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Commentary

Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products: An Overview of the PQRI Recommendations

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Abstract. The Product Quality Research Institute Leachables and Extractables Working Group includes pharmaceutical development scientists representing industry, government, and academia. The Working Group was created and constituted to address scientific and regulatory questions concerning the pharmaceutical development process for Orally Inhaled and Nasal Drug Products (OINDP) related to organic extractables and leachables. This effort has resulted in the creation of a detailed "Recommendation Document", which was submitted to the U.S. FDA for consideration in September 2006. The recommendations include proposed safety and analytical thresholds for leachables and extractables, as well as detailed "best practice" recommendations for various aspects of the OINDP pharmaceutical development process, including: materials selection for OINDP container closure system components, Controlled Extraction Studies, Leachables Studies, and Routine Extractables Testing. The Working Group's processes and the detailed and comprehensive recommendations that resulted from those processes, demonstrate that the Product Quality Research Institute collaborative process can result in consensus science-based and data driven recommendations that could have a positive effect on patient care. It is anticipated that the Working Group's recommendations will also contribute to the new "Quality by Design" pharmaceutical development paradigm. This commentary summarizes the best practice recommendations within the context of an overall pharmaceutical development process.

KEY WORDS: controlled extraction studies; leachables; OINDP; pharmaceutical development; PQRI.

BACKGROUND: LEACHABLES AND EXTRACTABLES IN ORALLY INHALED AND NASAL DRUG PRODUCTS

Leachables are chemical entities, either organic or inorganic, that migrate from pharmaceutical container closure system components into a drug product formulation. Since patients can be exposed to leachables during normal use of a drug product, leachables are of potential safety concern. Extractables are compounds that are forced out of container closure system materials and components under laboratory experimental conditions. All extractables from a given pharmaceutical container closure system and its components are, therefore, potential leachables in a drug product incorporating the same container closure system components. Regulatory concern regarding leachables and extractables is directly related to the potential for contamination and/or interaction of the drug product formulation with the container closure system, with greatest concern focused on Orally Inhaled and Nasal Drug Products (OINDP), which include Metered Dose Inhalers (MDIs), Dry Powder Inhalers (DPIs), inhalation solutions, suspensions and sprays, and nasal sprays (Container Closure Systems for Packaging Human Drugs and Biologics; Guidance for Industry; U.S. Food and Drug Administration Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER); May 1999; Draft Guidance for Industry. MDI and DPI Drug Products Chemistry, Manufacturing and Controls Documentation. FDA/CDER. October 1998; Guidance for Industry. Nasal Spray and Inhalation Solutions, Suspensions and Spray Drug Products. Chemistry, Manufacturing and Controls Documentation. FDA/CDER. July 2002.).

The views expressed in this document are not necessarily those of the U.S. Food and Drug Administration.

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The characterization and control of leachables and extractables represents possibly the most significant challenge facing a pharmaceutical development team responsible for the development, registration, and manufacture of an OINDP. Indeed, detecting, identifying, and quantifying organic leachables is a formidable task. In contrast to drug substance or excipient related impurities, organic leachables can represent a diversity of chemical structures and compound classes, and are potentially present at widely varying concentrations in any particular OINDP. Additionally, the information available to a pharmaceutical development team on container closure system component composition and processing, which is provided by the component supplier, is often incomplete. In some cases, the supplier may provide no information. Thus, when an extractables study is first undertaken, the development team may only have a limited idea of what to look for, and what extraction techniques and analytical methods to use for identification and assessment of potential leachables.

Historically, there has been little guidance available regarding the type and extent of leachables and extractables information required for development and registration of a drug product. In fact, not until the late 1980s did the OINDP industry and regulators realize that OINDP container closure system components might produce leachables in the drug product. Throughout most of the 1990s, OINDP manufacturers independently developed protocols for detecting, identifying, and reporting leachables and extractables, but no definitive regulatory guidance was available. The International Conference on Harmonisation (ICH) developed guidelines and thresholds for impurities in drug products, but these thresholds are not applicable to leachables and extractables, which are non-drug related impurities (Q3B(R) Impurities in New Drug Products; Guidance for Industry; U.S. Food and Drug Administration, CDER, November 2003).

In 1998 and 1999 the U.S. Food and Drug Administration (FDA) issued guidance documents addressing metered dose and dry powder inhalers and nasal sprays and inhalation solutions (see reference above). These documents provided much needed general guidance on FDA expectations for OINDP leachables and extractables evaluation. However, even with the availability of such guidance, uncertainties remained that were critical in pharmaceutical development programs and could complicate the regulatory review and approval process. For example, as the capabilities of modern analytical chemistry advance, chemists are able to detect compounds at increasingly lower levels, e.g., part-per-billion to part-per-trillion range. Thus, a typical extractables profile for an MDI container closure system component might include a "forest" of low level peaks, each representing an extractable present at minute levels (Figs. 1 and 2). This raises the obvious regulatory/safety questions:

- How low should one go to identify and quantify peaks in a given leachables/extractables profile?
- Is there an absolute level or threshold below which leachables in an OINDP would not represent a safety concern?
- What is meant by the term "correlation" between leachables and extractables, and how is such a "correlation" established?

These are but a few of the vexing questions that OINDP pharmaceutical development scientists have had to face.

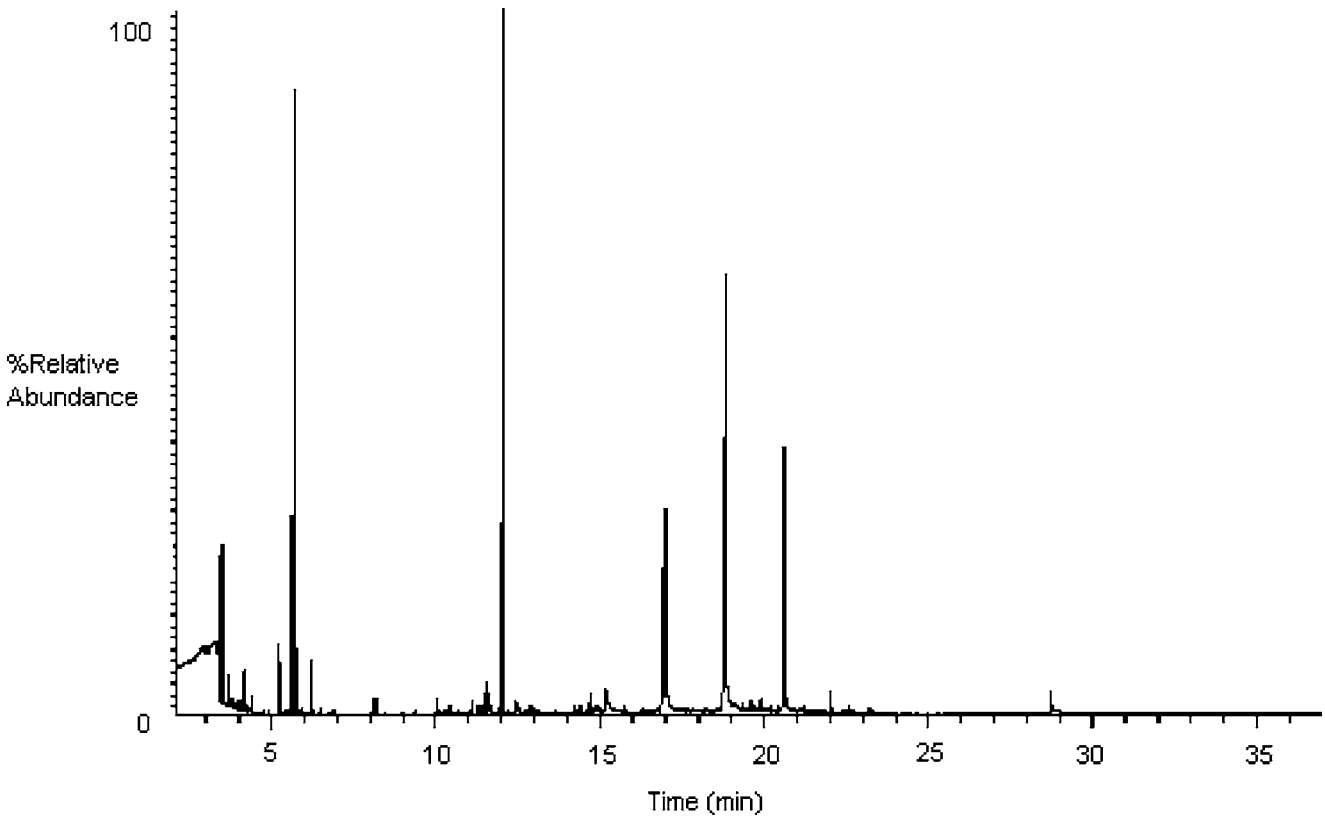

Fig. 1. GC/MS extractables profile (Total Ion Chromatogram, TIC) of a peroxide-cured elastomer, using isopropanol Soxhlet extraction.

