Definition and proper name

1. Staphylococcus toxoid is staphylococcus toxin (the sterile filtrate from a culture on a suitable medium of a toxigenic strain of *Staphylococcus*), the specific toxicity of which has been reduced to a low value by the action of chemical substances in such a manner that it retains efficient properties as an immunising antigen. Its proper name is "staphylococcus toxoid".

3RD SCH.—*cont.*

Staphylococcus toxoid may be issued either—

(*a*) undiluted; or

(*b*) already diluted with a saline solution to the strength suitable for injection.

Tests

2. Staphylococcus toxoid shall be submitted to each of the following tests and shall not be issued unless it passes all the tests:—

(*a*) *Tests to determine that the specific toxicity of the toxin used in its preparation has been sufficiently reduced*

(i) 1 volume of the undiluted staphylococcus toxoid shall be added to 4 volumes of physiological saline solution; equal volumes of this dilution of staphylococcus toxoid and of a 2 per cent. suspension of washed red blood corpuscles of the rabbit shall be mixed; when the mixture is heated to 37° C. for 1 hour there shall be no significant haemolysis.

(ii) 0.2 millilitre of the undiluted staphylococcus toxoid shall be injected intracutaneously into a healthy rabbit or guinea-pig; this injection may cause a slight local reaction but shall not produce necrosis.

(iii) 2 rabbits shall be injected intravenously with doses of staphylococcus toxoid calculated at the rate of 2.5 millilitres per kilogram body weight; this injection shall not cause the death of either rabbit within 3 days.

(*b*) *Test for non-specific toxicity*

3 healthy mice shall be injected intraperitoneally with 0.5 millilitre of the undiluted toxoid; this injection shall not cause the death of any of the animals within 7 days.

(*c*) *Tests for potency as an immunising antigen*

1 millilitre of the undiluted staphylococcus toxoid shall be injected into each of not less than 9 healthy guinea-pigs on each of two occasions separated by an interval of not more than 4 weeks; at a date not later than 2 weeks after the second injection the staphylococcus antitoxin present in the serum of each guinea-pig shall be determined.

If the serum of each of two-thirds or more of the guinea-pigs tested contains 0.5 unit or more of staphylococcus antitoxin per millilitre of serum or, alternatively, if the serum of each of one-third or more of the guinea-pigs tested contains 1 unit or more of staphylococcus antitoxin per millilitre of serum, the toxoid shall be accepted as sufficiently potent.

Labelling

3. The label on the container shall indicate the dose, or doses, appropriate for administration at one injection into a human subject.

## PART XIV

## PROVISIONS APPLICABLE TO TETANUS TOXOID

Definition and proper name

1. Tetanus toxoid is tetanus toxin (the sterile filtrate from a culture on nutrient broth of *Clostridium tetani*) the specific toxicity of which has been completely removed by the action of chemical substances in such a manner that it retains efficient properties as an immunising antigen. The proper name of the substance in the form of a simple solution is "tetanus toxoid". The proper name of the substance in any form other than that of simple solution is "tetanus toxoid" together with a phrase indicating the nature of the additional process to which it has been subjected, e.g. "tetanus toxoid, alum precipitated", or "alum precipitated tetanus toxoid".

Tests of tetanus toxoid

2. Tetanus toxoid shall be submitted to each of the tests prescribed in this paragraph and shall not be issued unless it passes all the tests.

3RD SCH.—*cont.*

(*a*) *Tests for sterility*

In addition to the tests for sterility prescribed by part IV of these regulations, tetanus toxoid shall be tested on media and under conditions approved by the licensing authority as being specially favourable for the growth of *Clostridium tetani.*

(*b*) *Tests to determine that the specific toxicity of the toxin used in its preparation has been completely removed*

5 millilitre of the tetanus toxoid shall be injected into each of not less than 5 healthy guinea-pigs, each weighing not more than 350 grammes. If this injection produces any symptom of tetanus in any of the animals injected within 21 days of injection the tetanus toxoid shall be held not to have passed the test.

(*c*) *Tests for potency as an immunising antigen*

The tests shall be carried out on not less than 9 healthy guinea-pigs, each weighing not more than 350 grammes. Each guinea-pig shall receive the tetanus toxoid by injection, either in one dose of 5 millilitres or in 2 doses each of 0.1 millilitre on each of two occasions separated by an interval of not more than 4 weeks. The tetanus antitoxin present in the serum of each guinea-pig shall be determined, in the case of those which received the said one dose not more than 6 weeks after the injection, and in the case of those which received the said 2 doses not later than 2 weeks after the second injection. If the serum of each of two-thirds or more of the guinea-pigs tested contains 0.05 international unit or more of tetanus antitoxin per millilitre of serum, or alternatively, if the serum of each of one-third or more of the guinea-pigs tested contains 0.5 international unit or more of tetanus antitoxin per millilitre of serum, the tetanus toxoid shall be accepted as sufficiently potent.

Tests of tetanus toxoid in forms other than simple solution

3.—(1) When tetanus toxoid is prepared for administration in a form other than simple solution, the tetanus toxoid from which such a form is prepared shall be submitted to the tests for sterility and for absence of specific toxicity prescribed in sub-paragraphs (*a*) and (*b*) of the last foregoing paragraph.

(2) Such a form, after precipitation or other process used for its final preparation, shall again be subjected to the said sterility tests with such modifications as the nature of the product may require to make the test effective.

(3) Such a form, after the precipitation or other process used for its final preparation, shall be subjected to the tests for absence of specific toxicity and for potency as an immunising antigen prescribed in sub-paragraphs (*b*) and (*c*) of the last foregoing paragraph, with the modification that the dose injected in the test for absence of specific toxicity and in the test for potency as an immunising antigen, when a single dose is administered, shall be 1 millilitre.

Labelling

4. The label on the container of tetanus toxoid shall indicate the dose, or doses, appropriate for administration at one injection to a human subject.

