Consultation Document

Reference No. 2018/06/12

Consultation on setting limits of sulphur dioxide residues in Chinese herbal medicines and related measures for implementation

Background

The application of sulphur dioxide (SO_2) produced by burning sulphur to fumigate Chinese herbal medicines can be used to prevent insects, mildew and browning, rendering them easy to preserve. Although such application has a long history, it may also cause problems of sulphur dioxide residues in herbal medicines.

2. Health baseline guidelines for sulphur dioxide are established based on the assessment conducted by Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the daily allowable intake (ADI) is 0 - 0.7 mg/kg (body weight). According to the list of carcinogens published by International Agency for Research on Cancer (WHO), sulphur dioxide is included in the list of Class 3 carcinogens which are suspected of being carcinogenic to humans but lack adequate human or animal research data. In addition, sulphur dioxide is also a common food preservative and will not adversely affect health under normal use.

3. Since sulphur dioxide is soluble in water, sulphur dioxide residues in Chinese herbal medicines will significantly be reduced after washing, soaking and decocting. However, excessive sulphur dioxide residues may cause harmful effects to individuals, especially those who have allergic reactions to sulphur dioxide, which may trigger asthma and other symptoms such as headache or nausea. Also, long-term exposure to sulphur dioxide with level exceeding the limit can induce respiratory diseases and cause multiple tissue damage. Therefore, there is a need to establish a quality standard for the limits of sulphur dioxide residues in Chinese herbal medicines due to their potential risks.

Background on the regulation of sulphur dioxide residues in Chinese herbal medicines in the Mainland China

4. With reference to the standards of various international organizations and the situation of the application of sulphur dioxide in China, the "Chinese Pharmacopoeia Commission" (Commission) has established limits for sulphur dioxide residues in

Chinese herbal medicines (crude drugs) and their decoction pieces. The Commission issued public notices in June 2011 and April 2012 to seek opinion on limits of sulphur dioxide residues in Chinese herbal medicines and their decoction pieces. The limits were included in the second supplement of the 2010 edition of the Chinese Pharmacopoeia (CP2010) published in 2013 and came into effect in December of the same year. Subsequently, the Commission conducted further research and consultation on the testing method for determination of sulphur dioxide residues, and changed the testing method (iodometric titration) stated in CP2010 to three methods (acid-base titration, gas chromatography and ion chromatography) stated in the 2015 edition of the Chinese Pharmacopoeia (CP2015).

5. According to CP2015, unless otherwise specified, sulphur dioxide residues in Chinese herbal medicines and their decoction pieces (except minerals) shall not exceed 150 mg/kg.

6. CP2015 also stipulates that sulphur dioxide residues of Achyranthis Bidentatae Radix, Puerariae Thomsonii Radix, Asparagi Radix, Gastrodiae Rhizoma, Trichosanthis Radix, Bletillae Rhizoma, Paeoniae Radix Alba, Atractylodis Macrocephalae Rhizoma, Codonopsis Radix as well as "Mao Shanyao" and "Guang Shanyao" under Dioscoreae Rhizoma[Note1] shall not exceed 400 mg/kg while that of "Shanyao Pian" under Dioscoreae Rhizoma[Note1] shall not exceed 10 mg/kg.

7. Besides, the three methods for determination of sulphur dioxide residues namely "acid-base titration", "gas chromatography" and "ion chromatography" have been documented in the General Chapter 2331 of CP2015 (Please see Appendix 1 for details).

8. In the case that the sulphur dioxide residues in Chinese herbal medicines and their decoction pieces are found not complied with the requirements, drug regulatory authorities in the Mainland China will take actions such as seizure, and require the relevant units to suspend the sale of sub-quality products and issue the announcement.

Background on the regulation of sulphur dioxide residues in Chinese herbal medicines in Hong Kong

9. Since the Commission has issued a public notice on the consultation of limits

[Note1] Dioscoreae Rhizoma is not a Schedule 1 or 2 Chinese herbal medicine under the Chinese Medicine Ordinance.

of sulphur dioxide residues in Chinese herbal medicines and their decoction pieces in 2011, the Chinese Medicine Council of Hong Kong (CMCHK) requested the Department of Health (DH) to keep in view of the progress and monitor the safety and quality of Chinese herbal medicines locally. In the same year, the "Scientific Committee" and the "International Advisory Board" under the "Hong Kong Chinese Materia Medica Standards" (HKCMMS) Project have discussed the testing of sulphur dioxide in herbal medicines, and conducted research on the determination and quantification of sulphur dioxide residues, including different testing methods for determination of sulphur dioxide residues to be adopted by HKCMMS, the situation of Mainland and Hong Kong regarding the sulphur dioxide residues in herbal medicines, the risk assessment and management of sulphur dioxide residues in herbal medicines.

