JP	KP	CP	VP
Microscopic examination	Microscopic examination	Microscopical Identification for Crude Drugs and Patent Medicines	MICROSCOPICAL IDENTIFICATION FOR CRUDE DRUGS AND PATENT MEDICINES
		with ocular micrometer. (1) Ocular micrometer (2) Stage micrometer (3) Mark of ocular micrometer (4) Measurements	coincide, then look for another coincident lines to the right. Measurements of cells and cell contents The value (μm) of I ocular micrometer division can be calculated on the basis of divisions of the two micrometer scales between the coincident lines. To measure the object, multiply the number of object-measuring divisions of ocular micrometer by the value (μm) of each division. Generally, it is carried out under a high power objective, but a low power objective would be more convenient to measure the length of longer fibres and non-glandular hairs. etc. Record the maximal and minimal values (μm), permitting a few numerical values slightly higher or lower than the values specified in pharmacopoeial requirement. Detection of cell wall *Lignified cell wall* *Suberized or Cuticularized cell wall* *Cellulose cell wall* *Siliceous cell Wall* Detection of cell contents *Starch* *Aleuronic* *Fatty oil, volatile oil or resin* *Inulin* *Calcium oxalate crystals* *Calcium carbonate* Silicum Insoluble in sulphuric acid Identify the patent medicines made from pulverized drugs, slides for powders are prepared according to the method for powder slides mentioned above; for pills and tablets, ets..., grind 2 -3 pills (tablets) into fine powder, to a small quantity of the sample add drop wise the required test solutions, stair thoroughly to separate the stuck cells and tissues, then carry out the identification method for powder characters, slides of honeyed pills can be prepared directly by picking a little sample, or de-honeyed with hot water for the examination.
Arsenic Limit Test	Arsenic Limit Test	Limit Test for Arsenic	LIMIT TESTS FOR IMPURITIES (ARSENIC)
The Arsenic Limit Test is a limit test of arsenic contained in drugs. The limit is expressed in terms of arsenic (III) trioxide (As_2O_3). In each monograph, the permissible limit for arsenic (as As_2O_3) is described in terms of ppm in parentheses. Preparation of the test solution Unless otherwise specified, proceed in the following. (1) Method 1 Weigh the amount of the sample direct in the monograph, add 5 mL of water, dissolve by heating if necessary, and designate the solution as the test solution. (2) Method 2 Weigh the amount of the sample directed in the monograph, add 5 mL of sulfuric acid except in the cases that the samples are inorganic acids. Add 10 mL of sulfurous acid solution, transfer to a small beaker, and evaporate the mixture on a water bath until it is free from sulfurous acid is reduced to about 2 mL in volume. Dilute with water to make 5 mL, and designate it as the test solution. (3) Method 3 Weigh the amount of the sample directed in the monograph, and place it in a crucible of platinum, quartz or porcelain. Add 10 mL of a solution of magnesium nitrate hexahydrate in ethanol(95)(1 in 50), ignite the ethanol, and heat gradually to incinerate. If carbonized material still remains by this procedure, moisten with a small quantity of nitric acid, and ignite again to incinerate. After cooling, add 3 mL of hydrochloric acid, heat on a water bath to dissolve the residue, and designate it as the test solution.	The Arsenic Limit Test is a limit test of arsenic contained in druge. The limit is expressed in terms of arsenic (III) trioxide (As_2O_3). In each monograph, the permissible limit for arsenic (as As_2O_3) is described in terms of ppm in parentheses. Preparation of the test solution Unless otherwise specified, proceed in the following. 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After cooling, add 3 mL of hydrochloric acid, heat on a water bath to dissolve the residue, and designate it as the test solution.	Method 1 (Gutzeit's method) Apparatus A is a 100 ml conical flask with standard ground joint : B is a standard hollow ground glass stopper connected to glass conduit C (external diameter 8.0 mm, internal diameter 6.0 mm), the total length of B and C is about 180 mm. D is a plastic screw, the upper part of which has an aperture 6.0 mm in diameter and the lower part of which has an aperture 8.0 mm in diameter; E is a plastic screw cap which has an aperture 6.0 mm in diameter. A wad of lead acetate cotton wool weighting about 60 mg is packed into tube C to a depth of about 60~80 mm. A disc of mercuric bromide test paper is placed between the contacting surfaces of D and E. Arsenic standard stain Place 2 ml of standard arsenic solution, accurately measured, in flask A, add 5 ml of hydrochloric acid and 21 ml water. Then add 5 ml of potassium iodide TS and 5 drops of acid stannous chloride TS, allow to stand at room temperature for 10 minutes and add 2 g of zinc granules. Insert the stopper B and conduit C into the mouth of flask A and immerse the flask in a water bath at 25~40℃ for 45 minutes. Remove the mercuric bromide test paper. Procedure Transfer the preparation prepared as described under individual monographs to flask A and proceed as described under Arsenic standard stain, beginning with the wards "Then add 5 ml of potassium iodide TS ...". Any stain produced is not more intense than the standard stain. Method 2 (Silver diethyldithiocarbamate method) Apparatus A is a 100 ml conical flask with standard ground joint; B is a standard hollow ground glass stopper connected to glass conduit C (at one end, the external diameter is 8.0 mm and the internal diameter is 6.0 mm; the other end is in length of 180 mm, in external diameter of 4 mm and in internal diameter of 1.6 mm, the internal diameter of sharp end is 1 mm). D is a glass tube with flat bottom (length 180 mm, internal diameter 10 mm, and with a graduation at 5.0 ml). A wad of cotton wool previously moistened with lead acetate TS and dried weighing about 0.1 g is packed into conduit C to a depth of about 80 mm, and measure 3 ml of silver diethyldithiocarbamate TS in tube D. Standard arsenic reference solution Transfer 2 ml of arsenic standard solution as described under Method I	Use Method A unless otherwise directed in the monograph Method A The Apparatus consists of a 100 ml conical flask closed with ground-glass stopper through which passes a glass tube about 200 mm long and 5 mm in internal diameter. The lower part of the tube is drawn to an in internal diameter of 1 mm. 15 mm from its tip there is a lateral orifice 2 to 3 mm in diameter. When the tube is in position in the stopper the lateral orifice should be at least 3 mm below the lower surface of the stopper. The upper end of the tube has a perfectly flat, ground surface at right angles to the axis of the tube. A second glass tube of the same internal diameter and 30 mm long, with a similar flat ground surface, is placed in contact with the first and held in position by two spiral springs. *Procedure* : Into the longer tube insert 50 to 60 mg of lead acetate cotton R, Between the flat surfaces of the 2 tubes place a disc or a small square of mercury (II) bromide paper R large enough to cover the orifice of the tube, hold the 2 tubes in position by two spiral springs. In the conical flask dissolve or dilute the prescribed quantity of the substance being examined n sufficient water to produce 25 ml. Add 15 ml of hydrochloric acid R, 0.1 ml of tin (II) chloride solution As TR and 5 ml of a 20% solution of potassium iodide R. Allow to stand for 15 minutes and add 5 g of arsenic-free zinc R. Immediately assemble the two parts of the apparatus and immerse the flask in a water bath at a temperature such that a uniform evolution of gas is maintained. Prepare a standard at the same time and in the same manner using 1 ml of arsenic standard solution (1 ppm As) in place of the substance being examined and diluted to 25 ml with water. After not less than 2 hours compare the stains produced on the mercury (II) bromide papers. Any stain produced on the paper of the test flask is not more intense than that of the standard. Method B Add the prescribed quantity of the substance being examined to a test tube containing 4 ml of hydrochloric acid R and about 5 mg of potassium iodide R and add 3 ml of hydrophosphite solution R. Heat the mixture on a water bath for 15 minutes, shaking occasionally. Prepare a standard at the same time and in the same manner using 0.5 ml of arsenic standard solution (1 ppm As) in place of the substance being

