

UNITED STATES PHARMACOPŒIA.

ABSTRACT OF PROPOSED CHANGES WITH NEW STANDARDS AND DESCRIPTIONS.
ELEVENTH REVISION.

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PART I—INORGANIC CHEMICALS.

The Pharmacopœial Convention of 1930 recommended that "abstracts of changes proposed for the U. S. P. XI and new standards and descriptions" be published before final adoption, that those who are not members of the Revision Committee may have an opportunity for comment and criticism.

In compliance with this recommendation, the following abstracts are submitted. The nomenclature and the exact wording does not necessarily represent that to be finally adopted, and doses have not been appended.

Comments should be sent to the Chairman of the Revision Committee.

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I. GENERAL TESTS.

1. *Hydrogen-Ion Concentration.*—A chapter on "Hydrogen Ions and p_H " has been prepared for inclusion in the section of the Pharmacopœia dealing with special tests. This monograph treats in a general way the theoretical considerations involved and sets forth in detail the colorimetric procedure for the determination of p_H . The colorimetric method has been adopted as the official procedure. However, owing to the fact that in many of the colored solutions of the Pharmacopœia this method is inapplicable, the potentiometric method is recognized as an alternative procedure. A table is included containing the salt-error corrections, and, also, suitable directions for the preparation of buffer solutions and indicator solutions accompany the chapter.

The advisability of incorporating a monograph of this kind into a modern pharmacopœia requires no defense. Precedent has already been established by the British Pharmacopœia of 1932, which has included such a monograph. The policy of Sub-Committee No. 7 in respect to the application of the principles of hydrogen-ion concentration to Pharmacopœial substances warrants comment. The Sub-Committee has not employed statements of p_H in the individual monographs for informative purposes only. If the information does not contribute to the tests for identity or purity, it has not been included in the official monograph. When, however, the information is useful as a means of identification or in establishing purity, the p_H of the substance has been included in the individual monograph. For the purposes of increasing stability and pharmaceutical elegance, p_H adjustment has been included in certain monographs.

In addition to the application of the foregoing policy of the Sub-Committee in respect to the individual monographs, an informative table setting forth the p_H of many of the official drugs in aqueous solution will be included in the section of "General Tests."

2. *Electrolytic Determinations.*—The U. S. P. X recognizes the electrolytic deposition methods as alternative analytical procedures for the determination of zinc, silver, mercury and copper salts. After much discussion and experimental work, the Sub-Committee decided to delete these electrolytic methods on the ground that the volumetric and gravimetric methods used to assay these salts were better suited for U. S. P. purposes than the electrolytic procedures.

3. *Heavy Metals Test.*—With certain minor modifications this test has been recommended for U. S. P. XI. After mixing the hydrogen sulphide T.S. and the liquid in question, the mixture is allowed to stand 10 minutes at room temperature instead of 30 minutes at 35° C. before examining for the appearance of a brown to black coloration.

4. *Assay for Acids (Alkalimetric).*—This general test has been deleted and more specific directions have been given under the individual acids.

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5. *Assay for Chlorides, Bromides and Iodides.*—This general test has been deleted and more specific directions have been included under the individual salts.

6. *Assay for Alkali Benzoates and Salicylates.*—This general test has been deleted and special assays included for sodium benzoate and salicylate under the individual monographs. These assays depend upon the titration of the alkali bound to the organic acid with half-normal acid in the presence of a large amount of ether. Methyl orange T.S. is employed in the assay of sodium benzoate and Brom.phenol Blue T.S. is used as the indicator in the assay of sodium salicylate. The precipitated organic acid is instantly dissolved in the ether by vigorous stirring and hence the vitiating of the end-point is obviated. This procedure with certain minor modifications is essentially the process employed in the British Pharmacopœia of 1932.

7. *The Arsenic Test.*—The arsenic test has been changed in many of its minor descriptive details. Throughout this revision an effort was made to harmonize the U. S. P. test with the arsenic test description and directions set forth in the Book of Methods of the Association of Official Agricultural Chemists 3rd Edition (1930), page 307.

Bettendorf's Arsenic Test has been deleted. This is recognized in the U. S. P. X for bismuth salts and antimony and potassium tartrate. It was observed that the general arsenic test was applicable to bismuth salts. Fleitmann's modification of the arsenic test has been included for antimony and potassium tartrate. The method depends upon the generation of hydrogen in alkaline medium; under this condition, arsine is formed but stibine is not formed. Hence antimony does not interfere in the test.

