

Guidance on Physicochemical Equivalence Test (Guidance for industry)

April 2024



MINISTRY OF FOOD AND DRUG SAFETY

National Institute
of Food and Drug Safety Evaluation

Bioequivalence Evaluation Division
Drug Evaluation Department

This guidance provides considerations on equivalence evaluation of pharmaceutical products that replaces bioequivalence studies with physicochemical equivalence test data in more plain language and represents the current stance of the MFDS on this topic.

This document should be viewed as only recommendations since it is not intended to be legally binding and does not impose any obligations upon industry despite the word 'should' used herein. Besides, since this guidance is written based on the established scientific and technological experiences, and valid laws as of April 30, 2024, its interpretation and application may vary if necessitated by revision of relevant laws and/or new scientific discoveries, etc.

※ An MFDS guidance for industry is a document published to promote understanding of applicable statutes or administrative rules in more plain language or to present the current stance of the MFDS, internally and externally, on specific applications or any equivalent ones from industry filed with the agency [Article 2 of *Regulation on the Management of MFDS Guidance Documents, etc.*].

※ For comments or questions regarding this guidance document, please contact the MFDS at the phone numbers below.

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Document History

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1	Guidance-0993-01	Nov. 27, 2019	Establishment
2	Guidance-0993-02	Mar. 29, 2021	<p>To change guidance name*, standardize format and update contact information in accordance with the revision of relevant regulations</p> <p>* Guidance on Physicochemical Equivalence Test assessment (Guidance for industry) → Guidance on Physicochemical Equivalence Test (Guidance for industry)</p> <p>** Integration of the guide on how to prepare physicochemical equivalence test results report (abolished) into this guideline</p>
3	Guidance-0993-03	Apr. 26, 2023	To provide detailed information on considerations for evaluating physicochemical equivalence and updating contact information considering recent review cases
4	Guidance-0993-04	Apr. 30, 2024	To reflect revision of regulations, describe detailed information, and clarify content

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1. Introduction

1.1. Objectives and Scope

- (Objectives) This guidance is intended to assist the understanding of applicants and reviewers as a reference for preparing the physicochemical equivalence test result report submitted when applying for drug product approval and notification (including changes).
- (Scope) This guidance is applied when it is desired to replace data on safety and efficacy for drug product (which fall under Article 25 (2) of the 'Regulation on Pharmaceuticals Approval, Notification, and Review') approval and notification (including changes) with physicochemical equivalence test data in accordance with Article 27 of the same regulation or when it falls under Article 3 (1) ④ of the 'Standard on Pharmaceutical Equivalence Test'.
 - As differences in quantitative and qualitative composition of excipients may affect the safety and efficacy of the drug, including absorption and action of active substances, the test product should be formulated taking into account quantitative and qualitative composition of excipients of the reference product, unless otherwise provided clinical evidence.
 - If quantitative and qualitative composition of excipients in dosage forms such as injections, ophthalmic solutions, and otic solutions are identical to those of already approved (notified) ingredients, the bioequivalence test data or comparative clinical trial results can be replaced with physicochemical equivalence test data.
 - However, the physicochemical equivalence test can be applied to drug products with changes in quantitative and qualitative composition of excipients of which changes are allowed in Article 27 (3) of the 'Regulation on Pharmaceuticals Approval, Notification, and Review'
 - In addition, for other excipients, if quantitative composition of those inactive ingredients is the same but the concentration difference is within $\pm 5\%$ of those used in the listed reference products, this concentration difference can be recognized as being the same.

1.2. Glossary

1. "Pharmaceutical equivalence test" means an *in vivo* or *in vitro* test such as bioequivalence study, comparative dissolution test, and comparative disintegration test performed to prove the equivalence of two pharmaceutical products with the same active substances, strength and dosage form under Article 2 ① of 'Standard on Pharmaceutical Equivalence Test'.
2. "Test product" means a drug product to be tested under Article 2 ② of the 'Standard on Pharmaceutical Equivalence Test', and has the same active substances (including salts and isomers), strength and route of administration as those of reference product.
3. "Reference product" means a drug product to be compared with the test product under Article 2 ③ of the 'Standard on Pharmaceutical Equivalence Test', and its safety and efficacy are previously established as its manufacturing (importing) had already been approved, or its validity as a reference product is listed by the Minister of Food and Drug Safety.
4. "Physicochemical equivalence test" means a equivalence test under Article 2 ③ of the 'Standard on Pharmaceutical Equivalence Test', and it is a test under Article 5 of the Standard. It is conducted in cases that fall under Article 26 of the Standard, and is generally an *in vitro* test conducted to prove that the physicochemical properties of the reference product and the test product are at the same level considering the dosage form.
5. In this guidance, "compendium" means 「Korean Pharmacopoeia」 (Notice of the Ministry of Food and Drug Safety) or compendium listed by the Minister of Food and Drug Safety under the [Appendix 1-2] of "Regulation for Approvals, Notification and Reviews of Pharmaceuticals".

