

*DEVELOPMENT OF
SAFETY THRESHOLDS,
SAFETY EVALUATION,
AND QUALIFICATION
OF EXTRACTABLES
AND LEACHABLES IN
ORALLY INHALED AND
NASAL DRUG
PRODUCTS*

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OVERVIEW OF LEACHABLES AND EXTRACTABLES IN ORALLY INHALED AND NASAL DRUG PRODUCTS

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1.1 INTRODUCTION

The purpose of this book is to provide a historical perspective on the development and application of safety thresholds in pharmaceutical development, and to discuss the development and implementation of safety thresholds for the qualification of organic leachables, a particular class of drug product impurity, in orally inhaled and nasal drug products (OINDPs). The book will also describe and consider the United States Food and Drug Administration (FDA) and international regulatory perspectives concerning the qualification of organic leachables in OINDP. Although the book is written specifically for OINDP, the principles used in defining safety thresholds could be applied to organic leachables in other drug product types.

Since the environmental movement of the 1970s, analytical chemistry and analytical techniques have become increasingly sophisticated and sensitive, capable of detecting, identifying, and quantifying both organic and inorganic chemical entities at ultratrace (i.e., parts per trillion) levels.¹ However, it is generally accepted that there are levels of many chemicals below which the risks to human health are so negligible as to be of no consequence. This rationale has been a strong impetus for development of safety thresholds for regulating chemicals to which humans are exposed, most notably in the federal regulations for food packaging.^{2,3} Safety thresholds have also been developed for application to pharmaceuticals, including organic impurities in drug substances⁴ (process and drug related), drug products,⁵ and residual solvents in drug substances and drug products.⁶ Note that the international regulatory guidance for drug product impurities specifically excludes from consideration “impurities . . . leached from the container closure system.”⁵

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Figure 1.1 Patients using metered dose inhaler (top) and dry powder inhaler (bottom) drug products. Note that each patient's mouth is in direct contact with the drug delivery device/container closure system, and that doses of drug formulation are delivered directly into each patient's mouth for inhalation. (Images provided by Bepak, a division of Consort Medical plc; www.bepak.com.)

OINDPs are developed for delivery of active pharmaceutical ingredient (API or drug substance) directly to the respiratory or nasal tract, to treat either a respiratory or nasal condition, or a systemic disease. Examples of OINDP include metered dose inhalers (MDIs), dry powder inhalers (DPIs), solutions/suspensions for nebulization, and nasal sprays (see Figs. 1.1 and 1.2). These drug product types incorporate complex delivery devices and container closure systems whose function and



Figure 1.2 Patient using a nasal spray drug product. Note that the patient's nasal mucosa is in direct contact with the drug delivery device/container closure system, and that doses of drug formulation are delivered directly into the patient's nasal passages for inhalation. (Image provided by Bespak, a division of Consort Medical plc; www.bespak.com.)

performance are critical to the safety and efficacy of the drug product. Components of OINDP delivery systems can be composed of polymers, elastomers, and other materials from which minute quantities of chemicals can migrate (i.e., leach) into the drug product formulation and be delivered to the sensitive surfaces of the respiratory and/or nasal tract along with the therapeutic agent. FDA guidance considers these drug product types high risk for containing leachables, which are delivered to the patient, because of the route of administration and because of the direct interaction of packaging and/or device components with drug formulation.⁷ While every effort is usually taken to reduce the levels of leachables, complete removal is neither practical nor desirable as many of these chemical entities perform important functions in container closure system components. Since leachables are non-drug-related impurities, there is an increased concern regarding the human risk associated with inhaling them on a daily basis, often for many years or decades. Historically, acceptable levels of leachables in OINDP have been set by negotiation with regulatory authorities on a case-by-case basis with no standard guidelines available. Recently, however, safety thresholds for risk assessment of organic leachables have been developed through a joint effort of scientists from the FDA, academia, and industry.^{8,9} This book will address the concepts, background, historical use, and development of safety thresholds and their utility in qualifying organic leachables in OINDP.

1.2 LEACHABLES IN OINDP: THE ISSUE IN DETAIL

The FDA guidance documents for MDIs/DPIs,¹⁰ and nasal spray, and inhalation solution, suspension and spray drug products¹¹ state that *leachables* are “compounds that leach from elastomeric, plastic components or coatings of the container and closure system as a result of direct contact with the formulation,” and *extractables* are “compounds that can be extracted from elastomeric, plastic components or coatings of the container and closure system when in the presence of an appropriate solvent(s).”

