
ITFG/IPAC-RS Collaboration

CMC Leachables and Extractables Technical Team

Leachables and Extractables Testing: Points to Consider

A Response to the FDA draft Guidances for Industry:

Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation; and

Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation

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I. OVERVIEW

- In November 1998 and June 1999, the FDA issued for public comment two draft CMC Guidances for Industry: 1) Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls (CMC) Documentation¹; and 2) Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation² (here referred to as the “draft MDI/DPI Guidance” and “draft Nasal/Nebulizer Guidance”, respectively).
- Following the issuance of the draft Guidances, two organizations with expertise in inhalation and nasal drug products - the Inhalation Technology Focus Group of the American Association of Pharmaceutical Scientists (ITFG) and the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) - initiated a scientific, data-driven collaboration to address specific issues in the draft Guidances in order to contribute constructively to the Agency’s development of guidance documents for orally inhaled and nasal drug products.
- The CMC Leachables and Extractables Technical Team of the ITFG/IPAC-RS Collaboration and its Toxicology Working Group carefully reviewed the draft Guidances, conducted confidential surveys of drug product manufacturers and suppliers of pharmaceutical device components, and prepared recommendations on leachables and extractables testing.
- This report is focused on the following topics:
 - (1) Control Extraction Studies
 - (2) Leachables Studies
 - (3) Routine Extractables Testing
 - (4) Biological Safety Qualification of Leachables (Qualification of Leachables)
- For each of the four focus areas, the Team has identified sections of the draft Guidances that could be strengthened by rewording of the existing text or by addition of further clarifying statements. This report contains proposed alternate language drafted by the Team for the Agency’s consideration, for inclusion in the CMC guidances for inhalation and nasal products.
- A key concept that is introduced in the report is a proposal for the establishment of reporting and qualification thresholds for leachables. These thresholds are consistent with current industry practices and are supported by a thorough safety justification, provided here.
- This report also offers certain general recommendations for leachables and extractables testing based on best industry practices.
- The Leachables and Extractables Technical Team and the Toxicology Working Group respectfully encourage the Agency to consider the recommendations developed by the Team and to incorporate the same in the next version of the draft CMC Guidance documents.

¹ <http://www.fda.gov/cder/guidance/2180dft.pdf>

² <http://www.fda.gov/cder/guidance/2836dft.pdf>

II. INTRODUCTION

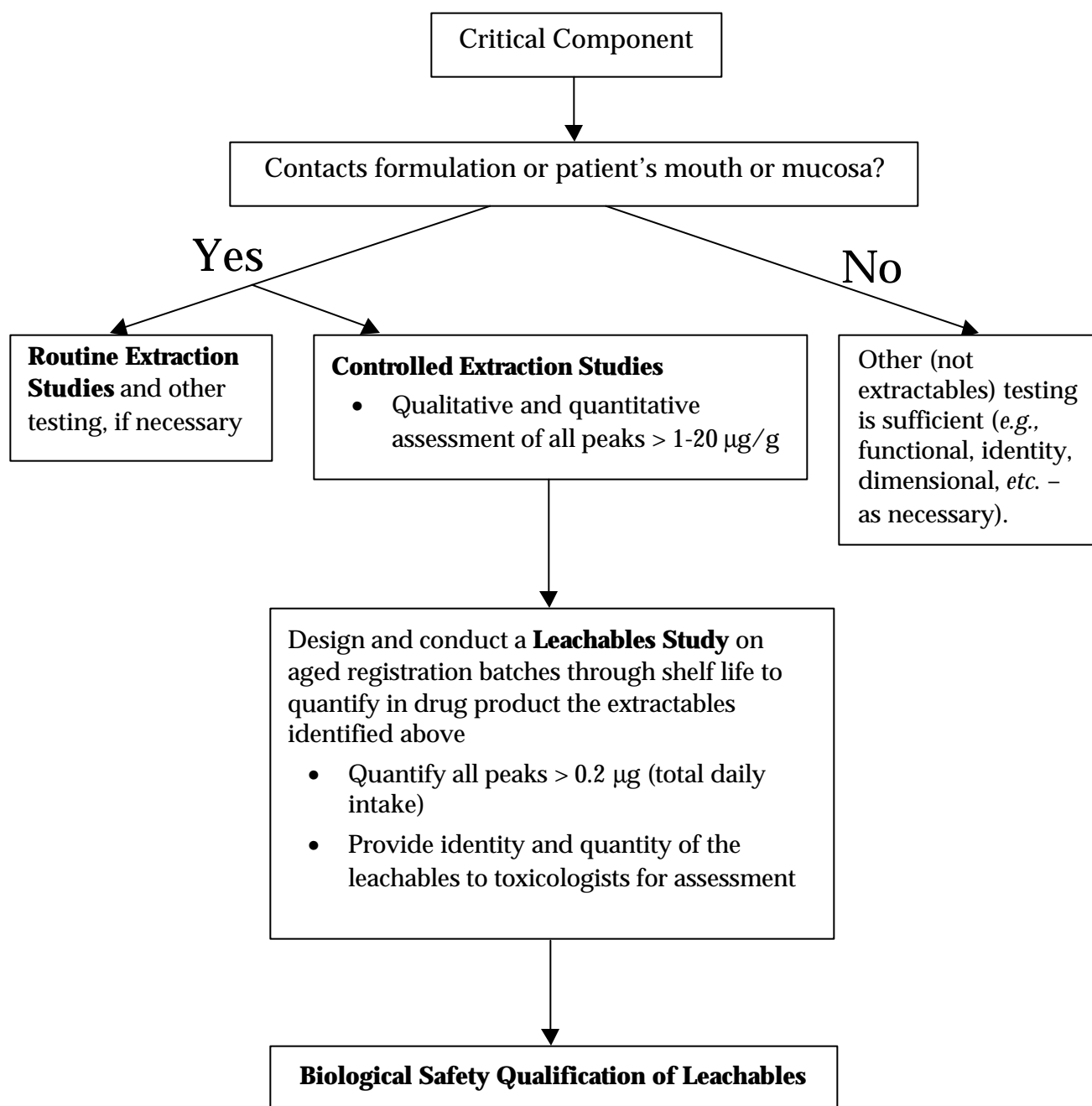
The ITFG/IPAC-RS Leachables and Extractables Technical Team presents its findings regarding leachables and extractables studies for orally inhaled and nasal drug products. In this document the Team proposes new, clarifying language recommended for adoption in the revised draft Guidances. The proposed alternate language describes a step-wise approach to investigating and controlling extractables and leachables in inhalation and nasal drug products. The proposed approach was developed based on best industry practices and science.

The approach is summarized as follows: first, the Team presents recommendations for controlled extraction studies, performed to obtain an extractables profile. This is followed by the Team's proposals for a one-time leachables study. The Team recommends that if a correlation between leachables and extractables is demonstrated, a specification for leachables in drug product should not be required. The Team also proposes a definition of a "correlation" between extractables and leachables. Next, the Team makes general recommendations for routine extractables testing and methodology. Finally, the Team proposes a strategy for the biological safety qualification of leachables.

