

PQRI Workshop

Thresholds and Best Practices for Parenteral and Ophthalmic Drug Products (PODP)

February 22-23, 2011
Hyatt Regency Bethesda



Thresholds and Best Practices Workshop for Parenteral and Ophthalmic Drug Products (PODP)

It is well established that substances extracted by drug products from their container closure systems can affect the drug product's safety and efficacy. Regulatory authorities have provided limited direction regarding the analysis and toxicological safety assessment (*i.e.*, qualification) of such substances. The Product Quality Research Institute (PQRI) has issued a recommendation entitled "Safety Thresholds and Best Practices for Extractables and Leachables in Orally Inhaled and Nasal Drug Products (OINDP)." This recommendation provides a scientific rationale and process to identify, quantify, and qualify leachables and/or extractables where appropriate, in OINDP. Included in this recommendation are experimental protocols, and the results thereof, for establishing best demonstrated practices for the performance of controlled extraction studies, specifically relevant of the OINDP dosage forms. Recognizing that the OINDP recommendations could have general applicability across other dosage forms, the PQRI Parenteral and Ophthalmic Drug Products (PODP) Leachables and Extractables Work Group (WG) was commissioned to extend the spirit, if not necessarily the detail, of the OINDP recommendations to PODP. In considering this task, the PODP WG developed a set of hypotheses:

►Threshold concepts that have been developed for safety qualification of leachables in OINDP can be extrapolated to the evaluation and safety qualification of leachables in PODP, with consideration of factors and parameters such as dose, duration, patient population, and product dependent characteristics unique to various PODP types.

►The science-based best demonstrated practices established for the OINDP pharmaceutical development process can be extrapolated to PODP container closure systems.

►Threshold and best practices concepts can be integrated into a comprehensive process for characterizing container closure systems with respect to leachable substances, and their associated impact on PODP safety.

This workshop is the first opportunity for the PQRI PODP Work Group to present and discuss its charter and accumulated data. The workshop will leverage the accumulated knowledge and insights of its participants to collaboratively consider the implications of the data in terms of drafting recommendations via working sessions, led by regulators and/or scientific experts, which will consider specific PODP dosage forms, such as pre-filled syringes, small and large volume parenterals, and ophthalmics. The experiences and insights shared at these working sessions will contribute to ongoing development of the PODP recommendations.

Planning Committee

Diane Paskiet, West Pharmaceutical Services
PODP Work Group Chair

Dennis Jenke, Ph.D., Baxter HealthCare
PODP Work Group - Chemistry Chair

Douglas J. Ball, M.S., D.A.B.T., Pfizer
PODP Work Group - Toxicology Chair

Stephen A. Barat, Ph.D., Forest Research Institute

William P. Beierschmitt, Ph.D., D.A.B.T., Pfizer, Inc.

Jim F. Castner, Lantheus Medical Imaging

Thomas Egert, Boehringer Ingelheim Pharma GmbH & Co. KG

Thomas N. Feinberg, Ph.D., Catalent Pharma Solutions

Alan D. Hendricker, Ph.D., Catalent Pharma Solutions

Frank Holcombe, Jr., Ph.D., U.S. Food and Drug Administration

Christopher Houston, Ph.D., Bausch & Lomb

Desmond G. Hunt, Ph.D., U.S. Pharmacopeia

Jacqueline A. Kunzler, Baxter Healthcare

Michael P. Lynch, Ph.D., Pfizer

Kumudini Nicholas, B.Sc., M.Sc., Health Canada

Daniel Norwood, M.S.P.H., Ph.D., Boehringer Ingelheim Pharmaceuticals, Inc.

Mary Richardson, Ph.D., Bausch and Lomb

Mike Ruberto, Ph.D., Material Needs Consulting, LLC

Edward J. Smith, Ph.D., Packaging Science Resources

Alisa Vespa, Ph.D., Health Canada

Tuesday, February 22

8:30 am - 8:45 am

Opening Remarks

Reggie Saraceno, Ph.D.

Boehringer Ingelheim Pharmaceuticals, Inc.

8:45 am - 10:00 am

Session I:

Leachables and Extractables Impact to Pharmaceutical Quality Systems

Moderator:

Diane Paskiet

West Pharmaceutical Services

It is prudent to assess the critical quality attributes of materials in contact with drug product during pharmaceutical development to enable identification and management of risks associated with patient safety. Packaging and process materials have the potential to compromise drug product quality if substances from these components leach into the drug product.

Selection of materials that could have an impact on the drug product quality should be guided by an understanding of the chemistry of materials through properly conducted extractable studies and linking that knowledge to patient safety. This session will provide a background on the scientific principles used for the assessment of leachables and consider the strategic aspects of the PODP leachable and extractable Work Plan. Such a discussion will provide a general overview whose details will be enumerated in the forthcoming Sessions.