3RD SCH.—*cont.*

## PART XV

### SPECIAL PROVISIONS APPLICABLE TO OLD TUBERCULIN

#### Definition and proper name

1. Old tuberculin is the concentrated filtrate from the growth of *Mycobacterium tuberculosis* on a suitable nutrient broth. For its preparation the bacillus shall be grown at approximately 37° C. for a period, usually not less than 6 weeks, sufficient to allow the surface of the fluid medium to become covered by a thick growth of the bacillus. At the end of this period the fluid medium, from which the bacilli may or may not have been previously separated by filtration, shall be concentrated by evaporation to one-tenth of its original volume, and then filtered. If the required test for potency shows that the preparation so concentrated is more potent than the standard preparation, the potency may be reduced to the required degree by appropriate dilution. If the test shows that the potency is less than that of the standard preparation, it shall not be increased by further evaporation. The proper name of the preparation is " old tuberculin ", with or without a suffix such as T., or P.T. The suffix T. will indicate that a strain of *Mycobacterium tuberculosis* var. *hominis* was used in preparing the tuberculin, and the suffix P.T. that a strain of *Mycobacterium tuberculosis* var. *bovis* was used.

#### Standard preparation

2. The standard preparation of old tuberculin is a quantity of old tuberculin kept in the National Institute for Medical Research, London.

#### Unit of standardization

3. The unit of old tuberculin for the purposes of this part of this schedule 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 as exactly equivalent to the unit accepted for international use.

#### Tests for potency

4.—(1) Each batch of old tuberculin shall be tested for potency in comparison with the standard preparation in guinea-pigs rendered specifically hypersensitive to old tuberculin.

(2) Old tuberculin shall not be issued if it contains less than 100,000 units of old tuberculin per millilitre.

#### Test for non-specific toxicity

5. Each batch of old tuberculin shall be tested for the absence of non-specific toxicity by the subcutaneous injection of 0.5 millilitre into a healthy guinea-pig weighing not more than 350 grammes and shall be treated as having passed the test if the injection does not produce any serious effects within 4 days.

#### Labelling

6. The label on the container shall state the number of units of old tuberculin per millilitre of the preparation.

## PART XVI

### SPECIAL PROVISIONS APPLICABLE TO PURIFIED PROTEIN DERIVATIVE OF TUBERCULIN

#### Definition and proper name

1. Purified protein derivative of tuberculin is prepared by fractional precipitation with ammonium sulphate, trichloroacetic acid or other suitable protein precipitant of a fluid medium on which *Mycobacterium tuberculosis* var. *hominis* has been grown, and from which the bacilli have been removed by filtration. The proper name of the substance is " tuberculin P.P.D.".

#### Test for potency

2.—(1) Each batch of tuberculin P.P.D. shall be tested for potency in comparison with the standard preparation of old tuberculin in guinea-pigs rendered specifically hypersensitive to old tuberculin and tuberculin P.P.D.

(2) Tuberculin P.P.D. shall not be issued if it contains less than 40,000 units of old tuberculin per milligram.

3RD SCH.—*cont.*

Test for non-specific toxicity

3. Each batch of tuberculin P.P.D. shall be tested for the absence of non-specific toxicity by the subcutaneous injection of 0.5 millilitre into a healthy guinea-pig weighing not more than 350 grammes, and shall be treated as having passed the test if the injection does not produce any serious effects within 4 days.

Labelling

4. The label on the container shall state the number of units of old tuberculin per millilitre in the case of liquid preparations, and per milligram in the case of solid preparations, to which the preparation of tuberculin P.P.D. is equivalent.

## FOURTH SCHEDULE

### SERA AND ANTITOXINS

### PART I

### PROVISIONS APPLICABLE TO THE PRODUCTION OF ALL SERA FROM LIVING ANIMALS

Staff of establishment

1. The establishment in which the sera are prepared shall be under the complete direction and control of an expert in bacteriology and serology.

Buildings and equipment

2.—(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

3.—(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.

(2) Every new animal intended to be use 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:

4TH SCH.—*cont.*

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.

4.—(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 II

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

Definition

1. This part of this schedule applies 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

2. The proper name of any antibacterial serum to which this part of this schedule 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 organism from which the toxin was prepared, and followed, if desired, by a term indicating the source or the strain of that organism, for example, "streptococcus antitoxin (scarlatina)".

Cultures

3. 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.

Tests for freedom from abnormal toxicity

4. Each batch of serum shall be subjected to the following tests for freedom from abnormal toxicity:—

(*a*) 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 treated as having passed the test for freedom from an excess of bacteriostatic if the injection does not produce any serious effects within four days; and

(*b*) a dose of not less than 5 millilitres of the serum shall be injected subcutaneously or intraperitoneally into a healthy guinea-pig weighing not more than 350 grammes and the serum shall be treated as having passed the test for freedom from other abnormal toxic constituents if the injection does not produce any serious effects within 4 days.

Quality

5.—(1) Any such serum 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

4TH SCH.—*cont.*

(*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

6.—(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 treat the performance of any test recorded under sub-paragraph (1) (*c*) of this paragraph as determining the date of completion of manufacture for the purposes of regulation 7 of these regulations, he shall submit full particulars of the proposed test to the licensing authority and obtain their approval.

Labelling

7.—(1) The label on the container shall indicate the total number of millilitres 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 native serum or purified serum proteins.

## PART III

### GENERAL PROVISIONS APPLICABLE TO THE SUBSTANCES TO WHICH THE SUCCEEDING PARTS OF THE SCHEDULE RELATE

Proper names

1. Where an antitoxin or antiserum to which any of the succeeding parts 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 therein followed by the common name of the animal from which it is prepared.

Standard preparation

2. The standard preparation of an antitoxin or antiserum to which any of the said parts relates is a quantity of the dried antitoxin or antiserum kept in the National Institute for Medical Research, London.

Unit of standardisation

3. The unit for the purpose of these regulations of an antitoxin or antiserum 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:

4TH SCH.—*cont.*

Provided that in the case of an antitoxin or antiserum 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 and freedom from abnormal toxicity

4.—(1) The potency in units of an antitoxin or antiserum 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.

(2) Any such antitoxin or antiserum shall be tested for freedom from abnormal toxicity in the manner provided by paragraph 4 of part II of this schedule.

Quality

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

(*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 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 sub-paragraph (*d*) of paragraph (2) of regulation 7 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 millilitre 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 millilitres 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.

## PART IV

### SPECIAL PROVISIONS APPLICABLE TO 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 ".

4TH SCH.—*cont.*

Strength

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

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.

## PART V

## SPECIAL PROVISIONS APPLICABLE TO 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.—(1) Tetanus antitoxin having a potency of less than 500 units per millilitre in the case of liquid preparations, or less than 5,000 units per gramme in the case of dried preparations, shall not be issued for prophylactic use.

