A-05

Handling of the Study Results for determination in the Evaluation of New Chemical Substances etc.

(Ministry of Health, Labour and Welfare (MHLW) Pharmaceuticals and Food Safety Bureau (PFSB) Notification 0331 No. 9 dated March 31, 2011, Ministry of Economy, Trade and Industry (METI) Manufacturing Industries Bureau Notification No. 7 dated March 29, 2011, and Ministry of the Environment (MOE) Environmental Health Policy Planning and Management Division Notification No. 110331011)

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Guideline for Handling of Study Results

1. General Rules

(1) Among from the test results to be reviewed for the determination in the evaluation pursuant to the provisions of Article 4 and 5 of *"Act on the Regulation of Manufacture and Evaluation of Chemical Substances"* (hereinafter referred to as "the Act"), the results of the tests on the properties of the priority assessment chemical substances pursuant to Paragraph (1) of Article 10 of the Act, and the study results on the hazardous properties pursuant to Paragraph (2) of Article 10 and Paragraph (1) of Article 14 of the Act, the results obtained by conducting the tests for obtaining the knowledge stipulated in the Paragraph (1)(i)(a) of Article 1 of "*Ministerial Ordinance Specifying Items for Tests Pertaining to New Chemical Substances and Studies Pertaining to the Hazardous Properties of Priority Assessment Chemical Substances and Monitoring Chemical Substances*" (Prime Minister's Office, Ministry of Health and Welfare, Ministry of International Trade and Industries, Ministerial Ordinance No. 1 of July 13, 1974) (hereinafter referred to as "the Ministerial Ordinance"), the studies pursuant to the Paragraph (1)(ii), (2) and (3) of Article 1, and Article 2, 3 or 4 of the Ministerial Ordinance, or the studies for the investigation pursuant to the Article 5 or 6 of the Ministerial Ordinance (hereinafter referred to as "GLP Applicable Study Results ") shall be conducted and put together in the test facility which comply, in principle, with "*the Good Laboratory Practice for test facilities conducting tests of New Chemical Substances etc.*" (hereinafter referred to as "GLP Standards ") stipulated in the "*Notice of the Good Laboratory Practice for test facilities conducting tests of New Chemical Substances etc.* (MHLW PFSB Notification No. 0331-8 dated March 31, 2011, METI Manufacturing Industries Bureau Notification No. 6 dated March 29, 2011, and MOE Environment Environmental Health Policy Planning and Management Division Notification No. 110331010)"; (hereinafter referred to as " GLP Study Results"); provided, however, that the tests conducted for obtaining the knowledge stipulated in Paragraph (1) (i) of Article 1 of the Ministerial Ordinance or the tests specified in Paragraph (1) (i) of Article 4 of the Ministerial Ordinance shall be limited to tests provided in the Paragraph 1 of the Annex the "Guidelines on the GLP Compliance Confirmation of the test facility".

(2) When the GLP Applicable Study Results are attached in the notification concerning manufacture, import or export of a new chemical substance under the provision of Article 3 or Article 7 of the Act, in the submission of documents describing the results of the test for the properties of priority assessment chemical substances based on Paragraph (1) of Article 10 of the Act, or in the report of the results of the study of the hazardous properties pursuant to Paragraph (2) of Article 10 or Paragraph (1) of Article 14 of the Act, the document detailing following materials should be appended. However, in the case that the GLP Applicable Study Results are treated as GLP Study Results according to the (2) or (3) of section 2, the materials in (i) and below shall not always be attached.

(i) Name (concerning the test facility : the same shall apply hereinafter), address, date of establishment, articles of association or act of endowment, organization, personnel organization, site area, number of stories and total floor area of the buildings that have facilities, layout of facilities and apparatus, outline of type and

contents. If a brochure showing the exterior view of the building and major facilities is available, the said brochure.

(ii) Name and responsibilities of the personnel engaged in the relevant study (including Study Director), and their resume, research career, academic societies or scientific bodies to which theybelong.

(iii) Name, title, and position of the Quality Assurance personnel of the relevant study.

(iv) Statement of the Test Facility Management or the Study Director certifying that the such results were tested and put together in accordance with the GLP Standards (For the foreign study results , the GLP standards of the said country that are deemed to be compliant with the OECD Principles of GLP may be acceptable).

