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BRIEFING

〈1664.1〉 Assessment of Leachables in Orally Inhaled and Nasal Drug Products. This proposal is based on the version of the chapter official as of August 1, 2015. It is proposed to revise this chapter to address specific, evolving considerations for leachables in orally inhaled and nasal drug products (OINDPs), including metered-dose inhalers (MDIs), nasal sprays, inhalation solutions, suspensions, sprays, and dry powder inhalers (DPIs). Updates include sections on elemental impurities, nitrosamines, and testing of additional leachable time points over the shelf life. The chapter considers organic and elemental leachables from two primary sources: process equipment used to produce the dosage form and container closure systems used to package the dosage form during its shelf life.

Additionally, minor editorial changes have been made to update the chapter to current *USP* style.

(GCDF: R. Kaja)

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The following Briefing list includes monographs and/or chapters that both reference the General Chapter under revision and require revision to keep references to the General Chapter accurate. Other monographs and/or chapters may also be listed, even where the reference to the General Chapter remains unchanged, as additional notice to stakeholders where there is believed to be potential for the change in the general chapter itself to affect pass-fail determinations for particular monograph articles.

Show Chapter Dependencies

〈1664.1〉 ASSESSMENT OF LEACHABLES IN ORALLY INHALED AND NASAL DRUG PRODUCTS

Change to read:

~~INTRODUCTION~~

~~This section addresses specific considerations for leachables in orally inhaled and nasal drug products (OINDP), including metered dose inhalers (MDIs); nasal sprays; inhalation solutions, suspensions, and sprays; and dry powder inhalers (DPIs). Although OINDP can be a combination of products that are comprised of drug and device constituent parts, the primary mode of action is typically through the drug. For this reason OINDP are treated as drugs from a regulatory perspective. Regulatory guidance documents and detailed best practice recommendations specific to OINDP are available (1–4). Note that the following discussion is primarily devoted to organic leachables. For consideration of inorganic (i.e., elemental) leachables, see *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems 〈1664〉*.~~

~~KEY TERMS~~

~~In addition to the key terms listed in 〈1664〉, some additional key terms more specific to OINDP are the following:~~

- ~~*Critical components* are packaging components that contact either the drug product formulation or the patient, or that affect the mechanics of the overall performance of the packaging and delivery system, including any necessary secondary packaging. The identification of critical components for a particular OINDP dosage form is the responsibility of the applicant in consultation with appropriate regulatory authorities.~~
- ~~*Special case compounds* are individual (or classes of) compounds that have special safety or historical concerns as drug product leachables in OINDP, and therefore must be evaluated and controlled as leachables (and extractables) by specific analytical techniques and technology-defined thresholds.~~

~~Additional terminology and associated definitions specific to OINDP are available in the cited references (1–4).~~

~~LEACHABLES ASSESSMENT RATIONALE FOR ORALLY INHALED AND NASAL DRUG PRODUCTS~~

OINDP are generally categorized as high-risk dosage forms due to safety considerations related to the route of administration and high probability of packaging component interaction with the formulation (see *Table 1* in 〈1664〉). The packaging systems used in these drug products incorporate components of various types, including components composed of polymeric (plastic or elastomeric) raw materials with complex chemical compositions and therefore a variety of potential leachables. Chemical entities may migrate (i.e., leach) into the formulation when there is direct contact with the primary packaging and delivery components for extended periods of time. In certain cases, there is also the potential for leaching from secondary and tertiary packaging. In addition, for OINDP, contact of the delivery device with mucosal tissue (mouth or nasal) is generally expected. Leachables studies for some OINDP may be considered separately for packaging components that are in continuous contact with the formulation (e.g., vials, bottles, blisters, metering valve components) versus those that are only in transient contact (e.g., DPI mouthpiece, MDI mouthpiece).

OINDP typically require:

- A leachables stability study for drug product registration that supports intended storage and use conditions throughout the proposed shelf-life (see *Table 1*), ideally on primary drug product stability batches manufactured with the same lots of packaging components used in extraction studies (in order to facilitate a leachables–extractables correlation)
- Sensitive, selective, and fully validated leachables analytical methods
- Leachables assessments based on safety thresholds [Safety Concern Threshold (SCT): 0.15 µg/day, and Qualification Threshold (QT): 5 µg/day total daily intake (TDI) for an individual organic leachable; however, for exceptions see *Special Case Compounds*]
- Complete qualitative and quantitative leachables–extractables correlations (which require that extractables assessments be accomplished on all critical packaging components; see *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems—〈1663〉*)
- Leachables specifications including acceptance criteria (assumes a complete extractables assessment for each critical packaging component). (Note that in many cases routine extractables testing for release of critical components can be used to control drug product leachables in lieu of routine drug product leachables testing, providing that a comprehensive leachables–extractables correlation is established.)

For OINDP dosage forms based on formulations with relatively lower leaching potential for organic compounds (e.g., aqueous formulations, dry powder formulations), the above requirements should be considered and evaluated on a case-by-case basis, including consultations with the appropriate regulatory authorities.

Table 1. Example Stability Storage Conditions and Testing Time Points for an OINDP Registration Leachables Study (*4*)

Condition (temperature/relative humidity)	Time Points (months)
25 ± 2°C/60 ± 5%RH	3, 6, 12, 18, 24, 36 (to end of shelf life)
30 ± 2°C/65 ± 5%RH	3, 6, 12, 18, 24, 36 (to end of shelf life)
40 ± 2°C/75 ± 5%RH	3, 6

ORALLY INHALED AND NASAL DRUG PRODUCTS DOSAGE FORM TYPES

Metered Dose Inhaler

MDIs or pressurized MDIs (pMDIs) are defined as "drug products that contain active ingredient(s) dissolved or suspended in a propellant, a mixture of propellants, or a mixture of solvent(s), propellant(s), and/or other excipients in compact pressurized aerosol dispensers" (*2,4*). Typical MDIs include a metal canister (stainless steel or aluminum; coated or uncoated), a fixed-volume metering valve (with plastic or elastomeric components), elastomeric seals, and a plastic actuator or mouthpiece (see *Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests—〈601〉*). MDIs are multidose drug container closure and delivery systems that can contain sufficient formulation for up to several hundred actuations (label claim) per container. Because many of the critical packaging components are in continuous contact with an organic solvent-based formulation, the MDI has the highest risk for formulation-packaging component interaction, and therefore the highest risk for leachables, of all OINDP dosage forms (or any other dosage form). Because of the leaching potential of their organic solvent-based formulations, MDIs would typically be expected to show complete qualitative and quantitative leachables–extractables correlations. Leachables in MDIs should be characterized (i.e., identified and quantitated) at levels above a calculated analytical evaluation threshold (AET). An AET can be calculated for any OINDP dosage form with consideration of the SCT for OINDP (i.e., 0.15 µg/day for an individual organic leachable). An example AET calculation for an MDI follows.

Given an MDI drug product with 200 labeled actuations per canister, a maximum recommended patient exposure of 12 actuations per day, and a critical valve component mass per valve of 200 mg, for an individual organic leachable derived from this valve component, the following AET can be estimated:

$$\text{Estimated AET} = \left(\frac{0.15\,\mu g/\text{day}}{12\ \text{actuations/day}}\right) \times (200\ \text{labeled actuations/canister})$$

Leachables Estimated AET = 2.5 µg/canister

To convert to an estimated AET, which would be a useful guide for characterizing potential leachables via extraction studies of this particular valve component (see 〈1663〉):

$$\text{Extractables Estimated AET} = (2.5\ \mu g/\text{Canister}) \times \left(\frac{1\ \text{canister/value}}{0.2\ g\ \text{elastomer/value}}\right)$$

Extractables Estimated AET = 12.5 µg/g

The AET calculation should not be modified to account for variables, such as manufacturing overfill in the canister to compensate for leak rate or fill variability, unless such modification can be scientifically justified.