8:45 am - 9:30 am

Regulatory Perspectives on Extractables and Leachables

REGULATORY SPEAKER INVITED

9:30 am - 10:00 am

Overview of PODP Objectives, Testing Strategies, and Milestones

Dennis Jenke, Ph.D.

Baxter HealthCare

10:00 am - 10:15 am

Refreshment Break

10:15 am - 12:15 pm

Session II:

Leachables and Extractables Thresholds and Best Practices Strategies and Rationale

Moderator:

Rajendra (Raj) Uppoor, R.Ph., Ph.D.
U.S. Food and Drug Administration

Leachables are those substances which actually migrate from the components and into the drug product, and are generally regarded to be a sub-set of the extractable profile. There are instances where substances initially identified as extractables are either not present as actual leachables in the drug product or, if present, are at levels so low that they represent a negligible risk for patient safety. In order to facilitate the evaluation of leachables in drug products, scientifically justifiable safety thresholds can be developed and applied to the various categories of drug product. The successful execution of such an approach is, however, dependent upon a requisite degree of analytical support. One of the primary factors that dictate the success of a leachables assessment is the analytical investigation and determination of the critical extractables profile for a given material. The level to which extractables have to be discovered, identified, and quantitated should be driven by the knowledge of the materials along with the configuration, type of drug product, and intended use. This session will discuss the relationship between these two mutually-dependent disciplines as applicable to the evaluation of leachables for POPDs.

10:15 am - 10:45 am

Threshold Establishment and Rationale

Douglas J. Ball, M.S., D.A.B.T.
Pfizer

10:45 am - 11:15 am

Integration Toxicology/ Chemistry-AET Concept

Daniel Norwood, M.S.P.H., Ph.D.
Boehringer Ingelheim Pharmaceuticals, Inc.

11:15 am - 12:15 pm

PODP Approach to Acquire Extractable Profile Data

Thomas Egert
Boehringer Ingelheim Pharma GmbH & Co. KG

Christopher Houston, Ph.D.
Bausch & Lomb

Alan D. Hendricker, Ph.D.
Catalent Pharma Solutions

- ▶PODP Extractables Protocol
- ▶Summary and Discussion of Results
- ▶Best Practice Recommendations for Extractables Testing

12:15 pm - 1:30 pm

Lunch & Poster Exhibit

Typical materials that may be used in container closure and delivery systems were evaluated to support the Working Group's Best Demonstrated Practices. Multiple solvents, extraction and analytical techniques were employed which resulted in a significant amount of extractables data. Posters will display key data for each type of material in order to provide additional background to support the PODP hypothesis.

1:30 pm - 4:45 pm

Session III:

Leachables and Extractables Problem Solving Breakouts

Moderator:

Desmond G. Hunt, Ph.D.
U.S. Pharmacopeia

The extractable profile is a cornerstone for the suitability of a container closure or delivery system. The principles of a controlled extraction study when extrapolated to PODP thresholds must consider parameters such as dose, duration, patient population and other product/user attributes. The selection and evaluation of product contact material is dependent on the risk to patient safety which has unique challenges for the various dosage forms and routes of administration.

This is an interactive session that will highlight how best practices and thresholds can be interpreted using scenarios based on data acquired for particular materials and drug products. Extraordinary challenges exist for certain dosage forms and examples will be given for these cases and special considerations will be discussed.

1:30 pm - 3:00 pm

Qualification of Drug Product Contact Materials used in Large Volume Parenteral (LVP): Chemistry and Toxicology Considerations

Alisa Vespa, Ph.D.
Health Canada

Dennis Jenke, Ph.D.
Baxter HealthCare

Jacqueline A. Kunzler
Baxter Healthcare

- ▶Case Study Overview
- ▶Regulatory Perspective
- ▶Chemistry Findings
- ▶Toxicological Impact

3:00 pm - 3:15 pm

Refreshment Break

3:15 pm - 4:45 pm

Selection and Qualification of a Product Specific Small Volume Parenterals (SVP): Chemistry and Toxicology Considerations

Desmond G. Hunt, Ph.D.
U.S. Pharmacopeia

Frank Holcombe, Jr., Ph.D.
U.S. Food and Drug Administration

Edward J. Smith, Ph.D.
Packaging Science Resources

William P. Beierschmitt, Ph.D., D.A.B.T.
Pfizer, Inc

- ▶Case Study Overview
- ▶Regulatory Perspective
- ▶Chemistry Findings
- ▶Toxicological Impact