10. The results of the study on the sulphur dioxide residues in herbal medicines under HKCMMS, including the testing method, the research data and limits of sulphur dioxide residues, were reviewed by the "International Advisory Board" in 2017. The recommendations were also endorsed by the "Scientific Committee" in January 2018. Relevant limits of sulphur dioxide residues and testing method for determination of sulphur dioxide residues will be published by HKCMMS in the third quarter of 2018.

11. Limits of sulphur dioxide residue recommended by HKCMMS are the same as those documented in CP2015. That is, unless otherwise specified, the sulphur dioxide residue of all herbal medicines (except minerals) shall not exceed 150 mg/kg. The sulphur dioxide residues of Achyranthis Bidentatae Radix, Puerariae Thomsonii Radix, Asparagi Radix, Gastrodiae Rhizoma, Trichosanthis Radix, Bletillae Rhizoma, Paeoniae Radix Alba, Atractylodis Macrocephalae Rhizoma, Codonopsis Radix shall not exceed 400 mg/kg. It is recommended to use “acid-base titration method” in CP2015 as the method to determine sulphur dioxide residues.

Current regulatory status in Hong Kong

12. Chinese Medicine Division of DH conducts market surveillance of Chinese herbal medicines specified in Schedules 1 and 2 of the Chinese Medicine Ordinance (Cap. 549 of the Laws of Hong Kong). The testing items include morphological examination, pesticide residues and heavy metals content.

13. At present, there is no standard for sulphur dioxide in Chinese herbal medicines in Hong Kong. Therefore, market surveillance programme of Chinese herbal medicines does not include the testing of sulphur dioxide residues. However,

when DH receives notifications on any incidents related to Chinese medicines from different sources (including reports of adverse reactions to Chinese medicines, public complaints, referrals from other government departments, and notifications from foreign drug regulatory authorities), DH will immediately conduct risk analysis, management, notification and related investigations.

14. Regarding the sulphur dioxide residues in Chinese herbal medicines, if the residue is found to be "unfit for human consumption" in the investigation, for example, exceeding the daily allowable intake (ADI) of 0.7 mg/kg (body weight), it may contravene Section 54 of the Public Health and Municipal Services Ordinance (Cap. 132 of the Laws of Hong Kong), that is, anyone who sells or possesses any drug intended for use by human but unfit for that purpose, is liable on conviction to a maximum penalty of level 5 fine of HK$50,000 and imprisonment for 6 months. DH may take actions, including requesting drug trader to recall problematic drugs, initiating prosecution, referring case to CMCHK for follow-up, and issuing relevant press release.

15. In addition, all imported Chinese herbal medicines must meet the statutory regulatory requirements of the place where the supplier locates. Otherwise, DH will require the importer to recall the problematic Chinese herbal medicines and notify the relevant drug regulatory authority.

Laboratory services in Hong Kong

16. At present, 15 laboratories in Hong Kong have been accredited for different testing parameters on Chinese herbal medicines according to the Hong Kong Laboratory Accreditation Scheme (HOKLAS). However, only one laboratory has been accredited to conduct the Method I (acid-base titration) on determination of sulphur dioxide residues in CP2015. Another laboratory has been accredited for testing sulphur dioxide residues in Chinese herbal medicines by using in-house method and in general food items. Other five laboratories have been accredited for the determination of sulphur dioxide in general food items, they have also been accredited under HOKLAS for other testing parameters on Chinese medicines (e.g. heavy metals or pesticide residues).

17. The principles of the method for determination of sulphur dioxide residues in food (AOAC Official method 990.28) and Method I in CP2015 are "acid-base titration", but there are slight differences in equipment used for extraction, sample weight and pre-treatment as well as extraction time, reagent concentration and quantity of reagents.

Therefore, the capability of local laboratories to test the sulphur dioxide residues in Chinese herbal medicines needs to be further improved in order to meet the demand as a result of setting limits of sulphur dioxide residues in Chinese herbal medicines.