In short, extractables are chemical entities that are derived from container closure and/or device components *under laboratory conditions*. Leachables are chemical entities derived from container closure and/or device components when they are *part of the final drug product and under patient-use conditions*. Leachables are, therefore, either a subset of extractables or can be correlated indirectly with extractables (e.g., via chemical reaction), and all extractables are *potential leachables*. Patients can be exposed to leachables through the normal use of the drug product.

OINDPs are used in the treatment of a variety of lung- and nasal-related conditions such as asthma, chronic obstructive pulmonary disease (COPD, such as emphysema or chronic bronchitis), and allergic rhinitis, as well as systemic diseases such as diabetes. This latter therapeutic application suggests that the inhalation route has potential for wider use in the treatment and management of a variety of disease states.

All OINDP types include a drug product formulation (API along with excipients) in direct contact with areas of the container closure system and parts of the drug product device that facilitate accurate dose delivery for inhalation by the patient and/or protect the integrity of the formulation. Figure 1.3 shows a schematic diagram of an MDI drug product, and Figure 1.4 shows a “cutaway” view of a dose metering valve. The MDI consists of a solution or suspension formulation containing a drug substance (API), chlorofluorocarbon (CFC), or hydrofluoroalkane (HFA) propellant to facilitate aerosol dose delivery, and surfactants, co-solvents and other excipients to help stabilize the formulation. The container closure and device system includes a metal canister to contain the pressurized formulation, a valve to meter the dose to the patient, elastomeric components to seal the valve to the canister, and an actuator/mouthpiece to facilitate patient self-dosing. The formulation and container closure system are closely integrated in the MDI drug product, and leachables may be derived from the elastomeric seals between the valve and metal canister (e.g., gaskets), plastic and other types of polymeric valve components (e.g., metering chamber, valve stem), and organic residues or coatings on the surfaces of the metal canister and metal valve components. As shown in Figure 1.1, the patient’s mouth is also in contact with the actuator/mouthpiece during normal use of the drug product.

Although the DPI can be a more complex device/container closure system than the MDI (see Fig. 1.5), the potential for leachables issues is significantly reduced. This is because the drug product formulation in the DPI is by definition a dry powder and, therefore, contains no solvent systems such as the organic propellants and co-solvents in the MDI formulation, which can facilitate leaching. However, DPI doses are usually contained in unit dose blister packs, capsules, and similar packaging systems, which include plastic, foil, and/or laminate overwraps that contact the drug

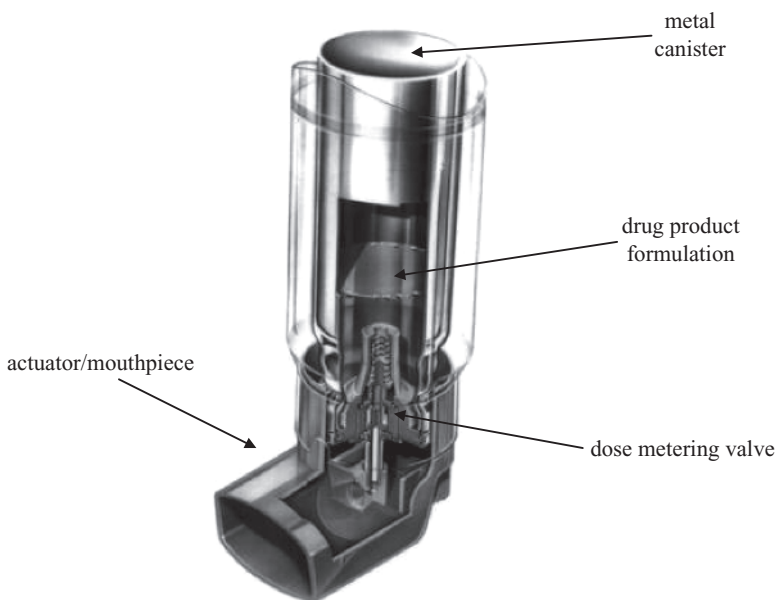


Figure 1.3 Schematic diagram of a metered dose inhaler (MDI) drug product. Note that the elastomeric, plastic, and metal components of the dose metering valve, as well as the metal canister inner surfaces, are capable of leaching chemical entities into the drug product formulation. The actuator/mouthpiece is in contact with the patient's mouth (see Fig. 1.1). (Images provided by Bepak, a division of Consort Medical plc; www.bepak.com.)

