PQRI Research Project Proposal:

Reporting and Qualification Thresholds for Leachables in Parenteral and Ophthalmic Drug Products

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I. INTRODUCTION

Leachables in parenteral and ophthalmic drug products (PODP) are those compounds (both organic and inorganic) that are present in the drug product due to leaching from packaging systems (container closure systems, CCS) and/or their components or materials of construction that are in direct or indirect contact with the PODP. Leachables typically correlate with extractables, which are those compounds that can be extracted from the packaging system and/or its associated components and materials of construction under experimental conditions using appropriate solvents and extraction conditions. Because some leachables may present safety risks during use of the final drug product, regulatory guidance has provided some recommendations regarding the analysis and toxicological safety assessments (*i.e.*, safety qualification) of such compounds.

In May 1999, the FDA issued *Container Closure Systems for Packaging Human Drugs and Biologics – chemistry, manufacturing and controls documentation guidance for industry*. In November 1998 and May 1999, the FDA issued two CMC draft Guidances addressing OINDP[1]: (i) the draft *Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products, Chemistry, Manufacturing, and Controls Documentation* (referred to here as the "MDI/DPI draft Guidance"); and (ii) the draft *Guidance for Industry, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation.* In addition, the European Medicines Agency (EMEA) issued its *Guideline on Plastic Immediate Packaging Materials* in May, 2005.[2]

These guidance documents have provided manufacturers a high level strategic process to assess and qualify the safety of extractables and leachables in various dosage forms. Such a high level process involves three primary steps (for example, Figure 1):

- Performing an extraction study to identify all extractables,
- Performing a migration study to measure the levels of leachables in the PODP under conditions of use, and
- Performing a toxicological assessment of the extractables and/or leachables information to specifically address the safety impact of the specific leachables at their specific accumulation levels under the specific conditions and dosing associated with product use.

A fourth step that is commonly included in this process is a reconciliation or correlation of the extractables and leachables information for the purpose of predicting worst case scenarios and component control.

The practical implementation of this process is problematic because it suggests that *all extractables and/or leachables, regardless of their accumulation levels,* must be reported and undergo full toxicological safety assessments. However some extractables may not be present in the final

[1] Available at http://www.fda.gov/cder/guidance/index.htm
[2] Available at http://www.emea.europa.eu/pdfs/human/qwp/435903en.pdf

drug product (*i.e,* they are not leachables), and some leachables may be present in the final drug product at levels so low as to be of no risk to human safety. Thus, these guidance documents appear to require full toxicological assessment on compounds for which the patient will either never be exposed, or which might exist at levels that present negligible safety risk.

In September 2006, PQRI issued a Recommendation entitled "Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products"[3]. This Recommendation provided a scientific rationale and process to identify, report and qualify extractables and leachables in orally inhaled and nasal drug products (OINDP). The fundamental concept proposed by PQRI was a Safety Concern Threshold (SCT) which would establish a limit below which leachables are not considered for toxicological safety qualification, as any leachable existing at levels below this threshold would present no safety concerns for the patient. A Qualification Threshold (QT) would establish a limit below which the leachable is not considered for safety qualification unless it presents structure-activity relationship (SAR) or other safety concerns. Both these thresholds assume that toxicological (safety) qualification should be performed on leachables and not on extractables. The SCT is used to develop an Analytical Evaluation Threshold (AET), which allows the SCT to be applied to leachables profiles of particular drug products. The general application of these concepts is illustrated in Figure 2.

The threshold concept utilizes a risk management approach which is consistent with the recommendations of PQRI and FDA guidance documents for container closure systems as well as the 2006 Guidance for Industry: Quality Systems Approach to Pharmaceutical CGMP Regulation. In addition, the rational for threshold concepts can be applied to support comprehensive studies for certain drug products as outlined in the EMEA Guideline on Plastic Immediate Packaging. Therefore, we propose a three-point hypothesis:

1. Threshold concepts that have been developed for safety qualification of leachables in OINDP and the existing FDA/EMEA guidance documents can be extrapolated to the evaluation and safety qualification of packaging systems (such as container closure systems, CCS) for PODP.
2. The "good science" best demonstrated practices that were developed for the OINDP pharmaceutical development process can be extrapolated to packaging systems for PODP.
3. Threshold and best practices concepts can be integrated into a comprehensive process for characterizing packaging systems with respect to leachable substances and their associated impact on PODP safety.

