STATUTORY INSTRUMENTS

1963 No. 1455

THERAPEUTIC SUBSTANCES

The Therapeutic Substances (Manufacture of Hormone Products) 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

PRELIMINARY

Citation

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

Interpretation

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

"the Act" means the Therapeutic Substances Act 1956;

"the general regulations" means the Therapeutic Substances (Manufacture and Importation) General Regulations 1963(b);

"the licensing authority" has the same meaning as in the general regulations.

(2) Any reference in these regulations to any provision of the general regulations shall be construed as a reference to that provision as amended, extended or re-enacted by any subsequent regulations made under part I of the Act.

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

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

Inclusion of substances in schedule to Act

3.—(1) Notwithstanding the revocation by the general regulations of the Therapeutic Substances Amendment Regulations 1957(d) corticotrophin and preparations thereof shall continue to be included in schedule 1 to the Act.

(a) 4 & 5 Eliz. 2. c. 25. (b) S.I. 1963/1450 (1963 II, p. 2483). (c) 52 & 53 Vict. c. 63.
(d) S.I. 1957/550 (1957 II, p. 2553).

(2) Preparations of the synthetic active principles of pituitary (posterior lobe), or of derivatives of these principles with the same specific biological action, which are intended for use by injection are hereby added to schedule 1 to the Act as being substances the purity or potency of which cannot be adequately tested by chemical means.

PART II

GENERAL PROVISIONS

Labelling

4.—(1) The particulars specified in regulation 6(1)(*g*) and (*h*) of the general regulation shall be borne both by the container of any substance to which these regulations relate and by the package in which it is offered for sale.

(2) The particulars specified in sub-paragraphs (*a*), (*b*) and (*c*) of the said regulation 6(1) shall be borne by the container of any such substance.

(3) The particulars specified in sub-paragraphs (*e*), (*f*) and (*i*) of the said regulation 6(1) shall, subject to the provisions of regulation 44 of these regulations, be borne either by the container of any such substance or by the package in which it is offered for sale.

PART III

GENERAL PROVISIONS RELATING TO INSULIN

Definition and proper name

5. Insulin is a preparation of the specific antidiabetic principle of the pancreas. Its proper name is " insulin ".

Standard preparation

6. The standard preparation of insulin is one kept at the National Institute for Medical Research, London.

Unit of standardisation

7. 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.

Tests for sterility

8. Insulin and preparations thereof shall be tested for sterility in accordance with the general regulations:

Provided that in the case of any dry preparation of insulin the tests shall be applied with such modifications as the licensing authority consider appropriate for that preparation.

Quality

9. Insulin which is issued as a watery solution shall have a pH value lying between 3·0 and 3·5.

Test for potency

10. Insulin 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 estimated potency of the substance shall not be 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:

Provided that this regulation shall not apply to insulin used in the manufacture of a preparation which is to be tested for potency in pursuance of regulation 13 of these regulations.

Method of issue

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

PART IV

PROVISIONS RELATING TO ALL PREPARATIONS OF INSULIN

Definition and proper names

12. The proper name of a preparation of insulin, or of a mixture of insulin with another therapeutic substance, for which a proper name is not expressly provided in this schedule is "insulin" together with such words or abbreviations as may be approved by the licensing authority as descriptive of that preparation or mixture.

Test for potency

13. Preparations of insulin shall be tested biologically by comparison with the standard preparation of insulin in the manner provided by regulation 10 of these regulations:

Provided that the licensing authority may exempt any preparation of insulin from this requirement.

Method of issue

14. Preparations of insulin shall not be issued in a mixture with any other therapeutic agent without the consent of the licensing authority.

Labelling

15. In addition to the particulars required by regulation 4(1) and (2) of these regulations, particulars of the strength of a preparation of insulin shall be borne by the container thereof, stated—

(*a*) if it is a liquid preparation, as the number of international units of insulin per millilitre;

(*b*) if it is a solid preparation in tablet form, as the number of international units of insulin in each tablet.

PART V

GENERAL PROVISIONS RELATING TO LONG-ACTING INSULIN AND PREPARATIONS OF LONG-ACTING INSULIN

Definition

16. Long-acting insulin consists of insulin prepared in such a way or combined with such a substance or substances that its hypoglycaemic action after parenteral injection is prolonged.

Test for prolongation of action

17. Long-acting insulin shall be tested by comparison with the standard preparation of insulin, by a method approved by the licensing authority, for its power of prolonging insulin hypoglycaemia;

Provided that the licensing authority may exempt any preparation from this requirement.

