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Implementation of “the already available knowledge on the composition, properties, etc.”

(Pharmaceutical Safety and Environmental Health Notification 0313 No.8 Dated March 14th, 2018, 20180308 Manufacturing Bureau No.1, Environmental Health Planning No.1803124）

Final Revision July 1st, 2019

Pharmaceutical Safety and Environmental Health Notification 0701 No.1, 20190619 Manufacturing Bureau No.2, Environmental Health Planning No.1907011

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This document prescribes implementation of “the available knowledge on the composition, properties, etc.” stipulated in the Act on the Regulation of Manufacture and Evaluation of Chemical Substances (Act No.117, 1973. Hereafter referred to as the “Act”) Article 4-1 (including cases where it is applied mutatis mutandis pursuant to Article 7-2 of the Act) and Article 5-2. This document becomes effective from April 1st, 2018.

Implementation of “the available knowledge on the composition, properties, etc.” (Pharmaceutical and Food Safety Notification 0331 No.4 Dated March 31st, 2011, Manufacturing Bureau No.2, March 29th, 2011, Environmental Health Planning No.110331006. Joint Notification by the Director General, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare/the Director General, Manufacturing Industries Bureau, Ministry of Economy, Trade and Industry/the Director General, Environmental Policy Bureau, Ministry of the Environment) is repealed of March 31st, 2018.

Note

1 A 'Polymer' means a chemical substance consisting of molecules characterized by the sequence of one or more types of monomer units, comprising 50 weight % and more of the molecules containing at least three monomer units, and comprising less than 50 weight % of the molecules of the same molecular weight, and the number average molecular weight is 1,000 or more (hereafter referred to as a “polymer”). A polymer that meets the conditions of (1) and (2) as shown below, is considered as a chemical substance that is not likely to undergo a chemical transformation through natural processes and is not readily bioaccumulative. A polymer that meets all the conditions of (1) to (3) as shown below is considered as a substance that does not fall under (a) of item (ii) of paragraph (1) of article 4 of the Act. A polymer that meets the conditions of (1), (2) and (4) is considered as a chemical substance that falls under (b) of item (ii) of paragraph (1) of article 4 of the Act. Whether a chemical substance meets the conditions of (1) and (2) stated below is evaluated by the test methods for polymer stability assessment as shown in the

attached document.

（1） A polymer shall be confirmed stable based on “physicochemical stability tests”.

If there are any changes in the content of dissolved organic carbon (hereafter referred to as “DOC”) or its weight, physical and chemical stability such as no structural changes is confirmed using other analysis methods.

（2） A polymer shall fall under any of the items below.

(i) A polymer is confirmed to be insoluble to all the acids, alkalis, water, or organic solvents based on “solubility test in acid/alkali” and “solubility test in water and organic solvents”.

(ii) A polymer is confirmed to be soluble to water or any of the organic solvents based on “solubility test in water and organic solvents” and has less than 1% of its components having molecular weights less than 1,000, and that is not known to be highly bioaccumulative.

(iii) A polymer is confirmed to be soluble to water or any of the organic solvents based on “solubility test in water and organic solvents” and has equal to or more than 1% of its components having molecular weights less than 1,000, and that is not known to be highly bioaccumulative, and molecular weights less than 1,000 is not likely to be bioaccumulative.

（3） A polymer shall not include heavy metals and not be expected to pose a risk of harming human health if taken in continuously based on information regarding correlations between the chemical structure and chronic toxicity.

（4） A polymers shall not include heavy metals and not have cationic properties in the main structure when a polymer is soluble to water, acid, and alkali based on “solubility test in acid/alkali”, and not be expected to pose a risk of damage to the inhabitation and/or growth of flora and fauna based on information regarding correlations between the chemical structure and toxicity to flora and fauna.

2 A chemical substance that is inorganic compound and that does not readily undergo a chemical transformation in air or in water under unshaded condition is considered as a chemical substance that is not likely to undergo a chemical

transformation through natural processes.