(2) Tetanus antitoxin having a potency of less than 3,000 units per millilitre in the case of liquid preparations, or less than 15,000 units per gramme in the case of dried preparations, shall not be issued for the treatment of tetanus.

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

Labelling

4. The label on the container shall bear a statement that the international units indicated are those determined in July, 1950, and are equivalent to American units.

## PART VI

## SPECIAL PROVISIONS APPLICABLE TO 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 300 units per millilitre in the case of liquid preparations, or less than 3,000 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 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 3, 5, 6 and 7 of part III of this schedule.

4TH SCH.—*cont.*

## PART VII

### SPECIAL PROVISIONS APPLICABLE TO 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 300 units per c.c. in the case of liquid preparations, or less than 3,000 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 750 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 3, 5, 6 and 7 of part III of this schedule.

## PART VIII

### SPECIAL PROVISIONS APPLICABLE TO 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 1,000 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

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 3, 5, 6 and 7 of part III of this schedule.

## PART IX

### SPECIAL PROVISIONS APPLICABLE TO 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 α-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.

## FIFTH SCHEDULE

### ARSPHENAMINE (COMMONLY KNOWN AS SALVARSAN) AND ITS DERIVATIVES AND ANALOGOUS SUBSTANCES

### PART I

### GENERAL PROVISIONS APPLICABLE TO ARSPHENAMINE AND ITS DERIVATIVES AND TO ANALOGOUS SUBSTANCES

#### Standard preparation

1. The standard preparations of arsphenamine and of the derivatives thereof, and of analogous substances used for the specific treatment of infective disease, are quantities of those preparations kept in the National Institute for Medical Research, London.

#### Tests

2. Arsphenamine and its derivatives and such analogous substances as aforesaid, other than oxophenarsine salts, shall be subjected to the following tests—

(*a*) *Test 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 by a proportion higher than that determined by the licensing authority.

(*b*) *Test for potency.*

Samples from each batch shall be tested for potency in comparison with the standard preparation on a series of mice or rats infected with a suitable strain of pathogenic trypanosomes (*T. brucei, T. equiperdum*, &c.) in accordance with the following general method and with such detailed instructions as the licensing authority may issue:—

(i) such mouse or rat in the group on which the test is made shall be infected with the trypanosome employed to an approximately equal degree;

(ii) samples from each batch shall be tested by administration to the animals by a method approved by the licensing authority, and no batch shall be issued which shows a potency less than that of the standard preparation by a proportion higher than that determined by the licensing authority.

#### Method of issue

3. Arsphenamine and any derivative of arsphenamine and any such analogous substance as aforesaid, shall be issued in the form of a dry powder, the glass container being filled before being sealed with some inert gas to the exclusion of oxygen:

Provided that a particular derivative or analogous substance may be issued in some other form with the consent of the licensing authority.

### PART II

### SPECIAL PROVISIONS APPLICABLE TO DERIVATIVES OF ARSPHENAMINE AND ANALOGOUS SUBSTANCES OTHER THAN THOSE SPECIFIED IN THE SUCCEEDING PARTS OF THIS SCHEDULE

#### Nature of substance

1. In the case of any derivative of arsphenamine and any analogous substance used for the specific treatment of infective disease, other than those specified in the succeeding parts of this schedule, the applicant for a manufacturing or an import licence shall submit to the licensing authority with his application a statement of the true chemical nature and composition of the derivative or analogous substance, and a full and detailed account of the chemical tests by which that composition is determined and by which the uniformity of successive batches is secured.

5TH SCH.—*cont.*

Proper name

2. The applicant shall also submit with his application the name which he proposes to use for the derivative or analogous substance to which the application relates, and such name, if approved by the licensing authority, may be used as the proper name thereof.

Chemical tests

3. If a licence is granted for the manufacture of such a derivative or analogous substance, the licensee shall carry out on each batch thereof such, if any, of the chemical tests submitted with the application as are accepted by the licensing authority, and any others which the authority may direct as requisite for determining the composition and securing its constancy. No batch of the substance which fails to pass any of the tests so accepted or directed shall be issued.

Tests for toxicity and potency

4. Each batch of any such derivative or analogous substance shall also be tested by biological methods, for toxicity and potency, according to the methods prescribed in part I of this schedule. In the event of no standard preparation being available for a particular derivative or analogous substance, the tests shall be made in such form and their results interpreted in accordance with such criteria as the licensing authority may direct.

## PART III

## SPECIAL PROVISIONS APPLICABLE TO ARSPHENAMINE

Definition and proper name

1. Arsphenamine is the dihydrochloride of diamino-dihydroxy-arsenobenzene. Its proper name is " arsphenamine."

Quality

2. Arsphenamine shall have the following physical and chemical characteristics:—

(*a*) the substance shall be in the condition of a pale yellow to yellow, dry, amorphous powder, freely mobile in contact with glass surfaces, and without odour, except that due to traces of ether;

(*b*) if 0.5 gramme of the powder is added to 35 millilitres of distilled water, it shall dissolve completely within 15 minutes, yielding a clear pale yellow solution, not acid in reaction to Congo-red paper, and perfectly clear and free from flocculi, hairs, dust and suspended particles of every kind;

(*c*) when 1 millilitre of a 15 per cent. watery solution of sodium hydroxide is added to the solution described in sub-paragraph (*b*) of this paragraph, it shall cause a preliminary separation of the insoluble arseno base, which, if the mixture is gently agitated, shall redissolve in the excess of alkali to form a clear, bright yellow solution;

(*d*) the last mentioned solution, when diluted to 250 millilitres with a 0.5 per cent. solution of pure sodium chloride in distilled water, should give a clear light yellow solution;

(*e*) the dry powder, as taken directly from the sealed ampoules in which it is issued, shall contain not less than 30 per cent. nor more than 34 per cent. of arsenic, as determined by a method approved by the licensing authority.

Test for stability

3. The product, as filled into ampoules, shall be kept at a temperature of 56° C. for at least 24 hours, and shall retain its colour, physical properties and solubility, as specified in paragraph 2 hereof, substantially unchanged at the end of that period.