1.3. Related Regulations and Guidance

- 1) Article 31 (2) and (3), and Article 42 (1) of the Pharmaceutical Affairs Act (Act)
- 2) Article 4, Article 5, and Article 8 (1) of the Regulation on Safety of Pharmaceuticals, etc. (Ordinance of the Prime Minister)
- 3) Article 18 (2) ①, Article 21 (2), and Article 24 (2) of the Narcotics Control Act (Act)
- 4) Article 32, and Article 33 of the Enforcement Rule of the Narcotics

Control Act (Ordinance of the Prime Minister)

- 5) Article 25 (2), and Article 27 of the Regulation on Pharmaceuticals Approval, Notification, and Review (Notice of the Ministry of Food and Drug Safety)
- 6) Guidance on Pharmaceutical Equivalence Test (Guidance for industry)
- 7) Standard on Pharmaceutical Equivalence Test (Notice of the Ministry of Food and Drug Safety)

2. Considerations for Assessment of Physicochemical Equivalence

2.1. Reference Product

- It complies with Article 3-2 of the 'Standard on Pharmaceutical Equivalence Test'.
- It is advisable to select a representative batch in reference products to be used in test after identifying the deviations between multiple batches through evaluation of physicochemical properties.
- It is recommended that tests to identify deviations between reference product batches should be conducted at the same time, and if there is a difference, justification for each test parameter (e.g., intermediate precision or daily check of equipment (only in cases where validation is not required), etc.) should be provided.

2.2 Test Product

- It complies with Article 4 of the 'Standard on Pharmaceutical Equivalence Test'.
- For batch size, both characteristics of the dosage form and commercial scale can be taken into account.

e.g.) In the case of parenteral solutions, powders to be reconstituted before use for injection, ophthalmic drugs, and otic drugs, the batch size of the test product should be at least 10% of the commercial scale, 50 liters (for packaging units of 2.0 mL or more) or 30 liters (for packaging units of less than 2.0 mL), whichever is larger. In the case of oral solution, the batch size of the test product should be at least 10% of

the commercial scale. In the case of semi-solid topical products, the batch size of of the test product should be at least 100 kg or 10% of the the commercial scale, whichever is larger.

2.3 Test Parameters

- Various physicochemical properties that may affect safety and efficacy should be identified by considering the characteristics of the product (appearance, dosage form, composition of excipients, route of administration etc.) and appropriate test parameters that can identify the physicochemical properties of the drug product should be selected.
- Examples specified in Section 2.8 'Test parameters by Dosage Form' and the 'Product-specific guidance' are referred. If necessary, you can consult in advance with the Ministry of Food and Drug Safety (MFDS).

2.4. Test Methods

- If the test methods is listed in the compendium, the compendium and method name should be stated.
- For test methods not listed in the compendium, they should be an appropriate test method with validated and/or verification/calibration.
- For test methods not listed in the compendium, the test process should be described in detail step by step, and information on the principles of the test method, reagents and solutions, analytical instruments and conditions, and interpretation of results should also be provided.
- When conducting a physicochemical equivalence test, if reference product and test product should be prepared as reconstituted status, the relevant procedure should be established based on validated evidence. Labeling (e.g., solvents etc. that are recommended or prohibited considering the usage and dosage of the drug that required reconstitution) should be taken into consideration in the test process.
- For test parameters (e.g., particle size distribution, etc.) used for decision making based on statistical techniques, it is recommended to apply an appropriate number of samples (e.g., ≥ 3 batches of reference product and test product, ≥ 10 samples per batch, etc.) to obtain significant

results. Considering variability between and within batches, the evidence for determining that the representativeness of the reference product and test product is appropriately ensured should be provided. However, if it is difficult to properly use the drug product (e.g., ≥ 3 batches, etc.), some pilot-scale batches (at least 1/10 of the actual production batch) with the same raw materials, formulation, manufacturing process, and quality can be used.

2.5. Test Result

- For the test parameters of the physicochemical equivalence test, the acceptance criteria, test results, and final result of equivalence should be provided. All test results obtained by repeating all operations of the Test method set for the test product batch at least three times should be within the criteria.

2.6. Equivalence Acceptance Criteria

- The equivalence between two products(Reference/Test) is determined by comparing test results on the physicochemical properties of the reference product and the test product. Acceptance criteria are set comprehensively, considering the impact of test parameters on the quality, safety, and efficacy, but are generally set within $\pm 10\%$ of the result from the reference product. If independent acceptance criteria are applied, the evidence for setting the criteria should be provided.

2.7. Supporting Data and Documents

- Certificate of analysis (CoA) of drug product, CoA of drug substance used in manufacturing the test product, and detailed data on the manufacturing process of the test product can be submitted in the form of a common technical document (CTD) and should be written as 'refer to the relevant number'.

2.8. Test parameters for Dosage Forms

- Examples of parameters that require equivalence test between reference product and test product in a representative dosage form are as follows. Test parameters can be determined considering the example parameters

below, but other test parameters should be included depending on the characteristics of individual products.