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Arsenic Limit Test	Arsenic Limit Test	Limit Test for Arsenic	LIMIT TESTS FOR IMPURITIES (ARSENIC)
(4) Method 4 Weigh the amount of the sample directed in the monograph. and place it in a crucibleof platinum, quartz or porcelain. Add 10 mL of a solution of magnesium nitrate hexahydrate in ethanol (95)(1 in 10), burn the ethanol, heat gradually, and ignite to incinerate. If carbonized material still remains by this procedure, moisten with a small quantity of nitric acid, and ignite again to incinerate in the same manner. After cooling, add 3 mL of hydrochloric acid, heat on a water bath to dissolve the residue, and designate it as the test solution. (5) Method 5 Weigh the amount of the sample directed in the monograph, add 10 mL of N,N-dimethylform-amide, dissolve by heating if necessary, and designate the solution as the test solution.	(4) Method 4 Weigh the amount of the sample directed in the monograph. and place it in a crucible of platinum, quartz or porcelain. Add 10 mL of a solution of magnesium nitrate hexahydrate in ethanol (1→10), burn the ethanol, heat gradually, and ignite to incinerate. If carbonized material still remains by this procedure, moisten with a small quantity of nitric acid, and ignite again to incinerate in the same manner. After cooling, add 3 mL of hydrochloric acid, heat on a water bath to dissolve the residue, and designate it as the test solution. (5) Method 5 Weigh the amount of the sample directed in the monograph, add 10 mL of N,N-dimethylform-amide, dissolve by heating if necessary, and designate the solution as the test solution.	to flask A, accurately measured, add 5 ml of hydrochloric acid and 21 ml of water. Then add 5 ml of potassium iodide TS and 5 drops of acid stannous chloride TS, allow to stand at room temperature for 10 minutes and add 2 g of zinc granules. Connect conduit C into flask A immediately, and allow the evolved arsine to enter tube D. Immerse the flask A in a water bath at 25—40℃ for 45 minutes. Remove tube D, add chloroform to the graduation, mix well. Procedure Transfer the test preparation prepared as described under individual monographs to flask A and proceed as described under standard arsenic reference solution beginning with the words "Then add 5 ml of potassium iodide TS ...". Compare the above two solution against a white background. Any colour produced by the preparation is not more intense than produced by the standard arsenic reference solution. If necessary, determine the absorbance at the wavelength of 510 nm, with a suitable spectrophoto-meter or colorimeter, using silver diethyldithiocarbamate TS as the blank.	examined. Compare the colour produced in the test solution with that in the standard solution. Any colour produced in the test solution is not more intese than that obtained in the standard solution.
Heavy Metals Limit Test	Heavy Metals Limit Test	Limit Test for Heavy Metals	LIMIT TESTS FOR IMPURITIES (HEAVY METALS)
The Heavy Metals Limit Test is a limit test of the quantity of heavy metals contained as impurities in drugs. The heavy metals are the metallic inclusions that are darkened with sodium sulfide TS in acidic solution, as their quantity is expressed in terms of the quantity of lead (Pb). In each monograph, the permissible limit for heavy metals (as Pb) is described in terms of ppm in parentheses. Preparation of test solutions and control solutions Unless otherwise specified, test solution and control solution are prepared as directed in the following: (1) Method 1 Place an amount of the sample, directed in the monograph, in Nessler tube. Dissolve in water to make 40 mL. Add 2 mL of dilute acetic acid and water to make 50 mL, and designate it as the test solution. The control solution is prepared by placing the volume of Standard Lead Solution directed in the monograph in a Nessler tube, and adding 2 mL of dilute acetic acid and water to make 50 mL. (2) Method 2 Place an amount of the sample, directed in the monograph, in a quartz or porcelain crucible, cover loosely with a lid, and carbonize by gentle ignition. After cooling, add 2 mL of nitric acid and 5 drops of sulfuric acid, heat cautiously until white fumes are no longer evolved, and incinerate by ignition between 500℃ and 600℃. Cool, add 2 mL of hydrochloric acid, evaporate to dryness on a water bath, moisten the residue with 3 drops of hydrochloric acid, add 10 mL of hot water, and warm for 2 minutes. Then add 1 drop if phenolphthalein TS, add ammonia TS dropwise until the solution develops a pale red color, add 2 mL of dilute acetic acid, filter if necessary, and wash with 10 mL of water. Transfer the filtrate and washing to a Nessler tube, and add water to make 50 mL. Designate it as the test solution. The control solution is prepared as follows: Evaporate a mixture of 2 mL of nitric acid, 5 drops of sulfuric acid and 2 mL of hydrochloric acid on a water bath, further evaporate to dryness on a sand bath, and moisten the residue with 3 drops of hydrochloric acid. Hereinafter, proceed as directed in the test solution, then add the volume of Standard Lead Solution directed in the monograph and water to make 50mL. (3) Method 3 Place an amount of the sample, directed in the	The Heavy Metals Limit Test is a limit test of the quantity of heavy metals contained as impurities in drugs. The heavy metals are the metallic inclusions that are darkened with sodium sulfide TS in acidic solution, as their quantity is expressed in terms of the quantity of lead (Pb). In each monograph, the permissible limit for heavy metals (as Pb) is described in terms of ppm in parentheses. 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Cool, add 2 mL of hydrochloric acid, evaporate to dryness on a water bath, moisten the residue with 3 drops of hydrochloric acid, add 10 mL of hot water, and warm for 2 minutes. Then add 1 drop if phenolphthalein TS, add ammonia TS dropwise until the solution develops a pale red color, add 2 mL of dilute acetic acid, filter if necessary, and wash with 10 mL of water. Transfer the filtrate and washing to a Nessler tube, and add water to make 50 mL. Designate it as the test solution. The control solution is prepared as follows: Evaporate a mixture of 2 mL of nitric acid, 5 drops of sulfuric acid and 2 mL of hydrochloric acid on a water bath, further evaporate to dryness on a sand bath, and moisten the residue with 3 drops of hydrochloric acid. Hereinafter, proceed as directed in the test solution, then add the volume of Standard Lead Solution directed in the monograph and water to make 50mL. (3) Method 3 Place an amount of the sample, directed in the	The Term "heavy metals" refers to those metals that react with thioacetamide or sodium under the specified conditions to produce a coloured compound. Method 1 Unless otherwise specified, use two 25 ml Nessler cylinders. To cylinder A add the specified volume of lead standard solution and 2 ml of acetate BS (pH 3.5). dilute with water or other solvent as specified under individual monographs to 25 ml. To cylinder B add 25 ml of the test preparation containing a quantity of the substance being examined as specified under individual monographs. If the original test preparation is coloured, its colour can be matched by the addition of a few drops of dilute caramel solution or other suitable solution to cylinder A. To each cylinder add 2 ml of thioacetamide TS and mix well, allow to stand for 2 minutes, compare the colour produced by viewing down the vertical axis of the cylinder against a white background. The colour produced in cylinder B is not more intense than that produced in cylinder A. If the colour cannot be matched by the addition of caramel solution, duplicate the quantity of the substance being examined and the regent, add water or other solvent as specified under individual monographs to produce 30 ml of test preparation. Divide the test preparation into two equal portions and transfer to Nessler cylinder A and B. To cylinder B add sufficient water or other solvent as specified under individual monograph to produce 25 ml. To cylinder A add 2 ml of thioacetamide TS, mix well in porosity. To cylinder A add the prescribed volume of lead standard solution and dilute with water of other solvent as specified under individual monographs to produce 25 ml. Then add 2 ml of thioacetamide TS to cylinder B and 2 ml of water to cylinder A and compare the colour as described above. If the substance being examined contains a ferric salt which interferes the test, 0.5—1.0 g of ascorbic acid should be added to each cylinder. Unless otherwise specified, evaporate the same quantity of the same reagents to dryness in a porcelain dish. Dissolve the residue in 2 ml of acetate buffer (pH 2.5) and 15 ml of water. Transfer the solution to a Nessler cylinder, add the specified quantity of lead standard solution and water to 25 ml. The solution is used as reference solution for the test solution which is prepared by using more than 1.0 ml of hydrochloric acid or equivalent amount of dilute hydrochloric acid, 2 ml of ammonia TS orby treating with other regents. Method 2 Unless otherwise specified, use the residue obtained from the Determination of residue on ignition, add 0.5 ml of nitric acid, evaporate to dryness, heat until nitrous oxide fumes are no longer evolved (or alternatively, ignite a quantity of the substance being examined in crucible until thoroughly charred, cool, moisten the residue with 0.5—1.0 ml of sulfuric acid, ignite at a low temperature until sulfurous acid fumes are no longer evolved, add 0.5 ml of nitric acid, evaporate to dryness, heat until nitrous oxide fumes are no longer evolved and ignite at 500—600℃ until the incineration is complete). Cool, add 2 ml of hydrochloric acidevaporate to dryness on a water bath, add 15 ml of water, followed by ammonia TS dropwise until the solution is neutral to phenolphthalein IS, then add 2 ml of acetate BS (pH 3.5) and warm to effect dissolution. Transfer the resulting solution to Nessler cylinder B, dilute with water to 25 ml and produced as described under method I. The reference	Use one of the following methods as prescribed in the monograph. Method 1 To 12 ml of the prescribed solution in a tube, add 2 ml of acetate buffer pH 3.5 and mix. Add 1.2 ml of thioacetamide solution R, mix immediately and allow to stand for 2 minutes. Prepare a standard solution in the same manner using a mixture of 10 ml of either lead standard solution (1 ppm Pb) or lead standard solution (2 ppm Pb), as prescribed, and 2 ml of the solution being examined. Compare the colour produced in the test solution with that in the standard solution. Any brown colour produced in the test solution is not more intense than that obtained in the standard solution. The standard solution exhibits aslightly brown colour when compared to a blank solution prepared by traeting in the same manner a mixture of 10 ml water and 2 ml of the solution being examined. Method 2 Dissolve the specified quantity of the substance being examined in an organic solvent containing a minimum percentage of water, such as 1, 4-dioxan R or acetone R containing 15% of water. Carry out Method 1 but prepare the lead standard solution by diluting lead standard solution (100 ppm Pb) with the solvent used to prepare the test solution to contain 1 or 2 ppm of Pb, as specified. Method 3 Place the prescribed quantity (usually not more than 2 g) of the substance being examined in a silica crucible. Add 4 ml of a 25% solution of magnesium sulphate in 2 N sulphuric acid R. Mix using a fine glass rod and heat cautiously. If the mixture is liquid, evaporate gently to dryness on a water bath. Progressively heat to ignition, not allowing the temperature to exceed 800℃, and continue heating until a white or at most greyish residue is produced. Allow to cool, moisten the residue with 0.2 ml of 2 N sulphuric acid R, evaporate, ignition again and allow to cool. The total period of ignition must not exceed 2 hours. Dissolve the residue using two 5 ml quantities of 2 N hydrochloric acid R. Add 0.1 ml of phenolphthalein solution I and concentrated ammonia solution R dropwise until a pink colour is produced. Cool, add glacial acetic acid R until the solution is decolorized and add a further 0.5 ml. Filter if necessary and dilute the solution to 20 ml with water. To 12 ml of the resulting solution in a tube, add 2 ml of acetate buffer pH 3.5 and mix. Add to 1.2 ml of thioacetamide solution R, mix immediately and allow to stand for 2 minutes. Compare the colour produced in the test solution with that in a standard solution prepared simultaneously in the same manner. Any colour producedin the test solution is not more intensethan that obtained in the standard solution. Method 4 Mix the prescribed quantity of the substance being examined with 0.5 g of magnesium oxide R in a silica crucible. Ignite to dull red heat until a homogeneous white or greyish white mass is produced. If after 30 minutes of ignition the mixture remains coloured, allow to cool, mix with a fine glass rod and repeat the ignition. If necessary, repeat the operation. Finally heat at 800℃ for about 1 hour. Dissolve the residue using two 5 ml quantities of 5 N hydrochloric acid solution R and carry out the procedure described under Method 3 beginning at the word "Add 0.1 ml of phenolphthalein solution I...". To prepare the standard solution place the prescribed volume of lead standard solution (10 ppm Pb) in a silica crucible, add 0.5 g of magnesium oxide R and mix. Dry the mixture in an oven at 100℃ to 105℃, ignite as described above.

