STATUTORY INSTRUMENTS

1963 No. 1450

THERAPEUTIC SUBSTANCES

The Therapeutic Substances (Manufacture and Importation) General Regulations 1963

Made - - - -	*23rd August* 1963
Laid before Parliament	*2nd September* 1963
Coming into Operation	*16th September* 1963

The Joint Committee constituted by section 4(1) of the Therapeutic Substances Act 1956(a), in exercise of the powers conferred on them by sections 1 and 5 of the said Act, after consultation with the Advisory Committee constituted under section 4(2) of the said Act, hereby make the following regulations: —

PART I

GENERAL

Citation

1. These regulations may be cited as the Therapeutic Substances (Manufacture and Importation) General Regulations 1963 and shall come into operation on 16th September 1963.

Interpretation

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

" the Act " means the Therapeutic Substances Act 1956 ;

" 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 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 regulations as the proper name of the substance ;

" relative regulations ", in relation to a therapeutic substance, means any regulations made under part I of the Act which are specifically applicable to that substance ;

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

(a) 4 & 5 Eliz. 2. c. 25.

" therapeutic substance " or " substance " means one of the therapeutic substances specified in schedule 1 to the Act or for the time being included in that schedule by virtue of regulations made under part I of the Act.

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

(3) The Interpretation Act 1889(a) 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 schedule 1 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 2 years.

PART II

LICENCES FOR MANUFACTURE OF THERAPEUTIC SUBSTANCES

Conditions

4. 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, or for the proper carrying out of such stages in the manufacture as are undertaken by the licensee;

(*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 any therapeutic substance and the tests carried out thereon in such a form that the records will be easily identifiable with the substance when issued for sale by reference to the number of the batch as shown on each container;

(*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

(a) 52 & 53 Vict. c. 63.

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;

(*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 authorising 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 as regards strength, quality and purity with the provisions of part IV of these regulations and the relative 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 regulations, and with such further requirements, if any, as may be specified in any regulations which may be made under part I of 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

5.—(1) No therapeutic substance shall, except so far as may be otherwise provided by the relative regulations, 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.

(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 regulations relating to containers, and may impose such additional requirements as, having regard to the special nature of the preparation, the authority may deem necessary.

Labelling

6.—(1) No therapeutic substance shall be sold or offered for sale unless with the sealed container thereof there are issued such of the following particulars, and such further particulars (if any), as may be specified in the relative regulations:—

(*a*) the proper name of the substance in letters not less conspicuous than those in which the proprietary name, if any, is stated, and following immediately after or under any 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 regulation 4(*d*) of these regulations;

(*d*) a statement of the potency in units defined in terms of relation to the standard preparation specified in the relative regulations;

(*e*) the name and address of the manufacturer of the final product, or other person authorised by the manufacturer to distribute the product;

(*f*) subject to the provisions of paragraph (4) of this regulation, 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 regulations, or, if there is no definition in the relative regulations, as defined in paragraph (3) of this regulation;

(*g*) subject as aforesaid, the date up to which the substance, if kept under suitable conditions, may be expected to retain a potency not less than that required by the relative regulations, or not to acquire a toxicity greater than that permitted by the relative regulations, as the case may be;

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

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

(2) Where any such particulars are in pursuance of the relative regulations borne by the container of a therapeutic substance, they shall, except so far as the relative regulations otherwise provide, be printed or written in indelible ink on a label affixed to the container by the manufacturer, or by such other person as the licensing authority may in any particular case approve, or marked indelibly in the body of the container by the manufacturer or by such other person as may be so approved; and where any such particulars in pursuance of the relative regulations are borne by the package in which the therapeutic substance is offered for sale, they shall be printed or written in indelible ink either on the package in which the container is offered for sale or on a label affixed to the package by the manufacturer, or by such other persons as may be approved as aforesaid.

(3) For the purpose of paragraph (1)(*f*) of this regulation the date on which the manufacture of a batch is complete shall be—

(*a*) in a case where a test for potency or toxicity is required by the relative 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. or, in the case of smallpox vaccine, a temperature not exceeding −10° C., or, in the case of poliomyelitis vaccine (oral), a temperature not exceeding −20° 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 a case 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 a case to which sub-paragraph (*b*) of this paragraph applies, 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.

(4) Unless the relative regulations provide otherwise, it shall be sufficient for the purposes of paragraph (1)(*f*) and (*g*) of this regulation if, instead of the dates therein mentioned, the month and year are stated which include the date on which the manufacture of a batch was completed or, as the case may be, the month and year up to the end of which the substance may be expected to retain a stated potency or not to acquire excessive toxicity; and in relation to any case in which a month and year are stated in pursuance of this paragraph any reference in these regulations or the relative regulations to either of the dates referred to in the said sub-paragraphs (*f*) and (*g*) shall be construed accordingly.

