

The Product Quality Research Institute

Industry, government and academia collaborating for excellence in pharmaceutical research

The Product Quality Research Institute (PQRI) is a collaboration involving the FDA’s Center for Drug Evaluation and Research (CDER), US Pharmacopeia, industry, and academia. PQRI has been engaged in a range of collaborative initiatives since 1999. PQRI’s mission is to conduct research needed to generate scientific information in support of regulatory policy. PQRI initiatives help identify the types of product quality information to be submitted in regulatory filings.

The Institute is guided by a Steering Committee comprised of representatives of the following member organizations: American Association of Pharmaceutical Scientists; Biotechnology Industry Organization; Consumer Healthcare Products Association; International Pharmaceutical Aerosol Consortium on Regulation & Science; International Pharmaceutical Excipients Council of the Americas; Parenteral Drug Association; Pharmaceutical Research and Manufacturers of America; U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research; and the United States Pharmacopeia.

This document highlights a number of PQRI’s accomplishments and contributions. To learn more about PQRI and its current activities, please contact Vicki Penn, PQRI Executive Secretary, at PennV@pqri.org.

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PQRI consists of three Technical Committees that provide technical and scientific guidance, direction, and review for PQRI Working Groups. The Technical Committees consist of scientists and regulatory experts from industry and FDA, and make technical/scientific recommendations to the Steering Committee. Currently, there is a high level of activity among the various Working Groups (WG) established by their respective Technical Committee. A listing of current projects is presented below:

The Development Technical Committee

focuses on research projects which help to more clearly define the Quality by Design (QbD) concepts, science, or related activities through technical examples and applications .

Sulfonate Esters WG

Excipients WG

Stability Shelf Life WG

Container Closure System WG

Leachables and Extractables WG

Specification Design and Lifecycle Management WG

The Biopharmaceutics Technical Committee

deals with regulatory and scientific issues associated with pharmacokinetics.

Sequential Design WG

BCS Class III Compounds WG

Quality by Design for PK Studies WG

The Manufacturing Technical Committee

leverages our manufacturing expertise to define science-based approaches that appropriately integrate risk assessment and encourage innovation and continuous quality improvement in pharmaceutical manufacturing and flexibility in the associated regulatory processes.

Case Studies for Risk Management WG

Specification Design and Lifecycle Management WG

Biological Indicators for Use in Isolator Systems WG

Publications/White Papers

Biologics Inspection

- "Results of a Survey of Biological Drug and Device Industries Inspected by FDA under the Team Biologics Program", *PDA Journal of Pharmaceutical Science and Technology*, Vol. 61, No. 3, May-June 2007, pages 211-222.
- The Product Quality Research Institute (PQRI), in conjunction with the Food and Drug Administration (FDA), conducted an invitation-only anonymous survey of the biological products manufacturing industry inspected by Team Biologics, with emphasis in obtaining industry input on inspection and compliance aspects of program operations. The electronic survey was available from January through May 2006, and was deemed successful with a response rate of 30%. Representatives from all of the product specific manufacturing industries inspected under the Team Biologics program responded to the survey (vaccines; fractionated plasma proteins and recombinant analogs; allergenics; therapeutics and *in-vivo* diagnostics; and *in-vitro* diagnostics (IVDs), including blood grouping reagents.) Data and written feedback were obtained regarding each firm's interactions and experiences of Team Biologics inspections at their facilities over the past three years. The three areas most impacted by Team Biologic inspections were "Production and Process Controls", "Failure Investigations" and "Facility/Equipment Controls". Overall assessment of the Program was generally positive with 68% identifying a positive impact on the site operations and 88% assessing the inspections as being conducted fairly. The findings and conclusions of this report will be utilized by FDA to evaluate and further assess the impact of the Team Biologics Program and to implement any necessary changes.

Blend Uniformity:

- “Results of Statistical Analysis of Blend and Dosage Unit Content Uniformity Data Obtained from the Product Quality Research Institute Blend Uniformity Working Group Data-Mining Effort”, *PDA Journal of Pharmaceutical Science and Technology*, March/April 2004, p. 62.
- “The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends”, *PDA Journal of Pharmaceutical Science and Technology*, Vol. 57, No. 2, March/April 2003, p. 64.
- “Report on the Industry Blend Uniformity Practices Survey”, *Pharmaceutical Technology*, August 2001, p. 20.