Analytical methods for leachables testing of MDI drug products can be based on processes such as "cold filtration" of suspension formulations to remove active ingredient and excipient particles (5) or careful venting of the volatile organic propellant, which retains leachables in a residue within the canister (6). Because sample preparation procedures for MDI formulations can be complex and typically require the volatile propellant to be reduced to dryness at some point, creating the possibility for loss of leachables before sample analysis, it is particularly important to demonstrate adequate recoveries of leachables through the use of spiked MDI samples.

Although it is unlikely to contribute leachables to the emitted drug product aerosol plume, potential patient exposure to chemical entities from the MDI plastic actuator or mouthpiece should be assessed at a threshold of 20 µg/g (see 〈1663〉). Additional studies and references required to assess patient exposure to actuator- or mouthpiece-derived chemicals include reference to indirect food additive regulations and the application of *Biological Reactivity Tests, In Vitro* 〈87〉 and *Biological Reactivity Tests, In Vivo* 〈88〉 (2). Note that "spacers" and other devices designed for use with MDIs should also be characterized if a particular device is specified on the drug product label.

When constructed from materials acceptable for food contact, MDI actuators and mouthpieces, "spacers", and other components and devices specified in the drug product labeling generally only require appropriate characterization (i.e., extraction studies and routine extractables testing) in order to assure continued consistent composition of the component or device.

In addition, based on applicable regulatory guidance (2), drug product applicants should consider the following (see 〈1663〉):

- Development and validation of surface organic residue release tests for incoming uncoated metal canisters, with appropriate acceptance criteria
- Development and validation of extractables release tests for the inner surfaces of incoming coated canisters, with appropriate acceptance criteria
- Development and validation of extractables release tests for incoming metering valve critical components, with appropriate acceptance criteria
- Development and validation of extractables profile release tests for incoming actuators or mouthpieces, with appropriate qualitative and quantitative acceptance criteria.

Nasal Sprays

Nasal sprays are defined as "drug products that contain active ingredients dissolved or suspended in a formulation, typically aqueous-based, which can contain other excipients and are intended for use by nasal inhalation" (1,4). Nasal sprays include a plastic container and components (usually plastic) that are responsible for formulation metering, atomization, and delivery to the patient (see 〈601〉). Critical components include those that are in constant contact with the formulation (e.g., the container, dip tube) and components that are in the liquid pathway during actuation of the device and that do not permit quick evaporation of residual surface liquid (3). Because nasal sprays are typically aqueous-based formulations, and the vast majority of potential organic leachables are relatively lipophilic, the risk for formulation-packaging component interaction is lower relative to the organic propellant-based MDIs, and the risk for organic leachables is lower. Leachables in nasal sprays should be characterized (i.e., identified and quantitated) at levels above a calculated AET. An AET can be calculated for any OINDP dosage form with consideration of the SCT for OINDP (i.e., 0.15 µg/day for an individual organic leachable). An example AET calculation for a nasal spray follows.

Given a nasal spray drug product with 120 labeled actuations per container, a maximum recommended patient exposure of 4 actuations per day, and a critical component (plastic dip tube) mass of 250 mg, for an individual organic leachable derived from this component, the following AET can be estimated:

$$\text{Estimated AET} = \left(\frac{0.15\ \mu g/\text{day}}{4\ \text{actuations/day}}\right) \times (120\ \textit{labeled}\ \text{actuations/container})$$

Leachables Estimated AET = 4.5 µg/container

Given a total fill volume of 10 mL:

Estimated AET = (4.5 µg/container)/(10 mL/container)

Estimated AET = 0.45 µg/mL

To convert to an estimated AET, which would be a useful guide for characterizing potential leachables via extraction studies of this particular plastic dip tube (see 〈1663〉):

$$\text{Extractables Estimated AET} = (4.5\ \mu g/\text{container}) \times \left(\frac{1\ \text{container}}{0.25\ g\ \text{material/tube}}\right)$$

Extractables Estimated AET = 18 µg/g

The AET calculation should not be modified to account for variables, such as manufacturing overfill, unless such modification can be scientifically justified.

All nasal spray packaging system critical components should be subjected to extractables assessments (see 〈1663〉). Potential patient exposure to chemical entities from nasal spray critical components not in continuous contact with the drug product formulation should be assessed at a threshold of 20 µg/g (see 〈1663〉). Additional studies and references required to assess patient exposure to nonformulation contact critical component derived chemicals include reference to indirect food additive regulations and the application of 〈87〉 and 〈88〉 (*1*).

When constructed from materials acceptable for food contact, nasal spray critical components not in continuous contact with the drug product formulation generally only need to be appropriately characterized (i.e., extraction studies and routine extractables testing) in order to assure continued consistent composition of the component.

In addition, based on applicable regulatory guidance (*1*), drug product applicants should consider the following (see 〈1663〉):

- Development and validation of extractables release tests for incoming container closure and pump critical components, with appropriate qualitative and quantitative acceptance criteria.

Inhalation Solutions, Suspensions, and Sprays

Inhalation solutions, suspensions, and sprays are defined as "drug products that contain active ingredients dissolved or suspended in a formulation, typically aqueous based, which can contain other excipients and are intended for use by oral inhalation" (*1,4*). Inhalation solutions and suspensions are intended for use with a nebulizer (*1,4*). Inhalation sprays, like MDIs and nasal sprays, are combination products where the components responsible for the metering, atomization, and delivery of the formulation to the patient are a part of the container closure system (*1,4*). Critical components include components that are in constant contact with the formulation and components that are in the liquid pathway during actuation of the device and that do not permit quick evaporation of residual surface liquid. Leachables in inhalation sprays should be characterized (i.e., identified and quantitated) at levels above a calculated AET. An AET can be calculated for any OINDP dosage form with consideration of the SCT for OINDP (i.e., 0.15 µg/day for an individual organic leachable). An example AET calculation for an inhalation spray follows.

Given an inhalation spray drug product with 120 labeled actuations per container, a maximum recommended patient exposure of 4 actuations per day, and a critical component (plastic dip tube) mass of 400 mg, for an individual organic leachable derived from this component, the following AET can be estimated:

$$\text{Estimated AET} = \left(\frac{0.15\,\mu g/\text{day}}{4\,\text{actuations/day}}\right) \times (120\ \textit{labeled}\ \text{actuations/container})$$

Leachables Estimated AET = 4.5 µg/container

Given a total fill volume of 4.5 mL:

Estimated AET = (4.5 µg/container)/(4.5 mL/container)

Estimated AET = 1 µg/mL

To convert to an estimated AET, which would be a useful guide for characterizing potential leachables via extraction studies of this particular plastic dip tube (see 〈1663〉):

$$\text{Estimated AET} = \left(\frac{0.15\,\mu g/\text{day}}{4\,\text{actuations/day}}\right) \times (120\ \textit{labeled}\ \text{actuations/container})$$

Extractables Estimated AET = 11.3 µg/g

The AET calculation should not be modified to account for variables, such as manufacturing overfill, unless such modification can be scientifically justified.