(5) The licensing authority may modify or dispense with any requirement of this regulation in its application to a container which is intended for export or to a package in which such a container is offered for sale.

(6) Any person named as the distributor of a product in pursuance of paragraph (1)(*e*) of this regulation shall, if so requested in writing by the licensing authority, furnish the name and address of the manufacturer of the product.

Prohibition of sale of substance after prescribed date

7. No person shall sell any therapeutic substance after the date borne by the container or by the package in which the container is offered for sale as being 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 relative regulations, 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 or the package 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

8.—(1) A therapeutic substance intended for sale shall conform with the standards of strength, quality and purity applicable to it under these regulations and the relative regulations, and the tests for determining conformity therewith shall, except so far as the relative regulations may otherwise provide, be applied to samples taken from the final product after every manufacturing process has been completed:

Provided that if the licensing authority approves that any of the tests may be applied, in the case of a preparation of any kind, at an earlier stage in the manufacture, that test may be applied to preparations of that kind at such earlier stage as may be approved by the said authority.

(2) A therapeutic substance intended for sale shall not contain any foreign matter:

Provided that the substance shall be deemed to comply with this paragraph if the amount of any foreign matter contained in it is, in the opinion of the licensing authority, negligible.

Tests for sterility

9. Where a therapeutic substance is required by the relative regulations to be tested for sterility in accordance with these regulations, then, except so far as may be otherwise provided by the relative regulations, the substance shall be tested for the presence of living aerobic or anaerobic micro-organisms in accordance with the provisions of schedule 2 to these regulations:

Provided that—

(*a*) 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 therapeutic substance, 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 the said schedule, 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;

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

Tests for freedom from pyrogenic substances

10. Where a therapeutic substance is required by the relative regulations to be tested for freedom from pyrogenic substances in accordance with these regulations it shall be tested in the manner described in schedule 3 to these regulations.

PART V

LICENCES FOR IMPORT OF THERAPEUTIC SUBSTANCES

Undertaking by manufacturer

11. 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 regulation 4(*a*) to (*e*) inclusive 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*) any 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 regulations, 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 part I of 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 part I of the Act and of which the licensing authority has given to the licensee not less than one month's notice.

Conditions

12. An import licence shall be subject to the conditions specified in regulation 4(*g*) (*h*) and (*i*) of these regulations 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 part I of the Act and of which the licensing authority has given to him not less than one month's notice.

Revocation and suspension

13.—(1) The licensing authority may revoke an import licence or suspend it for such period as he thinks fit if, in his opinion,—

(*a*) the licensee has failed to comply with the conditions subject to which the licence was issued ; or

(*b*) the manufacturer has failed to comply with the undertaking provided by him under regulation 11 of these regulations.

(2) Any such revocation or suspension may apply to all the substances to which the licence applies or to some one or more of them.

PART VI

RESEARCH LICENCES

Conditions

14. A 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 part I of the Act and of which the licensing authority has given to the licensee not less than one month's notice.

Revocation and suspension

15. The licensing authority may revoke a research licence or suspend it for such period as he thinks fit if, in his opinion, the licensee has failed to comply with the conditions subject to which the licence was issued.

PART VII

THERAPEUTIC SUBSTANCES MANUFACTURED OR IMPORTED FOR EXPORT ONLY

Dispensation with requirements of regulations

16.—(1) Subject to the provisions of paragraph (2) of this regulation, where any person licensed under the Act to manufacture or import a therapeutic substance certifies to the licensing authority that the substance, or a specified consignment of the substance, is being manufactured exclusively for sale outside the United Kingdom or is being imported exclusively for re-export, the licensing authority may as respects that substance or consignment dispense with any of the requirements of these regulations or the relative regulations if satisfied that such dispensation is desirable having regard to the nature of any arrangements in force in the country to which the substance is to be exported.

(2) Any dispensation granted under the foregoing paragraph shall be of no effect unless the substance or consignment is dealt with in accordance with the terms of the certificate furnished to the licensing authority.

PART VIII

THERAPEUTIC SUBSTANCES INTENDED FOR VETERINARY PURPOSES ONLY

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

17.—(1) A 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 part I of 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 human body

18.—(1) A container of, and a package containing a container of, 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 conspicuous manner in indelible red ink the words " non-sterile surgical ligature " or " non-sterile surgical suture ", as the case may be, followed in each case by the words " not to be used for operations upon the human body unless sterilized ".