5TH SCH.—*cont.*

## PART IV

### SPECIAL PROVISIONS APPLICABLE TO NEOARSPHENAMINE

#### Definition and proper name

1. Neoarsphenamine is the sodium salt of diamino-dihydroxy-arsenobenzene-methylene-sulphoxylic acid. Its proper name is "neoarsphenamine."

#### Quality

2. Neoarsphenamine shall have the following physical and chemical characteristics:—

(*a*) the substance shall be in the condition of a yellow, dry powder, freely mobile in contact with glass surfaces, and without odour, except such as is due to traces of ether or alcohol;

(*b*) the substance shall be soluble in water, but insoluble in absolute ethyl alcohol and in ether;

(*c*) if 0.6 gramme of the substance is added to 1 millilitre of distilled water, it shall dissolve rapidly and completely and form a clear, yellow solution, mobile and free from gelatinous particles and suspended matter of any kind;

(*d*) a normal solution of sodium carbonate or a 5 per cent. solution of anhydrous sodium carbonate, added in equal volume to a 10 per cent. watery solution of neoarsphenamine, shall not produce a precipitate;

(*e*) dilute hydrochloric acid (10 per cent. HCl.) added in equal volume to a 10 per cent. watery solution of neoarsphenamine must give a yellow precipitate of the free acid from neoarsphenamine and if the mixture is warmed, sulphur dioxide must be evolved so as to be detected by iodate-starch paper;

(*f*) when a solution of 0.2 gramme of neoarsphenamine in 10 millilitres of water is acidified with phosphoric acid and distilled to about one-half its volume and 5 drops of a 1 per cent. watery solution of phenol is added to the distillate and a layer of sulphuric acid is run under the mixture, formaldehyde shall be detected in the distillate by a red ring formed at the interface;

(*g*) the dry powder, as taken directly from the ampoules in which it is issued, shall contain not less than 18 per cent. nor more than 21 per cent. of arsenic, as determined by a method approved by the licensing authority.

#### Test for stability

3. The product as filled into ampoules shall be kept at a temperature of 56° C. for at least 24 hours and shall retain its colour, physical properties and solubility substantially unchanged at the end of that period.

## PART V

### SPECIAL PROVISIONS APPLICABLE TO SULPHARSPHENAMINE

#### Definition and proper name

1. Sulpharsphenamine is the disodium salt of diamino-dihydroxy-arsenobenzene-methylene-sulphurous acid. Its proper name is "sulpharsphenamine."

#### Quality

2. Sulpharsphenamine shall have the following physical and chemical characteristics:—

(*a*) the substance shall be in the condition of a yellow, dry powder, freely mobile in contact with glass surfaces, and without odour, except that due to traces of ether or alcohol;

(*b*) the substance shall be soluble in water but insoluble in alcohol and in ether;

(*c*) if 0.6 gramme of the substance is added to 1 millilitre of distilled water, it shall dissolve rapidly and completely, and form a clear, yellow solution, mobile and free from gelatinous particles and suspended matter of any kind;

5TH SCH.—*cont.*

(*d*) a normal solution of sodium carbonate or a 5 per cent. solution of anhydrous sodium carbonate, added in equal volume to a 10 per cent. watery solution of sulpharsphenamine, shall not produce a precipitate;

(*e*) five volumes of dilute hydrochloric acid (10 per cent. HCl.) added to one volume of a 10 per cent. watery solution of sulpharsphenamine shall give, after a few minutes, a yellow precipitate of the free acid from sulpharsphenamine, and if the mixture is boiled, sulphur dioxide shall be so evolved as to be detected by iodate-starch paper;

(*f*) when a solution of 0.2 gramme of sulpharsphenamine in 10 millilitres of water is acidified with phosphoric acid and distilled to about one-half its volume and 5 drops of a 1 per cent. watery solution of phenol is added to the distillate and a layer of sulphuric acid is run under the mixture, formaldehyde shall be detected in the distillate by a red ring formed at the interface;

(*g*) on addition of an equal volume of 1 in 10,000 indigo-carmine solution, a 10 per cent. watery solution of sulpharsphenamine shall not reduce the indigo-carmine in 5 minutes at 50° C.;

(*h*) the dry powder, as taken directly from the ampoules in which it is issued, shall contain not less than 18 per cent. nor more than 21 per cent. of arsenic, as determined by a method approved by the licensing authority.

Test for stability

3. The product as filled into ampoules shall be kept at 56° C. for at least 24 hours and shall retain its colour, physical properties and solubility substantially unchanged at the end of that period.

## PART VI

### SPECIAL PROVISIONS APPLICABLE TO OXOPHENARSINE SALTS

Definitions and proper names

1.—(1) Oxophenarsine hydrochloride is the hydrochloride of 3-amino-4-hydroxyphenylarsine oxide ($C_6H_6O_2NAs$, HCl). Its proper name is "oxophenarsine hydrochloride".

(2) Oxophenarsine tartrate is the hydrogen tartrate of 3-amino-4-hydroxyphenylarsine oxide ($C_6H_6O_2NAs$, $C_4H_6O_6$, $2H_2O$). Its proper name is "oxophenarsine tartrate".

Quality

2. The substances mentioned in the foregoing paragraph shall have the following physical and chemical characters:—

(*a*) the substance shall be a white or nearly white odourless powder;

(*b*) the substance shall be soluble in water, in watery solutions of alkali hydroxides and carbonates and in dilute mineral acids, and, in the case of oxophenarsine tartrate, in alcohol;

(*c*) when 250 milligrams of sodium hydrosulphite is added to a solution of about 50 milligrams of the substance in 3 millilitres of distilled water, a yellow precipitate or a salmon-coloured precipitate changing rapidly to yellow shall be formed;

(*d*) when 50 milligrams of the substance is added to 5 millilitres of acetone in a test-tube, a loose plug of cotton wool inserted and the contents gently boiled, the issuing vapours shall not turn moistened blue litmus paper red;

(*e*) the substance shall not lose more than 1 per cent. by weight after exposure for 24 hours to phosphorus pentoxide at a pressure not exceeding 5 millimetres of mercury.

3.—(1) Oxophenarsine hydrochloride, after such exposure as is mentioned in sub-paragraph (*e*) of the last foregoing paragraph, shall contain not less than 30 per cent. nor more than 32 per cent. of arsenic, not less than 29.5 per cent. nor more than 32 per cent. of trivalent arsenic, and not less than 14.8 per cent. nor more than 16 per cent. of chlorine.

