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PQRI SPECIAL SECTION: The following article is an invited contribution submitted by the Product Quality Research Institute (PQRI) Leachables and Extractable Working Group. The article was internally reviewed by PQRI and FDA members and their affiliated companies and not peer-reviewed by the PDA Journal.

COMMENTARY

Perspectives on the PQRI Extractables and Leachables “Safety Thresholds and Best Practices” Recommendations for Inhalation Drug Products

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ABSTRACT: In 2006, the Product Quality Research Institute’s (PQRI) Leachables and Extractables Working Group released a comprehensive and detailed recommendation document related to leachables and extractables for inhalation drug products. The document includes best pharmaceutical development practice recommendations regarding container closure/delivery system component composition and selection, controlled extraction studies, drug product leachables studies, and routine extractables testing for component release. Also included in the document are two safety-based thresholds for leachables in inhalation drug products, the *qualification threshold* (QT) and the *safety concern threshold* (SCT), the first such safety-based thresholds for leachables in any drug product type. A process was described for converting the SCT into an analytically useful threshold for leachables/extractables characterization, the *analytical evaluation threshold* (AET), with consideration of individual drug product dosing parameters and container closure system component characteristics.

This commentary presents the history and evolution of this recommendation document starting from the propellant changeover (chlorofluorocarbons to hydrofluorocarbons) in metered dose inhaler drug products, which helped prompt interest in inhalation drug product leachables, through the work process of the PQRI group. The overall positive acceptance of the PQRI recommendations is discussed, along with a brief summary of regulatory initiatives influenced by the recommendations. Also presented and discussed are certain key issues and questions that have arisen since the recommendation document was released. The extension and application of best practice recommendations to other high risk drug product types (e.g., large and small volume parenterals, ophthalmics), led by the PQRI Parenteral and Ophthalmic Drug Product Working Group, is introduced and considered.

KEYWORDS: Extractables, Leachables, Inhalation, OINDP, PQRI, Qualification threshold, Safety concern threshold, Analytical evaluation threshold.

LAY ABSTRACT: The recommendation document released by the Product Quality Research Institute’s (PQRI) Leachables and Extractables Working Group in 2006 includes the first safety-based thresholds for leachables in any drug product type, along with comprehensive best practice recommendations for inhalation drug product pharmaceutical development related to extractables and leachables. The best practice recommendations encompass a number of important functional areas, including container closure/delivery system component composition and selection, controlled extraction studies, drug product leachables studies, and routine extractables testing for component release. This commentary presents the history and evolution of this recommendation document starting from the propellant changeover (chlorofluorocarbons to hydrofluorocarbons) in metered dose inhaler drug products, which helped prompt interest in inhalation drug product leachables, through the work process of the PQRI group. The overall positive acceptance of the PQRI recommendations is discussed, along with a brief summary of regulatory initiatives influenced by the recommendations. Also presented and discussed are certain key issues and questions that have arisen since the recommendation document was released. The extension and application of best practice recommendations to other

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drug product types (e.g., large- and small-volume parenterals, ophthalmics), led by the PQRI Parenteral and Ophthalmic Drug Product Working Group, is introduced and considered.

Introduction

The 1970s saw a dramatic increase in awareness regarding human civilization's effects on the environment, along with an equally dramatic increase in awareness of the environment's effects on human health. Concerns in both the scientific community and general public led to advances in the understanding and control of air and water pollution, toxic wastes in soil and groundwater, and trace level contaminants in drinking water. Incidences of disease including certain cancers and respiratory conditions were unambiguously correlated with environmental factors such as exposure to trace levels of xenobiotic chemicals. One of the most significant reports of that "decade of the environment" came in 1974 when Stolarski and Cicerone described a theory linking chlorine with ozone depletion in the stratosphere through a free radical chain reaction (1–3). The ozone layer, which surrounds the earth in the upper atmosphere, filters out the majority of UV-B radiation from the sun and thereby protects the earth's ecosystems and organisms (2, 3). Depletion of the ozone layer would subject humans to increasing risk for potentially serious health problems such as skin cancer and cataracts, as well as other health and environmental problems (2, 3). Subsequent to the initial theory of ozone depletion, Molina and Rowland (4) suggested that chlorofluorocarbons (CFCs) acted as a primary source of ozone-destroying chlorine free radicals in the stratosphere. At that time, CFCs were widely used industrial chemicals with applications in refrigeration, air conditioning, and foam blowing; and as solvents, fire suppressants, and propellants in aerosol consumer products (3). Ominously for the pharmaceutical industry and patients with chronic respiratory diseases, CFCs (i.e., CFC-11, CFC-12, CFC-114) were also used as propellants in metered dose inhaler (MDI) drug products. The MDI, because of its effectiveness, low cost, and ease of use, was and continues to be a preferred delivery system for inhaled therapies to treat the hundreds of millions of people worldwide with asthma and COPD (chronic obstructive pulmonary disease, including emphysema and chronic bronchitis) (2).

The world's governments responded to the environmental consequences of CFCs by adopting the "Montreal Protocol" in 1987, which set restrictions on the

production of CFCs (2) and in 1992 extended the Protocol to phase out CFC production for all but "essential uses" by 1996 (2). The use of CFCs as MDI propellants was granted a temporary essential use exemption to allow time for development of CFC-free alternatives (2). In response to the Montreal Protocol's mandate, the pharmaceutical industry launched a massive effort to identify alternatives for CFCs, as well as alternative delivery systems for respiratory drugs. The so-called HFCs (hydrofluorocarbons; alternatively HFAs, hydrofluoroalkanes) HFC-134a and HFC-227 were identified as potentially viable CFC replacements for use in MDIs. The switch from CFCs to HFCs has not been simple, requiring reformulation of each individual MDI drug product along with modifications to the MDI container closure/delivery systems. As of this writing, there are a number of CFC-free MDI drug products approved and available to patients worldwide. Alternative delivery systems for respiratory drugs have also been developed, approved, and are available. These include various types of dry powder inhalers (DPIs), inhalation sprays, and others.