8. *Turbidimetric and Clarity Tests.*—Apparatus has been described and procedure outlined to determine the degree of turbidity in various preparations and solutions. The sample is matched against suspensions of fuller's earth (200 powder) in distilled water. Turbidities are expressed in parts per million. A description of the turbidimeter is given by J. R. Baylis, *Ind. Eng. Chem.*, 18 (1926), 311, and also Claman, Carr and Krantz, *Jour. A. Ph. A.*, 21 (1932), 670.

II. GENERAL POLICIES.

1. *Descriptive Matter in Monographs.*—It was considered beyond the scope of the Pharmacopœia to include descriptive matter in the individual monographs which does not definitely contribute to the tests for identity or purity of the substances. These statements, some of them carried in the texts for three or four revisions, have been deleted. To illustrate this point with a specific case, the following statement in the U. S. P. X under Boric Acid has been deleted in its entirety:

"Heated to 100° C., Boric Acid loses water, forming metaboric acid (HBO_2) which slowly volatilizes at that temperature. Heated to about 160° C. Boric Acid fuses to a glassy mass of tetraboric or pyroboric acid ($\text{H}_2\text{B}_4\text{O}_7$). At about 185° C. the fused mass swells, loses all of its water, and becomes boron trioxide (B_2O_3), which fuses into a transparent non-volatile, hygroscopic mass."

2. *Concentration of Diluted Acids.*—The concentration of diluted acids is now based on a weight to weight percentage. For convenience in preparation, the concentration has been expressed on a weight to volume basis. Therefore, in the preparation of the diluted acids from the concentrated ones, the retail pharmacist need only measure a definite volume of the concentrated acid (corresponding to a definite weight) and make up to volume with distilled water.

3. *Working Formulas.*—Many working formulas for the preparation of inorganic chemicals have been deleted. It is believed that such substances as precipitated sulphur, exsiccated alum and granulated ferrous sulphate are not prepared by the small prescription counter methods any longer and, therefore, the recognition of these working formulas has outlived its usefulness.

III. INDIVIDUAL MONOGRAPHS.

1. *Acidum Boricum.*—The assay of boric acid has been modified by the addition of another 50 cc. of glycerin when the end-point of the titration is reached and then titrating further to the production of the pink color with phenolphthalein. Results obtained by this modified method are somewhat higher than those obtained by the U. S. P. X method and agree more closely with the theoretical value.

2. *Acidum Hydriodicum Dilutum*.—The working formula has been deleted. If this formula were retained, any sample of the acid which did not contain potassium acid tartrate, which remains as an impurity in the acid made by the official process, would be considered illegal. This view is taken owing to the ruling of the courts. The official definition contains also the statement: "Diluted Hydriodic Acid also contains not less than 0.6 Gm. or more than 1.0 Gm. of H_2PO_2 in 100 cc." An assay for the hypophosphorous acid content is included also in the monographs.

3. *Acidum Hydrochloricum*.—To conform with the concentration of commercial acids, the concentration has been changed from "31 to 33 per cent" to "35 to 38 per cent."

4. *Acidum Nitricum*.—To conform with the concentration of commercial acids, the concentration has been changed from "67 to 69 per cent" to "67 to 70 per cent."

5. *Acidum Phosphoricum*.—The argentimetric assay has been deleted. The alkali-metric assay using phenolphthalein as an indicator and saturating the titration mixture with sodium chloride is included. This assay is far more expeditious than the silver method and yields results sufficiently concordant for the purpose intended.

6. *Acidum Sulphuricum*.—To conform with the concentration of commercial acids, the concentration has been changed from "93 to 95 per cent" to "93 to 97 per cent."

7. *Aqua*.—A p_H range (5.6 to 8.3) has been included. The test for oxidizable substances has been deleted. This has been found to be unreliable when applied to various municipal-treated water supplies.

8. *Aqua Destillata*.—A p_H range (5.8 to 7.0) has been included. The test for oxidizable substances has been deleted.

9. *Arsenii Iodidum*.—This substance is assayed in the U. S. P. X argentimetrically. An oxidizing titration with tenth-normal iodine has been adopted. This conforms with the assay for arsenous oxide and determines the trivalent arsenic present.

10. *Arseni Trioxidum*.—The statement regarding the size of particles and physiological potency has been deleted.

11. *Barii Sulphas*.—The following "Bulkiness of Powder" test has been incorporated.

