Elastomers in orally inhaled and nasal drug products

Part I: Elastomer selection and qualification

A rationalized, risk-based approach to elastomer selection and qualification is critical for OINDP quality and safety. This is the first of a two-part series of articles on elastomers to be published by Inhalation.

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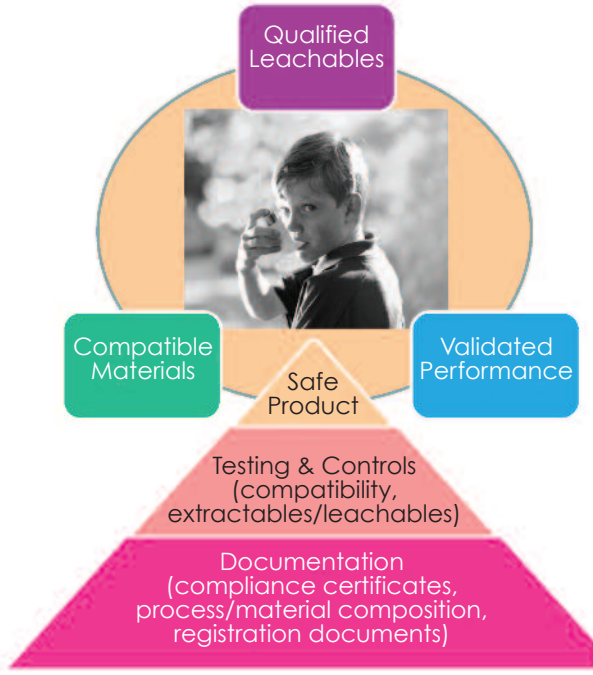
On behalf of the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS)



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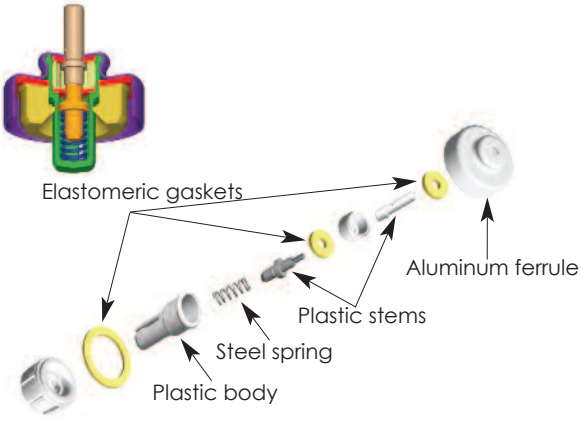
I. Introduction

Orally inhaled and nasal drug products (OINDPs) include metered dose inhalers (MDIs), dry powder inhalers (DPIs), inhalation solutions, soft-mist inhalers and nasal sprays. Elastomers have been used in OINDPs for more than 50 years. Constituting an integral part of OINDP container closure systems (CCSs) and/or delivery devices (DDs), they are important to the safety and performance of drug products. Inhalation products are typically complex, consisting of a drug product formulation within a CCS that may be external to or an integral part of a DD. For example, a typical MDI consists of a metal canister (containing the drug formulation), a plastic actuator/mouthpiece and a dose metering valve incorporating elastomeric seals and metal and plastic components (Figure 1). The quality of elastomeric components and their construction is essential for ensuring that a CCS/DD functions according to its intended use in the drug product and is not detrimental to a particular product's quality, safety or efficacy.

Elastomers are important to the proper function of inhalation products such as MDIs. Elastomeric seals in the MDI valve prevent leakage of the formulation, inhibit water ingress and help ensure the patient receives a correct dose of drug. However, because elas-

Figure 1

Example of an MDI valve in cross-section (top), with its various components (bottom). [Images courtesy of Aptar Group].