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Heavy Metals Limit Test	Heavy Metals Limit Test	Limit Test for Heavy Metals	LIMIT TESTS FOR IMPURITIES (HEAVY METALS)
monograph, in quartz or porcelain crucible, heat cautiously, gently at first, and then increase the heat until incineration is completed. After cooling, add 1 mL of aqua regia, evaporate to dryness on a water bath, moisten the residue with 3 drops of hydrochloric acid, add 10 mL of hot water, and warm for 2 minutes. Add 1 drop of phenolphthalein TS, add ammonia TS dropwise until the solution develops a pale red color, add 2 mL of dilute acetic acid, filter if necessary, wash with 10 mL of water, transfer the filtrate and washings to a Nessler tube, and add water to make 50 mL. Designate it as the test solution. The control solution is prepared as follows: Evaporate 1 mL of aqua regia to dryness on a water bath. Hereinafter, proceed as directed for the test solution, and add the volume of Standard Lead Solution directed in the monograph and water to make 50 mL. (4) Method 4 Place an amount of the sample, directed in the monograph, in a platinum or porcelain crucible, mix with 10 mL of a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 10), fire the ethanol to burn, and carbonize by gradual heating. Cool, add 1mL of sulfuric acid, heat carefully, and incinerate by ignition between 500℃ and 600℃. If a carbonized substance remains, moisten with a small amount of sulfuric acid, and incinerate by ignition. Cool, dissolve the residue in 3 mL of hydrochloric acid, evaporate on a water bath to dryness, wet the residue with 3 drops of hydrochloric acid, add 10 mL of water, and dissolve by warming. Add 1 drop of phenolphthalein TS, add ammonia TS dropwise until a pale red color develops, then add 2 mL of dilute acetic acid, filter if necessary, wash with 10 mL of water, transfer the filtrate and the washing to Nessler tube, add water to make 50 mL, and use this solution as the test solution. The control solution is prepared as follows: Take 10 mL of a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 10), and fire the ethanol to burn. Cool, add 1 mL of sulfuric acid, heat carefully, and ignite between 500℃ and 600℃. Cool, and add 3 mL of hydrochloric acid. Hereinafter, proceed as directed in the test solution, then add the volume of Standard Lead Solution directed in the monograph and water to make 50 mL.	monograph, in quartz or porcelain crucible, heat cautiously, gently at first, and then increase the heat until incineration is completed. After cooling, add 1 mL of aqua regia, evaporate to dryness on a water bath, moisten the residue with 3 drops of hydrochloric acid, add 10 mL of hot water, and warm for 2 minutes. Add 1 drop of phenolphthalein TS, add ammonia TS dropwise until the solution develops a pale red color, add 2 mL of dilute acetic acid, filter if necessary, wash with 10 mL of water, transfer the filtrate and washings to a Nessler tube, and add water to make 50 mL. Designate it as the test solution. The control solution is prepared as follows: Evaporate 1 mL of aqua regia to dryness on a water bath. Hereinafter, proceed as directed for the test solution, and add the volume of Standard Lead Solution directed in the monograph and water to make 50 mL. (4) Method 4 Place an amount of the sample, directed in the monograph, in a platinum or porcelain crucible, mix with 10 mL of a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 10), fire the ethanol to burn, and carbonize by gradual heating. Cool, add 1mL of sulfuric acid, heat carefully, and incinerate by ignition between 500℃ and 600℃. If a carbonized substance remains, moisten with a small amount of sulfuric acid, and incinerate by ignition. Cool, dissolve the residue in 3 mL of hydrochloric acid, evaporate on a water bath to dryness, wet the residue with 3 drops of hydrochloric acid, add 10 mL of water, and dissolve by warming. Add 1 drop of phenolphthalein TS, add ammonia TS dropwise until a pale red color develops, then add 2 mL of dilute acetic acid, filter if necessary, wash with 10 mL of water, transfer the filtrate and the washing to Nessler tube, add water to make 50 mL, and use this solution as the test solution. The control solution is prepared as follows: Take 10 mL of a solution of magnesium nitrate hexahydrate in ethanol (95) (1 in 10), and fire the ethanol to burn. Cool, add 1 mL of sulfuric acid, heat carefully, and ignite between 500℃ and 600℃. Cool, and add 3 mL of hydrochloric acid. Hereinafter, proceed as directed in the test solution, then add the volume of Standard Lead Solution directed in the monograph and water to make 50 mL. (5) Method 5 Unless otherwise specified, in the monograph, place 0.3 g of extract or 1.0 g of fluidextract in a platinum or porcelain crucible, evaporate to dryness on a water bath, incinerate by ignition between 500℃ and 600℃. Cool, dissolve the residue in 3 mL of hydrochloric acid by warming, filter and wash the residue 5 mL of water two times. Transfer the filtrate and washings to a Nessler tube, add 1 drop of phenolphthalein TS, add ammonia TS dropwise until a pale red color develops, then add 2 mL of dilute acetic acid, and add water to make 50 mL, Designate it as the test solution. The control solution is prepared as follows: add 3 mL of hydrochloric acid. Hereinafter, proceed as directed in the test solution, then add 3.0 mL of Standard Lead Solution and water to make 50 mL.	preparation should be prepared as follows. Place the same quantity of the same regents used for the preparation of test solution in a porcelain dish and evaporate to dryness, heat gently and dissolve in 2 ml of acetate BS (pH 3.5) and 15 ml of water, transfer to the Nessler cylinder A and add the specified volume of standard lead solution, dilute with water to 25 ml. Method 3 Unless otherwise specified, dissolve a quantity of the substance being examined in 5 ml if sodium hydroxide TS and 20 ml of water. Transfer the solution to a Nessler cylinder, add 5 drops of sodium sulphide TS and mix well the colour produced is not more intense than of a referencepreparation containing the specified volume of lead standard solution and treated in the same manner. Method 4 Apparatus The filter holder is compared of tightly sealed upper and lower parts with screw thread, washer, filter A is the upper cap part pf the filter holder the entrance may be fitted with a 50 ml syringe; B is joint : C is washer (external diameter is 10 mm, internal diameter is 6 mm) : D is filter membrane with 10 mm in diameter and 3.0 mm of porosity, soaked in water for more than 24 hours before use: E is auxiliary filter plate made of No.3 sintered glass filter plate with 10 mm in diameter and 1 mm in thickness; F is the lower part of the filter holder, the exit is fitted with a suitable rubber tube. Lead standard stain Measure accurately a quantity of lead standard solution to a small beaker, dilute to 10 ml with water or other solvent as and 1.0 ml of thioacetamide TS, mix well, allow to stand for 10 minutes. Transfer to a filter holder with a 50 ml syringe and filter it on applying an even pressure (filter rate is about 1 ml per minute), then place the filter membrane on a piece of filter paper and dry it. Procedure Transfer 10 ml of the test preparation prepared as described under individual monographs and proceed as described under Lead standard stain, beginning with the words "add 2 ml of acetate BS (pH 3.5)". Any stain produced is not more intense than the standard stain. If the test preparation is coloured or turbid, filter membrane is contaminated, replace it with another filter membrane and repeat the filtration until the filter membrane remains uncontaminated. Proceed as described under Lead standard stain, beginning at the words "add 2 ml of acetate BS (pH 3.5)", using 10 ml of filtrate, and compare the stain as described above.	Dissolve the residue using two 5 ml quantities of 5 N hydrochloric acid solution R and carry out the procedure described under Method 3 from the substance "Add 0.1 ml of phenolphthalein solution I..." and use a mixture of 10 ml of the above treated lead standard solution and 2 ml of the test solution. Method 5 Use a membrane filter holder, the dimensions of which are shown in Figure, fitted with a 50 ml syringe. The membrane filter disk (C) is made of a suitable material with a nominal pore diameter of 3 μm and protectedby a prefilter (B) that is made of borosilicate glass wire. Dissolve the prescribed quantity of the substance being examined in 30 ml of water unless otherwise specified in the monograph. Filter the solution applying an even pressure. Dismantle the holder and check that the membrane filter remains uncontaminated; if necessary replace the membrane filter and repeat the filtration. To the whole filtrate, or the prescribed volume of the filtrate, add 2 ml of acetate buffer pH 3.5 and add to 1.2 ml of thioacetamide solution R, mix and allow to stand for 10 minutes. Invert the order of the filters, and filter the solution applying slow and even pressure. Remove the membrane filter is not move intense than that obtained by standard which is treated using the prescribed volume of lead standard solution (1 ppm Pb) in the same manner from the sentence "Add 2 ml of acetate buffer pH 3.5...".
		General Quality Control Method for Crude Drugs	
		General quality control method for crude drugs includes the "Description", "Identification", "Tests", "Determination of Extractives" and "Assay" of crude druge. A scheme for the examination of crude	