It is noted that this hypothesis is supported by the fact that OINDP and PODP products are jointly classified by the FDA in the quadrant of highest/high concern with respect to the risk associated with undesirable packaging system – drug product interactions (see Figure 3). While OINDP and PODP products may share a central or common high level strategic approach to risk assessment for leachables and extractables, as reflected in the PQRI proposal, the specific tactical aspects of the risk assessments (e.g., numerical values for quantities such as SCT, QT

[3] Available at http://pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf

and AET) will differ due to the differing characteristics (e.g., composition and dosing) of these products.

II. APPROACH

The collaborative activities of participants from industry, academia and government regulatory agencies have, in the case of OINPD, resulted in comprehensive and all-encompassing strategic and tactical recommendations for leachables/extractables assessments aimed at ascertaining the product safety impact of interactions between OINPD drug products and their associated packaging systems. Because the toxicological risks associated with parenteral and injectable drug products are of similar magnitude to those associated OINPD products, it is reasonable to suggest that the general outline of the OINPD Recommendations is directly applicable to PODP products as well. It is also reasonable to note, however, that tactical Recommendations for OINPD products may require modification when applied to PODP products, given the significant differences between these two product classes.

We therefore propose that a PQRI Working Group (comprised of toxicologists, chemists and regulators) be established that will:

- Form a toxicology subgroup that will extrapolate the SCT and QT concepts previously developed by PQRI and determine how they can be utilized to qualify the safety of leachables in PODP.
- Form a chemistry subgroup that will extrapolate the AET concept for its utility in the evaluation of extractables and leachables in PODP. The subteam will investigate issues such as but not limited to:
    * Addition of water and aqueous systems to the solvent systems considered in the OINDP document
    * Addition of materials, components and/or packaging systems applicable to PODP
    * Consideration of extraction and/or analysis methods which have unique applicability to PODP
- The subteams will come together to develop a consensus-based leachables approach (chemical data generation and toxicological interpretation) for PODP.

III. OUTCOME

From this investigation, the work team will develop a science-based best practices approach. This approach will extrapolate the SCT, QT and AET principles previously developed by PQRI for OINDP to PODP and will include best demonstrated practice recommendations for conducting chemical assessments for the discovery, identification and quantitation of CCS-derived leachables and extractables in PODP.

Benefits:

- Establish a uniform, consistent, quantitative and science-based process to evaluate and qualify L&E in PODP.
- Establish a threshold-based approach to the safety qualification of L&E in PODP.
- Establish best demonstrated practices related to the analytical aspects of L&E investigations.
- Establish a consistent, industry-wide approach, across all dosage forms, to address current regulatory expectation. A possible result may include a matrix to help establish a uniform and risk based approach.

Risk: Lack of a threshold-based approach currently leads to:

- Inefficient product development processes.
- Ineffective safety qualifications.
- Increased costs associated with unnecessarily long product development timelines.
- Delayed product approvals.

IV. PROJECT TIMELINE

The PODP project is expected to take approximately three years to complete. The Working group would be formed directly after notification of PQRI approval of the proposal. The process for nomination of the Working Group is anticipated to take 60 days. Once the Working group has been organized the project milestones can be established the estimated timeframe is as follows.

Timeframe

- 4-6 months for the Hypothesis and Work Plan to be submitted to the DPTC and PQRI Steering Committee for approval.
- 1 year to acquire the chemistry and toxicology data
- 1-1.5 years to evaluate the data, come to consensus, write, review and submit the documents to the PDA for presentation to PQRI DPTC/Steering Committee
- 6 month review period after submission to the FDA requiring a PDA interface.

Resources:

- At least 12 face-to-face meetings of the Working Group over the course of the project (approximately 20 participants lasting 1 day for each meeting). Various companies and organizations represented on the Working Group (including the PDA) will be solicited for meeting locations and logistics.
- Approximately one teleconference per month of the Working Group over the course of the project . Various companies and organizations represented on the Working Group (including the PDA) will be solicited for teleconference capabilities.
- Any laboratory work required by the project will be solicited from various companies and organizations represented on the Working Group on a volunteer basis.
- Additional administrative and project management support will be provided by the Working Group members and their respective organizations, as appropriate.

Figure 1. Partial Decision Tree on the Presentation of the Documentation of Plastic Packaging Materials. From the EMEA Guideline (ref. 2). The numbers in () refer to specific sections in the EMEA Guideline. Note that and Interaction Study consists of two components, a migration study to assess leachables and a sorption study to assess drug binding.

