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International Harmonization of Compendium Monographs of Pharmaceutical Excipients: Its Progress and the Matters at Issue*

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의약품 첨가제의 공정서 각조의 국제 규격화 : 그 진행과 문제점

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일본의약품첨가제위원회, 신월화학 (주) 의약원료부

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These days, it is not uncommon that a same kind of drug is circulated globally. However, the qualities of excipients used in the same drug have to be sometimes different depending on the different requirements in the qualities stipulated by each country. For a supplier of pharmaceutical excipients, it is generally necessary to carry out different tests on the same kind of testing criteria depending on the country of destination. Thus, the discrepancies between compendium requirements of pharmaceutical excipients create severe problems in various area of industrial activities. The decision of the United States Pharmacopoeia, European Pharmacopoeia and Japanese Pharmacopoeia Commissions to harmonize the requirements is a unique chance for the industries to overcome these problems. On the other hand, discrepancies of general test methods and requirements in each monograph of pharmaceutical excipient between the compendia valid at present are in most cases extensive. Consequently their harmonization needs a lot of detailed work requiring strong support from the industry. Based on these circumstances, pharmaceutical excipients councils have been established first in U.S.A. and successively in Europe and in Japan to contribute to the harmorization process. We should like to review here the progress since the Orlando Conference in 1991 and comment about the matters at issue with regard to the international harmonization of pharmaceutical excipients.

I would like to express my sincere thanks to the members of the organizing committee of the symposium for giving me an opportunity to make this presentation. As it is well known, the harmonization project for pharmaceutical excipients was initiated at the conference in Orlando, Florida in the USA in 1991 where authorities from the United States Pharmacopeia, European Pharmacopoeia, British Pharmacopoeia, and the Pharmacopoeia of Japan attended. I have been participating in this project from a nongovernmental position on behalf of the Japan Pharmaceutical Excipient Council (JPEC) since the beginning of 1992. Based on my work, I would like to bring you up to date on the present status and matters at issue with regard to the project.

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Slide: 1

I have used the phrase "Compendium Monographs" in the title of my presentation as shown in this slide. However, another phrase "Pharmacopoeial Monographs" may be as equally adequate. At first I would like to ask you to understand that there is a situation where not all the monographs concerned with the harmonization are admitted to pharmacopoeias. Sometimes articles admitted to other standards are subjects of the harmonization.

Slide: 2

The content of harmonization in the field of pharmaceutical excipients is summarized in this slide. That is:

An adjustment of requirements laid down in the excipient monographs of the United States Pharmacopeia/National Formulary (USP/NF), European Pharmacopoeia (EP), Pharmacopoeia of Japan (JP), and Japanese Standards of Pharmaceutical Ingredients (JSPI) with regard to testing criteria specifications/limits, and analytical methods

In the case of the JSPI, which doesn't belong to any pharmacopoeia in a strict sense, but it is used as an official standard to be cited or followed at the time of an application for Drug Manufacturing Approval. Some of the articles for the subject of harmonization are admitted in this standard.

Slide: 3

Let me briefly summarize where present differences between different compendium requirements create problems and where industry as a whole will benefit from harmonization.

They are manufacturing approval of drugs and related products import and export, quality agreements beetween suppliers and users, production costs for different qualities of excipients, testing expenditure or its cost and time, and the rejection rate at purchasing.

Slide: 4

I would like to exemplify some of the differences between the present general test methods as well as the excipient monographs of the EP, USP and JP.

Residue on ignition is a typical case in which the differences in the testing conditions between the pharmacopoeias are severe. The differences between the pharmacopoeias are summarized in this slide. In the first place the name of the test is different. Though this point isn't included in this slide, the EP uses "Sulfated Ash" while USP and JP use "Residue on Ignition".

We sometimes experience that the JP method yields a higher value of sulfated ash as compared with the USP method when our cellulose derivatives products are tested. This may be caused mainly by the difference in the ignition temperature. the USP applies 800℃ while the JP applies from 450℃ to 550℃.

Incidentally, harmonization of the general test methods like this residue on ignition hasn't been started yet.

Slide: 5

Viscosity is one of the important functional factors for cellulose derivative products such as methylcellulose or hydroxypropyl methylcellulose. However, a problem is that the results according to the USP and JP on the one hand and those according to the EP on the other hand aren't directly comparable. As a characteristic of the solution of cellulose ether, its viscosity value varies depending on various factors such as the type of viscometer, capillary diameter when using a capillary tye viscometer, and the shear rate when using a rotating type viscometer.

This slide shows the relationship between the shear rate and the apparent viscosity of a solution of HPMC substitution type 2208.

The horizontal axis shows the shear rate and the vertical axis shows the viscosity value. As shown here, generally the viscosity value decreases as the shear rate increases. The effect of the shear rate on the viscosity becomes more significant as the viscosity value becomes higher.

