

*Edited by* Douglas J. Ball, Daniel L. Norwood,  
Cheryl L. M. Stults, and Lee M. Nagao

# Leachables and Extractables Handbook

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*Safety Evaluation, Qualification,  
and Best Practices Applied  
to Inhalation Drug Products*



*LEACHABLES AND  
EXTRACTABLES  
HANDBOOK*



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# *LEACHABLES AND EXTRACTABLES HANDBOOK*

Safety Evaluation, Qualification, and  
Best Practices Applied to Inhalation  
Drug Products

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## *ROBERT KROES: IN MEMORIAM*

This book is dedicated to the memory of Professor Robert Kroes whose scientific contributions played a vital role in developing the concept of the threshold of toxicological concern and the application of that concept to important societal issues including the safety evaluation of inhalable pharmaceutical products.

Robert Kroes, known as Bobby to his friends and colleagues around the world, was a native of The Netherlands. He received his Doctor of Veterinary Medicine in 1964. His training in Veterinary Medicine provided him with a solid scientific basis for a career grounded in comparative medicine, toxicology, and risk assessment, with a focus on the promotion of human health. In 1964, he was appointed Research Scientist at the National Institute of Public Health, which later became the National Institute of Public Health and Environment (known by the Dutch acronym, RIVM) in Bilthoven, The Netherlands. In 1970, he received a PhD in experimental pathology. He became a certified toxicologist in 1988 and a certified laboratory animal pathologist in 1989.

In 1972, he became Head of the Department of Oncology in the National Institute of Public Health. During this time in his career, he made important scientific contributions to understanding carcinogenicity. Moreover, he soon became a key contributor to major scientific committees within The Netherlands and on the international scene including the Benelux, the European Community, the Food and Agricultural Organization of the United Nations, and the World Health Organization. He was a member and, ultimately, Chair of the Dutch Scientific Council on Cancer Research of The Netherlands Academy of Science. He was a key contributor in the development of the first cancer research policy plan (1980–1984) of the Dutch Organization for Cancer Research.

In 1977, he was appointed Deputy Director of the Central Institute for Food and Nutrition Research (CIVO-TNO). In that position, he provided critical leadership for stimulating research in carcinogenesis, toxicology, biochemistry, and nutrition. In 1980, he became Director of the CIVO-TNO Institute for Toxicology and Nutrition. In 1983, he was appointed as a Director of RIVM with responsibility for managing the Institute's toxicology and pharmacology programs. He was also responsible for guiding the institute's advisory mission to the government with respect to the safety of chemicals. In 1988, he developed the Center for Epidemiology, further broadening the scope of RIVM's activities. In 1988, he began a part-time association as a Professor of Biological Toxicology in the Research Institute for Toxicology of the University of Utrecht. In 1989, he became Deputy Director-General of RIVM. In 1995, he retired from his leadership roles at RIVM. In that year, he became the Scientific Director of the Institute for Risk Assessment Sciences (IRAS) of the University of Utrecht. He retired from IRAS in 2005.

The use of the word “retired” certainly did not apply to Bobby’s scientific activities. He continued to play a prominent role in many scientific advisory groups in The Netherlands and on the international scene. He had a key role in the National Institute of Toxicology. Of special note are the key roles he played in the International Life Sciences Institute (ILSI) and the related ILSI Risk Science Institute, as well as the International Union of Toxicology. He served the latter organization in multiple roles including service as president-elect and was scheduled to assume the position of president in 2007. Unfortunately, Bobby lost a courageous battle with cancer and died on December 28, 2006.

During his scientific career spanning over four decades, Bobby’s many important scientific contributions to the fields of oncology, toxicology, comparative medicine, and risk assessment are well documented in some 200 publications he authored or coauthored. As noteworthy as those contributions are, his most significant contributions came from his ability to rise above the scientific details and understand how to synthesize and integrate science and relate it to important societal health issues. He took a pragmatic view and focused on concepts and solutions to resolving complex issues. He was truly a problem solver.