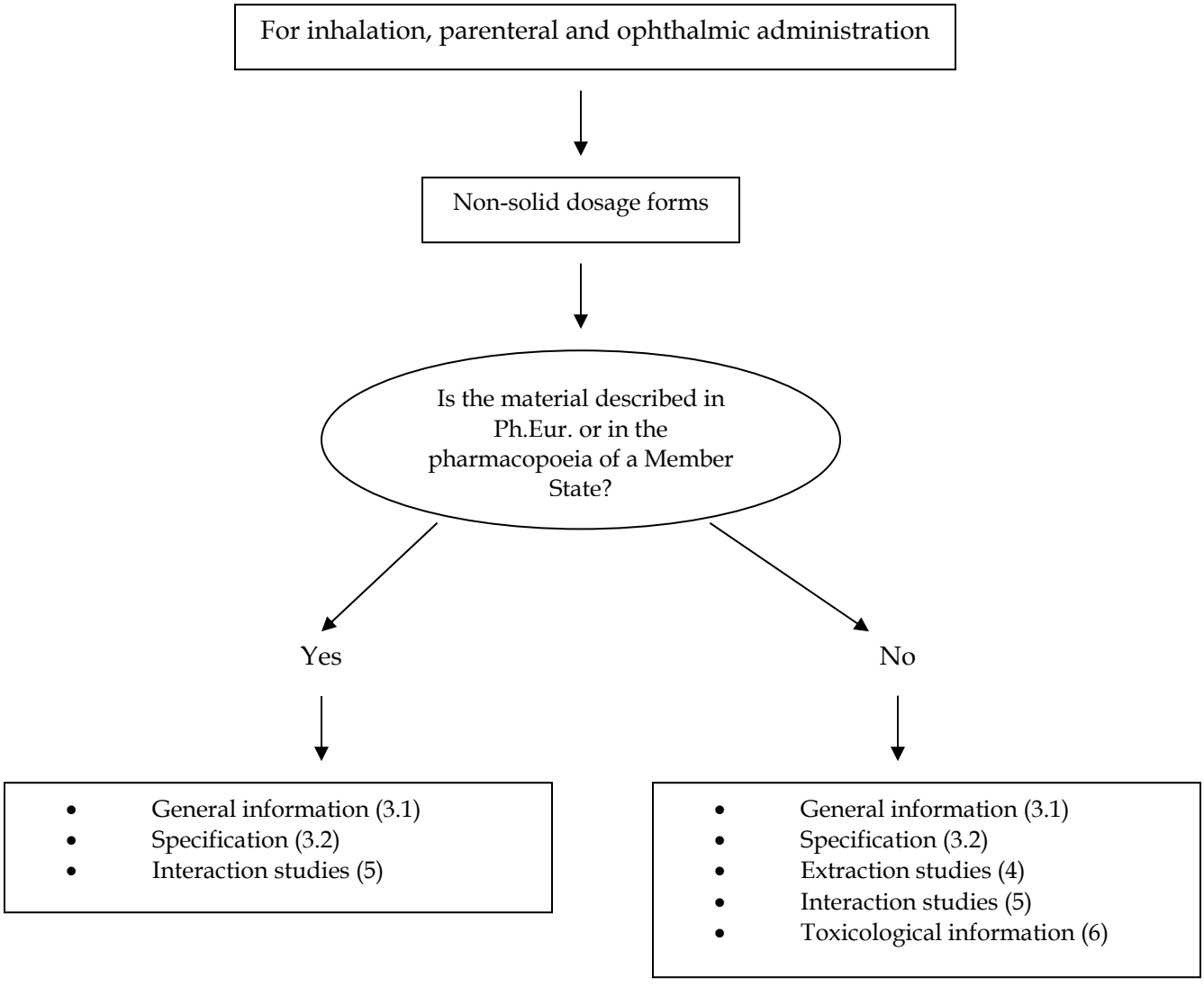

Figure 2. Partial Decision Tree on Qualification of Leachables. From the PQRI Recommendations (ref. 3). TDI = Total Daily Intake; SAR = Structure Activity Relationship.