The Team believes that reasonable reporting, identification and qualification thresholds for extractables and leachables should be established, and that there are appropriate processes for establishing such thresholds. Therefore, for controlled extraction studies, the Team proposes identification thresholds for extractables. In the *Leachables Studies* section of this paper, the Team proposes reporting and identification thresholds for leachables. In the *Qualification of Leachables* section, the Team proposes that only those leachables present above the proposed reporting threshold should be considered for potential biological safety qualification. Finally, the Team proposes a qualification threshold. These thresholds are consistent with current industry practices and are supported by a thorough safety justification.

A flowchart outlining the proposed process is presented in figure 1 on page 5. A summary table of the Team's recommended strategies for leachables and extractables testing for different dosage forms is contained in section VII (pages 31-33).

Figure 1. Summary Flowchart for Leachables and Extractables Evaluation Process*



* For detailed description and justification of each step, see text.

III. CONTROL EXTRACTION STUDIES

A. General Recommendations

The ITFG/IPAC-RS Leachables and Extractables Technical Team offers for the Agency's consideration the following observations and recommendations for control extraction studies:

1. The Team recommends that the term *controlled* extraction study be used in place of the term *control* extraction in order to avoid confusion with tests that are conducted as part of a routine control strategy.
2. Sections referring to "control extraction studies" are found throughout the draft Guidances (e.g., lines 822-834, 869-878, 986-1002, 1070-1080, 1165-1181 in the draft MDI/DPI Guidance and lines 827-831, 889-933, 939-942, in the draft Nasal/Nebulizer Guidance). We recommend that for clarity and ease of use, these sections be consolidated into one section, in each of the draft Guidances.
3. Furthermore, the draft Guidances introduce several key concepts in the cited sections, such as "critical component" and "correlation" between extractables and leachables. These key concepts should be more clearly defined for each type of delivery system. Currently, the term "critical component" is only defined for DPIs (see lines 1158-1161 of the draft MDI/DPI Guidance).
4. The Team recommends that controlled extraction studies should be conducted only on those critical components of the container closure system which either contact the formulation or the patient's mouth or nasal mucosa.
5. The current text of the draft Guidances requires the identification and quantitation of *each detected peak*. This requirement should be clarified. The Guidances should include identification criteria and reporting thresholds for extractables in controlled extraction studies.

B. Proposed Alternate Language for CMC Guidances for OINDP

A controlled extraction study is typically conducted during the early phases of drug development. The purpose of the study is to characterize the extractable compounds derived from the critical components of the drug delivery system which are either in contact with the formulation or with the patient's mouth or nasal mucosa.

In certain cases, secondary packaging critical for the performance of the drug product should also be included in a controlled extraction study. For example, a laminate overwrap used as secondary packaging for inhalation solutions, particularly when the primary packaging is semi-permeable. For DPIs, however, controlled extraction studies on secondary packaging are most appropriately addressed on a case-by-case basis.

In general, a controlled extraction study of a packaging component involves exposing a sample of the component to an appropriate solvent system at elevated temperature, followed by chemical analysis. The purpose of using elevated temperature is to increase the rate of extraction, so that a short experimental time may simulate a longer exposure time at room temperature, and/or to maximize the amount of extractable compounds obtained from a sample.

The methods employed to analyze the resulting extracts vary depending on the purpose of the extraction study and the nature of the packaging component. Typically, extraction solvents with a range of polarity are used, which should include a solvent with a polarity similar to the drug product vehicle. Solvent systems with higher solvating power than the dosage form are also included in order to generate sufficient levels of extractables for structure elucidation. Typical solvents are listed in Table 1:

Table 1. Typical solvents used for controlled extraction studies

<i>Components for the Following Dosage Forms</i>	<i>Typical Extraction Solvents For Controlled Extraction Studies</i>
MDIs	Hexane, methylene chloride, isopropanol
Inhalation solutions, nasal sprays, DPIs	Isopropanol, water, ethanol
Mouthpieces and actuators	Methylene chloride, isopropanol, water

A qualitative chemical analysis of the component extracts should be conducted. The identification of extractables is most commonly achieved by techniques such as gas chromatography – mass spectrometry (GCMS) and liquid chromatography-mass spectrometry (LCMS). The information that is typically obtained from these experiments is outlined in Table 2:

Table 2. Typical chemical identification data from analysis of extracts

<i>Identification Category</i>	<i>Typical Identification Data</i>
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

A combination of spectral interpretation, spectral library searching, and a knowledge of the materials studied are typically used in order to assign structures for the observed chromatographic peaks. The degree of certainty in the assignment of a structure is dependent on the identification data that has been obtained. Reasonable efforts should be made to assign structures as outlined in Table 3.

Table 3. Assignment of chemical structure related to extractable level

<i>Extractable Level in Component</i>	<i>Assignment Category*</i>
> 100 mg/g	Structure Confirmed
20 – 100 mg/g	Confident
< 20 mg/g	Tentative

**Assignment category:*

Structure confirmed: identification categories A, B (or C), and D (or E) (see Table 2) are positive.

Confident: sufficient data to preclude all but the most closely related structures.

Tentative: data is consistent with a class of molecule only.

The levels listed in Table 3 are consistent with current industry practices, and with the capabilities of the analytical techniques mentioned above. Whenever possible, the structures of significant extractables (> 100 mg/g) should be confirmed with authentic materials.

A quantitative analysis of the component extracts should be conducted. Reasonable efforts should be made to quantify peaks down to the 1-20 mg/g level. The test methods should be documented in sufficient detail to permit duplication

and verification by Agency laboratories. It is recognized that authentic materials for extractables may not be available. In such instances, it is acceptable to employ individual identified extractables as representative of compound classes as quantitation standards.

Note that for certain elastomeric formulations, much lower detection limits and dedicated methods may be required for specific compounds with known toxicity [e.g., nitrosamines, polynuclear aromatics (PNAs), mercaptobenzthiazole, etc.].

IV. LEACHABLES STUDIES

The draft MDI/DPI Guidance describes the requirements for leachables studies in lines 715–725, and 803–840. The draft MDI/DPI Guidance requires that

“Appropriate acceptance criteria for the levels of leached compounds in the formulation should be established...Identity and concentration profiles of the leachables in the drug product or placebo formulation...should be determined through the end of the drug product’s shelf life and correlated, if possible, with the extractables profiles of the container and closure components determined under the various control extraction study conditions. Such a correlation may obviate the need to evaluate leachables in the drug product formulation in future routine stability studies.”