Slide: 5

This slide summarizes the differences in the testing conditions of the viscosity of cellulose ethers between the pharmacopoeias. Though the sample preparation, concentration of solution and temperature are practically identical as shown in this table, the EP method yields a lower viscosity value as compared with the USP/JP method when

it exceeds a certain value. This is caused by the difference in the viscometer utilized in the test, i.e. the EP method specifies the use of a rotating type viscometer with a shear rate of 10 per second while the USP/JP method specifies the use of an Ubbelohde viscometer.

Slide: 6

This slide exemplifies the relationship of the viscosity value between the EP method and the USP method. The horizontal axis shows the viscosity value by the USP method and the vertical axis shows the viscosity by the EP method.

For example 20000 cp by the USP method corresponds to only approximately 9000 cp by the EP method. This difference can easily be explained by the effect of the shear rate shown in the previous slide. In the low viscosity range, however, it is obvious that both viscosity values become closer.

Slide: 7

In addition to the general test methods, differences between excipient-monographs are substantial in general. Lactose is one of the articles where the stage of harmonization is most advanced. Allow me to select lactose by as an example to see the extent of the difference. This slide shows the comparisons of requirements for lactose between the compendia. The USP adopts the style of a family monograph admitting a monograph covering anhydrous, monohydrate and also a product obtained by the spray-dried process. On the other hand, only monohydrate is covered in the EP and JP monographs. In the case of Japan, anhydrous lactose is admitted in the Japanese Standards of Pharmaceutical Excipients. This JSPI is also an official standard to be cited or followed at the time of application for Drug Manufacturing Approval as explained previously.

Slide: 8

This slide is a continuation of the former slide. Concerning specific rotation, this criterion has nothing in common with regard to the specification limit. In addition, the JP applies a different temperature of 25℃ while the others apply 20℃. Differences in the measuring method for moisture content and their specification limits are also remarkable.

Slide: 9

This slide is also a continuation of the former. Only the USP has specifications for a microbial limit. The need for the microbial limit test is becoming a general practice today, and it is also true for pharmaceutical excipients. The JP specifies limits for glucose, sucrose and starch or dextrin. These criteria seem to have been included in the monograph because of a possibility of admixing with these materials intentionally. Actually, such criteria seem not so meaningful today. Concerning the content of β-lactose in anhydrous lactose, the limit of 80% is important from the functional viewpoint especially concerning the storage stability of active ingredients which are sensitive to moisture. This criterion is going to be included in the consensus monograph of the harmonized monograph of anhydrous lactose based on the proposal from the JP. As shown by taking lactose as an example, there is a fundamental difference in the choice of testing criterion. We think it is important to compose the testing criteria from the scientific viewpoint.

Slide: 10

I would like to introduce one of typical examples where the harmonization process is not easy but when once harmonization is completed the effect is not small.

This slide shows principal differences in pharmacopoeial requirements for titanium dioxide.

Especially, the USP specifies a high purity titanium dioxide. In this case the quality is also corresponding to that specified in the Code of Federal Regulations of the USA. For example the USP specifies 99.0 to 100.5% of assay and not more than 2 ppm of antimony. Therefore, a special high purity grade of titanium dioxide is distributed in the field of food, pharmaceuticals and cosmetics in the USA. Consequently, if the harmonized monograph has severe specifications like that of the USP, pharmaceutical companies may find it necessary to change the supplier of the product.

Slide: 11

This slide is also a continuation of the former slide.

As shown in these tables, in the case of the titanium dioxide monograph, generally the USP and the EP include more testing criteria with regard to impurities as compared with the JP.

Slide: 12

Hydroxypropyl methylcellulose having the abbreviation of HPMC is one of the widely used excipients in the world. Though there are only three suppliers in the world, the differences in the pharmacopoeial requirements are significant as shown in this table. For example, the JP specifies a narrow viscosity range of 80 to 120% of the nominal value for all viscosity types or a smaller chloride content of not more than 0.284%. So there is a problem that a product which meets one pharmacopoeia sometimes doesn't meet other pharmacopoeias. The EP doesn't include an assay test. This sometimes gives problems such as in arranging the quality between a supplier and users.

Also HPMC is a subject for harmonization. In the harmonization committee of the International Pharmaceutical Exipients Council America, we have a working group that is studying the harmonized monograph for HPMC where all the manufacturers and some pharmaceutical companies are participating. In the study, they are making experiments on the various testing criteria using the same samples supplied by all the manufacturers. The fact is, today and tomorrow they are having their third meeting in Washington, where they will be discussing the experimental data.

Slide: 13

In the Pharmacopoeial Discussion Group Meeting consisting of authorities from the USP, EP and the JP, the top 25 excipients were selected from those used most frequently and agreed to be harmonized. This slide shows the list of the top 25 excipients. As compared with several hundreds of pharmaceutical excipients actually in use, the number of the top 25 excipients seems very small. However, among the monographs of the top 25, 13 cover a whole family of individual excipient, thus the present project actually covers in reality at least 70 excipients. Considering that the top 25 are basic excipients used in many different products and that the harmonization process requires a tremendous amount of detailed works, this selection seems reasonable at this stage.