This pragmatic, science-based approach was exemplified by Professor Kroes championing the use of the concept of “threshold of toxicological concern” (TTC) and its application to the safety of food and pharmaceuticals. The TTC concept refers to the establishment of a generic human exposure threshold for groups of chemicals below which there would be no appreciable risk to human health. He recognized that such a value could be identified for many chemicals, including those of unknown toxicity, by considering their chemical structure and drawing analogies from the known toxicity and modes of action of many chemicals that have been extensively studied. In December 2005, the Product Quality Research Institute organized a workshop to address the use of the TTC concept in evaluating the safety of inhalable pharmaceuticals. The organizers were unanimous in deciding that Professor Kroes should be invited to give an opening presentation to set the stage for the workshop. He gave a marvelous review of the developing field. His presentation served to energize activities that culminated in preparation of this volume. Therefore, it is indeed fitting that this volume be dedicated to the memory of Professor Robert Kroes. In using the science-based concepts championed by Professor Kroes, we celebrate the value of his contributions as a scientist and, for many of us, also have the opportunity to recall a wonderful friend who lived life to its fullest.

*Roger O. McClellan, DVM, DSc (Honorary), DABVT, DABT, FATS*



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# *PREFACE*

The establishment of data-based safety thresholds for leachables and extractables in orally inhaled and nasal drug products (OINDPs) is an important scientific advancement that helps OINDP manufacturers make knowledge-based safety and risk assessments for extractables and leachables and ensure the safety of their products for patient use. This book describes the development and application of these safety thresholds for OINDP and best practices for the chemical evaluation and management of extractables and leachables throughout the pharmaceutical product life cycle. Although the book addresses OINDP-specific thresholds and best practices, many of the general concepts presented can be applied to extractables and leachables assessments for other drug product types and dosage forms. The purpose of this book is to provide the reader with practical knowledge regarding how and why the thresholds were developed and how they can be applied, as well as practical approaches to management of extractables and leachables. This book is useful to analytical chemists, packaging and device engineers, formulation development scientists, component suppliers, regulatory affairs specialists, and toxicologists, all of whom must work together in the pharmaceutical development process to identify, qualify, and manage extractables and leachables.

Management of extractables and leachables in OINDP is a critical part of the OINDP life cycle. By “management” we mean a thorough understanding of (1) potential and actual extractables from a given container closure system or device material for the purposes of eliminating or limiting the levels of leachables from such materials and (2) potential safety concerns associated with these extractables and/or leachables. These issues highlight the key regulatory and industrial concern regarding leachables in OINDPs as well as other drug products—that of patient safety. Regulatory guidance identifies patient exposure to leachables via OINDPs as an area of high importance in risk assessments for these products. Over the last 30 years, scientific and regulatory thought has evolved on the best ways to approach both chemical and safety assessments of extractables and leachables in the OINDP pharmaceutical development process. A vexing challenge in these assessments has been knowing “how low to go” in determining what concentrations of extractables and leachables should be evaluated for safety assessments; that is, is there a threshold of safety that can be established for the majority of compounds that could be found as leachables or extractables in OINDPs, such that compounds existing at levels below the threshold need not undergo safety evaluation? This question has become increasingly important with the continuous advancement of chemical analysis techniques, which have been, for the past four decades, able to detect chemical compounds at picogram levels and below.

In 2006, the Product Quality Research Institute's (PQRI) Leachables and Extractables Working Group, consisting of scientists from the United States Food and Drug Administration (FDA), academia, and industry, answered this question by developing data-based safety and analytical thresholds for OINDP extractables and leachables, and corresponding best practices for analytical evaluation of these compounds. This book is based on the information contained in the Working Group's recommendations (publicly available through PQRI); but it provides further, more in-depth context and background, case studies, and specific regulatory perspectives and extends the concepts to practices that may be implemented across the industry.