The CFC-to-HFC switch coincided with an increase in regulatory concern regarding leachables in inhalation drug products, and in MDIs in particular (5). *Leachables* are chemical entities that migrate into a drug product formulation from the packaging or delivery system and its components, and are subsequently delivered to patients along with each dose of medication. Leachables, therefore, present potential safety risks for patients, and in particular for the sensitive patient population using inhalation drug products to treat chronic diseases (6, 7). The timing of the HFC reformulation effort for MDIs allowed modifications of MDI container closure/delivery systems to address the issue of leachables. However, in 1990 there was little, if any, scientific or regulatory guidance as to how to characterize or control leachables in MDIs or any other drug product/dosage form type.

This commentary describes the process of collaboration between industry and regulatory authorities through the Product Quality Research Institute (PQRI), which resulted in a comprehensive best practices recommendation/guidance (8) for leachables characterization and control in inhalation drug products, including MDIs, and the current status of this

guidance some 6 years after its release. The degree of acceptance of the PQRI recommendations, identified technical questions, and the degree to which the recommendations can and are being applied to other drug product types such as parenterals and injectables are considered.

Industry Consortia—IPAC and IPAC-RS

In 1989, MDI manufacturers from both the United States and Europe formed a group called the International Pharmaceutical Aerosol Consortium (IPAC) to address issues related to the phase-out of CFCs and the MDI reformulation effort (2). IPAC joined with the Pharmaceutical Aerosol CFC Coalition in 1990 to undertake toxicology testing of HFC-134a, forming the International Pharmaceutical Aerosol Consortium for Toxicology Testing of HFA-134a (IPACT-I) (2). Ironically, one of the most attractive features of the CFCs, their chemical stability which helps impart extremely low toxicity, also allows them to migrate into the upper atmosphere without chemical degradation, thus being available for ozone depletion. A second consortium (IPACT-II) was later formed to accomplish toxicology testing on HFC-227 (2).

Regulatory concern regarding leachables in inhalation drug products began in the late 1980s when the U.S. Food and Drug Administration (FDA) became aware of reports concerning polyaromatic hydrocarbons (PAHs; or polynuclear aromatic hydrocarbons, PNAs) in certain elastomers used as seals in MDI drug products (6, 7). The FDA then became aware of the presence of PAHs as leachables in MDI drug product formulations (7, 9). These PAHs were present in trace level amounts in the carbon black that was commonly used as a “filler” in the sulfur-cured elastomeric seals used in MDIs at that time. Later, the FDA also became aware of the potential presence of N-nitrosamines in these same sulfur-cured elastomers (7). N-nitrosamines are trace-level reaction byproducts of the vulcanization process for rubber, and are derived from curing agents such as thiurams (10, 11). In considering the rubber-curing process in greater detail, the FDA further became aware of the potential presence of curing agents/accelerators such as 2-mercaptobenzothiazole (2-MBT) in elastomers, along with other chemical classes of potential leachables in both the elastomeric and plastic components of MDIs (7).

In the early 1990s, the pharmaceutical industry responded to regulatory concern regarding leachables in

MDIs by initiating research programs to characterize leachables and potential leachables in MDI drug products under development. This included MDI drug products in the process of transition to alternate propellants, as well as those being developed with CFC propellants. Characterization of potential leachables was accomplished by extraction of MDI components and analysis of the corresponding extracts. Potential leachables characterized in this way were (and are) referred to as *extractables*. In addition, consideration was given to creating “cleaner” MDIs by prewashing (pre-extraction) of MDI valve rubber components, implementation of improved degreasing processes for MDI aluminum and stainless steel canisters, and designing MDI components with optimized curing and compounding processes to minimize potential leachables. Concern regarding leachables in MDIs prompted the pharmaceutical industry to begin to work more closely with component suppliers to engineer improved components and processes, as well as to secure the packaging component supply chain.

To assist with the processes of MDI propellant transition and in dealing with the leachables issue, inhalation drug product manufacturers also wanted regulatory guidance. In addition, regulatory guidance was needed regarding the development of other inhalation drug product types, particularly DPIs and inhalation sprays. There were many questions posed, including

- How should extractables/leachables be characterized and controlled, both in MDIs as well as other inhalation drug product types?
- Down to what level should such characterization and control be accomplished? (i.e., “How low should you go?”)
- How should extractables/leachables be qualified for safety?

To address these questions, the FDA prepared and issued three draft guidances, including a general packaging guidance (12) and two related specifically to inhalation product development (13, 14).

Inhalation product manufacturers had comments and questions regarding these regulatory guidances, and in 1999 IPAC member companies formed an organizational structure to address these. The resulting International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) undertook a mission to

advance consensus-based and scientifically driven standards and regulations for orally inhaled and nasal drug products (OINDPs; i.e., inhalation drug products). IPAC-RS, which was officially constituted as a separate consortium from IPAC in 2001, began a collaboration in 1999 with the Inhalation Technology Focus Group (ITFG) of the American Association of Pharmaceutical Scientists (AAPS), in order to directly address the draft inhalation product guidances (note that the “MDI/DPI guidance” (13) remains in draft form as of this writing, and the “Nasal Spray guidance” (14) was finalized in 2002). The IPAC-RS/ITFG Collaboration created a number of technical teams to address various aspects of the guidances, including a Leachables and Extractables Technical Team.