3 A chemical substance with a molecular weight of 800 or more (a molecular weight of 1,000 or more for compounds that include 2 or more halogen elements in its chemical structure) is considered as a compound that is not bioaccumulative. However, this is not apply to cases where this is not appropriate based on the structure of chemical substances.

4 Among chemical substances(including elements) that are generated by biodegradation tests by microorganism, those that are considered as not corresponding to item (i) of paragraph (2) of Article 2 or (b) 1 of item (ii) of paragraph (1) of Article 4 of the Act, or those that are not suspected to fall under (a) of item (i) of paragraph (3) of Article 2 of the Act are prescribed as below.

（1）Chemical substances shall not be considered to fall under item (i) of paragraph (2) of Article 2 and (b) 1 of item (ii) of paragraph (1) of Article 4 of the Act and not be suspected to fall under (a) of item (i) of paragraph (3) of Article 2 of the Act are listed below:

Na^{+}, K^{+}, NH_4^{+}, Mg^{2+}, Ca^{2+}, BO_3^{3-}, SiO_4^{4-}, PO_4^{3-}, SO_4^{2-}, F^{-}, Cl^{-}, Br^{-}, I^{-}

（2）Chemical substances shall not be considered to fall under item (i) of paragraph (2) of Article 2 and (a) of item (i) of paragraph (3) of Article 2 of the Act are listed below:

Fe^{2+}, Fe^{3+}, Zn^{2+}, Al^{3+}

Appendix

Test methods for the polymer stability assessment

(Polymer Flow Scheme)

Ⅰ Terminology

The terms used in the test methods are in accordance with the Japan Industrial Standards (JIS K 0211 (Technical terms for analytical chemistry (General part)), JIS K 0215 (Technical terms for analytical chemistry (analytical instrument part)), JIS K 7252 (Plastics - Determination of average molecular mass and molecular mass distribution of polymers using size-exclusion chromatography), and JIS Z 8801 (Test sieves, etc.,).

Ⅱ Preparation of test substances

A chemical substance with the smallest average molecular weight is selected as a test substance. However, if it is dissolved or dispersed in a solvent during polymer synthesis, the polymer isolated from the solvent without changing the properties of the chemical substance shall be used as the test substance.

Ⅲ Test method

1 Physicochemical stability test and solubility test in acid/alkali

(1) Granularity of test substances: The test substance shall be targeted to have particle size of between 60 to 80 mesh.

(2) pH of test solutions and its preparation: The pH values of 4.0 and 9.0, which are adopted in the OECD (Organization for Economic Cooperation and Development) Guidelines for Testing of Chemicals (OECD Council Decision [C(81)30 Final Appendix 1]) 111 “Hydrolysis as a Function of pH” (hereafter referred to as “TG111”) shall be used. The pH4.0 test solution may also be prepared by inorganic solvents that are not prescribed in TG 111 under the condition that pH level is confirmed to be maintained before and after the test.

(3) Test temperature: 40±2 ℃

(4) Light: Indoor light

(5) Air: The test solution shall be stirred to facilitate contact between the test substance and air.

(6) Test period: 2 weeks

(7) The concentration of the test substance shall be 1,000 mg/L. However, if there are any difficulties in conducting the test with test concentration 1,000mg/L due to the nature of test substance, the test concentration can be altered within the range of 100mg/L to 10,000mg/L.

(8) Number of cycles (repetition): 2 cycles

(9) Analysis: The DOC, IR spectrum and molecular weight distribution shall be analyzed before and after the test in order to examine whether there is any chemical change, and when a test substance has any side chains that can be hydrolyzed, a direct analysis shall be conducted to assess its physicochemical stability. However, if DOC analysis is not applicable; the test substance is an inorganic polymer or a buffer solution adopted in TG111 is applied for pH4.0 test solution, the weight shall be analyzed. However, some deviation may be allowed for cases with inevitable reasons.

