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Guideline for Controllable Additives Used in Plastic Pharmaceutical Packaging Materials and Application

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CHINA NATIONAL PHARMACEUTICAL PACKAGING ASSOCIATION
中国医药包装协会

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Foreword

This standard is drafted in accordance with the rules listed in GB/T 1.1-2020 Directives for standardization- Part 1: Rules for the structure and drafting of standardizing documents.

Please be aware that some contents in this standard may be patentable. China National Pharmaceutical Packaging Association shall not be held responsibility for identifying patent rights.

This standard was proposed by and is under the jurisdiction of China National Pharmaceutical Packaging Association.

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Introduction

Plastic additives are chemical substances that are intentionally added to plastic materials to achieve a physical or chemical effect during processing of the plastic or in the final material or container. They may consist of a single chemical substance, a polymeric substance or a defined mixture of different.

The types and amounts of plastic additives directly affect the medicine's quality and the patient's safety. Annex 4 of the State Food and Drug Administration 〔2012〕 No. 267 Technical Guideline for Research on Compatibility of Chemical Injection and Plastic Packaging Materials(Trial) lists the commonly used additives in injection packaging for polyethylene and polypropylene plastics and the additives permitted content in plastics. China National Standard GB 9685-2016 National Food Safety Standard: Standard for the Use of Additives in Food Contact Materials and Articles and the related announcements list the allowable additives with their use requirements that can be used in food contact plastic materials and their products. At present, there is no complete list and use requirements of additives for plastic pharmaceutical packaging materials in China.

European Pharmacopoeia (EP) series general chapter 3.1 materials used for the manufacture of containers list 48 additives and their maximum permitted content used in 7 plastic materials, 27 of which are European Pharmacopoeia Plastic Additives as described in general chapter 3.1.13. EP General Chapters require that unless otherwise justified and authorized, additives are chosen from the list, and meet the limit requirement specified for each substance. United States Pharmacopoeia (USP) General Chapter <661.1> Plastic Additives for Plastic Component Materials lists 27 additives and their limit requirements for 9 plastic materials. These additives information are important references for appendix A and appendix C of this guideline.

This guideline introduces the commonly used additives for plastic pharmaceutical packaging materials, summarizes the additives and usage limitation for plastic pharmaceutical packaging materials recorded in domestic and foreign pharmacopoeias, and partially adopts food contact materials and product additives for oral preparations. The controllable additives listed in this guideline are intentionally added rather than introduced accidentally, and do not include their reaction or degradation products, or residues from the plastic polymerization process. The additive list in this guideline refers

to the list of controllable additives used in plastic pharmaceutical packaging materials listed in Appendix A. The additives listed in this guideline are consistent with the Center for Drug Evaluation, NMPA(CDE) guideline of "Technical Guideline for Research on Compatibility of Chemical Injection and Plastic Packaging Materials(Trial)", and a more complete additives list and use requirements for plastic pharmaceutical packaging materials is listed with the reference of domestic food standards and domestic and foreign pharmacopoeia standards. This guideline provides guidance for the application of additives for plastic pharmaceutical packaging materials.

Safety is the primary condition for selecting additives for plastic pharmaceutical packaging materials. The assessment is described in the further application explanation of additives for plastic pharmaceutical packaging materials in Chapter 6 of this guideline. This guideline is used to guide packaging material manufacturers to select the types and use contents of additives for plastic pharmaceutical packaging materials. The maximum permitted content is the maximum allowable use content, and the most stringent requirements are given by referring to major regulatory documents at home and abroad. If a compatibility study is required, the maximum permitted content cannot replace the compatibility study.

This guideline can not cover all additives used in plastic pharmaceutical packaging materials, and with the continuous development of science and technology, additives not included in the list may will be used, and the relevant content of this guideline will also be adjusted appropriately. This guideline doesn’t include the administrative matters of registration approval and is not enforceable as a regulation. This guideline shall be used in compliance with relevant regulations.

Guideline for Controllable Additives Used in Plastic Pharmaceutical Packaging Materials and Application

1. Scope

This guideline provides the content of classification of additives used in plastic pharmaceutical packaging materials, list and application of controllable additives used in plastic pharmaceutical packaging materials, further application explanation of additives used in plastic pharmaceutical packaging materials.

This guideline is applicable to plastic pharmaceutical packaging material manufacturers to select controllable additives for plastic pharmaceutical packaging materials and guides plastic pharmaceutical packaging material manufacturers on the usage of controllable additives. It is also a reference for pharmaceutical preparation companies.

2. Normative references

No normative references.

3. Terminology

The following terms and definitions are applicable to this document.

3.1 Plastic additives

Chemical substances that are intentionally added to plastic materials to achieve a physical or chemical effect during processing of the plastic or in the final material or container. They may consist of a single chemical substance, a polymeric substance or a defined mixture of different.

3.2 Maximum permitted content

The maximum permitted quantity of a certain additive or a certain class of additives added during the production of a plastic pharmaceutical packaging materials, expressed as a mass fraction (%).

4. Classification of additives used in plastic pharmaceutical packaging materials

Depending on the intended use of a material, they may contain additives to optimize their processing or their chemical, physical and mechanical properties. Substances present that have not been added intentionally are considered to be impurities and include reaction and degradation products, which may be limited by a suitable specification.