While strongly supporting the efforts of the FDA in drafting useful guidance documents that addressed leachables and extractables in OINDPs, the IPAC-RS/ITFG technical team identified several key areas of the draft guidances that would benefit from further investigation and dialogue. To facilitate this dialogue, the team, among other activities, collected drug product-specific leachables and extractables data from IPAC-RS member companies, formed a toxicology working group to address toxicology issues for leachables, and investigated current supplier practices for control of component composition and extractables profiles. Finally, in March 2001 the team submitted a technical paper entitled *Leachables and Extractables Testing: Points to Consider* (15) to the FDA, which included proposals for

- Reporting and safety qualification thresholds for leachables (the first such threshold proposals for leachables in any drug product); and
- A leachables safety qualification process.

In response to the proposals in the *Points to Consider* document, the FDA suggested that IPAC-RS submit a project proposal to PQRI.

The Product Quality Research Institute (PQRI)

PQRI is a nonprofit organization established in 1996 to serve as a forum for academia, industry, and regulatory authorities to work cooperatively outside the formal regulatory process on scientific and regulatory issues for the overall advancement of drug product quality and development. PQRI is an organization of member organizations, currently including FDA/

CDER (Center for Drug Evaluation and Research), AAPS, Health Canada, the Consumer Healthcare Products Association (CHPA), the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas), and the United States Pharmacopeia (USP). IPAC-RS was also a member organization of PQRI during the period in which the aforementioned recommendations were developed (8). The result of a typical PQRI working group effort is a formal recommendation document designed to have an impact on pharmaceutical regulatory science, which is submitted to the FDA.

Following the suggestion from FDA, IPAC-RS representatives drafted a proposal to develop thresholds and examine best practices for leachables and extractables in OINDPs. The proposal was accepted by PQRI and a working group was formed in 2001, led by IPAC-RS scientists and consisting of chemists and toxicologists from the FDA, industry, and academia. The working group began by developing a formal hypothesis and workplan (8) which were approved by PQRI in 2002. As a final work product, the working group prepared a recommendation document entitled *Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products*, which was submitted to PQRI leadership and FDA in 2006 (8). The Working Group also presented a public workshop based on this recommendation document in December 2005 (16).

Content of the PQRI OINDP Recommendations

The PQRI OINDP recommendations include the first safety-based thresholds for leachables and extractables evaluation and qualification in any drug product type, developed from a consensus process including pharmaceutical industry representatives, regulators, and academics. Note that the existing guidance for drug product impurity evaluation (ICH Q3B) specifically excludes “impurities. . . extracted or leached from the container closure system. . .” (17).

The proposed thresholds are the

- *safety concern threshold* (SCT): 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 SCT for an individual organic leachable in any OINDP is 0.15 $\mu\text{g}/\text{day}$ TDI (total daily intake).

- *qualification threshold (QT)*: the threshold below which a given non-carcinogenic leachable is not considered for safety qualification (toxicological assessments) unless the leachable presents structure–activity relationship (SAR) concerns. The QT for an individual organic leachable in any OINDP is 5 µg/day TDI.
- *analytical evaluation threshold (AET)*: the threshold at or above which a particular extractable and/or leachable should be identified, quantified, and reported for potential toxicological assessment.

From an analytical chemistry perspective, an important issue is defining “how low to go” in the characterization of drug product leachables, and by extension, potential drug product leachables (i.e., extractables). The SCT answers this question, after it is converted to a quantity useful in the analytical laboratory by taking into account drug product dosing parameters and container closure/delivery system properties. This quantity is the AET.

Along with the safety-based thresholds for leachables, the PQRI OINDP recommendations define best pharmaceutical development practices in the following areas:

- Early evaluation of OINDP container closure system components for ingredients that could produce leachables of possible safety concern,
- Controlled extraction studies for characterization of container closure/delivery system component extractables (i.e., potential leachables),
- Leachables studies on drug product, and,
- Routine extractables testing for release of container closure/delivery system components.

Note that the thresholds and best practice recommendations have also been published in the peer-reviewed scientific literature (18, 19). A comprehensive book has also been published (edited by PQRI and IPAC-RS scientists) that discusses the issue of leachables and extractables in detail, along with the derivation of the safety thresholds and best practice recommendations, and includes the laboratory data acquired by the working group (20).

Acceptance of the PQRI OINDP Recommendations

Since its issuance in 2006, the OINDP industry has used the PQRI OINDP recommendations (8) to guide its management of leachables. The recommendations clearly filled a conspicuous gap, since previously there were no detailed, science-based, and experience-based guidances regarding extractable and leachable evaluations, safety qualifications, and risk assessments. While it is generally understood that industry has embraced the recommendations (judging from the significant number of industry presentations and publications referring to the application of the recommendations, the number of scientific meetings specifically related to extractables and leachables in which the recommendations are discussed, and the contract research organizations that advertise their ability to apply the recommendations), there is less in the public record regarding the extent of application, consideration, and acceptance of the recommendations by international regulatory authorities. It does appear, based on anecdotal evidence from IPAC-RS representatives (and others, including the authors of this commentary) related to product application meetings with regulatory agencies, that the FDA, Health Canada, and European regulators are generally supportive of the recommendations and believe that they represent good guidance and practice for OINDPs. Formal presentations at various scientific meetings have noted that the PQRI OINDP recommendations are a useful extractables/leachables reference (21), and have referred to the regulatory application of the recommendations and in particular, the SCT (22). Additionally, in a chapter addressing regulatory perspectives on the application of safety thresholds for qualification of leachables, it was noted (23) that “although this field of science is still evolving and is being continuously discussed at international meetings, the safety threshold concept proposed by PQRI is considered suitable to qualify a CCS (container closure system) intended for a pharmaceutical product”. Finally, a panel discussion at the 2011 IPAC-RS Leachables and Extractables Workshop, including representatives of the pharmaceutical industry and regulatory authorities, appeared to concur with the PQRI recommendations’ perspectives on the importance of controlled extraction studies in providing necessary information as well as supporting quality-by-design concepts (24).