Because inhalation solutions and suspensions are similar to nasal spray and inhalation spray drug products in that they are typically aqueous based formulations, and the vast majority of potential organic leachables are relatively lipophilic, the risk for formulation packaging component interaction is lower relative to the organic propellant-based MDIs, and the risk for organic leachables is lower. However, unlike MDIs, nasal and inhalation spray drug products, inhalation solutions, and suspensions are typically packaged in plastic unit dose containers (i.e., nebules). Leaching can potentially occur from the unit dose container [e.g., low-density polyethylene (LDPE)], which is in long-term continuous contact with the drug product formulation. It is also possible that organic chemical entities associated with paper labels, adhesives, inks, etc. in direct contact with the permeable unit dose container can migrate through the container and into the formulation. Leachables from tertiary packaging systems (e.g., cardboard shipping containers) are also possible. Leachables in inhalation solutions and suspensions should be characterized (i.e., identified and quantitated) at levels above a calculated AET. An AET can be calculated for any OINDP dosage form with consideration of the SCT for OINDP (i.e., 0.15 µg/day for an individual organic leachable). An example AET calculation for an inhalation solution follows.

Given an inhalation solution with 3 mL of drug product contained in a LDPE unit dose vial (1 g total weight of LDPE), with a maximum recommended patient exposure of three vials per day, for an individual organic leachable derived from this component, the following AET can be estimated:

$$\text{Estimated AET} = \left(\frac{0.15\,\mu g/\text{day}}{3\,\text{doses/day}}\right) \times (1\,\textit{labeled}\,\text{dose/container})$$

Leachables Estimated AET = 0.05 µg/container

Estimated AET = (0.05 µg/container)/(3 mL/container)

Estimated AET = 0.017 µg/mL

To convert to an estimated AET, which would be a useful guide for characterizing potential leachables via extraction studies of this particular plastic unit dose vial (see 〈1663〉):

$$\text{Extractables Estimated AET} = (0.05\,\mu g/\text{container}) \times \left(\frac{1\ \text{container}}{1\ \text{g material/container}}\right)$$

Extractables Estimated AET = 0.05 µg/g

The challenge of characterizing drug product leachables at levels of 17 ng/mL in an aqueous drug product is considerable, even given the capabilities of modern analytical chemistry. For this particular inhalation solution example, it might be appropriate to implement a simulation study (see 〈1663〉 and 〈1664〉) to facilitate the discovery and identification of probable leachables, with actual drug product leachables being quantitated (if required) with high-sensitivity target compound analytical techniques and methods.

All inhalation solution, suspension, and spray packaging system critical components should be subjected to extractables assessments (see 〈1663〉). Potential patient exposure to chemical entities from inhalation solution, suspension, and spray critical components not in continuous contact with the drug product formulation should be assessed at a threshold of 20 µg/g (see 〈1663〉). Additional studies and references required to assess patient exposure to nonformulation contact critical component-derived chemicals include reference to indirect food additive regulations and application of 〈87〉 and 〈88〉 (*1*). When constructed from materials acceptable for food contact, inhalation solution, suspension, and spray critical components not in continuous contact with the drug product formulation generally only need be appropriately characterized (i.e., extraction studies and routine extractables testing) in order to assure continued consistent composition of the component. Critical components of nebulizers and other devices designed for use with inhalation solutions and suspensions should also be characterized with respect to extractables and leachables if a particular device is specified in the drug product labeling.

Based on applicable regulatory guidance for inhalation solutions, suspensions and sprays (*1*), drug product applicants should consider the following (see 〈1663〉):

- Development and validation of extractables release tests for incoming container closure and pump critical components, with appropriate qualitative and quantitative acceptance criteria
- Consideration of validated tests for probable leachables from labels, inks and adhesives, etc., with appropriate acceptance criteria (should these be appropriate and applicable).

Dry Powder Inhalers and Inhalation Powders

DPIs are defined as “drug products designed to dispense powders for inhalation” (*2,4*). The drug substance in an inhalation powder has a particle size distribution in the respirable range, and may be a physical mixture of active pharmaceutical ingredient(s) with carrier particles or a formulated combination of active ingredient and excipients (see 〈601〉). The powder may be contained in a unit dose packaging system (e.g., capsule, blister), or reside in bulk in a reservoir inside the delivery device itself. In the latter case, the dose is metered by the device. The delivery device may actively disperse the powder from the container or rely on patient inspiration to supply the energy necessary to disperse the particles. The components and the design of the device are integral to the aerosol characteristics (i.e., mass and particle size distribution) of the formulation delivered to the patient. There is a wide diversity of DPI designs and characteristics (*2*).

Of all OINDP, the DPI has the lowest risk of exposing a patient to leachables at significant levels. The reasons for this are:

1. The DPI drug product formulation is a dry powder, and contains no solvent, either organic or aqueous, which can promote leaching of organic (or inorganic) chemical entities.
2. In a unit dose DPI, the drug product formulation is contained in a separate packaging system, and is usually only in transient contact with critical components of the device itself.

The most likely source of leachables in a unit dose DPI would be the material composing the unit dose container, such as a foil laminate blister or capsule material, or the material composing the drug product reservoir in a multidose DPI (including antistatic surface additives). Leaching would have to occur either via direct contact of the drug product powder with the packaging material, via volatilization of organic chemical entities from the container closure material with deposition on the dry powder, or via migration of organic chemical entities through the primary packaging material with deposition on the dry powder. The possibility of observing leachables from the DPI unit dose container is best evaluated with detailed extraction studies on the container material to identify potential leachables, which could possibly migrate to the dry powder by either solid-solid contact or volatilization and have potential safety concerns.

The device and packaging materials are typically evaluated for potential leachables by extraction and simulation studies (see 〈1663〉) to determine whether there are chemical entities at levels that would pose a safety concern. The evaluation of materials that contain the inhalation powder must consider the inks and any other processing aids used in the manufacture of the container so that all potential leachables are characterized. The types of compounds of greatest concern for inhalation powders are those that may migrate from the primary packaging (i.e., unit dose container or multidose reservoir) into the formulation. Extraction and simulation studies should consider all possible mechanisms of leaching, including volatilization. Actual and potential leachables in inhalation powders derived from critical

components of the packaging system or device that may have continuous long-term contact with the drug product formulation should be characterized (i.e., identified and quantitated) at levels above a calculated AET. An AET can be calculated for any OINDP dosage form with consideration of the SCT for OINDP (i.e., 0.15 µg/day for an individual organic leachable). An example AET calculation for an inhalation powder follows:

Given a DPI containing 13 mg of inhalation powder in a unit dose blister with 50 mg of blister material either in direct contact with the formulation or capable of volatilizing leachables into the headspace above the formulation, with a maximum recommended daily exposure of 2 actuations per day, for an individual organic leachable derived from this material, the following AET can be estimated:

$$\text{Estimated AET} = \left(\frac{0.15\,\mu g/\text{day}}{2\ \text{doses/day}}\right) \times (1\ \textit{labeled}\ \text{dose/blister})$$

Leachables Estimated AET = 0.075 µg/blister

To convert relative to the total mass of drug product in a blister:

Estimated AET = (0.075 µg/blister)/(0.013 µg drug product/blister)

Estimated AET = 5.8 µg/g drug product

To convert to an estimated AET, which would be a useful guide for characterizing potential leachables via extraction studies of this particular blister material (see 〈1663〉):

$$\text{Extractables Estimated AET} = (0.075\,\mu g/\text{blister}) \times \left(\frac{1\ \text{blister}}{0.05\ g\ \text{material/blister}}\right)$$

Extractables Estimated AET = 1.5 µg/g

The challenge of characterizing drug product leachables at levels of 5.8 µg/g in an inhalation powder is considerable, even given the capabilities of modern analytical chemistry. For this particular DPI example, it might be appropriate to implement a simulation study (see 〈1663〉 and 〈1664〉) to facilitate the discovery and identification of probable leachables from the blister material, with actual drug product leachables being quantitated (if required) with high-sensitivity target compound analytical techniques and methods.