- For other dosage forms, test parameters should be determined considering the pharmaceutical characteristics of the dosage forms, the example parameters below, and the 'Product-specific guidance 'It may be advisable to consult with the MFDS in advance, if necessary.
- If applicable, both the reference product and the test product should be considered for the test parameter being applied. Even if it is not related to the test product, if it is related to the reference product, test parameters should be included.

1) Injections (solutions or powder for injectables.)

No.	Test parameter	Note
1	Appearance	
2	pH	
3	Specific gravity or density	
4	Osmolality	
5	Buffer capacity	When containing a buffer or substance affecting buffer capacity
6	Viscosity	When containing viscosity controlling agent, polymeric substance, or a substance affecting viscosity
7	Reconstitution time	For reconstitution
8	Other	Test parameters additionally required considering the characteristics of the product

2) Ophthalmic drugs and otic drugs

No.	Test parameter	Note
1	Appearance	
2	pH	
3	Specific gravity or density	
4	Osmolality	When osmolality is required to be considered (refer to the composition of drug product, dosage and administration, indication, and warnings and precautions in the labeling)
5	Buffer capacity	When containing a buffer or substance affecting buffer capacity
6	Viscosity	When containing viscosity controlling agent, polymeric substance, or a substance affecting viscosity
7	Drop volume	
8	Other	Test parameters additionally required considering the characteristics of the product e.g.) Suspension particle size, dissolution test, etc.

3) Oral solutions (solutions or powder for solutions that are dissolved and taken before use. However, emulsions and suspensions are excluded)

No.	Test parameter	Note
1	Appearance	
2	pH	
3	Specific gravity or density	
4	Osmolality	When containing substances affecting osmolality or it is an excipient affecting the absorption of active substance in oral liquid
5	Buffer capacity	When containing a buffer or substance affecting buffer capacity
6	Viscosity	When containing viscosity controlling agent, polymeric substance, or a substance affecting viscosity
7	Reconstitution time	For reconstitution
8	Other	Test parameters additionally required considering the characteristics of the product

4) Topical drug products

(1) Solutions

No.	Test parameter	Note
1	Appearance	
2	pH	
3	Specific gravity or density	
4	Osmolality	When osmolality is required to be considered (refer to composition of drug product, dosage and administration, indication, and warnings and precautions in the labeling) However, preparations applied to the skin are excluded.
5	Buffer capacity	When containing a buffer or substance affecting buffer capacity
6	Viscosity	When containing viscosity controlling agent, polymeric substance, or a substance affecting viscosity
7	Drop volume (or spraying volume and particle size)	In the case of drop form (or for spray)
8	Other	Test parameters additionally required considering the characteristics of the product

(2) Semi-solid preparations (creams, ointments and gels, etc.)

No.	Test parameter ¹⁾	Note
1	Appearance	
2	pH	
3	Specific gravity or density	
4	Viscosity	
5	Particle size or particle size distribution	
6	Rheological properties	Selection of test parameters considering product characteristics e.g.) Flow curve (relationship between shear stress and shear rate), spreadability (soft formulation), penetration (hard formulation), etc.
7	Release test	
8	Other	Test parameters additionally required considering the characteristics of the product e.g.) Distribution coefficient, etc.

¹⁾ If conducting the test is proven to be impossible or irrelevant, it may be substituted with scientifically valid test data.

**3. Standard Format for
Physicochemical Equivalence Test Report**

**Physicochemical Equivalence Test
Report**

- Product Name (Substance Name) -

Principal Investigator

*(Quality Control Manager or Equivalent
Responsible Person for Submission)*

○ ○ ○
(Signature)

XXX Pharmaceutical Company

< Overview >

Title of Testing	<i>Physicochemical equivalence test report of product name (drug substance name)</i>
Purpose of Testing	<i>Specify the purpose of the physicochemical equivalence test, such as marketing authorization (notification)</i>
Period of Testing	MM.DD.YY – MM.DD.YY
Testing Site (Location)	<i>QC Department of XXX Pharmaceutical Company (address)</i>
Principal Investigator	<i>Quality Control Manager or Equivalent Responsible Person for Submission (incl. PI from contract research organization (CRO) in case of CRO)</i>
Test Result	<i>Equivalent</i> – <i>Data on physicochemical properties (pH, specific gravity, density, osmolality, viscosity and dissolution test)</i>

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1. Overview of Test

1.1. Title of Testing

Physicochemical equivalence test of the product name (drug substance name)

1.2. Summary of Test Purpose

Describe in detail the background and purpose of performing the physicochemical equivalence test.

1.3. Reference Product

e.g.) Rama Injection (XXX Hydrochloride), XXX Pharmaceutical Co. Ltd.

1.4. Test parameter

e.g.) Appearance, pH, specific gravity, density, osmolality, buffer capacity, and viscosity were selected as test parameters based on the Guidance of Physicochemical Equivalence Test.

1.5. Summary of Test Result

Test parameters and acceptance criteria were determined based on the physicochemical properties of the reference product. Physicochemical equivalence tests were conducted on one batch of the test product, Gana Injection (XXX hydrochloride) of XX Pharmaceutical Co., Ltd, and one batch of a reference product, Rama Injection (XXX hydrochloride) of YY Pharmaceutical Co., Ltd. According to the test results, the test product met the acceptance criteria in all test parameters, proving that the two drugs are physicochemically equivalent.