The plastic materials involved in this guideline include polyolefin [polyethylene (PE), polypropylene

(PP), etc.], cyclic olefins [cycloolefin copolymer (COC), cyclic olefin polymer (COP), etc.], polyvinyl chloride (PVC), poly (ethylene - vinyl acetate) (EVA), etc., and the composite materials formed by compounding of the materials.

Types of additives commonly used in plastic pharmaceutical packaging materials mainly include antioxidants, light stabilizers, heat stabilizers, plasticizers, antistatic agents, colorants, process aids and others (such as nucleating agents, impact modifiers) etc.

a) Antioxidants and light stabilizers: plastic aids that are added to plastic materials to effectively inhibit or reduce the thermal oxidation and light oxidation reaction rate of plastic macromolecules, significantly improve the heat resistance and light resistance of plastic materials, delay the degradation and aging process of plastic materials, and prolong the service life of plastic products.

b) Heat stabilizers: aids added to prevent plastics from degrading due to heat during high-temperature processing, which is mainly used in PVC.

c) Plasticizers: a class of fine chemical products that can increase the plasticity of a polymer system. It's the most important additive used during processing of polymer materials, especially of PVC plastics, to enhance the flexibility and facilitate processing.

d) Antistatic agents: chemicals that reduce the surface resistance of plastic objects and evacuate the surface charge of objects. With high surface resistivity and low permittivity, the plastic surface is inclined to have charge accumulated and therefore antistatic agents are needed to solve the problem caused by static electricity.

e) Colorants: additives that can change the color of plastics into various colors such as white, yellow, green, blue, red, black, etc. Colorants can be classified into two categories according to the different physical properties: pigments that are insoluble in the medium used and dyes that are soluble in the medium used.

f) Processing aids: usually refer to additives used to improve the processing performance of plastics. They mainly take effect when the polymer substrate is molten, including compounds that reduce the viscosity of the molten object without increasing the quantity of the plasticizer (viscosity inhibitors), compounds that offer additional stability by increasing the internal adhesion of the heterogeneous system or emulsion (emulsifiers/surfactants), or aids that offer

lubrication during processing(slip agents), etc.

5. List and application of controllable additives used in plastic pharmaceutical packaging materials

5.1 General rules

The list of additives in this guideline refers to the Technical Guideline for Research on Compatibility of Chemical Injection and Plastic Packaging Materials(Trial), relevant general rules of pharmacopoeias at home and abroad and relevant standards in domestic food field. Detailed information refers to normative Appendix A. The application of controllable additives used in plastic pharmaceutical packaging materials should comply with the content stipulated in 5.3.

5.2 List of controllable additives used in plastic pharmaceutical packaging materials

Appendix A includes CAS number (Chemical Abstracts Service), name and maximum permitted content of controllable additives used in plastic pharmaceutical packaging materials. Appendix A is sorted in order of the CAS number of the additives, and informative Appendix B also provides an index sorted by the Chinese name of the additives. Appendix C summarizes the information of applied plastic materials and examples of general application scenarios. The general application scenarios of additives are not all described in the referenced additive documents, see Appendix C.3 of this guideline for details.

Appendix A and C are summaries of priori knowledge, which provide reference for pharmaceutical packaging materials manufacturing enterprises to choose the types and use contents of additives. Choosing suitable additives for plastic pharmaceutical packaging materials and meeting the requirements of dosages provide a reasonable basis for selecting materials when designing packaging systems and minimize the risk of systematic inapplicability caused by material additives.

The additives summarized in Appendix A are widely used in industry. With the development of science and the application of new additives, the content of Appendix A can be adjusted appropriately.

5.3 Application of controllable additives used in plastic pharmaceutical packaging materials

5.3.1 general rules

The application of controllable additives listed in Appendix A should meet the content stipulated in 5.3.2 and 5.3.3.

5.3.2 Basic principles for the application of controllable additives used in plastic pharmaceutical packaging materials

Plastic pharmaceutical packaging materials contain additives to achieve certain processing, physical, chemical and mechanical effects. However, due to the particularity of drugs and the diversity of dosage forms and formulations, the use of additives of plastic pharmaceutical packaging materials should at least follow the following basic principles:

a) When plastic pharmaceutical packaging materials contact with drugs under the recommended conditions of use, the levels of additives and impurities migrated to drugs should not endanger human health.

b) The content of additives in plastic pharmaceutical packaging materials should be reduced as much as possible under the expected effect, while the stability and quality of the final materials and containers should be ensured.

c) Additives to be used should conform to the corresponding quality specifications, the acceptable criteria for identification, physical and chemical properties, impurities and assay should be specified.

d) When the substances listed in Appendix A are allowed to be used as additives for plastic pharmaceutical packaging materials, they should not produce technical functions for the drugs themselves.

5.3.3 Regulations on the application of controllable additives used in plastic pharmaceutical packaging materials

Regulations on the application of controllable additives used in plastic pharmaceutical packaging materials are as follows.

a) The use of controllable additives used in plastic pharmaceutical packaging materials should comply with the provisions of Appendix A, refer to the content of Appendix C. Appendix C provides more detailed information for Appendix A.

b) This guideline is a recommended standard, the additives listed in Appendix A should be preferred for plastic materials, and the corresponding use requirements should be met.

c) The limit in Appendix A refers to the maximum permitted content of one or a class of additives contained in plastic pharmaceutical packaging materials, which provides reference for the selection of additives. Each plastic resin may contain at most 3 antioxidants, and the total of antioxidant additives does not exceed 0.3%.

d) Using the additives in Appendix A and meeting the maximum permitted content requirements does not necessarily apply to all categories of drugs. It should be based on the risk level of the packaged drugs, and further evaluation of additives may be required according to the principles in Chapter 6. If a compatibility study is required, the maximum permitted content cannot replace the compatibility study.