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		General Quality Control Method for Crude Drugs	
		drugs is outlined below. 1. Carry out the method for sampling of crude drugs to take the drugs being examined. 2. Use a reference drug concerned which complies with the requirements specified under individual monograph to verify the result of tests or assays of a crude drug. 3. If the crude drugs being examined are broken, they should comply with the general requirement, except that described under "Description" in the monograph concerned. 4. "Description" consists of the form, size, colour, surface characters, texture, cut surface or fracture characters, odour and taste. 5. Identification indicates the methods for the examination of the identify of crude drugs, consisting of the traditional experiential, microscopic, physical and chemical methods. 6. Tests refers to test for the purity of crude drugs, such as the content of water, ash or foreign matter. 7. Determination of extractive refers to determine the content of soluble substances in crude drugs extracted with water or other solvents. 8. Assay refers to examine the crude drugs quantitively with chemical, physical or biological methods, including the determination of volatile oils, the content of active principles and potency by biological assay.	
		The Processing of Crude Drugs	THE PROCESSING OF CRUDE DRUGS
		Processing of crude drugs is to make the crude druge into small processed pieces through processing procedures such as cleaning, cutting and stir-baking, so that to obtain the processed drugs fulfilling the requirements of therapy, dispensing and making preparations thus assuring the safety and efficacy of the druge. The water used for processing should be unpolluted drinking water. Unless specified otherwise, the processing should meet the following requirements. 1. Cleaning The crude drugs after cleaning are called "clean crude druge". Clean crude druge should be used in cutting, processing, dispensing or compounding. The crude drugs can be cleaned with the method of sorting, winnowing, washing, sifting, cutting, scraping, paring, rejecting, brushing, rubbing and grinding, soaking, rinsing etc. to reach the quality standard on the basis of specific conditions. 2. Cutting Unless cutted in fresh or dry form, the crude drugs should be moistened to soft for cutting, it is better to keep moisten than to soak in water to prevent the elimination of active principles, the crude drugs should be treated separately and appropriately according to their size, diameter and hardness, nothing the temperature, quantity of water and duration of treatment. The drugs should be dried in time after cutting. The crude drugs may be cut into slices, sections, pieces and slivers, etc. Their size and thickness are generally as follows. *Slices* Less than 0.5 mm in thickness for very thin slices, 1-2 mm in thickness for thin slices; more than 2-4 mm in thickness for thick slices. Sections or segments 10-15 mm in length. *Pieces* Cubes of 8-12 mm. *Slivers* 2-3 mm in width for barks; 5-10 mm in width for leaves. The crude drugs other than those treated by cutting are usually treated by pounding. 3. Roasting and Broiling Unless specified otherwise, the general methods and requirments are as follows. (1) Stir-baking (2) Scalding (3) Calcing (4) Carbonizing (5) Steaming (6) Boiling (7) Stewing (8) Blanching in boiling water (9) Processing with wine (10) Processing with vinegar (11) Processing with soft-water (12) Stir-baking with ginger juice (13) Stir-baking with honey (14) Stir-baking with oil (15) Frost-like powder (16) Levigating (17) Roast	In traditional Vietnamese medicine, the medicaments used by oral administration are always to undergo stages of processing. *Preprocessing* (preliminary processing): The preprocessing aims at removing parts that are not indented for medicinal use (rootlets, cores, roots, stones...) or stabilising the crude drugs right away at the beginning (exposure to sunlight, drying, sulphuration...). Thus, after preprocessing the initial materials are obtained and called "raw drugs" that however have to comply with certain requirements of quality standard. *Complex-processing* (processing): This is more complicated process with a view to reducing toxicity, adverse and side effects or changing therapeutic categories, increasing channel tropism and still affecting very often the active ingredient structure and effects of the crude drugs to be processed. Thus, after complex-processing the materials with officinal meaning are obtained and called "processed drugs", complying with the requirement of therapy. Aqueous methods (water-processing) *Washing* *Soaking* *Wrapping up* *Levitating* Thermal methods (fire-processing) *Stir-baking* *Simple stir-baking* *Stir-baking with gentle heat* *Stir-baking to yellowing* *Stir-baking to yellowing and laying down on the ground* *Stir-baking to yellowing with darkened fractures* *Stir-bakint with nature presevation (Stir-baking to darkening)* *Stir-baking to carbonizing* *Stir-baking with liquid excipients* *Stir-baking with wine* *Stir-baking with vineger (processing with vineger)* *Stir-baking with honey* *Stir-baking with ginger juice* *Stir-baking with ginger loses* *Stir-baking with milk* *Stir-baking with rice-washing water* *Stir-baking with urine* *Stir-baking with black-bean water* *Stir-baking through an intermediary* *Stir-baking in a sand-bath* *Stir-baking in a bath of powdered talc or clam-shell* *Broiling* *Burning with ethanol* *Calcinating* Drying *Drying in a stove at normal pressure* *Drying over a cooking fire or charcoal oven*