All inhalation powder packaging system and DPI device critical components should be subjected to extractables assessments (see 〈1663〉). Potential patient exposure to chemical entities from inhalation powder packaging system and DPI device critical components not in continuous contact with the drug product formulation should be assessed at a threshold of 20 µg/g (see 〈1663〉). Additional studies might be required to assess patient exposure to nonformulation contact critical component derived chemicals, including reference to food additive regulations and application of 〈87〉 and 〈88〉 (2).

When constructed from materials acceptable for food contact, inhalation powder packaging system and DPI device critical components not in continuous contact with the drug product formulation generally only need be appropriately characterized (i.e., extraction studies and routine extractables testing) to assure continued consistent composition of the component.

In addition, for DPIs and inhalation powders, and based on applicable regulatory guidance (2), drug product applicants should consider the following (see 〈1663〉):

- Development and validation of extractables release tests for incoming inhalation powder packaging system and DPI device critical components, with appropriate qualitative and quantitative acceptance criteria.

ADDITIONAL CONSIDERATIONS

Analytical Uncertainty

An AET is that concentration above which unknown leachables should be characterized and reported for toxicological assessment. Target leachables (previously characterized as potential or probable leachables from extractables or simulation studies) will have known safety profiles and previously established leachables thresholds. In addition, reference compounds for previously characterized potential leachables will allow for accurate and precise quantitation of those target leachables as actual drug product leachables. Characterization of unknown leachables requires consideration of analytical uncertainty, as the location of an AET in a given leachables profile (e.g., a gas chromatography/mass spectrometry [GC/MS] chromatogram) must be accomplished relative to an internal standard(s) within the leachables profile. Analytical uncertainty for a particular analytical technique or method can be estimated based on the analysis of a series of reference compounds to create a response factor database. The reference compounds included in this database should represent all known potential leachables (i.e., as determined from extractables assessments). For OINDP, it is recommended (4) that the estimated AET be lowered by a factor defined as 1% relative standard deviation in an appropriately constituted response factor database, or a factor of 50% of the estimated AET, whichever is greater. Detailed examples of response factor databases and AET determinations are available (4).

Special Case Compounds

Polycyclic Aromatic Hydrocarbons (PAHs) or Polynuclear Aromatics (PNAs), *N*-nitrosamines, and 2-mercaptobenzothiozole (2-MBT) are considered to be "special case" compounds (i.e., compounds with special safety and historical concerns), requiring special characterization studies using specific analytical techniques and methods (1,2,4). Thresholds for characterization of these compounds as extractables or leachables in OINDP are typically based on the limits of these specific analytical techniques and methods. *Table 2* lists the PNAs and *N*-nitrosamines that, along with 2-MBT, are typically investigated as extractables and leachables in OINDP.

Table 2. PAHs, PNAs, and *N*-Nitrosamines Typically Investigated as Extractables and Leachables for OINDP

Target PAHs/PNAs	Target *N*-nitrosamines
Naphthalene	*N*-Nitrosodimethylamine
Acenaphthylene	*N*-Nitrosodiethylamine
Acenaphthene	*N*-Nitrosodi-*n*-butylamine
Fluorene	*N*-Nitrosomorpholine
Phenanthrene	*N*-Nitrosopiperidine
Anthracene	*N*-Nitrosopyrrolidine
Fluoranthene	—
Pyrene	—
Benzo(*a*)anthracene	—
Chrysene	—
Benzo(*b*)fluoranthene	—
Benzo(*k*)fluoranthene	—
Benzo(e)pyrene	—
Benzo(*a*)pyrene	—
Indeno(123-*cd*)pyrene	—
Dibenzo(*ah*)anthracene	—
Benzo(*ghi*)perylene	—

PNAs have been associated with carbon black filler used in many types of elastomer. Analysis of PNAs, either as elastomer extractables or as drug product leachables, usually involves quantitative extraction followed by highly specific and sensitive analysis of resulting extracts. GC/MS with selected ion monitoring has been reported for analysis of target PNAs as leachables in MDI drug products, for example (*5*). *N*-Nitrosamines are reaction products between specific organic precursor molecules, secondary amines (R_2NH), and a "nitrosating agent". In the compounding of rubber, secondary amines are likely formed from certain vulcanization accelerators such as thiurams and dithiocarbamates. Potential nitrosating agents include NO^+, N_2O_3, N_2O_4, etc., certain of which can be formed from commonly used chemicals such as sodium nitrite ($NaNO_2$), which has many industrial uses. Analysis of *N*-nitrosamines in rubber as potential leachables involves quantitative extraction followed by analysis of extracts with gas chromatography/thermal energy analysis detection (GC/TEA) (*7*). Analysis of *N*-nitrosamines as leachables in MDI drug products using GC/TEA has been reported (*6*). The 2-MBT is a vulcanization accelerator, which is used in certain sulfur-cured elastomers, and can be analyzed by extraction followed by LC/MS (*4*).

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7. ~~AOAC International Official Methods of Analysis. *N*-Nitrosamines in baby bottle rubber nipples. Official Method 987.05, Chapter 48, 7–8; Gaithersburg, MD, 2000.~~

▲1. INTRODUCTION

This chapter addresses specific considerations for leachables in orally inhaled and nasal drug products (OINDPs), including metered-dose inhalers (MDIs), nasal sprays, inhalation solutions, suspensions, and sprays, and dry powder inhalers (DPIs). Although OINDPs can be a combination of products comprised of drug and device constituent parts, the primary mode of action is typically through the drug. For this reason, OINDPs are treated as drugs from a regulatory perspective. Please note that the following discussion primarily focuses on organic leachables. For consideration of inorganic (i.e., elemental) leachables, see *Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems* 〈1664〉.

OINDPs refer to drug products delivered through the nose or lungs using devices such as inhalers or nasal sprays, for local or systemic effects, as defined and described in *Pharmaceutical Dosage Forms* 〈1151〉 and *Inhalation and Nasal Drug Products—General Information and Product Quality Tests* 〈5〉, *Table 1*. General classes of OINDPs have the following compositions:

- *Metered dose inhalers*—Drug product–device combination products in which the drug product contains active ingredient(s) dissolved or suspended in a propellant, a mixture of propellants, or a mixture of solvent(s), propellant(s), and/or other excipients, in compact pressurized aerosol dispensers
- *Nasal sprays*—Drug products that contain active ingredients dissolved or suspended in a formulation, typically aqueous-based, which can contain other excipients and are intended for use by nasal inhalation
- *Inhalation solutions, suspensions, and sprays*—Drug products that contain active ingredient(s) dissolved or suspended in a formulation, typically aqueous-based, that may contain other excipients and are intended for use by oral inhalation
- *Dry powder inhalers and inhalation powders*—Drug product–device combination products in which the drug-containing particles in an inhalation powder have a particle size distribution in the respirable range and may be a physical mixture of active pharmaceutical ingredient(s) with carrier particles or a formulated combination of active ingredient and excipients

2. PACKAGING FOR OINDPS

2.1 Key Terms

CRITICAL COMPONENTS

Critical components are packaging components that contact either the drug product formulation or the patient, or that affect the mechanics of the overall performance of the packaging and delivery system, including any necessary secondary packaging. The identification of critical components for a particular OINDP dosage form is the responsibility of the applicant in consultation with appropriate regulatory authorities.