(2) Surgical ligature or suture to which the provisions of the preceding paragraph apply shall not, except for the purpose of that paragraph, be deemed to be added to schedule 1 to the Act.

PART X

SUPPLEMENTARY

Revocation

19. The regulations specified in schedule 4 to these 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 any approval, consent, determination, dispensation, exemption, authorisation, licence or requirement in force 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, imposed or made under these regulations or the relative regulations, as the case may be.

SCHEDULE 1

FORM 1

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

Therapeutic Substances Act 1956

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

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* 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, Alexander Fleming House, Elephant and Castle, London, S.E.1.; in the case of Scotland to the Licensing Authority (Therapeutic Substances), Scottish Home and Health Department, 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.

FORM 2

Form of Manufacturing Licence

Therapeutic Substances Act 1956

The Minister of Health [*or* the Secretary of State *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 part I of 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 .

Given under the official seal of the
on , 19

FORM 3

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

Therapeutic Substances Act 1956

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 substances:—

I/We enclose with this application an undertaking signed by or on behalf of the said as required by regulation 11 of the Therapeutic Substances (Manufacture and Importation) General Regulations 1963.

Signature

Date

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* 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, Alexander Fleming House, Elephant and Castle, London, S.E.1.; in the case of Scotland to the Licensing Authority (Therapeutic Substances), Scottish Home and Health Department, 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.

FORM 4

Form of Import Licence

Therapeutic Substances Act 1956

The Minister of Health [*or* the Secretary of State *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 substances:—

This licence is granted subject to the conditions pertaining to the importation of the above-named substances set out in any regulations made under part I of the said Act and for the time being in force. It may be suspended or revoked if the licensee contravenes or fails to comply with any of those conditions or if the manufacturer of the substances fails to comply with any undertaking provided by him in accordance with any such regulations as aforesaid. The licence will, unless previously suspended or revoked, continue in force until

Given under the official seal of the
on , 19

FORM 5

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

Therapeutic Substances Act 1956

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

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* 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, Alexander Fleming House, Elephant and Castle, London, S.E.1.; in the case of Scotland to the Licensing Authority (Therapeutic Substances), Scottish Home and Health Department, St. Andrew's House, Edinburgh; 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, pharmaceutics or biochemistry or pharmaceutical chemistry in a university in Great Britain or Ireland or in a college in Great Britain or Ireland which is incorporated by royal charter.

FORM 6

Form of Research Licence

Therapeutic Substances Act 1956

The Minister of Health [*or* the Secretary of State *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. The 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 part I of 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 .

Given under the official seal of the
on , 19 .

SCHEDULE 2

STERILITY TESTS

Application of tests for sterility

1.—(1) The tests for sterility shall be applied to a sample from each batch of the substance, consisting of such number of filled containers as specified in the next following sub-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

2.—(1) The tests referred to in the last foregoing paragraph shall be made on a fluid medium which, as sterilized 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.

(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 sub-paragraph (2) of the last foregoing paragraph, 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 unless or until the material has been re-sterilized and has passed the foregoing tests.

(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 unless or until the material has been re-sterilized and has passed the foregoing tests.

(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 paragraph.

Testing in emergency and testing of unstable substances

3. Notwithstanding anything contained in the last foregoing paragraph, 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; or

(*c*) a substance is declared by the relative regulations to be a substance to which this paragraph applies;

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 paragraph, provided that he complies with the following conditions:—

(i) in a case to which sub-paragraph (*a*) of this paragraph 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 paragraph 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 5 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 paragraph containing such particulars of the circumstances in which the issue is made as the licensing authority may require.

SCHEDULE 3

TEST FOR FREEDOM FROM PYROGENIC SUBSTANCES

1. In this schedule—

"maximum temperature", in relation to a rabbit which has been injected as mentioned in paragraph 6 of this schedule, means the highest temperature reading recorded for the rabbit in the 3 hours after the injection;

"mean initial temperature", in relation to such a rabbit, means the average of the temperature readings recorded for the rabbit in the 40 minutes immediately before the injection;

"response", in relation to such a rabbit, means the difference between its mean initial temperature and its maximum temperature.

2. A test for freedom from pyrogenic substances (in this schedule called "a pyrogen test") shall be made with a group of 3 healthy rabbits of either sex, each weighing not less than 1·5 kilograms and having immediately before the test a rectal temperature not exceeding 39·8° C.