Slide: 14

I think that the working procedure for the international harmonization is already known. However, I would like to briefly repeat the procedure here for your information. The content of this slide is quoted from the report contributed by Dr. Terao, Vice Director General of the National Institute of Hygienic Sciences, in the Japanese Pharmacopoeial Forum, No. 1 of Vol. 1 published in 1992.

Slide: 15

Slide: 16

(Contents of the slides are read out.)

Slide: 17

Under the leadership of the three Pharmacopoeia Commissions, the harmonization project has reached the status shown in this slide. Second draft monographs or revised draft monographs for magnesium stearate, lactose, sucrose and povidine are published in the Pharmacopoeial Fora. Concerning the articles shown at the bottom, i.e. microcrystalline cellulose, powdered cellulose, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, dibasic calcium phosphate and sodium chloride are in the stage of the first draft monograph.

Slide: 18

In the case of the JP, we are responsible for 8 articles. Those are povidone, dibasic calcium phosphate, disodium calcium edetate, hydroxypropyl methylcellulose, methylcellulose, titanium dioxide, colloidal silicone dioxide and rice starch.

In the next JP Forum which will be published in October, the first draft monograph of disodium calcium edetate is going to be printed.

Slide: 19

I would like to speak about the role of the JPEC in the International Harmonization.

As shown in this slide, we are asked to prepare the preliminary draft monograph for the articles assigned to the JP. And it is our actual responsibility to have to coordinate the opinions of the manufacturers of pharmaceutical excipients with regard to matters raised in relation to preparing

the draft monographs or in arranging comments at each stage of the harmonization for every article.

Slide: 20

I think it could be suitable to explain the relation of the JPEC and the pharmaceutical administration in Japan in order to facilitate the understanding of the working procedure for harmonization. As shown in this slide: in the Ministry of Health and Welfare (which has the abbreviation of MHW), the Safety Division controls the JP. Members from the JP and the National Institute of Hygienic Sciences attend the Pharmacopoeial Discussion Group Meeting. As shown in this figure, the Safety Division organizes the Discussion Committee on the International Harmonization of Pharmaceutical Excipients in cooperation with the Pharmaceuticals & Cosmetics Division where I am participating on behalf of the JPEC.

Allow me to explain about the JSPI. This standard is controlled by the Pharmaceutical and Cosmetic Division. I must add that all the pharmaceutical excipients in the JSPI have just been transferred to a new standard, titled "Japanese Pharmaceutical Excipients" while accompanying a new admission of approximately 100 articles. The Pharmaceutical and Cosmetics Division is organizing the Discussion Committee on Pharmaceutical Excipients. In the Committee, discussions are being made to provide authorized monographs of pharmaceutical excipients which haven't been admitted to the JP or Japanese Pharmaceutical Excipients (JPE) but have already received approvals.

Slide: 21

This slide shows the reasons for providing such authorized monographs of pharmaceutical excipients which haven't been admitted to the JP or JPE. The number of such articles is estimated to reach around 1000. MHW is planning to change the system of manufacturing approval of drugs to a paperless computerized system from 1995. To comply with the system, all pharmaceutical excipents must be identified with a code number while providing authorized specifications and test methods. Also it has been decided that the completed monographs are to be admitted to the JPE successively in each year.

Slide: 22

Here I would like to introduce the three Pharmaceutical Councils which are called the three PECs, as an abbreviation. Those are the JPEC, IPEC-America and IPEC-Europe.

The three PECs were established first in the USA in 1991 and successively in Europe at the same time in 1991 and then in Japan in 1992 to contribute to the harmonization process. Actually, the three PECs have been intensively supporting these activities by proposing drafts for harmonized monographs that are discussed inside the pharmacopoeial institutions. They are also providing various documents which reflect the comprehensive technical expertise and experiences within the associations of excipient manufacturers and users. The three PECs are cooperating closely to ensure harmonization.

Slide: 23

In this slide I would like to introduce some examples on the contents of a harmonized monograph.

Lactose is one of the articles for which harmonization is most advanced. This slide shows the summary of second draft monographs of lactose.

As shown in this slide three monographs of lactose monohydrate, lactose monohydrate modified and anhydrous lactose are proposed. Inclusion of all types of lactose now available would make it more convenient for pharmaceutical companies to obtain drug manufacturing approval.

Slide: 24

Chemical analysis tests are replaced with a simple IR test for the identification test. The IR test will not be able to distinguish the three types of lactose. However a combination of the IR test with other tests contained in the monograph will cover this point.

slide: 25

It is proposed to include the particle size distribution and specific surface area as functional factors. However, a problem is that generally the test results relating to the functional factors differ more or less depending on the kind of apparatus utilized and test conditions applied. In order to

incorporate the functionality tests, we think it is important to first establish a test method having sufficient reproducibility. Inclusion of tests for organic volatile impurities and microbial limits seems also appropriate at this time as the interests in these are growing.