5.4 Application of additives not listed in Appendix A

The application of additives not listed in Appendix A is as follows.

a) The additives listed in Appendix A are widely used in industry and are adopted in regulatory documents. With the development of science and the application of new additives, the content of Appendix A can be adjusted appropriately.

b) If plastic pharmaceutical packaging materials manufacturing enterprises use the additives not listed in Appendix A, they should provide a reasonable explanation or relevant research information.

6. Further application explanation of additives used in plastic pharmaceutical packaging materials

In addition to meeting the requirements of 5.3 of this guideline, the selection of additives for plastic packaging materials should also evaluate the safety risks, such as the type of additives, the maximum use content, etc.

Safety is the primary condition for selecting additives for plastic pharmaceutical packaging materials. The safety evaluation of additives for plastic pharmaceutical packaging materials refers to the following risk assessment model.

a) Collecting the relevant information, the additives information provided by suppliers or obtained experimentally about the additives contained in the material itself and/or added during the processing, is essential for the use of additives.

b) And then, it should be considered whether the additive is in the list and whether the amount meets the maximum permitted content.

c) Conducting the safety assessment based on the risk level of the packaged drugs.

1) For plastic pharmaceutical packaging additives used in non-high-risk preparations, such as oral preparations, it's suggested to refer to the requirements of relevant food packaging materials in various countries, such as the feasibility of reference of GB 9685 and related announcements, and the use standards for additives used in food in other countries.

2) For plastic pharmaceutical packaging additives for high-risk preparations, such as pharmaceutical packaging materials for inhalation preparations, injections, and ophthalmic preparations. It is not necessarily applicable to all categories of drugs that the additives in packaging materials are listed in Appendix A and meet the dosage requirements. The packaging materials may have been suffered different processing and sterilization treatment, so that an additive may undergo different chemical changes when applied to different products, such as oxidation and degradation. Extractable/leachable studies and corresponding toxicological risk assessments may be required.

Appendix A

(Normative)

Controllable Additives Used in Plastic Pharmaceutical Packaging Materials and Application Limitation Guideline

A.1 This appendix provides a tabular summary of the allowable additives for plastics listed in the CDE guidelines, the United States Pharmacopoeia and the European Pharmacopoeia. Additives should comply with all requirements in the columns of Table A.1.

A.2 The list of controllable additives for plastic pharmaceutical packaging materials sorted by CAS number and the application limitation guideline are shown in Table A.1. The additives in Table A.1 are sorted by CAS number. The additives which have no CAS number are listed at the end of Table A.1 and sorted by the characters, digits, English letters, and the first letter of the Chinese phonetic alphabet.

A.3 The names of additives in Table A.1 comply with the United States Pharmacopoeia and/or the European Pharmacopoeia. Some additives that may contain different designations, the CAS number shall prevail.

A.4 Some additives may have more than one CAS number due to isomers or different proportions of ingredients. Additives with multiple Chinese names are distinguished according to CAS number, which without CAS number are distinguished according to Chinese name.

A.5 Each resin may contain at most 3 antioxidants, and the total of antioxidant additives does not exceed 0.3 percent.

A.6 Except the controllable additives used in plastic pharmaceutical packaging materials listed in Table A.1, for oral solid and liquid preparation, the plastic pharmaceutical additives approved by regulations in the food industry can be appropriately cited, such as the requirements of Table A.1 of Appendix A of GB 9685-2016.

Table A.1 Controllable Additives Used in Plastic Pharmaceutical Packaging Materials and Application Limitation Guideline Sorted by CAS Number

Additives NO.	CAS No.	Name	Maximum Permitted Content
1	[50-70-4]	Sorbitol	Not more than 1.5%
2	[57-11-4]	Stearic Acid	Not more than 0.5%
3	[112-84-5]	Erucamide	Not more than 0.5%, not more than 0.2% for EVA
4	[117-81-7]	Di(2-ethylhexyl) phthalate	Not more than 40%
5	[123-28-4]	Didodecyl 3,3′-thiodipropionate	Not more than 0.3%
6	[128-37-0]	2,6-di-tert-butyl-4-methylphenol	Not more than 0.125%
7	[136-53-8]	Zinc Octanoate	Not more than 1%
8	[301-02-0]	Oleamide	Not more than 0.5%, not more than 0.2% for EVA
9	[471-34-1] or [1310-58-3]	Calcium Carbonate or Potassium Hydroxide	Not more than 0.5%, calcium carbonate is not more than 1% when used in non-plasticised PVC
10	[532-32-1]	Sodium Benzoate	Not more than 0.5%