product formulation directly during storage. Also, the dry powder can contact certain surfaces of the DPI device during dose delivery, and as with the MDI, the patient's mouth contacts the mouthpiece (Fig. 1.1). Nasal spray and inhalation spray drug products can also include device/container closure system components with leaching potential (i.e., plastic containers and tubes, elastomeric seals); however, these drug product formulations are typically aqueous based and therefore have a generally reduced leaching potential compared with the organic solvent-based MDI drug products. Inhalation solutions are also mostly aqueous based and typically packaged in unit dose plastic containers (e.g., low-density polyethylene). Delivery of inhalation solution drug product to patients is usually accomplished via commercially available nebulizer systems. It is interesting to note that certain types of plastic, such as low-density polyethylene, can allow gaseous chemical substances from the surrounding environment to penetrate into the drug product. As a result of this, many inhalation solutions are stored in secondary packaging systems such as foil pouches.

The variety and complexity of OINDP and the different potentials for container closure system leaching among the various OINDP types should be clear from the above discussion. The organic chemicals that can appear as extractables and leachables represent an additional level of complexity. Extractables and leachables are generally low-molecular-weight organic chemicals either purposefully added to the packaging or device materials during synthesis, compounding, or fabrication (e.g.,

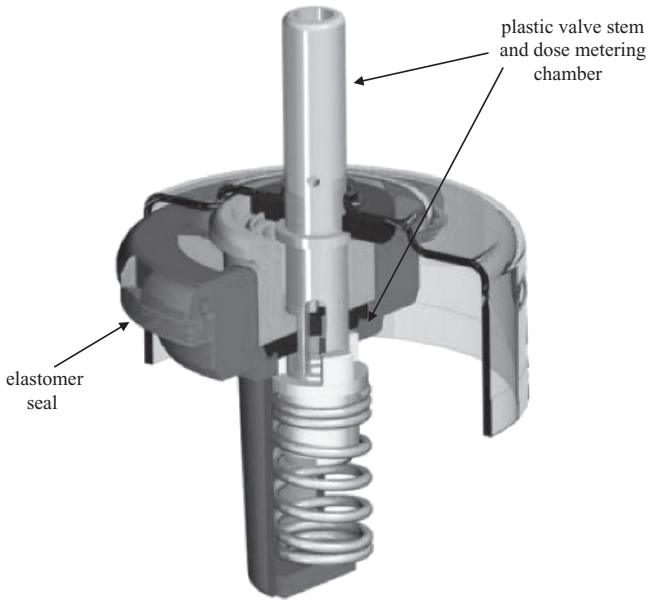


Figure 1.4 Cutaway diagram of a metered dose inhaler (MDI) dose metering valve showing the various metal, plastic and elastomeric components potentially in contact with the drug product formulation. (Images provided by Bespak, a division of Consort Medical plc; www.bespak.com.)



Figure 1.5 Cutaway diagram of a dry powder inhaler (DPI) showing the internal complexity of the device/container closure system and its many components. Many DPI components are plastic or elastomeric and therefore potentially capable of leaching. (Images provided by Valois Pharma.)

polymerization agents, fillers, antioxidants, stabilizers, and processing aids), or present in the materials as a by-product of synthesis, compounding, or fabrication (e.g., oligomers, additive contaminants such as polyaromatic hydrocarbons [PAHs] or polynuclear aromatics [PNAs] and reaction products such as *N*-nitrosamines). All of these chemical entities have the capacity to move from the packaging or device components into the OINDP formulation, and thus be delivered to the patient. Table 1.1 provides examples of potential sources of extractables and leachables from OINDP.¹² Unlike drug-substance-related impurities, leachables can represent a wide variety of chemical types (see some examples in Fig. 1.6) and be present in drug products at widely variable concentration levels, from perhaps several tens of micrograms per canister in the case of named additives to an MDI valve elastomeric seal,