*Douglas J. Ball*  
*Daniel L. Norwood*  
*Cheryl L.M. Stults*  
*Lee M. Nagao*

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*DEVELOPMENT OF  
SAFETY THRESHOLDS,  
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ORALLY INHALED AND  
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# OVERVIEW OF LEACHABLES AND EXTRACTABLES IN ORALLY INHALED AND NASAL DRUG PRODUCTS

*Douglas J. Ball, Daniel L. Norwood, and Lee M. Nagao*

## 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.<sup>1</sup> 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.<sup>2,3</sup> Safety thresholds have also been developed for application to pharmaceuticals, including organic impurities in drug substances<sup>4</sup> (process and drug related), drug products,<sup>5</sup> and residual solvents in drug substances and drug products.<sup>6</sup> Note that the international regulatory guidance for drug product impurities specifically excludes from consideration “impurities . . . leached from the container closure system.”<sup>5</sup>

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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](http://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 Bepak, a division of Consort Medical plc; [www.bepak.com](http://www.bepak.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.<sup>7</sup> 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.<sup>8,9</sup> 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,<sup>10</sup> and nasal spray, and inhalation solution, suspension and spray drug products<sup>11</sup> 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



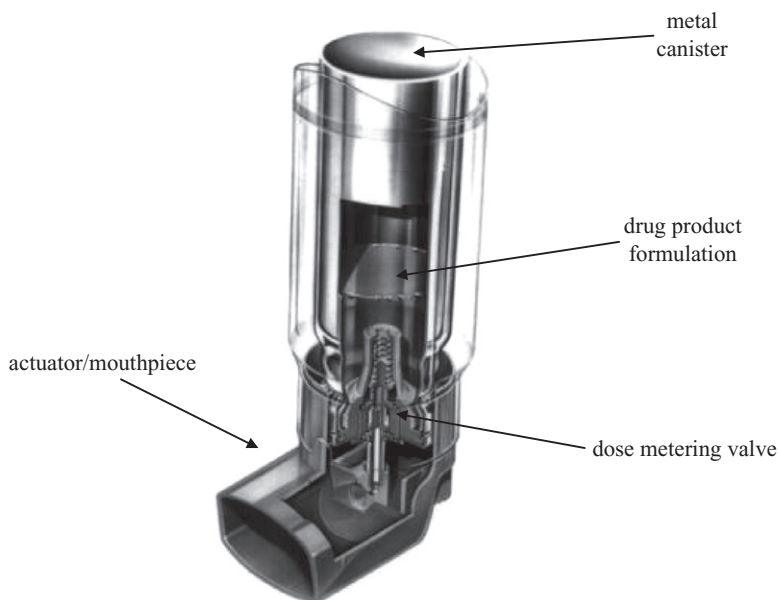


Figure 1.3 Schematic diagram of a metered dose inhaler (MDI) drug product. Note that the elastomeric, plastic, and metal components of the dose metering valve, as well as the metal canister inner surfaces, are capable of leaching chemical entities into the drug product formulation. The actuator/mouthpiece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