Additives NO.	CAS No.	Name	Maximum Permitted Content
11	[693-36-7]	Dioctadecyl 3,3′-thiodipropionate	Not more than 0.3%
12	[1309-48-4]	Magnesium Oxide	Not more than 0.2%
13	[1314-13-2]	Zinc Oxide	Not more than 0.5%
14	[1344-00-9]	Sodium Silico-Aluminate	Not more than 0.5%
15	[1592-23-0]or [557-05-1]	Calcium Stearate or Zinc Stearate or a mixture of both	Not more than 0.5%, not more than 1%for plasticised PVC
16	[1709-70-2]	1,3,5-trimethyl-2,4,6-tris(3,5-di-tert-butyl-4-hydroxybenzyl)benzene	Not more than 0.3%, Not more than 0.2% for EVA
17	[2082-79-3]	Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate	Not more than 0.3%, not more than 0.2% for EVA
18	[2500-88-1]	Dioctadecyl Disulfide	Not more than 0.3%
19	[3319-31-1]	Tris(2-ethylhexyl) trimellitate	Not more than 45%
20	[3806-34-6]	2,2′-bis(octadecyloxy)-5,5′-spirobi[1,3,2- dioxaphosphinane]	Not more than 0.3%
21	[5518-18-3]/ [110-30-5]	N,N′-diacylethylenediamines(acyl means in particular palmitoyl and stearoyl)	Not more than 0.5%
22	[6422-86-2]	Bis(2-ethylhexyl) terephthalate	Not more than 45%
23	[6683-19-8]	Pentaerythrityl tetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate]	Not more than 0.3%, not more than 0.2% for EVA
24	[7601-54-9]	Trisodium Phosphate	Not more than 0.5%
25	[7631-86-9]	Silica	Not more than 0.5%
26	[8013-07-8]	Epoxidised Soya Oil	Not more than 10% or the total amount of both should be no more than 10%
27	[8016-11-3]	Epoxidised Linseed Oil	
28	[8020-83-5]	Liquid Paraffin	Not more than 0.5%
29	[12304-65-3]	Hydrotalcite	Not more than 0.5%
30	[13463-67-7]	Titanium Dioxide	Not more than 4%
31	[14807-96-6]	Talc	Not more than 0.5%
32	I [26401-97-8] II [26401-86-5]	I: di(isooctyl) 2,2'–[(dioctylstannylene)bis(thio)] diacetate II: tri(isooctyl) 2,2',2''-[(monooctylstannylidyne)tris(thio)] triacetate	The tin content should be not more than 0.25%
33	[27676-62-6]	1, 3, 5-tris-(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2, 4, 6-(1H, 3H, 5H)-trione	Not more than 0.3%

Additives NO.	CAS No.	Name	Maximum Permitted Content
34	[31570-04-4]	Tris (2, 4-di-tert-butylphenyl) phosphite	Not more than 0.3%, no more than 0.2% for EVA
35	[32509-66-3]	ethylene bis [3, 3-bis [3-(1, 1-dimethylethyl)-4-hydroxyphenyl] butanoate]	Not more than 0.3%
36	[57455-37-5] (TSCA)/ [101357-30-6] (EINECS)/Pigment blue 29 (CI 77007)	Ultramarine Blue	When using colorants, ultramarine blue should be used, or other suitable coloring materials.
37	[58446-52-9] or [52047-59-3] or [36265-41-5]	1-phenyleicosane-1, 3-dione(benzoylstearoylmethane) or 2-(4-dodecylphenyl) indole or didodecyl1, 4-dihydropyridine-2, 6-dimethyl-3, 5-dicarboxylate	Not more than 1% or the total amount of both should be no more than 1%. When used in oral solid formulations, benzoyl stearyl methane should be no more than 1%.
38	[64033-89-2] or [763042-48-4] or [26523-78-4]	2, 4-dinonylphenyl phosphite or di(4-nonylphenyl) phosphite or tris(nonylphenyl) phosphite	Not more than 1%
39	[65447-77-0]	Copolymer of dimethyl succinate and (4-hydroxy-2, 2, 6, 6-tetramethylpiperidin-1-yl) ethanol	Not more than 0.3%
40	[82469-79-2]	Butyryl tri-n-hexyl citrate	Not more than 45%
41	[119345-01-6]	Mixture of 7 products corresponding to reaction product of di-*tert*-butyl phosphonite with phosphorous trichloride, reaction products with 1,1' -biphenyl and 2, 4-di-tert-butylphnol	Not more than 0.1%
42	[166412-78-8]	Cyclohexane 1, 2-dicarboxylic acid, diisononyl ester	Not more than 45%
43	/	Calcium, Magnesium or Zinc salts of Aliphatic Fatty Acids with more than 7 carbon atoms	Not more than 1.5% or total amount no more than 1.5%
44	/	Colloidal Silica	Not more than 0.2%
45	/	Macrogol Ester	Not more than 1.5%
46	/	Waxes	Not more than 4%, no more than 1.5% for non-injection aqueous solutions
47	/	Fatty Acid Esters or Salts	Not more than 0.5%
48	/	Hydrogenated Oils or Esters of	Not more than 2%

Additives NO.	CAS No.	Name	Maximum Permitted Content
		Aliphatic Fatty Acids	

Appendix B

(informative)

Controllable Additives Used in Plastic Pharmaceutical Packaging Materials Index Directory

Table B.1 sorts the additives according to the characters, digits, English letters, and the first letter of the Chinese phonetic alphabet, lists the Chinese name, CAS number and additive number of the additives in Table A.1.

