
## Leachables and Extractables Working Group

**Spring 2002**

# PROPOSED WORK PLAN

***Development of Scientifically Justifiable Thresholds for Leachables and Extractables***

*Finalized by Working Group on 20 February 2002*

*Forwarded for review to DPTC on 20 February 2002*
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## I. BACKGROUND

Leachables in orally inhaled and nasal drug products (OINDP) are compounds which are present in the drug product due to leaching from container closure system components. Extractables are compounds that can be extracted from OINDP device components, or surfaces of the OINDP container closure system when in the presence of an appropriate solvent(s) and/or condition(s). Leachables are often a subset of, or are derived directly or indirectly from extractables. Extractables may, therefore, be considered as potential leachables in OINDPs. Some leachables may affect product quality and/or present potential safety risks, therefore regulatory guidance has provided some recommendations regarding the analysis and toxicological safety assessment (*i.e.*, qualification) of such compounds.

In November 1998 and May 1999, the FDA issued two CMC draft Guidances addressing OINDP: (i) the draft *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation*[1] (referred to here as the "MDI/DPI draft Guidance"); and (ii) the draft *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation*[2] (referred to here as the "Nasal Spray draft Guidance").

Currently, the draft Guidances recommend that the sponsor identify, report, and conduct toxicological analyses on all extractables found in the controlled extraction study (referred to in the draft Guidances as a "control extraction study"). Examples of these recommendations are described in the draft MDI/DPI Guidance regarding MDI canisters, valves, and actuators (lines 883-884; 990-991; and 1073):

> *…the profile of each extract should be evaluated both analytically and toxicologically.*

This recommendation is problematic because it suggests that *all extractables* must be reported and undergo toxicological safety assessments. However, some of these extractables may not be present in the final drug product (*i.e.*, they are not leachables), or may exist as leachables at levels so low as to be of negligible risk to human safety. Thus, the draft guidances appear to recommend toxicological assessments on compounds for which the patient will either never be exposed, or which might exist at levels that present negligible safety risk. Further, the draft Guidances do not offer advice as to the concentration levels (*i.e.*, thresholds) at which extractables/leachables should be identified, quantified, reported, and qualified for safety purposes.

[1] *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products* Chemistry, Manufacturing, and Controls Documentation, CDER/FDA, October 1998, (Docket No. 98D-0997), available at http://www.fda.gov/cder/guidance/2180.pdf.

[2] *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products* Chemistry, Manufacturing, and Controls Documentation, CDER/FDA, May 1999, (Docket No. 99D-1454), available at http://www.fda.gov/cder/guidance/2836.pdf.

## II. RESEARCH OBJECTIVE

### A. Why Work is Being Done

Regulatory and industry resources will have greatest impact when focussed on toxicological issues related to those compounds that are introduced to the patient (*i.e.*, leachables), as well as consideration of the levels of such compounds that may affect human safety. A logical way to address this is to develop thresholds for reporting and safety qualification of *leachables*.

A reporting threshold with associated identification and quantitation thresholds for leachables would be established to support toxicological safety qualification. A qualification threshold would establish a limit below which the leachable is not considered for safety qualification unless it presents structure-activity relationship (SAR) concerns. Note that certain classes of potential leachable compounds with special toxicological concerns [*e.g.*, nitrosamines, polynuclear aromatics (PNAs), mercaptobenzthiazole, etc.] would require development of reporting thresholds on a case-by-case basis. Both these thresholds assume that toxicological qualification should be performed on leachables and not on extractables.

The establishment of reporting and qualification thresholds for leachables would then naturally lead to reporting thresholds for extractables. This would facilitate the development of appropriate quality control strategies for extractables at the component level, which would then in turn provide indirect control of leachables in drug products without the need for routine analytical testing of leachables.