"Place 5 Gm. of Barium Sulphate, previously sifted through a No. 60 sieve, in a 50-cc. graduated cylinder provided with a glass stopper. The extent of the graduation of the cylinder should be about 14 cm. Add distilled water until a 50-cc. volume is obtained. Agitate the mixture briskly for exactly one minute and set it aside for sedimentation. Within fifteen minutes the Barium Sulphate should not settle below a volume of 12 cc. (bulkiness of powder)."

12. *Calx*.—Calcium oxide has been deleted and calcium hydroxide, for the preparation of lime water, has been included.

13. *Calcii Bromidum*.—The argentimetric assay has been deleted. The substance is directed to be assayed by the oxalate, permanganate method now employed for calcium carbonate.

14. *Calcii Chloridum*.—The argentimetric assay has been deleted. The substance is directed to be assayed by the oxalate, permanganate method now employed for calcium carbonate.

15. *Carbonii Dioxidum*.—Carbon dioxide of medicinal purity (99 per cent CO_2) has been admitted. The absence of carbon monoxide is required and an appropriate assay has been described.

16. *Ferri et Ammonii Citras*.—In the assay for iron in this substance a change in procedure has been adopted. Instead of allowing the hydrochloric acid solution of the sample to remain in contact with the potassium iodide for 30 minutes at 40° C., the titration of the iodine is begun without preliminary heating. The results obtained by this modification are practically identical with those obtained by the more lengthy process.

17. *Liquor Ferri Chloridum*.—The indigocarmine test for nitrate has been added to replace the ferrous sulphate test.

18. *Liquor Hydrogenii Dioxidum*.—The purity rubric has been changed from not less than 3 per cent to not less than 2.5 Gm. or more than 3.5 Gm. of H_2O_2 in each 100 cc.

19. *Liquor Magnesii Citratis* (Description and Assay).—Minor modifications of the assay have been included. The preliminary evaporation and carbonizing of the solution has been

omitted. A maximum and minimum magnesium oxide content will be incorporated. The (minimum total citric acid) test has been omitted. An identity test for citric acid has been included. An assay for the citric acid content has been included.

20. *Liquor Potassii Arsenitis*.—The maximum and minimum standards have been changed from 0.975 to 1.025 Gm. of As_2O_3 to 0.950 to 1.050 Gm. of As_2O_3 in each 100 cc.

21. *Magma Magnesiae*.—The working formula has been omitted.

Methyl orange T.S. has been replaced by methyl red T.S. in the limit of soluble alkalies test.

The test for soluble salts and soluble alkalies has been modified.

Limits of heavy metals and arsenic have been included.

Limit of calcium test has been included.

22. *Magnesii Carbonas*.—The purity rubric has been changed from "not less than 39.2 per cent MgO " to not less than 40 per cent or more than 42 per cent MgO .

The limit of calcium oxide permitted to be present has been reduced from 0.8 per cent to 0.4 per cent. The cumbersome oxalate precipitation method employed for the determination of calcium has been replaced by a simple calcium sulphate precipitation procedure.

23. *Magnesii Oxidum*.—The limit of calcium oxide permitted to be present has been reduced from 2 per cent to 1 per cent.

The cumbersome oxalate precipitation method employed for the determination of calcium has been replaced by a simple calcium sulphate precipitation procedure.

24. *Massa Ferri Carbonatis* (Definition and Assay).—The purity rubric of not less than 35 per cent of $FeCO_3$ has been changed to not less than 36 per cent and not more than 41 per cent of $FeCO_3$.

Diphenylamine T.S. as an inside indicator in the assay has replaced potassium ferricyanide as an outside indicator.

25. *Nitrogenii Monoxidum*.—The following purity rubric has been incorporated: "Nitrogen Monoxide contains not less than 97 per cent by volume of N_2O ."

A test for the absence of oxidizing impurities has been included. This test has been added to preclude the possibility of the higher oxides of nitrogen being present.

A detailed description of an assay has been added. This assay depends upon the differential solubility of N_2O in water contrasted with the solubilities of the generally occurring impurities.

26. *Oxygenium*.—The purity rubric has been increased from 98 per cent O by volume to 99 per cent O by volume.

A test to identify the presence of traces of carbon monoxide in oxygen has been developed. This test depends upon the reduction of iodine pentoxide and the detection of the liberated iodine. Description of the apparatus and a diagram accompanies the test. Carbon monoxide in concentrations of 1 to 100,000 are easily detectable by this method.

The assay has been described in complete detail. The alkaline pyrogallol absorption method has been replaced by the more easily manipulated ammonio-copper solution absorption method.

27. *Pilulae Ferri Carbonatis* (Assay).—Diluted phosphoric acid has been used in place of diluted sulphuric acid for the solution of the pills.