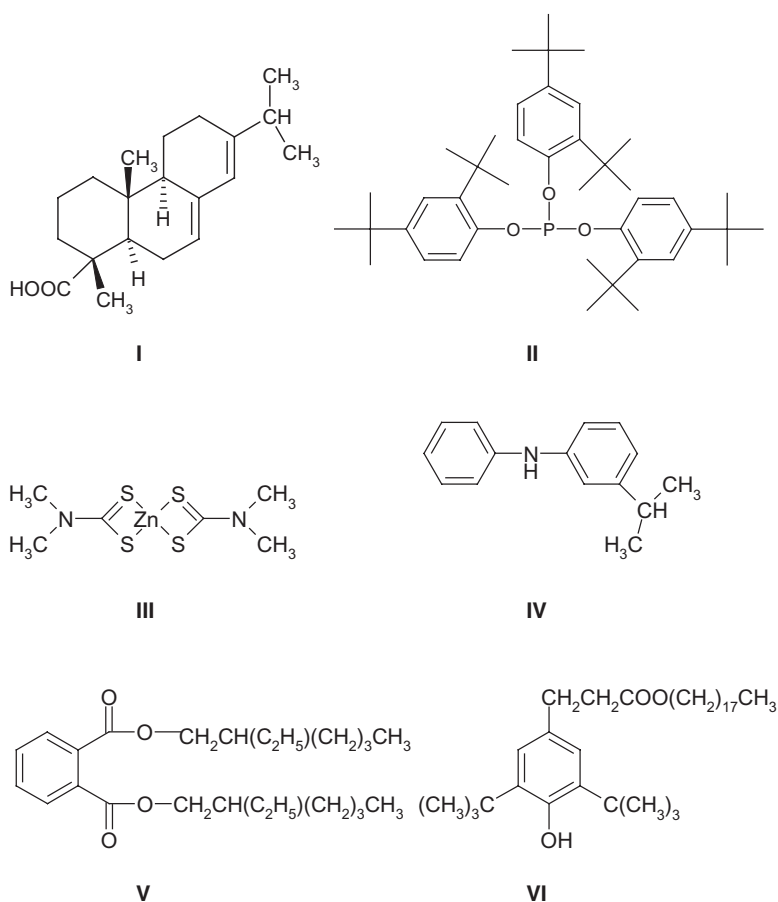


Figure 1.6 Some examples of chemical entities that can appear as extractables and/or leachables associated with OINDP. (I) Abietic acid (a filler for certain elastomers); (II) Irgafos 168 (a phosphite antioxidant); (III) zinc tetramethyldithiocarbamate (an accelerator for certain sulfur-cured elastomers); (IV) isopropylidiphenylamine (an antioxidant); (V) di-2-ethylhexylphthalate (a plasticizer); (VI) Irganox 1076 (an antioxidant).

to several nanograms per canister in the case of a volatile *N*-nitrosamine rubber polymerization by-product. Additional detailed discussions are available regarding the variety and origins of extractables and leachables.^{8,12}

1.3 REGULATORY BACKGROUND

The U.S. regulatory history of extractables and leachables in OINDP was summarized and discussed by Dr. Alan Schroeder of the FDA Center for Drug Evaluation and Research (CDER), at a workshop on the topic in 2005.¹³ Regulatory attention was focused in two general areas: clinical and quality control. Clinical concerns resulted from the fact that the majority of OINDPs are administered to a sensitive and already compromised patient population, that is, patients with asthma or COPD. It is known that some of these patients can experience a condition known as *paradoxical bronchospasm*. Bronchospasm is defined as a condition in which the airways suddenly narrow, causing coughing or breathing difficulty, like an asthma attack.¹⁴ Paradoxical bronchospasm is a relatively rare event in which a medicine prescribed to treat bronchospasm or the underlying condition, has the effect of causing bronchospasm, which can be life threatening. Some hypothesized that patient sensitivity to leachables in the drug product could contribute to this condition. Beyond paradoxical bronchospasm, regulators were concerned that OINDPs are often prescribed for chronic use, and therefore, patients would potentially be exposed to leachables over many years. Clinical concerns can be linked to quality control issues, such as control of the OINDP manufacturing process, the consistency of container closure system materials and components, and the control of unintended contaminants.

Schroeder added that regulatory concern and regulation of OINDP leachables have evolved over time as problems were observed in specific drug products and increased knowledge regarding component materials and manufacturing processes was acquired. The first example dates to the mid- to late 1980s and involved the observation of PNAs (PAHs) in extracts of an MDI elastomeric valve component following the detection of PNAs as leachables in the corresponding drug product. The resulting increased awareness and understanding of leachables led FDA to request that MDI manufacturers investigate an additional class of known elastomeric extractables of potential safety concern, the volatile *N*-nitrosamines. *N*-nitrosamines are trace-level reaction by-products of certain sulfur “curing agents” used in rubber vulcanization (cross-linking) processes. *N*-nitrosamines had previously been found in baby bottle rubber nipples at trace (parts per billion) levels, and had been regulated by the FDA as extractables from these components (see Reference 12 for a more detailed discussion and additional references regarding *N*-nitrosamines). Additional concern and investigation centered on 2-mercaptobenzothiazole, another rubber vulcanization reaction by-product and sometimes known rubber additive, again in MDI drug products. As knowledge and understanding built through the 1990s, concern broadened to include other classes of extractables/leachables (Table 1.1), metal component organic residues, as well as the previously mentioned issue of migration of extraneous organics through container walls. For the latter concern, Schroeder described a case study involving the migration of vanillin derived from