3. A rabbit shall not be used in a pyrogen test—

(*a*) if it has been used in a pyrogen test in the preceding 3 days; or

(*b*) if it has been used in the preceding 3 weeks in a pyrogen test in which the substance under examination failed to pass the test; or

(*c*) if it has been used at any time in a pyrogen test in which the average responses of the rabbits in the group exceeded 1·2° C.; or

(*d*) if it is a rabbit which has not been used for a pyrogen test within the preceding 2 weeks, unless within 3 days before the test it has been injected intravenously with 10 millilitres per kilogram of its body weight of pyrogen-free physiological saline and has shown no undue rise or fall in temperature.

4. The measurement of the temperatures of the rabbits in a pyrogen test shall be by a clinical thermometer complying with the requirements of British Standard 691: 1953 (Clinical Maximum Thermometers) or by any other suitable instrument of at least equal precision, inserted in the rectum to a depth of not less than 6 centimetres and not more than 9 centimetres, the depth of insertion being constant for any one rabbit in any one test. If the instrument is left in the rectum throughout the test, the rabbit may be restrained only with a loosely fitting neck-stock, so designed that the rabbit sits in a normal posture.

5. A pyrogen test shall be conducted in a quiet room which has a temperature within 3° C. of that of the rabbits' living quarters or a temperature at which the rabbits have been kept for at least 18 hours before the test. The rabbits used in the test shall not be fed during the period beginning with the night before the test and ending with the completion of the test and shall be given no water during the test.

6. A pyrogen test shall be made by—

(*a*) injecting intravenously into each of the 3 rabbits in the group such quantity of the substance under examination as is specified in the relevant regulations, dissolved or suspended in not more than 5 millilitres of pyrogen-free water or physiological saline or treated by such other method as the licensing authority may approve;

(*b*) taking the temperature of each of the rabbits at regular intervals of not more than 30 minutes over a period beginning at least 90 minutes before the injection and ending 3 hours after the injection.

7. The test may be repeated on a substance so often as the aggregate of the responses of the rabbits used in the test or tests so far made exceeds the amount shown in the second column of the table at the end of this schedule in relation to the number of rabbits so far used but does not exceed the amount shown in the third column thereof in relation thereto:

Provided that not more than 4 tests in all may be made.

8. The substance shall be deemed to be free from pyrogenic substances if after the first test, or after any subsequent test permitted by the last foregoing paragraph, the aggregate of the responses of the rabbits used in the test or tests does not exceed the amount shown in the second column of the said table in relation to the number of rabbits so used.

TABLE

Number of rabbits used	Aggregate of responses	
	Pass if not exceeding	Limit for further test
3	1·15°	2·65°
6	2·80°	4·30°
9	4·45°	5·95°
12	6·60°	

SCHEDULE 4

REGULATIONS REVOKED

The Therapeutic Substances Regulations 1952	S.I. 1952/1937 (1952 III, p. 3420).
The Therapeutic Substances Amendment Regulations 1953	S.I. 1953/1172 (1953 II, p. 2289).
The Therapeutic Substances Amendment Regulations 1954	S.I. 1954/1645 (1954 II, p. 2384).
The Therapeutic Substances Amendment Regulations 1956	S.I. 1956/1131 (1956 II, p. 2364).
The Therapeutic Substances Amendment Regulations 1957	S.I. 1957/550 (1957 II, p. 2553).

These regulations were made by the aforesaid Joint Committee on 23rd August 1963.

J. Enoch Powell,
Michael Noble,
Wm. J. Morgan,
Members of the Joint Committee.

B. H. Betts,
Clerk to the Joint Committee.

EXPLANATORY NOTE

(This Note is not part of the Regulations, but is intended to indicate their general purport.)

These regulations, made under part I of the Therapeutic Substances Act 1956 form part of a comprehensive code relating to the manufacture and importation of therapeutic substances. The code of regulations consolidates in a different form and with certain amendments and additions the Therapeutic Substances Regulations 1952 to 1957.

These regulations reproduce with minor amendments those requirements of the previous regulations which apply to all therapeutic substances and in particular provide for:—

(*a*) granting of licences for manufacture, research and importation;

(*b*) requirements as to containers, labelling and sale;

(*c*) standards of, and tests relating to, the strength, quality and purity of therapeutic substances.

Other regulations contain provisions appropriate to particular groups of substances, these groups at present being antibiotics; arsphenamine and analogous substances; enzymes and enzyme inhibitors; hormone products; preparations of human blood; dextran solution; sera and antitoxins; surgical materials; and vaccines, toxins and antigens.

The substances included in schedule 1 to the 1956 Act by the previous regulations continue to be so included, with the exception of

(*a*) organic substances having the specific biological action of curare on neuro-muscular transmission and preparations thereof;

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

(*c*) heparin not intended for parenteral injection and preparations thereof.