

PQRI to Gather Data on RFID Effects

Radio Frequency Identification devices (RFID) were thrust into the pharmaceutical zeitgeist when U.S. retailer Wal-Mart mandated in 2003 that its top one-hundred suppliers label packages with the tracking and control technology, including finished pharmaceutical products. Following the retailer's lead, FDA recommended use of RFID as a tool to combat counterfeiting (<http://www.fda.gov/oc/initiatives/counterfeit/>). In November 2004, the Agency issued a guidance for industry on RFID, entitled "Radiofrequency Identification Feasibility Studies and Pilot Programs for Drugs" (http://www.fda.gov/oc/initiatives/counterfeit/rfid_cpg.html).

In anticipation of the widespread use of RFID, several pharmaceutical companies have started efforts to investigate whether use of the technology could affect the quality of their products. For its part, FDA requested that broader studies on potential effects of RFID use on the quality, safety and efficacy of drugs be conducted in order to provide a basis for future regulatory decisions in this area. PQRI has stepped forward to carry out the necessary RFID research and identify any potential impacts on pharmaceutical products.

The RFID initiative at FDA is overseen by Office of the Commissioner Medical Officer Paul Rudolf. Spearheading the effort for CDER are Moheb Nasr and Guirag Poochikian. Toby Massa (Bristol-Myers Squibb), Chair of the PQRI Board of Directors, is leading the effort within PQRI. He explained that a Working Group under the Drug Product Technical Committee (DPTC) is developing a research plan, which should be forwarded to the DPTC and PQRI Steering Committee for review and approval by the early January.

In its simplest form, an RFID is a tag containing a small metal coil that can receive and reflect radio signals. The device can store some identifying information about the package to which it is attached. Like a familiar bar-code label, an RFID tag must be "interrogated" by a "reader" system—in this case a radio emitter interfaced with a computer—in order to reveal the identifying information. Essentially, the ID provided by the RFID allows the reader to look up in its database the documentation on the tagged package. This documentation may include the description of the product, its origin, shipping log, distribution details, etc.

Implementation of RFID technology requires several hardware and software components, along with well-developed manufacturing, tracking and maintenance systems. While there are many issues to be considered, PQRI will provide recommendations only on areas that might have a bearing on the quality of drug products.

One area of concern is the heat generated by RFID tags. When the interrogating radio signal reaches

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RFID, from Cover

the RFID tag, the metal coil antenna (and possibly other metal parts of the product’s packaging) may heat up slightly. The level of exposure to this additional thermal energy, as well as to the non-thermal component of the radio signal itself, might appear inconsequential. However, no definitive data exists demonstrating whether or not, under worst-case scenario conditions, such exposures would affect the quality, safety or efficacy of pharmaceutical products. Of particular concern are vaccines and other protein-containing products because both thermal and non-thermal electromagnetic energy may interfere with the secondary structure of proteins and with their proper folding, which in turn may influence the immunogenicity and efficacy of the drug product.

Among the technical questions to be studied first by the PQRI Working Group are the following:

- ❖ How should the temperature increase be measured?
- ❖ How does the temperature increase depend on the mutual orientation and proximity of the receiving and transmitting antennas, length of exposure, environmental humidity and other conditions?
- ❖ Does the effect depend on the dosage form (e.g., solid oral dosage forms, solutions, creams and ointments)?

For the first phase of the workplan, the PQRI Working Group will draw upon existing guidelines and literature related to stability testing, thermal cycling, electrophoresis, etc. Based on this preliminary research, the group will work on a sound protocol for testing, which will be carried out in the second phase. Dr. Massa expects that the first-phase will be completed around May 2005, whereupon the second

phase will commence. The outcome of PQRI’s research will help FDA form its opinion, which will likely be communicated in the form of a guidance or a letter to manufacturers.

“Everybody is excited about creating a definitive study and definitive data upon which FDA will make a regulatory decision,” says Dr. Massa, “Data will tell us what the story is.”