TABLE 1.1. Potential Sources of Extractables and Leachables from OINDP^a

Potential sources	MDI	DPI	Inhalation solutions, suspensions, and sprays	Nasal sprays			
Metal components (MDI valve components, canisters, etc.) <ul style="list-style-type: none"> • Residual cleaning agents, organic surface residues • Coatings on internal canister surface 							
Elastomeric container closure system components (gaskets, seals, etc.) <ul style="list-style-type: none"> • Antioxidants, stabilizers, plasticizers, and so on • Monomers and oligomers • Secondary reaction products from curing process 							
Plastic container closure system components (plastic MDI valve components, mouthpieces, plastic container material) <ul style="list-style-type: none"> • Antioxidants, stabilizers, plasticizers, and so on • Monomers and oligomers from the polymeric material • Pigments 							
Processing aids, for example, chemicals applied to surfaces of processing/fabrication machinery, or directly to components <ul style="list-style-type: none"> • Mold release agents • Lubricants 							
Blisters or capsules containing individual doses of drug product <ul style="list-style-type: none"> • Chemical additives • Adhesives and glues 							
Labels, for example, paper labels on inhalation solution plastic containers <ul style="list-style-type: none"> • Inks • Adhesives/glues 							

^a Shading means that source is relevant for a given dosage form.

cardboard shipping containers through the low-density polyethylene packaging system of an inhalation solution drug product. Vanillin is associated with lignin, which is a major component of wood from which paper is derived.¹⁵

As knowledge of the identities and origins of extractables and leachables associated with OINDP increased, regulatory interest and concern both increased and broadened. The initial focus on PNAs in MDI drug products has now evolved into a general interest and concern regarding safety and quality control for all leachables and potential leachables in every OINDP type.

1.4 WHY DO WE NEED SAFETY THRESHOLDS?

Modern analytical chemistry has enormous capability for analyzing extractables and leachables in OINDP and other drug product types. Analytical challenges of this general type are best approached as problems in the field of trace organic analysis (TOA).¹ TOA can be defined as the qualitative and/or quantitative analysis of a complex mixture of trace level organic compounds contained within a complex matrix.¹⁶ Solving TOA problems generally requires knowledge of the chemical nature of the analyte mixture; removal or extraction of the analyte mixture from its matrix; separation of the analyte mixture into individual chemical entities; and compound-specific detection of the individual chemical entities.¹⁶ Analytical techniques capable of separating, detecting, identifying, and quantifying individual organic extractables and leachables include gas chromatography/mass spectrometry (GC/MS), (high-performance) liquid chromatography/mass spectrometry (LC/MS or HPLC/MS), and (high-performance) liquid chromatography/diode array detection (LC/DAD or HPLC/DAD). These advanced analytical technologies are now in routine use in pharmaceutical development laboratories (see Fig. 1.7), and have been applied to extractables/leachables problems for almost 20 years (e.g., see Norwood et al.¹⁷ regarding analysis of PNAs in MDI drug products by GC/MS).

A GC/MS extractables “profile” from a laboratory-controlled extraction study⁸ conducted on an elastomeric container closure system component material is shown in Figure 1.8. The display in Figure 1.8 is normalized to the most concentrated individual extractable. An expanded view of a similar GC/MS profile is shown in Figure 1.9. The problem faced by the OINDP pharmaceutical development scientist should now be obvious. As Figures 1.8 and 1.9 suggest, a single extractables mixture derived from a single type of container closure system component material and analyzed with a single analytical technique, can result in an extractables profile with perhaps hundreds of individual chemicals to identify and quantify. Under today’s typical pharmaceutical development practice, this single mixture would be analyzed by a variety of analytical techniques as described above, resulting in several equally complex extractables profiles. Furthermore, OINDP container closure systems often contain many components with leaching potential (see Fig. 1.10). This consideration does not include the original issues of PNAs, volatile *N*-nitrosamines, and 2-mercaptobenzothiazole, which are still considered as “special case” compounds⁸ by the FDA and require special scrutiny by ultrasensitive and specific analytical technologies. Given the enormity of these challenges, it is clear that a more rational approach is needed—one that tells the pharmaceutical development scientist “how low to go” in the search for extractables and leachables.