tomeric seals can be in contact with drug product formulations, it is possible that various organic chemicals (e.g., oligomers, additives or degradants from the elastomers) can migrate or leach into the formulation. Because elastomeric components are critical to the quality and performance of inhalation drug products, and leached impurities from elastomers can pose a safety issue, OINDP manufacturers must carefully select elastomers based on functionality, formulation compatibility and safety implications of potential leachables. This material selection and safety qualification process is begun early in drug product development and is an important part of any CCS/DD risk management plan. OINDP manufacturers must characterize potential leachables by performing Controlled Extraction Studies on elastomeric components; identifying and quantifying actual leachables by accomplishing Leachables Studies on the final drug product; and implementing Routine Extractables Testing as required to control the quality of incoming elastomeric components. The OINDP manufacturer must also ensure that the composition of materials used in the drug product for registration and marketing is the same as that used for non-clinical safety studies and clinical studies. The selection and safety qualification of materials; verification of CCS/DD performance, functionality and compatibility with the formulation; performance of Controlled Extraction and Leachables Studies; and development of Routine Extractables Testing for quality control are complex processes that can take years to accomplish.

There are several considerations and evaluations that OINDP manufacturers must accomplish in order to adequately assess the functionality, compatibility and safety of elastomers for use in OINDPs. These activities are enhanced by specific types of information that OINDP manufacturers must exchange with elastomer suppliers to adequately meet the requirements for selection and qualification. This article describes the quality and safety expectations OINDP manufacturers have for their products, focusing on the extensive activities performed to select and qualify elastomers.

II. Selection and qualification of elastomer component materials

Multiple criteria must be considered and evaluated in selection and qualification of appropriate elastomeric component materials for use in OINDP CCS/DDs. These include:

Functional/mechanical product requirements Elastomeric components must have appropriate physical properties to meet the functional and mechanical characteristics required for the CCS/DD. These include tensile strength, modulus, hardness, compression set and "manufacturability" (i.e., the material can be readily molded or processed into the required shape).

Compatibility with the formulation Depending on the design of the CCS/DD, elastomers may be in direct contact with the formulated drug product, and as a consequence, their chemical composition may impact the stability of the formulated drug product and vice versa. For example, migration of the drug or key excipients into or onto the elastomers through absorption or adsorption may adversely affect accurate dose delivery or the stability of the formulation. Migration of compounds (leaching) out of elastomers into the drug formulation can affect the efficacy and/or stability of the formulation (e.g., by causing changes in the active ingredient particle size or degradation of the active ingredient. Failure of an elastomeric seal could allow ingress of water into the formulation and affect drug product stability (i.e., by causing aggregation of drug particles in suspension formulations, thus affecting formulation homogeneity and impacting delivered dose uniformity or causing drug or excipient degradation). Elastomers must be resistant to changes in physical properties (e.g., swelling, brittleness) caused by contact with drug product formulation constituents, such as MDI propellants (hydrofluoroalkane) and excipients (ethanol). Elastomers can also be made resistant to physical changes by incorporation of an impervious coating.

Safety—leachables and potential leachables (extractables) During the elastomeric component selection process, a basic requirement for assessing safety is information gained from *in vitro* and *in vivo* biological reactivity tests, according to the US Pharmacopeia's[1, 2] General Chapters <87> and <88> or ISO 10993.[3] The appropriate tests are dictated by the duration and nature of patient contact as well as any other special considerations for intended use and may be used to assess the potential for toxicity (e.g., systemic or genotoxicity) and biological reactivity (e.g., sensitization, irritation).
Depending on the test, the elastomer itself may be tested, or more commonly, a specified extract of the elastomer is tested. For OINDPs, Controlled Extraction Studies and Leachables Studies are critical safety assessment tools. Leachables migrate into a formulation from

Definitions

Extractable	Chemical entities that are forcibly "pulled out" or extracted from CCS/DD components under laboratory conditions, often with application of solvents and heat. These are potential leachables.
Leachable	Chemical entities that migrate out of the CCS/DD into the drug product over the shelf-life of the drug product. These are typically, but not always, a subset of extractables.

components of the CCS/DD, including elastomeric components, as a result of direct or indirect contact with the formulation over the shelf-life of the drug product. Along with the compatibility issues mentioned above, leachables may be inhaled by the patient and can have safety implications.