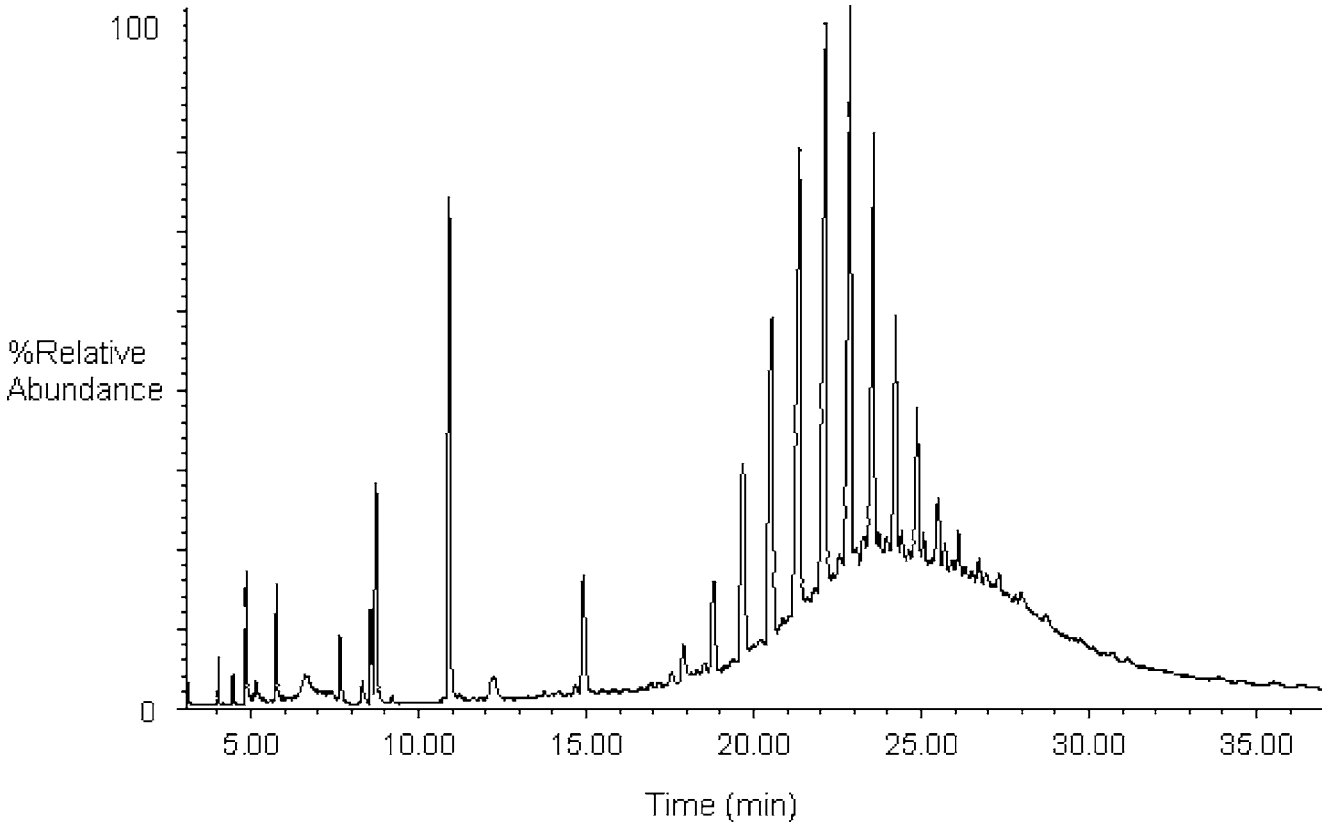

Fig. 2. GC/MS extractables profile (Total Ion Chromatogram, TIC) of a second peroxide-cured elastomer, using 2-propanol reflux extraction.

At the 1999 AAPS/FDA/USP Workshop, the International Pharmaceutical Aerosol Consortium (IPAC) and the AAPS Inhalation Technology Focus Group (ITFG) agreed to work collaboratively to address some of these questions and uncertainties. The IPAC-ITFG Leachables and Extractables Technical Team, composed of both chemists and toxicologists, developed a technical paper entitled *Leachables and Extractables Testing: Points to Consider* (Leachables and Extractables Testing: Points to Consider, IPAC-RS March 2001, http://www.ipacrs.com/PDFs/Points_to_Consider_FINAL.PDF. Accessed July 2007). This paper, submitted to the FDA in 2001, proposed (i) clarification and consolidation of requirements for leachables and extractables; and (ii) "reporting" and "qualification" thresholds for leachables. The development and proposal of thresholds for leachables was a ground-breaking exercise. The FDA subsequently suggested that IPAC, which in 2000 had become a separate consortium, the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), sponsor an L&E Working Group within the Product Quality Research Institute (PQRI).

PQRI is a collaboration between FDA, the pharmaceutical industry, and academia, to address critical issues for pharmaceutical product quality and generate data and recommendations in support of science-based regulatory policy (http://www.pqri.org/. Accessed June 2007). The PQRI Leachables and Extractables Working Group was established with the intent of reducing as much as possible the remaining uncertainty in the OINDP pharmaceutical development process for leachables and extractables, using science based and data driven approaches. The Working Group is made up of toxicologists, analytical chemists, and others, from industry, government, and academia. At the outset of its efforts, the Working Group proposed a two-part hypothesis:

1. Scientifically justifiable thresholds based on the best available data and industry practices can be developed for:
   (a) the reporting and safety qualification of leachables in orally inhaled and nasal drug products, and
   (b) the reporting of extractables from the critical components used in corresponding container closure systems.
2. Reporting thresholds for leachables and extractables should include associated identification and quantitation thresholds.
3. Safety qualification of extractables would be scientifically justified on a case-by-case basis.

To investigate this hypothesis, the Working Group performed analytical laboratory experiments and toxicology/safety database reviews, taking into consideration the IPAC/ITFG work. The Working Group toxicologists collected and assessed data from well-established databases of safe exposure levels and applied conservative risk analysis procedures

to these data. Through this process, they developed an individual organic leachable Safety Concern Threshold (SCT) of 0.15 μg/day and a Qualification Threshold (QT) of 5 μg/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 leachable is not considered for safety qualification unless the leachable presents structure–activity relationship (SAR) concerns.

The processes used to establish both the SCT and QT are discussed in detail in the Working Group's comprehensive recommendation document (Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products. PQRI Leachables and Extractables Working Group, http://www.pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf. Accessed June 2007) and an additional Working Group publication (1). It is important to note that the SCT and QT, as well as the analytical threshold described below, address only individual leachables.

The Working Group chemists conducted protocol-based Controlled Extraction Studies and simulated Leachables Studies, using elastomer and plastic test articles specially formulated and manufactured for use by the group. They optimized and validated the analytical methods for the quantitative Controlled Extraction Studies, and collected and assessed the data generated from both the extraction and leachables studies. Finally, they proposed a process for establishing what they termed an "Analytical Evaluation Threshold" (AET) based directly on the SCT. The AET, which is based on safety considerations, is designed to answer the question: How low should one go? Unlike the SCT, which is an absolute exposure value, the AET takes into consideration drug product dependent parameters such as dosing schedule as described in patient instructions, and the particular analytical technique/method used to produce a particular leachables (or extractables) profile. From their laboratory studies, the Working Group chemists also developed "Best Practice Recommendations" for leachables and extractables studies within the context of a comprehensive pharmaceutical development process.