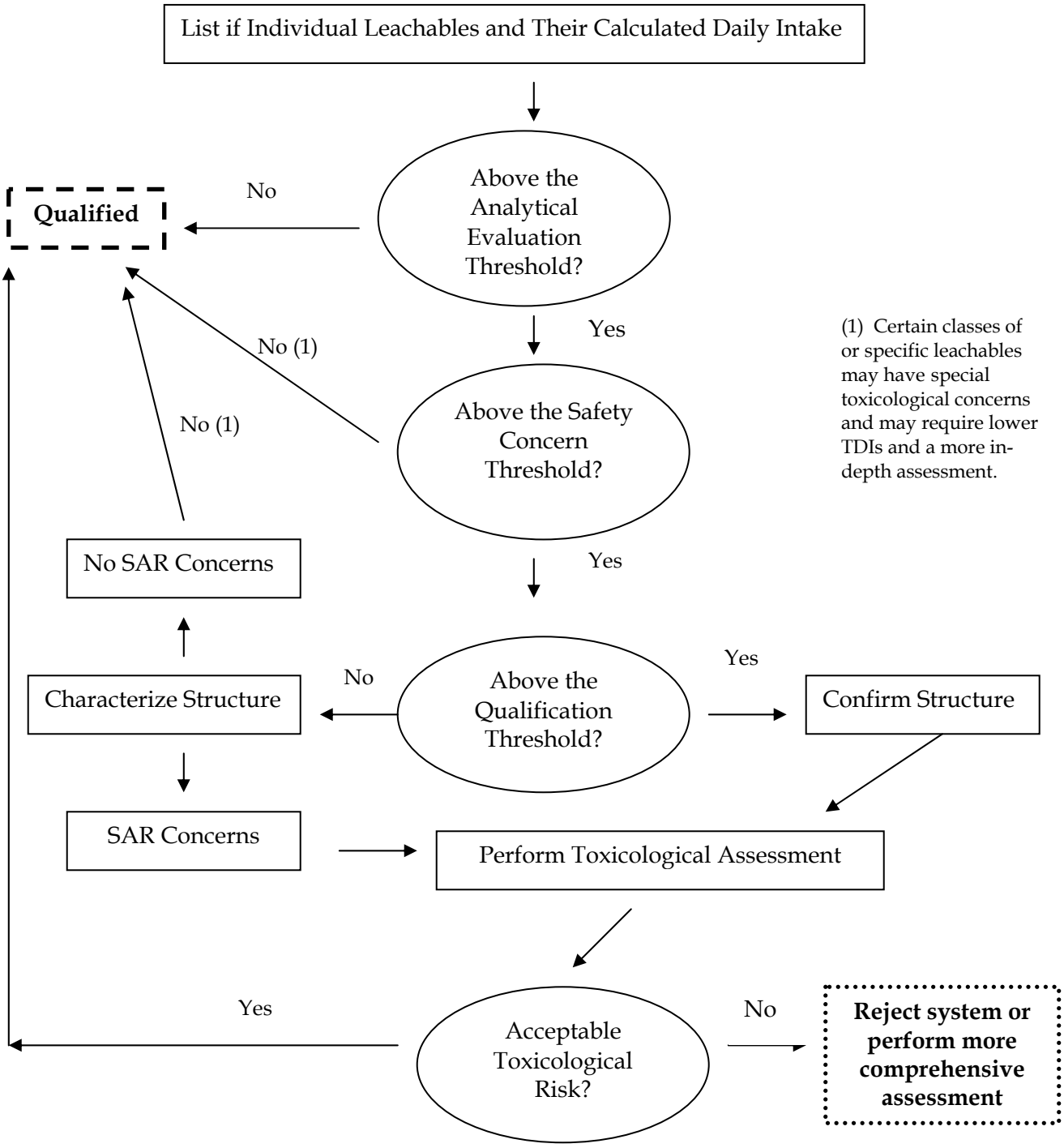

Table 1. Examples of Packaging Concerns for Common Classes of Drug Products. (1)			
Degree of Concern Associated with the Route of Administration	**Likelihood of Packaging Component-Dosage Form Interaction**		
	High	**Medium**	**Low**
Highest	Inhalation Aerosols and Solutions; Injections and Injectable Suspensions[a]	Sterile Powders and Powders for Injection; Inhalation Powders	
High	Ophthalmic Solutions and Suspensions; Transdermal Ointments and Patches; Nasal Aerosols and Sprays		
Low	Topical Solutions and Suspensions; Topical and Lingual Aerosols; Oral Solutions and Suspensions	Topical Powders; Oral powders	Oral Tablets and Oral (Hard and Soft Gelatin) Capsules

Notes: (1) From Guidance for Industry. Container Closure Systems for Packaging Human Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration; Rockville, MD, May, 1999.[2]
[a] For the purpose of this table, the term suspension is used to mean a mixture of two immiscible phases (e.g., solid in liquid or liquid in liquid). As such, it encompasses a wide variety of dosage forms such as creams, ointments, gels, and emulsions, as well as suspensions in the pharmaceutical sense.