2. Inspection, etc.

(1) The Director-General of MHWL, the Director-General of METI or the Director-General of MOE shall conduct, as necessary, the inspection of the test facility, document examination of the GLP Applicable Study Results (Study Audit) or interview from the Test Facility Management (hereinafter collectively referred to as the " Inspection, etc.") to ensure the quality of the GLP Applicable Study Results.

(2) Among from the GLP Applicable Study Results, the study results obtained by the test facility of which compliance with the GLP Standards has been confirmed prior to the initiation of such study in accordance with the Annex "The Guidelines for Confirmation of Compliance with the GLP Standards by the Test Facility" and kept being confirmed once within 3 years until last inspection conducted within the past 3 years (including the test facilities for which the effectiveness of the confirmation is considered to remain valid in accordance with the provisionary clause in 3 (4) of the Attachment titled The Guidelines on GLP Compliance Confirmation of the Test Facility) and which submitted the required notification during the period, shall be treated , in principle, as the GLP Study Results.

Also, the study results obtained by the test facility of which compliance with the GLP Standards has been confirmed in accordance with the Annex "The Guidelines on GLP Compliance Confirmation of the Test Facility", and subject to the document examination in conjunction with the inspection conducted for the said compliance confirmation, shall be treated as the GLP Study Results.

(3) The study results shall be treated as the GLP Study Results when a document stating that by inspection within 3 years prior to the initiation of said study, a government authority in said country or equivalent authority confirmed that said test facility is in compliance with the GLP standards of the said country that are deemed to be compliant with the OECD Principles of GLP (hereinafter referred to as " the Statement ") is attached.

However, the study results obtained by the test facility confirmed by Competent Authorities listed in SECTION II of Part B of "Sectoral Annex on Good Laboratory Practice (GLP) for Chemicals" of 'The Agreement on Mutual Recognition Between Japan and the European Community' and an appropriate competent authority in the United Kingdom, which is listed in Section II of Part B of the Sectoral Annex “Good Laboratory Practice (GLP) for Chemicals” of the Letters concerning Mutual Recognition in the Agreement between the United Kingdom of Great Britain and Northern Ireland and Japan for a Comprehensive Economic Partnership shall be treated, in principle, as the GLP Study Results regardless of whether the Written Verification is attached or not.

(4) However, in each of (2) or (3) cases above, the inspections etc. to confirm the quality of the study results shall not be precluded, and if this lead to the result of non-compliance with the GLP Standards, the said study results shall not be deemed as the GLP Study Results in principle.

3. Handling of the GLP Applicable Study Results which partly fail to be in compliance with the GLP Standards

(5) When the GLP Applicable Study Results which partly fail to be in compliance with the GLP Standards are submitted, a person who gives a notification for manufacture, import or export of said new chemical substance or a person who reports the results of said study of hazardous properties (hereinafter referred to as "Notifier")

shall be required to submit the document to show that the quality of the study results would not be affected by the part of non-compliance with the GLP Standards, or that the effect would be tolerable. If necessary, an inspection shall be conducted. If said study results are found to be reliable by these, they shall be treated as materials for evaluations.

In this case, for foreign study results, the same shall apply, if results of inspection conducted by a government authority in said country or an equivalent authority is submitted and said study results are found to be reliable by these.

(6) Foreign study results which are impossible or extremely difficult to be attached by the documents prescribed in 2 (3) or the material or results of inspections prescribed in 3 (1) for due reason such that there is no GLP standards in said country or others, shall be treated pursuant to the provisions then in force.

4. Exclusion from the Evaluation

If it is judged that the quality of the submitted study results could not be confirmed or is compromised since they fall under any of the following items, the said study results may be excluded from the materials for evaluations of notification concerning manufacture, import or export of a new chemical substance concerning said test or the materials for determination of the study results for a study of hazardous properties concerning said study.

(a) Materials prescribed in 3 (1) above have not been submitted by the Notifier, or are deemed inadequate if submitted.
(b) Inspections pertaining to 2 or 3 (1) above was refused by the said test facility, or the quality of the study results is compromised, judging from the inspection results (for foreign test results, results of inspection conducted by a government authority in said country or an equivalent authority).