1.5 SAFETY THRESHOLDS AND THEIR APPLICATION TO LEACHABLES IN OINDP

Safety thresholds for OINDP leachables would provide a means of determining just “how low to go” in their evaluation and management, allowing the pharmaceutical development scientist to confidently identify from the full universe of leachables



Figure 1.7 Typical GC/MS (top) and LC/MS (bottom) systems in common use in pharmaceutical development laboratories. Such systems are used to identify and quantify drug- and excipient-related impurities and metabolites, as well as extractables and leachables.

only a subset of compounds (i.e., those above a given threshold) that should undergo risk assessment and safety qualification, while still providing an ample margin of assurance that those leachables below the threshold pose no safety concern for patients. Safety thresholds have been developed for other applications where control of human exposure to specific chemicals is important. These include the thresholds for indirect food additives and International Conference on Harmonisation (ICH) thresholds for APIs and residual solvents.^{4-6,18} Furthermore, it is well established that there are levels at or below which organic chemical entities in drug product represent no safety concern to patients. Therefore, the establishment of safety thresholds that are protective of patients for OINDP leachables and extractables can be justified and are believed to be necessary to limit unreasonable and extended evaluations of chemicals present at levels that cannot harm patients.

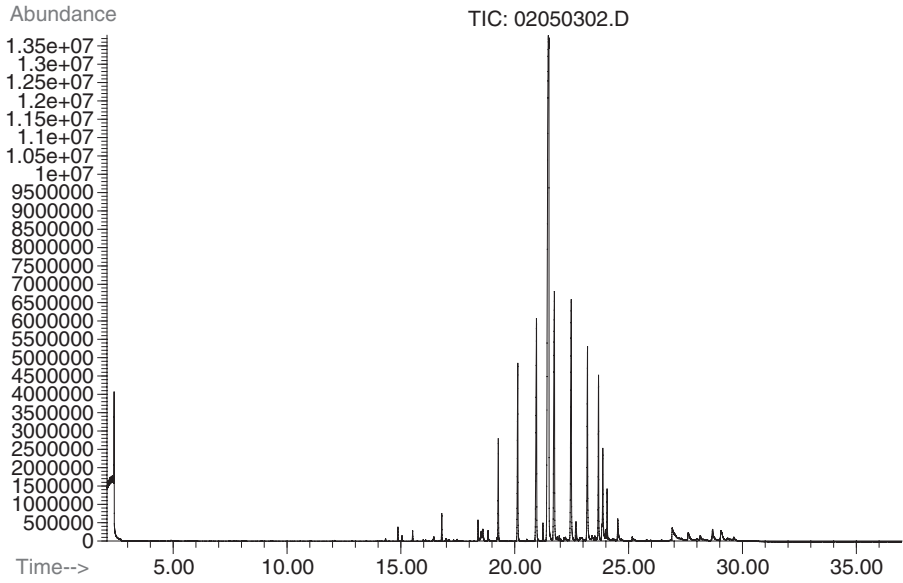


Figure 1.8 A GC/MS extractables “profile” of an elastomer (total ion chromatogram of a solvent extract).

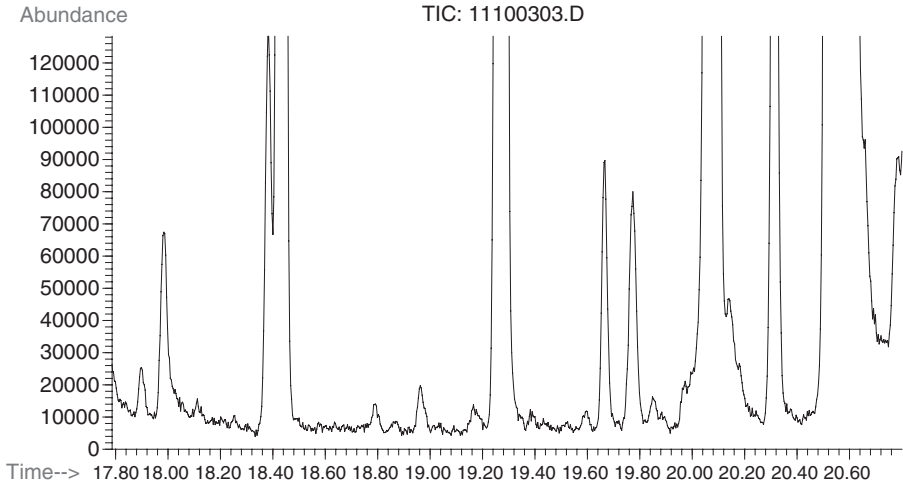


Figure 1.9 Expanded region of a GC/MS extractables “profile” of an elastomer (total ion chromatogram of a solvent extract).