Table B.1 Controllable Additives Used in Plastic Pharmaceutical Packaging Materials Index Directory Sorted by Chinese Name

Name	CAS No.	Additive No（refer to Table A）
1,3,5-tris-(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2,4,6-(1H,3H,5H)-trione	[27676-62-6]	33
1,3,5-Trimethyl-2,4,6-tris(3,5-di-tert-butyl-4-hydroxybenzyl)benzene	[1709-70-2]	16
1-phenyleicosane-1,3-dione (benzoylstearoylmethane) or 2-(4-dodecylphenyl)indole or didodecyl 1,4-dihydropyridine-2,6-dimethyl-3,5-dicarboxylate	[58446-52-9] or [52047-59-3] or [36265-41-5]	37
2,2′-bis(octadecyloxy)-5,5′-spirobi[1,3,2- dioxaphosphinane]	[3806-34-6]	20
2,4-dinonylphenyl phosphite, or di(4-nonylphenyl) phosphite or tris(nonylphenyl) phosphite	[64033-89-2] or [763042-48-4] or [26523-78-4]	38
2,6-di-tert-butyl-4-methylphenol	[128-37-0]	6
Zinc Octanoate	[136-53-8]	7
octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate	[2082-79-3]	17
dioctadecyl 3,3′-thiodipropionate	[693-36-7]	11
didodecyl 3,3′-thiodipropionate	[123-28-4]	5
I: di(isooctyl) 2,2′-[(dioctylstannylene)bis(thio)]diacetate II: tri(isooctyl) 2,2′,2″-[(monooctylstannylidyne)tris(thio)]triacetate	I [26401-97-8] II [26401-86-5]	32
N,N′-diacylethylenediamines (acyl means in particular palmitoyl and stearoyl)	[5518-18-3]/ [110-30-5]	21
Sodium Benzoate	[532-32-1]	10
Copolymer of dimethyl succinate and (4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethanol	[65447-77-0]	39
Butyryl Tri-n-hexyl Citrate	[82469-79-2]	40
bis(2-ethylhexyl) terephthalate	[6422-86-2]	22
ethylene bis[3,3-bis[3-(1,1- dimethylethyl)-4-hydroxyphenyl]butanoate]	[32509-66-3]	35

Name	CAS No.	Additive No（refer to Table A）
Silica	[7631-86-9]	25
Titanium Dioxide	[13463-67-7]	30
Dioctadency Disulfide	[2500-88-1]	18
Sodium Silico-Aluminate	[1344-00-9]	14
Calcium, Magnesium or Zinc salts of Aliphatic Fatty Acids with more than 7 carbon atoms	/	43
mixture of 7 products corresponding to reaction product of di-*tert*-butyl phosphonite with phosphorous trichloride, reaction products with 1,1'-biphenyl and 2,4-di-tert-butylphnol	[119345-01-6]	41
Talc	[14807-96-6]	31
cyclohexane 1,2-dicarboxylic acid, diisononyl ester	[166412-78-8]	42
Epoxidised Soya Oil	[8013-07-8]	26
Epoxidised Linseed Oil	[8016-11-3]	27
Hydrotalcite	[12304-65-3]	29
Colloidal Silica	/	44
Erucamide	[112-84-5]	3
Macrogol Esters	/	45
di(2-ethylhexyl) phthalate	[117-81-7]	4
Trisodium Phosphate	[7601-54-9]	24
tris(2-ethylhexyl) trimellitate	[3319-31-1]	19
Ultramarine Blue	[57455-37-5](TSCA)/[101357-30-6] (EINECS)/Pigment blue 29 (CI 77007)	36
tris(2,4-di-tert-butylphenyl)phosphite	[31570-04-4]	34
Sorbitol	[50-70-4]	1
Waxes	/	46
pentaerythrityl tetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate]	[6683-19-8]	23
Calcium Carbonate or Potassium Hydroxide	[471-34-1] or [1310-58-3]	9
Magnesium Oxide	[1309-48-4]	12
Zinc Oxide	[1314-13-2]	13
Liquid Paraffin	[8020-83-5]	28
Stearic Acid	[57-11-4]	2

Name	CAS No.	Additive No（refer to Table A）
Calcium Stearate or Zinc Stearate or a mixture of both	[1592-23-0] or [557-05-1]	15
Oleamide	[301-02-0]	8
Fatty Acid Esters or Salts	/	47
Hydrogenated Oils or Esters of Aliphatic Fatty Acids	/	48

Appendix C

(informative)

Controllable Additives Used in Plastic Pharmaceutical Packaging Materials Source Index

C.1 Additives No., CAS No., and name of Table C.1 is consistent with Table A.1

C.2 The types of plastic resins to which additives can be applied were listed in the column *Types of Plastics* (①CDE Guidelines, ②USP, ③EP) and denoted by resin abbreviations. The resin abbreviation marks①②③ respectively represent the resins listed by ①*Technical Guideline for Research on Compatibility of Chemical Injection and Plastic Packaging Materials(Trial)*(NMPA-I-[2012] No. 267), ②USP general rules <661.1> and ③EP material related general rules.