Current members of the PQRI RFID Working Group include representatives of FDA, USP, MIT, and Michigan State University. The Working Group also interacts with vendors of RFID technology, who could contribute pertinent data and technical expertise. PQRI and FDA recognize that other initiatives involving RFID are under way, and plan to coordinate with them as appropriate. This could be facilitated by the current working group members, several of whom have been involved with an RFID program called Jump Start led by a private consulting firm Accenture. Dr. Massa stressed that although other initiatives have generated interesting information, there has been no worst-case exposure study. Nevertheless, the previously accumulated knowledge could provide useful insights, help avoid “dead-end” alleys in PQRI’s research, and expedite harmonization of final recommendations with existing approaches and practices.

At present, the PQRI RFID Working Group is comprised of the following individuals: Chris Allen (Bayer), Rafik H. Bishara (Eli Lilly), Peter Calcott (Chiron), Stephen Hess (Merck), Ashok.V. Katdare (Morton Grove Pharmaceuticals), William F. Kluttz (Eli Lilly), Tobias Massa (Bristol-Myers Squibb), Denise Miller (Eli Lilly), Guirag Poochikian (FDA), Frederick Razzaghi (CHPA), Fred Sexton (Kos), Robert H. Seevers (Eli Lilly), Mark R. Seitz (Eli Lilly).

Stay tuned for this newsletter’s updates on the PQRI RFID initiative!

Don’t miss the Leachables/Extractables Workshop
Fall of 2005
 Watch our web site (www.pqri.org) for more information!

The State-of-the-State: PQRI Projects Moving Forward

The PQRI Steering Committee gathered in September for its third strategic visioning session of the year. The meeting was hosted by the Generic Pharmaceutical Association (GPhA) at the law offices of McKenna, Long and Alrich.

These meetings are used by Steering Committee members to further define PQRI initiatives. In September, the group reviewed current projects and PQRI's role and strategies for moving forward in 2005. "The Steering Committee is always looking to keep PQRI moving in a direction that benefits all our stakeholders," stated PQRI Steering Committee Chair, Gordon Hansen (Boehringer-Ingelheim). "Strategic visioning meetings allow us to assess current projects and identify the latest issues confronting stakeholders, like RFID."

The Technical Committee Chairs presented a timeline of current and future projects, including:

Drug Product Technical Committee (DPTC)

Terrence Tougas, PhD, Chair, reporting

Container/Closure Working Group

- ❖ This Working Group is developing test methods and evaluation criteria in direct support of FDA's PACPAC guidance document. They recently published a stimuli article "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 PQRI Container-Closure Working Group" in the January edition of the *Pharmaceutical Forum*.
- ❖ The group is now focused on providing experimental support for the proposals made in the PF article.

Leachables/Extractables Working Group (LEWG)

- ❖ The LEWG composed of chemists and toxicologists is focused on proposing reporting and qualification thresholds for leachables in orally inhaled and nasal drug products (OINDP). It is anticipated that the LEWG will submit its recommendation to the FDA in late 2005.
- ❖ A workshop is planned for fall of 2005.

Mass Balance Working Group (MPWG)

- ❖ The MBWG is preparing recommendations on the appropriate use of mass balance determinations connected with aerosol particle size determinations for OINDP. It is anticipated that the MBWG will submit recommendations to FDA 2nd quarter of this year.

Profile Comparisons Working Group (PCWG)

- ❖ The PCWG is addressing the development of statistically robust methods for comparison of aerosol particle size distributions in OINDP. The work to date is being summarized in a paper for publication, and is anticipated to be submitted in the first half of 2005.
- ❖ The group hopes to make a final recommendation to FDA by the end of 2005.

Excipients Working Group

- ❖ This working group is assessing (i) current industry practice for excipient control to comply with CFR and USP-NF requirements, (ii) use of reduced testing, and (iii) availability and use of simple, reliable, extra-monograph excipient tests to determine excipient processability.
- ❖ A work plan was approved by the SC in November 2004 and work is currently underway to survey industry regarding current practices.

Radio Frequency Identification Working Group (RFID)

- ❖ The RFID Working Group has recently submitted a proposed work plan to the DPTC to investigate: the potential thermal and electromagnetic field effects of radio frequency exposure on different types of drug products in various presentations

Drug Substance Technical Committee (DSTC)

Pat Tway, PhD, Chair, reporting

Specifications Working Group

- ❖ A draft BACPAC II proposal was forwarded to the FDA in June 2004.

