Standard of Japanese Pharmaceuticals

Abstracted from J. P. and J. N. F.

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FOREWORD

We believe that those persons abroad who are interested in pharmaceutical products desire to be informed of the quality standards of Japanese pharmaceuticals and how this quality is controlled and maintained.

Concerning drugs, we, the Japan Pharmaceutical, Medical and Dental Supply Exporters' Association, in cooperation with Japan External Trade Recovery Organization, have prepared this publication in order to inform you of the Japanese standards and how the manufacture of drugs are supervised.

Pharmaceuticals of which properties, purity, assay, indications, etc., are clearly known have been standardized by The Pharmacopoeia of Japan and The National Formulary of Japan. Regarding 1,144 drugs listed in these standards, their manufacture and distribution are licensed, provided their specifications meet the requirements of these standards. With reference to antibiotics and biologics, Minimum Requirements of Antibiotic Products and Minimum Requirements of Biologic Products are established under the Pharmaceutical Law of Japan. Through inspections are made so that the quality of antibiotics and biologics is maintained at a high level. These standards of Japan were established after a thorough study of U.S.P., B.P. and other official standards of foreign countries. We are confident that these Japanese standards are comparable with respective standards mentioned above.

The drugs described in this publication were selected by a committee of experts on each individual subject listed in the four official standards of Japan. This was done in view of the exportability and possible interest of overseas customers. Therefore, we hope this publication will be useful as a reference of the Japanese pharmaceutical business and will serve in assisting you to under-

stand the high quality of drugs manufactured in Japan. We hope you will find this book of use and assistance and will be pleased, if by its study, you will understand and appreciate the value and quality of our Japanese pharmaceutical products.

Chibei Takeda

President
Japan Pharmaceutical, Medical and
Dental Supply Exporters' Association

CONTENTS

Part I

THE PHARMACOPOEIA OF JAPAN

This part consists of 102 items abstracted from 672 items of J. P. VI

The serial number given to each item shows the manufacturers or dealers thereof, whose name and address are shown in the directory section.

GENERAL NOTICE

1. The title of this book, including Supplements thereto, the Pharmacopoeia of Japan, Sixth Revised Edition. This title may be abbreviated Japan Pharmacopoeia VI, or J.P. VI, or its synonym in the Japanese language.
2. Titles of monographs in this Pharmacopoeia include, besides Latin and Japanese (or English) names, non-official or commonly used names, if any.
3. Uuless otherwise provided for, a drug is to be tested as directed under the pertinent monograph on the basis of General Notice, General Rules for Preparations and General Tests for its conformity to the Pharmacopoeia. However, the solubility, specific gravity, boiling point, melting point, opitical rotation, refractive index and pH, given under the paragraph entitled Description in each monograph, should not be taken as standards for the conformity to the Pharmacopoeia. They are given merely for information.
4. All articles incorporated in the Pharmacopoeia shall have on the label the words "Pharmacopoeia of Japan" and the designation of each article (in Japanese) or its equivalent in Latin (or English), as given in the Pharmacopoeia. However, the words "Pharmacopoeia of Japan" may be abbreviated to "J.P.". In ampuls of less than 2-cc. capacity or below, or of over 2-cc. but less than 10-cc. capacity or glass containers of such sizes, in which the designations are printed directly on the ampuls or glass containers, some of the words may be abbreviated according to general usage.

   A preparation whose standards include requiment regarding the amount of content or unit, and/or effective period to appear on the label shall have a label standing such amount of units, and/or the effective period.

Deviation Permitted

5. In the manufacture of any official preparation, deviation in detail from the official directions is permissible, provided the finished preparation conforms to the standards prescribed by the Pharmacopoeia, and to those produced by following the official directions.
6. The official standards of strength, quality, purity, or packaging speci-

fication do not apply to crude drugs when used solely for the manufacture or isolation of volatile oils, alkaloids, glycosides, or other active principles.