C.3 The chapter number and specified application scenarios of additives in USP and EP were listed in the column of indexes in Table C.1. USP: 661.1(Unrestricted) refers to the application scenarios of plastic additives are not restricted by USP general chapter of 661.1, EP: 3.1.13 (Unrestricted Plastic additives) refers to the plastic materials and application scenarios are not restricted by EP general chapter of 3.1.13, 3.1.3 (unrestricted polyolefin) refers to the application scenarios in polyolefin are not restricted by EP general chapter of 3.1.3, and other application scenarios are described in Table C. The plastic additives included in CDE guideline (NMPA-I-〔2012〕No. 267 Technical Guideline for Research on Compatibility of Chemical Injection and Plastic Packaging Materials(Trial)()are applicable to polyethylene and polypropylene plastics, so it's not listed in the table duplicately.

C.4 The relevant USP and EP general chapter name listed in indexes of Table C as follows,

a) USP 661.1 Plastic Materials of Construction
b) EP 3.1.3 Polyolefin
c) EP 3.1.5 Polyethylene with Additives for Containers for Parenteral Preparations and for Ophthalmic Preparations
d) EP 3.1.6 Polypropylene for Containers and Closures for Parenteral Preparations and Ophthalmic Preparations
e) EP 3.1.7 Poly(ethylene - vinyl acetate) for containers and tubing for total parenteral nutrition preparations
f) EP 3.1.10 Materials Based on Non-plasticised Poly(vinyl chloride) for Containers for Non-injectable Aqueous Solutions
g) EP 3.1.11. Materials Based on Non-plasticised Poly(vinyl chloride) for Containers for Solid Dosage Forms for Oral Administration
h) EP 3.1.13 Plastic Additives
i) EP 3.1.14 Materials Based on Plasticised Poly(vinyl chloride) for Containers for Aqueous Solutions for Intravenous Infusion

Table C.1 Controllable Additives Used in Plastic Pharmaceutical Packaging Materials Source Index

Additives NO.	CAS No.	Name	Types of Plastics (CDE guidelines, USP, EP)	Indexes
1	[50-70-4]	Sorbitol	Non-plasticised PVC②③	USP: 661.1 (Unrestricted), EP: 3.1.10 (Materials based on non-plasticised poly(vinyl chloride) for containers for non-injectable, aqueous solutions) 3.1.11 (Materials based on non-plasticised poly(vinyl chloride) for containers for solid dosage forms for oral administration)
2	[57-11-4]	Stearic Acid	PE①③, PP①③, COC②, Polyolefin ③, EVA③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations) 3.1.7 (Poly(ethylene-vinyl acetate) for containers and tubing for total parenteral nutrition preparations)
3	[112-84-5]	Erucamide	PE①②③, PP①②③, EVA②③, COC②, Polyolefin③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations) 3.1.7 (Poly(ethylene-vinyl acetate) for containers and tubing for total parenteral nutrition preparations)
4	[117-81-7]	Di(2-ethylhexyl) phthalate	Plasticised PVC②③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.14 (Materials based on plasticised

Additives NO.	CAS No.	Name	Types of Plastics (CDE guidelines, USP, EP)	Indexes
				poly(vinyl chloride) for containers for aqueous solutions for intravenous infusion)
5	[123-28-4]	Didodecyl 3,3′-thiodipropionate	PP①②③, PE①③, COC②, Polyolefin③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
6	[128-37-0]	2,6-di-tert-butyl-4-methylphenol	PE①②③, PP①②③, EVA②③, COC②, Polyolefin③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations) 3.1.7 (Poly(ethylene-vinyl acetate) for containers and tubing for total parenteral nutrition preparations)
7	[136-53-8]	Zinc Octanoate	Plasticised PVC③	EP: 3.1.13 (Plastic additives are not restricted) 3.1.14 (Materials based on plasticised poly(vinyl chloride) for containers for aqueous solutions for intravenous infusion)
8	[301-02-0]	Oleamide	PE①②③, PP①②③, EVA②③, COC②, Polyolefin③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations

Additives NO.	CAS No.	Name	Types of Plastics (CDE guidelines, USP, EP)	Indexes
				and ophthalmic preparations) 3.1.7 (Poly(ethylene-vinyl acetate) for containers and tubing for total parenteral nutrition preparations)
9	[471-34-1] or [1310-58-3]	Calcium Carbonate or Potassium Hydroxide	Non-plasticised PVC②③, EVA③	USP: 661.1 (Unrestricted) EP: 3.1.7 (Poly(ethylene-vinyl acetate) for containers and tubing for total parenteral nutrition preparations) 3.1.11 (Materials based on non-plasticised poly(vinyl chloride) for containers for solid dosage forms for oral administration)
10	[532-32-1]	Sodium Benzoate	PE①③, PP①③ , Polyolefin③	EP: 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
11	[693-36-7]	Dioctadecyl 3,3′-thiodipropionate	PP①②③, PE①③, COC②, Polyolefin③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
12	[1309-48-4]	Magnesium Oxide	PE①③, PP①③ , Polyolefin③	EP:3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
13	[1314-13-2]	Zinc Oxide	PE①③, PP①③ , Polyolefin③	EP:3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations)