18. The Hong Kong Accreditation Service (HKAS) points out that the actual time required between the submission of an application and the granting of accreditation will depend very much on the applicant's conformity with the HKAS requirements, the range of tests/inspection fields covered in the scope of accreditation, the effectiveness and efficiency of the organization in addressing any non-conformities identified during the assessment, etc. For a well prepared application, the accreditation process normally takes 6 months.

Laboratory services in the Mainland China

19. In 2016, Certification and Accreditation Administration of the People's Republic of China (CNCA) announced that 46 institutions in the Mainland have been accredited for passing the capability testing on determination of sulphur dioxide residues in Chinese herbal medicines, including 7 institutions(Guangdong Institute for Food and Drug, Guangdong Detection Center of Microbiology, Foshan Institute for Food and Drug, Inspection and Quarantine Comprehensive Technology Centre of Foshan Entry-Exit Inspection & Quarantine Bureau, Guangdong Shantou Institute for Food and Drug Control, Guangzhou Kingmed Center for Clinical Laboratory Co. Ltd., Dongguan Institute For Food and Drug Control) located in Guangdong Province, and they adopt the determination methods documented in the Chinese Pharmacopoeia.

Proposed measures for implementation

20. After considering the above background and the current situation of the industry, DH is now consulting on the following measures for implementation:

(1) Limits and testing methods for determination of sulphur dioxide residues

(i) It is recommended to refer to the Chinese Pharmacopoeia and the HKCMMS for limits of sulphur dioxide residues and their determination method to set the limits in Chinese herbal medicines as specified in Schedules 1 and 2 of the Chinese Medicine Ordinance (Cap. 549 of the Laws of Hong Kong) and their decoction pieces. (Please see Table 1 below for details).

Table 1: Proposed Hong Kong limits of sulphur dioxide residues in Chinese herbal medicines* and their decoction pieces to be set by CMCHK

Name of Chinese herbal medicine	Limits of sulphur dioxide residues
All Chinese herbal medicines (except for those otherwise specified and minerals)	not more than 150 mg/kg
1. Radix Asparagi	not more than 400 mg/kg
2. Radix Trichosanthis	
3. Rhizoma Gastrodiae	
4. Radix Achyranthis Bidentatae	
5. Rhizoma Bletillae	
6. Rhizoma Atractylodis Macrocephalae	
7. Radix Paeoniae Alba	
8. Radix Codonopsis	
9. Radix Puerariae	For root of Pueraria thomsonii Benth (that is Puerariae Thomsonii Radix in CP2015), not more than 400 mg/kg
	For root of Pueraria lobata (Willd.) Ohwi (that is Puerariae Lobatae Radix in CP2015), not more than 150 mg/kg

* According to the Chinese Medicine Ordinance, "Chinese herbal medicine" means the toxic Chinese herbal medicines specified in the Schedule 1 and the commonly used Chinese herbal medicines specified in the Schedule 2.

(ii) It is recommended that the industry refers to the "acid-base titration" in CP2015 which will be adopted by the HKCMMS or other methods documented in CP2015 ("gas chromatography" or "ion chromatography") for the determination of sulphur dioxide residues in Chinese herbal medicines and their decoction pieces.

(2) Implementation date

(iii) In view of the fact that only a few private laboratories in Hong Kong have been accredited for related tests, the date of implementation for relevant standards is subject to consultation with industries of Chinese medicines and laboratory service. It is proposed that the implementation date of the above regulatory measures is two years later (excluding the consultation period).

(iv) Before the official implementation, DH will communicate with the traders through various platforms to explain the limits of sulphur dioxide residues, determination methods and regulatory measures. DH will also educate the public on the precautions for the purchase and decoction of Chinese herbal medicines. When DH receives notifications on any incidents related to Chinese medicines (including reports of adverse reactions to Chinese medicines, public complaints, etc.), DH will immediately conduct risk analysis and related investigations. If the sulphur dioxide residues in Chinese herbal medicines are found to be "unfit for human consumption", prosecution will be initiated under section 54 of the Public Health and Municipal Services Ordinance (Cap. 132). In addition, all imported Chinese herbal medicines must meet the statutory regulatory requirements of the place where the supplier locates. Otherwise, DH will require the importer to recall the problematic Chinese herbal medicines and notify the relevant drug regulatory authority.

(v) After official implementation, DH will incorporate sulphur dioxide residues as a testing parameter into market surveillance programme of Chinese herbal medicines. A grace period of one year from the date of implementation for relevant standards is recommended.