Additional evidence of support for the utility and application of the PQRI recommendations comes from the fact that the USP is currently in the process of

preparing and proposing new general chapters related to both extractables and leachables which are intended to incorporate the essence of the PQRI OINDP recommendations.

Scientific and Regulatory Initiatives Since 2006

Since the original public presentation of the PQRI recommendations in 2005 (16), additional scientific and regulatory initiatives have been undertaken. These have focused on providing regulatory guidance specifically for inhalation products and more generally dealing with the quality of materials used in inhalation product container closure/delivery systems. Although there were several draft or issued guidance documents for different types of inhalation products in the U.S. (13, 14, 25), the European and Canadian health authorities issued a harmonized, single, formal guidance document (26, 27) for inhalation products in 2006. There are some differences between this harmonized document and some of the expectations presented in the U.S. documents. The Canadian/European guidance specifies extractables only for non-compendial materials characterization, whereas the U.S. draft MDI/DPI guidance (13) and PQRI recommendations point to extractables as a means of characterization and control for all inhalation product critical components. Similarly the Canadian/European guidance specifies leachables on liquid formulations but not dry powders, and the PQRI recommendations consider leachables for all inhalation product types. This difference in expectations is understandable in light of the differences in suitability criteria for pharmaceutical packaging materials. For example, the European Pharmacopoeia (Chapter 3) (28) lists specific additives that are allowed in plastics along with specific tests to be performed, whereas USP — (29) only provides general tests that are to be performed on the finished components of a container closure system.

The regulatory landscape for inhalation products with respect to extractables and leachables is complex and continues to evolve, as it is a combination of specific guidelines for inhalation products and general food/pharmaceutical packaging and device regulations. For example, the ISO 10993-1 standard was recently revised (2009) (30) to allow a risk-based approach to biological evaluation of medical devices. This revision takes into account the utilization of extractables assessment results to reduce or eliminate unnecessary animal testing and is applicable to inhalation delivery systems that are considered to be medical devices. In

the case of packaging, both the EMEA guideline on plastic immediate packaging materials (31) and the FDA packaging guidance (12) require compliance to food additive regulations and the pharmacopoeias. The European guideline for materials intended to come into contact with food (32) was recently revised to include substances used in multi-material multi-layers (e.g., multi-laminate materials), which are very often used in inhalation product packaging. The complexity of regulatory expectations is anticipated to evolve further as regulations and pharmacopoeias in the emerging markets continue to develop and address issues associated with products at higher risk for leachables issues. To address the complexity of the global regulatory landscape it will be important to identify areas where harmonization might be possible.

IPAC-RS has sponsored several initiatives geared toward developing harmonized and scientifically sound approaches to ensuring the quality of materials in inhalation products. In an effort that ran in parallel with the development of the PQRI recommendations, IPAC-RS developed and published, in 2006, a good manufacturing practice (GMP) guideline for OINDP suppliers (33). Subsequent to its publication, many public workshops were held to introduce the concepts of controls for potential leachables in the manufacturing environment, change control to minimize the risk of unexpected material changes and the use of supplier agreements, and Drug Master Files to protect proprietary information. As of September 2011 the elements of this supplier guideline were formally incorporated into the British standard, PS9000-2011.

In a second initiative, and after several workshops and discussions with suppliers, pharmaceutical companies, and regulators to discuss the topic of material quality, a set of baseline requirements for OINDP materials was developed and endorsed by IPAC-RS member companies. The document, published on the IPAC-RS website (34), includes the expectations for security of supply, change management, compendial and regulatory requirements relevant to chemical and biocompatibility attributes, and a testing paradigm for different types of materials at different points in the supply chain. It is anticipated that this type of a baseline set of requirements, to which items may be added or taken away, may be useful for other high-risk drug products (e.g., injectables, parenterals, and ophthalmics).

The introduction of the FDA's Pharmaceutical Quality for the 21st Century and ICH tripartite guidelines on

pharmaceutical development ICH Q8, quality risk management ICH Q9, and pharmaceutical quality systems ICH Q10 (35–38), coupled with the concerns about managing potential leachables, led to a third IPAC-RS initiative in 2008. The focus of this initiative was to investigate how quality could be designed into container closure/delivery system components so that potential leachables could be effectively managed. A working group was formed based on the hypothesis that an approach using traditional development concepts could be integrated with risk-based approaches to develop a paradigm for managing extractables and subsequently be applied to management of drug product leachables. The group developed a decision tree for classifying components and then undertook a case study to demonstrate how the use of designed experiments and statistical analysis could be implemented to develop numerical models to evaluate the impact of manufacturing process parameters on potential leachables in a critical component (39).

Throughout the pharmaceutical industry several initiatives were catalyzed by the issuance of the PQRI recommendations, although their scope is not confined to OINDPs. One example is the Extractables and Leachables Safety Information Exchange (ELSIE) Consortium that was formed in May 2007 (40). This industry-driven initiative was founded on the premise that safety evaluation is both time- and resource-consuming and could be done more efficiently if all generally available toxicological information for extractable or leachable compounds was accessible in a central database (launched in 2011).

The PQRI OINDP recommendations have also acted as a basis for scientific/regulatory initiatives related to other types of drug products. In a recent book that discusses all of the pharmaceutical development aspects of extractables and leachables within the context of compatibility, Jenke incorporates the essence of the PQRI best practice recommendations when discussing various categories of drug product (including injectables and parenterals) (41). The French Society of Pharmaceutical Science and Technology Working Group on Container–Content Interaction has published some proposed guidance (including for extractables and leachables studies) which purports to “meet both European and U.S. requirements, and allows consistent and standardized information to be presented by the industry to the regulators” (42). Also, the Extractables and Leachables Subcommittee of the Bio-Process Systems Alliance has published an article, “Rec-

ommendations for extractables and leachables testing. Part 1: Introduction, regulatory, and risk assessment”, related to development and manufacture of biological drug products (43). Both of these efforts mention and reference the PQRI OINDP recommendations.