5TH SCH.—*cont.*

(2) Oxophenarsine tartrate, after such exposure as aforesaid, shall contain not more than 19.6 per cent. of arsenic, and not less than 19 per cent. nor more than 19.6 per cent. of trivalent arsenic.

4. Oxophenarsine tartrate shall have the following further chemical characters:—

(*a*) when 20 milligrams of the substance is added to a mixture of 2 millilitres of sulphuric acid, 4 drops of a 2 per cent. solution of resorcinol in water and 4 drops of a 10 per cent. solution of potassium bromide in water and the mixture is warmed on a water bath for 5 to 10 minutes, an intense blue colour shall be produced which changes to pink on pouring the mixture into water;

(*b*) when 400 milligrams of the substance is dissolved in 50 millilitres of distilled water, not less than 20.5 nor more than 21.4 millilitres of deci-normal sodium hydroxide solution shall be required for neutralisation, using bromthymol blue as indicator.

Potency and maximum toxicity

5. Oxophenarsine hydrochloride and oxophenarsine tartrate shall have a potency not less than, and toxicity not exceeding, those of the standard preparation by proportions higher than those determined by the licensing authority, and, if so required by the licensing authority, shall be subjected to the tests specified in paragraph 2 of part I of this schedule.

Labelling

6. If either of the substances mentioned in paragraph 1 of this part of this schedule, as issued for sale, is mixed with any substance, the label on the container shall state the nature of that substance and the proportion thereof contained in the mixture.

## SIXTH SCHEDULE

### INSULIN

### PART I

### GENERAL PROVISIONS APPLICABLE TO INSULIN AND PREPARATIONS OF INSULIN

Definition and proper name

1.—(1) Insulin is a preparation of the specific antidiabetic principle of the pancreas. Its proper name is "insulin".

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

Standard preparation

2. The standard preparation of insulin is a quantity of insulin kept at the National Institute for Medical Research, London.

Unit of standardization

3. The unit of insulin for the purposes of these regulations is the specific activity contained in such an amount of the standard preparation of insulin as the Medical Research Council may from time to time indicate as the quantity exactly equivalent to the unit accepted for international use.

Quality

4. Insulin which is issued as a watery solution shall have a pH value lying between 2.5 and 3.5.

6TH SCH.—*cont.*

Tests for potency

5. Insulin and preparations of insulin other than protamine zinc insulin and such other preparations of insulin as may be exempted from compliance with this paragraph by the licensing authority, shall be tested biologically by comparison with the appropriate standard preparation, and the potency and the fiducial limits of error (P = 0.95) of the potency shall be calculated from the results of the test. The estimated potency of a preparation shall be not greater than 111 per cent. and not less than 90 per cent. of the stated potency. The fiducial limits of error (P = 0.95) of the estimated potency shall lie between 80 and 125 per cent. of the stated potency.

Method of issue

6. Insulin and preparations thereof shall not be issued in a mixture with any other therapeutic agent without the consent of the licensing authority.

Labelling

7. In the case of liquid preparations of insulin, the label on the container shall indicate the strength as the number of units per millilitre, and in the case of solid preparations in tablet form, as the number of units in each tablet.

PART II

SPECIAL PROVISIONS APPLICABLE TO GLOBIN INSULIN

Definition and proper name

1. Globin insulin is a preparation of the zinc salt of insulin combined with ox globin. Its proper name is " globin insulin ".

Standard preparation

2. The standard preparation of globin insulin is a quantity of dry globin zinc insulin kept at the National Institute for Medical Research, London.

PART III

SPECIAL PROVISIONS APPLICABLE TO PROTAMINE ZINC INSULIN

Definition and proper name

1. Protamine zinc insulin is the complex produced by the interaction of insulin with a suitable protamine and zinc chloride. Its proper name is " protamine zinc insulin ".

Test for potency

2. In addition to the test required by paragraph 5 of part I of this schedule, the liquor from which the precipitate of protamine zinc insulin has been removed shall be tested biologically by comparison with the standard preparation of insulin, and shall contain not more than 3.75 per cent. of the insulin from which the protamine zinc insulin was manufactured.

Test for delayed action

3. The preparation shall be tested, by comparison with the standard preparation of insulin, by a method approved by the licensing authority, for its power of prolonging the insulin hypoglycaemia in rabbits.

## SEVENTH SCHEDULE

PITUITARY (POSTERIOR LOBE) EXTRACT

Definition and proper name

1. Pituitary extract is the watery extract prepared from the separated posterior lobe of the pituitary body, or the watery solution of one or more of the separated active principles of that lobe. The proper name of the complete watery extract is " pituitary (posterior lobe) extract ". The proper name of a solution containing one of the separated active principles is " oxytocic principle of the pituitary

7TH SCH.—*cont.*

posterior lobe" or "pressor principle of the pituitary posterior lobe" or such other name descriptive of such a solution as the licensing authority may in any particular case approve.

Standard preparation

2. The standard preparation is a quantity of dried pituitary (posterior lobe) extract kept in the National Institute for Medical Research, London.

Unit of standardisation

3.—(1) The unit of pituitary extracts for the purposes of these regulations is the specific activity corresponding to that yielded by 0.5 milligram of the standard preparation when extracted by the method approved by the licensing authority under this schedule.

(2) When the preparation is a solution of a separated active principle, the unit employed in indicating the strength shall be the amount of that active principle yielded to extraction by 0.5 milligram of the standard preparation as determined by the appropriate biological test.

Quality

4. The prepared watery extract shall have a pH value lying between 3.0 and 4.0.

Method of preparation

5. The method used for preparing pituitary posterior lobe extract shall be such as the licensing authority may from time to time approve.

Tests

6. Pituitary posterior lobe extract shall be submitted to such biological tests as the licensing authority shall from time to time approve.

Labelling

7. The label on the container shall indicate the strength of the extract as the number of units per millilitre.

## EIGHTH SCHEDULE

### SURGICAL LIGATURE AND SURGICAL SUTURE

Definition and proper name

1. Surgical ligature or suture is any ligature or form of binding material prepared from the gut or any tissue of an animal and offered or intended to be offered for sale for use in surgical operations upon the human body. When such ligature or suture is offered or intended to be offered for sale as sterile and ready for use, the proper name of the substance shall be "sterilised surgical ligature" or "sterilised surgical suture" followed, in brackets, by the accepted scientific name or a title descriptive of the true nature and origin of the substance as, for example, "sterilised surgical ligature (catgut)" or "sterilised surgical suture (horsehair)".