1.6. Testing Site *(incl. PI from contract research organization (CRO) in case of CRO)*

- Name: Representative of XXX Co. Ltd.
- Address:
- CEO:

1.7. Analytical Devices and Equipment used in the Test *(Example)*

Test parameter	Used device	Manufacturer	Model	Note
pH	pH meter	PHMT	P-100	
Osmolality	Freezing point depression osmometer	AAA	BBB	
Density	Specific gravity bottle	CCC	DDD	
Viscosity	Capillary viscometer	EEE	FFF	
Other				

1.8 Principal Investigator (PI) *(incl. PI from contract research organization (CRO) in case of CRO)*

- Name: XXX
- Affiliation:
- Position:

2. Test Methods

- *Describe the basis for setting the test method and the detailed test method, and attach data that can justify the test method.*
- *The selection criteria for test parameters are prepared based on dosage form, purpose of compounding, and characteristics of excipient.*
- *Refer to 'CTD 3.2.P.5.2. Analytical Procedure' and 'CTD 3.2.P.5.3 Validation of Analytical Procedure or provide the detailed reason for setting the test method for each parameter and the specific test process.*
- *For test method listed in the compendium, the compendium and name of test method should be included as data that can justify the the test method, or if necessary, the validation criteria and results should be summarized.*
- *(Example) osmolality test*

According to the test method for osmolality in the Korean Pharmacopoeia general test, after cleaning the sample cell and thermistor, measure the freezing point using the sample solution, obtain the osmolality from the concentration dependence of the freezing point depression, and use this as the osmolarity.

3. Test Result

3.1. Details on Test Products and Reference Products

3.1.1. Overview

Category	Test Product	Reference Product
Manufacturer (Manufacturing country)		
Product name	<i>Gana Injection (XXX Hydrochloride)</i>	
Manufacturer of Active substance		
Standard & Analytical Procedure		
Lot No.		
Batch size (Production scale)	<i>100,000 vials (100kg)</i>	-
Manufacturing date (Expiration date)		
Labeled amount of active substance		
Assay result		
Type of excipients		

3.1.2 Test product: XXX injection

3.1.2.1 Composition (drug substance and quantity)

In 1 mL (or mg) of the drug					
Purpose of compound ing	Substance name	Specificati on	Qty.	Unit	Note
Active substance				mg	
Buffer					
...					

3.1.2.2 Details on the active substance used in the manufacture of the test product

- *The name and location of the manufacturer of the active substance in the manufacturing method in the application should be the same as those listed on the Certificate of Analysis (CoA) for the drug substance. In this case, the location of the manufacturer should be the address of the manufacturing site, not the*

headquarters.

- It can be written as 'Refer to CTD 3.2.S.4.4 Batch analyses.'
- (Example) Manufacturer/Manufacturing site: AB Pharmaceutical / ○○-○, ○○-dong, ○○-gu, Yongin-si, Gyeonggi-do, South Korea
Lot No.: 100214
CoA for the raw materials: Appendix 1

3.1.2.3 Detailed data on the manufacturing process of the test product

- It can be written as 'Refer to CTD 3.2.P.3.3 Description of Manufacturing Process and Process Control.'
- Submit data verifying that the product is manufactured as labeled.

3.1.3 Reference Product

3.1.3.1 Selection of reference product batch

- Identify batch variations with physicochemical evaluation based on characteristics, and select a representative batch.
- (Example)

Test parameter	Test Result			Note
	Batch No.:(Manufacturing date)	Batch No.:(Manufacturing date)	Batch No.:(Manufacturing date)	
Appearance				
pH				
Specific gravity (g/mL)				
Osmolality (Osmol/kg)				
Buffer capacity (Eq/L)/ΔpH				
Viscosity (Centi poise)				
Other parameters				

3.1.4. Data on Quality Control Test

3.1.4.1. Summary of quality control test results

- (Example)

<Test product>

<i>Test parameter</i>	<i>Standard</i>	<i>Test Product (AB001)</i>
<i>Appearance</i>	<i>Clear, yellowish emulsion contained in a colorless and transparent vial</i>	<i>Pass</i>
<i>Identification test</i>	<i>1) HPLC: Retention time of the standard solution and test solution is the same. 2) TLC: The main spot Rf of the standard solution and test solution is the same.</i>	<i>1) Same 2) Same</i>
<i>pH</i>	<i>6.0~8.0</i>	<i>7.0</i>
<i>Moisture</i>	<i>≤ 2.0%</i>	<i>0.9%</i>
<i>Impurities</i>	<i>Individual impurities: ≥ 0.2% Total impurities: ≥ 0.5%</i>	<i>Individual impurities: ≥ 0.2% Total impurities: ≥ 0.5%</i>
<i>Uniformity of dosage units test</i>	<i>≥ Labeled amount (20mL)</i>	<i>20.5 mL</i>
<i>Endotoxin Test</i>	<i>≥ 0.06 EU/mg</i>	<i>≥ 0.06EU/mg</i>
<i>Sterility test</i>	<i>No microbial growth observed</i>	<i>Pass</i>
<i>Test for insoluble foreign matter</i>	<i>Visually clear with no observable particulate matter</i>	<i>Pass</i>
<i>Test for insoluble particulate</i>	<i>≥10μm: 6000 or less/vial ≥25μm: 600 or less/vial</i>	<i>≥10μm: 500/vial ≥25μm: 20/vial</i>
<i>Assay</i>	<i>95.0~105.0%</i>	<i>100.5%</i>

