STATUTORY INSTRUMENTS

1964 No. 1432

THERAPEUTIC SUBSTANCES

The Therapeutic Substances (Manufacture of Hormone Products) Amendment Regulations 1964

Made - - - -	*7th September* 1964
Laid before Parliament	*15th September* 1964
Coming into Operation	*16th September* 1964

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:—

Citation, Commencement and Interpretation

1.—(1) These regulations may be cited as the Therapeutic Substances (Manufacture of Hormone Products) Amendment Regulations 1964 and shall come into operation on 16th September 1964.

(2) The Therapeutic Substances (Manufacture of Hormone Products) Regulations 1963(b) (hereinafter referred to as "the principal regulations") and these regulations may be cited together as the Therapeutic Substances (Manufacture of Hormone Products) Regulations 1963 and 1964.

(3) In these regulations and in the principal regulations the expression "parenteral injection" in relation to any substance includes any administration of the substance by insertion into the body by any route other than that of the gastro-intestinal tract but does not include any application of the substance to the skin.

(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

2.—(1) Chorionic gonadotrophin and other gonadotrophins of biological origin, preparations thereof, and mixtures which include any of the foregoing are hereby added to schedule 1 to the Therapeutic Substances Act 1956 as being substances the purity or potency of which cannot be adequately tested by chemical means.

(2) For paragraph (2) of regulation 3 of the principal regulations there shall be substituted the following paragraph:—

"(2) Preparations of pituitary (posterior lobe) or of the active principles thereof (whether obtained by fractionation of the gland or by synthesis) or of derivatives of those principles with the same specific biological

(a) 4 & 5 Eliz. 2. c. 25. (b) S.I. 1963/1455 (1963 II, p. 2529). (c) 52 & 53 Vict. c. 63.

action, which are intended for use by parenteral injection are hereby added to schedule 1 to the Act as being substances the purity and potency of which cannot be adequately tested by chemical means.".

Insulin

3. For regulation 9 of the principal regulations (which relates to the quality of insulin) there shall be substituted the following regulation:—

" *Potency and quality*

9.—(1) Insulin shall have a potency of not less than 22 units per milligram calculated with reference to the dried substance.

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

(3) Insulin shall contain not more than 0·04 milligram of zinc per 100 units of insulin.".

Globin zinc insulin, protamine zinc insulin, isophane insulin and insulin zinc suspensions

4. For parts VI to IX of the principal regulations there shall be substituted the following:—

" 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 ".

Quality

18A.—(1) The preparation shall not contain less than 1·3 nor more than 1·8 per cent. w/v of glycerin.

(2) The preparation shall not contain less than 0·25 nor more than 0·35 milligram of zinc for each 100 units of 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 2·5 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.

(4) The preparation shall not contain less than 0·2 nor more than 0·25 milligram of zinc for each 100 units of insulin.

(5) The preparation shall not contain less than 1·3 nor more than 1·8 per cent. w/v of glycerin.

Labelling

20A. In addition to the particulars required by regulation 4(1) and (2) of these regulations, a statement to the effect that the contents should be shaken immediately before use shall be borne by the container of a substance to which this part of these regulations relates.

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.

(3) The preparation shall contain not less than 1·4 nor more than 1·8 per cent. w/v of glycerin.

(4) The liquor from which the precipitate of isophane insulin has been removed shall not contain more than 2·5 per cent. of the stated activity of the original isophane insulin.

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.

Labelling

23A. In addition to the particulars required by regulation 4(1) and (2) of these regulations, a statement to the effect that the contents should be shaken immediately before use shall be borne by the container of a substance to which this part of these regulations relates.

PART IX

SPECIAL PROVISIONS RELATING TO INSULIN ZINC SUSPENSIONS

Definition and proper names

24.—(1) 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 parenthesis 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 and, when not followed by a word in parenthesis, the term " insulin zinc suspension " shall denote a buffered suspension of seven parts of insulin zinc suspension (crystalline) with three parts of insulin zinc suspension (amorphous).

(2) Insulin zinc suspension (crystalline) is a buffered suspension of insulin with zinc chloride in the form of crystals insoluble in water.