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- ❖ FDA is preparing a detailed comparison between the PQRI document and its own in-house documents.

Impurities Working Group

- ❖ A publication was prepared based on the results of an industry survey on the appropriate level of characterization of impurities in the drug substance during the early stages of clinical development.
- ❖ Document has been submitted to *Pharmaceutical Research* for publication.
- ❖ Work was done in conjunction with Dr. Lloyd Snyder to develop a model to demonstrate column equivalency. Two articles are being published in the *Journal of Chromatography*.
- ❖ The team is currently working with USP on a recommendation for column equivalency to be published in a PF Stimuli article 1Q05.

Particle Size Working Group

- ❖ A draft publication has been prepared on the selection of suitable particle size analysis techniques, development and validation, and the establishment of acceptance criteria for particle size of API used in oral solid dosage forms.
- ❖ The publication will be released for wider industry review 1Q05.

Manufacturing Technical Committee (MTC)

Bruce Bird, PhD, Chair, reporting

Aseptic Processing Working Group

- ❖ Original work has been completed; however, the WG is now drafting a work plan for post-approval changes.

Biological Indicators Working Group

- ❖ Proposal is being drafted for approval by the TC by the end of 2004.

Process Robustness Working Group

- ❖ A white paper relative to critical parameters is being drafted. It is anticipated that it will be forwarded to the MTC for approval in March-April 2005.

Regulatory Process Working Group

- ❖ This project start date is contingent upon the

- completion of the process robustness work due to the sequential nature of the projects. It is anticipated that this work would focus initially on solid dosage forms only. WG would also look at resource loading.
- ❖ Some of this work would be cross-functional.

Risk Management Workshop

- ❖ Will be held on January 31 – February 2 at the Renaissance Washington Hotel in Washington, DC.
- ❖ Depending upon what actions/outcomes that come from the workshop, there may be additional WGs formed to further that work.
- ❖ Future projects could include PAT implementation protocol; determination of industry implementation for a current product from a process roadmap view; how to take existing products, translate into PAT and then implement.

Continuous Quality Verification/Validation

- ❖ With the advent of the CPG guidance being released, this may be a good opportunity for a PQRI WG to redefine terminology, along with the science that needs to be conducted in this area.
- ❖ A work plan is expected in early 2005.
- ❖ Some of the work relating to API projects could be shared by MTC and DSTC (i.e., process robustness would be a parallel project).

Biopharmaceutical Technical Committee (BTC)

Alan Parr, PhD, Co-Chair, reporting

Sequential Design Working Group

- ❖ A work plan is scheduled for drafting in October, with a majority of the work being completed by the 4th quarter of 2005.

Immediate Release Oral Drug Products Working Group (IRODP)

- ❖ Future meetings are being set.

Dissolution Specifications Working Group

- ❖ Meetings with Dr. Ajaz Hussain, FDA, are anticipated.
- ❖ Future possible projects include variability evaluation.

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PQRI Specifications Workshop – March 16-18, 2005

The “desired state” of pharmaceutical manufacturing in the 21st Century, as proposed in ICH’s quality guideline “Q8”, *Pharmaceutical Development*, specifies that: product quality and performance should be achieved and assured by design of effective and efficient manufacturing processes; that product specifications should be based on mechanistic understanding of how formulation and process factors impact product performance; and that manufacturers have the ability to effect continuous improvement.

To ensure that this “desired state” can be met, there needs to be a more modern evaluation of specifications and how they are established and used. The PQRI Specifications Workshop will consider the fundamentals of specifications to determine:

- ❖ Future relevance with respect to ensuring design of product and processes and setting, and
- ❖ Changing specifications in order to ensure that product performance can be maintained without variation throughout the lifecycle.

The workshop will explore specifications as applied by both the innovator and generic industries and focus on the specific principles that must be observed in order to maintain high quality pharmaceutical products in the future.

Plenary sessions will describe the “desired state” and how specification setting may be affected. These sessions will include a case study on specification setting in other industry sectors and the results of the recent FDA specifications workshop for biotechnology and biological products. There will also be discussions of the European Union’s approaches to developing and using specifications and the current role of compendial standards.