<Reference product>

<i>Test parameter</i>	<i>Standard</i>	<i>Reference product (CP020)</i>
<i>Appearance</i>	<i>Clear, yellowish emulsion contained in a colorless and transparent vial</i>	<i>Pass</i>
<i>Assay</i>	<i>95.0~105.0%</i>	<i>99.2%</i>

3.1.4.2. Assay

The results of testing the test product and the reference product according to the in-house standards and *test method* of the test product are as follows.

Category	Test Product	Reference Product
Manufacturer (Manufacturing country)	XX Pharmaceutical Co. Ltd. (Korea)	YY Pharmaceutical Co. Ltd. (Korea)
Product name	Gana Injection (XXX Hydrochloride)	Rama Injection (XXX Hydrochloride)
Specifications of drug	In-house standard	In-house standard
Lot No.	AB001	CP020
Labeled amount of active substance	Rama Injection (XXX Hydrochloride) 22.8mg/vial	Rama Injection (XXX Hydrochloride) 22.8mg/vial
Assay result	100.5%	99.2%

3.2. Acceptance Criteria, Test Results, and Equivalence Determination

3.2.1. Physicochemical equivalence test assessment report

- *Enclose Attachment 1.*
- *The acceptance criteria should apply the standards established in Section '2.6 Equivalence Acceptance Criteria' and all results from a minimum of three repeated tests conducted using the test method established for the test product batch should conform to the standards.*
- *If the acceptance criteria are set outside the range of $\pm 10\%$ of the reference product results, the rationale should be documented. (If based on literature or separate test data, the data should be included as other attachment).*

4. Discussion and Comprehensive Opinion on the Acceptance Criteria and Test Results

- *(Example) For marketing authorization of Gana Injection (XXX Hydrochloride) (manufactured), according to the physicochemical properties of Rama Injection (XXX Hydrochloride), the results of a comprehensive analysis of the physicochemical equivalence test conducted by setting the test parameters and*

acceptance criteria were obtained. For test product, when all operations of the test method were repeated 3 times, all test parameters met the acceptance criteria and met the physicochemical equivalence standard. Therefore, the test product Gana Injection (XXX Hydrochloride) and the reference product Rama Injection (XXX Hydrochloride) are physicochemically equivalent.

Principal Investigator: Department Name (Signature)

Signature of the Contract Test Manager for a Contract Test

(Attachment 1)

Physicochemical Equivalence Assessment Report

MM.DD.YY

	Company name	Product name	Lot No.	Lot size	Manufacturing date (Expiration date)	Strength (%)		
Reference product	YY Pharmaceutical Co. Ltd.	Rama Injection (XXX Hydrochloride)	CP020	-	MM.DD.YY (Expiration date)			
Test product	XX Pharmaceutical Co. Ltd.	Gana Injection (XXX Hydrochloride)	AB001	100,000 vials (100kg)	MM.DD.YY.			
Composition (drug substance and quantity)	Reference product				Test product			
	Purpose of compounding	Raw material name	Specification	Qty.	Purpose of compounding	Raw material name	Specification	Qty.
	Active substance	XXX Hydrochloride	KP	00 mg	Active substance	XXX Hydrochloride	KP	00 mg
					000	00000	KP	00 mg
Testing site	QC Department of XXX Pharmaceutical Company		Principal Investigator			[Name]		
Physicochemical equivalence test result								
Selection of test parameter								
No.	Test parameter	Reasons and rationale for selection			Analytical Procedure			
1	Appearance							
2	pH							
3	Specific gravity g/mL							
4	Osmolality Osmol/L							
5	Buffer capacity (Eq/L)/ΔpH							
6	Viscosity CPS							
7	Other parameters							
Review comment	The reason for selection is valid according to the Guidance on Physicochemical Equivalence Test.							
Test result								
Test parameter	Test result (Test period: -)				Test result	Acceptance criteria	Decision	
	Reference product	Test product (Batch No., Manufacturing date)						
	Batch No. (Manufacturing date:)	Test 1	Test 2	Test 3				
Appearance							Equivalent	
pH					~	~ (±10%)	Equivalent	
Specific gravity g/mL					~	~ (±10%)	Equivalent	
Osmolality Osmol/L					~	~ (±10%)	Equivalent	
Buffer capacity (Eq/L)/ΔpH					~	~ (±10%)	Equivalent	
Viscosity CPS					~	~ (±10%)	Equivalent	
Other parameters					~	~ (±10%)	Equivalent	
Test period	2000.00.00.~00.			Final determination date	2000.00.00.~00.			
Special note								
Review comment	Pass							