Test for sterility

2. Every batch of surgical ligature or suture shall consist entirely of material collected under uniform conditions and simultaneously subjected or intended to be subjected to the same process or series of processes for rendering it sterile.

3.—(1) The provisions of regulations 13 and 14 of these regulations, except paragraphs (6) and (7) of regulation 14, shall apply to surgical ligature and surgical suture, with the modification that in paragraph (4) of regulation 14 the expression "12 days" shall be substituted for the expression "5 days".

(2) The tests required by those provisions as so applied shall be applied to the whole of the ligature or suture in the container.

(3) If any growth of micro-organisms is found during the period of the test, the batch from which the sample was taken shall not be issued.

8TH SCH.—*cont.*

Labelling

4. For the purpose of sub-paragraph (*b*) of paragraph (2) of regulation 7 of these regulations, the date on which the manufacture of the batch is completed shall be the date on which the test for sterility was completed.

## NINTH SCHEDULE

### ANTIBIOTICS

### PART I

### GENERAL PROVISIONS APPLICABLE TO ANTIBIOTICS

Scope of schedule

1. This schedule relates to any antimicrobial substance synthesized by bacteria fungi or protozoa, and any substance the chemical properties of which are identical with or similar to any such antimicrobial substance but which is not produced by living organisms, being a substance which is used in the specific treatment of human infections. Any such substance is hereinafter referred to as an antibiotic.

Standard preparation

2. The standard preparation is a quantity of the antibiotic in such form as may be prescribed by the part of this schedule specifically relating to it, kept at the National Institute for Medical Research, London:

Provided that in the case of a derivative of an antibiotic for which biological assay in the terms of the said standard preparation is invalid, the standard preparation shall be such preparation of the antibiotic as may be approved by the licensing authority as suitable for the assay of that derivative.

Unit of standardisation

3. The unit of an antibiotic for the purpose of these regulations is the activity contained in such an amount of the standard preparation as may be indicated from time to time by the Medical Research Council:

Provided that in the case of an antibiotic 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.

Strength

4.—(1) Subject to the provisions of sub-paragraph (2) of this paragraph, an antibiotic shall be tested for potency by comparative tests in relation to the standard preparation by a method approved by the licensing authority.

(2) An antibiotic whose potency can be adequately tested by chemical or physical means may be tested by those means instead of by the tests mentioned in the foregoing sub-paragraph:

Provided that a licensee shall not use any chemical or physical means for testing the potency of an antibiotic unless he is satisfied that, if the antibiotic when tested by those means will satisfy the relative requirements as to potency of this schedule, it will also satisfy those requirements if tested in accordance with the foregoing sub-paragraph.

(3) The potency shall be expressed in units per milligram in the case of an antibiotic in solid form and in units per millilitre in the case of solutions or suspensions:

Provided that if the licensing authority approves the expression of the potency in any other manner the potency may be expressed in that other manner.

9TH SCH.—*cont.*

(4) Where the part of this schedule containing special provisions relating to an antibiotic provides a minimum potency for an antibiotic the licensing authority may authorise, with or without conditions, the issue for specified purposes of such an antibiotic which does not satisfy the said standards of potency.

Test for freedom from abnormal toxicity

5. An antibiotic shall be free from abnormal toxicity and if so required by the licensing authority shall be subjected to the following test for freedom from such toxicity:—

A quantity of the antibiotic containing such number of units as is specified by the part of this schedule specifically relating to it, dissolved, in the case of the antibiotic in solid form, in a volume not exceeding 0.5 millilitre of a watery solution, shall be injected intravenously into each of five healthy mice each weighing between 17 and 22 grammes. The sample shall be treated as having passed the test if either—

(*a*) the injection does not cause death in any of the mice within 24 hours, or

(*b*) the injection having caused death in one only of the mice within that period, further such injections in 5 other such mice do not cause the death of any of those mice within 24 hours.

Test for freedom from pyrogenic substances

6. An antibiotic shall be free from pyrogenic substances and if so required by the licensing authority shall be subjected to the following test for freedom from such substances:—

There shall be injected intravenously into each of 3 healthy rabbits each weighing not less than 1.5 kilograms a quantity of the antibiotic containing, in the case of each rabbit, such number of units as is specified in the part of this schedule specifically relating to it, dissolved, in the case of the antibiotic in solid form, in not more than 5 millilitres of water or physiological saline. The body temperature of the rabbits shall be recorded at least once during the hour before, and three times in the 3 hours after, the injection, one such record being made between 75 and 90 minutes after the injection. The sample shall be treated as having passed the test if the average maximum increase of temperature shown by the 3 rabbits does not exceed 0.6° C.

Labelling

7. If an antibiotic as issued for sale has been mixed with any substance, the label on the container shall state the nature of that substance and—

(*a*) in the case of a preparation issued as a solution or suspension, the minimum number of units of the antibiotic per millilitre of the solution or suspension;

(*b*) in the case of a preparation issued in solid form, either the minimum total number of units of the antibiotic in the container or the minimum number of units thereof per milligram of the mixture.

PART II

SPECIAL PROVISIONS APPLICABLE TO PENICILLIN

Definition

1. Penicillin is any antimicrobial acid which —

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

(*b*) loses its antimicrobial activity on hydrolysis by the penicillinases which destroy the antimicrobial activity of the substances 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.

9TH SCH.—*cont.*

Proper name

2. The proper name of penicillin or a preparation containing penicillin is "penicillin" qualified by a word or words approved by the licensing authority as indicating the nature of the preparation.

Standard preparation

3. The standard preparation is a quantity of dry penicillin salt.

Strength

4.—(1) Salts of penicillin with inorganic bases, if in solid form, shall not be issued with a potency of less than 1,100 units per milligram.

(2) In the case of other salts or derivatives of penicillin, the minimum permitted potency shall be such as shall be determined by the licensing authority.

Test for freedom from abnormal toxicity

5. The number of units of penicillin for the purpose of the test for freedom from abnormal toxicity shall be not less than 1,000.