2 Solubility test methods in water and organic solvents

(1) Test solvents

(i) Water

(ii) Tetrahydrofuran (hereafter referred to as “THF”) and dimethylformamide (hereafter referred to as “DMF”).

(Note 1) The solubility in n-octanol and n-heptane (affinity index to fat) can be determined by the solubility in THF and DMF.

(Note 2) Dimethyl sulfoxide (hereafter referred to as “DMSO”) or 1-methyl-2-pyrrolidone (hereafter referred to as NMP) can be used in place of DMF.

(2) Test temperature: Between 35℃ to 40℃.

(3) Test period: 1 hour of stirring

(4) Equilibrium: Maintain equilibrium for 24 hours at 25±2℃.

(5) Test concentration of test substances: 2,000mg/L

(6) Granularity: The test substance shall be targeted to have particle size of between 60 to 80 mesh

(7) Number of cycles (repetition): 2 cycles

(8) Stirring: The test solution should be gently and constantly stirred or agitated in order to facilitate contact between the test substance and air.

(9) Analysis:

(i) The DOC analysis shall be conducted for the water test solution. However, if the DOC analysis is not applicable for water test solution, the weight change shall be assessed on constant weight of residue sample obtained by filtering the test solution. If the filtering method cannot be used due to the nature of the test substance such as swelling and adherence to test vessel, etc., other methods can be used to separate the test solution and the residue sample. If the weight analysis of the residue samples is not feasible, the weight analysis can be carried out on test sample obtained by drying filtrate.

(ii) For THF and DMF test solution, the weight change shall be assessed on constant weight of residue sample obtained by filtering the test solution. If filtration is not applicable due to the nature of the test substance such as swelling and adherence to test vessel, etc., another method can be used to separate the test solution and the residue sample. If the weight analysis of the residue samples is not feasible, the weight analysis can be carried out on test sample obtained by drying filtrate.

(10) Solubility assessment: Insolubility is, in principle, confirmed by the fact that the test substance is insoluble in water and in 2 organic solvents. If the substance dissolves in 1 out of the 3 types of solvents (water and 2 organic solvents), the water solubility shall be provided.

3 Measurement method for molecular weight distribution

When the test sample is confirmed to be soluble in accordance with (2) J., Size-Exclusion Chromatography method (hereafter referred to as “SEC”) is carried out with consideration of the following points.

(1) Eluant: Any of the following general eluants shall be used. If where the test substance does not dissolve in the eluants, the special eluants prescribed in item (ii) shall also be considered. If the test substance does not dissolve at the temperature prescribed by Japan Industrial Standards (JIS K 7252), solubility study can be carried out with o-dichlorobenzene (hereafter referred to as “ODCB”), toluene, DMF, or water under heated condition.

(i) General eluants: THF, chloroform, dichloromethane, DMF, water (including buffer solutions), etc.

(ii) Special eluants: 1, 1, 1, 3, 3, 3, hexafluoro-2-propanol (HFIP), 1, 2, 4-trichlorobenzene (TCB), ODCB, toluene, 1,2-dichloroethane, NMP, m-cresol, benzene, DMSO, tetrachloroethylene, 2-chlorophenol, trifluoroethanol, etc.

(2) Method to convert the molecular weight: A method shall be selected from the following methods that is suitable for the test substances.

(i) Methods using standard samples of monodisperse molecular weight. (Polyethylene oxide, polystyrene,, etc. shall be used as standard samples.)

(ii) Methods using standard samples of polydisperse molecular weight: 1 to 2 types of standard samples with number average molecular weight, weight average molecular weight, and Z average molecular weight determined by absolute method (membrane osmotic method, light scattering method, ultracentrifugal method, etc) shall be used.

(iii) Methods using elongated chain length

(iv) Methods using hydrodynamic volume

(v) SEC-viscosity detector method

(vi) The SEC-LS method

(3) Stability: The baseline shall be linear.