III. Leachables and extractables

Extractables are chemical entities that are *forcibly "pulled out"* or extracted from CCS/DD components *under laboratory conditions,* often with application of solvents and heat. Leachables are chemical entities that migrate out of the CCS/DD *into the drug product* over the *shelf-life* of the drug product. Extractables are therefore *potential leachables* and leachables are typically a subset of extractables. Regulatory authorities expect OINDP manufacturers to understand and manage leachables in inhalation products because some leachables at certain levels may pose safety issues. Extractables (and thus leachables) can result, not only from the base elastomer material, but from additives and processing aids used to provide the needed physical properties and/or manufacturability mentioned above. Thus, a key input is detailed knowledge and understanding of the qualitative and quantitative composition of the elastomer, including:

Identity of the base elastomer material (e.g., isoprene, butyl, halobutyl, ethylene propylene diene, etc.);

Identities and amounts of additives, such as curing or cross-linking agents (e.g., sulfur, peroxide), fillers (e.g., carbon black), processing aids (e.g., fatty acids, erucamide), plasticizers (e.g., silicone oil, wax, hydrocarbon oils), pigments, and stabilizers (e.g., antioxidants, UV stablizers). Consideration should be given to sources of so-called "special case" compounds[4] (e.g., polynuclear aromatic hydrocarbons (PAHs or PNAs) in carbon black filler, N-nitrosamines or mercaptobenzothiazole in sulfur-cured elastomers) (Figure 2);

Additive chemistry, including trace level contaminants/impurities and reaction/degradation products of additives, as well as secondary reaction products from the curing and/or shaping process; and

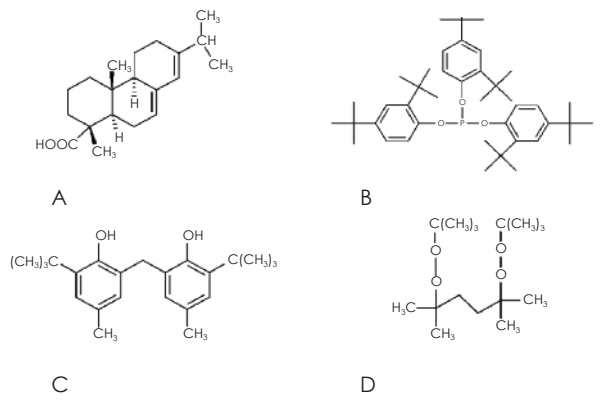
Post-manufacturing processes (e.g., sterilization or washing of finished components).

A. Controlled extraction studies

Armed with appropriate and complete information, OINDP manufacturers and/or component suppliers accomplish Controlled Extraction Studies on CCS/DD components in order to develop qualitative and quantitative profiles of extractables. In these studies, compounds that are extracted from elastomeric components in the presence of appropriate solvents under relatively vigorous conditions are analytically evaluated. Best practice recommendations[4] suggest that extractions be performed using multiple solvents of varying polarity and multiple extraction techniques (e.g., Soxhlet or reflux) to achieve so-called asymptotic levels for extractables. The resulting extracts are typically analyzed chromatographically (e.g., using gas chromatography and/or high performance liquid chromatography) to identify and quan-

Figure 2

Various polymer additives (potential leachables), including A) a filler (abietic acid), B) a phosphite antioxidant (Tris (2,4-di-tert-butylphenyl) phosphite, tradename: Irgafos 168), C) a phenolic antioxidant (2-t-butyl-6-[[3-(1,1-dimethylethyl)-2-hydroxy-5-methylphenyl]methyl]-4-methyl-phenol), and D) a peroxide curing agent (2,5-di(t-butylperoxy)-2,5-dimethylhexane).