MDIs

Typical MDIs include a metal canister (stainless steel or aluminum; coated or uncoated), a fixed-volume metering valve (with a metal spring, a metal ferrule, and additional components, which can be either metal with plastic or elastomeric components), elastomeric seals, and a plastic actuator or mouthpiece with or without integrated devices, such as a spacer, a dose counter, or an actuation mechanism. MDIs are container closure and delivery systems for multidose drug products that can contain a sufficient amount of drug product for up to several hundred actuations (label claim) per container.

NASAL SPRAYS

Nasal spray products, either multidose or unit dose, typically include the drug product, the container closure system, a pump, and an actuator. The container closure system for nasal sprays comprises a plastic container and other components (typically plastic) that are responsible for formulation metering, atomization, and delivery to the patient. Critical components include those that are in constant contact with the formulation (e.g., the container and dip tube) and components that are part of the liquid pathway during device actuation but do not permit quick evaporation of residual surface liquid.

INHALATION SOLUTIONS, SUSPENSIONS, AND SPRAYS

Inhalation solutions and suspensions are intended for use with a nebulizer. Inhalation sprays, like MDIs and nasal sprays, are combination products in which the components responsible for the metering, atomization, and delivery of the formulation to the patient are a part of the container closure system. Critical components include those that are in constant contact with the formulation and those in the liquid pathway during device actuation, but which do not permit the quick evaporation of residual surface liquid.

Many inhalation solutions and suspensions are contained in blow-fill-seal low-density polyethylene (LDPE) ampules or vials, which are semipermeable. Due to the semipermeable nature of LDPE, volatile compounds from the inner layers of foil laminate overwraps can migrate into the ampules or vials and accumulate in the formulation; therefore, the foil laminate overwraps used with them are considered critical secondary packaging components.

DPIs

The powder may be contained in a unit-dose packaging system (e.g., capsule, blister) or reside as a powder bulk in a reservoir inside the delivery device itself. In the latter case, the dose is metered by the device. DPIs can be active or passive. Active DPIs use an internal source, such as compressed air, to disperse powders. The dose delivery from a passive device may rely on patient inspiration to supply the energy

necessary to disperse the particles. The components and the design of the device are integral to the aerosol characteristics (i.e., mass and particle size distribution) of the formulation delivered to the patient. There is a wide diversity of DPI designs and characteristics. Critical components are those that come into contact with the inhalation powder and with the mouthpiece (or area contacted by the patient's mouth).

3. REGULATORY GUIDELINES FOR OINDPS

Regulatory guidance documents and detailed best practice recommendations specific to OINDPs are available (2–4).

4. CHEMICAL ASSESSMENT REQUIREMENTS FOR OINDP PACKAGING

4.1 General Discussion

OINDPs are generally categorized as high-risk dosage forms due to safety considerations related to the route of administration. Furthermore, the risk for liquid dosage forms (solutions, suspensions, sprays) is high due to the high probability of interaction between the packaging components and the formulation. However, the risk for solid dosage forms (e.g., DPI) is considered low due to the low probability of solid-solid interactions (see *Table 1* in 〈1664〉). The packaging systems used in these drug products incorporate components of various types, including components composed of polymeric (plastic or elastomeric) raw materials with complex chemical compositions and, therefore, a variety of potential leachables. Chemical entities may migrate (i.e., leach) into the formulation when there is direct contact with the primary packaging and delivery components for extended periods. In certain cases, there is also the potential for leaching from secondary and tertiary packaging (e.g., Inhalation solution/suspension in LDPE ampules/vials). Additionally, for OINDP, contact of the delivery device with mucosal tissue (such as the mouth or nasal passages) is generally expected. Leachables studies for some OINDPs may be considered separately for packaging components that are in continuous contact with the formulation (e.g., vials, bottles, blisters, metering valve components) versus those that are only in transient contact (e.g., DPI mouthpieces, MDI mouthpieces).

For regulatory submissions, OINDPs typically require:

- A leachables stability study for drug product registration that supports intended storage and use conditions throughout the proposed shelf-life (see *Table 1* for the proper testing schedule), ideally on primary drug product stability batches manufactured, when possible, with the same lots of packaging components used in extraction studies (in order to facilitate a leachables–extractables correlation).
- Sensitive, selective, and fully validated leachables analytical methods.
- Leachables assessments based on safety thresholds. Although a safety concern threshold (SCT) of 0.15 µg/day and a qualification threshold (QT) of 5 µg/day total daily intake (TDI) for an individual organic leachable were previously published in the Product Quality Research Institute's OINDP best practices (4), current regulatory practice is an SCT of 1.5 µg/day. For exceptions to these SCT and QT values, see *4.7 Special Case Compounds*. Applicants are recommended to consult with the regulatory agency before leachables or extractables studies are performed, to clarify or justify expectations regarding study design topics such as the SCT.
- For liquid dosage forms: Complete qualitative and quantitative leachables–extractables correlations (which require that extractables assessments be accomplished on all critical packaging components; see *Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems* 〈1663〉.
- For liquid dosage forms: Leachables specifications including acceptance criteria (assumes a complete extractables assessment for each critical packaging component). (Note that in some cases, routine extractables testing for release of critical components can be used to control drug product leachables in lieu of routine drug product leachables testing, providing that a comprehensive leachables–extractables correlation is established).
- For drug products packaged in semipermeable containers (e.g., low density polyethylene) without protective packaging that are intended for storage under controlled room temperature conditions, and, drug products intended for storage in a refrigerator, refer to FDA's *Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products—Chemistry, Manufacturing, and Controls Documentation* (1).

For OINDP dosage forms based on formulations with relatively low leaching potential for organic compounds (e.g., aqueous formulations or dry powder formulations), the above requirements should be considered and evaluated on a case-by-case basis, including consultations with the appropriate regulatory authorities.

Table 1 shows an example of stability storage conditions and testing time points for an OINDP registration leachables study for a drug product intended for storage under controlled room temperature conditions and not packaged in semipermeable containers (6).

Table 1. Example of Stability Storage Conditions and Testing Time Points

Condition (Temperature and Relative Humidity)	Time Points (Months)
25 ± 2° 60 ± 5% RH	3, 6, 9, 12, 18, 24, 36 (to the end of shelf life)
30 ± 2° 65 ± 5% RH	3, 6, 9, 12

Condition (Temperature and Relative Humidity)	Time Points (Months)
40 ± 2° 75 ± 5% RH	3, 6

4.2 MDIs

Because many critical packaging components for MDIs are in continuous contact with an organic solvent-based formulation, MDIs have the highest risk of formulation–packaging component interaction, and therefore the highest risk of leachables, among all OINDP dosage forms (or any other dosage form). MDIs have the highest risk of interactions between packaging components and the dosage form because they include a propellant. The presence of an organic propellant in MDI formulations could enhance leaching of compounds from the valve or canister components into the formulation. Thus, MDIs would typically be expected to show complete qualitative and quantitative correlations between leachables and extractables. Leachables in MDIs should be characterized (i.e., identified and quantitated) at levels above a calculated analytical evaluation threshold (AET).

An AET can be calculated for any OINDP dosage form by applying the OINDP SCT (i.e., 1.5 µg/day for an individual organic leachable). An example AET calculation for an MDI is provided below.