The best practices and safety thresholds derivation and justification were submitted to the U.S. FDA in September 2006 as a comprehensive recommendation document (Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products). The best practices recommendations summarized here and described in detail in the recommendation document, provide guidance on how to conduct Controlled Extraction Studies and Leachables Studies, establish correlations between extractables and leachables profiles, and establish and use analytical thresholds (the AET) based on the safety thresholds.

THE PHARMACEUTICAL DEVELOPMENT PROCESS

Details of the pharmaceutical development process for leachables and extractables in OINDP will differ among companies. However, the process generally consists of materials selection for container closure systems, Controlled Extraction Studies, Leachables Studies, safety qualification of leachables (and sometimes extractables), and Routine Extractables Testing with establishment of specifications and acceptance criteria for extractables and leachables. The PQRI L&E Working Group provided an example of the general pharmaceutical development process shown in Fig. 3. Several aspects of this process flowchart are important to note. First, informed materials selection is a critical part of the development process. OINDP developers should understand to the extent possible, the composition of container closure system materials and components and be aware of safety concerns posed by potential leachables. Building and maintaining strong relationships and effective communications with materials and component suppliers will significantly aid OINDP developers in establishing materials composition knowledge.

Second, the chart shows that safety assessment should be an integral part of every stage of this process, starting with materials selection. Historically, involvement of toxicologists in the process was often limited to assessment and qualification of leachables. The Working Group concluded, however, that input on safety should begin early and remain integrated throughout the process. This approach would allow early knowledge of potential safety concerns at the materials selection stage, and allow manufacturers to make knowledge-based decisions regarding the types of materials to use in their products, and to decrease the risk of potential safety concerns in the latter stages of product development. Third, the figure shows that analytical and safety thresholds can be used in the pharmaceutical development process, and can be applied to safety evaluation of extractables and leachables. Finally, careful and thorough Controlled Extraction Studies are of great importance to the pharmaceutical development process because they allow early knowledge of potential leachables of safety concern and establishment of an extractables and leachables correlation, which can then be used to manage the quality of final drug product via Routine Extractables Testing with appropriate specifications and acceptance criteria.

The following sections of this commentary summarize in greater detail the Working Group's "Best Practice" recommendations. For additional detail, the reader is referred to the comprehensive recommendation document.

CONTAINER CLOSURE SYSTEM COMPONENT SELECTION

An OINDP pharmaceutical development program should begin with a thorough understanding of the drug product formulation, excipients, the intended use of the product including recommended patient dosing, and the container closure system. The container closure system for an OINDP includes *primary packaging components*, which are defined as those that are, or may be, in direct contact with the formulation (including those in the formulation pathway), and *secondary packaging components*, which are defined as those that are not or will not be in direct contact with the formulation (Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation; Guidance for Industry. U.S. FDA). Primary packaging components for OINDP include, for example: MDI canisters and valves (with their respective metal, elastomeric and polymeric components), MDI mouth-

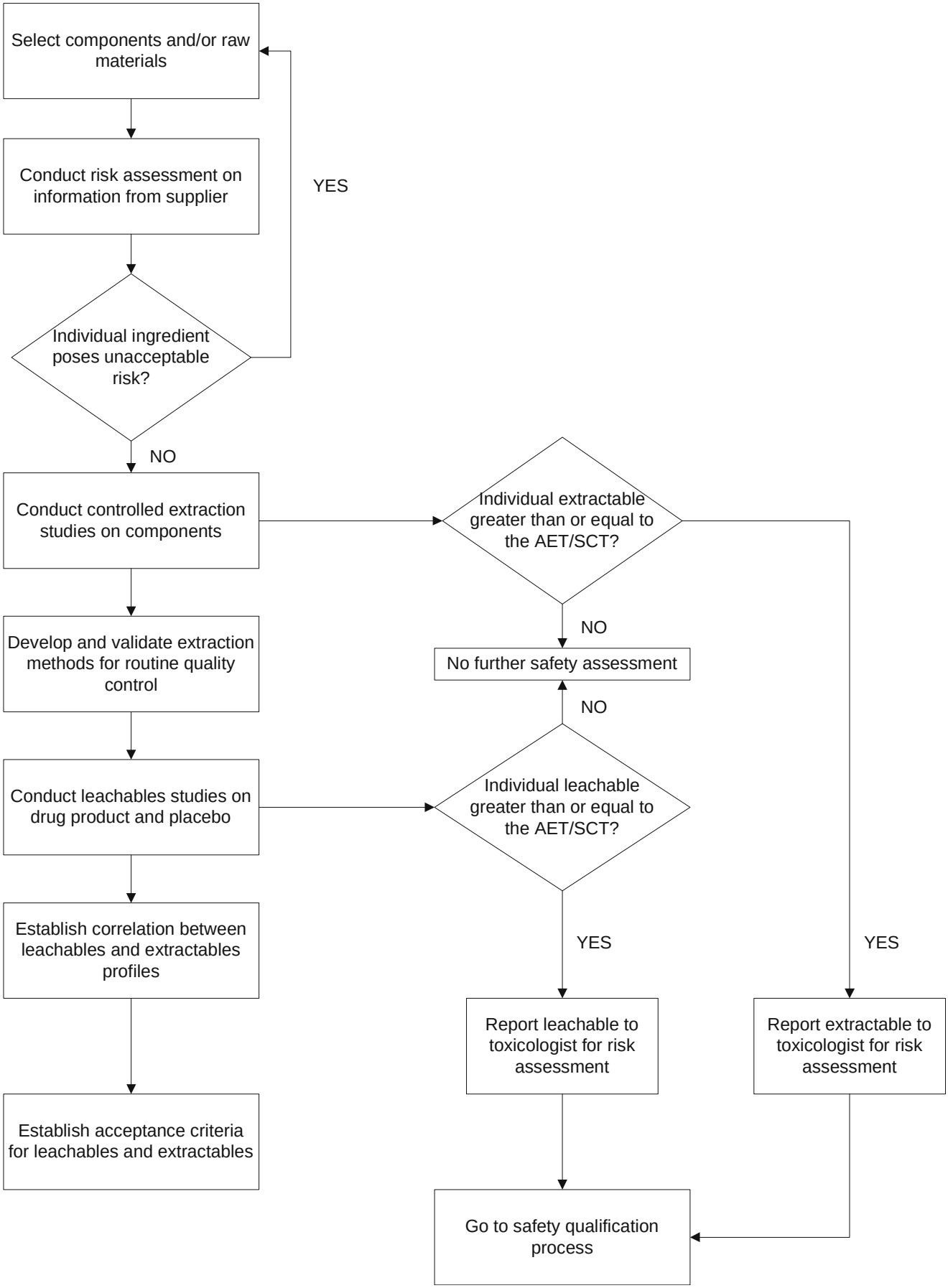

Fig. 3. Example of the pharmaceutical development process for extractables and leachables evaluation in OINDP.

pieces, plastic nebules designed to contain inhalation solutions, nasal spray pump, bottles, and nosepieces, and DPI unit dose blisters and drug reservoirs. Secondary packaging components include, for example, inhalation solution foil laminate overwrap, labels on containers, and even cardboard shipping containers under certain circumstances. Packaging component selection is an important step in the OINDP pharmaceutical development process since these and their materials of construction are the principal sources of extractables and leachables, and may be in direct contact with the formulation and/or the patient's mouth or nasal mucosa (Container Closure Systems for Packaging Human Drugs and Biologics; Guidance for Industry. U.S. FDA). For example, the inner surfaces of MDI canisters may have traces of heavy oils used for fabricating the canisters, and cleaning agents used to degrease the canisters. Elastomeric gaskets and seals used in MDI valves and DPIs contain chemical additives, such as antioxidants. Mouthpieces and plastic containers also contain chemical additives or colorants, and both elastomeric and plastic components can contain residual monomers and oligomers. Labels, inks and glues applied to containers fabricated from semi-permeable plastic materials may also be sources of organic extractables and leachables.