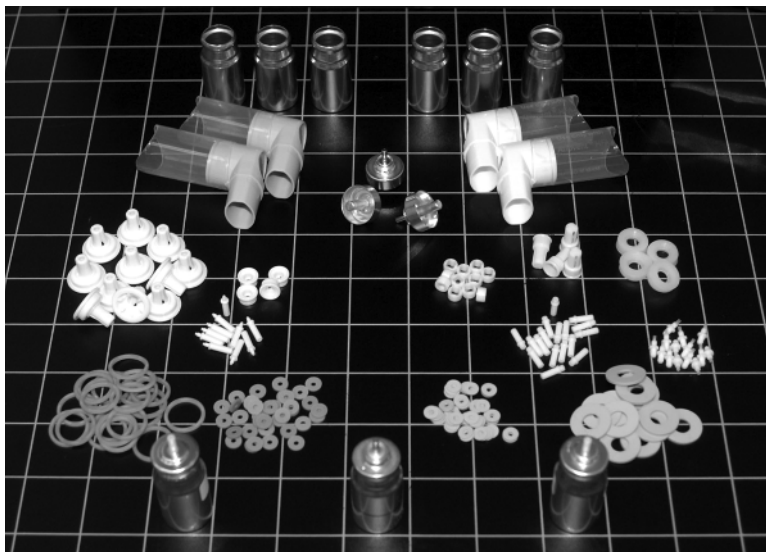


Figure 1.10 Components of the container closure system of an MDI drug product capable of contributing leachables and potential leachables (i.e., extractables).

1.5.1 Context

The first MDI was introduced by Riker Laboratories in the mid-1950s.¹⁹ At that time, there were no regulatory guidance documents that specifically focused on leachables in OINDP. From a safety perspective, however, it is important to note that general guidelines from the federal regulations were available. These explained that drug product is deemed adulterated “if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health.”^{7,20}

As previously mentioned, leachables were treated as common impurities until the 1980s when known leachables issues (e.g., PNAs leached from carbon-black-containing elastomers) raised awareness that MDI container closure system components could affect the overall safety and quality of the drug product. Through the 1990s, the FDA became increasingly concerned about leachables issues in particular drug products. In 1999, the agency issued its guidance on container closure systems,⁷ which calls for drug product manufacturers to provide information showing that the proposed container closure system and its component parts are suitable for their intended use. The type and extent of information that should be provided in an application will depend on the dosage form and the route of administration. The guidance also proposed a safety classification based on the type of drug product with the drug products of highest concern having the more stringent safety requirements (Table 1.2).

Shortly thereafter, in 1999 and 2002, FDA issued its specific guidance for pulmonary and nasal products,^{10,11} addressing leachables and extractables in detail, stating that

TABLE 1.2. Safety Characterization of Extractables for Various Routes/Dosage Forms

Route/dosage form	Safety category	Typical safety data provided
Inhalation aerosol Inhalation solution Nasal spray	Case 1s	USP Biological Reactivity Test data, extraction/toxicological evaluation, limits on extractables, batch-to-batch monitoring
Injection Suspension/powder for injection Sterile powders Ophthalmic solution/suspension	Case 2s	USP Biological Reactivity Test data; possibly extraction/toxicological evaluation
Topical delivery system Topical solution/suspension Topical and lingual aerosols Oral solutions/suspensions	Case 3s	<i>Aqueous-based solvents</i> Reference to indirect food additive regulations <i>Nonaqueous solvents and co-solvents</i> Reference to indirect food additive regulations Additional suitability information
Topical powders Oral tablets and capsules	Case 4s	Reference to indirect food additive regulations
Inhalation powders	Case 5s	Reference to indirect food additive regulations, USP Biological Reactivity testing for mouthpiece

- the profile of *each critical component extract* should be evaluated both analytically and toxicologically;
- the toxicological evaluation should include appropriate *in vitro* and *in vivo* tests;
- a rationale, based on available toxicological information, should be provided to support acceptance criteria for components in terms of the extractables profile(s);
- safety concerns will usually be satisfied if the components that contact either the patient or the formulation meet food additive regulations and the mouthpiece meets the USP Biological Reactivity Test criteria (USP <87> and <88>); and
- if the components are not recognized as safe for food contact under appropriate regulations, additional safety data may be needed.