(3) Grace period

(vi) During the grace period, if Chinese herbal medicines are found not complied with the limits of sulphur dioxide residues set by CMCHK in market surveillance or investigation, neither prosecution nor disciplinary hearing will be conducted in the cases where do not have any public health risks. Letter will be issued to the Chinese medicine supplier as a reminder and the trader will be requested to recall the relevant batch of Chinese herbal medicine. However, prosecution under section 54 of the Public Health and Municipal Services Ordinance (Cap. 132) and appropriate actions will be conducted if the sulphur dioxide residues in Chinese herbal medicines are found to be "unfit for human consumption".

(vii) After the expiration of the grace period, if Chinese herbal medicines are found not complied with the limits of sulphur dioxide residues set by CMCHK in market surveillance or investigation, DH will conduct enforcement and refer to the Chinese Medicines Board for disciplinary action. The relevant legislation is section 52 of the Public Health and Municipal Services Ordinance (Cap. 132), that is, selling to the prejudice of a purchaser a drug which is not of the quality of the drug demanded by the purchaser. Upon conviction, the maximum penalty is level

3 fine of HK$10,000 and imprisonment for 3 months. In addition, prosecution under section 54 of the Public Health and Municipal Services Ordinance (Cap. 132) and appropriate actions will be conducted if the sulphur dioxide residues in Chinese herbal medicines are found to be "unfit for human consumption".

Consultation period

21. In response to the wide variety of Chinese herbal medicines and the wide range of stakeholders involved (including local wholesalers and retailers of Chinese herbal medicines and laboratory service industry), a six-month industry consultation is conducted to understand the concerns of various sectors.

Opinions sought

22. If the industry has any comments on setting limits of sulphur dioxide residues in Chinese herbal medicines and related measures for implementation, please send their opinions to the Chinese Medicine Division of the Department of Health by post, fax or email by 12 December 2018 (Address: 16/F, AIA Kowloon Tower, Landmark East, 100 How Ming Street, Kwun Tong, Kowloon; Fax no.: 2778 1085; Email Address: cmd@dh.gov.hk).

Chinese Medicine Division of the Department of Health
June 2018

Disclaimer: This consultation document has been translated into English. If there is any inconsistency or ambiguity between the Chinese version and the English version, the Chinese version shall prevail.

Appendix 1

General Chapter 2331 of CP2015

2331 Determination of Residue of Sulfur Dioxide

The methods refer to acid-base titration, gas chromatography and ion chromatography for determination of sulfur dioxide residue in medicines or decoction pieces fumigated with sulphur, respectively as method Ⅰ, method Ⅱ and method Ⅲ. Proper method may be selected according to specific conditions to carry out the determination of residue of sulfur dioxide.

Method Ⅰ (Acid-base Titration)

The method refers to that traditional chinese medicines are treated via distillation. After the sulfite substances in the sample are converted to sulfur dioxide via acidification, they are carried together with nitrogen to an absorption bottle with hydrogen peroxide and oxidized through by hydrogen peroxide to sulfate ions. Determine and calculate the amount of sulfur dioxide residue in the medicine or decoction pieces via acid-base titration.

Apparatus Shown in Fig. 1 A is a 1000 ml double-neck round-bottom flask; B is a vertical reflux condensing tube; C is a separating funnel (with scale); D is the nitrogen connecting inlet; E is the sulfur dioxide gas outlet. In addition, an electric jacket, a nitrogen source and a gas flow meter are provided.

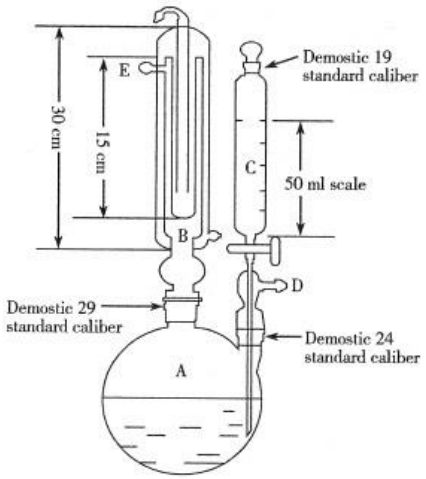

Fig 1. Apparatus for Determination of Sulfur Dioxide (Acid-base Titration)