7. Substances, unless otherwise provided in the individual monograph, may be added to pharmacopoeial preparations to assure the permanency or usefulness of the products, but these substances must be non-toxic and harmless in the amounts administered and must not interfere with the therapeutic efficacy of the preparations, or with testing.
8. In the manufacture of tablets, pills and capsules, it is permissible to use suitable diluents, bulking agents, colors, lubricants, and adhesives, such as starches, lactose, sucrose, and other innocuous materials, but these substances must be non-toxic and harmless in the amounts administered and must not interfere with the therapeutic efficacy of the preparations, or with testing.
9. In official ointments, plasters, and suppositories, the proportions of diluents or excipients may be varied to maintain a suitable consistence under different climatic conditions, provided that the proportion of active ingredients is not varied.
10. For the preservation of solutions intended for parenteral administration or topical application, in addition to Injections, there may be added to the solutions, unless otherwise directed in the monograph, not more than 0.5 per cent of phenol, chlorobutanol, cresol, sulfur dioxide, sodium bisulfite, or other suitable preservative. The presence and proportion of a preservative shall be plainly declared on the label of the container in which the product is sold or dispensed. Not more than 0.9 per cent of sodium chloride may be present, and the air in the container may be evacuated or be replaced by carbon dioxide, or by nitrogen, in which case no declaration is necessary on the label.

Weights, Measures and Temperatures

11. The metric system of weights and measures is the official system used in this Pharmacopoeia. The units of the metric system commonly employed are designated by abbreviations as follows:

m. =meter	Kg. =kilogram	L. =liter
dm. =decimeter	Gm.=gram	dl.=deciliter
cm. =centimeter	mg. =milligram	cc. =cubic centimeter (equivalent to milliliter).
mm.=millimeter	γ =gamma =0.001 mg.	

12. Percentage concentrations of solutions are expressed as follows: Per cent weight in volume (w/v), expresses the number of grams of an active constituent in 100 cc. of solution. Per cent volume in volume (v/v), expresses the number of cc. of an active constituent in 100 cc. of solution. These are sometimes expressed as "per cent by weight", or "per cent by volume", respectively.
13. Units of official preparations show a definite biological efficacy and differ according to each preparation. The units are determined by comparison with each Reference Standards by biological means. When otherwise specified, the word unit used in the Formulary (the Pharmacopoeia and the National Formulary of Japan) indicates the unit by Pharmacopoeia of Japan, which may be abbreviated to the word "Unit" in all articles incorporated in the Formulary (the Pharmacopoeia and the National Formulary of Japan).
14. Unless otherwise specified, all temperatures in this Pharmacopoeia are expressed in centigrade degrees.
15. All measurements are made at 25° unless otherwise directed, ordinary temperatures being taken in the range of 15° to 25°, and slight warmth, in the range of 30° to 40°. Water is called hot when its temperature is between 60° and 70°, and boiling, when its temperature is about 100°. The term heat on or in a water bath indicates that the water of the bath shall be boiling, unless otherwise specified. When a water bath is directed, a bath of actively flowing steam corresponding to about 100°, may be used.
16. Maceration or digestion with a cold solvent shall be carried out at a temperature between 15°, and 25°, and that with a warm solvent, or with application of heat, at 35° to 45°.
17. A cold place, unless otherwise directed in the monograph, shall be a place having a temperature not exceeding 15°.
18. In dispensing prescriptions, slight changes in volume owing to variations in room temperatures may be disregarded.

Degrees of Cutting and Powdering and Sieves

19. The degrees of cutting and powdering as used in drugs and the specifications for sieves are given below:

Sieve No.	Mesh Opening			Wire Diameter		Degree of Grind or Powder which has passed through the respective sieve	Approx Mesh No.
	Size mm.	official variation		diam. mm.	official variation mm.		
		mean	max.				
1	4.8	±2.5	10	1.4	±0.04	coarse ground	4
2	2.8	±3	10	0.90	±0.03	medium ground	7
3	2.0	±3	10	0.80	±0.03	finely ground	10
4	0.85	±5	25	0.40	±0.025	coarse powder	20
5	0.30	±6	30	0.18	±0.015	medium powder	50
6	0.15	±6	40	0.10	±0.015	fine powder	100
7	0.075	±8	50	0.05	±0.010	very fine powder	200

Testing

20. All testing shall be carried out with the chemicals as specified in General Tests, and distilled water shall be used where water is referred to in the tests.
21. Unless otherwise specified in the individual monograph, all solutions referred to are aqueous solutions.
22. The term "parts" referred to in the monograph represents parts by weight.
23. Unless otherwise specified, the reaction of solutions are tested with blue or red litmus paper.
24. Concentrations of solutions for testing, expressed by (1:3), (1:10), (1:100), etc., are understood to mean that 1 part by volume of a liquid is to be diluted with, or 1 part by weight of a soild dissolved in, sufficient of the solvent to make the volume of the finished solution 3, 10 or 100 parts by volume. For example, a diluted solution of hydrochloric acid (1:5) means 1 cc. of hydrochloric acid (35 to 38 per cent) diluted to 5 cc. with water, and a solution of sodium hydroxide (1:25) means a solution in which 1 Gm. of sodium hydroxide has been dissolved in sufficient water to bring the volume of the solution to 25 cc.
25. Solubilities are expressed by the following general usage:

