Guidance for Extractable Study on Packaging System of Inhalation Aerosols (Draft for Comments)

Introduction

An inhalation drug combines the characteristics of inhaled formulations and aerosols, while interaction between the drug formulation and packaging system bears the highest level of risk. Inhaled aerosol drug formulations are mainly based on organic media phase, and the packaging system has a complicated structure, involving plastics, rubber, metal and other materials. These factors determine that inhalation aerosol packaging system and drug compatibility study is always the focus and challenge of study of pharmaceutical industry domestically and internationally.

A drug and packaging material compatibility study mainly includes three aspects: extraction study, interaction study (including migration tests and adsorption tests) and safety studies. Extraction studies of packaging material of inhaled aerosols can not be used to screen analytical methods for leachable study, to create potential extraction profile in extreme cases, lay the essential foundation for leachable study and subsequent risk assessment, but also to characterize construction material of key components of packaging systems , to support routine quality monitoring of extractable, and potential studies on changes in the packaging system.

The extraction of key components of inhaled aerosols primarily takes into account the extraction studies of components that are in long term contact with the drug. In the process of extraction, the components are classified and separately extracted in order to facilitate explain the source of the extractable according to different material or component. Meanwhile, with subsequent risk assessment, especially the toxicological risk assessments indicating high risk from potential leachable, these information helps to identify and consider components to be replaced. Based on extraction study of key components, further extraction studies of the inhalation aerosol packaging system may be optionally conducted. However, such

studies are generally used for further verification and validation, rather than regulatory requirements.

To the date, there is no technical guidance for the study of packaging system and drug compatibility for inhaled aerosols in China.

The overall approach and strategy on the compatibility study of inhaled aerosols can be referred to the relevant domestic and foreign technical guidelines and regulations, such as "Technical Guideline for Compatibility Study of Chemical Injection and Plastic Packaging Materials ", "Technical Guideline for Compatibility Study of Chemical Drugs and Elastomers and Closures", "Technical Guideline for Compatibility Study of Chemical Injection and Glass Packaging Materials", USP<1663> ASSESSMENT
OF EXTRACTABLES ASSOCIATED WITH PHARMACEUTICAL PACKAGINGDELIVERY
SYSTEMS, "Compatibility of Drug and Packaging Materials", "Handbook of Leachable and Extractable", etc.

This guideline is formulated based on existing packaging materials, production techniques and analytical techniques in the domestic market. With new material development and application of new technologies and the advancement of modern analytical techniques, users may consider the real situation and conduct study with other effective compatibility study approaches. Inhalation Aerosol

Guideline of Extraction Study for Packaging System of Inhaled Aerosols

1. Scope

This standard applies to the extraction of packaging systems for inhaled aerosols, including packaging components and packaging materials.

This standard provides information on terms and definitions related to the extraction of inhalation aerosol packaging systems, general principles, information collection of extraction studies, selection and determination of extraction parameters, preparation of extraction media for analysis, characterization of extracts and a list of commonly used additives for components of packaging system for inhalation aerosols.

2. Terms and Definitions

2.1 Metered Dose Inhalation (MDIs): "A formulation of APIs solution or suspension contained in propellant or mixed propellants and other excipients, forming aerosol by pressure for delivery. "

2.2 Packaging system: also known as container closure system, refers to the totality of packaging components and packaging materials that contain and protect drugs. It includes primary packaging components (direct contact) and secondary packaging components as additional protection for the drug.

2.3 Packaging component: Refers to any component of the container closure system. Packaging components are divided into packaging component in direct contact with the drug and the secondary packaging component. Secondary packaging component refers to the packaging components that are not in direct contact with the drug.