(4) Response sensitivity of detector: The response sensitivity shall not have any molecular weight dependency. (The response sensitivity shall be calibrated if any dependency observed.)

(5) Separation: The peaks of polymers shall not be overlapped by any other peaks (additives and other impurities in solvents,

etc.). However, it shall not apply to cases where it is technically not feasible to separate the peaks and the molecular weight is calculated up to a point that represents a range corresponding to the whole molecular weight region including monomers and oligomers. In this case, if it is clearly confirmed that the peaks are originating from additives or other impurities, etc. in the solvent, such peaks can be excluded from the molecular weight calculation.

(6) The method used to draw the baseline for low molecular ranges: Calculations shall be made for 2 charts with stable baseline and the average value shall be obtained.

(7) Data processing: The number average molecular weight (Mn), weight average molecular weight (Mw), Z average molecular weight (Mz), dispersity(Mw/Mn), and the concentration of molecules with molecular weight under 1,000 shall be determined based on the data acquired by the SEC method or any other measurement methods.

Ⅳ Summary of the results: The results shall be summarized in the appended forms and the test report shall be attached to the form.

Appendix

Name of new chemical substance:

（1） Purity, impurity, concentrations of impurities, and granularity of test samples

Purity	
Impurities and its contained amount	
Granularity	

（2） Name of monomers constituting the test samples and Official gazette notification number (MITI No.), etc.

Monomer name	Official gazette notification number (MITI No.)	Other numbers

（3） Molar ratio and Weight ratio of the test samples per monomer

Structural formula	
Molar ratio	
Weight ratio	

（4） Physicochemical stability test results and acid/alkali solubility test results.

Test solution	DOC change				Weight change *2				IR spectrum change			Change in molecular weight distribution						
	DOC content（mg/L）			Organic carbon solubility rate (%) *1	Weight (mg)			Weight change rate (%)	Pre-test	Post-test	Presence or absence of change	Average molecular weight (mean value)						Change
												Mn		Mw		Mw/Mn		
	Pre-test	Post-test	Δ DOC		Pre-test	Post-test	ΔW					Pre-test	Post-test	Pre-test	Post-test	Pre-test	Post-test	
pH= 4.0																		
pH= 9.0																		

1 Organic carbon solubility rate (%)＝(ΔDOC/theoretical value)×100

* Theoretical value (mg/L)＝Test concentration of the test substances(mg/L)×Content of organic carbon (%)

*2 Weight change shall be reported when DOC analysis is not appropriate.

Test solution pH4.0	Type*3	Preparation method *4

*3 Eluants or inorganic solvents adopted in TG 111 shall be reported.

*4 The preparation methods when using inorganic solvents shall be reported.

（5） Results of solubility tests in water/organic solvents

Measurement solvent	DOC change					Weight change *6				
	DOC content (mg/L)			Organic carbon solubility rate (%) *5	Average (%)	Weight (mg)			Weight change rate (%)	Average (%)
	Pre-test	Post-test	ΔDOC			Pre-test	Post-test	ΔW		
Water										

5 Organic carbon solubility rate (%)＝(ΔDOC/theoretical value)×100

*Theoretical value (　　mg/L)＝Test concentration of the test substances (　　mg/L)×Content of organic carbon (　　%)

*6 Weight change shall be reported when DOC analysis is not appropriate.

Measurement solvent	Weight change				
	Weight (mg)			Weight change rate (%)	Average (%)
	Pre-test	Post-test	ΔW		
Tetrahydrofuran					
Dimethylformamide					

（6）Molecular weight and the concentration of components in molecules having molecular weight of 1,000 or less.

Molecular weight distribution	
Number average molecular weight (Mn)	
Weight average molecular weight (Mw)	
Z average molecular weight (Mz)	
Degree of dispersion (Mw/Mn)	
Concentration of components in molecules having molecular weight of 1,000 or less	
Eluant	
Method to convert the molecular weight	