The amount of the solvent needed to dissolve 1 Gm. or 1 cc. of the solute	Designations
below 1 cc.	Very easily soluble
1 to 10 cc.	Easily soluble

10 to 30 cc.	Soluble
30 to 100 cc.	Slightly soluble
100 to 1000 cc.	Very sparingly soluble
1000 to 10,000 cc.	Practically insoluble
over 10,000 cc.	Almost insoluble

26. For the counting of the number of drops, an apparatus giving 20(±1) drops from 1 Gm. of distilled water at 15° is to be used.
27. Specific gravity, unless otherwise stated, is the ratio of the weight of a substance in air at 25° to that of an equal volume of water at the same temperature.
28. The term "dried or ignited to constant weight" means that two consecutive weighings do not differ by more than 0.5 mg. per Gm. of substance taken for the determination, the second weighing following an additional 1 hour of drying, or ignition.
29. The word "about", used in stating the quantities to be used for assays, is used to indicate that this amount need not be the exact quantity specified, but it should not deviate more than plus or minus 10 per cent. This quantity is accurately weighed, and the result of the test or assay is based upon this exact weight.
30. Unless otherwise specified, all measurements are made at an ordinary temperature, observations being made immediately following operation.
31. Identification tests, unless otherwise specified, shall be made in a test tube of about 1.5 cm. in inside diameter, in which 5 cc. of the solution to be tested shall be placed.
32. A pharmacopoeial substance soluble or miscible in a solvent means that it dissolves or mixes with that solvent to form a clear solution, and the presence of a very minute amount of dusts or fibers are not questioned.
33. In the Description of pharmacopoeial substances, the term "white" or "colorless" indicates that the substance is white or colorless, or almost white or almost colorless, usually tested by taking 1 to 3 Gm. of the sample. In the case of liquids, testing of color or clarity of solution is measured in a test tube of aboht 1.5 cm. in inside diameter, and viewed downward in a layer of about 3 cm.
34. The term "odorless" in the paragraph of Description in the monographs indicates that the substance is free from odor or is almost free from odor, determination to be made in the same manner as for the foregoing tests.

Crude Drugs

(omitted)

Packaging, Storage and Preservation

40. The container is the device which holds the drug and which is or may be in direct contact with the drug. The closure of the container is a part of the container.

    The container shall not interact physically or chemically with the drug which it holds so as to alter the strength, quality, or purity of the drug beyond the official requirements.

41. A well-closed container shall protect the contents from extraneous solids or from loss of the drug under the ordinary or customary conditions of handling or storage. Where a well-closed container is specified, it may be replaced by a tight container.

42. A tight container shall protect the contents from contamination by extraneous solids or moisture, from loss of the drug and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling or storage, and shall be capable of tight reclosure. Where a tight container is specified, it may be replaced by a hermetic container.

43. A hermetic container shall be impervious to air or any other gas under the ordinary or customary conditions of handling or storage.

44. A light-resistant container is a container which is opaque, or provided with opaque covering, and designed to prevent photochemical deterioration of the contents beyond the official limits of strength, quality, or purity, under the ordinary or customary conditions of handling or storage.

Doses

45. The usual doses stated in this Pharmacopoeia are those which may be expected ordinarily to produce the therapeutic effect for which the ingredient or preparation is most commonly employed. Unless otherwise specified, the usual doses are for oral administration to human adults. These doses are intended solely as information to users.

46. The maximal doses stated in this Pharmacopoeia, unless otherwise specified, are for oral administration to human adults. Prescription of doses over and above this dose by physicians and dentists must be so indicated in the prescription by **Caution!** mark.

47. The contents given under the paragraph on Preparations are the contents of ingredients in preparations usually available on the market.

48. (omitted).
49. (omitted).

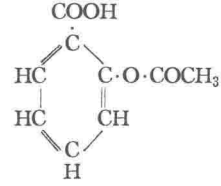
Note *The above mentioned "General Notices" are those of J.P. IV.*

ACIDUM ACETYLSALICYLICUM

Acetylsalicylic Acid

Acid. Acetylsal.