JP	KP	CP	VP
		The Processing of Crude Drugs	THE PROCESSING OF CRUDE DRUGS
			Aqueous-thermal methods Stewing *Steaming* *Boiling* *Quenching*
		Determination of Tanninoids	DETERMINATION OF TANNINOIDS IN HERBAL DRUGS
		This experiment should be processed without illumination. Preparation of reference solution Place 50 ml reference substance solution of gallic acid, accurately measured, in 100 ml brown measuring flask, dissolve and dilute to volume with water. Place 5 ml, accurately measured, in 50 ml brown measuring flask, dilute to volume with water, shake well (0.05 g gallic acid per ml). Preparation of standard curve Place 1.0 ml, 2.0 ml, 3.0 ml, 4.0 ml 5.0 ml reference substance solution, in 25 ml brown measuring flask, add 1 ml phosphotungstomolybdic acid respectively, then add 11 ml, 10 ml, 9 ml, 8 ml, 7 ml water respectively, dilute to volume with 29% sodium carbonate, shake well. With corresponding reagents as blank, measure the absorbance at 760 nm according to the Ultraviolet Spectrophotometry and Colourimetry. Draw the standard curve with the absorbance as ordinate and concentration as abscissa. Preparation of test solution Place a quantity of the powdered material (according to the prescription under the individual monograph), accurately weighed, in a 250 ml brown measuring flask, add 150 ml water, stand overnight, treat with ultrasound for 10 minutes, allow to cool, dilute to volume with water, shake well, keep standing (for solids depositing), filter and throw away the first 50 ml of filtrate. Place 20 ml of the filtrate, accurately measured, in 100 ml brown measuring flask, dilute to volume with water. Procedure Total phenol Place 2 ml solution being examined, accurately measured, into 25 ml brown measuring flask. Follow the steps in preparation of standard curve, from "add 1 ml phosphotungstomolybdic acid", add 10 ml water, measure the absorbance according to the method and calculate the content of gallic acid in the test solution using the standard curve. Non-adsorbed polyphenol Place 25 ml solution being examined, accurately measured, in 100 ml stoppered conical flask, previously added 0.6 g casein, and stopper well. Stay at 30℃ for 1 hour on a water bath, shake well, then allow to cool, filter and throw away the frontal filtrate. Place 2 ml of the filtrate, accurately measured, in 25 ml brown measuring flask. Follow the steps in Preparation of standard curve, from "add 1 ml phosphotungstomolybdic acid", add 10 ml water, measure the absorbance and calculate the content of gallic acid in the solution being examined using the standard curve. Use this following formula to calculate the content of tannnin in the test solution. Total tannin = (Total phenol) - (Non-adsorbed polyphenol)	Weigh accurately a quantity of powdered crude drug (passed through a N0 355 sieve) containing about 1g of tannoids. Place in a conical flask, add 150 ml of water and heat on a bath for 30 minutes. Allow to cool, transfer the mixture to a 250 ml volumetric flask. Dilute to volume with water, filter and use the filtrate as the test solution. Determination of total water-soluble extractives Take accurately 25 ml of the test solution, evaporate to dryness, dry the residue at 105℃ for 3 hours. Weigh (T1 g). Determination of water-soluble extractives not bound with hide powder To 100 ml of the test solution, measured accurately, add 6 g of dry hide powder R. Shake well fore 15 minutes and filter, Take accurately 25 ml of the filtrate, evaporate to dryness, dry the residue at 105℃ for 3 hours. Weigh (T2 g). Determination of water-soluble extractives of hide powder To 100 ml of water, measured accurately, add 6 g of dry hide powder (R). Shake well fore 15 minutes and filter, Take accurately 25 ml of the filtrate, evaporate to dryness, dry the residue at 105℃ for 3 hours. Weigh (T0 g). Calculate the percentage of tanninoids in herbal drugs from the expression: (T1-T2+T0) x 10/a x100 where: a is the mass taken (in g) of the drug being examined, calculated on the dried basis.
		Determination of Cineol	DETERMINATION OF CINEOLE IN THE VOLATILE OIL
		Carry out the method for gas chromatography. Chromatographic system and system suitability Pack a column with 7:3 (g/g) of 10.0% polyethylene glycol (PEG)-20M and 2.0% silicon (OV-17), with PEG at the end of injection; maintain the column temperature 110±5℃; the number of theoretical plate of the column is not less than 2500, calculated with reference to cineol; the resolution factor of the peaks of cineol and its neighbouring impurities should meet the requirement. Determination of the correction factor Dissolve a quantity of cyclihexanone, accurately weighed, in *n* -hexane to make a solution containing 50 mg per ml as the internal standard. Weigh accurately about 100 mg of cineol CRS to a 10 ml volumetric flask, add accurately 2 ml of the internal standard solution, dilute with *n* -hexane to volume, shake well, inject 1 ml of the solution to the column for 3-5 times, and calculate the correction factor by the average area of peaks. Preparation and determination of the test solution Weigh accurately about 100 mg of the sample to a 10 ml volumetric flask, add accurately 2 ml of the internal standard solution, dilute with *n* -hexane to volume, shake well, use it as the test solution. Inject 1 ml of the solution to the column and calculate the content of cineol.	Weigh 3.00g of the sample, recently dried with anhydrous sodium sulphate R, into a dry test tube and add 2.10g of melted o-cresol. Place the tube in the apparatus for the determination of freezing point and allow to cool, stirring continuously. When crystallisation takes place there is a small rise in temperature; note the highest temperature reached (t1). Remelt the mixture on a water bath ensuring that the temperature douse not exceed t1 by more than 5℃ and place the tube in the apparatus maintained at a temperature 5℃ below t1. When recrystallisation takes place, or when the temperature of the mixture has fallen 3℃ below t1, stair continuously, note the highest temperature at which the mixture freezes (t2). Repeat the operation until the tow highest values obtained for t2 not differ by more than 0.2℃. If super cooling occurs, induce crystallisation by the addition of small crystal of a complex consisting of 3.00 g of cineol and 2.10 g of melted o-cresol. If t2 is below 27.4℃, repeat the determination after the addition of 5, 10g of the complex. Determine the percentage (m/m) of cineole correspondent to the freezing point (2) from the Table, obtaining intermediate values by interpolation. If 5.10g of the cineol o-cresol complex was added, calculate the percentage m/m of cineole from the expression 2 (A-50), where A is the value corresponding to a freezing point of t2 taken from the Table.