(3) Insulin zinc suspension (amorphous) is a buffered suspension of insulin with zinc chloride in the amorphous form insoluble in water.

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 any of the insulin zinc suspensions mentioned in regulation 24 of these regulations has been removed shall not contain more than 2·5 per cent. of the stated activity of the original zinc suspension.

(3) The liquor from which the precipitate of any of the insulin zinc suspensions mentioned in regulation 24 of these regulations has been removed shall not contain more than 0·0055 per cent. w/v of zinc in preparations containing 40 units of insulin per millilitre nor more than 0·007 per cent. w/v of zinc in preparations containing 80 or more units of insulin per millilitre.

(4) The amount of insulin extractable with a suitably buffered acetone solution from any centrifuged precipitate of insulin zinc suspension (crystalline) shall be not greater than 15 per cent. of the total insulin present.

(5) The amount of insulin extractable with a suitably buffered acetone solution from any centrifuged deposit of insulin zinc suspension shall lie between 27 and 40 per cent. of the total insulin present.

Labelling

25A. In addition to the particulars required by regulation 4(1) and (2) of these regulations, a statement to the effect that the contents should be shaken immediately before use shall be borne by the container of a substance to which this part of these regulations relates.".

Corticotrophin

5. In Part XV of the principal regulations before regulation 45 there shall be inserted the following regulation:—

" *Quality*

44A.—(1) Corticotrophin shall not be issued with a potency of less than 24 units per milligram in preparations where the ox or the sheep gland is used as the source of the preparation, or less than 45 units per milligram where the pig gland is used as the source.

(2) Corticotrophin when dissolved according to the manufacturer's directions, or, if there are no such directions, in water, shall have a pH value lying between 3·0 and 5·0.".

6. In regulation 46(2) of the principal regulations (which relates to the toxicity testing of corticotrophin) for the expression "3·0 units" there shall be substituted the expression "9·0 units".

7. After regulation 55 of the principal regulations there shall be inserted the following regulation:—

"*Quality*

55A.—(1) Long-acting corticotrophin as a preparation of corticotrophin with gelatin shall have a pH value lying between 4·5 and 7·0.

(2) Long-acting corticotrophin as a preparation of corticotrophin with zinc hydroxide shall have a pH value lying between 7·6 and 8·1.

(3) A preparation of corticotrophin with zinc hydroxide shall not contain more than 3·0 milligrams of zinc per millilitre.

(4) The liquor obtained by centrifugation of a preparation of corticotrophin with zinc hydroxide shall not contain more than 0·1 milligram of zinc per millilitre.".

8. After regulation 58 of the principal regulations there shall be added the following regulations:—

"PART XIX

GENERAL PROVISIONS APPLICABLE TO CHORIONIC GONADOTROPHIN AND PREPARATIONS OF CHORIONIC GONADOTROPHIN

Definition and proper name

59.—(1) Chorionic gonadotrophin is a dry sterile preparation of the gonad-stimulating substance obtained from the urine of pregnant women.

(2) The proper name of chorionic gonadotrophin is "chorionic gonadotrophin".

Methods of preparation and of sterilisation

60. Chorionic gonadotrophin shall be prepared from the urine of pregnant women and shall be sterilised by filtration.

Standard preparation

61. The standard preparation of chorionic gonadotrophin is one of dried chorionic gonadotrophin kept at the National Institute for Medical Research, London.

Unit of standardisation

62. The unit of chorionic gonadotrophin for the purpose of these regulations is the specific activity contained in such an amount of the standard preparation as is for the time being indicated by the licensing authority, on the advice of the Medical Research Council, as the quantity exactly equivalent to the unit accepted for international use.

Strength

63. Chorionic gonadotrophin in solid form shall have a potency not less than 1,500 units per milligram.

Tests for sterility

64. Chorionic gonadotrophin and preparations thereof shall be tested for sterility in accordance with the general regulations.

Test for freedom from oestrogens

65.—(1) Chorionic gonadotrophin shall be tested for freedom from oestrogens in accordance with this regulation.