4. References

- 1) EMA, Guideline on the Investigation of Bioequivalence, Aug. 2010
- 2) EMA, Draft guideline on quality and equivalence of topical products, 18 Oct. 2018.
- 3) FDA, ANDA Submissions-Refuse-to-Receive Standards Guidance for Industry, Dec. 2016
- 4) FDA, The BE Table Comparative Physicochemical Data of Ophthalmic Solution Drug Products in Module 2.7 of the ANDA
- 5) Health Canada, Guidance for Industry ; Pharmaceutical Quality of Aqueous Solutions, 18. Feb. 2005.
- 6) PMDA, Guideline for Bioequivalence Studies of Generic Products for Topical Use, 7. July. 2003.
- 7) PMDA, 点眼剤の後発医薬品の生物學的同等性評価に関する基本{的考え方, 11. Nov. 2018.

Appx. Frequently Asked Questions

1. Approval of generic drugs with different composition and concentration of excipients from reference products

When submitting an application for generic drug approval for injections, ophthalmic drugs, and otic drugs, what type of data should the applicant submit if the composition and concentration of excipients of the drug product are different from the reference product?

- ☞ For injections, ophthalmic drugs, and otic drugs, the safety and efficacy of submitted physicochemical equivalence test data can be recognized, basically, when the composition and concentration¹⁾ of inactive ingredients of the drug product is the same as the reference product. If the composition and concentration of preservatives, buffers, antioxidants, and pH adjusters in injections are different, or if the composition and concentrations of preservatives, buffers, substance to adjust tonicity, thickening agent, and pH adjusters in ophthalmic drugs or otic drugs are different, sufficient information (e.g., stability data, etc.) should be submitted to prove that the difference does not affect the action of the active substance. For excipients other than those mentioned above, if the composition is same as the reference product but only the concentration is different, objective evidence such as a foreign pharmaceutical compendia should be submitted.

Note 1) If the concentration of each excipient is within $\pm 5\%$ of the publicly announced reference product, it can be recognized as the same concentration.

When submitting an application for a topical drug generic products (excluding liquids), what kind of data should the applicant submit if the quantitative and qualitative composition of excipients is different from the reference product?

- ☞ For a topical drug products, excluding solutions, physicochemical equivalence test data can be recognized as safety and efficacy data, when the quantitative and qualitative composition of excipients is the same as the reference product. However, preservatives, antioxidants, colorants and flavoring agents may differ from those in the reference product. If composition of excipients other than those mentioned above is different from the reference product, data (e.g., skin pharmacokinetic test data, pharmacodynamic test data, etc.) should be submitted to prove that the excipient does not affect the safety and efficacy of the drug product. [Enforcement date: October 15, 2023]

2. Test product available for physicochemical equivalence test

Are there any requirements for test products that can be used for physicochemical equivalence test?

- ☞ The test product should be manufactured using the same raw materials, composition, and process as it is marketed, and should be selected as a batch manufactured in compliance with the Regulation on Safety of Pharmaceuticals, etc. (Pharmaceutical Manufacturing and Quality Control Standards). However, it can be used considering both the characteristics of the dosage form and commercial scale. For example, in the case of parenteral solutions, powders to be reconstituted before use for injection, ophthalmic drugs, and otic drugs, the batch size of the test product should be at least 10% of

the commercial scale, 50 liters (for packaging units of 2.0 mL or more), or 30 liters (for packaging units of less than 2.0 mL), whichever is larger. In the case of oral solution, the batch size of the test product should be at least 10% of the commercial scale. In the case of semi-solid topical products, the batch size of the test product should be at least 100 kg or 10% of the commercial scale, whichever is larger.

3. Common Technical Document (CTD)

Where should the data for the physicochemical equivalence test, which compares and evaluates physicochemical properties, be included in the CTD?

- ☞ The data for the physicochemical equivalence test, which substitutes for bioequivalence studies or comparative clinical study results, should be included in Module 3 or Module 5 of the CTD.

4. Injections imported as drug products

Is it necessary to conduct a physicochemical equivalence test when importing injections as drug products?

- ☞ Imported parental solution should also be tested for physicochemical equivalence under the relevant regulations, in the same way as domestically manufactured pharmaceuticals, if they fall under the category requiring such a test.

5. Conducting a physicochemical equivalence test for each packaging unit when developing generic drugs

For generic drugs, when the concentration of the active substance and excipients are the same but there are multiple packaging units, is it required to submit data on physicochemical equivalence test for each packaging unit?

- ☞ When the strength per unit dosage form is the same but there are various packaging units (filling amount), a physicochemical equivalence test can be conducted on one packaging unit.

6. Physicochemical equivalence test conducted abroad

For imported drug products, is it possible to submit physicochemical equivalence test data conducted by a foreign manufacturer?

- ☞ Physicochemical equivalence test data conducted abroad can be submitted if it meets domestic regulations. It is essential to ensure that the quality control outsourcing contract with the foreign CRO, the comprehensive opinion and signature of the foreign PI, and the raw data, including the date and time of the test, should be included. When submitting foreign documents not in English, a translation may be required.