Clearly, there are many sources and potential sources of extractables and leachables for OINDP. It is therefore vital that a pharmaceutical development team obtain as much information as possible on the composition and manufacturing process(es) for the "critical" components of the OINDP. "Critical" components are defined as those that are in direct contact with the formulation, the patient's mouth or nasal mucosa, or affect the functionality of the device. OINDP come in a wide variety of designs and can be complex. Therefore, manufacturers must carefully determine for their own products, which components are "critical" and work with regulators to confirm this determination.

The most important part of component and packaging materials selection is developing, to the extent possible, a thorough understanding of materials composition. Manufacturers should work closely with component and packaging suppliers to achieve this understanding. Ideally, suppliers will, under appropriate agreements, share with manufacturers the specific ingredients and relative amounts of those ingredients in the component and packaging materials. This information sharing is extremely important because it allows early risk assessment on potential leachables of safety concern. Safety assessments, done during materials selection, allow manufacturers to make an informed, risk-based selection of materials to use in their drug product early in the development process, lowering the risk that safety concerns will appear later in development or even post-market. Further, knowledge of materials ingredients allows analytical chemists to compare results of Controlled Extraction Studies with the known compositions of components and packaging materials. This is a powerful process for investigating extractables of concern and optimizing extraction and analytical methods.

The PQRI L&E Working Group acquired a sulfur-cured elastomer, two peroxide-cured elastomers, and a polypropylene to use as test articles for developing best practices recommendations. These materials were custom made for the Working Group's use. Ingredients and their relative amounts were divulged to the Working Group for all of these articles to illustrate the importance of this information in designing Controlled Extraction Studies, highlighting important compounds or potential degradation products to look out for, and conducting early safety assessments. The ingredients for the sulfur-cured elastomer are listed in Table I.

Table I. Ingredients in Sulfur-Cured Elastomer Test Article

Ingredient	Registry #(s)	Percent (w/w)
Calcined clay	308063-94-7	8.96
Blanc fixe (barium sulfate)	7727-43-7	25.80
Crepe	9006-04-6	38.22
Brown sub mb (ingredients below)	NA (not available)	16.84
Brown sub loose	NA	33.30
Crepe	9006-04-6	66.70
1,722 mb (ingredients below)	NA	2.11
SMR (Standard Malaysian Rubber)	NA	60.00
FEF carbon black (low PNA)	1333-86-4	40.00
Zinc oxide	1314-13-2	4.04
2, 2′ methylene-bis (6-tert-butyl-4-ethyl phenol)	88-24-4	0.56
Coumarone-indene resin	164325-24-0 140413-58-7 140413-55-4 68956-53-6 68955-30-6	1.12
Paraffin	8002-74-2 308069-08-1	1.12
Tetramethylthiuram monosulfide	97-74-5	0.11
Zinc 2-mercaptobenzothiazole	149-30-4 155-04-4	0.29
Sulfur	7704-34-9	0.84

Information important to planning effective Controlled Extraction Studies is readily available from this list. For example, carbon black and sulfur-curing agents should alert the chemist to the potential presence of polynuclear aromatics (PNAs) and N-nitrosamines, respectively. These compounds are carcinogenic, of special safety concern, and should be investigated with special, highly sensitive analytical methods. Paraffin, another ingredient, while not of obvious safety concern, presents other challenges—it is a natural product and may therefore produce very complex extractables or leachables profiles consisting of many related compounds.

The list of ingredients and relative amounts in Table I is enough to allow an estimate of a "worst-case" exposure for any given compound in the table. For example, a worst-case total daily intake can be calculated using the drug product configuration, e.g., total number of doses, recommended doses per day, weight of the test article or component used, and the relative amount of the compound in the test article. This information can be used with structure–activity relationship and literature data to provide an early risk assessment of potential leachables from this material. The benefits of compositional information are demonstrated further in the

Controlled Extraction Studies that the PQRI L&E Working Group conducted on the sulfur-cured elastomer.

CONTROLLED EXTRACTION STUDIES

Controlled Extraction Studies are an extremely important part of the pharmaceutical development process for OINDP, and should be performed on critical components as identified by the manufacturer and regulatory authority. As stated in the PQRI L&E Recommendations: "A Controlled Extraction Study is a laboratory investigation into the qualitative and quantitative nature of extractables profiles of critical components of an OINDP container closure system. The purpose of a Controlled Extraction Study is to systematically and rationally identify and quantify potential leachables, i.e., extractables, to the extent practicable, and within certain defined analytical threshold parameters" (Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products).

Controlled Extraction Studies result in extractables profiles of OINDP components, examples of which are the GC/MS Total Ion Chromatograms shown in Figs. 1 and 2. Extractables profiles contain information which allows the identification, to the extent possible, and quantitation of individual extractables from a given component, and therefore an early indication of potential leachables of concern. Controlled Extraction Studies generally establish a basis for the development and validation of routine quality control methods and specifications/acceptance criteria for critical component extractables profiles; establish a basis for the development and validation of leachables methods suitable for use in drug product leachables studies and for potential use as routine quality control methods for drug product leachables; and finally, allow for the "correlation" of extractables and leachables profiles (Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products). Although information on component composition from suppliers is very useful, helping to inform component selection and guide Controlled Extraction Studies, such knowledge does not provide a complete extractables profile and therefore does not alleviate the requirement for Controlled Extraction Studies no matter how "complete" the information might appear to be.

It is, therefore, critical that Controlled Extraction Studies be performed properly and thoroughly. Specific expectations for "proper and thorough" Controlled Extraction Studies will ultimately depend on the nature of the OINDP being developed. However, the PQRI L&E Working Group was able to establish some general best practice recommendations for OINDP Controlled Extraction Studies, based on data that the Group generated by conducting its own Controlled Extraction Studies on the elastomer and polymer test articles, and from the extensive experience of Working Group members. These recommendations are:

- Controlled Extraction Studies should employ vigorous extraction with multiple solvents of varying polarity.
- Controlled Extraction Studies should incorporate multiple extraction techniques.
- Controlled Extraction Studies should include careful sample preparation based on knowledge of analytical techniques used.
- Controlled Extraction Studies should employ multiple analytical techniques.
- Controlled Extraction Studies should include a defined and systematic process for identification of individual extractables.
- Controlled Extraction Study "definitive" extraction techniques and methods should be optimized.
- During the Controlled Extraction Studies, sponsors should revisit supplier information describing component formulation.
- Controlled Extraction Studies should be guided by Analytical Evaluation Thresholds (AET) that are based on an accepted safety concern threshold.
- Qualitative and quantitiative extractables profiles should be discussed with and reviewed by toxicologists so that any potential safety concerns regarding individual extractables, i.e., potential leachables, are identified early in the development process.
- Polynuclear aromatics (PNAs), N-nitrosamines, and 2-mercaptobenzothiazole (MBT) are "special case" compounds, requiring evaluation by specific analytical techniques and technology defined thresholds.

Detailed discussion of each of these recommendations is included in the PQRI L&E Working Group's best practices document, however, the reader is invited to consider the following:

Controlled Extraction Studies should employ vigorous extraction with multiple solvents of different polarity and multiple extraction techniques. Use of multiple solvents with varying polarity allows for extraction of a wide range of compounds, and provides a means to maximize the number and concentration of extractables. The drug product formulation, and component composition and function can guide selection of solvents. For example, the Working Group chose methylene chloride and isopropyl alcohol as extraction solvents to mimic cholorofluorocarbon or hydrofluoroalkane propellants and ethanol co-solvent in MDIs, respectively.