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分担研究報告書

分担研究課題　臨床試験報告における漢方製剤の記載法に関する研究

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研究要旨：臨床報告は、副作用についての症例報告から、有効性を主とするランダム化比較試験(randomized controlled trial: RCT)までの多様な研究デザインに関連する。そこでの漢方製剤の記載法はグローバルに見ると herbal medicine の characterization の一部とみなすことができる。この characterization に関して、世界で進行中の、1) Uppsala Monitoring Center の Herbal ATC (HATC) classification project、2) WHO/WPRO による IST (WHO/WPRO International Standardization of Terminology of Traditional Medicine)、3) Forum for Herbal Harmonization (FHH)、4) CONSORT statement: herbal / TCM extension、5) ICH M5 (Data Elements and Standards for Drug Dictionaries の 5 つのプロジェクトについてその歴史と現状、またその相互関係を明らかにし、漢方製剤の記載法の標準化にむけての基礎資料を整えた。さらに中国医学系の薬物の分類の推移についての歴史的分析の予備調査を行った。

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A. 研究目的

1990 年代後半からのエビデンスに基づく医療(evidence-based medicine: EBM)の潮流の中で「過去に行われた臨床試験の十分なレビューがなされないまま新たに臨床試験を実施することは非倫理的である」と言われるようになった。すなわち、各国での医療サービスの中での医薬品に対するニーズがどのようなものであり、それがどの程度強いかを知り、これに答える既存の臨床試験からのエビデンスを知り、今後どんな臨床試験がなされるべきかを計画するのである。漢方製剤などの herbal medicines についても同様のことがいえる。

Herbal medicines は世界的に使われているものであるが、上記のレビューを行うに当たり、その記載法や分類が標準化していないという問題がある。副作用についての単一の症例報告から、ランダム化比較試験(randomized controlled trial: RCT)のような有効性を主とする研究デザインの双方に関係する。これらを harmonize させることを目的とした project には、複数のものが存在するがその歴史や現状、また相互の関係が明確ではない。

漢方製剤はいずれグローバル化すると考えられる。そこで、これらの project について調査し、現状を明らかにすることを第 1 の目的とする。

この作業の中で明らかになった中国医学系の薬物の分類の推移についての歴史的分析の予備調査を第 2 の目的とする。

B. 研究方法

(1) Medline や医中誌 web による関連文献の収集。
(2) 英国・ロンドンの Kew Garden における関係者とのインタビュー
(3) オランダ・アムステルダムにおける関係者とのインタビュー
(4) ノルウェー・オスロで 2007.10.24-25 に開催された "The 22nd meeting of the WHO International Working Group for Drug Statistics Methodology への参加。
(5) 中国人・中医学研究者との議論

(倫理面への配慮)

直接的に患者や健常人に対する調査は行わず、この点での倫理的な配慮は必要としない。

C. 研究結果

以下の5つのプロジェクトがherbal medicinesの記載法として進行中であることが明らかとなった。

(1) Herbal ATC project

グローバルレベルと日本国内の動きに分けて述べる。

1) グローバルレベルのHerbal ATC project

Herbal ATC (HATC)は、2つのWHO協力センターが関係している。一つはオスロにある医薬品統計学方法論WHO協力センター（WHO Collaborating Centre for Drug Statistic Methodology)である。このセンターは新薬にATC分類に基づきコードを付与している。ATC分類とはAnatomical, Therapeutic, and Chemical classificationのことである。コードが決まるとそれに対する1日平均維持量（Defined Daily Dose: DDD）も決められる。

基本的にはオスロのセンターが毎年2回会議をもちATCとDDDの決定をしている。会議は世界各地域から全部で12人のメンバーとセンターのスタッフからなる。

ただし、ハーブに関するATCだけはスウェーデンのウプサラにあるUppsala Monitoring Centre（UMC）が担当している。UMCは、国際医薬品モニタリングWHO協力センター(WHO Collaborating Centre for International Drug Monitoring)でもあり、日本を含む世界各国からのADR reportの収集と分析、また伝達の世界の中心的な役割を果たしている。300万件以上のADRレポートがVigibaseというデータベースに蓄積されている。

この中には、ハーブや生薬や漢方薬のADR reportも1万件以上含まれる。しかし名称が統一されていない。またUMCのシステムはRoman alphabetでしか運用されていない。そこでデータベースを全体として解析するためには世界共通コードが必要になる。

2002年5月27日に、ハーブについてATCをつける第1回目の会議が開かれ、HATCコード付与を開始することになった。ここでハーブとは西洋ハーブのみならず生薬や漢方処方などの伝統薬全体を含む。3人のメンバーとUMCのスタッフが参加した。第2回の会議は、ロンドンで2005年4月に開催された。ここにはハーブ関係の副作用の世界的研究者であるオランダのPeter de Smetも参加した。彼が1992-1993に纏めた"Adverse effects of herbal drugs 1& 2"（Springer-Verlag）はこの領域の古典とも言われるものである。UMCのHATC projectももともと彼のアイデアで始まったものである。この間、いくつかの冊子が出版された。単味のハーブについては着実にコード化が進んだ。

2) 日本におけるHATCプロジェクトと漢方処方のローマ字表記の標準化

日本側HATCのプロジェクトは2002年から開始された。日本では単味の生薬よりも漢方処方として製剤化して使われる方がはるかに大きい。そこで漢方処方のATC分類からスタートした。また翌2003年からは漢方処方のローマ字表記のプロジェクトも始まった。

関係者らの協力によりこの2つのプロジェクトは平行して進んだ。明確な結果としては「漢方処方名ローマ字表記法2005」（Standard Kampo Formula Nomenclature" (SKFN)が先に2005年3月に完成した。この内容は、日本東洋医学会の「日本東洋医学雑誌」、日本生薬学会の"Herbal Medicines"、和漢医薬学会の"Journal of Traditional Medicines"と3つの学会誌の投稿規定に入るなどして、2005年から使われ始めた。また翌2006年3月の「第15改正日本薬局方」に初めて漢方処方が6種収載された時にもこのローマ字表記は用いられた。

一方、漢方処方のATCコードは、『一般用漢方処方の手引き』(1975)にある210処方とそれ以外に医療用として販売されている漢方処方18の計228処方に付けられた。2002年のウプサラ会議で、コードは多くて3つまでと決められており、日本で漢方処方を分類するときもこれにしたがった。するとコードが一つで済むものは、48処方、約20%に過ぎない。他は2つないし3つのコードが付いたのである。

これは、漢方医学の持つ医学システムによる。小柴胡湯は、肝炎につかうと消化器系であり、長引いたかぜに使うと呼吸器系であり、腎炎につかうと腎疾患系であり、それだけで3つのコードが付いてしまうのである。

また、漢方医学は中国医学の日本variationといえるものであるが、中国と日本はそのシステムが若干異なっており、また他の中国周辺諸国、ベトナムや韓国などとも違っている。そうすると同じ

漢方処方名であってもコードが異なることも生ずることになる。こうした状況では、コードを副作用情報の世界的な解析に用いようという本来の目的を達成することが困難になる。

(2) WHO/WPRO International Standardization of Terminology (IST)

WHO 伝統医学用語国際標準化プロジェクト、略称で IST とも称されているものである。最初の会議は、北京で 2004 年 2 月に開催された。その後、東京、韓国の大邱とつづき、また各国で対応する組織も設立され進んだものである。日本では、日本東洋医学サミット会議(Japan Liaison for Oriental Medicine: JLOM)が担当した。その後、2007 年 8 月に WHO 西太平洋地域事務局から"WHO Internal Standard Terminologies on Traditional Medicine in the Western Pacific Region"として出版された。同じものが同事務局の website [http://www.wpro.who.int/]から無料で download できる。ただし全 356 ページある。