7. Selection of reference product for physicochemical equivalence test

If there are significant variations in the test results between batches of the reference product, how should the tests be conducted?

- ☞ The batch used as the reference product should be representative of the product. Please select and test a batch that represents the physicochemical characteristics, considering the manufacturing date

and variations between batches.

If a product is a new drug approved after 1989 but has not been designated as a reference listed drug for the physicochemical equivalence test, how should the reference product be selected?

- ☞ Prescription drugs announced as new drugs after 1989 can be considered and used as the reference listed drug. However, when developing a generic drug for a product that has a formulation difference (such as powder vs. liquid) from a listed new drugs, it is required to justify the reference product by applying for designation of reference listed drug.

8. Physicochemical equivalence test in cases where the reference product is unavailable

When conducting a physicochemical equivalence test for generic drugs, how should the test be conducted if the reference listed drug is unavailable due to reasons such as discontinued production?

- ☞ If it is proven that the reference listed drug is unavailable due to reasons such as discontinued production, a request can be made to change to a new reference listed drug, and after confirming the status, it can be used for testing.

What should be done if a sufficient batch of the reference product is not available?

- ☞ It is recommended to select the reference product as a batch that represents physicochemical characteristics by testing at least three batches, if possible. However, if three batches of the reference product are not

available, it is possible to test physicochemical equivalence with less than three batches, provided that the reasons are submitted and justified.

9. Selection of test parameters

When submitting a physicochemical equivalence test data for approval, how should the parameters to test physicochemical characteristics be selected?

- ☞ The test parameters for the physicochemical equivalence test should be selected based on the characteristics of the product, such as appearance, dosage form, excipient composition and grade, and administration method. After identifying various physicochemical properties that may affect safety and efficacy, appropriate parameters should be selected. Test parameters can be set based on the 'Product-specific guidance', and consultation with the MFDS can be arranged in advance if necessary.

If the reference product does not include a viscosity controlling agent, can the viscosity test be excluded?

- ☞ Even if there is no viscosity controlling agent, if the active substance or excipients of the reference product or test product could affect viscosity (including polymers, viscous substances, mannitol, sorbitol, etc.), it is recommended to measure and compare the viscosity of the reference product and the test product.

Are there cases where the osmolality test must be included as a parameter in the physicochemical equivalence test?

- ☞ For injections, osmolality test must be conducted. For ophthalmic solutions, otic solutions, and topical liquid preparations, if the

reference product contains substances that significantly influence osmolality, or if there are statements related to osmolality in dosage and administration, indication, and warnings and precautions of the labeling (notification), it is recommended to measure and compare the osmolality of the reference product and the test product.

10. Excipients of oral solutions

What are examples of excipients that can affect the absorption of the active substance in oral solutions?

☞ Examples include vitamin E, sorbitol, mannitol, and surfactants.

- * References: Bioavailability and Bioequivalence studies submitted in NDAs or INDs (FDA 2014 draft guidance) and 4. Reference 1) Guideline on the Investigation of Bioequivalence (EMA 2010 Guideline)

How can equivalence be demonstrated when an oral solutions contains excipients that can affect the absorption of the active substance?

☞ Sugar alcohols (such as sorbitol, mannitol, maltitol), surfactants, and vitamin E are known to affect the absorption of the active substance. Depending on the differences from the reference product, the following data should be submitted.

Type	Quantity variation	Data for evaluation
Same	within $\pm 10\%$	Physicochemical equivalence test
	exceeding $\pm 10\%$	Physicochemical equivalence test and data proving that excipients do not affect absorption ¹⁾
Not same		Physicochemical equivalence test and data proving that excipients do not affect absorption ¹⁾

Note 1) Example: Human PK (including literature), animal PK (for reference product and test product), BCS class I supporting data, etc.

- * References: Bioavailability and Bioequivalence studies submitted in NDAs or INDs (FDA 2014 draft guidance) and 4. Reference 1) Guideline on the Investigation of Bioequivalence(EMA 2010 Guideline)

11. Test methods of test parameters

How should the test method be established for test parameters by dosage form?

- ☞ The test method for the test parameters should be either a method listed in the compendium or an appropriately validated, verified, and calibrated test method. The compendium includes USP, EP, and other compendia recognized by the MFDS.

How can the test method be justified to compare physicochemical characteristics?

- ☞ The validation data for the test method includes, if necessary depending on the test method, validation or verification and calibration data. For the test method comparing physicochemical characteristics, it can be considered to verify accuracy and precision by repeatedly testing existing products or standard solutions with known results.

Is there an appropriate method for measuring the drop volume of ophthalmic solutions and otic solutions?

- ☞ As an example, hold the container at a 90° angle and let it drop one drop at a time, measuring the mass at regular intervals (e.g., 1, 5, 10 drops). The drop volume can be found by dividing the mass by the pre-measured density to calculate the volume per drop.

Are there methods for measuring spray volume and particle size distribution in spray formulations?