Cascade Impactor Mass Balance:

- Good Cascade Impactor Practices – “Cascade Impactor APSD Mass Balance” in *Journal Aerosol Med*, 2003
- D. Christopher, P. Curry, B. Doub, K. Furnkranz, M. Lavery, K. Lin, S. Lyapustina, J. Mitchell, B. Rogers, H. Strickland, T. Tougas, Y. Tsong, and B. Wyka. 2003. “Considerations for the development and practice of cascade impaction testing including a mass balance failure investigation tree.” *J. Aerosol Med*. 16:235-247.
- Jolyon P. Mitchell, “Regarding the Development and Practice of Cascade Impaction Testing, Including a Mass Balance Failure Investigation Tree” *J. Aerosol Medicine*. Dec 2003, Vol. 16, No. 4: 433 – 433.
- B. Wyka, T. Tougas, J. Mitchell, H. Strickland, D. Christopher, and S. Lyapustina; Comparison of Two Approaches for Treating Cascade Impaction Mass Balance Measurements; *J. Aerosol Med*. Accepted for publication 2007.

Leachables and Extractables:

- G. Hansen, on behalf of the PQRI Leachables and Extractables Working Group. “Extractables And Leachables—The Regulatory Challenge Of Qualifying Novel Inhaler Components.” *RDD Europe* 2005:81-88.
- Proceedings of Symposium "Development of Safety Qualification Thresholds and Their Use in Drug Product Evaluation" for Society of Toxicology Annual Meeting (March 2006)
- D. Ball, J. Blanchard, D. Jacobson-Kram, R. O. McClellan, T. McGovern, D. L. Norwood, W. M. Vogel, R. Wolff, and L. Nagao. Development of Safety Qualification Thresholds and Their Use in Orally Inhaled and Nasal Drug Product Evaluation. *TOXICOLOGICAL SCIENCES* 97(2), 226–236 (2007). doi:10.1093/toxsci/kfm058; Advance Access publication March 16, 2007

Aerodynamic Particle Size Distribution Profile Comparisons:

- W.P. Adams, D. Christopher, D.S. Lee, B. Morgan, Z. Pan, G.J.P. Singh, Y. Tsong, S. Lyapustina. “Product Quality Research Institute Evaluation of Cascade Impactor Profiles of Pharmaceutical Aerosols, Part 1: Background for a Statistical Method”. *AAPS PharmSciTech*. 2007; 8(1): Article 4. DOI: 10.1208/pt0801004. Available online at <http://www.aapspharmscitech.org/view.asp?art=pt0801004> (2007)
- D. Christopher, W.P. Adams, D.S. Lee, B. Morgan, Z. Pan, G.J.P. Singh, Y. Tsong, S. Lyapustina. “Product Quality Research Institute Evaluation of Cascade Impactor Profiles of Pharmaceutical Aerosols: Part 2 - Evaluation of a Method for Determining Equivalence.” *AAPS PharmSciTech*. 2007; 8(1): Article 5. DOI: 10.1208/pt0801005. Available online at <http://www.aapspharmscitech.org/view.asp?art=pt0801005>. (2007)
- D. Christopher, W. Adams, A. Amann, C. Bertha, P. R. Byron, W. Doub, C. Dunbar, W. Hauck, S. Lyapustina, J. P. Mitchell, B. Morgan, S. Nichols, Z. Pan, G. J. P. Singh, T. Tougas, Y. Tsong, R. Wolff, and B. Wyka. “Product Quality Research Institute Evaluation of Cascade Impactor Profiles of Pharmaceutical Aerosols: Part 3– Final Report on a Statistical Procedure for Determining Equivalence”. *AAPS PharmSciTech*. 2007 Accepted for publication.

- DeLuca PP, Lyapustina S. Product Quality Research Institute Reports. *AAPS PharmSciTech*. 2007; 8(1): Article 6. Available at <http://www.aapspharmscitech.org/view.asp?art=pt0801006>. Accessed June 22, 2007.

Container/Closure:

- “Basis for Using Moisture Vapor Transmission Rate Per Unit Product in The Evaluation of Moisture-Barrier Equivalence of Primary Packages for Solid Oral Dosage Forms” — *Pharmacoepial Forum Vol 31 No 1 Jan-Feb 2005*; Pg 262.