Test for freedom from pyrogenic substances

6. The number of units of penicillin for the purpose of the test for freedom from pyrogenic substances shall be not less than 2,000 per kilogram of the rabbit's weight.

PART III

SPECIAL PROVISIONS APPLICABLE TO STREPTOMYCIN

Definition

1. Streptomycin is any antimicrobial complex organic base or mixture of such bases produced by *Streptomyces griseus* or other living organism which—

(*a*) yields on hydrolysis by mineral acids the base streptidine (*meso*-1 : 3-diguanido-2:4:5:6-tetrahydroxycyclohexane); and

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

and includes any salt or derivative, or salt of a derivative, of any such base, any mixture of any of the substances aforesaid, and any substance the chemical and biological properties of which are identical with or similar to those of any of the substances aforesaid but which is not produced by living organisms.

Proper name

2. The proper name of streptomycin is "streptomycin" qualified by a word or words approved by the licensing authority as indicating the nature of the preparation.

Standard preparations

3. The standard preparations are a preparation of streptomycin and a preparation of dihydrostreptomycin.

Strength

4.—(1) Salts of streptomycin with inorganic acids, if in solid form, shall not be issued with a potency of less than 600 units per milligram.

(2) In the case of other salts or derivatives of streptomycin the minimum permitted potency shall be such as shall be determined by the licensing authority.

Quality

5. A salt of streptomycin shall form a clear solution with a pH value lying between 5.0 and 7.0 when the dried substance is reconstituted with distilled water in a concentration of 200,000 units per millilitre.

9TH SCH.—*cont.*

Test for freedom from abnormal toxicity

6. The number of units of streptomycin for the purpose of the test for freedom from abnormal toxicity shall be not less than 1,000.

Test for freedom from pyrogenic substances

7. The number of units of streptomycin for the purpose of the test for freedom from pyrogenic substances shall be not less than 2,000 units per kilogram of the rabbit's weight.

Test for freedom from histamine-like substances

8. Streptomycin shall be free from histamine-like substances and if so required by the licensing authority shall be subjected to the following test for freedom from such substances:—

A solution of the streptomycin, containing not less than 3,000 units per millilitre, shall be injected intravenously into a cat anaesthetized with chloralose or a suitable barbiturate in a volume corresponding to 0.1 millilitre per kilogram of the cat's weight. The sample shall be treated as having passed the test, if the injection produces a smaller fall of arterial blood pressure than the injection into the same cat of an equal volume of a solution of a histamine salt containing 1 microgram of histamine base per millilitre.

## TENTH SCHEDULE

### PREPARATIONS OF HUMAN BLOOD

### PART I

### GENERAL PROVISIONS APPLICABLE TO PREPARATIONS OF HUMAN BLOOD

Definition

1. Preparations of human blood include any serum or plasma made from human blood, any protein or other substances separated from human blood and any dried product prepared from any such serum, plasma, protein or other substance.

Provisions as to donors of blood

2. 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

3. 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.

10TH SCH.—*cont.*

Method of preparation

4.—(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

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

Records

6. 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 part 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 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 millilitres.

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.

Labelling

6.—(1) 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;

10TH SCH.—*cont.*

(*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.

(2) For the purposes of sub-paragraph (*b*) of paragraph (2) of regulation 7 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.

## PART III

### SPECIAL PROVISIONS APPLICABLE TO 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 a 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 of 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.

10TH SCH.—*cont.*

## PART IV

### SPECIAL PROVISIONS APPLICABLE TO 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 a 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 subparagraph.

## PART V

### SPECIAL PROVISIONS APPLICABLE TO 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.

10TH SCH.—*cont.*

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.

PART VI

SPECIAL PROVISIONS APPLICABLE TO HUMAN FIBRIN, FIBRINOGEN, THROMBIN AND ANTIBODY 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 antibody globulin is soluble protein which is derived from human plasma or serum and has specific antibacterial, antiviral or antitoxic activity. Its proper name is "human antibody globulin".

Quality, storage and labelling

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

## ELEVENTH 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 TUBOCURARINE CHLORIDE AND PREPARATIONS THEREOF

#### Definitions and proper names

1.—(1) 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 following characteristics:—

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

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

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

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

(v) 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°;

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

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

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

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

#### Standard preparation

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

#### Test for potency

3. Tubocurarine chloride and preparations thereof shall be tested biologically for potency by comparison with the standard preparation and the potency and the fiducial limits of error (P = 0.95) of the potency shall be calculated from the results of the test. The stated potency of the substance shall be not greater than 107 per cent. and not less than 93 per cent. of the standard potency. The percentage fiducial limits of error (P = 0.95) of the estimated potency shall be between 85 and 115.

#### Labelling

4.—(1) The label on a container of tubocurarine chloride or of a solid preparation thereof shall state the total number of milligrams of tubocurarine chloride in the container.

(2) The label on a container of a solution or suspension of tubocurarine chloride shall state—

(*a*) the nature of the vehicle;

(*b*) the number of milligrams of tubocurarine chloride per millilitre of the solution or suspension.

11TH SCH.—*cont.*

(3) The label on a container of a preparation other than an oily injection, or the label or wrapper on the package thereof, shall state that the dose of tubocurarine chloride for an adult should not ordinarily exceed 15 milligrams.

(4) The label on the container of an oily solution or the label or wrapper on the package thereof, shall state that the preparation is for subcutaneous or intramuscular injection only, and that the dose of tubocurarine chloride for an adult should not ordinarily exceed 30 milligrams.

## PART II

### PROVISIONS APPLICABLE TO PREPARATIONS, OTHER THAN TUBOCURARINE CHLORIDE AND PREPARATIONS THEREOF, WHICH OWE THEIR ACTION ON NEURO-MUSCULAR TRANSMISSION TO TUBOCURARINE.

#### Unit of standardisation

1. The unit of tubocurarine chloride for the purposes of this part of this schedule is the specific activity contained in one milligram of the standard preparation.

#### Quality

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

#### Test for potency

3. Tubocurarine chloride and preparations thereof shall be tested biologically for potency by comparison with the standard preparation and the potency and the fiducial limits of error ($P = 0.95$) of the potency shall be calculated from the results of the test. The stated potency of the sample shall not be greater than 105 per cent. nor less than 95 per cent. of the estimated potency. The percentage fiducial limits of error ($P = 0.95$) of the estimated potency must lie between 90 and 111.