- ☞ It is recommended to primarily analyze using a light scatter measurement device. However, given the difficulty of using this method in practical environments, an alternative approach can be considered to spray in a consistent manner (with the same length, angle, etc.) and analyze the pattern stained with dye. Reference can also be made to the USP <601> 'Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders-Performance Quality Test.'

How are in vitro release and permeability tests conducted?

- ☞ Considering the characteristics of the formulation, the test method can be validated and performed using internationally recognized analytical procedure or literature. For example, in vitro release test methods include the USP dissolution test and methods using Franz Diffusion Cells, while in vitro permeability test methods also include methods using Franz Diffusion Cells. Reference can also be made to the 'Guidance on the Evaluation of Local Topical Drug Product Equivalence (Guidance for industry)' and the USP <601> 'Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders-Performance Quality Test.'

12. Acceptance criteria for tests

Should the acceptance criteria for all physicochemical properties be set as 'within $\pm 10\%$ of the reference product results'?

- ☞ Generally, acceptance criteria can be set as 'within $\pm 10\%$ of the reference product results,' but reasonable criteria can be established depending on the test parameters. For example, parameters such as 'appearance,' which cannot be quantified with numerical values in

the test method, should be set with criteria such as 'same as the reference product'. Therefore, considering the impact of the parameter on product quality and the accuracy of the test method comprehensively, if a separate criterion can be scientifically justified with supporting data, equivalence can be tested using methods other than 'within $\pm 10\%$ of the reference product results. In cases where needed, 'Product-specific guidance' can be referenced.

13. Viscosity test procedure and criteria for equivalence

How should the viscosity test procedure and criteria for equivalence be established?

- ☞ Generally, after confirming whether the fluid is Newtonian or non-Newtonian with preliminary testing, measurement methods and criteria depending on the formulation characteristics should be applied. (However, if it can be demonstrated that the formulation is of low viscosity (< 100 cP) based on formulation development data or literature, preliminary testing can be excluded.)

In cases where non-Newtonian behavior is confirmed and viscosity is measured using Method 2, it is required to ensure that the viscosity profile can be verified at various shear rates (e.g., 0.01 to 1000/s). For ophthalmic injection, the viscosity profile should be verified at various shear rates (e.g., 0.001 to 1000/s) considering the clinical use condition. Please refer to the table below for the measurement methods and acceptance criteria for each dosage form.

Dosage form		Category	Measuring method (measuring range)	Acceptance criteria
Injections	Low viscosity (< 100cP)	×	KP Method 1 or Method 2	±10% or within ±10cP
	Clear intravenous injection (IV)			
	Clear intramuscular injection (IM),	Newtonian	KP Method 1 or Method 2	±10%
	Viscous intra-articular injection, Viscous ophthalmic injection	Non-Newtonian	Method 2 (0.001 - 1000/s)	±10%
Ophthalmic drugs	Low viscosity (< 100cP)	×	KP Method 1 or Method 2	±10% or within ±10cP
	Suspension, high viscosity	Newtonian	KP Method 1 or Method 2	±10%
		Non-Newtonian	Method 2 (0.01 - 1000/s)	±10%
Oral solutions	Low viscosity (< 100cP)	×	KP Method 1 or Method 2	±10% or within ±10cP
	High viscosity	Newtonian	KP Method 1 or Method 2	±10%
		Non-Newtonian	Method 2 (0.01 - 1000/s)	±10%

* The acceptance criteria should be set as ±10% of the reference product; however, if different acceptance criteria are established, a detailed rationale and supporting evidence should be provided.

Is it necessary to submit viscosity measurement results at various shear rates (e.g., 0.01 - 1000/s) for low viscosity liquids (e.g., < 100 cP)?

☞ If it does not affect safety or efficacy, and if preliminary tests confirm that a low-viscosity liquid (e.g., < 100 cP) has low viscosity, it can be measured using Method 1 or Method 2 of the KP.

Is it acceptable to evaluate the viscosity profile (at shear rates of 0.01 - 1000/s) using specific shear rates (e.g., 0.01, 0.1, 1.0, 10, 100, and 1000/s, etc.) for equivalence test?

- ☞ It is recommended to measure the viscosity profile at sufficient points within the shear rate range of 0.01 to 1000/s (e.g., 30 to 50 points) and test equivalence with the reference product at all measurement points.

14. Supporting Data including Test Results

Is it required to submit the CoA and its raw data?

- ☞ The CoA for the test product should be submitted, but raw data for the test parameter do not have to be submitted. For the reference product's CoA, test parameters other than appearance, assay, or potency testing can be exempted.

15. Testing site

If an analytical device is not available, can some test parameters be outsourced to an external laboratory?

- ☞ Yes, it is possible. According to Article 5 (4) of the 'Standard on Pharmaceutical Equivalence Test' (MFDS Notification), physicochemical equivalence tests should be performed at the pharmaceutical manufacturing (importing) site or a place with the facilities and equipment, etc., necessary to perform the test, and every equipment used in the test should be equipped with audit trails that can maintain and retain all operation records.

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