2.4 Extractable: substances obtained from a packaging material obtained by an extraction study.

2.5 Leachable: substance migrating from packaging system or derived from the process through migration study
2.6 Extreme extraction: the amount of extract in the extraction media is less than 10% of the first extraction media, or when the cumulative extract quantification does not have significant further increase.
2.7 Permitted daily exposure (PDE): refers to the daily average maximum dose that is allowed to ingest without causing toxicity. PDE value of a specific substance is derived from response-free level, body weight adjustment coefficient, species difference coefficient, individual difference, and coefficient of variance of short-term exposure acute toxicity study.
2.8 Safety Concern Threshold (SCT): When the level of leachable is lower than this, carcinogenic and non-carcinogenic toxic effects and safety effects are negligible.
2.9 Analytical Evaluation Threshold (AET): According to the maximal individual daily exposure or safety threshold/limit, dosage and packaging characteristics of the drug product, limits for certain extractable and/or leachable in a single packaging container are derived. When the level of a certain extractable/leachable reaches or exceeds this amount, it is necessary to start the analysis of this extractable/leachable, and report to the relevant departments for safety assessment.

3. General Principle

3.1 Packaging system extraction study is a part of the compatibility study of inhaled aerosol drugs with its packaging system.
The guideline provides guidance for the extraction study of packaging systems for inhaled aerosols. Study conclusions obtained with reference to this guideline can be used to establish potential leachable profile in extreme cases, laying the essential foundation for leachable study and subsequent risk assessment.

3.2 Packaging system for inhalation aerosol generally includes components such as pressure vessel cans, metered valves, and actuators. The main components of metered valves include valve rod, valve body, metering chamber, sealing gasket, metal spring and metal cap, etc. Some metering valve is also equipped with a fluid collecting ring. Pressure canisters are mainly classified into metal cans and glass cans according to the construction materials. The most commonly used metal canister is aluminum alloy canister, which may be further divided into two types: coated and uncoated with different strategy of extraction study. The valve rod, valve body, metering chamber and collecting ring are generally made of plastic materials, sealing gasket rubber, and spring and cover metal (rod and body of certain valves are also made of metal).

3.3 In inhalation aerosol packaging system, components with long-term contact with drugs mainly include pressure can, rod of metering valve, valve bodies, metering chambers, fluid collecting rings, gaskets and metal springs, which are subject to extraction study as key components. Actuators have extremely short contact with the drug only when the patient is using it. It may not be included in extraction study unless specifically indicated.

3.4 An extraction study for the packaging system of inhalation aerosol generally include: principle of extraction, preparation of extraction media for analysis and characterization of extracts.

3.5 The extraction principle of key components is established based on the consideration of packaging system and its key components, inhalation aerosol drug information and selection of extraction parameters (including extraction media, extraction technique, component-media ratio and extraction time etc.).

Study on selected extraction parameters should be studied and justified.

4. Information Collection and Selection and Determination of Extraction Parameters for Extraction Studies

4.1 Information collection for extraction studies

The source of extractable generally includes additives for materials used in the construction material of components and impurities or degradation products thereof, monomers and oligomers of polymer materials, processing aids, and in some cases from the migrates of secondary or tertiary packaging materials (such as inks, label adhesives, volatile components, etc.). Due to the containers of inhalation aerosol packaging system are usually metal cans or glass cans, the risk of migration from secondary or tertiary packaging is mild.

The basic information for the extraction study of inhalation aerosol and packaging systems is divided into two categories, including: (1) names materials of critical components of extraction study, composition or code (stainless steel, aluminum), additive information, processing aid, information on cleaned/not cleaned and cleaning agents, coating materials (if any) and coating process information; (2)drug formulation, key processes (including the assembly process of aerosol packaging system after filling), strength, maximal daily dosage, frequency of dosing, and duration of treatment. These information is used to select and justify extraction parameters, calculation and evaluation of Analytical Evaluation Threshold (AET), explanation of source of extractable after identification, preliminary toxicology risk analysis and determination of potential leachables with risk.

4.2 Selection and determination of extraction parameters

The main extraction parameters to be considered in the extraction experiment include extraction media, extraction method, extraction ratio and extraction time.