Given an MDI drug product with 200 labeled actuations per canister, a maximum recommended patient exposure of 12 actuations per day, and a critical valve component mass per valve of 200 mg, for an individual organic leachable derived from this valve component, the following AET can be estimated:

$$\text{Estimated AET} = (1.5\,\mu\text{g/day} \div 12\ \text{actuations/day}) \cdot (200\,\text{labeled actuations/canister})$$

$$\text{Leachables estimated AET} = 25\,\mu\text{g/canister}$$

To convert to an estimated AET, which would be a useful guide for characterizing potential leachables via extraction studies of this particular valve component:

$$\text{Extractables estimated AET} = (25\,\mu\text{g/canister}) \cdot (1\,\text{canister/value} \div 0.2\,\text{g elastomer/value})$$

$$\text{Extractables estimated AET for component} = 125\,\mu\text{g/g}$$

Estimated AETs are converted to final AETs by adjusting the estimated AET with an uncertainty factor (UF).

Similarly, the AET for other nonelastomeric components—including the first stem gasket, second stem gasket, neck gasket, housing, metering chamber, lower stem, stem, and ring—as well as for the canister and actuator, can be calculated in the same way. For the actuator, this includes contact parts (such as the sump, actuator orifice, and mouthpiece) and noncontact parts (such as the sleeve for the canister).

The AET calculation should not be modified to account for variables, such as manufacturing overfill in the canister to compensate for leak rate or fill variability, unless such modification can be scientifically justified.

Analytical methods for leachables testing of MDI drug products can be based on processes such as “cold filtration” of suspension formulations to remove active ingredient and excipient particles (*5*) or careful venting of the volatile organic propellant, which retains leachables in a residue within the canister (*6*). Because sample preparation procedures for MDI formulations can be complex and typically require the volatile propellant to be reduced to dryness at some point, creating the possibility for loss of leachables before sample analysis, it is particularly important to demonstrate adequate recoveries of leachables through the use of spiked MDI samples. Although it is unlikely to contribute leachables to the emitted drug product aerosol plume, potential patient exposure to chemical entities from the MDI plastic actuator or mouthpiece should be assessed at a threshold of 20 µg/g (see 〈1663〉). Additional studies and references are required to assess patient exposure to actuator- or mouthpiece-derived chemicals, including references to indirect food additive regulations and the application of biological reactivity testing (*The Biocompatibility of Pharmaceutical Packaging Systems and Their Materials of Construction,* 〈1031〉). Note that “spacers” and other devices designed for use with MDIs should also be characterized if a particular device is specified on the drug product label.

When the delivery system is also considered a medical device, additional regulations may apply, and the appropriate authorities should be consulted.

Applicants should describe a control strategy that ensures the continued reproducibility of the delivery system. For example, if constructed from materials acceptable for food contact, MDI actuators and mouthpieces, “spacers”, and other components and devices specified in the drug product labeling generally may only need to be appropriately characterized (i.e., extraction studies and possibly routine extractables testing) to ensure continued consistent composition of the component or device.

In addition, based on applicable regulatory guidance, drug product applicants should consider the following (see 〈1663〉):

1. Development and validation of surface organic residue release tests for incoming uncoated metal canisters, with appropriate acceptance criteria.
2. Development and validation of extractables release tests for the inner surfaces of incoming coated canisters, with appropriate acceptance criteria.
3. Development and validation of extractables release tests for incoming metering valve critical components, with appropriate acceptance criteria.
4. Development and validation of extractables profile release tests for the incoming actuators or mouthpieces, with appropriate qualitative and quantitative acceptance criteria.

Any post-approval changes (for example, material, dimensions, or source of supplier) made to the container closure systems of MDIs require repetition of the above recommendation to establish that the changed systems conform to relevant quality standards.

4.3 Nasal Sprays

Because nasal sprays are typically aqueous-based formulations, and the vast majority of potential organic leachables are relatively lipophilic with low aqueous solubility, the risk of formulation–packaging component interaction is lower than that for organic propellant-based MDIs. Leachables in nasal sprays should be characterized (i.e., identified and quantitated) at levels above a calculated AET. An AET can be calculated for any OINDP dosage form by applying the OINDP SCT (i.e., 1.5 µg/day for an individual organic leachable).

An example AET calculation for a nasal spray is provided below.

Given a nasal spray drug product with 120 labeled actuations per container, a maximum recommended patient exposure of 4 actuations per day, and a critical component (plastic dip tube) mass of 250 mg, for an individual organic leachable derived from this component, the following AET can be estimated:

$$\text{Estimated AET} = (1.5\,\mu\text{g/day} \div 4\ \text{actuations/day}) \cdot (120\ \text{labeled actuations/container})$$

$$\text{Leachables estimated AET} = 45\,\mu\text{g/container}$$

Given a total fill volume of 10 mL:

$$\text{Estimated AET} = (45\ \mu\text{g/container}) \div (10\,\text{mL/container})$$

$$\text{Estimated AET} = 4.5\,\mu\text{g/mL}$$

To convert to an estimated AET, which would be a useful guide for characterizing potential leachables via extraction studies of this particular plastic dip tube (see 〈1663〉):

$$\text{Extractables estimated AET} = (45\ \mu\text{g/container}) \cdot (1\,\text{container} \div 0.25\,\text{g material/tube})$$

$$\text{Extractables estimated AET} = 180\,\mu\text{g/g}$$

Estimated AETs are converted to final AETs by adjusting the estimated AET with a UF.

The AET calculation should not be modified to account for variables, such as manufacturing overfill, unless such a modification can be scientifically justified.

Applicants should describe a control strategy that ensures the continued reproducibility of the delivery system. For example, all critical components of the nasal spray packaging system could be subjected to extractables assessments (see 〈1663〉). Potential patient exposure to chemical entities from nasal spray critical components not in continuous contact with the drug product formulation could be assessed at a threshold of 20 µg/g (see 〈1663〉). When constructed from materials acceptable for food contact, nasal spray critical components not in continuous contact with the drug product formulation may only need to be appropriately characterized (i.e., extraction studies and possibly routine extractables testing) to ensure a consistent composition of the component.

Additional studies and references are required to assess patient exposure to chemicals derived from nonformulation-contact critical components. These may include references to indirect food additive regulations and the application of biological reactivity testing, as outlined in 〈1031〉.

In addition, based on applicable regulatory guidance, drug product applicants should consider the following (see 〈1663〉):

- Development and validation of extractables release tests for incoming container closure and pump critical components, with appropriate qualitative and quantitative acceptance criteria.

4.4 Inhalation Sprays

Leachables in inhalation sprays should be characterized (i.e., identified and quantitated) at levels above a calculated AET. An AET can be calculated for any OINDP dosage form by applying the OINDP SCT (i.e., 1.5 µg/day for an individual organic leachable).

An example AET calculation for an inhalation spray is provided below.

Given an inhalation spray drug product with 120 labeled actuations per container, a maximum recommended patient exposure of 4 actuations per day, and a critical component (plastic dip tube) mass of 400 mg, for an individual organic leachable derived from this component, the following AET can be estimated:

$$\text{Estimated AET} = (1.5\ \mu\text{g/day} \div 4\ \text{actuations/day}) \cdot (120\,\text{labeled actuations/container})$$

$$\text{Leachables estimated AET} = 45\ \mu\text{g/container}$$

Given a total fill volume of 4.5 mL:

$$\text{Estimated AET} = (45\,\mu\text{g/container}) \div (4.5\ \text{mL/container})$$

$$\text{Estimated AET} = 10\,\mu\text{g/mL}$$

To convert to an estimated AET, which would be a useful guide for characterizing potential leachables via extraction studies of this particular plastic dip tube (see 〈1663〉):

$$\text{Estimated AET} = (45\ \mu\text{g/day} \div \text{container}) \cdot (1\ \text{container}/0.4\ \text{g})$$

$$\text{Extractables estimated AET} = 113\ \mu\text{g/g}$$

Estimated AETs are converted to final AETs by adjusting the estimated AET with a UF.