この過程中、2006 年の東京会議で、この用語集に生薬名、漢方処方名を入れるかどうかが議論された。この IST の案は、中国側で作成されたもので、主たる参考文献は、2004 年発行の謝竹藩の『中医薬常用名詞術語英訳』(English Translation of Common Terms in Traditional Chinese Medicine)である。IST の案には中薬が 21 分類全 493 種、方剤が 19 分類全 469 種入っていた。

Fig. 1 に中薬についてその分類名と中薬数、Fig. 2 に方剤について同じく分類名と方剤数を示す。

これらの分類法は、基本的には、中国の中医薬大学や中医学院で広く使われている「中薬学」と「方剤学」の教科書と同じものである。

まず生薬について議論されたが、ここで大きな問題になったのは生薬の局方名(pharmacopeia name)のラテン語表記の各国での違いである。例えば人参を薬局方の中で,中国やベトナムのように *Radix Ginseng* と表記する国もあれば、日本や韓国のように *Ginseng Radix* と表記する国もある。どちらがラテン語として正しいのであろうか？ドイツから来た薬学出身で、著名な中国医学の医史学者の Paul Unshuld によれば、ラテン語は彼の専門領域でもあり、双方とも正しいとのことである。

またこのプロジェクトのメンバーは各国の伝統医学の臨床家が多く、薬系の人はあまり多くない。各国の薬局方は各国の薬局方委員会が作成する国家的ドキュメントであり、それに反するようなことを会議の参加者は決めることはできないとなったのである。

大方の意見としては、生薬・中薬についても決められないのであるから、処方名・方剤名についても決めるのは憚られるということで、この生薬と方剤名については、将来の課題となった。

この議論から興味深い事実が浮かび上がった。この種の中国医学系の分類は、ある生薬や処方は必ずひとつの分類に収まり、2 つ以上の分類になることはない。これは、複数のコードが付いてしまうという ATC コードとは違う。ATC コードは、まず解剖学的臓器名、例えば消化器系や呼吸器系から分類がはじまり、つぎの段階が、治療的・薬理学的分類である。このためにある薬に 2 つ以上の分類コードが付いてしまう。これに対し、中国医学系の分類体系は、「解表」や「清熱」など、機能を主としているために分類がユニークに決まるのである。

ただし約 20 の分類名には、日本であまり見かけないものも存在する。だがそのうち約半分は日本でもある程度漢方医学を勉強したものには理解可能なものである。

このいわば「東アジア伝統薬分類体系」(east Asian herbal classification)はうまく育てれば、世界的な分類法になる可能性がある。それを、ATC コードと組み合わせリンクして、UMC のシステムに組み込むことも将来は考えられる。

そこで中国人・中医学研究者とともに、中国医学系の薬物の分類の推移についての歴史的分析を開始した。現在の中国における中薬や方剤の分類システムは清代に作られたものであり、日本でもおおよそ明治期まではほぼ同じものがいくらか用いられていたがその後ほとんど使われなくなっている。この予備的な研究結果は 2007 年 12 月 3 日に台北で開催された 14th International Congress of Oriental Medicine (ICOM, 国際東洋医学会学術大会)で報告された。

(3) Forum for the Harmonization of Herbal Medicines (FHH)

先の ATC はもともと WHO ヨーロッパ地域事務局(WHO Office for Europe: EURO)が関係していたものが、その後 WHO 本部が担当し現在は世界的なプロジェクトになったものである。一方、IST は WHO 西太平洋地域事務局(WHO /WPRO)のプ

ロジェクトである。

ここで紹介するFHHは、もともとWHO/WPROが企画したもので2002年に始まったものであるが、現在は、日本、韓国、中国、ベトナム、シンガポール、オーストラリアの6カ国に香港が加わり、“6+1”で実質的に運営されている。その名称は、日米EUを主にして1993年から動いている「日米EU医薬品規制調和国際会議」(International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH)からharmonisationの用語を借り、WHO西太平洋地域事務局の管理する国の間で生薬・漢方薬の種々のハーモナイゼーションを行おうというものである。なおICHは英語でharmonisationだが、FHHは米語でharmonizationとなっている。

現在、3つの分科会（Sub-committee）がある。Sub-committee Iは用語と標準化、Sub-committee IIは品質保証と情報、Sub-committee IIIは2005年から始まった副作用(adverse drug reaction)である。詳しい活動はソウル大学天然物科学研究所が管理しているwebsite (http://www.fhhm.net/)から見ることができる。

このFHHは、2年単位で活動しており各単位の終わりに国際ファーラムを開催している。安全性に関して、2004年9月の上海でのFirst HFF International Forum、2006年11月の東京でのSecond FHH International Forumなどで、HATCの世界的な動きとそれに対応した日本の現状について報告された。副作用についての他の国からの報告もあったが、通常の西洋薬の副作用自発報告制度も十分には整備されてない国が多く、初期的発展段階、まだこれから、というところである。

ただし漢方製剤に毒性を持つ物質が含まれて事故が起きるといった緊急的な状況への対応には、このFHHのネットワークは十分機能している。

(4) CONSORT extension for herbal medicines

CONSORT声明(CONSORT Statement)は世界的な「エビデンスに基づく医療」（evidence-based medicine: EBM）のながれの中で1996年に作成されたものである。

RCTを雑誌に投稿する際に、チェックリストを用いて必要な項目が記載されているかどうかを確認し、同じチェックリストを雑誌編集部や査読者も使うシステムである。また組入れられた試験参加者の脱落などを明示するためのフローチャートの論文への収載が要求される。これらによってRCT論文の質向上、さらにはRCTそのものの質向上を期待するものである。

2001年に改定され現在は22項目からなっている。多くの世界的な医学雑誌は投稿規定でこのCONSORT声明を取り入れ、著者が使うことを要求している。各国語に翻訳され、web (http://www.consort-statement.org)で公開されている。日本語訳も存在する。

このアイディアは種々の方向に発展した。ひとつは、RCTに限らず他の研究デザインでの同様なチェックリストの作成である。メタアナリシス、観察研究、非劣性試験、などに展開した[]。

もうひとつの流れは、広く相補代替医療(complementary and alternative medicine: CAM)の領域でのチェックリストの開発である。特に「介入」(intervention) についてより詳しく書きその論文に記載されたエビデンスの使用可能性を高めるものである。鍼のSTRICTA声明(http://www.stricta.info)では、針の太さや刺入の深さ、また鍼師がどの程度、何年間の臨床経験があるかなども記載するようになっている。

ハーブ関係でも動きがあり、一つは単味の生薬についてで、2006年3月にGagnirらによって発表された。ここでは、生薬の植物名、部位、加工法、品質管理の方法などの記載が求めれている。

同年5月には香港のBianらにより、方剤を含み広く中薬(Chinese Herbal Medicines: CHM)についてのものが報告された。22項目を3項目に拡大し、配合理由、弁証論治の内容、など中国医学システムに応じた項目が含まれている。

これらは、CONSORT声明が拡張してできたチェックリストということでCONSORT extensionと総称される。手にした臨床研究の論文のエビデンスがどの程度のものか？ そのエビデンスを目の前の患者に使えるのか？ といったユーザー指向の考えに基づくものである。行政は関与しないが、論文発表の段階で、そのハーブ・生薬がどういうものかなどを記載に標準化し、いわば学術情報の流通の段階での品質管理をおこなおうとするもので、今後、大きな発展が期待される。

(5) M5: Data elements and standard for drug dictionaries

先に述べたICHは基本的に新薬開発のためのガイドラインを作成するものであるが、Quality、Safety、Efficacy、Multi-disciplinaryの4つのカテゴリーに分けて作業が進んでいる。このうちMulti-disciplinary(複合領域)の5つ目のプロジェクトで、M5 Data elements and standard for drug dictionaries (医薬品辞書のためのデータ項目及び

基準)と称するプロジェクトのうちでherbal substance（植物由来の物質）やherbal preparation（植物製剤）が、2.2.2 Active Ingredients Controlled Vocabulary (有効成分管理用語集)の項で議論されている。