A. General Recommendations

The Leachables and Extractables Team offers the following recommendations regarding leachables studies:

1. Since the draft MDI/DPI Guidance requires that a correlation between leachables and extractables be demonstrated in order to avoid the requirement for leachables testing on a routine basis, we recommend that the draft Guidances include a clear working definition of how such a correlation is established.
2. The Guidances should also include appropriate reporting, identification and qualification thresholds for leachables. (Qualification thresholds for leachables are discussed in section IV.D of this document).
3. The Team also strongly recommends that the control of leachables be accomplished by applying suitable controls and procedures during component manufacture, not after the manufacture of drug product. As the proper understanding of extractable profiles and toxicity issues is established through developmental studies, routine control of extractables is achieved primarily by current Good Manufacturing Practices (cGMPs). The cGMPs require that quality be built into all aspects of the manufacturing process as is necessary to ensure the product possesses the purported quality and purity.³

The first two recommendations have been addressed in the proposed alternate language provided below.

³ The Leachables and Extractables Team is working with the ITFG/IPAC-RS Supplier Quality Control Team to address this recommendation.

B. Proposed Alternate Language for CMC Guidances for OINDP

A leachables study should be conducted as a one-time study in support of a new drug application (NDA) or abbreviated new drug application (ANDA) submission, and may also be conducted on drug product intended for pivotal toxicological studies, and clinical trials. The purpose of the study is to determine the identity and concentration of leachables in the drug product or placebo formulation, through the end of the shelf life of the drug product. Accelerated temperature conditions may be employed to predict the leachables profile prior to reaching the end of product shelf life. The leachables study is carried out after the completion of the qualitative and quantitative characterization of extractables in the delivery system components.

For DPI's and inhalation solutions, the leachables study should be conducted on the drug product packaging configuration employed for long term stability studies (e.g., capsule with blister, low density polyethylene vial with overwrap).

An in-use study should be conducted in order to determine the leachables derived from components which are in contact with either the formulation or the patient's mouth or nasal mucosa only during administration (such as mouthpieces and actuators).

The analytical methods employed for the leachables studies should be validated for target compounds representative of those identified in the controlled extraction studies, following the International Conference on Harmonization (ICH) requirements for the validation of analytical methods for impurities. An assessment of the formulation may be done to investigate target leachables. Reasonable attempts should be made to evaluate method performance at or near the expected leachable levels.

Method quantitation limits should be sufficient for the detection of predicted leachable levels (based on component extractables data).

Table 4 presents guidance for reporting and identification thresholds for leachables in inhaled and nasal drug products. These levels are consistent with current industry practices, and with the capabilities of the previously mentioned analytical techniques. The risk assessment and justification for these levels are presented in section VI of this document.

Table 4. Reporting and identification thresholds for leachables

	Reporting threshold for leachables	Identification threshold for leachables (tentative structures)	Identification threshold for leachables (confident structures)	Identification threshold for leachables (confirmed structures)
Leachable level based on total daily intake (TDI)	~0.2 mg/day	~0.2 mg/day	> 0.2 mg/day to < 2 mg/day	~2 mg/day

Confirmed Structures: identification categories A, B (or C), and D (or E) (see Table 2) are positive.

Confident Structures: sufficient data to preclude all but the most closely related structures.

Tentative Structures: data is consistent with a class of molecule only.

Note that for certain classes of potential leachable compounds with special toxicological concerns (e.g., nitrosamines, PNA's, mercaptobenzthiazole, etc.), much lower reporting thresholds, dedicated methods, and appropriate specifications may be required.

The identities and levels of leachables should be determined in the drug product (or placebo) after storage at or near expiry. The identities and profiles of leachables should be compared with the elastomeric and plastic component extractables profiles obtained from the controlled extraction studies.

Provided that a correlation between leachables and extractables can be demonstrated, a specification for leachable compounds in the drug product will not be required. *A correlation is established when each leachable in the drug product can be assigned qualitatively, directly or indirectly, to an extractable.*

The level and profile of leachables in drug product will be controlled by routine extractables testing of components in order to ensure that no new extractables are introduced and that there is no significant increase in the level of extractables.

V. ROUTINE EXTRACTABLES TESTING

A. General Recommendations

Routine extractables testing is addressed in lines 898-905, 1004-1014, 1081-1089, and 1182-1190 of the draft MDI/DPI Guidance, and lines 924-942 of the draft Nasal/Nebulizer Guidance.

The Leachables and Extractables Team recommends that routine control of extractables be dictated primarily by current Good Manufacturing Practices (cGMPs). The cGMPs require that quality be built into all aspects of the manufacturing process as is necessary to ensure the product possesses the purported quality and purity.

B. Proposed Alternate Language for CMC Guidances for OINDP

The purpose of routine component extractables testing is to ensure that the extractables profiles of the components used for commercial drug product manufacture remain consistent with the profiles of the components evaluated as part of the development controlled extraction study. This testing is not a substitute for suitable elastomer and plastic formulation controls, which are the responsibility of the component supplier.

Routine extractables testing is required on those components which contact either the drug product and/or the patient's mucosa. Critical components which do not contact the patient's mouth or nasal mucosa or the drug product should be controlled by tests which are relevant to their performance or functional attributes. Routine extractables testing of these components is not required.

Routine extractables testing should be performed at the earliest point possible. Preferably, this testing should take place at the component manufacturer, and become a part of a system of manufacturing controls, along with in-process controls and supplier qualification. Routine extractables testing on plastic resins may be performed if a correlation can be established between the extractables profile of the resin and finished components.

Based on the analytical evaluation of the extractables from the controlled extraction study and the toxicological evaluation of leachables (see section VI), the applicant should establish discriminatory test methods and set appropriate acceptance criteria for the extractable profile(s) for routine testing of the incoming individual components.

The specifications should be established in order to control for significant changes as well as the appearance of new peaks in the extractables profile. The

test methods employed in routine extraction studies should be documented and validated in accordance with ICH requirements for impurities. It is recognized that authentic materials of extractables may not be available. In such instances, it is acceptable to employ individual compounds as representative of compound classes for validation studies and as quantitation standards. Method performance should be assessed at or near the expected extractables levels.

VI. QUALIFICATION OF LEACHABLES⁴

A. General Recommendations

The ITFG/IPAC-RS Toxicology Working Group has reviewed current industry practices of evaluating the safety of extractables and leachables. The Working Group compared these practices with the toxicological evaluation procedures in the two draft Guidances, and concluded that there are both areas of agreement and disagreement.

The following is a list of current industry practices that differ from those in the draft Guidances and that we recommend be adopted in the next version of the draft Guidances:

1. Qualification should be performed only on leachables.
2. Qualification should be conducted only on those leachables that occur above data-supported thresholds.
3. Qualification of a product-related leachable composite mixture is sufficient to qualify those leachables for registration.
4. For qualification, product samples should be qualitatively representative of the end-of-shelf life leachable profiles.
5. Risk assessment of leachables may come from one or more of the following data sources: in-silico, structure-activity relationships (SAR), literature, in-vitro or in-vivo testing.
6. For component suppliers, United States Pharmacopoeia (USP) <87> and <88> may have utility for extractable testing. However for a pulmonary drug product, USP <87> and <88> are not necessary when a more comprehensive in-vivo toxicological evaluation is available.
7. Acceptance criteria for components should be based on extractable profiles.

