PQRI’s Contributions to Science

Gordon Hansen
Past chair, PQRI Steering Committee

December 15, 2009
Why PQRI?

- Need for a safe harbor between scientists and regulators
- Initial concept proposed in 1995 by Roger Williams, then head of FDA’s Office of Pharmaceutical Sciences
- Concept initially proposed as Product Quality Research Initiative
History of PQRI Formation

- October 1996, Product Quality Research Initiative
- August 2, 1999, Product Quality Research Institute officially recognized by State of Virginia as nonprofit, tax-exempt corporation
PQRI Visionaries

- Roger Williams, FDA OPS, USP
- Helen Winkle, FDA OPS
- Ajaz Hussain, FDA
- Toby Massa, PhRMA
- Ed Fry, PDA
- Bill Bradley, CHPA
Purpose

"...serve as a forum for academia, industry and FDA to work cooperatively to conduct pharmaceutical product quality research and to support development of public standards..."
“PQRI is a tangible expression of a unique collaboration between academia, industry, and a governmental agency that brings us together for both the innovator and generic pharmaceutical companies.

This collaboration will identify the best practices for manufacturing of high quality pharmaceutical products. It’s an excellent means for leveraging FDA’s intellectual and laboratory resources; to promote regulatory research programs designed to enhance the science base that we need to provide, and

I am convinced it will be a win, win, win solution for the public, the industry, and the agency.”

Jane Henney, MD, former FDA Commissioner
Original Member Organizations

- **American Association of Pharmaceutical Scientists (AAPS)**
- **Consumer Health Products Association (CHPA)**
- Generic Pharmaceutical Industry Association (GPhIA)
- National Association of Pharmaceutical Manufacturers (NAPM)
- National Pharmaceutical Alliance (NPA)
- Parenteral Drug Association (PDA)
- Pharmaceutical Research and Manufacturers of America (PhRMA)
- **Center for Drug Evaluation and Research, FDA**
Additional Members

- **United States Pharmacopoeia (USP)**
- International Society of Pharmaceutical Engineers (ISPE)
- **International Pharmaceutical Excipients Council – Americas (IPEC-Americas)**
- **International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS)**
- Biotechnology Industry Organization (BIO)
- Health Canada
Current Member Organizations – an Organization of Organizations

- American Association of Pharmaceutical Scientists (AAPS)
- Consumer Healthcare Products Association (CHPA)
- U.S. Food and Drug Administration, Center for Drug Evaluation and Research (FDA)
- Health Canada
- International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)
- International Pharmaceutical Excipients Council of the Americas (IPEC)
- United States Pharmacopeia (USP)
- MOA: National Institute for Pharmaceutical Technology and Education (NIPTE)
Structure of PQRI

- Governed by a Board of Directors and a Steering Committee
  - Steering Committee has sole authority over all scientific activities
  - Each member organization is represented on the Steering Committee
- Technical work is carried out by Technical Committees and Working Groups
- Board has fiduciary responsibility
- Structure and responsibilities delineated in Bylaws
Organization

PQRI Board of Directors
Mario L. Rocco, Jr., Ph.D., Chair; Glenn Van Buskirk, Ph.D., Treasurer; Mary Oates, Ph.D.; Avi Yacobi, Ph.D.; Anthony DeStefano, Ph.D.

Steering Committee
Mary Oates, Ph.D., Chair; Anthony DeStefano, Ph.D., Vice-Chair (USP); Lynn Van Campen, Ph.D. (AAPS); Rachael Roehring, Ph.D. (CHPA); Terrence Tougas, Ph.D., (IPAC-RS); Robert Wiens (IPEC-Americas); Rich Levy, Ph.D.(PDA); Helen Winkle (FDA); Anita DiFranco (Health Canada)