### B. Hypothesis

Based on the above discussion, the following working hypothesis is proposed:

1. *Scientifically justifiable thresholds based on the best available data and industry practices can be developed for:*

   *(a) the reporting and safety qualification of leachables in orally inhaled and nasal drug products, and*

   *(b) reporting of extractables from the critical components used in corresponding container/closure systems.*

   *Reporting thresholds for leachables and extractables will include associated identification and quantitation thresholds.*

2. *Safety qualification of extractables, would be scientifically justified on a case-by-case basis.*

The work plan outline described below is designed to test this hypothesis through a process intended to develop these scientifically justifiable thresholds.

## C. Work Plan Outline

The essence of the proposed Work Plan is that in order to test the hypothesis that appropriate and scientifically justifiable thresholds exist, then the Working Group must engage in a process designed to develop these thresholds. It is envisioned that processes designed to develop qualification and reporting thresholds would proceed somewhat in parallel, with the former taking advantage of the toxicological expertise of particular Working Group members and the latter taking advantage of the analytical chemistry expertise of others in the Group. It is also considered likely that the development of reporting thresholds will require example data in the form of leachables and extractables profiles, etc., from various OINDPs. These data will be utilized to explore important concepts such as "correlation" of leachables and extractables. Every effort will be made to solicit appropriate existing data (industry, academic, or government sources), and as required to generate new data in laboratory facilities available to Working Group members, or others within PQRI.

The following Work Plan is proposed to test the hypothesis stated above:

### Task 1: Process Development

**Goal:** The Working Group will agree on the outline of a process (or processes) designed to test the stated hypothesis by attempting to develop appropriate and scientifically justifiable qualification and reporting thresholds related to leachables and extractables.

**Implementation:** The ITFG/IPAC-RS Collaboration engaged in a process which resulted in qualification thresholds for leachables, and reporting thresholds for extractables and leachables. These proposed thresholds and the processes used to develop them are described in the document *Points to Consider.*[3]

In its second face-to-face meeting, the Working Group will review the processes described in *Points to Consider* and through its own deliberation, design and agree on the outlines of processes that it will employ for threshold development. ITFG/IPAC-RS representatives who are also members of the Working Group will present and describe the processes that they employed for threshold development. It should be emphasized that the *Points to Consider* document will be used as a model for process development only. The Working Group will not at this point consider or debate the actual numerical thresholds proposed in this document. It is envisioned that the additional expertise and

[3] ITFG/IPAC-RS Collaboration, Leachables and Extractables Testing: Points to Consider, available at http://www.ipacrs.com/leachables.html

perspective available in the Working Group will result in enhanced processes for threshold development.

**Outcome:** The expected outcome from *Task 1* is the outline of a process(es) designed to develop qualification and reporting thresholds, and thereby test the hypothesis.

**Timeline:** **1 May 2002** for completion of *Task 1*.

**Required Resources:** It is envisioned that *Task 1* will require only facilities for face-to-face meeting(s) and teleconferences.

## Task 2: Process Implementation

Threshold development can be logically divided into two separate but related sub-tasks: (1) development of qualification thresholds and (2) development of reporting thresholds. It is envisioned that these two processes will proceed in parallel utilizing appropriate expertise from various Group members, with clear and continuous communication between the two sub-tasks.

### (1) Sub-task: Development of Qualification Thresholds

**Goal:** The Working Group will develop appropriate and scientifically justifiable qualification thresholds for leachables. A qualification process will be developed for extractables which can be employed as required on a case by case basis.

**Implementation:** The Working Group will employ the process outline from *Task 1* to develop qualification thresholds. The Group will consider and debate many questions during this process. Examples of these questions are as follows:

- Is it appropriate to use exposure standards for environmental pollutants for developing a qualification threshold for leachables/extractables in OINDP?
- Is there utility in other qualification threshold strategies (e.g., indirect food additive regulations) for OINDP application?
- Is there utility to be found from other sources (e.g., USP, ISO 10993, 21 CFR (174-178)) regarding risk assessment, qualification, and thresholding of leachables/extractables?
- What are the testing paradigms that could provide data for risk assessment of leachables/extractables in OINDP?
- Is there utility in the testing procedures described in USP<87> and <88> for safety qualification of any OINDP?
- Is there utility in considering other available qualification decision trees (e.g., ICH guideline for impurities) for the qualification of leachables/extractables?