PART VI

SPECIAL PROVISIONS RELATING TO GLOBIN ZINC INSULIN

Definition and proper name

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

PART VII

SPECIAL PROVISIONS RELATING TO PROTAMINE ZINC INSULIN

Definition and proper name

19. 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 ".

Quality

20.—(1) The quantity of protamine in the preparation shall not be less than 1·0 milligram nor more than 1·7 milligrams of protamine sulphate for each 100 units of insulin.

(2) The liquor from which the precipitate of protamine zinc insulin has been removed shall not contain more than 4 per cent. of the stated activity of the original protamine zinc insulin.

(3) The suspension shall have a pH value lying between 6·9 and 7·3.

PART VIII

SPECIAL PROVISIONS RELATING TO ISOPHANE INSULIN

Definition and proper name

21. Isophane insulin consists substantially of a crystalline complex of insulin, protamine and zinc, suspended in a buffered medium. Its proper name is " isophane insulin ".

Quality

22.—(1) The quantity of protamine in the preparation shall not be less than 0·3 milligram nor more than 0·7 milligram of protamine sulphate for each 100 units of insulin.

(2) The suspension shall have a pH value lying between 7·1 and 7·4.

Test for freedom from protaminase

23.—(1) Isophane insulin shall be tested in accordance with this regulation to ensure its freedom from contamination with protaminase.

(2) A sample of 40 millilitres of isophane insulin shall be divided into two equal portions. One portion shall be centrifuged and the deposit washed with alcohol, dried and weighed. The other portion shall be placed in an incubator at 37°C. and left for 30 days. It shall then be removed from the incubator and centrifuged, and the deposit similarly washed with alcohol, dried and weighed. The loss in weight after 30 days' incubation at 37°C. shall not exceed 10 per cent. of the initial weight.

PART IX

SPECIAL PROVISIONS RELATING TO INSULIN ZINC SUSPENSIONS

Definition and proper names

24. Insulin zinc suspensions are preparations of insulin with zinc in a suitable buffer, such that the insulin is in a form insoluble in water. The proper name of any such preparation is " insulin zinc suspension " followed in parentheses by the word " crystalline " if the insulin is almost wholly in crystalline form or by the word " amorphous " if the insulin is almost wholly in amorphous form.

Quality

25.—(1) The suspension shall have a pH value lying between 7·2 and 7·5.

(2) The liquor from which the precipitate of insulin zinc suspension has been removed shall not contain more than 4 per cent. of the stated activity of the original insulin zinc suspension.

PART X

GENERAL PROVISIONS RELATING TO PITUITARY (POSTERIOR LOBE)

Scope of this Part

26. This part of these regulations relates to preparations of pituitary (posterior lobe) which are intended for use by injection and to preparations of the active principles of pituitary (posterior lobe) intended for parenteral injection.

Standard Preparation

27. The standard preparation of oxytocic, vasopressor or antidiuretic substances is an acetone-dried powder of pituitary (posterior lobe) kept at the National Institute for Medical Research, London.

Unit of Standardisation

28. The unit for the purpose of this part of these regulations is the specific oxytocic, vasopressor or antidiuretic activity, as the case may be, contained in such an amount of the standard preparation of oxytocic, vasopressor or antidiuretic substances as the Medical Research Council may from time to time indicate as the quantity exactly equivalent to the unit accepted for international use.

Quality

29. Preparations of pituitary (posterior lobe), or of the active principles thereof, shall have a pH value lying between 3·0 and 4·0.

Tests

30. Preparations of pituitary (posterior lobe), or of the active principles thereof, shall be tested for sterility in accordance with the general regulations and shall be submitted to such other biological tests as the licensing authority may from time to time require.

Labelling

31. In addition to the particulars required by regulation 4(1) and (2) of these regulations, particulars of the strength of a substance to which this part of these regulations relates shall be borne by the container thereof, stated—

(*a*) in the case of preparations of pituitary (posterior lobe) and preparations of the active principles of pituitary (posterior lobe), other than preparations of vasopressin, as the number of units (oxytocic) per millilitre of the preparation ;

(*b*) in the case of preparations of vasopressin, as the number of units (vasopressor) per millilitre of the preparation.

PART XI

SPECIAL PROVISIONS RELATING TO PITUITARY (POSTERIOR LOBE) INJECTION

Definition and proper name

32. Pituitary (posterior lobe) injection is a watery extract of pituitary (posterior lobe). Its proper name is " pituitary (posterior lobe) injection ".

Method of preparation

33. The method used for preparing pituitary (posterior lobe) injection shall be such as the licensing authority may approve.