Figures 4, 5 and 6 show GC/MS Total Ion Chromatogram (TIC) extractables profiles from methylene chloride, 2-propanol, and hexane reflux extracts of the sulfur-cured elastomer. The profiles differ in number and intensity of peaks depending on the solvent used. The major peak in all three extractables profiles is the antioxidant 2,2′-methylene-bis-(6-*tert*-butyl)-4-ethylphenol, a known formulation ingredient (see Table I). Also note in Fig. 5, the peak at approximately 8 min which is not as apparent in Figs. 4 and 6. This extractable was identified as benzothiazole, and its presence in the 2-propanol extract at this higher concentration is likely the result of thermolysis of the known ingredient 2-mercaptobenzothiazole, under the relatively higher boiling temperature of 2-propanol (82.3°C), *versus* methylene chloride (40.1°C) and n-hexane (69.0°C). Note that examination of these three profiles, a basic understanding of organic chemistry, and supplier information

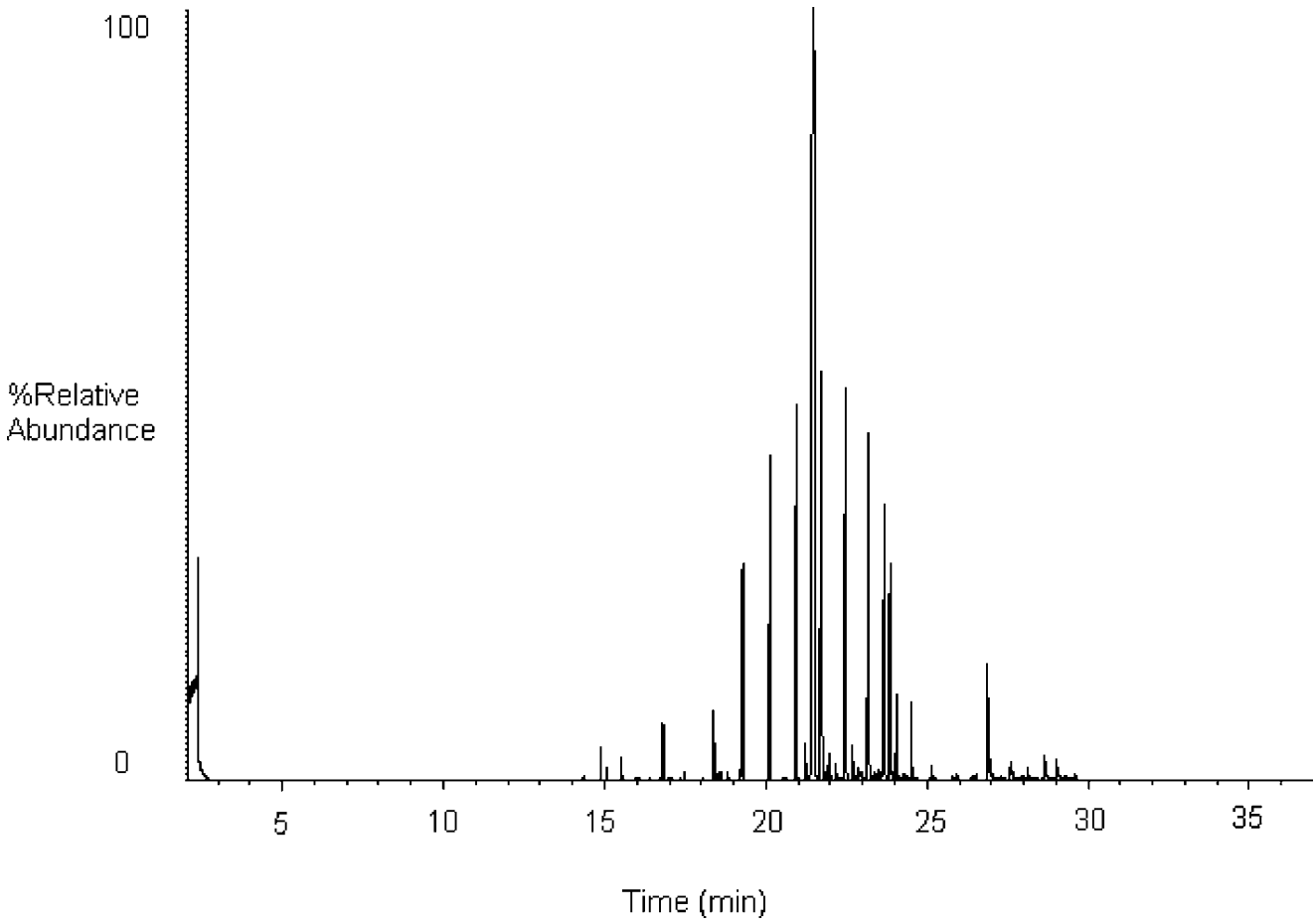

Fig. 4. GC/MS (Gas Chromatography/Mass Spectrometry) extractables profile (Total Ion Chromatogram, TIC) of the sulfur-cured elastomer test article, methylene chloride reflux extract.

on formulation ingredients help to alert the analytical chemist to the potential presence of the special case extractable 2-mercaptobenzothiazole.

Identification of extractables using a defined, systematic process. Identification of extractables should include three general considerations: (i) determination of how "low" one should go to identify the extractables (ii) development of a process for identification of the extractables; and (iii) reconciling extractables identification with supplier ingredient information.

The PQRI L&E Working Group developed the concept of the Analytical Evaluation Threshold (AET), which is based on the SCT, to address point (i) above. The AET is defined as the threshold at or above which a chemist should begin to identify a particular leachable and/or extractable and report it for potential toxicological assessment. While the SCT is an absolute value (0.15 μg/day), the AET will vary depending on the particular drug product configuration and the method(s) used to detect and quantify the extractables and leachables. The methods used will affect the AET value because of the analytical uncertainty inherent in the response factors of individual extractables or leachables analyzed by the methods. The AET applied to extractables allows the analytical chemist to determine which extractables need not be identified for safety reasons, and which extractables should be identified to the extent possible. A well-performed Controlled Extraction Study should provide a "worst-case" concentration of potential leachables in the profile, and therefore any extractables identified should be observed as leachables in final product either above or below the AET for leachables, but at concentrations lower than that found in the extractables profiles.

The AET for extractables is determined by converting the SCT from daily exposure to amount per unit, e.g., μg/canister for an MDI, μg/blister for a DPI. This can be done using the drug product configuration, e.g., maximum recommended dose per day, actuations per dose, actuations per canister. The resulting value is called the "Estimated AET." The Estimated AET for extractables is then adjusted by an uncertainty factor to yield the "Final AET." This uncertainty factor takes into account that the analytical response for each compound, with a given method, will depend on the nature of the compound, and that the concentrations of every single compound in the profile cannot be determined with authentic reference standards. The recommended process for AET determination is as follows (Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products):

