STATUTORY INSTRUMENTS

1963 No. 1452

THERAPEUTIC SUBSTANCES

The Therapeutic Substances (Manufacture of Arsphenamine and Analogous Substances) Regulations 1963

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

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

PART I

PRELIMINARY

Citation

1. These regulations may be cited as the Therapeutic Substances (Manufacture of Arsphenamine and Analogous Substances) 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.

PART II

GENERAL PROVISIONS RELATING TO ARSPHENAMINE AND ANALOGOUS SUBSTANCES

Standard Preparation

3. The standard preparation of arsphenamine and of any analogous substance is one kept at the National Institute for Medical Research, London.

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

Tests for Sterility

4. Arsphenamine and any analogous substance shall be tested for sterility in accordance with the general regulations.

Test for maximum toxicity

5.—(1) Arsphenamine and any analogous substance shall be tested for maximum toxicity in accordance with this regulation.

(2) Several separate containers from each finished batch shall be tested 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 specified by the licensing authority.

Test for potency

6.—(1) Arsphenamine and any analogous substance shall be tested for potency in accordance with this regulation.

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

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

(*b*) 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 specified by the licensing authority.

Method of issue

7. Arsphenamine and any analogous substance 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 analogous substance may be issued in some other form with the consent of the licensing authority.

Tests for stability

8. A substance to which these regulations relate shall, when filled into containers, be kept at a temperature of 56°C. for at least 24 hours and shall retain the colour, physical properties and solubility specified in the part of these regulations specifically relating to the substance substantially unchanged at the end of that period.

Labelling

9.—(1) The particulars specified in regulation 6(1)(*g*) of the general regulations shall be borne both by the container of arsphenamine or of any analogous substance, 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 arsphenamine or any analogous substance.

(3) The particulars specified in sub-paragraphs (*e*) and (*f*) of the said regulation 6(1) shall be borne either by the container of arsphenamine or any analogous substance, or by the package in which it is offered for sale.

PART III

SPECIAL PROVISIONS RELATING TO ARSPHENAMINE

Definition and proper name

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

Quality

11. 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 purified water, it shall dissolve completely within 15 minutes, yielding a clear pale yellow solution with a pH value of not less than 3·0 ;

(*c*) when 1 millilitre of a 15 per cent. watery solution of sodium hydroxide is added to the solution described in paragraph (*b*) of this regulation, 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 purified water, shall give a clear light yellow solution ;

(*e*) the dry powder, as taken directly from the sealed containers 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.

PART IV

SPECIAL PROVISIONS RELATING TO ANALOGOUS SUBSTANCES OTHER THAN THOSE SPECIFIED IN THE SUCCEEDING PARTS OF THESE REGULATIONS

Nature of substance

12. In the case of any substance analogous to arsphenamine other than those specified in the succeeding parts of these regulations, 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 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.

Proper name

13. The proper name of an analogous substance for which no proper name is provided by these regulations shall be such name as the licensing authority may approve as descriptive of the substance.

Chemical tests

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

Tests for Toxicity and potency

15. In relation to a substance for which there is no standard preparation, the tests for toxicity and potency shall be made in such form and their results interpreted in accordance with such criteria as the licensing authority may require.

PART V

SPECIAL PROVISIONS RELATING TO NEOARSPHENAMINE

Definition and proper name

16. Neoarsphenamine is the sodium salt of diamino-dihydroxy-arseno-benzene-methylene-sulphoxylic acid. Its proper name is " neoarsphenamine ".

Quality

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

(*a*) the substance shall be in the form 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 purified 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 shall give a yellow precipitate of the free acid from neoarsphenamine and if the mixture is warmed, sulphur dioxide shall 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 purified water is acidified with phosphoric acid and distilled to about one-half of 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 containers 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.

PART VI

SPECIAL PROVISIONS RELATING TO SULPHARSPHENAMINE

Definition and proper name

18. Sulpharsphenamine is the disodium salt of diamino-dihydroxy-arsenobenzene-methylene-sulphurous acid. Its proper name is " sulphar-sphenamine ".

Quality

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

(*a*) the substance shall be in the form 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 purified 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 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 evolved so as to be detected by iodate-starch paper;

(*f*) when a solution of 0·2 gramme of sulpharsphenamine in 10 millilitres of purified water is acidified with phosphoric acid and distilled to about one-half of 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 containers 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.

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

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

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

EXPLANATORY NOTE

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

These regulations, made under part I of the Therapeutic Substances Act 1956 form part of a comprehensive code relating to the manufacture and

importation of therapeutic substances and are to be read in conjunction with the Therapeutic Substances (Manufacture and Importation) General Regulations 1963.

These regulations consolidate with minor amendments those requirements of the Therapeutic Substances Regulations 1952 to 1957 which apply to arsphenamine and analogous substances and in particular provide for:—

(*a*) standards of quality;

(*b*) tests for sterility, maximum toxicity, potency and stability, and

(*c*) requirements as to labelling.