4.2.1 Extraction media is the most important parameter considered in the extraction experiment. Extraction study can be applied for a purpose. As extraction study stated by this guideline is primarily used for drug and packaging system compatibility assessments, so the selection of media should fully consider the characteristics of the drug, e.g. the polarity of the media should be chosen similar to the drug product or slightly higher to obtain as much qualitative and quantitative information as possible on the leachable profile. Media should be justified and selected based on material function and composition, together with information on drug formulation ingredients. For packaging components of inhalation aerosol, generally it is needed to discuss and select a variety of medias for simulation extraction, e.g., dichloromethane representing class of hydrofluoroalkane propellants in the formulation of inhaled aerosols (such as tetrafluoroethane, heptafluoropropane, etc.) , isopropanol simulating ethanol in the formulation, or directly with ethanol; in some cases, hexane simulating non-polar ingredients in the formulation.

4.2.2 Regular extraction techniques include reflux extraction, Soxhlet extraction, ultrasonic extraction, and accelerated extraction with sample enclosed in containers. Each extraction technique has its own advantages and disadvantages. For example, reflux extraction has higher extraction efficiency, but since the extraction temperature depends on the boiling point of the extraction media, it may cause heat degradation in some medias with high boiling temperature; similarly, heat generated during ultrasonic extraction is likely to cause similar problems, and therefore, ultrasonic extraction is generally done in ice water baths.

4.2.3 Extraction ratio refers to the ratio of the mass or surface area of the components of inhaled aerosol package to the extraction media. The general principle of determination extraction ratio is: the concentration of extraction obtained under the selected extraction

ratio is generally higher compared to the actual possible leachable of the drug. Another important consideration in the selection of extraction ratio is the sensitivity of proposed analytical technique and Analytical Evaluation Threshold (AET) levels. Analytical Evaluation Threshold means any extractable/leachable above this threshold should be qualified and quantified, and toxicologically evaluated. AET is usually derived from safety threshold. For inhaled aerosols, safety threshold is generally set to 0.15 μg / day. A typical derivation formula is as follows:
AET (ug/container) = ((0.15 ug / day) / (administered dose / day)) x (labeled dose / container).
Therefore, based on the analytical sensitivity, in order to obtain an AET value meaningful to operation, extraction ratio is an important consideration. Components samples for the extracted study are generally not to be cut.
4.2.4 Extraction time should not be determined until the above parameters are set. In general, the time should allow the concentration of the extracts to reach asymptotic level or extreme extraction. Asymptotic level or extreme extraction means the amount of extractable in the extract media is less than 10% of the first extraction media, or when the cumulative extract quantification does not have significant further increase.

5. Preparation of extraction media for analysis

In order to reduce the loss of extracts that may be brought about during the preparation, ideally extract fluid obtained should be feasible for direct injection. When dichloromethane or hexane is used to extract inhalation aerosol components for GC and GC/MS , direct injection is preferred. Similarly for extraction by alcohol for HPLC and LC/MS, direct injection is preferred. However, in some cases, the extract may need to be further prepared for subsequent

analysis. Preparation of an extract for inhalation aerosol analysis generally include: concentration of extracts, media conversion and derivatization.

When the analytical system does not have sufficient sensitivity, such as the sensitivity can not meet the AET requirements, the extract can also be concentrated. Commonly used concentration techniques include nitrogen blowing, rotary evaporation, etc.

For extracts that cannot be directly injected, such as dichloromethane or hexane extracts for reverse HPLC and LC/MS as the immiscibility of the extraction media and the mobile phase, media conversion and reconstitution are usually required before injection. The media is generally removed with suitable method, followed by being dissolved by the mobile phase or other media compatible with the mobile phase and injection. The reconstitution process also allows for the concentration of the extract if desired.

The response of certain compounds in analytical systems may be unsatisfactory, such as fatty acids. Alcohols or other derivatization reagents are usually used to derivatize them into esters for good response. As inhalation aerosol formulations usually contain ethanol as a co-solvent, so alcohol (such as isopropanol) is usually selected as one of the extraction medias. The media acts as a derivatizing reagent simultaneously during the analysis.

6. Characterization of extractable

Characterization of extractable refers to qualitative and quantitative studies of extracts beyond AET. Characterization of the extractable requires complete evaluation of the extractable spectrum by a variety of analytical techniques. Extractable characterization process generally includes non-specific analysis, extractable scouting, identification of extractable and quantification of extractable.