PF Impurities:

- The survey results data was published in February 2006 in *Pharmaceutical Research* (reference below).
- *Pharm Res*. 2006 Feb;23(2):438-44, “Report on the PQRI Impurity Characterization and Quantification Best Practices Survey”, Faustino P, Chan CC, Carrano J, Gosnell M, Gu ZQ, Maule A, Sigvardson K, Zhang YF.
- Impurity Characterization and Quantification Best Practices Survey, FDA Science Forum 2005.
- Impurities – Column Equivalency article in *Journal of Chromatography*. HPLC article in *Pharmacopeia Forum*— February 2005.
- Beta-testing of the equivalent column database was made available by USP to the contributors from PQRI Impurities Working Group. It is expected to be available free of charge to the scientific community in 1Q07.
- L.R. Snyder *et. Al.*, *J. Chrom A 1057 (2004) 49-57*, “A fast, convenient and rugged procedure for characterizing the selections of alkyl-silica columns”.
- USP Pharmacopeial Forum 31 (2), HPLC Column Classification 637-645p. Mar-Apr 2005.

Particle Size:

- PQRI Recommendations on Drug Substance Particle-Size Analysis of Oral Dosage Forms published in the *J. Pharm Sci*. Jan. 2007. This document provided information for the pharmaceutical industry and the Food and Drug Administration (FDA) regarding the selection of suitable particle-size analysis techniques, development and validation of particle-size methods, and the establishment of acceptance criteria for the particle size of drug substances used in oral solid-dosage forms. The document was intended for analysts knowledgeable in the techniques necessary to conduct particle-size characterization (a table of acronyms is provided at the end of the document).

Process Robustness:

- Paper on Process Robustness of Oral Solid Dosage Forms published in *Pharm. Eng*. Vol. 26, No. 6, Nov/Dec 2006. Also, posted on the PQRI website. Workshop on Robustness Principals, held at the GMP by the Sea Conference, August 2006.

Excipients:

PQRI Survey of Pharmaceutical Excipient Testing and Control Strategies, Used by Excipient Manufacturers, Excipient Distributors and Drug Product Manufacturers” — *Pharmaceutical Technology*, Vol. 30, No 9, September 2006, page 90.

PQRI conducted an open, publicly available, electronic survey of current excipient-control strategies among pharmaceutical excipient manufacturers, distributors and drug-product manufacturers. Among the major findings are: 1) most respondents supply global markets, and must meet substantially different test requirements for different regions; 2) most respondents use reduced-testing strategies employing equivalent methods; 3) most respondents perform additional tests on the excipients to determine physical and chemical properties; and 4) drug-product manufacturers use company procedures to qualify excipient suppliers. The survey provides insights about industry decisions for testing excipient quality and using excipients in manufacturing.

Cascade Impactor Mass Balance:

- The PQRI Mass Balance WG submitted a letter to FDA, which is publically available at [http://www.pqri.org/pdfs/mass Balance Submission to FDA 10 26 06.pdf](http://www.pqri.org/pdfs/mass%20Balance%20Submission%20to%20FDA%2010%2026%2006.pdf).

Surveys Conducted

Blend Uniformity:

Results published in the *PDA Journal of Pharmaceutical Science and Technology*, 2004 March-April, 58 (2), pages 62-74, entitled “Results of Statistical Analysis of Blend and Dosage Unit Content Uniformity Data Obtained from the PQRI Blend Uniformity Working Group Data-Mining Effort”.

Aseptic Processing:

An industry survey was conducted to gather specific information regarding aseptic filling practices. The responses from over 45 aseptic filling sites were received and collated for use by the team. Since then, several additional surveys have been received. The complete survey results, including the additional surveys received, will be submitted for publication in the near future.

Biologic Inspections:

"See previous notation in the publications section on biologics inspection survey results."

Formal Recommendations to FDA

Blend Uniformity:

A Draft Guidance for industry was issued in October 2003 by the FDA titled, “Powder Blends and Finished Dosage Units – Stratified In-Process Dosage Unit Sampling and Assessment.” This draft guidance was a result of recommendations made by PQRI.

Aseptic Processing:

Recommendations were submitted to FDA in March 2003 to address the FDA’s concept paper “Sterile Drug Products Produced by Aseptic Processing.” The recommendations were based on expert knowledge of the work group members, survey results, and publications. The recommendations enabled the FDA to finalize their guidance on aseptic processing.

BACPAC II:

- Final recommendation submitted to the FDA in June 2004. The Specifications and BACPAC Working Group under the guidance of the Drug Substance Technical Committee completed a report on “Setting Specifications and Evaluating Drug Substance Manufacturing Post Approval Changes after the Isolation of the Final Intermediate” also known as Bulk Actives Post Approval Changes II (BACPAC II). The PQRI report provides key points and specific recommendations on the post-approval manufacturing changes and appropriate technical data needed for filing and filing type for all four reporting mechanisms (NDAs, ANDAs, NADAs, and ANADAs) used in the pharmaceutical industry. The PQRI recommendations for BACPAC II are based on good science and the requirements of both the FDA and industry. The report was submitted to the FDA for review and comments and it will be considered during the preparation of the general GMP guidance currently underway with in the agency.