In addition, the Toxicology Working Group recommends that:

8. The draft Guidances should clarify the risk assessment modeling approach for carcinogenic extractables that are also leachables.
9. Each draft Guidance should include an additional section describing the recommended toxicological evaluation process, along with a flowchart and glossary.

Below, we present detailed recommendations reflecting these considerations:

- the proposed alternate language (see section B below);

⁴ *Qualification of leachables* is understood here to mean *biological safety qualification of leachables*.

- the proposed process of toxicological evaluation recommended for inclusion in the draft Guidances (see section C below); and
- a justification of the proposed qualification threshold for leachables (see section D below).

B. Proposed Alternate Language for CMC Guidances for OINDP

Text highlighted in **bold** indicates proposed new language.

For Inclusion in Draft MDI/DPI Guidance:

<i>Lines of Draft Guidance</i>	<i>Proposed Alternative Language for Draft Guidance on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products</i>
853-4	Toxicological evaluation, where appropriate, of the leached materials and residues
866	A toxicological appraisal of the leachables and residual materials should be...
883-4	For coated containers, controlled extraction studies should be performed and the profile of each extract should be evaluated analytically. Only extractables that are found to be leachables should be evaluated toxicologically.
888-9	A toxicological appraisal of the leachables should be provided. The results of USP Biological Reactivity Tests (USP <87> and <88>) should also be submitted, unless other data are available as an acceptable substitute.
895-7	A toxicological appraisal of leachable residues from manufacture or canister cleaning should be provided. The results of USP Biological Reactivity Tests (USP <87> and <88>) should be submitted, unless other data are available as an acceptable substitute.
899-902 (New text refers to residues and residue studies, and excludes requirement for toxicological evaluation of extractables)	Based on the analytical evaluation from the controlled extraction study, residue studies and toxicological evaluation of leachables and leachable residues, the applicant should establish discriminatory test methods and set appropriate acceptance criteria for the extractable profile(s) and the residues for routine testing of the incoming containers.
939	Toxicological evaluation of the leachables

Lines of Draft Guidance	Proposed Alternative Language for Draft Guidance on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products
951-2	A toxicological appraisal of the leachables ,
990-1	The profile of each extract should be evaluated analytically, but only leachables require a toxicological evaluation.
994-6	The toxicological evaluation should include appropriate in vitro and in vivo tests. The results of USP Biological Reactivity Tests (USP <87> and <88>) should be submitted, unless other data are available as an acceptable substitute.
999-1000	In those cases such as when some extractable components from rubber are known genotoxicants, known rodent carcinogens or have compelling structural alerts (e.g., nitrosamines, PNA's, mercaptobenzthiazole, etc.), appropriate risk assessment models may be needed to establish acceptance criteria if that extractable component is found as a leachable in drug product.
1005-8	Based on the analytical evaluation from the controlled extraction study and toxicological evaluation of leachables, the applicant should establish discriminatory test methods and set appropriate acceptance criteria for the extractable profile(s) for routine testing of the incoming individual valve components.
1049	Toxicological evaluation of the leachables
1073	The profile of each extract should be evaluated analytically, but only leachables require a toxicological evaluation.
1078-80	Safety concerns will usually be satisfied if the materials in the components meet food additive regulations and the actuator meets the USP Biological Reactivity Tests (USP <87> and <88>). However, if other acceptable data are available, then USP Biological Reactivity Tests (USP <87> and <88>) need not be performed.
1082	Based on the analytical evaluation from the controlled extraction study and toxicological evaluation of leachables, the applicant should establish discriminatory test methods and set appropriate acceptance criteria for the extractable profile(s) for routine testing of the incoming actuator component(s).
1132	Toxicological evaluation of the leachables

Lines of Draft Guidance	Proposed Alternative Language for Draft Guidance on Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products
1171-5	The profile of each extract from a critical component in contact with the formulation or the patient's mouth or nasal mucosa , should be evaluated analytically, but only leachables require a toxicological evaluation.
1175-8	Safety concerns will usually be satisfied if the components that contact either the patient or the formulation meet food additive regulations and the mouthpiece meets the USP Biological Reactivity Tests (USP <87> and <88>). However, if other acceptable data are available, then USP Biological Reactivity Tests (USP <87> and <88>) need not be performed.
1184	Based on the analytical evaluation from the controlled extraction study and toxicological evaluation of leachables , the applicant should establish discriminatory test methods and set appropriate acceptance criteria for the extractable profile(s) for routine testing of incoming individual critical device components

For Inclusion in Draft Nasal/Nebulizer Guidance:

Lines of Draft Guidance	Proposed Alternative Language for Draft Guidance on Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products
860	Toxicological evaluation of leachables
904-5	Extraction studies should be performed, and the profile of each extract should be evaluated analytically. Only extractables that are found to be leachables will be evaluated toxicologically.
908-10	A toxicological evaluation should be made of the leachables from the container, closure, and critical pump components (those in contact with either the formulation or the patient's mouth or nasal mucosa) and the results submitted in the application.
912-13	The results of USP Biological Reactivity Tests (USP <87> and <88>) should be submitted. However, if other acceptable data are available, then USP Biological Reactivity Tests (USP <87> and <88>) need not be performed.
919-920	Since some extractables may be carcinogenic, appropriate risk assessment models may be needed to establish acceptance criteria, if these extractable components are found to be leachables in the drug product.
926-29	Based on the analytical evaluation from the controlled extraction study and toxicological evaluation of leachables, the applicant should establish discriminatory test procedures and set appropriate acceptance criteria for the extractable profile(s) for routine testing for each container, closure, and individual pump components (those in contact with either the formulation or the patient's mouth or nasal mucosa).