4:45 pm - 5:00 pm
Close Day 1 & Wrap Up
Thomas N. Feinberg, Ph.D.
Catalent Pharma Solutions

6:00 pm - 7:00 pm
Reception & Poster Session

Wednesday, February 23

8:30 am - 12:00 pm
Session IV:
Leachables and Extractables Problem Solving Breakouts

Moderator:
Douglas J. Ball, M.S., D.A.B.T.
Pfizer

Continuing from the preceding session, Session IV will focus on two additional dosage forms each of which has its own unique issues and challenges. The discussion on Pre-Fillable Syringe drug products will include a presentation on the principles of Quality-by-Design (QbD), the envisioned but yet to be fully realized paradigm of the future for pharmaceutical development.

The following discussion of ophthalmic drug products will consider the long history of extractables/leachables assessment in these unique dosage forms, as well as introduce the issue of high potency drug products and the possible special considerations associated with these.

8:30 am - 10:00 am
Selection and Qualification of Product Specific Pre-Fillable Syringe Components: Chemistry and Toxicology Considerations
Kumudini Nicholas, B.Sc., M.Sc.
Health Canada

Mike Ruberto, Ph.D.
Material Needs Consulting, LLC

Stephen A. Barat, Ph.D.
Forest Research Institute

- ▶ Case Study Overview
- ▶ Regulatory Perspective
- ▶ Chemistry Findings
- ▶ Toxicological Impact

10:00 am - 10:30 am
Refreshment Break

10:30 am - 12:00 pm
Qualification Challenges for Drug Products Administered via Ophthalmic Route of Administration: Chemistry and Toxicology Considerations
Linda Ng, Ph.D.
U.S. Food and Drug Administration

Mary Richardson, Ph.D.
Bausch & Lomb

Michael P. Lynch, Ph.D.
Pfizer

Christopher Houston, Ph.D.
Bausch & Lomb

- ▶ Current Regulatory Expectations for Ophthalmics
- ▶ Considerations for Ophthalmic Drug Products in Semi-permeable Packaging
- ▶ Current Industry Challenges and Case Studies
- ▶ Looking Forward: Potential Application of Toxicological Qualification Thresholds

12:00 pm - 1:00 pm
Lunch

1:00 pm - 3:00 pm
Session V:
Summary of Findings from Case Study Break-Outs/Panel Discussion

Moderator:
Jim F. Castner
Lantheus Medical Imaging

1:00 pm - 1:45 pm
Significance of Leachables and Extractables to Pharmaceutical Quality
REGULATORY SPEAKER INVITED

1:45 pm - 3:00 pm
Highlights of Day1 and Day 2 Case Study Break-Out Leaders

3:00 pm - 3:15 pm
Refreshment Break

3:15 pm - 4:30 pm
Session VI:
Future Considerations for Leachables and Extractables

Moderator:
Daniel Norwood, M.S.P.H., Ph.D.
Boehringer Ingelheim Pharmaceuticals, Inc.

3:15 pm - 4:00 pm
Extractables and the USP: Past and Future
Roger L. Williams, M.D.
U. S. Pharmacopeia

4:00 pm - 4:30 pm
PODP Accomplishments and Next Steps
Diane Paskiet
West Pharmaceutical Services

- ▶ Thresholds Concepts
- ▶ Best Demonstrated Practices
- ▶ QbD Principles

PQRI Mission Statement

The Product Quality Research Institute (PQRI) is a non-profit consortium of organizations working together to generate and share timely, relevant, and impactful information that advances drug product quality and development.

By virtue of its diverse membership, PQRI provides a unique forum to focus critical thinking, conduct research, exchange information, and propose methodology or guidance to pharmaceutical companies, regulators, and standard setting organizations.

PQRI Member Organizations

AAPS

American Association of Pharmaceutical Scientists

CHPA

Consumer Healthcare Products Association

FDA/CDER

U.S. Food and Drug Administration, Center for Drug Evaluation and Research

HC

Health Canada

IPAC-RS

International Pharmaceutical Aerosol Consortium on Regulation & Science

IPEC-Americas

International Pharmaceutical Excipients Council of the Americas

USP

United States Pharmacopeia

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The workshop is being held at the Hyatt Regency Bethesda and reservations may be made by calling **1-888-421-1442** and referring to the PQRI Workshop on PODP. Hotel reservations can also be made online at <https://resweb.passkey.com/go/PQRI>.

Registration for the workshop can be made by going to the Sign Me Up website at <https://www.signmeup.com/site/reg/register.aspx?fid=392VYJ7>.

For additional information, please contact Vicki Penn at Pennv@pqri.org.