Finally, PQRI itself has followed up on the OINDP effort by forming a second working group to address extractables and leachables in parenteral and ophthalmic drug products. Termed the *PODP Working Group*, this effort is on-going at the time of this writing and has held a recent public workshop devoted to proposals for extending the PQRI OINDP recommendations to these additional drug product types (44). A timeline depicting the evolution of OINDP extractables/leachables concern, and guidances related to extractables and leachables in OINDPs, is presented in Figure 1.

Specific Questions and Uncertainty

Although the PQRI recommendations, including the safety based thresholds and best practices, have been generally accepted by both industry and regulators for inhalation drug products, certain questions and concerns have been raised since their initial release. The most significant of these are presented and discussed below.

The Nature of the Safety Concern Threshold (SCT)

The SCT has received considerable discussion and debate since its formal proposal in 2006. The SCT, along with the qualification threshold (QT), are both based on a broad scientific consensus of industry, regulators, and academics. Prior to the proposals for the SCT and QT, pharmaceutical development scientists dealing with extractables and leachables issues in inhalation drug products (or any other drug product types) had no guidance as to “how low to go” with characterization studies. Without guidance, pharmaceutical development scientists conducting leachables and extractables studies were forced to rely on the known capabilities of modern trace organic analysis (which are considerable), drug product-specific guidance from regulatory authorities (often after a regulatory filing), and guesswork. The available ICH guidances specifically excluded leachables and extractables from consideration as drug product impurities, and thus ICH thresholds and guidance did not apply (17).

The SCT is similar in concept to the *threshold of toxicological concern* (TTC), which is defined as “a level of exposure for all chemicals, whether or not there are chemical-specific toxicity data, below which

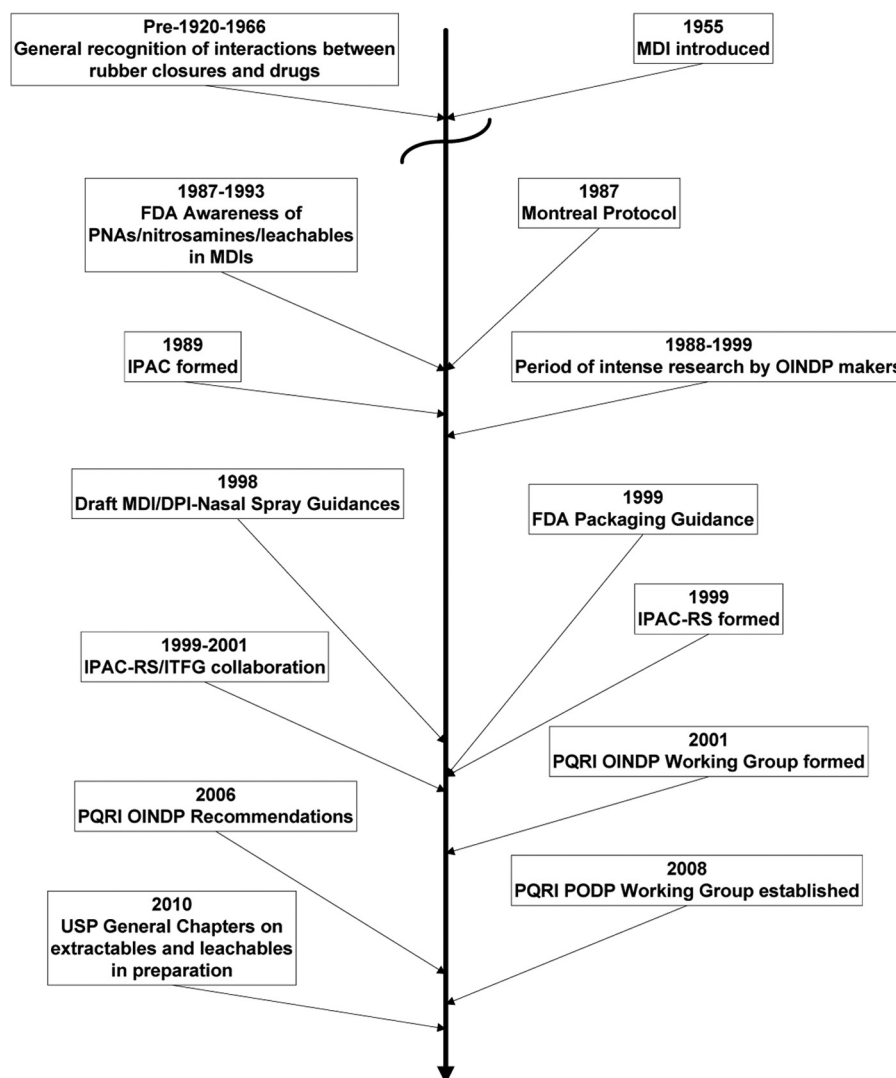


Figure 1

Pictorial representation of key events in the evolution of the PQRI OINDP Recommendations, and beyond.