C. Proposed Toxicological Evaluation Process

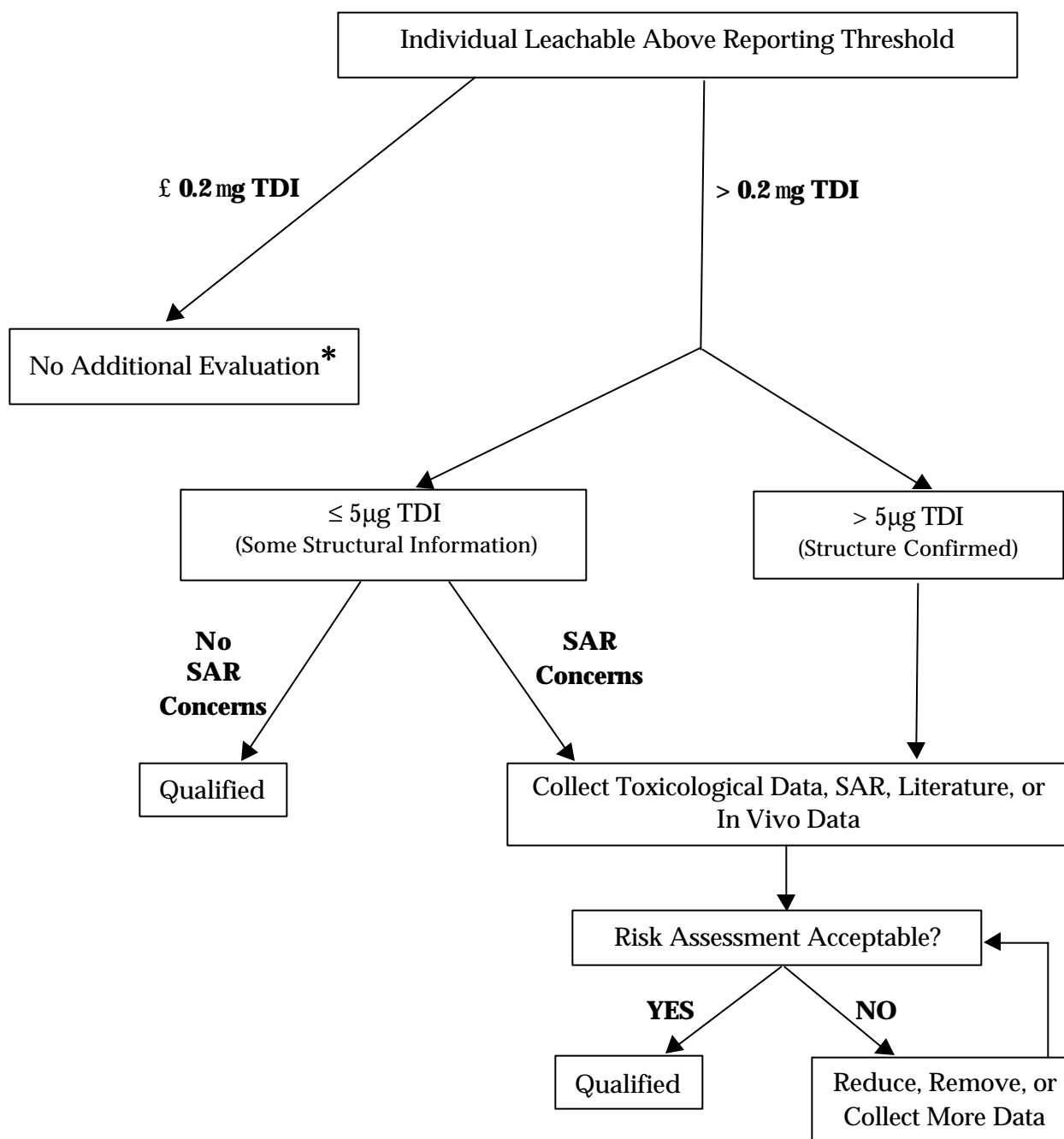
The Toxicology Working Group is proposing an approach to evaluation of leachables that recognizes the importance of regulations and guidelines that focus resources on substantive matters concerned with the benefits and safety of inhaled products to patients. The approach also recognizes a threshold below which trace leachables need not be evaluated unless there are special concerns about the structure.

The Toxicology Working Group recommends that the following flowchart (Figure 2), description of the toxicological evaluation process and glossary entries be incorporated in the revised draft Guidances.

The Working Group recognizes that like all guidelines, the following recommendations may not cover all situations and that special, case-by-case considerations may be warranted in some instances.

A key element in the safety evaluation process is defining a threshold below which leachables would not need to undergo qualification. A rationale for the proposed qualification threshold for leachables is contained in Section D.

Figure 2. Decision flowchart for evaluating toxicity and risk evaluation (recommended for incorporation in CMC guidances for OINDP)



*Note that for certain classes of potential leachable compounds with special toxicological concerns [i.e., nitrosamines, polynuclear aromatics (PNAs), mercaptobenzthiazole, etc.] much lower reporting thresholds, dedicated methods, appropriate specifications, and appropriate qualifications and risk assessments may be required.

DESCRIPTION OF TOXICOLOGICAL EVALUATION PROCESS (Recommended for incorporation in CMC guidances for OINDP)

1. Collection of Toxicology Data

Evaluate the potential toxicity of each leachable above the qualification threshold based on the intended route of administration (mostly through inhalation, although ingestion through swallowing is also likely), duration of treatment in patients, and the patient population (men, women of child-bearing potential, pediatrics, etc) at risk.

Where sufficient toxicological information is not available in the literature on a specific leachable, but the class of chemical presents a structural alert, based upon structure activity relationship (SAR) analysis, additional safety testing may be warranted. The toxicology studies to be considered, depending on the alert, may include in vitro genotoxicity assays and 2-13 week general toxicity studies in the most appropriate species, using the drug product and the leachable (at a concentration, where possible, greater than or equal to that which will be present in the drug product at the end of the shelf life).

2. Qualification and Reporting Thresholds and Risk Assessment

Based on the concentration of the leachable present in the drug product, calculate the total daily intake (TDI) of the leachable that a patient will be exposed to according to the maximum daily dose of the drug product. Use the assumption that the entire inhaled dose is delivered to the lung.

If a leachable is present at a level below the reporting threshold (usually 0.2 mg TDI, see Table 4), it is considered qualified and no toxicological assessment is required. In general, a leachable with a TDI of 0.2 mg or less will have a dose so low as to present no safety concerns for patients using the product. However for certain classes of potential leachable compounds with special toxicological concerns [e.g., nitrosamines, polynuclear aromatics (PNA's), mercaptobenzthiazole, etc.], much lower reporting thresholds, dedicated methods, appropriate specifications and appropriate qualifications and risk assessments may be required. Such leachables will be considered on a case-by-case basis.

If a leachable is present at level that will result in a TDI greater than 0.2 mg and less than or equal to 5 mg, SAR should be performed to determine if the leachable shows a structural alert. The amount of structural information available for SAR is dependent upon the TDI (see Table 4). For instance, for a leachable present at a TDI of approximately 0.2 mg the data available may only be sufficient to assign the structure to a chemical class. As the level of a leachable increases, up to 2 mg TDI, the degree of certainty in the assignment would be expected to

increase until finally, for a TDI of approximately 2 mg or greater, the structure of the leachable can be confirmed.

If a leachable shows no structural alert or no known class effect for carcinogenicity/genotoxicity or immediate hypersensitivity, and it is present at a level that will result in a TDI greater than 0.2 mg and less than or equal to 5 µg, it is considered qualified and no toxicological assessment is required.

If a leachable shows a structural alert or a class effect for carcinogenicity/genotoxicity or immediate hypersensitivity, and it is present at a level that will result in a TDI greater than 0.2 mg and less than or equal to 5 mg, a toxicology risk assessment should be performed. Compare the TDI of the leachable to study results, or the toxicology data reported in the literature, to see if a sufficient safety margin exists.

If any leachable is present at a level that will result in a TDI of greater than 5 µg, a toxicology risk assessment should be performed. Compare the TDI of the leachable to study results, or the toxicology data reported in the literature, to see if sufficient safety margin exists.