(2) A solution containing not less than 100 units of chorionic gonadotrophin in not more than 0·5 millilitre of physiological saline shall be injected subcutaneously into each of 3 rats or 3 mice which have been prepared by ovariectomy not less than 14 days prior to the injection. The preparation shall pass the test if vaginal smears taken from all the rats or mice on each of the third, fourth and fifth days following the injection show no signs of positive oestrus response.

Test for freedom from abnormal toxicity

66.—(1) Chorionic gonadotrophin shall be tested for abnormal toxicity in accordance with this regulation.

(2) A solution containing not less than 1,000 units of chorionic gonadotrophin in not more than 0·5 millilitre of physiological saline shall be injected intravenously over a period of time not exceeding one minute into each of 5 healthy mice, each weighing between 18 and 20 grammes. The preparation shall pass the test either if none of the injected mice dies within 48 hours after the injection, or if 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.

Labelling

67. The labelling requirements of regulation 4 of these regulations shall not apply in respect of chorionic gonadotrophin or preparations of chorionic gonadotrophin, but instead the following requirements shall apply:—

(*a*) the particulars specified in regulation 6(1)(*a*), (*b*), (*c*) and (*d*) of the general regulations shall be borne by the container thereof;

(*b*) the particulars specified in sub-paragraph (*f*) of the said regulation 6(1), together with a statement regarding the precautions necessary for best preserving the properties of the contents shall be borne both by the said container and by the package in which it is offered for sale;

(*c*) the particulars specified in sub-paragraph (*e*) of the said regulation 6(1) shall be borne either by the said container or by the said package.

PART XX

SPECIAL PROVISIONS RELATING TO CHORIONIC GONADOTROPHIN AND PREPARATIONS THEREOF INTENDED FOR PARENTERAL INJECTION

Method of preparation

68. Preparations of chorionic gonadotrophin intended for parenteral injection shall be prepared from chorionic gonadotrophin complying with the preceding part of these regulations. They shall be sterilised by filtration.

Potency

69. Preparations of chorionic gonadotrophin intended for parenteral injection shall be assayed in their final form, in terms of units defined

in regulation 62 of these regulations, 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.

Freedom from pyrogenic substances

70.—(1) Chorionic gonadotrophin intended for parenteral injection shall, if so required by the licensing authority, be tested for freedom from pyrogenic substances in accordance with the general regulations, and in any event shall be free from such substances to such an extent that, if so tested, it would pass the test.

(2) The number of units of chorionic gonadotrophin for the purpose of the test for freedom from pyrogenic substances shall be not less than 1,500 per kilogram of the weight of each rabbit used in the test.

Labelling

71. The labelling requirements of regulation 67 of these regulations shall not apply in respect of chorionic gonadotrophin or preparations of chorionic gonadotrophin intended for parenteral injection, but instead the following requirements shall apply:—

(*a*) the particulars specified in regulation 6(1)(*a*), (*b*) and (*c*) of the general regulations shall be borne by the container thereof, and, in addition—

(i) in the case of a solid preparation, the total number of units in the container and the nature of the vehicle for mixing with the preparation and the volume to be added; or

(ii) in the case of a liquid preparation, the total number of units in the solution, the total volume in the container and the nature of the vehicle included in the mixture

shall be shown on the container;

(*b*) the particulars specified in regulation 6(1)(*e*), (*f*), (*g*) and (*h*) of the general regulations, together with the details of any substances which have been added, shall be borne either by the said container or by the package in which it is offered for sale.".

These regulations were made by the aforesaid Joint Committee on 7th September 1964.

Anthony Barber,
Wm. Craig,
Michael Noble,
Members of the Joint Committee.

W. Turner,
Clerk to the Joint Committee.

EXPLANATORY NOTE

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

These regulations amend the Therapeutic Substances (Manufacture of Hormone Products) Regulations 1963 so as to bring the requirements of those regulations into line with recent advances in practice as regards the manufacture of hormone products.

In addition chorionic gonadotrophin and other gonadotrophins of biological origin are added to the list of substances included in schedule 1 to the Therapeutic Substances Act 1956 as being substances the purity or potency of which cannot be adequately tested by chemical means. The regulations prescribe standards of purity and potency and labelling requirements for the added substances.