Determination method Place about 10 g of medicine or fine powder of decoction pieces (sample amount may be reduced appropriately if the amount of sulfur dioxide residue is relatively high, for example more than 1000 mg/kg, but not less than 5 g), weighed accurately into a double-neck round-bottom flask, add 300 to 400 ml of water. Open the reflux condensing tube and feed in water, connect the upper opening E of the condensing tube with a rubber gas guide tube to the bottom of a 100 ml conical flask. Add 50 ml of 3% hydrogen peroxide solution into the conical flask as absorption liquid (end of the rubber gas guide tube shall be below the absorption liquid level). Prior to use, add three drops of methyl red ethanol solution indicator (2.5 mg/ml) into the absorption liquid, and titrate with 0.01 mol/L sodium hydroxide until the solution turns yellow (i.e. final point; the absorption solution in excess of the final point shall be discarded). Open nitrogen and adjust its flow to about 0.2 L/min with a flow meter, and open the piston of separating funnel C to allow 10 ml of hydrochloric acid solution (6 mol/L) to flow into the distilling flask. Heat the solution in the double-neck flask immediately to boiling and keep at a slight boiling state. Stop heating after the solution inside the flask is boiled for 1.5 h; cool the solution naturally, titrate the absorption liquid with sodium hydroxide (0.01 mol/L) VS until yellow colour does not disappear within 20 s; and correct the titration results with blank test. Calculate according to the following formula:

Amount of sulfur dioxide residue in test sample ($\mu g/g$) = (A-B) ×C×0.032×1000000/W

Where A refers to the volume of titrant sodium hydroxide consumed by the test sample, ml;

B refers to the volume of titrant sodium hydroxide consumed by blank test, ml;

C refers to the mol concentration of titrant sodium hydroxide, mol/L;

0.032 refers to the mass of sulfur dioxide equivalent to 1 ml of titrant sodium hydroxide (1 mol/L), g;

W refers to the weight of test sample, g.

Method Ⅱ (Gas Chromatography)

The method refers to determination of the sulfur dioxide amount of residue in medicines and decoction pieces with gas chromatography ⟨*0521*⟩.

Chromatographic system and system suitability Use GS-GasPro bonded silica gel porous layer open tubular chromatographic column (such as GS-GasPro, column length 30 m, inner diameter 0.32 mm) or equivalent column and thermal conductivity detector. The detector temperature is 250℃. Temperature programming: keep at initial temperature 50 ℃ for 2 min, then raised the temperature to 200℃ at a rate of 20℃/min, and keep at 200℃ for 2 min; The injection port temperature is 200℃, the carrier gas is helium and the flow rate is 2.0 ml/min. Headspace sampling utilizing gas-tight syringes (syringe temperature 105℃); the balance temperature of headspace bottle is 80℃; and the equilibrium time is all 10 min. The system suitability test shall meet the requirements of gas chromatography.

Preparation of reference solutions Accurately weigh 500 mg of reference substance sodium sulfite and place it into a 10 ml measuring flask; add in a mixed solution containing 0.5% mannitol and 0.1% disodium ethylene diamine tetraacetic acid (disodium EDTA) to dissolve the reference substance; dilute it to the volume and shake up evenly to prepare a reference stock solution with sodium sulfite content of 50.0 mg/ml. Accurately measure 0.1, 0.2, 0.4 and 1.2 ml of reference stock solution respectively and place them into a 10 ml measuring flask; dilute them with a mixed solution containing 0.5% mannitol and 0.1% disodium ethylene diamine tetraacetic acid (disodium EDTA) to reference solutions with sodium sulfite contents of 0.5 mg/ml, 1 mg/ml, 2 mg/ml, 5 mg/ml and 10 mg/ml respectively. Accurately weigh 1 g of sodium chloride and 1 g of solid paraffin (fusing point 52 to 56 ℃) and place them into a 20 ml headspace sample bottle respectively. Accurately add 2 ml of 2 mol/L hydrochloric acid solution into the bottles; place the bottles into 60 ℃ water bath and remove when the solid paraffin is dissolved completely; cool naturally to room temperature to cure and seal solid paraffin on the acid liquid layer (blow off acid mist condensed on bottle wall with air). Accurately weigh 100 μl of the above reference solutions with sodium sulfite contents of 0.5 mg/ml, 1 mg/ml, 2 mg/ml, 5 mg/ml and 10 mg/ml and place them above the paraffin layer respectively; finally seal to obtain the reference solutions.