Some of the leachables (e.g., phthalates, ethyl acetate) may be present in the environment at considerable concentrations where daily ingestion (through food or water) and inhalation (through air) occur. If the TDI of a leachable is estimated to be greater than 5 µg but lower than that reported for humans through environmental exposure, and the epidemiology data do not indicate adverse effects, then it may be possible to justify a higher level of qualification on a case-by-case basis.

GLOSSARY

<u>Qualification</u>	All data from testing (e.g., toxicology data, literature data, SAR data, clinical safety experience).
<u>Toxicological Studies</u>	Includes animal studies and in-vitro studies beyond those available in the literature.
<u>Risk Assessment</u>	Evaluation of data obtained through qualification and toxicological studies (as defined above) to define potential risks relative to therapeutic use of the product.

D. Justification of Proposed Qualification Threshold

1. Introduction

This section provides a scientific rationale, based on available data, for the toxicological qualification and acceptance of leachables (non-drug-related impurities) in inhaled drug products using a threshold value of 5 µg per leachable for a total daily exposure irrespective of age and disease severity.

We first provide a brief overview of the concept of inhaled drug product leachables, and some background information on the current regulatory approaches to controlling these leachables. We follow with a brief summary of typical sources of leachables, then provide a rationale and process for establishing the 5 µg threshold value. We then examine the significance of this threshold in the context of two marketed inhaled drug products, and also compare it to threshold data for compounds in some approved inhaled drug products.

2. Background

Inhalation drug products are developed for delivery of drug substance directly to the respiratory tract to treat either a local condition [e.g., asthma or chronic obstructive pulmonary disease (COPD)] or a non-respiratory disease (e.g., diabetes). Inhaled drug substances are, by far, some of the most potent chemical entities that are administered to humans. These drugs are usually presented in delivery devices, (e.g., metered dose inhalers, dry powder inhalers or nasal spray inhalers/pumps). These devices may contain polymers, elastomers, and other components from which minute quantities of material may migrate (leach) into the product and be delivered to the sensitive surfaces of the respiratory tract along with the therapeutic agent. While every effort is taken to reduce the levels of these leachables, complete removal is not possible.

ICH guidelines, Q3A and Q3B cover the internationally agreed principles for impurities in drug substances and products, respectively and the ICH Q3C⁵ guideline covers the acceptable levels of residual solvents allowable. These guidelines are being considered by the FDA, and have been published in the Federal Register. According to the guidelines, *the level of any degradation product present in a new drug product that has been adequately tested and found safe in safety and/or clinical studies is considered qualified*. However, identification and qualification limits of leachable materials associated with a pulmonary product have been held to a higher standard. This is most likely because leachables are non-drug related impurities and may possess toxicity characteristics unlike those associated with the drug substance or drug product.

For instance, a metered dose inhaler (MDI) has been demonstrated to accurately deliver low doses of drug substance to the lung. However, it is also understood that the propellants

⁵ <http://www.ifpma.org/ich5q.html#Impurity>; ICH Guidelines Q3A, Q3B, and Q3C were published in the Federal Register on 4 January 1996, 19 May 1997 and 24 December 1997, respectively. Revised versions of Q3A and Q3B were published in the Federal Register on 20 July 2000 and 19 July 2000, respectively.

employed in MDIs are reasonably good solvents and will cause a certain amount of materials to leach from the rubber-based and polymeric components in MDI delivery devices. Because these are non-drug-related impurities, there could be an increased concern for human risk by inhaling these leachates on a daily basis.

Historically, acceptable levels of leachables in a pulmonary drug product have been set by negotiation on a case-by-case basis with no standard guidelines available.

3. Potential Sources of Leachables

Historically, leachables in inhaled drug products tend to arise from:

- Polymers
- Elastomers
- Adhesives and curing agents
- Metal components
- Dyes and pigments
- Mould release agents

During product development, careful consideration is given to the choice and rationale for selection of the components that go into the final drug product. The selection criteria are outside the detailed scope of this document. However, we recommend, wherever possible, that the materials selected comply with accepted materials for food contact or incidental food use and/or generally recognized as safe (GRAS) materials.

4. Rationale for Setting a Qualification Threshold

Analytical techniques are increasingly sophisticated and capable of detecting and identifying chemicals at picogram quantities. However, it is generally accepted that there are levels of many chemicals below which the risks to human health are so negligible as to be of no consequence.

The premise of this document is that leachables present in inhalable drug products when held below a qualification level are not of concern.

5. Establishment of a Threshold Limit (Qualification Limit)

In this section the approach to establishing a threshold limit (qualification limit) is reviewed. The factors influencing the potential dose of an inhalable drug product and leachables contained in the product are reviewed. Next, representative data from the scientific literature are used to calculate volumes of air inspired by individuals. In the next step, the quantity of inhalable

particles respired by representative individuals exposed to levels of ambient air particles in a typical clean United States city are calculated. These levels are well below the standards established by the United States Environmental Protection Agency (USEPA) as being protective of public health, including sensitive sub-populations, with an ample margin of safety.

Finally, these levels of inhaled particulate matter are compared to a proposed threshold limit or qualification limit of 5 µg per day. The resulting comparison shows that the proposed qualification limit of 5 µg per day represents a small fraction of the quantity of material individuals are normally inhaling.

The likely patient dose of a leachable from an inhaled drug product will be related principally to the following factors:

- Concentration of leachable in the inhaler
- Number of doses taken each day
- Inspiratory volume of the patient
- Weight of the patient
- Disease state.

We have considered the data in the context of each of these factors. Table 5 defines the respiratory values that have been taken into consideration:

Table 5. Ventilation rate (m³/h) of patients related to age and exercise

Age	Resting(Sleeping) Males/Females*	Sitting awake M/F	Light exercise M/F	Heavy exercise M/F
1 year	0.15	0.22	0.35	-
10 years	0.31	0.38	1.12	2.22/1.84
30 years	0.45/0.32	0.54/0.39	1.5/1.26	3.0/2.7

*Data quoted for males and females separately where given in original reference.⁶

The same paper⁷ indicates the daily-inhaled volumes for different ages and mixed daily activities and may be used for estimating likely human exposures. These data are for “normal” healthy subjects. In contrast, patients using inhalers, by definition, have compromised respiratory function. The *International Asthma Guidelines*⁸ have been used as an approximation, to adjust these normal volumes for compromised patients. These guidelines define patients with mild asthma as

⁶ Roy, M., Age Related Aspects of Physiology in Respiratory Tract Modeling, in *Radiation Protection Dosimetry*, **41** (2/4), pp 93-98, 1992; Nuclear Technology Publishing.

⁷ *Ibid.*

⁸ Expert Panel Report 2, *Guidelines for the Diagnosis and Management of Asthma*, National Asthma Education Program, National Institutes of Health, National Heart, Lung and Blood Institute, pp. 1-13, 1997.

having a peak expiratory flow rate (PEFR) of > 80% of normal, moderate asthma as a PEFR as 60-80% and severe asthma as < 60% of normal.