there would be no appreciable risk to human health” (45, 46). Based on studies of known carcinogenic chemicals in various carcinogenic potency databases, the European Medicines Agency used the TTC concept to establish a value of 1.5 $\mu\text{g}/\text{day}$ as an acceptable daily exposure limit for genotoxic impurities in drug substances, which corresponds to a 10^{-5} lifetime excess risk of cancer (47). The SCT is based on a 10^{-6} lifetime excess risk of carcinogenicity that was considered to be justified based on the diversity of chemical types which could appear as leachables and potential leachables, a focus on genotoxic carcinogens with the probability of their existence as leachables and proper evaluation of species sensitivity, and the profiles of patient populations that typically require inhalation drug therapy. In addition, it was recognized

that inhalation drugs are delivered directly to the diseased organs of sensitive patient populations, and that many of these patients would require such inhalation therapies for decades or for their lifetimes. Toxicity issues beyond carcinogenicity, such as paradoxical bronchospasm (i.e., irritation), were also evaluated and considered to be of negligible safety concern if the carcinogenicity threshold was met. Further, leachables were considered as providing no benefit to patients. For a complete discussion of the derivation of the SCT for leachables, the reader is referred to Chapter 4 (48) in the *Leachables and Extractables Handbook* (20). Detailed discussions of the TTC concept for genotoxic and carcinogenic impurities in drug substances and drug products can be found in the applicable regulatory guidances (47, 49).

Table I
OINDP Special Case Compounds

Polyaromatic Hydrocarbons	N-nitrosamines	Other
Naphthalene	N-nitrosodimethylamine	2-mercaptobenzothiazole
Acenaphthylene	N-nitrosodiethylamine	
Acenaphthene	N-nitrosodi-n-butylamine	
Fluorene	N-nitrosomorpholine	
Phenanthrene	N-nitrosopiperidine	
Anthracene		
Fluoranthene		
Pyrene		
Benzo(a)anthracene		
Chrysene		
Benzo(b)fluoranthene		
Benzo(k)fluoranthene		
Benzo(e)pyrene		
Benzo(a)pyrene		
Indeno(123-cd)pyrene		
Dibenzo(ah)anthracene		
Benzo(ghi)perylene		

The SCT is designed to represent a safety based benchmark for analytical chemists and other pharmaceutical development scientists dealing with extractables and leachables in inhalation drug products. In order to be drug product-specific, an SCT value (derived from safety data relevant to that dosage form, for example, 0.15 $\mu\text{g}/\text{day}$ TDI for OINDPs) can be translated into an AET with consideration of the specific dosing parameters and packaging system attributes of that specific drug product—see Chapter 5 (50) of the *Leachables and Extractables Handbook* (20).

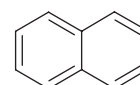
Given the preceding discussion, there are several points of clarification regarding the SCT:

- *The SCT is designed primarily to assist pharmaceutical development scientists in developing analytical methods for leachables and extractables studies. In that context, it can be considered as an “identification threshold” or “reporting threshold”.*
- *The SCT is not intended to represent a “control limit” for drug product leachables, whether they are genotoxic or otherwise; and it was never presented or described as such. Leachables and potential leachables identified above the SCT are presented for compound-specific safety assessment.*

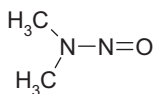
- *This particular SCT value of 0.15 $\mu\text{g}/\text{day}$ was developed for inhalation drug products only (i.e., OINDP). The extension of the SCT/QT concept to other drug product types is a subject of current investigation, and is discussed briefly below.*

Why Special Case Compounds?

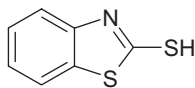
It has been recognized that some chemical structure types are of such high potency that exposures below the TTC could be associated with the potential for significant carcinogenic risks (46, 47). These chemical types include N-nitroso-, azoxy-, and aflatoxin-like-structures (47). Likewise, the FDA recognized in the late 1980s and early 1990s that certain chemical structure types were of particular concern for inhalation drug products (7). Thus, the PQRI recommendations identify the so-called *special case compounds*, which include polyaromatic hydrocarbons (PAHs or PNAs), N-nitrosamines, and 2-mercaptobenzothiazole (see Table I):



Naphthalene (a PAH)



N-nitrosodimethylamine (an *N*-nitrosamine)



2-mercaptobenzothiazole

Special case compounds in inhalation drug products should be “evaluated and controlled (either as extractables, leachables, or both) by specific analytical techniques and technology defined thresholds” (8, 51). Note that specific analytical techniques and methods exist for all special case compounds and compound classes (9–11, 52). As of this writing, there are no designated special case compounds or compound classes of leachables for other drug product types.

Best Practices for Controlled Extraction Studies

The *controlled extraction study* is defined in the PQRI OINDP recommendations as a laboratory investigation into the qualitative and quantitative nature of extractables profiles from critical components of a container closure/delivery system (8). The central purpose of a controlled extraction study is to systematically and rationally identify and quantify potential leachables, that is, extractables, to the extent practicable, and within certain defined analytical threshold parameters (8). The extraction studies accomplished by the PQRI OINDP Working Group in support of the development of best practice recommendations are reported and described in detail in Chapters 15 and 16 (52, 53) of the *Leachables and Extractables Handbook* (20). The controlled extraction study and best practice recommendations (see Table II) related to these studies are discussed in Chapter 14 (54). Although these studies were in fact designed with MDI rubber and plastic componentry in mind, the best practice recommendations were intended to be, and are, generally applicable to all types of extraction studies related to any drug product type. The MDI model was employed for these studies because the MDI is the only drug product type in which there is an almost certain 1:1 correlation (either direct or indirect; see reference 8) between critical component extractables (i.e., potential leachables) and actual identified leachables. Organic solvent extraction studies were employed because these are most applicable to the MDI; however, there was no intention to exclude any extraction technique (e.g.,

static headspace or accelerated solvent extraction) or extracting solvent choice (e.g., water), which could be more applicable to other drug product types, and this has also been discussed (54). The term “vigorous” when applied to extraction conditions does not imply total deformation of an extracted component (54), and is really intended as “rigorous” relative to the conditions of the drug product. The best practice recommendations were developed to ensure that extraction studies were accomplished with the appropriate “due diligence”, such that potential leachables were not overlooked, while balancing the level of effort required to characterize extractables that are unlikely potential leachables.