1. Convert the SCT (0.15 μg/day for an individual organic leachable) to an Estimated AET (μg/canister for an

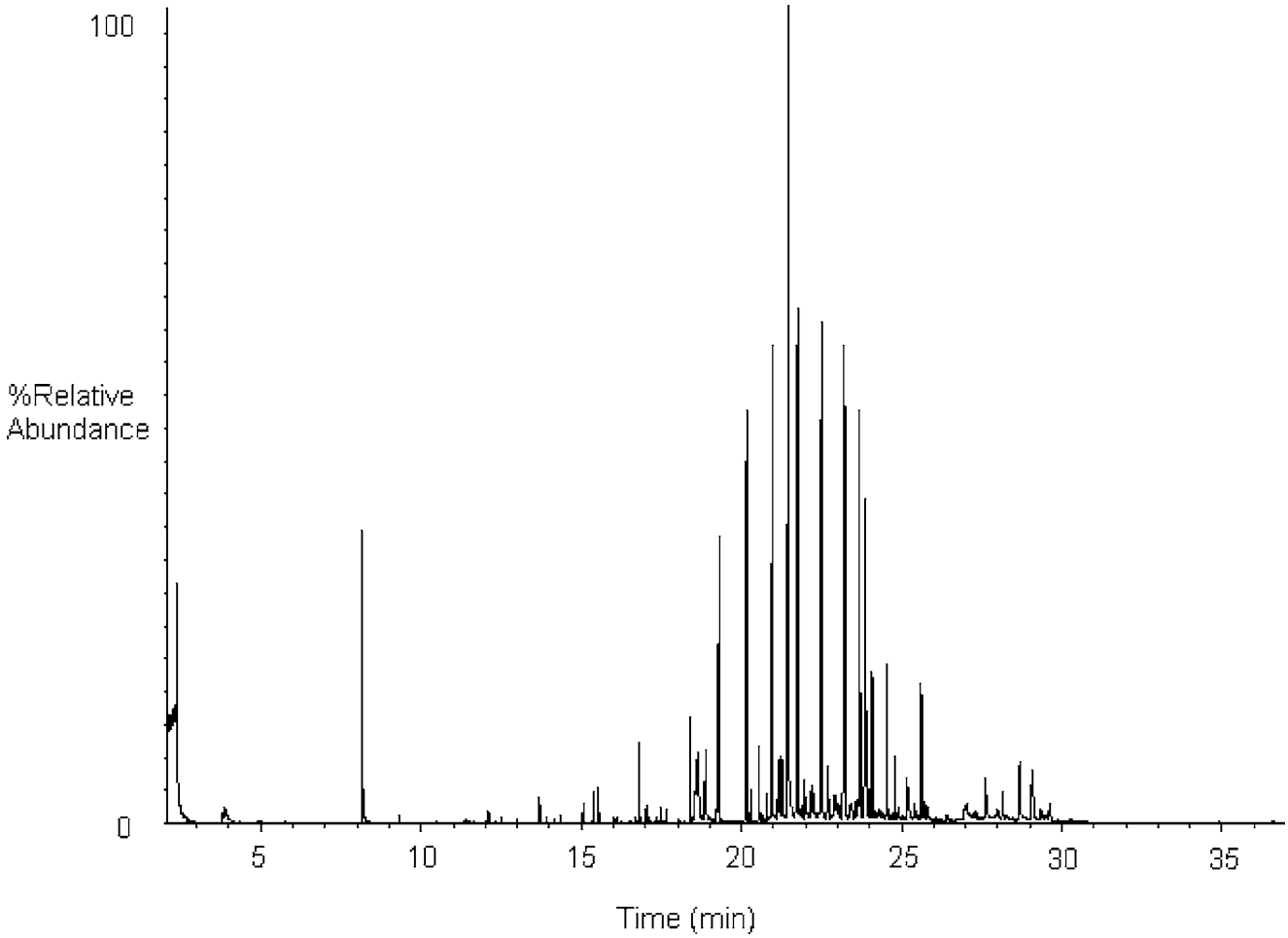

Fig. 5. GC/MS (Gas Chromatography/Mass Spectrometry) extractables profile (Total Ion Chromatogram, TIC) of the sulfur-cured elastomer test article, 2-propanol reflux extract. Sample reconstituted in methylene chloride prior to GC/MS analysis.

individual organic leachable in an MDI, for example) by considering the dosing and other parameters of the particular OINDP.

2. Convert the Estimated AET for leachables to an Estimated AET for extractables (μg/g elastomer for an individual organic extractable, for example) by considering the parameters of the particular OINDP container closure system, e.g., weight of elastomer per MDI valve.
3. Locate the Estimated AET on a particular leachables or extractables profile, e.g., a GC/MS Total Ion Chromatogram.
4. Evaluate the uncertainty of the particular analytical technique/method, e.g., GC/MS response factors for various potential extractables/leachables.
5. Convert the Estimated AET to a Final AET by considering this analytical uncertainty.

The uncertainty factor can be calculated in any number of ways, one of which is to develop the percent relative standard deviation (%RSD) of relative response factors from reference compounds analyzed by the analytical method under consideration. The PQRI L&E Working Group recommends that the analytical uncertainty in the Estimated AET be defined as one %RSD in an appropriately constituted and acquired response factor database, or 50% of the Estimated AET, whichever is greater. Several examples of AET calculations are provided in the full PQRI Recommendations. Some Estimated AET values for a selection of marketed OINDP are shown in Table II.

Extractables above the AET should be identified to the extent possible, using a clearly defined process for identification. Such a process should ideally allow for different levels of identification, since it is unlikely that in all cases all extractables above the AET can be fully identified. The PQRI L&E Working Group proposed a systematic process for GC/MS and LC/MS (Liquid Chromatography/Mass Spectrometry) extractables profile evaluation, presented in Table III. Table III shows how GC/MS and LC/MS data can be assigned "Identification Categories," which can then be used to assign descriptive identification terms such as *Confirmed*, *Confident*, or *Tentative*.

A *Confirmed* identification means that identification categories A, B (or C), and D (or E) have been fulfilled. A *Confident* identification means that sufficient data to preclude all but the most closely related structures have been obtained.

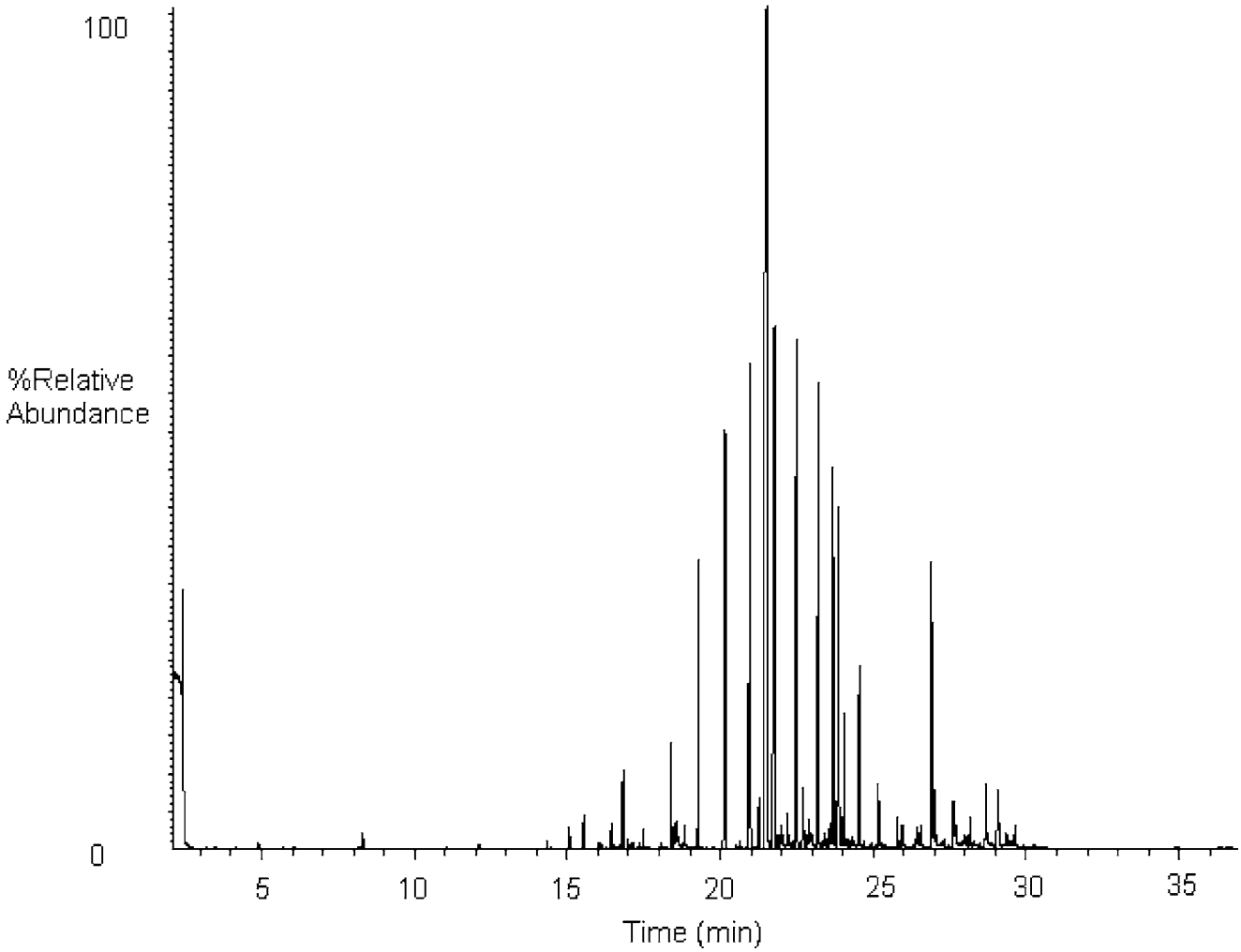

Fig. 6. GC/MS (Gas Chromatography/Mass Spectrometry) extractables profile (Total Ion Chromatogram, TIC) of the sulfur-cured elastomer test article, hexane reflux extract.