Visibility / Outreach
Mary Oates, Chair

Executive Secretary
Vicki Penn

Development Technical Committee
Reggie Saraceno, Ph.D., Chair

PODP Leachables & Extractables
Diane Paskiet, Ph.D., Chair

Stability Shelf Life Work Group
Jim Schwenke & Patrick Forenzo, Co-Chairs

Container Closure Work Group
Dan Malinowski, Chair

Sulfonate Esters Work Group
Andrew Teasdale, Ph.D., Chair

Biopharmaceutics Technical Committee
Erika Stippler, Ph.D., Chair

Sequential Design Work Group
Alan Parr, Ph.D., Chair

BCS III Classification Work Group
Alan Parr, Ph.D., Chair

Manufacturing Technical Committee
Margaret Szymczak, Chair

Specifications Design & Life Cycle
Gordon Munhead, Chair

Risk Management Case Studies Work Group
Ted Frank, Chair

QbD Work Group
CPP and CQA issues
The mission of the DTC is to conduct research projects which help to more clearly define through technical examples and applications the Quality by Design (QbD) concepts, science or related activities associated with QbD. The DTC incorporates projects formerly managed by the Drug Product and Drug Substance Technical Committees.
The MTC leverages manufacturing expertise to define science-based approaches that appropriately integrate risk assessment and encourage innovation and continuous quality improvement in pharmaceutical manufacturing as well as flexibility in the associated regulatory processes.
The mission of the BTC is to promote research in the area of biopharmaceutics. Areas of interest include: linkage of in-vitro drug dissolution/release methods to in-vivo drug bioavailability and bioequivalence, methods for the determination of bioavailability and bioequivalence, pharmacokinetic-pharmacodynamic relationships and comparative clinical trials.
History

- Historically, PQRI was focused on influencing FDA regulations
- Several impactful projects have been completed by PQRI over the past 10 years (e.g., leachables and extractables, blend uniformity, process robustness)
# DTC Projects

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<th>Outcomes</th>
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<td>• White paper issued on the use of Moisture Vapor Transmission Rates (MVTR)</td>
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<tr>
<td>Leachable/Extractables</td>
<td>• Recommendations to FDA on the characterization of Leachables and Extractables in Orally Inhaled and Nasal Drug Products (OINDP)</td>
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<td></td>
<td>□ Training courses</td>
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<tr>
<td>Mass Balance</td>
<td>• Recommendations to FDA on a science-based rationale for the use of mass balance measurement in OINDP cascade impactor testing</td>
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<td>Profile Comparisons</td>
<td>• Publications</td>
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<tr>
<td>PODP</td>
<td>• Reporting and Qualification Thresholds for Leachables in Parenteral and Ophthalmic Drug Products</td>
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DTC Projects, continued

| Excipients | •Publication of industry survey and FDA concepts on Excipient Control Strategies
  □Workshop on current industry and regulatory practices |
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<tr>
<td>RFID</td>
<td>•White paper</td>
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| Blend Uniformity | Recommendations to FDA
  □Publications
  □Workshop |
| Impurities characterization | □Publication in Pharm. Research |
| HPLC Column comparison | •USP publication
  □J. Chrom publication |
| Specifications (BACPAC II) | •Recommendations to FDA |
| Sulfonate Esters | •Publications |
| Stability Shelf Life | •Publication
  □Presentations
  □Webinar |
## MTC Projects

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<td>Post Approval Changes for Aseptic Processes</td>
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<td>Process Robustness</td>
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<tr>
<td>Case Studies for Risk Management</td>
<td>• Workshop on Risk Management in Solid Dosage Form Manufacture</td>
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<tr>
<td></td>
<td>□ Whitepaper</td>
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<tr>
<td>Specification Design and Lifecycle Management</td>
<td>□ Activities in Progress</td>
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<tr>
<td>Biological Inspection Survey</td>
<td>□ Survey of inspection impact and effectiveness conducted with FDA</td>
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<tr>
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<td>□ Publication</td>
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## BTC Projects

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<td>BA/BE Sequential Design</td>
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<td>BCS Class III Compounds</td>
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Highlights

- Blend Uniformity
- Aseptic Processing
- Leachables and Extractables
Blend Uniformity Testing

- Project initiated in response to FDA proposal to test all blends for content uniformity and reject any batch that did not meet established criteria
- First PQRI project with significant outcome
- Working Group conducted extensive data mining and statistical analyses
- WG proposed enhanced tablet-testing scheme, adopted by FDA in 2003 as an alternative to BU testing
- Proposal resulted in significant cost savings to Industry while addressing Agency quality concerns
Aseptic Processing