Estimated versus Final AET—The Issue of Analytical Uncertainty

For any particular drug product, the SCT can be converted into an AET with appropriate consideration of the dosing parameters of that particular drug product. The calculation process for accomplishing this conversion is described in detail in both the PQRI OINDP Recommendations (8) and Chapter 5 of the *Leachables and Extractables Handbook* (50). However, while both the SCT and the resulting calculated AET are absolute values, assigning a numerical value to the AET in a particular leachables/extractables profile from any particular analytical technique/method—for example, a chromatogram from a gas chromatography/mass spectrometry (GC/MS) analysis of drug product leachables—requires an estimation based on the known response of an internal standard or other reference compound(s) (see Figure 2). An AET assigned in this way in an extractables/leachables profile is referred to as the *estimated AET*, and by definition incorporates a degree of analytical uncertainty. The PQRI working group believed that the AET should be corrected with appropriate consideration of this analytical uncertainty. In order to accomplish this, the working group proposed a process that incorporates criteria for selecting appropriate internal standard(s), selection of reference compounds, and evaluation of analytical uncertainty through analysis of reference compounds and creation of response factor databases (8, 50). The estimated AET could then be converted to a *final AET* by correcting for analytical uncertainty. The PQRI recommendations proposed that the analytical uncertainty should be defined as either one relative standard deviation derived from an appropriately constituted response factor database of reference compounds and applied to the AET as a percentage, or

Table II
PQRI Best Practice Recommendations (with comments) for Controlled Extraction Studies (CES)

Best Practice Recommendation	Comments
<ul style="list-style-type: none"> • <i>CESs should employ vigorous extraction with multiple solvents of varying solvating power.</i> 	<ul style="list-style-type: none"> • A due diligence criterion. The term “vigorous” does not imply deformation, but rather a “rigorous” study design. Solvents should be chosen with the drug product formulation in mind.
<ul style="list-style-type: none"> • <i>CESs may incorporate multiple extraction techniques.</i> 	<ul style="list-style-type: none"> • A due diligence criterion. “Multiple extraction techniques” can include Soxhlet, reflux, sonication, headspace, automated solvent extraction, microwave, etc.
<ul style="list-style-type: none"> • <i>CESs should include careful sample preparation based on knowledge of analytical techniques to be used.</i> 	<ul style="list-style-type: none"> • This is simply good practice of trace organic analysis.
<ul style="list-style-type: none"> • <i>CESs should employ multiple analytical techniques.</i> 	<ul style="list-style-type: none"> • A due diligence criterion. In general, gas and liquid chromatography in combination are adequate.
<ul style="list-style-type: none"> • <i>CESs should include a defined and systematic process for identification of individual extractables.</i> 	<ul style="list-style-type: none"> • This is simply good practice of trace organic analysis.
<ul style="list-style-type: none"> • <i>CES “definitive” extraction techniques/methods should be optimized.</i> 	<ul style="list-style-type: none"> • A due diligence criterion. This implies the so-called “asymptotic levels” (i.e., equilibrium levels).
<ul style="list-style-type: none"> • <i>During the CES process, sponsors should revisit supplier information describing component formulation.</i> 	<ul style="list-style-type: none"> • A due diligence criterion.
<ul style="list-style-type: none"> • <i>CESs should be guided by an AET that is based on an accepted SCT.</i> 	<ul style="list-style-type: none"> • A due diligence criterion which takes the safety-based leachables thresholds into account.
<ul style="list-style-type: none"> • <i>Special case compounds such as PAHs (or PNAs), N-nitrosamines, and 2-MBT require evaluation by specific analytical techniques and technology-defined thresholds.</i> 	<ul style="list-style-type: none"> • Compounds of particular potency as recognized by the TTC concept.
<ul style="list-style-type: none"> • <i>Qualitative and quantitative extractables profiles should be discussed with and reviewed by pharmaceutical development team toxicologists so that any potential safety concerns regarding individual extractables, that is, potential leachables, are identified early in the pharmaceutical development process.</i> 	<ul style="list-style-type: none"> • A due diligence criterion. Safety assessment should be an integral part of every phase of an extractables/leachables assessment.

50% of the *estimated AET*, whichever gives the lower *final AET*. In laboratory studies involving GC/MS and gas chromatography/flame ionization detection (GC/FID), both Mullis et al. (55) and Jenke and Odufu (56) generally supported this method for estimating analytical uncertainty. It is clear, however, that analytical

uncertainty for more selective techniques such as liquid chromatography with UV detection is more difficult to determine.

The SCT, and, by extension, the AET can be considered as a pragmatic tool in the same way that the TTC

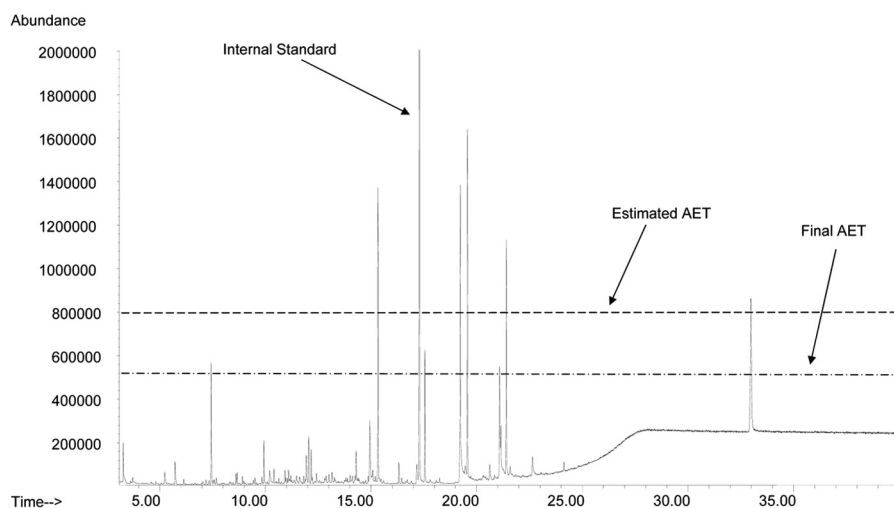


Figure 2

A representation of the estimated and final AETs in a hypothetical MDI GC/MS (gas chromatography/mass spectrometry) leachables profile. Note that the AETs are positioned relative to an internal standard.