A *Tentative* identification means that data have been obtained that are consistent with a class of molecule only.

A final important step in the identification process is to compare the extractables profile(s) from the Controlled Extraction Study with supplier information on component ingredients. Such a comparison allows the chemist to identify extractables that may not be included in supplier information, to consider whether the extraction and analytical methods are not optimal or appropriate for the given material, and to understand if some compounds have been consumed in the materials manufacturing process. Ultimately this confirmatory step provides a deeper understanding of the extractables profile and make-up of the component material. As an example, during Controlled Extraction Studies of the sulfur-cured elastomer, the L&E Working Group determined that tetramethylthiuram monosulfide (TMTS) was not detected in any of the extractables profiles, even though this compound was listed as a formulation ingredient (see Table I). An authentic reference standard of TMTS was analyzed by GC/MS under the same analytical conditions used to characterize elastomer extracts, and a peak for this standard was clearly visible in the resulting total ion chromatogram (TIC), indicating that it would likely be detected in GC/MS profiles of sulfur-cured elastomer extracts. The Working Group concluded that TMTS was consumed during the elastomer polymerization/cross-linking process.

LEACHABLES STUDIES

A Leachables Study is a laboratory investigation into the qualitative and quantitative nature of a particular OINDP leachables profile(s) over the proposed shelf-life of the product. The purpose of a Leachables Study is to systematically identify and quantify drug product leachables to the extent practical, and within certain defined analytical threshold parameters (Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products). The goals of a Leachables Study should be to help establish a correlation between extractables and leachables profiles; to understand the trends in leachables levels over the product shelf-life; to determine maximum leachables levels up to the product's proposed end of shelf-life; to support safety evaluation of drug product leachables; and to

Table II. Estimated AET Values for Various OINDP

MDI Drug Product	Estimated Formulation Parameters from Product Labeling		Estimated AET Corresponding to SCT of 0.15 μg/day (μg/can)
	Number of Actuations Per Can	Maximum Actuations Per Day	
Flovent 110	60	8	1.1
Alupent	100	12	1.3
Beconase[a]	80	8	1.5
QVAR	100	8	1.9
Nasacort[a]	100	8	1.9
Tilade	104	8	2.0
Azmacort	240	16	2.3
Proventil HFA	200	12	2.5
Ventolin HFA	200	12	2.5
Combivent	200	12	2.5
Atrovent	200	12	2.5
Serevent[b]	120	4	4.5
Maxair	400	12	5.0

These estimates are for illustrative purposes only and should not be used for decision making because they may not reflect actual MDI formulation parameters. Estimated AET (μg/can) at 0.15 μg/day= 0.15 μg/day×Actuations/can÷Actuations/day
[a] Nasal inhalation drug product.
[b] No longer marketed in US.

establish drug product leachables specifications and acceptance criteria, if required.

The PQRI L&E Working Group recommends that for Leachables Studies:

- Analytical methods for the qualitative and quantitative evaluation of leachables should be based on the analytical techniques/methods used in the Controlled Extraction Studies, and should be fully validated according to accepted parameters and criteria.
- Leachables Studies should be guided by an AET that is based on an accepted safety concern threshold.
- A comprehensive correlation between extractables and leachables profiles should be established.
- Specifications and acceptance criteria should be established for leachables profiles in OINDP.
- Qualitative and quantitative leachables profiles should be reviewed by toxicologists so that potential safety concerns of leachables are identified as early as possible in the pharmaceutical development process.

The Working Group recognizes that the requirements for Leachables Studies will differ depending on the type of OINDP. The Group recommends that Leachables Studies should always be performed for MDIs, and should generally be performed for Nasal Spray and Inhalation Spray drug products. If scientifically justified, Leachables Studies may not need to be done for particular Nasal Spray or Inhalation Spray drug products, provided that there are no changes in the composition of materials, or compounding/fabrication processes, or supplier(s) of the component(s), during the pharmaceutical development process. Any such changes would necessitate reconsideration of the need for Leachables Studies. Leachables Studies (either stability studies or "one-time" characterization studies) are recommended for DPIs only if potential leachables, i.e., extractables, of safety concern are identified in the Controlled Extraction Studies at or above the AET level from the unit dose container closure system and other critical components of the device which may have continuous long term contact with the drug product formulation.

For Inhalation Solution and Suspension products, Leachables Studies are not recommended if it can be scientifically demonstrated that aqueous and/or drug product formulation extracts of inhalation solution direct formulation contact container closure system materials yield no extractables, under appropriate stress conditions, at Final AET levels, or no extractables above final AET levels with safety concern; AND if there is no evidence for migration of organic chemical entities through the unit dose container into the drug product formulation. This recommendation again assumes that there are no changes in the composition of materials, or compounding/fabrication processes, or supplier(s) of the component(s) during the pharmaceutical development process.

Identification of leachables is an important aspect of the Leachables Study. If Controlled Extraction Studies have been performed properly and thoroughly, then any leachables in the leachables profile above the leachables AET, should already have been identified. In some cases a leachable may react with elements of the drug product formulation, e.g., the active pharmaceutical ingredient, solvents, to produce a leachable derivative. In these cases the chemist would still understand the origins of the leachable from having performed a careful Controlled Extraction Study.

An AET for leachables can be established to determine which leachables in the profile should be reported for safety qualification. Preliminary safety information such as *in-silico* and/or literature-based risk assessments on these leachables may already have been completed if these leachables were reported as extractables of concern during the Controlled Extraction Studies phase.

Establishing a correlation between extractables and leachables profiles is important and extremely useful, since a correlation allows for detection of potential changes in a leachables profile through understanding of changes in an extractables profile. The Working Group has proposed that a qualitative correlation can be established if all leachables detected can be qualitatively linked directly or indirectly to an extractable. A quantitative correlation can be established

Table III. Identification Categories for Structure Elucidation of Extractables and Leachables by GC/MS and LC/MS

Category	Supporting Identification Data
A	Mass spectrometric fragmentation behavior
B	Confirmation of molecular weight
C	Confirmation of elemental composition
D	Mass spectrum matches automated library or literature spectrum
E	Mass spectrum and chromatographic retention index match authentic specimen

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.

The Working Group suggests that qualitative and quantitative correlations should include multiple batches of container closure system critical components and multiple batches of drug product to end of shelf-life (including multiple stability time-points, stability storage conditions and drug product orientations). To establish a correlation, the development team should compare leachables profiles from at least three drug product definitive registration batches using specific batches of critical components, with qualitative and quantitative extractables profiles of those specific component batches; and leachables profiles from multiple drug product registration batches with extractables profiles from multiple batches of critical components (which may not have been used in the drug product registration batches), in order to confirm the consistency of correlations between extractables profiles from multiple component batches and leachables profiles from multiple drug product batches. The extraction conditions should be optimized to achieve approximate asymptotic levels of extractables (relative to a zero slope line) to provide adequate extractables data for an extractables/leachables correlation.

If a qualitative and quantitative correlation cannot be established, the source of the problem should be corrected. Potential sources include excessive variability in component composition and/or manufacturing processes (strong supplier-pharma relationships are important in encouraging decreased variability), changes in drug product formulation, inadequate Controlled Extraction Studies, and poorly validated leachables and extractables methods.