#### 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 tubocurarine chloride per milligram in the case of a solid preparation or per millilitre in the case of a liquid, and

(*b*) that one unit of tubocurarine chloride is equivalent to one milligram 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 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 TUBOCURARINE

Extent of part III

1. This part of this schedule applies to organic substances having the specific biological action of curare on neuro-muscular transmission, and preparations thereof, being substances the purity or potency of which cannot be adequately tested by chemical means and being substances 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.

## TWELFTH SCHEDULE

DIMERCAPROL

PART I

GENERAL PROVISIONS APPLICABLE TO DIMERCAPROL

Definition and proper name

1. Dimercaprol is 2:3-dimercaptopropanol. Its proper name is "dimercaprol".

Quality

2. Dimercaprol shall have the following physical and chemical characteristics:—

(*a*) the substance shall be a colourless, or slightly yellow, clear liquid with an alliaceous odour;

(*b*) the substance shall be soluble in water at 15° C. in a concentration of at least 6 per cent. (w./v.);

(*c*) a saturated solution of the substance in water at a temperature of 20° C. shall have a pH value lying between 4.5 and 6.0;

(*d*) the substance shall have a weight per c.c. at 20° C. of not less than 1.235 grammes and not more than 1.255 grammes;

(*e*) the substance shall contain not less than 52.5 per cent. and not more than 54.0 per cent. of thiol, calculated as the thiol radical; and

(*f*) the substance shall contain not more than 0.1 per cent. of bromine and not more than 20 parts per million of iron.

Standard preparation

3. The standard preparation is a quantity of dimercaprol kept at the National Institute for Medical Research, London.

Test for stability

4. Preparations of dimercaprol shall be heated and kept at a temperature of 140° C. for 2 hours under conditions approved by the licensing authority and shall not have lost more than 5 per cent. of their thiol content at the end of that period.

12TH SCH.—*cont.*

Test for freedom from abnormal toxicity

5. Dimercaprol shall be tested biologically by comparison with the standard preparation and the toxicity and fiducial limits of error (P = 0.95) of the toxicity shall be calculated from the results of the test. The estimated toxicity of the sample shall not be greater than 110 per cent. of the toxicity of the standard preparation. The upper fiducial limit of error (P = 0.95) shall not be greater than 120 per cent. of the estimated toxicity.

PART II

SPECIAL PROVISIONS APPLICABLE TO OILY INJECTION OF DIMERCAPROL

Definition and proper name

1. Oily injection of dimercaprol is dimercaprol dissolved in a solution of benzyl benzoate in arachis oil, and stabilized by the addition of ammonia. Its proper name is "oily injection of dimercaprol".

Quality

2.—(1) The oily injection shall be clear and free from deposit.

(2) In the case of oily injections containing 5 per cent. w./v. of dimercaprol, the solvent shall be 10 per cent. (v./v.) benzyl benzoate in arachis oil, or such other proportion as the licensing authority may approve, and the final concentration of dimercaprol shall be between 4.9 and 5.1 per cent.

(3) In the case of oily injections containing 10 per cent. w./v. of dimercaprol, the solvent shall be 20 per cent. (v./v.) benzyl benzoate in arachis oil, or such other proportion as the licensing authority may approve, and the final concentration of dimercaprol shall be between 9.8 and 10.2 per cent.

(4) In the case of oily injections containing proportions of dimercapril other than those mentioned in the foregoing provisions of this paragraph, the proportions of benzyl benzoate and arachis oil, and the final concentration of dimercaprol, shall be such as the licensing authority shall approve.

Test for freedom from abnormal toxicity

3. Oily injections of dimercaprol shall be tested for abnormal toxicity in accordance with provisions of part I of this schedule.

Containers

4. Oily injections of dimercaprol shall be issued in single-dose glass containers sealed by fusion of glass and containing an atmosphere of nitrogen.

Labelling

5. The label on the container shall state:—

(*a*) the nature of the solvent;

(*b*) the number of grammes of dimercaprol per millilitre of the solution;

(*c*) that the solution is intended for subcutaneous or intramuscular injection only.

These regulations were made by the aforesaid Joint Committee this seventh day of November nineteen hundred and fifty-two.

Iain Macleod,
James Stuart,
Dehra Parker
Members of the Joint Committee.

W. G. Honnor,
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 consolidate with amendments (mainly of a drafting character) the regulations specified in the first schedule.

They also add to the Schedule to the Act (see regulation 22, 9th schedule part III, and 12th schedule)—

(*a*) dimercaprol and its derivatives, and preparations thereof ;

(*b*) preparations of streptomycin which are intended for parenteral injection.

New parts of schedules contain special provisions for a number of substances already within the schedule to the Act but hitherto only covered by general provisions, namely B.C.G. vaccine (3rd schedule part II), tuberculin P.P.D. (3rd schedule part XVI), oxophenarsine salts (5th schedule part VI), and globin insulin and protamine zinc insulin (6th schedule parts II and III).

# TOBACCO

## 1952 No. 2226

## The Manufacture of Tobacco Regulations, 1952

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|---|---|
| *Made* - - - - | *22nd December*, 1952 |
| *Laid before Parliament* | *23rd December*, 1952 |
| *Coming into Operation* | *1st January*, 1953 |

The Commissioners of Customs and Excise in pursuance of the powers conferred on them by subsection (1) of section one hundred and seventy-seven of the Customs and Excise Act, 1952(**a**), and of all other powers enabling them in that behalf, hereby make the following Regulations:—

**1.** A tobacco manufacturer (hereinafter referred to as a manufacturer)—

(*a*) before commencing to trade as a manufacturer of tobacco shall make entry of the premises, rooms and places intended to be used by him for the manufacture and storage of tobacco and shall include in such entry any premises which adjoin such premises, rooms and places and are intended for the storage and sale of tobacco ;

(*b*) shall not withdraw such entry while any unmanufactured or partly manufactured tobacco remains in such premises.

**2.** A manufacturer shall not receive into his entered premises—

(*a*) any leaf or other unmanufactured tobacco or stalks of tobacco, otherwise than—

(i) from a warehouse or from the approved premises of a licensed tobacco grower or curer, and on payment of the duty, and

(a) 15 & 16 Geo. 6. & 1 Eliz. 2. c. 44.