Slide: 26

This slide shows comparisons of the requirements for povidone among the USP, EP, JP and the second draft for the harmonized monograph. Needless to say this article has various names as shown in this title name, like povidone, polyvidone and polyvinylpyrrolidone. In the case of this article, the JP was assigned as the lead Pharmacopoeia. As we received many comments from all over the world on our first draft monograph, we had to make thorough revisions in the second draft. By the way, in tomorrow's presentation by Dr. Lang from BASF, properties of povidone will be detailed. we also received great deal of cooperation from BASF in completing the second draft. Povidone has many product types which are differentiated by its K value. The USP and EP adopt a family monograph admitting a monograph covering the K values from 10 to 95. On the other hand, the JP admit monograhs of K-25, K-30 and K-90 separately. Though we proposed the family monograph in the draft of the harmonized monograph, the range of K values couldn't be included. This is because, the different K values that have so far received approval aren't in common in various countries. The promotion of international harmonization from the list of actually aplicable excipients hasn't been decided yet. Concerning the identification test shown at the bottom, each pharmacopoeia specifies at least three chemical tests. We proposed only the IR test in the harmonized monograph. We believe that by carrying out other tests contained in the monograph in addition to the IR test, the purpose of identification can be completely attained.

Slide: 27

This is a continuation of the former slide. You may have doubts about the significant differences in the limits of aldehyde and vinyl pyrrolidone monomer between Those in the present pharmacopoeias and the proposed draft respectively. these are simply based on applying modern analytical techniques and also improvements in manufacturing technologies.

Slide: 28

This is also a continuation of the former slide. there is a possibility that the criterion water would be replaced with loss on drying. Loss on drying is specified only in the EP. There is a comment that the test of loss on drying is more advantageous.

Concerning the nitrogen test, there is a comment that this test should be omitted. The proposed specification, 11.5 to 12.8% corresponds to an assay of 91.3 to 101.6% which is far below the effective purity of the substance. On the other hand the method is time consuming and the laboratory personnel has to handle hazardous reagents which are problematic from an ecological point of view.

Slide: 29

I would like to conclude by conveying some important matters at issue which are faced at present with regard to the international harmonization of pharmaceutical excipients. The first is relating to cooperation with the Pharmaceutical Excipients Councils. Because the harmonization process requires a tremendous amount of works for improving the quality standards, as well as incorporating modern analytical techniques, and applying functionality tests, the establishment of routes of cooperation from industries is important. However, understanding from the industry side seems not always sufficient. Participation from industries through the Pharmaceutical Excipients Councils by providing manpower are greatly expected at present. The second is cooperation with legal authorities. As shown in the example of titanium dioxide, sometimes pharmacopoeial monographs are not always legally binding. Therefore, to truly harmonize requirements of such articles, we would have to have the assistance of legal authorities, if we feel that the established limits are unacceptable to other parts of the world. The third is cooperation from worldwide suppliers of excipients. Sometimes the manufacturing method

of an excipient differs among suppliers. Cooperation from the suppliers with respect to supplying samples and information about the manufacturing method are indispensable for incorporating adequate test criteria, establishing adequate test methods and also their limits.

Slide: 30

May I emphasize as a conclusion that the industries should understand that this is a unique opportunity for innovation and elimination of severe obstacles from the existing discrepancies and they should keep watch and also cooperate on the process.

Slide 1

International Harmonization of Compendium Monographs of Pharmaceutical Excipients : Its Progress and the Matters at Issue

Slide 2

Content of Harmonization in the Field of Pharmaceutical Excipients

Adjustment of requirements laid down in the excipient monographs of the

United States Pharmacopeia/
National Formulary(USP/NF)

European Pharmacopoeia(EP/Ph. Eur)

Pharmacopoeia of Japan(JP)
Japanese Standards of Pharmaceutical Ingredients(JSPI)

with regard to

Testing criteria
Specifications/limits
Analytical methods

Slide 3

Examples of Problem Areas due to Differences of Compendium Requirements

- Manufacturing approval of drugs and related products
- Import/Export
- Quality agreements with suppliers
- Production costs for different qualities of excipients
- Testing expenditure and time
- Purchasing (rejection rate)

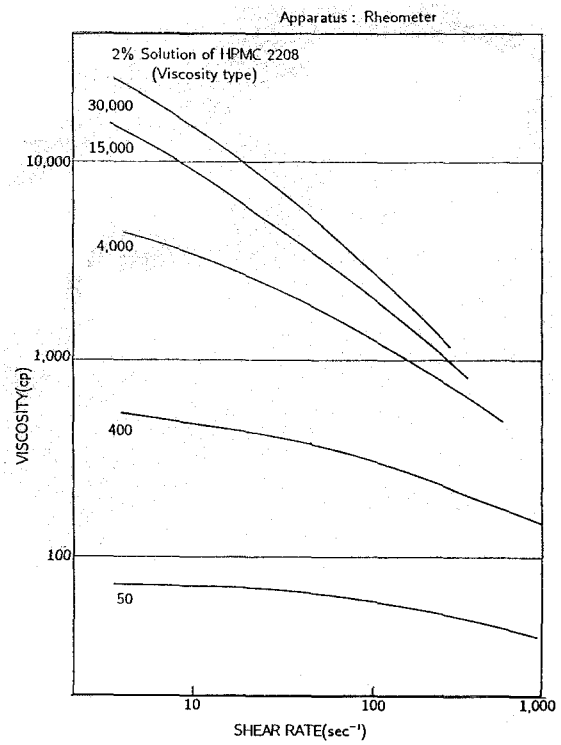
Slide 4

Sulfated Ash/Residue on Ignition – Testing Conditions

Pharmacopoeia	EP	USP XXII	JP XII
First heating with addition of H_2SO_4	yes	no	yes
Temperature	600℃	800±25℃	450~550℃
Final addition of Ammonium Carbonate	yes	no	no
Means of heating	water bath, then flame	not specified	not specified