In 2001, in response to this guidance, the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) and the Inhalation Technology Focus Group of the American Association of Pharmaceutical Scientists, developed a Points to Consider document proposing safety thresholds for OINDP leachables, as well as a justification for the thresholds, based on human exposure studies of inhaled particulate matter.²¹ Specifically, the document proposed that qualification be performed on only those leachables that occur above data-supported thresholds (>0.2 µg total daily intake [TDI]).

1.5.2 Safety Thresholds for OINDP

At the suggestion of the FDA, and with the desire to develop a wider consensus on safety thresholds for OINDP leachables that would include regulators and other stakeholders from industry and the scientific community, IPAC-RS proposed the development of safety thresholds for OINDP as a project for the Product Quality Research Institute (PQRI).

In 2001, PQRI accepted the proposal and commenced this project.²² At the time, there was no regulatory guidance available for drug products that applied such thresholds. The ICH thresholds for impurities are not applicable to leachables and extractables.⁴⁻⁶

The PQRI Leachables and Extractables Working Group, consisting of toxicologists and chemists from industry, FDA, and academia, developed a safety concern threshold (SCT) and a qualification threshold (QT) for leachables; an analytical evaluation threshold (AET) for extractables and leachables; processes for applying these thresholds; and best practices for selecting OINDP container closure system components and conducting controlled extraction studies, leachables studies, and routine extractables testing. These “recommendations” provided, for the first time, data-based safety thresholds for extractables and leachables in OINDP, established with a broad stakeholder consensus.⁸ Furthermore, the recommendations provided a comprehensive and rationalized approach to applying these thresholds within the context of the OINDP pharmaceutical development process.

The PQRI SCT was proposed to be 0.15 $\mu\text{g}/\text{day}$, and the QT was 5 $\mu\text{g}/\text{day}$. The SCT is the threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and noncarcinogenic toxic effects. The QT is the threshold below which a given noncarcinogenic leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents structure–activity relationship (SAR) concerns. Below the SCT, identification of leachables generally would not be necessary. Below the QT, leachables without structural alerts for carcinogenicity or irritation would not require compound-specific risk assessment.

The recommendations also describe how the SCT can be translated into an AET, using individual product parameters such as dose per day, actuations per canister, and so on. The AET is defined as the threshold at or above which an analytical chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment. The AET allows the pharmaceutical development scientist to determine, based on safety considerations, “how low to go” in identifying and quantifying peaks in leachables and extractables profiles from OINDP. In 2006, the PQRI recommendations were submitted to the FDA for consideration in the agency’s development of regulatory recommendations for OINDP.

1.6 SUMMARY

OINDPs have been available to patients for more than 50 years. Increasingly sophisticated liquid aerosol and DPIs have been developed to provide precise dosing of

potent medicines to asthmatic and COPD patients. In parallel, a diverse number of elastomers and polymers have been used in the construction of these inhalers, each with unique extractables and leachables profiles. The application of thresholds such as the SCT, QT, and AET has provided scientifically justified approaches to identifying, reporting, and qualifying extractables and leachables in OINDP.

This book discusses in detail the concepts of safety-based thresholds and their application to leachables in OINDP, extractables from OINDP critical components, and concepts and approaches addressing best practices for management of extractables and leachables from OINDP and OINDP components. Part I of this book addresses development of safety thresholds and their application. Chapter 2 provides the context for safety qualification of extractables and leachables, describing the suitability for intended use requirements for materials used in pharmaceutical products and therefore describing fundamental concepts for understanding extractables and leachables and why evaluation and qualification of these compounds are so important for certain drug products, including OINDP. Background on the development and application of thresholds for various consumer products in general is provided in Chapter 3. Chapter 4 then provides details of the concepts and approaches used to develop safety thresholds for OINDP leachables. Following this, Chapter 5 provides a description of the development and application of the AET for extractables and leachables. Chapter 6 describes the history of safety qualification of OINDP extractables/leachables, from an industry perspective, and also describes, at a high level, how the safety thresholds for OINDP can be applied in the pharmaceutical development process. Chapter 7 provides further detail on the application of safety thresholds, providing case studies on how the chemist and toxicologist can collaborate in the development process to evaluate extractables and leachables, and how in specific cases, thresholds may be applied. Chapter 8 provides a perspective on the FDA's application of safety thresholds in its review of OINDP. Finally, Chapter 9 provides a regulatory perspective from Health Canada on extractables and leachables in drug products as well as the application of safety thresholds. Chapter 10 provides a detailed introduction to Part II of this book, which focuses on the aforementioned best practices.

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