Using the data from Table 5 and applying such correction factors for disease state, estimates of the daily inhaled volumes for different patients may be made as shown in Table 6.

Table 6. Approximation of daily-inhaled volume (m³) for patients of different ages and disease states.

Age	Mild Asthma (80% of normal)	Moderate Asthma (70% of normal)	Severe Asthma (60% of normal)	Normal * (for comparison)
1 year	4.11	3.60	3.08	5.14
10years	12.2	10.7	9.18	15.3
30 years	14.2	12.5	10.7	17.8

*Adapted from Roy, M., 1992

In the next step, the estimated quantities of air respired are combined with typical concentrations of airborne particulate material that might be inhaled by individuals. The USEPA under the authority of the *Clean Air Act* establishes National Ambient Air Quality Standards (NAAQS) for particulate matter. These standards are set to protect public health, including sensitive sub-populations, with an ample margin of safety.

The current NAAQS⁹ for PM₁₀ (the inhalable fraction) is set at 150 µg/m³, twenty-four hour average, and 50 µg/m³, annual average. The PM_{2.5} (the fine particle fraction) is set at 65µg/m³, twenty-four hour average, and 15 µg/m³, annual average. The inhalable fraction, PM₁₀, is assumed to include the range of particle sizes present in inhalable products and, thus, the PM₁₀ fraction is used for comparison calculations.

A concentration of 18 µg/m³ is used for calculation of comparison values. The 18 µg/m³ value was reported by Dockery, *et. al.*¹⁰ for Portage, Wisconsin, the cleanest of six cities studied intensively to establish an association between air pollution and adverse health outcomes. This was a key study used in setting the NAAQS for particulate matter. Portage had the best air quality and the least cardio-respiratory disease. It was therefore used as the “control” city, against which other cities were compared. For reference, as reported by Daniels *et. al.*,¹¹ people living in the twenty largest cities in the United States would all be exposed to higher concentrations of particulate matter than people in Portage.

⁹ Environmental Protection Agency, National Ambient Air Quality Standards for Particulate matter; *Fed. Regist.*; Volume **62**, No. 138, 1997.

¹⁰ Dockery, DW; Pope, CA III; Xu, X; An Association Between Air Pollution and Mortality in Six U.S. Cities; *N. Engl. J. Med.*; **329**, pp. 1753-9, 1993.

¹¹ Daniels, MJ; Dominici, F; Samet, JM; *et al.*, Estimating Particulate Matter-Mortality Dose Response Curves and Threshold Levels: An Analysis of Daily Time-Series for the 20 Largest US Cities; *Am. J. Epidemiol.*, **152** (5) pp397-406, 2000

Using the Portage air concentration for PM₁₀ (18 µg/m³), and the respiratory values from Table 6, the daily exposure of patients to environmental inhalable particles is calculated (Table 7) for total exposure (µg) and relative to body weight (µg/kg). These results have been based, where possible, on the FDA guidelines for bodyweight (1 year, 10 kg; 10 years, 25 kg; and 30 years, 50 kg). Obviously, the values in Table 7 would be even larger if the allowable twenty-four hour average NAAQS for PM₁₀ (150 µg/m³) had been used to make the calculations.

Table 7. Estimates of the daily inhalable quantities (µg) of environmental particulates for patients using Portage WI, USA, inhalable particle concentrations (18 mg/m³)

Age		Mild Asthma (80% of normal)	Moderate Asthma (70% of normal)	Severe Asthma (60% of normal)	Normal (for comparison)
1 year	(µg)	74.0	64.8	55.4	92.5
	(µg/kg)	7.40	6.48	5.54	9.25
10 years	(µg)	220	193	165	275
	(µg/kg)	8.8	7.72	6.6	11.0
30 years	(µg)	256	225	193	320
	(µg/kg)	10.2	9.0	7.72	12.8

Based on these data we propose a limit of 5mg per day of a leachable. Below this limit no qualification should be required. A 5 µg per day intake of a leachable would represent an amount of between 1 and 0.1 µg/kg/day and is between 2 and 10% of the estimated inhalable quantities of environmental particulate matter for mild to severe asthmatics described above.

Table 8 shows the 5 µg qualification limit as a percent of environmental particulate matter inhaled from ambient air, for different populations. These percentages would be even smaller if the comparison were being made to air concentrations of PM₁₀ in major cities, or to concentrations equal to the NAAQS for PM₁₀, a value considered to be protective of public health with an ample margin of safety even for sensitive sub-populations.

Table 8. 5 mg qualification limit expressed as a percentage of the potential daily particulate inhaled from ambient air

Age	Mild Asthma (80% of normal)	Moderate Asthma (70% of normal)	Severe Asthma (60% of normal)	Normal (for comparison)
1 year	6.8	7.7	9.0	5.4
10years	2.3	2.6	3.0	1.8
30 years	1.9	2.2	2.6	1.6

As seen, even for the severe asthmatic patient, the 5µg qualification limit represents a small fraction of particulate material the individual may inhale from ambient air. The 5µg per day limit, taking into consideration the risk/benefit to MDI patients, represents a minor additional load on the respiratory tract compared to the daily environmental exposure. Additionally, 5µg is considered a worst case since, by design, it is considered a total respiratory tract burden, and does not take into account differential lung deposition, oral deposition and swallowing.

6. Threshold Applied to Typical Inhaled Drug Products

We examine the significance of the threshold for inhaled drug products by applying it to ATROVENT® Inhalation Aerosol and FLOVENT® Inhalation Aerosol - two marketed products that represent a low and high range of TDI for an inhaled product. When taken as recommended, ATROVENT® Inhalation Aerosol delivers 18 µg/actuation and up to 12 actuations can be administered for a total daily dose of 216 µg/day. Following the rationale outlined above, 5µg of a leachable would represent 2% of the TDI. For FLOVENT® Inhalation Aerosol, the highest recommended TDI is 1960 µg/day. In this case, a leachable present at 5 µg would represent just 0.3% of the TDI.

7. Other Considerations

The 5 µg/day (< 1 µg/kg) threshold for a leachable in an inhaled drug product can be put into perspective by considering other compounds in some approved inhaled drug products.

The proposed FDA specifications for the alternative propellant HFA 134a, include limits of 5 ppm for “total unsaturates”¹² in the propellant. Unsaturated compounds are highly reactive species and a patient could easily receive 16 actuations a day (4 doses of a steroid, 4 of a long acting β₂-agonist and 8 actuations or more of a rescue medication). Under these circumstances the patient could inhale 8 µg of an unsaturated compound, which is more than the proposed leachable threshold.

¹² *Guidance for Industry, Metered Dose Inhaler(MDI) and Dry Powder Inhaler (DPI) Drug Products; Chemistry, Manufacturing, and Controls Documentation; draft Guidance; FDA, p. 13, 1998*

Another example can be drawn from a typical valve leachable. 2,2,4,6,6-pentamethyl-hept-3-ene (CAS 123-8-8) is a typical leachable present in some MDI formulations. Takagi *et. al.*,¹³ quoted a no-effect oral dose of 0.03% in the diet during chronic preclinical studies of up to 18 months duration. This represented doses of approximately 18 mg/kg/day. Applying the Agency's safety factors of 100¹⁴ an acceptable daily intake would be equivalent to NOEL/100 or 0.18 mg/kg/day some 360-1800 times greater than the proposed threshold.