Additives NO.	CAS No.	Name	Types of Plastics (CDE guidelines, USP, EP)	Indexes
				3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
14	[1344-00-9]	Sodium Silico-Aluminate	PE①③, PP①③, Polyolefin③	EP:3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
15	[1592-23-0]或 [557-05-1]	Calcium Stearate or Zinc Stearate or a mixture of both	Polyolefin③, PE③, PP③, EVA③, Plasticised PVC③	EP:3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations) 3.1.7 (Poly(ethylene-vinyl acetate) for containers and tubing for total parenteral nutrition preparations) 3.1.14 (Materials based on plasticised poly(vinyl chloride) for containers for aqueous solutions for intravenous infusion)
16	[1709-70-2]	1,3,5-trimethyl-2,4,6-tris(3,5-di-tert-butyl-4-hydroxybenzyl)benzene	PE①②③, PP①②③, EVA②③, COC②, Polyolefin③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations) 3.1.7 (Poly(ethylene-vinyl acetate) for containers and tubing for total parenteral nutrition preparations)
17	[2082-79-3]	Octadecyl 3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate	PE①②③, PP①②③, EVA②③, COC②, Polyolefin③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted)

Additives NO.	CAS No.	Name	Types of Plastics (CDE guidelines, USP, EP)	Indexes
				3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations) 3.1.7 (Poly(ethylene-vinyl acetate) for containers and tubing for total parenteral nutrition preparations)
18	[2500-88-1]	Dioctadecyl Disulfide	PP①②③, PE①③, COC②, Polyolefin③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
19	[3319-31-1]	Tris(2-ethylhexyl) trimellitate	Plasticised PVC（for human blood or blood components）③	EP: 3.1.13 (Plastic additives are not restricted)
20	[3806-34-6]	2,2′-bis(octadecyloxy)-5,5′-spirobi[1,3,2-dioxaphosphinane]	PE①③, PP①③, Polyolefin③	EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
21	[5518-18-3]/ [110-30-5]	N,N′-diacylethylenediamines(acyl means in particular palmitoyl and stearoyl)	PE①, PP①, Plasticised PVC②③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.14 (Materials based on plasticised poly(vinyl chloride) for containers for aqueous solutions for intravenous infusion)
22	[6422-86-2]	Bis(2-ethylhexyl) terephthalate	Plasticised PVC（for human	EP: 3.1.13 (Plastic additives are not restricted)

Additives NO.	CAS No.	Name	Types of Plastics (CDE guidelines, USP, EP)	Indexes
			blood or blood components）③	
23	[6683-19-8]	Pentaerythrityl tetrakis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate]	PE①②③, PP①②③, EVA②③, COC②, Polyolefin③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations) 3.1.7 (Poly(ethylene-vinyl acetate) for containers and tubing for total parenteral nutrition preparations)
24	[7601-54-9]	Trisodium Phosphate	PE①③, PP①③, Polyolefin③	EP: 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
25	[7631-86-9]	Silica	PE①③, PP①③ Non-plasticised PVC②③, Polyolefin③	USP: 661.1 (Unrestricted) EP: 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations) 3.1.11 (Materials based on non-plasticised poly(vinyl chloride) for containers for solid dosage forms for oral administration)
26	[8013-07-8]	Epoxidised Soya Oil	Plasticized PVC②③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.14 (Materials based on plasticised poly (vinyl chloride) for containers for aqueous
27	[8016-11-3]	Epoxidised Linseed Oil		

Additives NO.	CAS No.	Name	Types of Plastics (CDE guidelines, USP, EP)	Indexes
				solutions for intravenous infusion)
28	[8020-83-5]	Liquid Paraffin	PE[①③], PP[①③], Non-Plasticized PVC[②③], Polyolefin[③]	USP: 661.1 (Unrestricted) EP: 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations) 3.1.10 (Materials based on non-plasticised poly (vinyl chloride) for containers for non-injectable, aqueous solutions) 3.1.11 (Materials based on non-plasticised poly(vinyl chloride) for containers for solid dosage forms for oral administration)
29	[12304-65-3]	Hydrotalcite	PE[①③], PP[①③], Polyolefin[③]	EP: 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
30	[13463-67-7]	Titanium Dioxide	Polyolefin[③], PE[①③], PP[①③]	EP: 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
31	[14807-96-6]	Talc	PP[①③], PE[①], Polyolefin[③]	EP: 3.1.3 (Polyolefins are not restricted) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
32	I [26401-97-8] II [26401-86-5]	I: di(isooctyl) 2,2'–[(dioctylstannylene)bis(thio)] diacetate II: tri(isooctyl) 2,2',2''-[(monooctylstannylidyne)tris(thio)] triacetate	Non-Plasticized PVC[②③]	USP: 661.1 (unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.10 (Materials based on non-plasticised poly (vinyl chloride) for containers for non-injectable, aqueous solutions) 3.1.11 (Materials based on non-plasticised

Additives NO.	CAS No.	Name	Types of Plastics (CDE guidelines, USP, EP)	Indexes
				poly(vinyl chloride) for containers for solid dosage forms for oral administration)
33	[27676-62-6]	1, 3, 5-tris-(3,5-di-tert-butyl-4-hydroxybenzyl)-s-triazine-2, 4, 6-(1H, 3H, 5H)-trione	PP①②③, PE①③, COC②, Polyolefin③	USP: 661.1 (unrestricted) EP: 3.1.13 (Unrestricted plastic additives) 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
34	[31570-04-4]	Tris (2, 4-di-tert-butylphenyl) phosphite	PE①②③, PP①②③, EVA②③, COC②, Polyolefin③	USP: 661.1 (unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations) 3.1.7 (Poly (ethylene - vinyl acetate) for containers and tubing for total parenteral nutrition preparations)
35	[32509-66-3]	ethylene bis [3, 3-bis [3-(1, 1-dimethylethyl)-4-hydroxyphenyl] butanoate]	PE①②③, PP①②③, COC②, Polyolefin③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
36	[57455-37-5] (TSCA)/ [101357-30-6] (EINECS)/P	Ultramarine Blue	Plasticized PVC③	EP: 3.1.13 (Plastic additives are not restricted) 3.1.14 (Materials based on plasticised poly (vinyl chloride) for containers for aqueous solutions for intravenous infusion)