現在、このM5トピックは2008年2月現在step 3の段階である。Step 3はstep2で出来たdraftに対するパブリックコメントを求めるものである。日本版の締め切りは2005年7月21日であり、現在step 4の最終版作成へ向けての作業進んでいるところである。Step 2の内容は、websiteから見ることが出来る (www.ich.org/ 日本語はhttp://www.pmda.go.jp/ich/ich_index.html)。

ラテン語による植物名、部位、加工法などを記載することになる。

なお、ICHは先に述べたように新薬開発を中心としたプロジェクトであり、一部市販後の副作用調査も含まれるが、このM5の医薬品辞書でherbal substanceやherbal preparationが含まれているのは、漢方薬の新薬開発を目的にしたものではない。臨床試験のプロトコールや症例調査票(case report form: CRF)で、併用薬としての漢方薬が記載される場合があるが、それが有効性や安全性に関係している場合がある。そこでそれらの記載法を標準化する必要があるというのが理由である。

D. 考察

上記した5つの他にも、国際標準化機構(International Organization for Standardization: ISO)での動きもあり、この種のハーモナイゼーションの国際的なプロジェクトは全部で6つである。用いる介入の「性格表示」(characterization)をどうするかについてのプロジェクトともいえる。

このようにハーモナイゼーションに係わるプロジェクトが同時並行で動いている現状であり、これらのハーモナイゼーションのプロジェクトのハーモナイゼーション(H^2)も必要と考えられる。

これらの間でいくつかリンクが取れているものもある。HATCを担当するUMCは、英国のキュー植物園(Royal Botanical Garden, Kew)と協力関係にある。UMCのVigibaseに入るハーブなどの名称の確認をキューが担当することになっている。WHO herbal ADR databaseのコンセプト図にherbal code number (HCN)と称する10桁のコードがある。植物名が5桁、部位が3桁、製法・剤形が2桁である。これらはキュウが担当するのである。ICH M5にもKewからメンバーが入っている。またUMCはISOとも関係している。HATCとFHH双方に関るものもいる。

ただしこれらのH^2はそれほど上手くいっているわけではない、先に述べた、HATCで一緒に活動しているオランダのDe SmetとH^2が必要だと意見が一致し、2007年12月に一緒にキューを訪問し現状調査したが、組織的・資金的問題がありそれほどスムーズには進んではいない。

アジアのまた中国文化圏・漢字文化圏の人間として感じるのは、各国の状況の多様性である。リスク評価はリスク認知から始まると述べたが、リスクを認知するためには、有害事象・副作用情報の収集がまず必要である。

日本は、毎年約3万件の副作用報告が厚生労働省に集まる。このうちUMCへ報告されるのはそのうちの約20%を占める「直接報告」すなわち医療機関などから直接、厚生労働省へ報告されるもののみである。残り約80%の「企業報告」はUMCへ送られていない。医薬情報担当者(MR)が関与する「企業報告」のほうが通常、情報の質が高いとも考えられるがそれが世界的には利用されていないのだ。生薬・漢方薬についても同様である。

これには、報告するには、全部、英語、ローマ字化しなければならずその手間が大変ということもある。現在では、先に紹介した2005年のStandard Kampo Formula Nomenclature（SKFN）が使われるようになったが、それ以前に一部ではあるがUMCに送られていた漢方薬の副作用情報は、用語が統一されておらず、SKFNとのマッピングの作業が必要である。

中国からは、多くのADR reportがUMCに届いているとのことであるが、中薬に関しては、用語の標準化やコード化がなされていないため、活用できない状態にある。ただし中国医薬品食品監督局(State Food and Drug Administration: SFDA)はUMCにスタッフを送りワークショップに参加させたり、また国内でもこの領域の教育をすでに開始している。

韓国はADR reportが十分には集まっていない。特に生薬・韓薬については少ない。これは韓国の西医師と韓医師からなるパラレルな医療システムに由来する。韓医師は病院勤務は少なく多くは開業医である。韓国は全ての医療機関が保険診療機関であるが混合診療が認められている。韓医師の収入の多くは煎じ薬を自費払いで用いること

で成り立つ。また患者も煎じ薬を好むところがある。このため、患者からの評判を重要視する韓医師は副作用報告をすることを好まないのである。典型的な under reporting の状態である。

このような各国の状態の理解の下にハーモナイゼーションや、H^2のプロジェクトを進める必要があるのである。

E. 結論

臨床報告は、副作用についての症例報告から、有効性を主とするランダム化比較試験(randomized controlled trial: RCT)までの多様な研究デザインに関連する。そこでの漢方製剤の記載法はグローバルに見ると herbal medicine の characterization の一部とみなすことができる。この characterization に関して、世界で進行中の、1) Uppsala Monitoring Center の Herbal ATC (HATC) classification project、2) WHO/WPRO による IST (WHO/WPRO International Standardization of Terminology of Traditional Medicine)、3) Forum for Herbal Harmonization (FHH)、4) CONSORT statement: herbal / CHM extension、5) ICH M5 (Data Elements and Standards for Drug Dictionaries の 5 つの project についてその歴史と現状、またその相互関係を明らかにし、漢方製剤の記載法の標準化にむけての基礎資料を整えた。さらに中国医学系の薬物の分類の推移についての歴史的分析の予備調査を行った。

F. 健康危険情報

なし。

G. 研究発表

1. 論文発表

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2. 学会発表

(1) Tsutani K, Tu Ya. The history and current situation of the classification of traditional Chinese medicine in China and Kampo drugs in Japan. 14th International Congress of Oriental Medicine (ICOM), Taipei, 3 December 2007. Abstract. p.40-1

H. 知的財産権の出願・登録状況

なし。

1. 解表薬	31	12. 活血祛瘀薬	41
2. 清熱薬	85	13. 化痰止咳平喘薬	42
3. 瀉下薬	16	14. 安神薬	10
4. 祛風湿薬	30	15. 平肝熄風薬	15
5. 化湿薬	10	16. 開竅薬	6
6. 利水滲湿薬	31	17. 補虚薬	61
7. 温裏薬	14	18. 収澁薬	20
8. 理気薬	33	19. 湧吐薬	2
9. 消食薬	7	20. 殺虫止痒薬	7
10.駆虫薬	6	21. 提膿祛薬	6
11.止血薬	20	total	493

Fig.1 中薬の分類名と中薬数

1. 解表剤	20	11. 理血剤	37
2. 清熱剤	86	12. 祛風剤	31
3. 瀉下剤	18	13. 治燥剤	4
4. 和解剤	16	14. 祛湿剤	38
5. 温裏剤	22	15. 祛痰剤	26
6. 補益剤	94	16. 消食剤	5
7. 固澁剤	14	17. 駆虫剤	20
8. 安神剤	8	18. 湧吐剤	2
9. 開竅剤	6	19. 明目剤	6
10.理気剤	35	total	469

Fig. 2 方剤の分類名と方剤数

研究成果の刊行に関する一覧表

原著論文

発表者氏名	タイトル名	発表誌名	巻、号	ページ	出版年
Kawahara, N.他	Comparative study on testing methods and specification values for crude drugs in Pharmacopoeias among four western pacific regional countries (Japan, China, Korea and Vietnam) (Ⅲ) Comparative study on general testing methods for crude drugs	Shoyakugaku Zasshi	61	44-57	2007
Itokazu, N.他	Actual Use Research, a new method for evaluating the effectiveness of OTC kampo drugs and its application to Kamishoyosan formulation	J. Trad. Med.	24	104-114	2007
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Tsutani, K.他	Regulatory sciences in herbal medicines and dietary supplements	Yakugaku Zasshi	128	accepted	2008
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Kawahara, N.他	Comparative study on testing methods and specification values for crude drugs in Pharmacopoeias among four western pacific regional countries (Japan, China, Korea and Vietnam) (IV) Comparative studies on TLC identification for crude drugs considering harmonization and clean analysis	Shoyakugaku Zasshi		submitted	2008

総説等

Goda, Y.	Actual use research (AUR), a new method for evaluating the effectiveness of OTC kampo formulations	Shoyakugaku Zasshi	62(1)	1-7	2008