Diphenylamine T.S. has been used as an inside indicator instead of potassium ferricyanide T.S. as an outside indicator, in the assay of these pills.

28. *Potassii Carbonas*.—The following test has been included to control the water content of the compound.

"Dry about 3 Gm. of Potassium carbonate, accurately weighed, to a constant weight at $180^\circ C.$: the loss is not less than 10 per cent or greater than 15 per cent (water)."

29. *Potassii Hydroxidum*.—In addition to sticks and fused masses, pellets and other forms of KOH have been recognized.

30. *Potassii Iodidum*.—The argentimetric assay has been deleted. The iodate direct titration method has been included. This latter method is specific for iodides and thus eliminates bromides and chlorides.

31. *Sodii Benzoas*.—The statement 1 Gm. of Sodium Benzoate is soluble in 61 cc. of alcohol at 25° C. has been changed to "1 Gm. is soluble in 50 cc. of a mixture of 47.5 cc. of alcohol and 3.7 cc. of distilled water at 25° C."

32. *Sodii Biphosphas*.—This salt is assayed argentometrically in the U. S. P. X. As with phosphoric acid, this assay has been deleted and the alkalimetric procedure employed.

33. *Sodii Hydroxidum*.—In addition to the sticks and fused masses, pellets and other forms of NaOH have been recognized.

34. *Sodii Iodidum*.—The limit of water has been reduced from 7 per cent to 5 per cent.

The argentimetric assay has been deleted. The iodate direct titration method has been included. The latter method is specific for iodides and thus eliminates bromides and chlorides.

35. *Sodii Nitris*.—The assay has been made to conform with the assay of ethyl and amyl nitrites. This assay depends upon the liberation of iodine by the action of the nitrite on potassium iodide in the presence of sulphuric acid and the subsequent titration of the iodine with tenth-normal sodium thiosulphate solution in an atmosphere of carbon dioxide.

36. *Sodii Phosphas*.—In place of the efflorescent duodecahydrated sodium phosphate, the more stable heptahydrate has been recognized.

The official definition is:

"Sodium Phosphate when dried to a constant weight at 110° C. contains not less than 98 per cent of Na_2HPO_4 . It contains not more than 50 per cent of water."

The argentimetric assay has been deleted and the more accurate magnesium pyrophosphate gravimetric procedure has been included.

37. *Spiritus Ammoniae Aromaticus (Definition and Assay)*.—The following definition has been included:

"Aromatic Spirit of Ammonia contains in each 100 cc. not less than 1.7 Gm. and not more than 2.1 Gm. of total ammonia and not less than 3.5 Gm. or more than 4.5 Gm. of normal ammonium carbonate $(\text{NH}_4)_2\text{CO}_3$."

The following assay has been included:

"*Total Ammonia*.—Measure accurately 10 cc. of Aromatic Spirit of Ammonia into a 200-cc. Erlenmeyer flask containing about 50 cc. of distilled water. Add 30 cc. of half-normal sulphuric acid and boil until the solution becomes clear. Cool and titrate the excess of acid with half-normal sodium hydroxide, using methyl red T.S. as an indicator. Each cc. of half-normal sulphuric acid corresponds to 0.0850 Gm. of NH_3 ."

"*Normal Ammonium Carbonate*.—Introduce another 10 cc. of the spirit, accurately measured, into a flask of about 300 cc. capacity. Add about 30 cc. of half-normal sodium hydroxide and boil this mixture, replacing the water lost by evaporation, until the vapors no longer turn moist, red litmus paper blue. Cool, add 6 drops of phenolphthalein T.S. and half-normal sulphuric acid until the color of the phenolphthalein is just discharged. Now add about 3 drops of methyl orange T.S. and titrate with half-normal sulphuric acid. Each cc. of half-normal sulphuric acid corresponds to 0.0480 Gm. of $(\text{NH}_4)_2\text{CO}_3$."

38. *Tinctura Ferri Chloridi (Assay, Description and Definition)*.—The official definition has been changed to read.

"A hydro-alcoholic solution containing about 13 Gm. of ferric chloride (FeCl_3) in 100 cc., corresponding to not less than 4.5 Gm. per 100 cc. of Fe."

The indigocarmine test for nitrate has been added to replace the ferrous sulphate test.

The assay has been simplified according to the procedure set forth by Oakley and Krantz, *JOUR. A. PH. A.*, 21 (1932), 468.

In the continual study and scrutiny of the monographs up until the time of publication, small changes in manipulation may be made and errors will be eliminated, but this survey contains the essential changes in the monographs reported.