- Project initiated in response to 2002 FDA concept paper “Sterile Drug Products Produced by Aseptic Processing”
- Working Group developed 8 clarifications and 10 recommendations based on survey results and available scientific literature
- Influenced outcome of final 2004 guidance document
Leachables and Extractables
1998/99 FDA Draft Guidances for Orally Inhaled and Nasal Drug Products (OINDP)

- Provided, for the first time, FDA expectations for testing of extractables and leachables (L&E) in OINDP

- Opportunity for dialogue between industry and FDA on L&E testing in OINDP
Initial Industry Efforts to Address 1998/99 Guidances

IPAC-RS in collaboration with the Inhalation Technology Focus Group (AAPS):

- Conducted confidential surveys of pharma industry and suppliers
- Developed and submitted to FDA *Points to Consider*, a response to the recommendations on L&E testing in the 1998/99 MDI/DPI Guidances.
IPAC-RS recognized the Product Quality Research Institute (PQRI) as a valuable opportunity to work with FDA in addressing topics of mutual interest in a scientific manner.

- IPAC-RS developed and submitted L&E proposal to PQRI
- L&E Project accepted into PQRI in 2001
1. Scientifically justifiable thresholds based on the best available data and industry practices can be developed for the reporting and safety qualification of leachables and extractables from critical components used in OINDP.

2. Safety qualification of extractables would be scientifically justified on a case-by-case basis.
Proposed analytical and safety qualification thresholds for assessment of L&E in OINDP

Proposed a pharmaceutical development process for analytical and safety assessment of L&E in OINDP

Addresses all OINDP (e.g., DPIs, MDIs, nasal sprays, solutions for nebulization, etc)

Encourages careful and informed selection of materials and integration of safety expertise in materials selection and analytical evaluation of extractables
Developing the Thresholds

- Used established safety databases and conservative assumptions
- Considered patient population and delivery mechanism
- Considered existing thresholds, e.g., CFSAN threshold for food additives
- Considered previous threshold approaches, e.g., for genotoxic impurities
PQRI L&E Working Group Members

Dan Norwood, Chair (IPAC-RS)  
Doug Ball (IPAC-RS)  
Jim Blanchard (IPAC-RS)  
Lidiette Celado (AAPS)  
Fran DeGrazio (PDA)  
T.J. Deng (Lab - PPD)  
Bill Doub (Lab - FDA)  
Tom Feinberg (AAPS)  
Alan Hendricker (Lab - Cardinal)  
Jeff Hrkach (AAPS)  
Roger McClellan (UNM)  
Tim McGovern (FDA)  
Diane Paskiet (PDA)  
David Porter (USP)  
Michael Ruberto (Lab - CIBA)  
Alan Schroeder (FDA)  
Mark Vogel (PhRMA)  
Charles Wang (PhRMA)  
Ron Wolff (IPAC-RS)  
Michael Golden (DPTC, IPAC-RS)  
Guirag Poochikian (DPTC, FDA)
Public Dissemination of L&E Outcomes

Final Recommendations submitted to FDA, 2006

Workshops and Training Courses
- Excipient Testing and Control Strategies, October 10-11, 2006
- Leachables and Extractables Best Practices, April 12-13, 2007
- Leachables and Extractables Best Practices (Basel, Switzerland), September 26-27, 2007
- Leachables and Extractables Best Practices (San Diego, CA), November 15-16, 2007

Publications in Peer-reviewed Journals
The Tally

- 21 Projects completed or on-going
- 100’s of dedicated volunteers
- 36 publications…. 
- 11 workshops, conferences, webinars…. 
Lessons Learned

- Impactful work can be done, but generally requires more time and resources than initially estimated
- We are all volunteers – PQRI comes “on top of” work back at the office
- Effective project management is key to success
- Reaching consensus with Regulatory Agencies may not be possible (e.g. Mass Balance Project)
Challenges

- The world has changed since the late 1990’s and so must we.
- Reduced Regulatory emphasis on Guidelines
- Increased access to Regulatory Scientists through CREDA’s, etc.
- Trade associations less focused on scientific issues
Acknowledgements

- Hundreds of volunteers who made all this possible
- Member Organizations
- Technical Committee chairs
- Steering Committee, Board of Directors
- Chris Allen