Preparation of test solution Accurately weigh 1 g of sodium chloride and 1 g of solid paraffin (fusing point 52 to 56℃) and place them into a 20 ml headspace sample bottle respectively. Accurately add 2 ml of 2 mol/L hydrochloric acid solution into the bottles; place the bottles into 60 ℃ water bath and remove when the solid paraffin is dissolved completely; cool naturally to re-cure the solid paraffin; take and accurately weigh 0.2 g of fine powder of the sample and place it above the paraffin layer; add 100 μl of a mixed solution containing 0.5% mannitol and 0.1% disodium ethylene diamine tetraacetic acid (disodium EDTA); finally seal to obtain the test solution.

Determination method Accurately measure 1 ml of headspace bottle gases of balanced reference solution and test solution, inject them into a gas chromatograph respectively, and record chromatogram. Quantify according to the external standard work curve method, calculate the sulfite content in sample and multiply the measured result with 0.5079 to obtain the sulfur dioxide content.

Method Ⅲ (Ion Chromatography)

According to the method, traditional Chinese medicines are handled with steam distillation, so that sulfite series substances in the sample which are converted to sulfur dioxide after acidification are absorbed by hydrogen peroxide and oxidized into sulfate ions; then such ions are measured and the amount of sulfur dioxide residue in the medicine or decoction pieces are calculated with ion chromatography *〈0513〉*.

Instrument and devices See Fig. 2 for ion chromatography steam distillation device. The distillation device needs to be customized and is provided with an additional electric jacket.

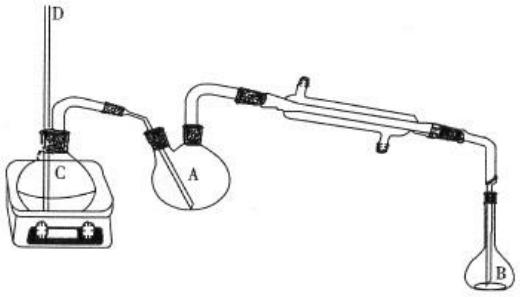

Fig 2. Apparatus for Determination of Sulfur Dioxide (Ion chromatography)
A. double-neck bottle; B. absorption bottle; C. round-bottom bottle; D. glass tube

Chromatographic system and system suitability Use ion chromatography. The chromatographic column is an anion exchange column (such as AS11-HC, 250 mm×4 mm) with alkanol quaternary ammonium as functional group and ethyl vinyl benzene-divinyl benzene polymer resin as filler, or equivalent column; the guard column uses the anion exchange column (such as AG11-HC, 50 mm×4 mm) with the same filler; the elluent is 20 mmol/L potassium hydroxide solution (produced by automatic elluent generator); if there is no automatic elluent generator, the elluent adopts a mixed solution with final concentration of 3.2 mmol/L Na_2CO_3 and 1.0 mmol/L $NaHCO_3$; the flow rate is 1 ml/min; and the column temperature is 30℃. Anion suppressor and electrical conductivity detector. The system suitability test shall conform to the requirements of ion chromatography.

Preparation of reference solution Take sulfate radical standard solution, add water and prepare into solutions with sulfate content of 1 μg/ml, 5 μg/ml, 20 μg/ml, 50 μg/ml, 100 μg/ml and 200 μg/ml respectively; feed 10 μl for each of the solutions and draw the standard curves.

Preparation of test solution Accurately weigh 5 to 10 g (not less than 5 g) of rough powder of the test sample; add bottle A (double-neck flask) and 50 ml of water; shake out to disperse the powder uniformly; connect the bottle with a water vapor distillation bottle C. Add 20 ml of 3% hydrogen peroxide solution to absorption bottle B (100 ml Nessler tube or measuring flask) as absorption liquid; insert the lower end of the absorption tube to below the absorption liquid level. Add 5 ml of hydrochloric acid to bottle A along the bottle wall, and seal the bottle quickly; start distillation; keep bottle C in boiling state and regulate the heating power of distillation to maintain the outflow rate of distillate at 2 ml/min. Distill till the total volume of the solution in bottle B is about 95 ml (time: around 30 to 40 min), wash the tail connecting tube with water and transfer it to the absorption bottle; dilute the solution to the volume and shake well; allow to stand for 1 h, filter the solution with a microfiltration membrane to obtain the product.

Determination method Accurately measure 10 μl of corresponding reference solution and test solution to determine and calculate the content of sulfate in the sample. Calculate the content of sulfur dioxide residue in the sample according to ($SO_2/SO_4^{2-}=0.6669$).