PART XII

SPECIAL PROVISIONS RELATING TO PREPARATIONS OF OXYTOCIN

Definition and proper name

34. This part of these regulations relates to preparations containing the oxytocic principle of pituitary (posterior lobe), whether obtained by fractionation from the glands of oxen or other mammals or by synthesis. The proper name of such a preparation is " oxytocin " qualified by a word or words approved by the licensing authority as indicating the nature of the preparation.

Test for freedom from vasopressor activity

35. Preparations of oxytocin shall be tested biologically for freedom from vasopressor activity by comparison with the standard preparation defined in regulation 27 of these regulations, and shall pass the test if they contain less than one unit of vasopressor activity per 20 units of oxytocin.

PART XIII

SPECIAL PROVISIONS RELATING TO PREPARATIONS OF VASOPRESSIN

Definition and proper name

36. This part of these regulations relates to injectable preparations containing the vasopressor and antidiuretic principles of pituitary (posterior lobe), whether obtained by fractionation from the glands of oxen or other mammals or by synthesis. The proper name of such a preparation is " vasopressin " qualified by a word or words approved by the licensing authority as indicating the nature of the preparation.

Test for freedom from oxytocic activity

37. Preparations of vasopressin shall be tested biologically for freedom from oxytocic activity by comparison with the standard preparation defined in regulation 27 of these regulations, and shall pass the test if they contain less than one unit of oxytocic activity per 20 units of vasopressin.

Labelling

38. Where the antidiuretic activity of a preparation of vasopressin has been determined by a method approved by the licensing authority, the number of units (antidiuretic) per millilitre may be stated on the container, in addition to the particulars required by regulation 31(*b*) of these regulations.

PART XIV

GENERAL PROVISIONS APPLICABLE TO CORTICOTROPHIN AND PREPARATIONS OF CORTICOTROPHIN

Definition and proper name

39.—(1) Corticotrophin is a substance obtained from the anterior lobe of the pituitary gland and contains the hormone that increases the rate at which corticoid hormones are secreted by the adrenal gland.

(2) The proper name of corticotrophin is "corticotrophin" and the proper name of a preparation thereof is "corticotrophin" qualified by such word or words or abbreviations as may be approved by the licensing authority as a description of that preparation.

Method of preparation

40. Corticotrophin shall be prepared from pituitary extracts by a method which includes absorption on oxycellulose or by such other methods as shall be approved by the licensing authority.

Standard preparation

41. The standard preparation of corticotrophin is one of dried corticotrophin kept at the National Institute for Medical Research, London.

Unit of standardisation

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

Tests for sterility

43. Corticotrophin and preparations thereof shall be tested for sterility in accordance with the general regulations.

Labelling

44. In addition to the particulars required by regulation 4(1) and (2) of these regulations, the following particulars shall be borne by a container of corticotrophin or a preparation of corticotrophin :—

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

(*b*) a statement of the species of animal from which the substance is derived;

(*c*) in the case of a solid preparation, the total number of units in the container and the volume to be added of the vehicle which is recommended for mixture with the preparation;

(*d*) in the case of a liquid preparation, the total number of units of the solution, the total volume in the container and the nature of the vehicle.

PART XV

SPECIAL PROVISIONS RELATING TO CORTICOTROPHIN

Test for potency

45.—(1) Corticotrophin shall, if so required, be tested for minimum potency by a method approved by the licensing authority and shall comply with the requirements set out in the following paragraph.

(2) Corticotrophin shall be assayed in terms of the units defined in regulation 42 of these regulations by injection into hypophysectomised or

otherwise specially prepared rats, by a method approved by the licensing authority, and the potency and fiducial limits of error of the potency shall be calculated from the results of the test. The estimated potency shall lie between 80 per cent. and 125 per cent. of the potency stated on the label. The fiducial limits of error (P = 0·95) shall lie between 64 per cent. and 156 per cent. of the potency stated on the label.

Test for freedom from abnormal toxicity

46.—(1) Corticotrophin shall be tested for abnormal toxicity in accordance with this regulation.

(2) A solution containing 3·0 units of corticotrophin in not more than 0·3 millilitre of physiological saline shall be injected intravenously into each of 5 healthy mice, each weighing between 18 and 20 grammes. The preparation shall pass the test if either none of the injected mice dies within 48 hours after the injection, or only one of the mice dies within that period and, after similar injections have been made into 5 other such mice, none of these mice dies within 48 hours after the injection.

Test for freedom from pressor activity

47. Corticotrophin shall be tested biologically for freedom from pressor activity by comparison with the Standard Preparation of Oxytocic, Vasopressor and Antidiuretic Substances by a method approved by the licensing authority and shall pass the test if it contains less than 5 units of vasopressor principle per 100 units of corticotrophin.