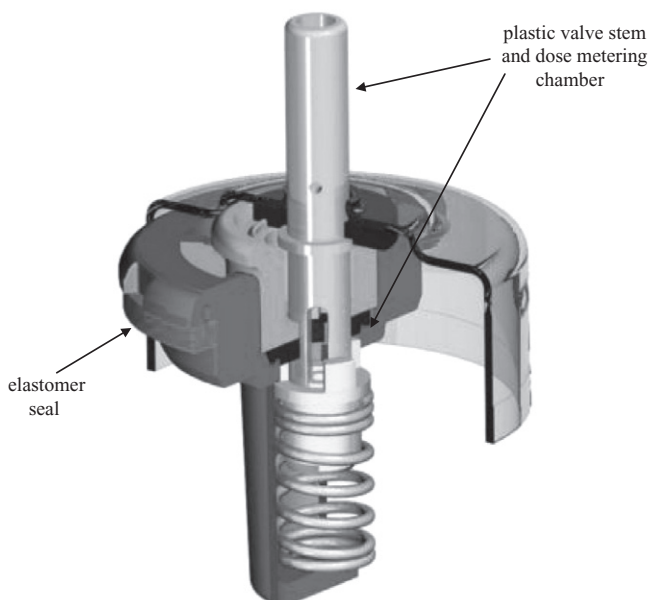


Figure 1.4 Cutaway diagram of a metered dose inhaler (MDI) dose metering valve showing the various metal, plastic and elastomeric components potentially in contact with the drug product formulation. (Images provided by Bespak, a division of Consort Medical plc; [www.bespak.com](http://www.bespak.com).)



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.<sup>12</sup> 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,

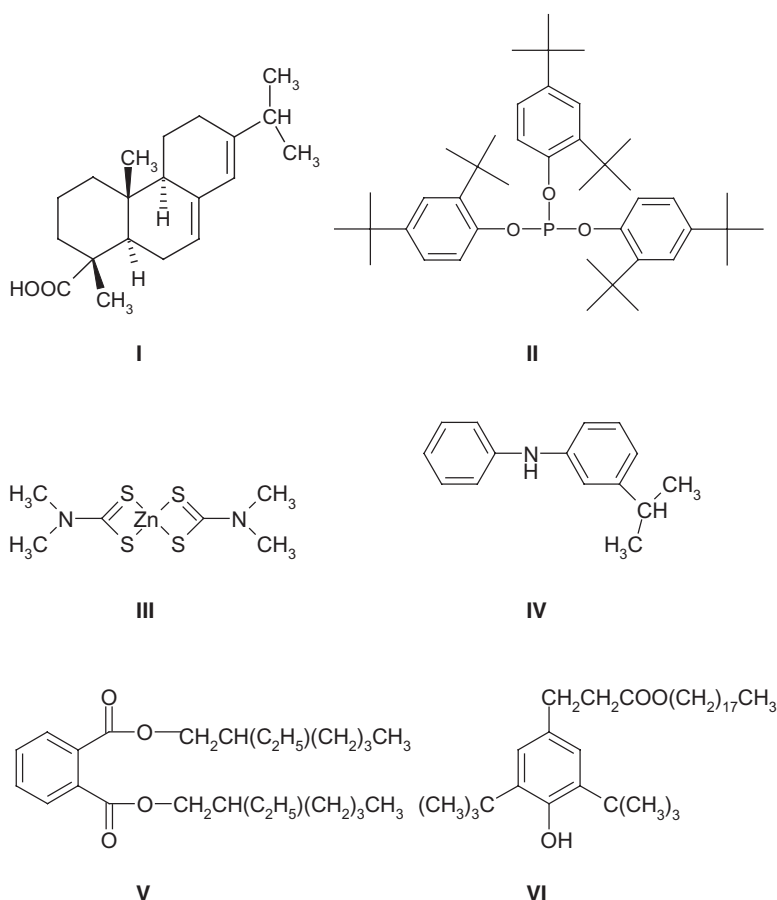


Figure 1.6 Some examples of chemical entities that can appear as extractables and/or leachables associated with OINDP. (I) Abietic acid (a filler for certain elastomers); (II) Irgafos 168 (a phosphite antioxidant); (III) zinc tetramethyldithiocarbamate (an accelerator for certain sulfur-cured elastomers); (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.<sup>8,12</sup>

### 1.3 REGULATORY BACKGROUND

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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.<sup>13</sup> 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.<sup>14</sup> 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<sup>a</sup>**

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

<sup>a</sup> 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.<sup>15</sup>

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?

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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).<sup>1</sup> 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.<sup>16</sup> 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.<sup>16</sup> 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.<sup>17</sup> regarding analysis of PNAs in MDI drug products by GC/MS).

A GC/MS extractables “profile” from a laboratory-controlled extraction study<sup>8</sup> 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” compounds<sup>8</sup> 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

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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