(Aspirin)



$C_9H_8O_4 = 180.15$

Acetylsalicylic Acid, when dried over sulfric acid for 5 hours, contains not less than 99.5 per cent of $C_9H_8O_4$.

Description—Acetylsalicylic Acid occurs as white crystals, commonly tabular or needle-like, or as a white, crystalline powder. It is stable in dry air; in moist air it gradually hydrolyzes into salicylic and acetic acids. It is odorless. One Gm. of Acetylsalicylic Acid dissolves in 6.5 cc. of alcohol, in 20 cc. of chloroform, and in 19 cc. of ether. It is hardly soluble in water. Acetylsalicylic Acid dissolves with decomposition in solutions of alkali hydroxides and carbonates.

Identification—(1) Heat Acetylsalicylic Acid with water for several minutes, cool, and add a drop or two of ferric chloride T.S.: a violet red color is produced (Salicylic Acid). (2) Boil about 0.5 Gm. of Acetylsalicylic Acid with 10 cc. of sodium hydroxide T.S. for a few minutes, cool, and add 10 cc. of diluted sulfuric acid: a white precipitate of salicylic acid is produced, and the odor of acetic acid is perceptible. Filter, add to the filtrate 3 cc. of alchol and 3 cc. of sulfuric acid, and warm: the odor of ethyl acetate becomes noticeable.

Purity—(1) **Chloride** Boil 1.5 Gm. of Acetylsalicylic Acid with 75 cc. of water for 5 minutes, cool, add sufficient water to restore the original volume, and filter. A 25 cc. portion of the filtrate shows no more **Chloride** than corresponds to 0.1 cc. of fiftieth-normal hydrochloric acid as specified in Section 23 of **General Tests.** (2) **Sulfate** A 25 cc. portion of the filtrate prepared for the test for **Chloride** shows no more **Sulfate** than corresponds to 0.2 cc. of fiftieth-normal sulfuric acid as specified in Section 23 of **General Tests.** (3) **Heavy metals** Dissolve 1 Gm. of Acetylsalicylic Acid in 25 cc. of acetone, add 1 cc. of water and

10 cc. of hydrogen sulfide T.S. Any color produced is not darker than that of a control made with 25 cc. of acetone, 1 cc. of standard lead solution, and 10 cc. of hydrogen sulfide T.S. (4) **Readily carbonizable substances** Dissolve 0.5 Gm. of Acetylsalicylic Acid in 5 cc. of sulfuric acid: the solution has no more color than matching fluid Q. (5) **Free salicylic acid** Dissolve 0.1 Gm. of Acetylsalicylic Acid in 1 cc. of alcohol, dilute the solution with 48 cc. of cold water (about 10°), and add at once 1 cc. of a freshly prepared diluted ferric ammonium sulfate solution (made by adding 1 cc. of normal hydrochloric acid to 2 cc. of ferric ammonium sulfate T.S. and diluting with water to 100 cc.): at the end of 30 seconds the color of the mixture is not more intense than that similarly observed in a control solution prepared as follows: Control Solution: Dissolve 100 mg. of salicylic acid in 1000 cc. of water, and add 1 cc. of glacial acetic acid: mix 1 cc. of this solution with 1 cc. of alcohol and 48 cc. of cold water (about 10°), and add 1 cc. of the diluted ferric ammonium sulfate solution previously employed. (6) **Substances insoluble in sodium carbonate T.S.** A solution of 0.5 Gm. of Acetylsalicylic Acid in 10 cc. of warm sodium carbonate T.S. is clear.

Loss on drying—When dried over sulfuric acid for 5 hours, Acetylsalicylic Acid loses not more than 0.5 per cent of its weight.

Residue on ignition—Acetylsalicylic Acid yields not more than 0.05 per cent of residue on ignition.

Assay—Place about 1.5 Gm. of Acetylsalicylic Acid, previously dried over sulfuric acid for 5 hours and accurately weighed, in a flask, add 50 cc. of half-normal sodium hydroxide, and boil the mixture gently for 10 minutes. Titrate the excess of sodium hydroxide with half-normal sulfuric acid, using 3 drops of phenolphthalein T.S. as the indicator. Determine the normality of the sodium hydroxide in the same manner as in the test. Each cc. of half-normal sodium hydroxide is equivalent to 45.04 mg. of $C_9H_8O_4$.

Packaging and storage—Preserve Acetylsalicylic Acid in well-closed containers.

Usual dose—Single: 0.5 Gm.; Daily: 1 Gm.

Serial number of firms: **17, 22.**