Slide 5

Relationship between the Shear Rate and the Apparent Viscosity of HPMC Solution



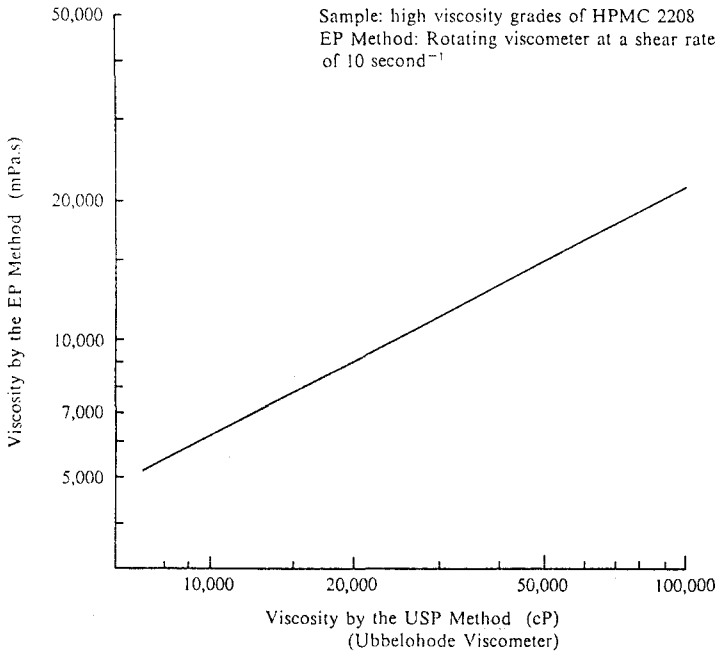
Slide 6

Viscosity of Cellulose Ethers – Testing Conditions

Pharmacopoeia	EP	USP XXII	JP XII
Concentration of solution	2.0%	2.0%	2.0%
Temperature	20±0.1℃	20±0.1℃	20±0.1℃
Type of viscometer	rotating viscometer	capillary type, Ubbelohde	capillary type, Ubbelohde
Shear rate	10 S^{-1}	—	—
Unit	cP(mPa·s)	cP(mPa·s)	cSt
Sample preparation	Very similar in all 3 Pharmacopoeia		

Slide 7

The Relationship between the Viscosity Values by the USP Method and Those by the EP Method



Slide 8

Pharmacopoeial Requirements for Lactose (1)

Compendium	USP XXII/NF XVII	EP	JP XII	JSPI 1991
Monograph Title	Lactose	Lactosum	Lactose	Lactose Anhydrous
Origin	anhydrous or monohydrate	monohydrate	monohydrate	anhydrous
Labeling	Label to indicate whether anhydrous or hydrous. Spray-dried process is available.	—	—	—
Identity test A (Moore's test) B (Cu^{++} test) C (thin-laler chromatography)	 + + —	 + + +	 + + —	 + + —
Aqueous solution, clarity	+(clear)(3 g+10 ml of boiling water)	+(clear)(1.0 g in 10 ml solution)	+(clear)(1.0 g+20 ml of boiling water)	+(clear)(1.0 g+20 ml of boiling water)

Slide 9 Pharmacopoeial Requirements for Lactose (2)

Compendium	USP XXII/NF XVII	EP	JP XII	JSPI 1991
Specific rotation	+54.8°~+55.5° (anhydrous basis) at 20°C, 10 g in 100 ml, with NH_3	+54.4°~+55.9° (anhydrous basis) at 20°C, 10.0 g in 100 ml, with NH_3	+52.0°~+52.6° at 25°C, 10 g dried, in 100 ml,with NH_3	+54.6°~+55.5° (anhydrous basis) at 20°C, 10 g in 100 ml, with NH_3
Acidity or alkalinity	30 g 100 ml of water, max. 1.5 ml of 0.1 N NaOH	6.0 g in 25 ml of water, max. 0.4 ml of 0.1 N NaOH	—	—
Water	anhydrous, max. 1.0% hydrous, max. 5.5%	4.5% – 5.5%	—	max. 1.0%
Loss on drying	—	—	max. 0.5% (80°C, 2 hr)	—
Residue on ignition Sulphated ash	max. 0.1%	max. 0.1%	max. 0.10%	max. 0.10%
Alcohol-soluble residue	max. 20 mg/2.5 g	—	—	—
Heavy metals	max. 5 ppm	—	max. 5 ppm	max. 5 ppm