Additives NO.	CAS No.	Name	Types of Plastics (CDE guidelines, USP, EP)	Indexes
	igment blue 29 (CI 77007)			
37	[58446-52-9] or [52047-59-3] or [36265-41-5]	1-phenyleicosane-1, 3-dione(benzoylstearoylmethane) or 2-(4-dodecylphenyl) indole or didodecyl1, 4-dihydropyridine-2, 6-dimethyl-3, 5-dicarboxylate	Non-Plasticized PVC②③	USP: 661.1 (Unrestricted), EP: 3.1.10 (Materials based on non-plasticised poly (vinyl chloride) for containers for non-injectable, aqueous solutions) 3.1.11 (Materials based on non-plasticised poly(vinyl chloride) for containers for solid dosage forms for oral administration)
38	[64033-89-2] or [763042-48-4] or [26523-78-4]	2, 4-dinonylphenyl phosphite or di(4-nonylphenyl) phosphite or tris(nonylphenyl) phosphite	Non-Plasticized PVC②③	USP: 661.1 (Unrestricted) EP: 3.1.10 (Materials based on non-plasticised poly (vinyl chloride) for containers for non-injectable, aqueous solutions) 3.1.11 (Materials based on non-plasticised poly(vinyl chloride) for containers for solid dosage forms for oral administration)
39	[65447-77-0]	Copolymer of dimethyl succinate and (4-hydroxy-2, 2, 6, 6-tetramethylpiperidin-1-yl) ethanol	PE①, PP①, COC②, Polyolefin③	USP: 661.1 (Unrestricted) EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted)
40	[82469-79-2]	Butyryl tri-n-hexyl citrate	Plasticized PVC (for human blood or blood components)③	EP: 3.1.13 (Plastic additives are not restricted)
41	[119345-01-6]	Mixture of 7 products corresponding to reaction product of di-*tert*-butyl phosphonite with phosphorous trichloride, reaction products with 1,1' -biphenyl and 2, 4-di-tert-butylphnol	PE①, PP①, Polyolefin③	EP: 3.1.13 (Plastic additives are not restricted) 3.1.3 (Polyolefins are not restricted)
42	[166412-78-	Cyclohexane 1, 2-	Plasticized PVC	EP: 3.1.13 (Plastic additives are not

Additives NO.	CAS No.	Name	Types of Plastics (CDE guidelines, USP, EP)	Indexes
	8]	dicarboxylic acid, diisononyl ester	(for human blood or blood components)③	restricted)
43	/	Calcium, Magnesium or Zinc salts of Aliphatic Fatty Acids with more than 7 carbon atoms	Non-Plasticized PVC②③	USP: 661.1 (Unrestricted), EP: 3.1.10 (Materials based on non-plasticised poly (vinyl chloride) for containers for non-injectable, aqueous solutions) 3.1.11 (Materials based on non-plasticised poly(vinyl chloride) for containers for solid dosage forms for oral administration)
44	/	Colloidal Silica	EVA③	EP: 3.1.7 Poly (ethylene - vinyl acetate) for containers and tubing for total parenteral nutrition preparations
45	/	Macrogol Ester	Non-Plasticized PVC②③	USP: 661.1 (Unrestricted) EP: 3.1.10 (Materials based on non-plasticised poly (vinyl chloride) for containers for non-injectable, aqueous solutions) 3.1.11 (Materials based on non-plasticised poly(vinyl chloride) for containers for solid dosage forms for oral administration)
46	/	Waxes	Non-Plasticized PVC②③	USP: 661.1 (Unrestricted) EP: 3.1.10 (Materials based on non-plasticised poly (vinyl chloride) for containers for non-injectable, aqueous solutions) 3.1.11 (Materials based on non-plasticised poly(vinyl chloride) for containers for solid dosage forms for oral administration)
47	/	Fatty Acid Esters or Salts	PP①③, PE①③, Polyolefin③	EP: 3.1.3 (Plastic additives are not restricted) 3.1.5 (Polyethylene with additives for containers for parenteral preparations and for ophthalmic preparations) 3.1.6 (Polypropylene for containers and closures for parenteral preparations and ophthalmic preparations)
48	/	Hydrogenated Oils or Esters of Aliphatic Fatty Acids	Non-Plasticized PVC②③	USP: 661.1 (Unrestricted) EP: 3.1.10 (Materials based on non-plasticised poly (vinyl chloride) for containers for non-injectable, aqueous

Additives NO.	CAS No.	Name	Types of Plastics (CDE guidelines, USP, EP)	Indexes
				solutions) 3.1.11 (Materials based on non-plasticised poly(vinyl chloride) for containers for solid dosage forms for oral administration)

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