The Working Group will develop a qualification strategy for leachables that will include testing strategies, risk assessment models, and decision trees; as appropriate.

Once the qualification strategy is generally agreed upon, the Working Group will devise a generic list of potential leachables for a "worst case scenario" OINDP. The compounds on the list and their exposure levels to patients will be based on the expertise and knowledge-base of Working Group members, and information solicited from represented industry/academic/government organizations. The list will then be used for a mock toxicological qualification and risk assessment to test the credibility of a qualification threshold. The list (termed Product X) will likely be designed to mimic an MDI (Metered Dose Inhaler) drug product which, of all OINDPs, is most likely to have an extensive leachables profile which correlates directly with its device components extractables profile(s). The Product X data set should also encompass special case leachables (i.e., nitrosamines and PNAs) as well as less often encountered leachables. The concentrations of leachables proposed for Product X should be within a range consistent with current manufacturing practices for OINDPs.

The mock toxicological qualification will assess whether the threshold argument adequately qualified leachables, as represented by the Product X profile/list. It should also determine if the proposed qualification/testing paradigm would adequately qualify leachables that fell outside the proposed threshold.

**Outcome:** The expected and potential outcomes from this sub-task are as follows:

- A qualification/testing paradigm for leachables/extractables in OINDPs.
- A decision tree for qualification of leachables/extractables in OINDPs.
- Thresholds for qualification of leachables/extractables in OINDPs.
- An example of a complete qualification for a representative leachables profile from a typical OINDP.

A consensus within the Working Group on qualification thresholds and the successful completion of the mock qualification will be considered a successful test of the hypothesis.

### (2) Sub-task: Development of Reporting Thresholds

**Goal:** The Working Group will develop appropriate and scientifically justifiable reporting thresholds for extractables and leachables.

**Implementation:** The Working Group will employ the process outline from *Task 1* to develop reporting thresholds. The Group will consider and debate many questions during this process. Examples of these questions are as follows:

- What analytical technologies and strategies are typically used by the industry for identification and quantification of extractables and leachables? What are the relative strengths and weaknesses of these technologies and strategies? What thresholds for detection/quantification do these technologies imply? What are appropriate target compounds for development and validation of specific analytical methods for leachables/extractables? Is there any utility in methods and strategies contained in ICHQ2B, USP<381>, USP<661>, ISO 10993 (draft), and 21CFR (170-180)? Is it appropriate for the Working Group to propose/recommend most appropriate technologies/strategies for identification and quantification of various classes of extractables/leachables?
- What does it mean to "identify" an extractable/leachable? Is it appropriate for the Working Group to propose/recommend criteria for identification of extractables/leachables?
- How does one design and implement a "controlled extraction" study for extractables? Is it appropriate for the Working Group to propose/recommend a most appropriate strategy for controlled extraction studies? Will this strategy depend on the particular OINDP dosage form (MDI, DPI, etc.) and the nature of the material being extracted?
- What is a "critical component" in an OINDP?
- Is it appropriate to use extractables tests as secondary controls on the composition of critical components in an OINDP? Are there better approaches?
- What are appropriate routine control technologies/strategies for extractables? Is it appropriate for the Working Group to propose/recommend a most appropriate technology/strategy for routine control of extractables? Under what circumstances will leachables controls be required?

It is envisioned that investigation of these questions will require data in the form of extractables/leachables profiles, as well as a body of information on current industry practices. All available sources of appropriate data and information will be solicited through the Working Group members and the organizations they represent. If new laboratory studies are required to generate data, these will be solicited through the laboratories of the Working Group members or their contacts.

It is also envisioned that the Working Group will assemble an advisory team of OINDP component manufacturers to provide appropriate input and data to the process.

**Outcome:** The expected and potential outcomes from this sub-task are as follows:

- Recommended technologies/strategies for extractables/leachables studies.
- Recommended criteria for identification of extractables/leachables.
- Thresholds for the identification and reporting of extractables/leachables.
- Thresholds for the quantification of extractables/leachables.

- Recommended control technologies/strategies for extractables/leachables.