Slide 10 Pharmacopoeial Requirements for Lactose (3)

Compendium	USP XXII/NF XVII	EP	JP XII	JSPI 1991
Lead	—	max. 0.5 ppm	—	—
Total bacterial count	max.100 per g	—	—	—
E. coli	not detectable	—	—	—
Salmonella	not detectable	—	—	—
Protein and light-absorbing impurities	—	1.0 g in aq. 100 ml, max. 0.25(210-220 nm), max. 0.07(270-300 nm)	—	—
Glucose	—	—	not detectable	not detectable
Sucrose	—	—	not detectable	not detectable
Starch or dextrin	—	—	not detectable	not detectable
Assay	—	—	—	min. 80%, batalactose

Slide 11 **Principal Differences in Pharmacopoeial Requirements for Titanium Dioxide**

	USP XXII	EP	JP XII
Title Name	Titanium Dioxide	Titanium Dioxide	Titanium Oxide
Assay	99.0~100.5%	98.0~100.5%	98.5%
Lead	<10 ppm(acid soluble)	No test	<60 ppm(total)
Arsenic	<1 ppm	<5 ppm	<10 ppm
Antimony	<2 ppm(acid soluble)	<100 ppm(total)	No test
Mercury	<1 ppm	No test	No test
Loss on ignition	<0.5%	No test	No test

Slide 12 **Principal Differences in Pharmacopoeial Requirements for Titanium Dioxide(continued)**

	USP XXII	EP	JP XII
Water solubles	<0.25%	<0.5%	<0.25%
Acid solubles	<0.5%	No test	No test
Loss on drying	<0.5%	No test	<0.5%
Colour/Opalescence	No test	Visual comparison	No test
Acidity/Alkalinity	No test	To comply	No test
Balium	No test	To comply	No test
Heavy metals	No test	<20 ppm (acid soluble)	No test
Iron	No test	<200 ppm(total)	No test

Slide 13 **Principal Differences in Pharmacopoeial Requirements for Hydroxypropyl Methylcellulose**

	USP XXII	EP	JP XII
Viscosity 1) Range of Nominal 2) Test Method	80.0~120.0% (100 cP or less) 75.0~140.0% (higher than 100 cP) Ubbelohde	75~140% Rotational	80~120% Ubbelohde
Chloride	No test	<0.5%	<0.284%
Iron	No test	No test	<100 ppm
Colour/Opalescence	No test	Visual comparison	Opalescence only, visual
Residue on ignition/ Sulphated ash	<1.5% (higher than 50 cP) <3% (50 cP or less)	<1.0%	<1.5%
pH	No test	5.5~8.0	5.0~8.0
Assay	hydroxypropoxyl and methoxyl contents are specified for each substitution type	No test	basically same as USP

Slide 14 **Top 25 Excipients**

Excipient Name

1. Magnesium Stearete
2. Microcrystalline Cellulose
3. Lactose
4. Starch
5. Cellulose Derivatives
6. Sucrose
7. Povidone
8. Stearic Acid
9. Dibasic Calcium Phosphate
10. Polyethylene Glycol
11. Hydrochioric Acid
12. Alcohol
13. Benzyl Alcohol
14. Talc
15. Sodium Chloride
16. Sodium Starch Glycolate
17. Sodium Hydroxide
18. Polysorbate 80
19. Calcium Disodium Edetate
20. Petrolatum
21. Colloidal Silicon Dioxide
22. Citric Acid
23. Methylparaben
24. Sodium Saccharin
25. Titanium Dioxide

Slide 15

Working Procedure for the International Harmonization of Pharmacopoeial Monographs (1)

1. (a) The Lead Pharmacopoeia who takes charge of preparing the draft monograph is assigned to each article of the Top 25 Excipients.
2. (a) The Pharmacopoeial institution in charge studies the valid monographs concerned with the article in each Pharmacopoeia.
   (b) The Pharmacopoeial institution prepares the first draft monograph while appending explanations and comments.
   (c) The Pharmacopoeial institution in charge announces publicly the first draft monograph while asking the connected institutions or groups for voluntary comments. Othter Pharmacopoeial institutions announce domestically the publication of the first draft monograph.

Slide 16

Working Procedure for the International Harmonization of Pharmacopoeial Monographs (2)

(d) The Pharmacopoeial institution in charge makes corrections in the first draft monograph by referring to comments received by suitable means.

(e) The Pharmacopoeial institution in charge prepares the second draft monograph while appending explanations and comments.

3. (a) The three Pharmacopoeial institutions (USP, EP and JP) announce publicly the second draft monograph almost simultaneously through their bulletins (like JP Forum).

(b) Each Pharmacopoeial institution studies the comments sent to them and send compiled comments to the Pharmacopoeial institution in charge.

Slide 17

Working Procedure for the International Harmonization of Pharmacopoeial Monographs (3)

(c) The Pharmacopoeial institution in charge prepares the Consensus monograph based on these comments.

4. (a) The three Pharmacopoeial institutions study the acceptance of the Consensus Monograph in accordance with the respective formalized procedure.