The AET calculation should not be modified to account for variables, such as manufacturing overfill, unless such a modification can be scientifically justified.

Based on applicable regulatory guidance for inhalation solutions, suspensions, and sprays, drug product applicants should consider the following (see 〈1663〉):

- Development and validation of extractables release tests for incoming container closure and pump critical components, with appropriate qualitative and quantitative acceptance criteria.
- Consideration of validated tests for probable leachables from labels, inks, adhesives, etc., with appropriate acceptance criteria, if such tests are appropriate and applicable.

4.5 Inhalation Solutions and Suspensions

Because inhalation solutions and suspensions are similar to nasal spray and inhalation spray drug products in that they are typically aqueous-based formulations, and the vast majority of potential organic leachables are relatively lipophilic, the risk of formulation–packaging component interaction is lower than that for organic propellant-based MDIs. The risk for organic leachables is therefore also lower. However, unlike MDIs, nasal and inhalation spray drug products, inhalation solutions, and suspensions are typically packaged in plastic unit dose containers (i.e., nebules). Leaching can potentially occur from the unit dose container (e.g., LDPE), which is in long-term continuous contact with the drug product formulation. It is also possible that organic chemical entities associated with paper labels, adhesives, and inks, in direct contact with the permeable unit dose container, can migrate through the container and into the formulation. Leachables from tertiary packaging systems (e.g., cardboard shipping containers) are also possible.

Leachables in inhalation solutions and suspensions should be characterized (i.e., identified and quantitated) at levels above a calculated AET. An AET can be calculated for any OINDP dosage form by applying the OINDP SCT (i.e., 1.5 µg/day for an individual organic leachable).

An example AET calculation for an inhalation solution is provided below.

Given an inhalation solution with 3 mL of drug product contained in an LDPE unit dose vial (1 g total weight of LDPE), with a maximum recommended patient exposure of three vials per day, for an individual organic leachable derived from this component, the following AET can be estimated:

$$\text{Estimated AET} = (1.5\ \mu\text{g/day} \div\ 3\ \text{doses/day}) \cdot (1\ \text{labeled dose/container})$$

$$\text{Leachables estimated AET} = 0.5\ \mu\text{g/container}$$

$$\text{Estimated AET} = (0.5\ \mu\text{g/container}) \div\ (3\ \text{mL/container})$$

$$\text{Estimated AET} = 0.17\ \mu\text{g/mL}$$

To convert to an estimated AET, which would be a useful guide for characterizing potential leachables via extraction studies of this particular plastic unit dose vial (see 〈1663〉):

$$\text{Extractables estimated AET} = (0.50\ \mu\text{g/container}) \cdot (1\ \text{container} \div 1\ \text{g material/container})$$

$$\text{Extractables estimated AET} = 0.50\ \mu\text{g/g}$$

Estimated AETs are converted to final AETs by adjusting the estimated AET with a UF.

The challenge of characterizing drug product leachables at levels of 0.17 µg/mL in an aqueous drug product is considerable, even given the capabilities of modern analytical chemistry. For this particular inhalation solution example, it might be appropriate to implement a simulation study (see 〈1663〉 and 〈1664〉) to facilitate the discovery and identification of probable leachables, with actual drug product leachables being quantitated (if required) with high-sensitivity target compound analytical techniques and methods.

An appropriate control strategy should be developed to ensure reproducibility of packaging materials. For example, all inhalation solution, suspension, and spray packaging system critical components should be subjected to extractables assessments. Potential patient exposure to chemical entities from inhalation solution, suspension, and spray critical components not in continuous contact with the drug product formulation should be assessed at a threshold of 20 µg/g (see 〈1663〉). Potential patient exposure to chemical entities from inhalation solution, suspension, and spray critical components not in continuous contact with the drug product formulation should be assessed at a threshold of 20 µg/g (see 〈1663〉). If constructed from materials acceptable for food contact, inhalation solution, suspension, and spray critical components not in continuous contact with the drug product formulation generally may only need to be appropriately characterized (i.e., extraction studies and possibly routine extractables testing) to ensure continued consistent composition of the component.

Additional studies and references are required to assess patient exposure to nonformulation contact critical component-derived chemicals, including references to indirect food additive regulations and the application of biological reactivity testing, as outlined in 〈1031〉.

Critical components of nebulizers and other devices designed for use with inhalation solutions and suspensions should also be characterized with respect to extractables and leachables if a particular device is specified in the drug product labeling.

Delivery systems that are considered medical devices may be subject to additional regulations; therefore, the appropriate authorities should be consulted.

Based on applicable regulatory guidance for inhalation solutions, suspensions and sprays, drug product applicants should consider the following (see 〈1663〉):

- Development and validation of extractables release tests for incoming container closure and pump critical components, with appropriate qualitative and quantitative acceptance criteria.

- Consideration of validated tests for probable leachables from labels, inks, and adhesives, etc., with appropriate acceptance criteria (should these be appropriate and applicable).

4.6 Dry Powder Inhalers and Inhalation Powders

Of all OINDPs, the DPI has the lowest risk of exposing a patient to leachables at significant levels. The reasons for this are:

- The DPI drug product formulation is a dry powder and contains no solvent, either organic or aqueous, which can promote leaching of organic (or inorganic) chemical entities.
- In a unit-dose DPI, the drug product formulation is contained in a separate packaging system and is usually only in transient contact with critical components of the device itself.

The most likely source of leachables in a unit-dose DPI would be the material composing the unit-dose container, such as a foil laminate blister, or the material composing the drug product reservoir in a multidose DPI (including antistatic surface additives). Leaching would have to occur either via direct contact of the drug product powder with the packaging material, via volatilization of organic chemical entities from the container closure material with deposition on the dry powder, or via migration of organic chemical entities through the primary packaging material with deposition on the dry powder. The possibility of observing leachables from the DPI unit dose container is best evaluated through detailed extraction studies on the container material to identify potential leachables that could potentially migrate to the dry powder by either solid-solid contact or volatilization, raising safety concerns.

The device and packaging materials are typically evaluated for potential leachables by extraction and simulation studies (see 〈1663〉) to determine whether there are chemical entities at levels that would pose a safety concern. The evaluation of materials that contain the inhalation powder must consider the inks and any other processing aids used in the manufacture of the container so that all potential leachables are characterized. The types of compounds of greatest concern for inhalation powders are those that may migrate from the primary packaging (i.e., unit dose container or multidose reservoir) into the formulation. Extraction and simulation studies should consider all possible mechanisms of leaching, including volatilization. Actual and potential leachables in inhalation powders derived from critical components of the packaging system or device that may have continuous long-term contact with the drug product formulation should be characterized (i.e., identified and quantitated) at levels above a calculated AET. An AET can be calculated for any OINDP dosage form by applying the OINDP SCT (i.e., 0.15 µg/day for an individual organic leachable).

An example AET calculation for an inhalation powder is provided below.