This workshop will provide the basis for future approaches to specification establishment and use and help in providing a sound foundation for ensuring the “desired state” in the 21st Century.

Goals and Objectives

- ❖ Explore the establishment and use of specifications under the “desired state” for pharmaceutical manufacturing to best assure the quality of pharmaceutical products throughout their lifecycle.
- ❖ Determine what changes in principles and practice are necessary in order to ensure specifications are set with appropriate mechanistic understanding.
- ❖ Identify the next steps for accomplishing harmonization between the innovator industry and the generic industry and globally for setting specifications.

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- ❖ It was determined that funding may be required for the IRODP project, but no other funding needs are anticipated for the other WGs.

Education, Communication and Assessment Subcommittee (ECAS)

Ms. Stacey May, Co-Chair, reporting

- ❖ There was discussion relative to how ECAS could best publicize the three upcoming PQRI workshops.
 - Risk Management – January 31 – February 2, 2005
 - Specifications Workshop – March 15-18, 2005
 - Leachables/Extractables – Fall 2005
- ❖ PQRI Newsletter

- The March 2005 newsletter will highlight PQRI volunteers.
- Financial contributors will be highlighted in June 2005.
- ❖ Color copies of the August newsletter were sent to volunteer labs and top management of those companies, along with a letter of appreciation from PQRI.

Other

- ❖ Global implications of proposed projects, data mining and safe harbor issues were also discussed.

If you have an idea for a future PQRI project, please send all written submissions to Gordon Hansen, Chair of the Steering Committee at gehansen@rdg.boehringer-ingelheim.com.

PQRI Primer: Meet the Board of Directors

PQRI would like to recognize its Board of Directors. Through their hard work, this unique collaborative body continues to play a positive and constructive role in the development of sound regulatory policy.

Of the five Directors, three are appointed by the Executive Council of the American Association of Pharmaceutical Scientists (AAPS) and two represent the PQRI Steering Committee. PQRI's current Board of Directors is as follows:

- ❖ Tobias Massa, Ph.D. (PhRMA), Chair
- ❖ Alexander Giaquinto, Ph.D. (AAPS)
- ❖ Gordon Hansen (IPAC-RS), Chair PQRI Steering Committee
- ❖ Robert Lipper, Ph.D., Treasurer (AAPS)
- ❖ Avraham Yacobi, Ph.D. (AAPS)

Directors serve for terms of two years each and there are currently no term limits. Sylvia Gantt, PQRI's Executive Secretary, acts as a non-voting member. Government representatives are not eligible to serve.

"It's been an honor and a privilege to serve on PQRI's Board of Directors," stated Chair, Toby Massa, Ph.D. (PhRMA). "In order for PQRI to function to the best of its ability, it is essential for the Board of Directors and the Steering Committee to work towards a common goal."

The Board's primary responsibilities focus on the administrative management and operation of the Institute, except for those activities involving scien-

tific decision making, which are delegated to the PQRI Steering Committee. The Board meets two to four times per year to provide oversight on backing of PQRI projects, fundraising activities, workshop approval, staffing, and financial management. Board members receive no compensation or expenses from the Institute for Institute activities.

Over the past few years, the board has worked tirelessly to ensure that PQRI is well funded and that current scientific programs can move forward. Due in large part to their efforts, the Institute has secured funding from the following companies:

- Abbott Laboratories
- AstraZeneca Pharmaceuticals
- Eli Lilly & Company
- F. Hoffmann-La Roche Ltd
- Pfizer Inc.
- Proctor & Gamble Pharmaceuticals, Inc.
- Schering Plough Research Institute
- The P.F. Laboratories
- Aventis Pharmaceuticals
- Bristol-Myers Squibb Company
- DuPont Pharmaceuticals Company
- Merck & Company
- Novartis Pharmaceuticals Corporation
- Penwest Pharmaceuticals Company
- Prasco Laboratories
- Savient Pharmaceuticals
- Powrex Corporation

Thanks to all of the PQRI Board Members for their efforts.

Interested in serving as a PQRI Volunteer? Contact

Sylvia Gantt at GanttS@PQRI.ORG.