6.1 Non-specific analysis of extractable include total organic carbon (TOC), UV absorption, residue weighting after evaporation of media, and infrared spectrum. This information is useful for providing a certain subsequent characterization of extractable and cross evidence.
6.2 Scouting for extractable in the extraction media is the process of analyzing the extraction media to obtain information of individual extractable, in other words, the process of finding a substance which represents instrument response. Usually analytical techniques used for trace organic or inorganic substances, including gas chromatography/hydrogen flame (GC/FID), gas chromatography/mass spectrometry (GC/MS),
High performance liquid chromatography/ultraviolet/diode array (HPLC/UV/DAD), liquid chromatography/mass spectrometry (LC/MS), atom absorption spectrophotometry (AAS), inductively coupled plasma spectroscopy (ICP), inductively coupled plasma spectrometry (ICP/MS), etc. are used. These analytical techniques generally enable testing for volatile/semi-volatile organics, non-volatile organics inorganic substances.
6.3 Extractable identification requires considering AET in the mean time. Identification can be a structural analysis of extractable, as well as qualitative analysis. Structural analysis is the process of interpreting and confirming the molecular structure of an unknown substance. Qualitative analysis is the process of matching and identifying unknowns by one or more analytical techniques using reliable reference standards. Identification of extractable commonly apply mass spectrometry in combination, such as GC/MS, LC/MS for identifying organics, and ICP/MS for identifying inorganics. The identification results are divided into different levels according to their reliability: a) tentative, ie the result of the identification only obtains molecular class information, such as an interpretation from the mass spectrometry fragment information or a match with the literature; b) confirmative, that is, by referring to other deterministic

information, such as molecular weight, elemental composition and other analytical techniques such as nuclear magnetic resonance NMR, the closest chemical structure is identified.

6.4 Extractable quantification process is to measure the concentration of identified compounds and compounds that fail to be identified. Usually a reliable external reference standard method or one or more internal standards can be used for quantification. In the case where a reliable reference standard is not available, relative response between extractable and internal standard can be used, or alternative reference with similar structure may be used for quantification. The quantitative technique or method used should be adequate for accuracy, precision and sensitivity.

6.5 As rubber is used for sealing gasket of inhalation aerosol packaging system, the extraction study needs to pay attention to special carcinogens such as polycyclic aromatic hydrocarbons (PAHs or PNAs), N-nitrosamines, mercaptobenzothiazoles (MBT), etc., it is advisable to develop a highly sensitive method to measure the residual amount of the above specific substances.

Appendix

Common Additives for Packaging System of Inhaled Aerosols

Chemical Name	Generic Name	CAS Number	Chemical Formula	Relative Molecular Weight
	Calcined clay	308063-94-7		
Barium sulfate	Barite powder	7727-43-7	$BaSO_4$	233.39
	FEF carbon black (low PNA)	1333-86-4	C	12.01
	Benzofuran-indene resin	164325-24-0、140413-58-7、140413-55-4、		