Slide 18

Status of the Harmonization Project (July 1993)

Revised draft monographs

Magnesium stearate
Lactose
Sucrose
Povidone

First draft monographs

Microcrystalline cellulose
Powdered cellulose
Cellulose acetate phthalate
Hydroxypropyl methylcellulose phthalate
Dibasic calcium phosphate
Sodium chloride

Slide 19

Present Status of the Harmonization for Articles Responsible to the JP

Povidone
Second draft monograph (JP Forum, Vol. 2, No. 2)

Dibasic Calcium Phosphate
First draft monograph (JP Forum, Vol. 2, No. 3)

Disodium Calcium Edetate
First draft monograph (JP Forum, Vol. 2, No. 4, arranged)

Hydroxypropyl Methylcellulose
Methylcellulose
Titanium Dioxide
Colloidal Silicon Dioxide
Rice Starch
First draft monographs are under prepartion.

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Role of JPEC in the International Harmonization

Preparation of the preliminary draft monograph for the articles assigned to the JP

Coordination of opinions of the manufactures of Pharmaceutical excipients with regard to matters raised.

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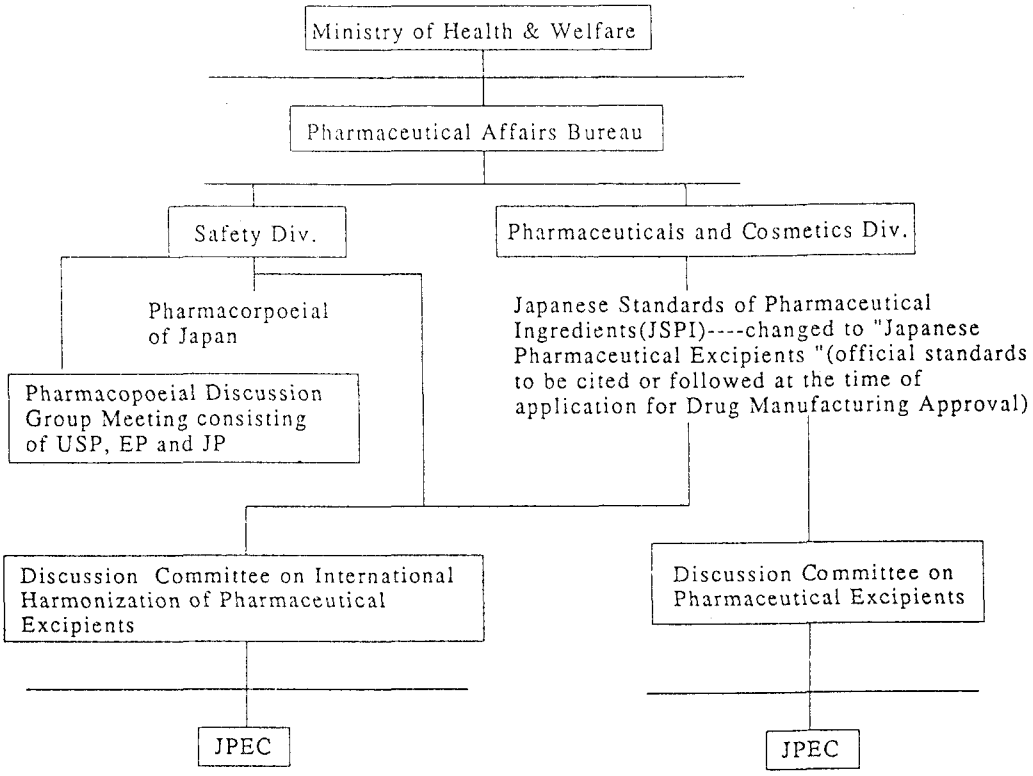
Relation of JPEC and Pharmaceutical Administration in Japan



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The Reasons for Providing Monographs of Pharmaceutical Exipients Which Have Been Approved But Not Admitted to the JP and JSPI

MHW is planning to change the system of manufacturing approval of drugs to a paperless computerized system.
All pharmaceutial excipients must be identified with a code number while providing authorized specifications and test methods. We don't have a system to refer the specifications which are included in the application for the approval of a drug. So, there haven't been any arthorized specifications or test method for pharmaceutical excipients which haven't been admitted to the JP or JSPI.