Select abbreviations

CHMP	Committee for Medicinal Products for Human Use
CVMP	Committee for Medicinal Products for Veterinary Use
EMA	European Medicines Agency; formerly known as EMEA, European Medicines Evaluation Agency
EP	European Pharmacopoeia
ISO	International Organization for Standardization
JP	The Japanese Pharmacopoeia
PQRI	Product Quality Research Institute
USP	United States Pharmacopeia

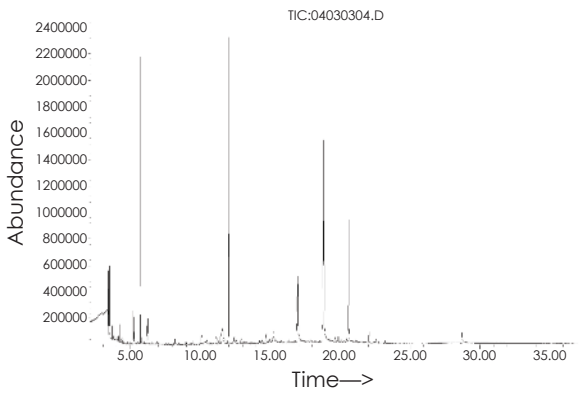
tify extractables (Figure 3). Inorganic extractables can also be determined by, for example, acid digestion of components and materials, followed by appropriate analyses of digests. Because extractables are potential leachables, Controlled Extraction Studies can allow prediction of a worst-case leachables profile. Based on the results of Controlled Extraction Studies, a safety assessment can be performed on individual identified potential leachables to determine whether the selected material remains suitable for its intended use. Additionally, the extractables profiles are assessed to determine chemical targets for Leachables Studies.

B. Leachables studies

After evaluating the results from the Controlled Extraction Studies, the OINDP manufacturer conducts Leachables Studies on the drug product to generate information about the identities and amounts of individual leachable compounds, allowing performance of a risk assessment on the actual observed leachables. The extractables profile is used as the basis for developing methods for this qualitative and quantitative evaluation of leachables. For individual leachable compounds, a safety concern threshold (SCT) of 0.15 µg per day has been proposed for OINDPs,[4] which can be used to determine the required sensitivity of the analytical method(s). Considering the drug product configuration (e.g., number of doses per day and total number of doses in a drug product unit), an analytical evaluation threshold (AET) is estimated by converting the safety concern threshold from µg/day to amount per product unit (µg/container). The analytical evaluation threshold in combination with the chemical targets identified from the extractables studies form the basis of leachables analytical methods.

Figure 3

Gas chromatography/mass spectrometry (GC/MS) extractables profile of an elastomer (2-propanol Soxhlet extraction for 16 hours).



Leachables data are generated by analysis of the drug product, when the CCS/DD components are stored in direct contact with the formulation over the anticipated shelf-life of the drug product, under conditions that represent intended use and accelerated stability conditions (i.e., temperature and humidity). At specific time-points, the drug product is analyzed using methods designed to quantify specified leachables and detect unspecified leachables. Qualitative and quantitative results of the Leachables Studies are assessed as part of the comprehensive safety evaluation of the drug product. Additionally, the toxicological assessment may show that there are specific leachables that need to be controlled, which may be possible by routine monitoring of the extractables that correlate to those leachables.

C. Extractables and leachables correlations

A qualitative extractables/leachables correlation can be established if all leachables detected can be qualitatively linked, either directly or indirectly, to corresponding extractables. A quantitative correlation can be established if the levels of individual leachables determined at the end of drug product shelf-life are less than or equal to the levels of corresponding extractables.[4] It is this quantitative relationship that can be used to establish appropriate control levels for a leachable via routine extractables testing.

D. Leachables and potential leachables safety evaluation

Safety evaluation is a critical aspect of the pharmaceutical development process, allowing safety assessment of leachables and potential leachables at early and appropriate stages of development. This evaluation should be performed at three key points in the pharmaceutical development process:

During the initial selection of components and materials, using already available composition information, certifications and associated toxicological data;

On extractables (potential leachables) identified during Controlled Extraction Studies; and

On actual leachables identified and quantified during Leachables Studies.

IV. Elastomer component supplier expectations

A. Information exchange with the supplier

From an OINDP manufacturer perspective, it is highly beneficial for all supply-chain entities (including base polymer manufacturers, additive manufacturers, elastomer compounders, component fabricators, etc.) to share all available information on elastomer composition and processing with the OINDP manufacturer and with each other. This sharing of information can facili-

tate risk assessment and materials selection, reduce redundant testing, enhance communication between suppliers and their customers about issues such as method development for extractables testing and establishing appropriate acceptance criteria, and, most importantly, help ensure the long-term safety and quality of the final drug product. It is important that OINDP manufacturers establish communication channels with immediate suppliers to make them aware of the intended uses of their materials or components and build a foundation for establishing control strategies.