RFID:

- Working Group’s final recommendation and report was submitted to FDA in March 2006, and posted at http://pqri.org/pdfs/RFID_Report_to_FDA_23Mar2006.pdf . The outcome of the work resulted in the finding that all of the information in this final report, taken together, provides ample evidence that exposure to RF energy due to the implementation of an RFID track and trace system represents a negligible risk to drug product quality, whether of small molecules or biological or protein-based drugs.

Leachables/Extractables:

- Final Recommendations to FDA were submitted on September 29, 2006, and posted at http://pqri.org/pdfs/LE_Recommendations_to_FDA_09-29-06.pdf.

Anticipated Publications/White Papers/Recommendations

Container/Closure:

- Final recommendation to FDA were submitted in late 2006.

Leachables and Extractables:

- Journal article summarizing the Best Practices recommendations will be submitted in the third quarter of 2007.
- Book on safety thresholds for drug products, is based on Society of Toxicology 2006 symposium is planned for publication in 2007-2008.
- Chapter contribution to book on leachables and extractables best practices, to be submitted in the fourth quarter of 2007.
- Article summarizing full Best Practices and Safety Recommendations submitted to American Pharmaceutical Review, June 2007.

Profile Comparisons:

- Interim Report papers to be published in scientific journal.

Excipients:

- White paper summarizing findings from the September 2007 workshop.

Post Approval Changes for Sterile Products:

- Submitted to the FDA Docket on Supplements and Other Changes to an Approved Application (#2006N-0525). Other publications planned.

Stability Shelf Life:

- Manuscript on the definition of shelf life is being prepared.

Organizational Structure

Member Organizations

AAPS	American Association of Pharmaceutical Scientists
BIO	Biotechnology Industry Organization
CHPA	Consumer Healthcare Products Association
IPAC-RS	International Pharmaceutical Aerosol Consortium on Regulation and Science
IPEC-Americas	International Pharmaceutical Excipients Council of the Americas
PDA	Parenteral Drug Association
PhRMA	Pharmaceutical Research Manufacturers of America
U.S. FDA	U. S. Food and Drug Administration, Center for Drug Evaluation and Research
USP	United States Pharmacopeia

PQRI

The outcomes of PQRI will be focused on research projects whose results provide a continuing scientific basis for regulatory policy. Research may support reduction in regulatory burden by decreasing the amount of information needed for a submission and/or regulatory filing while continually striving to improve the quality of drugs and their benefits to patients.

Board of Directors

The Board of Directors has authority over the collection and disbursement of funds and the administrative procedures required to ensure the effective operation of the institute.

Steering Committee

The PQRI Steering Committee has sole authority over all scientific activities undertaken in conjunction with the institute and is responsible for recommending all institute funds spent in conjunction with scientific activities, specifically for all research done under the auspices of the institute.

Technical Committees

PQRI consists of three Technical Committees that provide technical and scientific guidance, direction, and review for PQRI Working Groups. The Technical Committees consist of scientists and regulatory experts from industry and FDA, and make technical/scientific recommendations to the Screening Committee.

Working Groups

PQRI currently has several very active Working Groups operating under the guidance of a Technical Committee. These Working Groups consist of scientists from industry, academia, and the FDA, who generate, evaluate, discuss information or data, and develop PQRI recommendations, technical reports, and/or scientific papers.

Past PQRI Meetings

2001

PQRI Executive Training (January 2001)

2003

**Good Regulation Through Good Science
Workshop (August 2003)**

**Drug Quality System for the 21st Century
Workshop (April 2003)**

**Blend Uniformity Workshop
(December 2003)**

2005

**Risk Management Workshop
(January 2005)**

Specifications Workshop (March 2005)

**Leachables/Extractables Workshop
(Fall 2005)**

2006

**Leachables and Extractables Best
Practices Training Course
(September 2006)**

**Excipients Testing and Control Strategies
Workshop (October 2006)**

2007

**Leachables and Extractables Best
Practices Training Course (April 2007)**

Future PQRI Meetings

September 10-11, 2007

**IPEC-Americas Regulatory Affairs
Conference Findings of a PQRI
Working Group
Alexandria, VA**

Sept. 26-27

**Leachables and Extractables Best
Practices Training Course
Basel, Switzerland**

Nov. 15-16

**Leachables and Extractables Best
Practices Training Course
San Diego, CA**

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