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Outline of the Three-PECs

	JPEC	IPEC-America	IPEC-Europe
Chairman	Shun-ichi Koyanagi (Shin-Etsu Chemical Co., Ltd.)	Louis Blecher (International Specialty Products)	John Hogan (Colorcon)
Subcommittee	Membership committee	Communication Committee	Membership Committee
	Testing & Specifications Committee	Harmonization Committee	Harmonization Committee
	Safety Committee	Safety Committee	Safety Committee
	International Committee		

Note:
JPEC: Japan Pharmaceutical Excipients Council
IPEC: International Pharmaceutical Excipients Council

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Summary of second Draft Monographs of Lactose (1)

Monograph Title	Lactose Monohydrate	Lactose Monohydrate Modified	Anhydrous Lactose
Origin	natural disaccharide, obtained from milk	obtained by specified processing of monohydrate	primarily alpha lactose, bata lactose or amixture
Description and solubility	include crystallized, sieved, ground or powdered form	free flowing powder (Solubility is in common)	
Labeling	nominal particle size distribution and test method	method of modification, nominal particle size distribution and nominal specific surface area and test methods	same as lactose monohydrate
Clarity and color of solution	10%(w/v)solution : clear and colorless or nearly colorless, absorbance : max. 0.04	same as lactose monohydrate	same as lactose monohydrate

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Summary of second Draft Monographs of Lactose (2)

Monograph Title	Lactose Monohydrate	Lactose Monohydrate Modified	Anhydrous Lactose
Identification	IR method, comparison with a reference standard	same manner as lactose monohydrate	same manner as lactose monohydrate
Specific optical rotation	±54.8°~±55.8° 20℃, anhydrous basis, 10 g/100 ml	same as lactose monohydrate	same as lactose monohydrate
Microbial limit	total bacteria : max. 100/g, Salmonella and E. coli : not detectable	same as lactose monohydrate	same as lactose monohydrate
Acidity and alkalinity	30 g in 100 ml of water, max. 1.5 ml of 0.1 N NaOH	same as lactose monohydrate	same as lactose monohyrate

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Summary of second Draft Monographs of Lactose (3)

Monograph Title	Lactose Monohydrate	Lactose Monohydrate Modified	Anhydrous Lactose
Loss on drying	max. 0.5%(80℃, 2 hrs)	max. 1.0%(80℃, 2 hrs)	max. 0.1%(80℃, 2 hrs)
Water	4.5%~5.5%	4.5%~5.5%	max. 1.0%
Residue on ignition	max. 0.1%	max. 0.1%	max. 0.1%
Particle size distribution	within±10% of the label claim	within±10% of the label claim	within±10% of the label claim
Heavy metals	max. 5 ppm	max. 5 ppm	max. 5 ppm
Organic volatile impurities	meets the requirements	meets the requirements	meets the requirements
Protein and light-absorbing impurities	1%(w/v) : max. 0.25(210~220 nm), 0.07(270~300 nm)	same as lactose monohydrate	same as lactose monohydrate
Specific surface area	—	within±10% of the label claim	—

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Pharmacopoeial Requirements for Povidone(1)

	USP XXII	EP	JP XII	Second Draft Harmonized Monograph
Title Name	Povidone	Polyvidone	Polyvinyl-pyrrolidone K-25, K-30, K-90	Povidone
range of K-value	10~95	10~95	25, 30 and 90	—
Identification				
1) reaction with I	+	+	+	—
2) reaction with dichromate	+	+	+	—
3) reaction with Co^{++} and thiocyanate	+	—	+	—
4) reaction with dimethylamino-benzaldehyde	—	+	—	—
5) IR test	—	+	—	+
pH	3.0~7.0	No test	3.0~7.0	3.0~7.0

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Pharmacopoeial Requirements for Povidone(2)

	USP XXII	EP	JP XII	Second Draft Harmonized Monograph
Colour/Opalescence	No test	Visual comparison	Visual	Visual
Heavy metals	No test	<10 ppm	<10 ppm	<10 ppm
Lead	<10 ppm	No test	No test	No test
Aldehyde	<0.20% (titration)	<0.2% (titration)	<0.2% (titration)	<500 ppm (spectrophotometry)
Vinylpyrrolidone	<0.2% (titration)	<0.2% (titration)	<0.2% (titration)	<10 ppm (LC)
Peroxide	No test	<400 ppm(as H_2O_2)	No test	<400 ppm(as H_2O_2)
Hydrazine	<1 ppm	<1 ppm	No test	<1 ppm
Residue on ignition/ Sulphated ash	<0.1%	<0.1%	<0.10%	<0.10%
Water	<5.0%	No test	<5.0%	<5.0%

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Pharmacopoeial Requirements for Povidone(3)

	USP XXII	EP	JP XII	Second Draft Harmonized Monograph
Loss on drying	No test	<5.0%	No test	No test
Low-molecular fraction and /or High-molecular fraction	No test	No test	To comply	No test
K-value Range of nominal	85.0~115.0% (15 or less) 90.0~108.0% (more than 15)	85.0~115.0% (15 or less) 90.0~107.0% (more than 15)	Intrinsic viscosity K-25 : 0.15~0.19, K-30 : 0.19~0.25, K-90 : 1.3~1.6	85.0~115.0% (15 or less) 90.0~108.0% (more than 15)
Nitrogen content	11.5~12.8%	No test	11.5~12.8%	11.5~12.8%

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Matters at Issue in the Harmonization Project

1) Cooperation from three-PECs

2) Cooperation with legal authorities

3) Cooperation with worldwide suppliers of excipients

Coclusion

The industries should understand that the international harmonization of pharmaceutical excipients gives a unique opportunity for innovation and elimination of severe obstacles from the existing discrepancies and should keep watch and cooperate on the process.