Labelling

48. In addition to the particulars required by regulation 4(1) and (2) and regulation 44 of these regulations, a statement of the route of injection used in determining the potency of the preparation shall be borne by the container of corticotrophin.

PART XVI

SPECIAL PROVISIONS RELATING TO PREPARATIONS OF CORTICOTROPHIN INTENDED FOR INTRAVENOUS USE

Method of Preparation

49. Preparations of corticotrophin intended for intravenous use shall be prepared from corticotrophin complying with part XIV of these regulations. They shall be sterilised by a method approved by the licensing authority.

Potency

50. Preparations of corticotrophin intended to be given intravenously shall be assayed in their final form in terms of the units defined in regulation 42 of these regulations by intravenous injection into hypophysectomised or otherwise specially prepared rats, by a method approved by the licensing authority, and the potency and the fiducial limits of error of the potency shall be calculated from the results of the test. The estimated potency shall lie between 80 per cent. and 125 per cent. of the potency stated on the label. The fiducial limits of error (P=0·95) shall lie between 64 per cent. and 156 per cent. of the potency stated on the label.

Labelling

51. In addition to the particulars required by regulation 4(1) and (2) and regulation 44 of these regulations, the container of a substance to which this part of these regulations applies shall bear a statement that the preparation is intended for intravenous use only.

PART XVII

SPECIAL PROVISIONS RELATING TO PREPARATIONS OF CORTICOTROPHIN INTENDED FOR USE OTHER THAN BY INTRAVENOUS INJECTION

Method of Preparation

52. Preparations of corticotrophin for injection by other than the intravenous route shall be prepared from corticotrophin as defined in part XIV of these regulations. They shall be sterilised by a method approved by the licensing authority.

Potency

53. Preparations of corticotrophin intended for use other than by intravenous injection shall be assayed in their final form in terms of the units defined in regulation 42 of these regulations by subcutaneous injection into hypophysectomised or otherwise specially prepared rats, by a method approved by the licensing authority, and the fiducial limits of error of the potency shall be calculated from the results of the test. The estimated potency shall lie between 80 per cent. and 125 per cent. of the potency stated on the label. The fiducial limits of error (P=0·95) shall lie between 64 per cent. and 156 per cent. of the potency stated on the label.

Labelling

54. In addition to the particulars required by regulation 4(1) and (2) and regulation 44 of these regulations, the container of a substance to which this part of these regulations applies shall bear a statement that the preparation is for subcutaneous or intramuscular use only.

PART XVIII

SPECIAL PROVISIONS APPLICABLE TO LONG-ACTING PREPARATIONS OF CORTICOTROPHIN

Definition

55. Long-acting corticotrophin is a sterile preparation of corticotrophin combined with or dissolved in a substance or substances which prolongs or prolong the period of its activity in the body.

Potency

56. Long-acting preparations of corticotrophin shall be assayed by injection subcutaneously in terms of the units defined in part XIV of these regulations by a method approved by the licensing authority.

Test for prolongation

57. Long-acting corticotrophin shall be tested biologically by a method approved by the licensing authority as indicating its power of prolonging the specific effects of the corticotrophin contained therein if the licensing authority so directs.

Labelling

58. In addition to the particulars required by regulation 4(1) and (2) and regulation 44 of these regulations the container of a substance to which

this part of these regulations applies shall bear a statement that the preparation is for subcutaneous or intramuscular use only.

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

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

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

EXPLANATORY NOTE

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

These regulations, made under part I of the Therapeutic Substances Act 1956 form part of a comprehensive code relating to the manufacture and importation of therapeutic substances and are to be read in conjunction with the Therapeutic Substances (Manufacture and Importation) General Regulations 1963.

These regulations consolidate with minor amendments (except for the provisions relating to corticotrophin and preparations of corticotrophin, also pituitary (posterior lobe), which have been substantially revised) those requirements of the Therapeutic Substances Regulations 1952 to 1957 which apply to the hormone products mentioned in the following paragraph and in particular provide for:—

(*a*) standards of quality;

(*b*) tests for sterility, potency and other tests appropriate to the particular substance, and

(*c*) requirements as to labelling.

The substances to which the regulations relate are:—

(*a*) insulin and preparations thereof;

(*b*) pituitary (posterior lobe) and preparations thereof, and

(*c*) corticotrophin and preparations thereof.

Preparations of the synthetic active principles of pituitary (posterior lobe) or of derivatives of these principles with the same specific biological action, which are intended for use by injection are added to the substances listed in schedule 1 to the 1956 Act.