has been described as a “pragmatic risk management tool using a probabilistic methodology” (47). There is a high probability that an AET derived from the SCT that considers analytical uncertainty will detect any leachables and potential leachables that might impart a greater than 10^{-6} lifetime cancer risk to a patient. However, just as the TTC for genotoxic impurities “should not be interpreted as providing absolute certainty of no risk” (47), the AET calculated from the SCT should likewise not be interpreted as ensuring no risk. Given that the PQRI OINDP recommendations suggest (1) the use of multiple extracting solvents for controlled extraction studies, (2) the use of multiple extraction techniques for controlled extraction studies, and (3) the use of multiple analytical techniques/methods for the analytical evaluation of both extractables (i.e., potential leachables) and actual drug product leachables, there is a very high probability that any leachable of safety concern in a particular drug product will be identified, evaluated, and controlled.

Extension to Other Drug Product Types—“The AET Challenge”

While the actual safety threshold values for OINDP (i.e., QT = 5 $\mu\text{g}/\text{day}$; SCT = 0.15 $\mu\text{g}/\text{day}$) might not be applicable to all drug product types, particularly those deemed of lower risk for leachables issues (12), the overall threshold concept based on the TTC clearly is. The best practice recommendations for materials/component selection, controlled extraction studies,

leachables studies, and routine extractables testing are also applicable to all drug product types. For example, *if* a controlled extraction study is deemed required for a rubber stopper for an injection vial, *then* the OINDP recommendations can act as a guide for the conduct of that study. Further, *if* routine release of that particular stopper requires extractables testing, *then* the recommendations can act as a guide for that release quality attribute.

As stated above, both the SCT and AET are absolute values; however, while the SCT is a constant, the AET varies from one drug product to another depending on the dosing parameters of the individual drug product. While this is not an issue when dealing with a low-volume drug product with a relatively large number of doses (i.e., an MDI), it is potentially problematic when considering the application to other dosage forms such as a high-volume drug product with a relatively low number of doses (i.e., an LVP) which can result in an extremely low AET value. For example, an MDI with 120 labeled actuations per canister and a recommended dose of 8 actuations per day gives an estimated AET value of 2.25 $\mu\text{g}/\text{canister}$, which is a reasonable analytical target. However, an LVP with 1 L of drug product packaged in a container/bag, with a recommended dose of 1 container per day, gives an estimated AET of 0.15 $\mu\text{g}/\text{bag}$ or 150 ng/L. The PQRI PODP working group is developing proposals to address this analytical challenge. The group’s preliminary proposals were a subject of discussion and debate

at its 2011 workshop (44). The issue was recognized by the PQRI OINDP working group relative to inhalation solutions (8) (which are relatively high-volume/low-dose OINDPs), and a strategy was proposed as follows:

The Working Group recommends that if it can be scientifically demonstrated that

1. *Aqueous and/or drug product formulation extracts of inhalation solution direct formulation contact container closure system material yield no extractables at final AET levels, or no extractables above final AET levels with safety concern, AND*
2. *There is no evidence for migration of organic chemical entities through the unit dose container into the drug product formulation, THEN*

Drug product leachables studies are not required.

This strategy allows leachables studies to be avoided for inhalation solutions (aqueous-based formulations) with analytically challenging AET levels. Carefully designed controlled extraction studies, which are easier to deal with in the laboratory, can be used to demonstrate the lack of potential leachables at AET levels. Like inhalation solutions, large-volume parenterals tend to be aqueous-based. Note that a recent publication from Jenke that anticipates the PQRI PODP Working Group's recommendations is available (57).

Concluding Summary

Concern regarding leachables in inhalation drug products serendipitously coincided with the effort to switch MDI drug products from CFCs to alternate propellants as mandated by the Montreal Protocol. The CFC transition process, along with increased regulatory scrutiny of all MDI regulatory submissions, facilitated addressing the leachables issue through the development of improved and cleaner container closure systems and alternative delivery devices and packaging. Regulatory guidances developed in the 1990s led to increasing dialogue between industry and regulatory authorities, resulting in the PQRI OINDP Recommendations (8), which have been deemed useful and relevant, and appear to be widely accepted and applied to both inhalation drug products and other drug product types. Various subsequent regulatory guidance initia-

tives related to leachables and extractables were influenced by the PQRI recommendations. Although not intended to be proscriptive regarding details (e.g., extracting solvent selection, extraction conditions, etc.), the recommendations *were* intended to be proscriptive in the sense that good science and due diligence are proscriptive in pharmaceutical development. Several questions and concerns regarding the best practice recommendations and their application, particularly to dosage forms beyond OINDP, have been recognized and are being addressed. Given the continuing concern regarding leachables and their relationship to safety and compatibility in various dosage form types, including therapeutic proteins (58, 59) and other biological drug products, the significance of the PQRI OINDP Recommendations is apparent.

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Conflict of Interest Declaration

The authors declare that they have no competing interests.

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