B. Information needed from suppliers

There are several types of information that are useful to the OINDP manufacturer and may come from various points in the supply-chain:

Supplier certificates Compliance with indirect food additive regulations, pharmacopoeias and other regulations should be fulfilled. Therefore, it is important for elastomer suppliers to provide to OINDP manufacturers indirect food additive certificates and other compliance statements. Statements include: (i) compliance with food contact regulations and regulations for specific compounds, e.g., generally recognized as safe (GRAS), presence of phthalates or di(2-ethylhexyl) phthalate (DEHP) content;[5-7] (ii) conformance to physicochemical tests according to pharmacopoeias (USP, EP, JP);[8-11] (iii) biocompatibility of materials;[1-3, 12] (iv) conformance to guidelines for the use of tallow derived or other animal-sourced products to minimize the risk of conveying transmissible spongiform encephalopathy (TSE), including bovine spongiform encephalopathy (BSE);[13, 14] and (v) registration of medical devices according to relevant legislation.[15, 16] Elastomer suppliers should also provide toxicological data.

Composition and processing information In addition to the qualitative and quantitative information regarding the elastomer material/component composition (identity of the base elastomer material, identities and amounts of additives), suppliers should convey information related to manufacturing processes that could result in chemical modification of additives, the polymer or the components. These include: (i) the polymerization process, polymerization agents and additives/processing aids; (ii) the mixing process, temperatures, formulation ingredients and additive packages for curing and stabilization; (iii) the shaping/curing process, equipment (extruders, calenders, molding machines), equipment cleaning processes, processing and mould release aids, and process parameters; (iv) reagents, materials and processing temperatures used in treatments such as post-cure heating,

Synopsis of key points

Section	Key points
I. Introduction	• The quality of elastomeric components in OINDPs is essential for ensuring safe and effective administration of the drug product.
II. Selection and qualification	• The selection and qualification of elastomeric component materials must include consideration of the chemical nature of the materials in addition to functional/mechanical properties. • Chemical entities may leach into the product and result in formulation compatibility issues or have product safety implications.
III. Leachables and extractables	• Detailed information must be obtained regarding the chemical nature of elastomeric component materials and the associated manufacturing processes in order to adequately assess any impact on product safety. • Two specific types of characterization studies, Controlled Extraction and Leachables, are used to obtain quantitative estimates of chemical entities that can leach (extractables) and do leach into the product. • The results from these studies are used to perform toxicological assessments and develop control strategies for the product.
IV. Elastomeric component supplier expectations	• To ensure the long-term safety and quality of the product, it is important that information regarding the elastomeric component materials be shared among relevant parties in the OINDP manufacturer's supply chain. • The information expected to be shared includes intended use of materials, regulatory compliance statements or certificates, composition and processing information and extractables profiles. • Meeting these expectations enables the OINDP manufacturer to take a rationalized and risk-based approach to elastomeric component material selection and qualification.

coating, siliconization and/or cleaning/washing processes; (v) the storage/shipping environment for the components; and (vi) treatments such as coating, siliconization and/or cleaning/washing processes as these can either reduce potential leachables levels and/or introduce new potential leachables.

Extractables profile for material Component suppliers should provide (if available), extractables profiles of elastomeric components obtained with appropriate best practice procedures.[4] In an ideal situation, the supplier would control the extractables profile from batch to batch of component, accomplished with process controls and/or monitored by appropriate routine extractables testing.

V. Conclusion

A rationalized and risk-based approach to selection and qualification of OINDP CCS/DD elastomeric materials and components is critical in ensuring the quality and safety of OINDPs. This process must include appropriate and comprehensive sharing of information between suppliers and OINDP manufacturers. **Another key element of this process, change management, will be addressed in Part 2 of this article, to be published in the June 2012 issue of *Inhalation*.**

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