8. Conclusions

The information provided in this paper provides a scientific rationale to establish a qualification limit of 5 µg per leachable for TDI from individual inhalable drug products.

Based on the information provided in this technical review:

- The current ICH guideline (Q3B) for impurities and degradants in drug product is considered inappropriate for leachables; and
- A 5 µg TDI limit for qualification of a leachable will adequately protect the safety of patients.

The weight of scientific evidence strongly supports the use of a 5 µg TDI for qualification of leachables associated with inhaled pharmaceutical products. Establishment of a 5 µg TDI threshold will allow preclinical evaluations to focus on substantive issues related to product safety and avoid evaluation of trace leachables unless structural information indicates a basis for further evaluation. This strategy provides a high level of assurance that these products are safe for patient use.

¹³ Takagi, *et. al.*, Acute, Subchronic and Chronic Toxicity Studies of a Synthetic Antioxidant, *J. Toxicol. Sci. (Japan)*, **19** (2), pp 77-78, 1994

¹⁴ Kokoski CJ, *et. al.*, Methods Used in Safety Evaluation, in *Food Additives*, Chapter 15, pp 579-616, Branen AL, Davidson PM and Salminen S., eds.; Marcel Dekker, New York, 1990.

VII. SUMMARY TABLE OF RECOMMENDED LEACHABLES AND EXTRACTABLES TESTING

The following table summarizes the recommended strategy for leachables and extractables testing for different product types. The Leachables and Extractables Team recommends inclusion of this summary table in the CMC guidances for OINDP.

Product Type		Controlled Extraction Study	Leachables Study	Routine Extractables Testing	Routine Leachable Testing
MDI	Valve components (polymeric and in contact with formulation)	Yes	N/A	Yes	N/A
	Mouthpiece (including spacer, if attached)	Yes	No (one-time in-use study)	Yes	N/A
	Canister	Yes (if coated)	N/A	Yes (if coated)	N/A
	Drug product	N/A	Yes	N/A	No (if correlation with extractables)

Summary Table, continued

Product Type		Controlled Extraction Study	Leachables Study	Routine Extractables Testing	Routine Leachable Testing
DPI	Primary packaging	Yes	N/A	Yes	N/A
	Protective secondary packaging (critical to the performance of the drug product)	Case-by-case	N/A	Case-by-case	N/A
	Mouthpiece	Yes	No (one-time in-use study)	Yes	N/A
	Polymeric components (in direct contact with the formulation only during administration)	Yes	No (one-time in-use study)	Yes	N/A
	Drug product	N/A	Yes	N/A	No (if correlation with extractables)
Nasal Spray	Pump components (polymeric and in contact with formulation during administration)	Yes	No (one-time in-use study)	Yes	N/A
	Container	Yes	N/A	Yes	N/A
	Actuator (in contact with formulation during administration)	Yes	No (one-time in-use study)	Yes	N/A
	Drug Product	N/A	Yes	N/A	No (if correlation with extractables)

Summary Table, continued

Product Type		Controlled Extraction Study	Leachables Study	Routine Extractables Testing	Routine Leachable Testing
Inhalation Solution/Suspension (Intended for use with generic nebulizer)	Primary Packaging (polymeric)	Yes	N/A	Yes	N/A
	Protective Secondary Packaging (critical to the performance of the drug product)	Yes	N/A	Yes	N/A
	Drug Product	N/A	Yes	N/A	No (if correlation with extractables)
Inhalation Solution/Suspension (Intended for use with proprietary delivery system)	Primary Packaging (polymeric)	Yes	N/A	Yes	N/A
	Protective Secondary Packaging (critical to the performance of the drug product)	Yes	N/A	Yes	N/A
	Mouthpiece (including spacer, if attached)	Yes	No (one-time in-use study)	Yes	N/A
	Polymeric Components (in direct contact with the formulation only during administration)	Yes	No (one-time in-use study)	Yes	N/A
	Drug product	N/A	Yes	No	No (if correlation with extractables)

VIII. CONCLUSION

The Leachables and Extractables Technical Team and the Toxicology Working Group respectfully encourage the Agency to consider the recommendations developed by the Team and to incorporate the same in the next version of the draft CMC Guidance documents.

The Team would like to meet with the Agency in order to discuss these proposals and, in particular, discuss and agree on recommendations regarding reporting and toxicological qualification thresholds for leachables. Furthermore, if the Agency considers it valuable, the Leachables and Extractables Team, in collaboration with the Supplier Quality Control Technical Team, will propose a control strategy (including appropriate testing criteria) for ensuring the relevant performance and safety characteristics of critical device components.

The ITFG/IPAC-RS Collaboration supports the Agency's efforts to develop scientifically sound guidances for OINDP that will serve the needs of the Agency, industry, and patients.

IX. GLOSSARY

CAS	Chemical Abstracts Service
CMC	Chemistry, Manufacturing, and Controls
COPD	Chronic Obstructive Pulmonary Disease
DPI	Dry Powder Inhaler
Extractables	Compounds extracted from individual components of the drug delivery system, under appropriate solvent and temperature conditions. Extractables studies are therefore conducted during development on the components that will constitute the drug product.
GRAS	Generally Recognized As Safe
HFA	Hydrofluoroalkane
ICH	International Conference on Harmonization
Leachables	Compounds that migrate from the container/closure system of the drug product under normal conditions of use, or during stability studies. Leachables studies are therefore conducted on the final drug product.
MDI	Metered Dose Inhaler
NAAQS	National Ambient Air Quality Standards
NOEL	No Observed Effect Level
OINDP	Orally Inhaled and Nasal Drug Products
PEFR	Peak Expiratory Flow Rate
Picogram	10 ⁻¹² grams
PM₁₀	Particulate Material 10 micrometers: refers to particles collected with an aerodynamic sampling system with 50% efficiency for particles with a 10 micrometer aerodynamic size.

PM_{2.5}	Particulate Material 2.5 micrometers: refers to particles collected with an aerodynamic sampling system with 50% efficiency for particles with a 2.5 micrometer aerodynamic size.
PNA	Polynuclear Aromatic
Q3A	Guideline published by the International Conference on Harmonization (ICH) that addresses impurities in drug substances.
Q3B	Guideline published by the International Conference on Harmonization (ICH) that addresses impurities in drug products.
Q3C	Guideline published by the International Conference on Harmonization (ICH) that addresses acceptable levels of residual solvents in pharmaceuticals for the safety of the patient.
SAR	Structure Activity Relationship
TDI	Total Daily Intake
USEPA	United States Environmental Protection Agency
USP	United States Pharmacopeia