A consensus within the Working Group on reporting thresholds will be considered a successful test of the hypothesis.

**Timeline:** **1 May 2003** for completion of *Task 2* (including both sub-tasks).

**Required Resources:** It is envisioned that *Task 2* will require only facilities for face-to-face meeting(s) and teleconferences. Required information and data will be collected/generated with the resources available to members of the Working Group and their respective organizations and contacts.

**Task 3: Harmonization and Consensus**

**Goal:** The Working Group will thoroughly evaluate the results of the process implementation described under *Task 2* (including any data and other information employed) and come to consensus as to the validity of the hypothesis based on the testing criteria previously stated.

**Implementation:** The Working Group as a whole will critically evaluate the outcomes of *Task 2* and create a report for review within the PQRI process that will include all proposed outcomes as well as clearly stated recommendations for the Agency (FDA) to consider in the final implementation of their draft Guidances.

Other outcomes from *Task 3* may include publications and presentations at appropriate scientific meetings and forums. These additional outcomes will be discussed and agreed to at the appropriate time in the overall PQRI process.

**Timeline:** **1 September 2003** for completion of *Task 3.*

**Required Resources:** It is envisioned that *Task 3* will require only facilities for face-to-face meeting(s) and teleconferences. Additional required information and data will be collected/generated with the resources available to members of the Working Group and their respective organizations and contacts.

## III. SUMMARY OF REQUIRED RESOURCES

### A. Human Resources

Current members of the Working Group are:

Daniel L. Norwood (Boehringer Ingelheim), Chair
Gordon Hansen (Boehringer Ingelheim), PQRI Steering Committee
Doug Ball (Pfizer)

Tom Feinberg (Magellan Laboratories)
Jim Blanchard (Aradigm)
Fran DeGrazio (West)
Debby Miran (Miran Consulting)
Roxana Nikoui (Valois)
Roger McClellan (UNM)
David Porter (USP)
Diane Paskiet (Monarch Analytical)
Alan Schroeder (FDA)
Mark Vogel (Pharmacia)
Tim McGovern (FDA)

In addition, Guirag Poochikian (FDA) and Jeffery Blumenstein (Pfizer) serve as liaisons to the DPTC, and the IPAC-RS Secretariat provides administrative, logistical, and other support.

Members of the Working Group bring to the process a variety of expertise and experience, including analytical chemistry, inhalation toxicology, OINDP development, regulatory affairs, and device/drug product manufacturing. These resources will be supplemented, if required, by additional resources available to the represented organizations (*i.e.*, IPAC-RS, PDA, *etc.*). A plan is currently under consideration by the Working Group to create an Advisory Group of OINDP component supplier/manufacturer representatives to assist the Group in the proposed project.

### B. Laboratory Resources

As previously stated, required laboratory resources for the generation of original data will be solicited from the Working Group members and their contacts.

### C. Financial Resources

No additional financial resources from PQRI are requested at this time. In-kind donations of resources may be solicited from the Working Group member organizations.

## IV. POTENTIAL IMPACT

The establishment of reporting and qualification thresholds for leachables, and reporting thresholds for extractables, would enhance the utility of the draft Guidances, which would in turn facilitate drug development programs for OINDPs by reducing uncertainty, and thus making such programs more time and cost efficient. This would likely result in regulatory submissions of greater quality and consistency which would facilitate the review process. The end result to the patient will be continued improvement in product quality.

# V. GLOSSARY

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| **ICH Q2B** | ICH guideline on validation of analytical procedures: methodology |
| **ICH Q3B** | ICH guideline on impurities in new drug products |
| **ISO 10993** | International Standard Organization: biological evaluation of medical devices |
| **USP<1031>** | USP general information chapter for biocompatibility |
| **USP<87>** | USP general test chapter for in vitro biological reactivity tests |
| **USP<88>** | USP general test chapter for in vivo biological reactivity tests |
| **USP<381>** | USP general test chapter for elastomeric closures for injections |
| **USP<661>** | USP general test chapter for containers |
| **21CFR (170-180)** | Code of Federal Regulations, volume 21, parts 170-180: food additives and indirect food additives |