Given a DPI containing 13 mg of inhalation powder in a unit dose blister with 50 mg of blister material either in direct contact with the formulation or capable of volatilizing leachables into the headspace above the formulation, with a maximum recommended daily exposure of 2 actuations per day, for an individual organic leachable derived from this material, the following AET can be estimated:

$$\text{Estimated AET} = (1.5\ \mu\text{g/day} \div 2\ \text{doses/day}) \cdot (1\ \text{labeled dose/blister})$$

$$\text{Leachables estimated AET} = 0.75\ \mu\text{g/blister}$$

To convert relative to the total mass of drug product in a blister:

$$\text{Estimated AET} = (0.75\ \mu\text{g/blister}) \div (0.013\ \text{g drug product/blister})$$

$$\text{Estimated AET} = 58\ \mu\text{g/g drug product}$$

To convert to an estimated AET, which would be a useful guide for characterizing potential leachables via extraction studies of this particular blister material (see 〈1663〉):

$$\text{Extractables estimated AET} = (0.75\ \mu\text{g/blister}) \cdot (1\ \text{blister} \div 0.05\ \text{g material/blister})$$

$$\text{Extractables estimated AET} = 15\ \mu\text{g/g blister material}$$

Estimated AETs are converted to final AETs by adjusting the estimated AET with a UF.

As the challenge of characterizing drug product leachables in an inhalation powder may be considerable, even given the capabilities of modern analytical chemistry, it may be appropriate to implement a simulation study (see 〈1663〉 and 〈1664〉) to facilitate the discovery and identification of probable leachables from the blister material, with actual drug product leachables being quantitated (if required) using high-sensitivity target compound analytical techniques and methods.

All inhalation powder packaging systems and DPI device critical components should be subjected to extractables assessments (see 〈1663〉). Potential patient exposure to chemical entities from inhalation powder packaging system and DPI device critical components not in continuous contact with the drug product formulation should be assessed at a threshold of 20 µg/g (see 〈1663〉). Additional studies may be required to assess patient exposure to nonformulation contact critical component-derived chemicals, including reference to food additive regulations and the application of biological reactivity testing, as outlined in 〈1031〉.

Delivery systems that are considered medical devices may be subject to additional regulations; therefore, the appropriate authorities should be consulted.

When constructed from materials acceptable for food contact, the inhalation powder packaging system and DPI device critical components not in continuous contact with the drug product formulation generally only need to be appropriately characterized (i.e., extraction studies and routine extractables testing) to ensure a continued consistent composition of the component. In addition, for DPIs and inhalation powders, and based on applicable regulatory guidance (2), if leachables with safety concerns are identified, drug product applicants should consider the following (see 〈1663〉):

- Development and validation of extractables release tests for relevant incoming inhalation powder packaging systems and critical components of DPI devices, with appropriate qualitative and quantitative acceptance criteria.

4.7 Special Case Compounds

Special case compounds are individual compounds (or classes of compounds) that have special safety or historical concerns as drug product leachables in OINDPs and, therefore, must be evaluated and controlled as leachables (and extractables) by specific analytical techniques and technology-defined thresholds. The AET does not apply to special case compounds. Polycyclic aromatic hydrocarbons (PAHs) or polynuclear aromatics (PNAs), *N*-nitrosamines, and 2-mercaptobenzothiazole (2-MBT) are considered to be special case compounds (i.e., compounds with special safety and historical concerns), requiring special characterization studies using specific analytical techniques and methods. Thresholds for characterizing these compounds as extractables or leachables in OINDP are typically based on the limits of specific analytical techniques and methods. *Table 2* lists the PNAs and *N*-nitrosamines that, along with 2-MBT, are typically investigated as special case extractables and leachables in OINDP.

Table 2. PAHs, PNAs, and *N*-Nitrosamines Typically Investigated as Extractables and Leachables for OINDP

Target PAHs and PNAs
Lower Molecular Weight PAHs
Naphthalene
Acenaphthylene
Acenaphthene
Fluorene
Phenanthrene
Anthracene
Fluoranthene
Pyrene
Higher Molecular Weight PAHs
Benzo(*a*)anthracene
Chrysene
Benzo(*b*)fluoranthene
Benzo(*k*)fluoranthene
Benzo(*e*)pyrene
Benzo(*a*)pyrene
Indeno(123-*cd*)pyrene
Dibenzo(*ah*)anthracene
Benzo(*ghi*)perylene
Target *N*-Nitrosamines (*Nitrosamine Impurities* 〈1469〉)

PNAs have been associated with carbon black filler used in many types of elastomers. Analysis of PNAs, whether as elastomer extractables or as drug product leachables, typically involves quantitative extraction followed by highly specific and sensitive analysis of the resulting extracts. Gas chromatography/mass spectrometry (GC/MS) with selected-ion monitoring has been reported for the analysis of target PNAs as leachables in MDI drug products, for example (*5*). *N*-Nitrosamines are reaction products between specific organic precursor molecules, secondary amines (R_2NH), and a “nitrosating agent”. In the compounding of rubber, secondary amines are likely formed from certain vulcanization accelerators such as thiurams and dithiocarbamates. Potential nitrosating agents include nitrosonium ion (NO^+), dinitrogen

trioxide (N_2O_3), and dinitrogen tetroxide (N_2O_4), among others, some of which can be formed from commonly used chemicals such as sodium nitrite ($NaNO_2$), which has numerous industrial applications. Analysis of *N*-nitrosamines in rubber as potential leachables involves quantitative extraction, followed by analysis of the extracts using gas chromatography–thermal energy analysis detection (GC–TEA) (*6*). Analysis of *N*-nitrosamines as leachables in MDI drug products using GC–TEA has been reported (*7*). Guidelines for nitrosamines as impurities in drug products have been issued by both the USP and the FDA (*8*). The 2-MBT is a vulcanization accelerator used in certain sulfur-cured elastomers, which can be analyzed by extraction followed by LC–MS (*9*).

4.8 Elemental Impurities

Elemental impurities may be present in OINDPs as a result of their interaction with packaging systems. Packaging and critical packaging components for OINDPs should be tested for extractable elements, and OINDPs should be characterized over their shelf life for elemental impurities, consistent with the requirements and guidelines contained in International Council for Harmonisation (ICH) Q3D (*10*).

5. CHEMICAL ASSESSMENT REQUIREMENTS FOR OINDP MANUFACTURING COMPONENTS

Metallic, glass, or ceramic components used to manufacture OINDPs do not require qualification for organic extractables, as such components are not sources of organic extractables or leachables. The risk of such components leaching elemental impurities into OINDPs must be assessed. Assessments that conclude that there is a high risk of leaching of elements must be followed by appropriate extractables or leachables testing. If extractables testing does not reveal extracted elements in excess of the appropriate control threshold [e.g., 30% of the element's permitted daily exposure (PDE)], then testing manufactured drug products for manufacturing-related leached elements is not required.

Plastic components used to manufacture OINDPs, or their relevant materials of construction, must be well characterized:

- The manufacturing system itself, or all of its relevant materials of construction, complies with the relevant compendial monographs.
- The manufacturing system itself, or all of its relevant materials of construction, complies with the relevant food contact safety regulations (e.g., 21 CFR 174–186) and compliance is adequately justified (e.g., proposed use is consistent with regulations for food contact use, the leaching propensity of the OINDP process stream is similar or less than the extraction solvent(s) listed in a referenced regulation, and all specified testing results for the manufacturing system or material meet the specified acceptance criteria).

For plastic OINDP manufacturing components, the risk of such components leaching organic impurities into OINDPs must be assessed. If the assessments conclude that the risk is high, appropriate extractables or leachables testing must follow. Depending on the outcome of extraction studies, leachables studies may also be required on a case-by-case basis. *Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products 〈665〉* and *Characterization and Qualification of Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products 〈1665〉* should be consulted to facilitate the design and implementation of any necessary extractables and leachables studies for plastic manufacturing components.

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Topic/Question	Contact	Expert Committee
<1664.1> ASSESSMENT OF LEACHABLES IN ORALLY INHALED AND NASAL DRUG PRODUCTS	Ravikiran Kaja Senior Principal Scientist	GCPD2025 Packaging and Distribution
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