5. Relationship between the final reports pertaining to the GLP Standards and the materials concerning test results attached in notifying of New Chemical Substances, in submitting documents describing the test results for the properties of Priority Assessment Chemical Substance, or in reporting the results of the study of the hazardous properties

The GLP Applicable Study Results attached in notifying of New Chemical Substances, in submitting documents describing the test results for the properties of priority assessment chemical substances, or in reporting the results of the study of the hazardous properties shall not differ from the final reports in contents.

Annex

"The Guidelines on GLP Compliance Confirmation of the Test Facility"

The procedure to confirm the adherence level of the test facility to the GLP Standards (hereinafter referred to as "Confirmation") performed by the Director-General of MHWL, the Director-General of METI and the Director-General of MOE shall be as follows;

1. Study Items subject to the Confirmation

The Confirmation shall be conducted on each of the study items listed below from (1) through (4). For the studies from (2) through (4), the Confirmation may be conducted on a part of the study item, as appropriate.

(1)Biodegradation Test of Chemical Substances by Microbial Organisms (hereinafter referred to as "Biodegradation Test")

(2)Bioaccumulation Test of Chemical Substances in Fish and measurement of Octanol/Water Partition Coefficients (hereinafter referred to as "Bioaccumulation Test, etc.")

(3) Toxicity studies of Chemical Substances including the Chronic Toxicity Study, the Studies of reproductive potential and the influence on later generation, the Teratogenicity Study, the Mutagenicity Study, the Carcinogenicity Study, the Study on metabolic Fate, the Pharmacological Study and the Repeated Dose Toxicity Study in Mammals (hereinafter referred to as "Toxicity Studies")

(4) Toxicity tests for chemical substances including the Test on the Impact on Reproduction of Birds, the Fresh Water Algae Growth Inhibition Test, the Daphnia Acute Immobilization Test, the Fish Acute Toxicity Test, the Daphnia Magna Reproduction Test, the Effects on Inhabitation or Growth of Fish in Early Life Stage and other studies (hereinafter collectively referred to as "Ecotoxicity Test") that the Minister of Economy, Trade and Industry and the Minister of Environment find particularly necessary, considering the environmental residue levels of Priority Assessment Chemical Substances, for evaluating the effects on the inhabitation and growth of flora and fauna in the human living environment.

2. Application Procedure

(1) The person who intends to receive the Confirmation shall submit the Application using Form 1 with respect to each test facility and each study item and a copy thereof to the following competent Director-General of the designated Ministry, provided, however, that in cases where Biodegradation tests and Bioaccumulation Tests are conducted at the same test facility, the applications may be made by the single application form.

(i) For application concerning Biodegradation Test and Bioaccumulation Test, the Director-General, Manufacturing Industries Bureau, Ministry of Economy, Trade and Industry.

(ii) For application for concerning Toxicity Study, the Director-General, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare.

(iii) For application concerning Ecotoxicity Test, the Director-General, Environmental Policy Bureau, Ministry of the Environment.

The person, who intends to receive the Confirmation by the specific date, shall apply no later than 6 months prior to the said specific date.

(2) The Application form and its copy of (1) above shall be respectively attached by the following information:

(a) Date of establishment (concerning the test facility : the same shall apply hereinafter), entity that established the facility, articles of incorporation or act of endowment, site area, number of stories and total floor area of the buildings that have facilities;

(b) Plan view of the test facilities and physical layout of the main facilities, equipment and apparatus;

(c) Name, quantity, type, number, etc. of the main equipment and apparatus to be used for the study items concerning an application;

(d) Organization, personnel organization, Name and responsibilities of the key personnel (including Test Facility Management), and their resume, research career, academic societies or scientific bodies to which they belong;

(e) Provisions related to the internal audit and the status of the internal audit in the last three years;

(f) Status of the implementation of education and training of the personnel in the last three years.

(g) Status of the studies conducted in the last 10 years for the test items concerning applications.

3. Confirmation

(1) The Confirmation shall be conducted by evaluation of the application form and the submitted material provided in 2 above, and by the inspection of the test facilities concerning the application, provided, however, that for the test facility obtained the Confirmation, a part or all of inspection concerning study items other than that have been already confirmed may be omitted.

When the competent Director-General of the Ministry finds it appropriate, for the test facility which is in compliance with the GLP standards under other laws that are deemed to compliant with OECD Principles of GLP, a part or all of inspection may be omitted.

(2) Inspection shall be carried out by dispatching the person designated by competent Director-General of the Ministry to the said test facility.