Once a correlation has been established, specifications including acceptance criteria for leachables can be developed, which should include a validated analytical test method. Acceptance criteria should apply over the proposed shelf-life of the drug product, and should include quantitative limits for known drug product leachables monitored during product registration stability studies, and a quantitative limit for "new" or "unspecified" leachables not detected or monitored during product registration stability studies. Quantitative acceptance criteria should be based on leachables levels, and trends in leachables levels over time and across various storage conditions and drug product orientations during product registration stability studies.

A comprehensive correlation may eliminate the need for routine implementation of drug product leachables specifications including acceptance criteria, but only with adequate supplier information; a complete understanding and management of critical component fabrication and manufacturing processes; adequate and comprehensive Controlled Extraction Studies on all critical components; validated leachables analytical methods and a comprehensive Leachables Study; validated Routine Extractables Testing analytical methods and an adequate database of critical component extractables profiles; and finally, appropriate extractables specifications and acceptance criteria. The requirement for implementation of leachables specifications including acceptance criteria for any particular OINDP is up to individual regulatory authorities.

ROUTINE EXTRACTABLES TESTING

Routine Extractables Testing is performed on all critical components of OINDP container closure systems and is the process by which OINDP container closure system critical components are qualitatively and quantitatively profiled for extractables. Routine Extractables Testing is done to help establish acceptance criteria for extractables from critical components; to help ensure that the leachables profile in the drug product is maintained within appropriate limits; and to release critical components according to established specifications, including acceptance criteria. For Routine Extractables Testing, the PQRI Working Group recommends that:

- Routine Extractables Testing should be performed on critical components using appropriate specifications and acceptance criteria.
- Analytical methods for Routine Extractables Testing should be based on the analytical technique(s)/method(s) used in the Controlled Extraction Studies.
- Analytical methods for Routine Extractables Testing should be fully validated according to accepted parameters and criteria.

Acceptance criteria are used to manage the levels of extractables which were identified during Controlled Extraction Studies and to detect "unspecified" extractables which could be present as the result of, for instance, component ingredient changes, manufacturing process changes, or external contamination. Acceptance criteria for OINDP critical component extractables should include confirmation of extractables identified in Controlled Extraction Studies; quantitative limits for extractables identified in Controlled Extraction Studies; and quantitative limits for unspecified extractables. Acceptance criteria, should be established through a complete understanding of critical component composition, ingredients, and compounding/fabrication processes; comprehensive Controlled Extraction Studies; a significant database of extractables profiles obtained with fully optimized and validated Routine Extractables Testing analytical methods; and a complete leachables/extractables correlation. Note that there are many ways to establish acceptance criteria for Routine Extractables Studies using this type of information. How acceptance criteria are eventually set will depend on the type of OINDP. Note also that quantitative limits need not necessarily be established for all extractables identified in Controlled Extraction Studies, but could be established for major extractables representative of major chemical additives in the component formulation.

Failure of a particular batch of critical components to meet established acceptance criteria suggests either an unapproved change in critical component ingredients or compounding/fabrication processes. In order to prevent extractables profile failures, and to ensure that quality is maintained, it is extremely important that sponsors work closely with their suppliers to manage critical component compounding/fabrication processes. The sponsor should also clarify to the supplier the expectations regarding changes to component ingredients, compounding, fabrication, or other manufacturing processes, including prior notification of such

changes. Strong relationships and communication with suppliers is critical in ensuring the quality of the final drug product, and reducing surprises in Routine Extractables Study profiles.

Analytical methods for Routine Extractables Testing should be based on the analytical methods used in the Controlled Extraction Studies. Note that Routine Extractables Testing analytical methods have greater requirements for ruggedness and robustness than those for Controlled Extraction Studies. Therefore it is appropriate to use, for example, Gas Chromatography/Flame Ionization Detection (GC/FID) methods in Routine Extractables Testing, which are based on GC/MS Controlled Extraction Studies methods. The methods must be capable of detecting and quantifying all extractables characterized in Controlled Extraction Studies, and identifying "unspecified" extractables which could result from unanticipated changes in critical component ingredients or some external contamination. Finally, the methods should be fully validated according to accepted parameters and criteria, such as those described in the ICH guidelines for example (Q2(R1) Validation of Analytical Procedures: Text and Methodology, http://www.ich.org/LOB/media/MEDIA417.pdf. Accessed July 2007).

CONCLUSIONS

The PQRI best practices recommendations for leachables and extractables in OINDP are the result of collaboration and consensus-building among scientists from FDA, academia and industry, and provide science-based and experience-based guidance on best approaches to evaluating and managing extractables and leachables in an OINDP pharmaceutical development process. The Recommendations address component selection, Controlled Extraction Studies, Leachables Studies, Routine Extractables Studies, and the development and application of an analytical threshold (the AET) that is based on a safety threshold (the SCT). The Recommendations provide, for the first time, a comprehensive, rationalized and knowledge-based approach to managing extractables and leachables in these drug products, and shifts the extractables/leachables study paradigm to one of knowledge integration among suppliers, development chemists and toxicologists during the pharmaceutical development process.

The work of the PQRI Leachables and Extractables Working Group demonstrates that industry, academia and government can effectively collaborate to produce science-based guidance that benefits patients, regulators and industry. The development of a comprehensive recommendation document, representing a consensus among scientists from the various PQRI member organizations, demonstrates that an organization like PQRI can work effectively and to the benefit of patients. Additional contributions to the OINDP pharmaceutical development process by IPAC-RS and its technical teams have also appeared, including the IPAC-RS Good Manufacturing Processes Guideline for Suppliers of Components of OINDP (2).

THE FUTURE: OTHER DOSAGE FORMS AND "QUALITY BY DESIGN"

Regulatory concern regarding extractables and leachables is not limited to OINDP. The potential for formulation—container closure system interaction is also relatively high for other drug product types, such as injectable solutions, parenterals, and ophthalmics (Container Closure Systems for Packaging Human Drugs and Biologics; Guidance for Industry. U.S. FDA). It is attractive and logical to conclude that safety and analytical thresholds, as well as best practices for pharmaceutical development, could be developed for these other drug product types. At the time of this writing, a PQRI Working Group for parenteral and ophthalmic drug products (PODP) is forming. This Working Group will likely address these issues and produce an additional recommendation document.

The proposed pharmaceutical development process and best practice recommendations for OINDP also support a Quality by Design (QbD) approach to drug product development (3), for example in its proposal that management of extractables and leachables for OINDP should start with knowledge of critical container closure component composition, and early safety assessment using this information. Further, the process proposes that the AET is based on the SCT, that is, analytical approaches to quality are fundamentally based on considerations of drug product safety, not *vice versa*. The process and the recommendations do not explicitly describe how extractables and leachables information would affect the "Design Space" for OINDP, and how extractables and leachables acceptance criteria would be established and utilized within the Design Space paradigm. This concept is highly complex, and industry and regulators are only beginning to explore this issue (D. Norwood. Considerations for Leachables and Extractables in a QbD Environment. Inhalation and Nasal Drugs: The Regulatory Landscape. November 2006. http://www.ipacrs.com/conf2006.html)

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REFERENCES

1. D. Ball, J. Blanchard, D. Jacobson-Kram, R. McClellan, T. McGovern, D. L. Norwood, M. Vogel, R. Wolff, and L. Nagao. Development of safety qualification thresholds and their use in drug product evaluation. *Toxicol. Sci.* **97**(2):226–236 (2007).
2. IPAC-RS. Good manufacturing practices guideline for suppliers of components for orally inhaled and nasal drug products. International Pharmaceutical Aerosol Consortium on Regulation and Science(2006).
3. D. L. Norwood. Understanding the challenges of extractables and leachables for the pharmaceutical industry—safety and regulatory environment for pharmaceuticals. *Am. Pharm. Rev.* **10**(2):32–39 (2007).