		68956-53-6、68955-30-6		
paraffin		8002-74-2、308069-08-1		
sulfur		7704-34-9	S	32.07
Phenolic Resin		9003-35-4	$C_7H_6O_2$	122.12
1,1,3,3-tetramethylthiourea	Tetramethylthiourea	2782-91-4	$C_5H_{12}N_2S$	132.22
Tetramethylthiuram monosulfide	TMTMS	97-74-5	$C_6H_{12}N_2S_3$	208.01
Tetrabenzylthiuram disulfide		10591-85-2	$C_{30}H_{28}N_2S_4$	544.11
2-mercaptobenzothiazole	2-MBT	149-30-4	$C_7H_5NS_2$	166.99
Zinc 2-mercaptobenzothiazole		155-04-4	$C_{14}H_8N_2S_4Zn$	397.90
Tetramethylthiuram disulfide		137-26-8	$C_6H_{12}N_2S_4$	239.99
Zinc oxide		1314-13-2	ZnO	81.38
Magnesium oxide		1309-48-4	MgO	40.30
Octadecanoic acid	Stearic acid	57-11-4	$C_{18}H_{36}O_2$	284.27
Polyethylene glycol PEG4000		25322-68-3	$HO(CH_2CH_2O)nH$	697.61
Hexadecanoic acid	Palmitic acid	57-10-3	$C_{16}H_{32}O_2$	256.24
Myristic acid	Myristic acid	544-63-8	$C_{14}H_{28}O_2$	228.21
Eicosanoid	Arachidonic acid	506-30-9	$C_{20}H_{40}O_2$	312.53
Octadecenoic acid		112-80-1	$C_{18}H_{34}O_2$	282.25
Calcined kaolin		1340-68-7	$Al_2O_3 .SiO_2 .nH_2O$	
talcum powder		14807-96-6	$3MgO.4SiO_2.H_2O$	379.27
Precipitated silica		10279-57-9	$SiO_2 .nH_2O$	
Light calcium carbonate		471-34-1	$CaCO_3$	100.09
Epoxy soybean oil		8013-07-8		
Calcium stearate		1592-23-0	$C_{36}H_{70}CaO_4$	607.02
Dibutylhydroxytoluene; 2,6-di-tert-butyl-4-methylphenol	AntioxidantBHT	128-37-0	$C_{15}H_{24}O$	220.18
Pentaerythritol 3-(3,5-di-	Antioxidant1010	6683-19-	$C_{73}H_{108}O_{12}$	1176.78

tert-butyl-4-hydroxyphenyl)propionate		8		
Octadecyl 3,5-bis(1,1-dimethylethyl)-4-hydroxyphenylpropionate	Antioxidant1076	2082-79-3	$C_{35}H_{62}O_3$	530.86
Tris(2,4-di-tert-butylphenyl) phosphite	Antioxidant168；Irgafos168	31570-04-4	$C_{42}H_{63}O_3P$	646.93
Triethylene glycol ether-bis(3-tert-butyl-4-hydroxy-5-methylphenyl)propionate	Antioxidant245	36443-68-2	$C_{34}H_{50}O_8$	586.35
2,4-bis(1,1-dimethylethyl)-phenol-1,1',1''-phosphite	Irgafos168phosphite	95906-11-9	$C_{42}H_{63}O_4P$	662.92
3,3' thiodipropionate	IrganoxPS800	123-28-4	$C_{30}H_{58}O_4S$	514.84
4,4'-1,1-biphenyl-ylidene diphosphonic acid-tetrakis(2,4-di-tert-butylphenyl) ester	PEPQ	38613-77-3	$C_{68}H_{92}O_4P_2$	1035.41
1,3,5-trimethyl-2,4,6-tris(3,5-tert-butyl-4-hydroxybenzyl)benzene	Irganox1330	1709-70-2	$C_{54}H_{78}O_3$	775.20
Hexanediol bis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate]	Antioxidant259	35074-77-2	$C_{40}H_{62}O_6$	638.92
2,2-methylenebis(6-tert-butyl-4-cresol)	Antioxidant2246	119-47-1	$C_{23}H_{32}O_2$	340.24
2,2-methylene-bis(6-tert-butyl-4-ethylphenol)		88-24-4	$C_{25}H_{36}O_2$	368.27
Bis(2,4-di-tert-butylphenyl)pentaerythritol diphosphite	AntioxidantTHP-24，AntioxidantUltranox626	26741-53-7	$C_{33}H_{50}O_6P_2$	604.69
2(3)-tert-butyl-4-methoxyphenol	BHA	25013-16-5	$C_{11}H_{16}O_2$	180.25
2,4-di-tert-butylphenol		96-76-4	$C_{14}H_{22}O$	206.17
Cis-9-octadecylamine	Oleic acid amide	301-02-0	$C_{18}H_{35}NO$	281.27
13-docosaenoic acid amide	Erucamide	112-84-5	$C_{22}H_{43}NO$	337.33
	Monostearate	31566-31-1	$C_{21}H_{42}O_4$	358.56
1,3:2,4-bis(3,4-dimethylbenzylidene)-D-sorbitol	Nucleating transparent agentTH-3988	135861-56-2	$C_{24}H_{30}O_6$	414.49
Rosin acid		514-10-3	$C_{20}H_{30}O_2$	302.45