(3) The competent Director-General of the Ministry shall give the notice, when the said test facility is deemed to be in compliance with the GLP Standards as the results of the Inspection pertaining to (1) above, to the applicant of the confirmation. If it is not deemed to be in compliance, it shall be notified.

(4) The confirmation shall remain valid for the period of time specified in the notification made above in (3). However, in case the application in 2 (1) was made not later than six months before the expiration date of the validity period and the notification in (3) was not received by the day before the expiration date of the validity period due to any disaster or other unavoidable reasons, the validity of the confirmation shall be deemed to remain valid even if there is a blank period for confirmation of the test facility only if the test facility is found meeting GLP as a result of inspection for the application made. In addition, those test facilities that are found to meet GLP-compliant on other laws and regulations approved to conform to the OECD Principles of GLP may be treated as approved as appropriate by the Director-General of the competent authority if any blank period would take place

during the term of validity of confirmation about the test facilities

4. Change of test facility

A person, who has received notice of the confirmation of 3 above, when following matters change, shall notify that effect to the competent Director-General of the Ministry in the Form 2 without delay.

(1) Name or identity of the applicant, and in the case of a juridical person, the name of the representative, the name and address of the test facility.

(2) Changes related to the organization, personnel organization, facility, equipment, instruments, management and operation which might cause an effect on the quality of the study results concerning study items subject to the Confirmation.

5. Abolition of test facility

A person, who has received notice of the confirmation of 3 above, when the test facility concerning the said Confirmation abolished a part or all of business concerning study items subject to the confirmation (including reconstruction, movement, complete renovation of the test facility etc.), shall notify that effect to the competent Director-General of the Ministry in the Form 3 without delay.

(Reference 1) Competent Authorities of the European Union
(Excerpts from Sectoral Annex on Good Laboratory Practice (GLP) for Chemicals of The Agreement on Mutual Recognition between Japan and the European Community (EC) (Japan-EC Mutual Recognition Agreement (MRA)) in effect since January 1, 2002)

Competent Authorities of the European Community are the following authorities of the Member States of the European Community or authorities succeeding them:

Belgium	Institut Scientifique de la Santé Publique
Denmark	Erhvervsfremme Styrelsen Laegemiddelstyrelsen
Germany	Bundesministerium für Umwelt, Naturschutz und nukleare Sicherheit
Greece	General Chemical State Laboratory
Spain	Agencia Española de Medicamentos y Productos Sanitarios, Subdirección General de Seguridad de Medicamentos
	Ministerio de Agricultura, Pesca y Alimentación, Dirección General de Agricultura
	Ministerio de Ciencia y Tecnologia, Subdirección General de Calidad y Seguridad Industrial
	Ministerio de Sanidad y Consumo, Subdirección General de Seguridad Alimentaria
	Ministerio de Sanidad y Consumo, Subdirección General de Sanidad Ambiental y Salud Laboral
France	Groupe Interministériel des Produits Chimiques
	Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)
	Agence Française de Sécurité Sanitaire des Aliments (AFSSA)
	Agence Nationale du Médicament Vétérinaire (ANMV)
Ireland	National Accreditation Board
Italy	Ministero della Salute
Netherlands	Ministerie van Volksgezondheid, Welzijn en Sport,
	Inspectie voor de Gezondheidszorg (GLP - afdeling)
Austria	Bundesministerium für Land- und Forstwirtschaft, Umwelt

	und Wasserwirtschaft
Portugal	Instituto Português da Qualidade (IPQ) Ministério da Economia Instituto Nacional da Farmácia e do Medicamento (INFARMED)
Finland	Sosiaali- ja terveydenhuollon tuotevalvontakeskus / Social- och halsovardens producttillsynscentral
Sweden	Laegemiddelstyrelsen Styrelsen för ackreditering och teknisk kontroll (SWEDAC)

(Reference 2) Competent Authorities of the United Kingdom
(Excerpts from Sectoral Annex on Good Laboratory Practice (GLP) for Chemicals in the Protocol on Mutual Recognition of the Agreement between the United Kingdom of Great Britain and Northern Ireland and Japan for a Comprehensive Economic Partnership which came into effect on January 1, 2021)

For all: Department of Health and Social Care (Medicines and Healthcare Products Regulatory Agency) or authority succeeding it