

Bringing Value to the Patient in a Changing World

2011 Conference Report

Rockville, Maryland, USA
March 29-31, 2011

INTRODUCTION

The International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS) held a conference entitled "Bringing Value to the Patient in a Changing World" on March 29-31, 2011 to discuss future directions and challenges of developing Orally Inhaled and Nasal Drug Products (OINDP). The conference was attended by more than 190 participants from 14 countries. The program featured an exceptional faculty of speakers, moderators and panelists from industry, academia and government. Through a combination of podium presentations, panel discussions, and poster sessions, participants reviewed and discussed key issues facing the OINDP industry, and the efforts that are being made to address these issues.

Plenary sessions at the IPAC-RS conference took a multi-faceted approach to assessing the current OINDP context and challenges by incorporating the perspectives of patients, physicians, health insurers, industry, and regulators. The first day included detailed discussions of patient needs, adherence, and patient centered product design. The second day focused on efforts to advance OINDP quality and characterization approaches and to improve and enhance their development. Practical solutions and efforts to address these topics were presented by the following IPAC-RS Working Groups: Analytical Methods, Cascade Impaction (CI), Delivered Dose Uniformity (DDU) and Parametric Tolerance Interval Testing (PTIT), Materials, and Supplier Quality.

After two days of plenary discussions, participants attended three specialty workshops, which provided an opportunity for in-depth coverage and interactive discussions on (1) leachables and extractables and OINDP material selection; (2) abbreviated impactor measurements and efficient data analysis of aerodynamic particle size distributions; and (3) patient, payor/healthcare purchaser industry and health-care professional perspectives on patient adherence with inhaled therapies.

Judging by spontaneous feedback and submitted evaluation forms, the IPAC-RS 2011 Conference met its goal of making the voice of the customer more central in dialogue between industry and regulators regarding best scientific and regulatory approaches to OINDP.

Slide presentations and posters are available at:
<http://ipacrs.com/2011%20Conference.html>



IPAC-RS 2011 Conference Organizing Committee:

Sue Holmes, Co-Chair, GlaxoSmithKline

Cheryl Stults, Co-Chair, Novartis

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Frank Cerasoli, Pfizer

Tim Chesworth, AstraZeneca

Frank Koppenhagen, Teva

Paul Lucas, Pfizer

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Martin Shott, Vectura

Mary Ann Smith, Novartis

Patricia Watson, Boehringer Ingelheim

Eileen Wyka, MannKind Corporation

Day 1 Morning Focus: Voice of the Customers

Session Chairs:
Martin Shott (Vectura) and
Mary Ann Smith (Novartis)

Key Messages and Recommendations

- For asthma and COPD patients, quality of life is important.
- Arthritis : RA is different from OA. Likewise, asthma has different phenotypes.
- A greater investment in COPD treatment, might help reduce overall healthcare costs.
- Greater patient specificity may lead to greater predictability in clinical trials.
- One could get 50% fewer exacerbations without any improvement in FEV1.
- A good picture (in patient instructions) is worth a thousand words.
- Misunderstanding during patient training and of labeling is higher for complex orally inhaled drugs.
- Match device to the patient not patient to the device.
- Patients would be more compliant if there were only three steps in patient instructions.

Summaries of presentations:

Asthma and its Many Unmet Needs: Directions for Novel Therapeutic Approaches

William W. Busse, M.D. Professor of Medicine; Allergy, Pulmonary and Critical Care Medicine, University of Wisconsin

Dr. Busse explained that “asthma” is not one disease but many. Accordingly, future medicines will have to be more precise in targeting the specific underlying cause (which in some cases is not well understood yet).

William W. Busse, M.D.

Professor of
Medicine; Allergy,
Pulmonary and Critical
Care Medicine, University
of Wisconsin



COPD Patient's Needs

Stephen I. Rennard, M.D., Professor, University of Nebraska Medical Center

Dr. Rennard emphasized the high burden that COPD exerts on individual patients and the society. He views COPD patients as largely under-served today, and encouraged all attendees to devote more efforts to development of effective medications.

A Global Perspective on Patient Educational Requirements and Needs Related to Inhaled Therapies

Monica Fletcher, Chief Executive, Education for Health

Ms. Fletcher described her organizations efforts to improve respiratory health of patients in both developed and developing countries.

Matching Patient to the Device

Søren Pedersen, M.D., Ph.D., Dr. Med. Sci, on behalf of ADMIT. Department of Pediatrics, Kolding Hospital; Professor of Pediatric Respiratory Medicine, University of Southern Denmark

Dr. Pedersen convincingly argued that design of devices should better take into account the needs of individual patients, so that devices are more intuitive and easier to use. He also encouraged the medical community to ensure that patients are checked regularly for verification and reinforcement of their inhalation techniques. Dr. Pederson's key recommendation was that “Focus should be redirected from in-vitro characterization to production and assessment of which inhalers are easiest to use correctly by various groups of patients and the importance of the individual steps in inhalation instructions.”

FDA Efforts on Liaising with Patients

Deborah J. Miller, Ph.D., RN, Health Programs Coordinator, Office of Special Health Issues, Food & Drug Administration

Dr. Miller reviewed the history of creation and growth of one of FDA's newer offices, focusing on Special Health Issues, especially for patients with HIV/AIDS. Current efforts with patient liaising focus on the patient representative program which is linked to Advisory Committee meetings.

Summary of the 2010 ISAM/IPAC-RS Equivalence Workshop, with a Focus on Patient-Related Aspects

Dennis O'Connor, Clinical Supplies Release Officer, Boehringer Ingelheim Pharmaceuticals; ISAM/IPAC-RS Workshop Organizing Committee

This presentation highlighted patient-related messages from the ISAM/IPAC-RS workshop (<http://ipacrs.com/beworkshop.html>) that explored requirements for demonstration of equivalence in orally inhaled products (OIPs) – such as when changes to a product are introduced post-approval, or when a generic manufacturer wishes to develop a copy of the brand-name drug.

Day 1 Afternoon Focus: Patient Interface

Session Chairs: Sue Holmes (GSK) and Paul Lucas (Pfizer)

Key Messages and Recommendations

There are many potential reasons for patients' poor adherence with medication. For orally inhaled therapies, the patient/device interface may present an additional challenge. This session focused on interface-related aspects of adherence, discussed potential solutions, and presented regulatory recommendations as well as industry's best practices regarding user testing of OIPs. Key insights included the following:

- Device usability is clearly critical, but is just one aspect of patient adherence. To improve overall adherence industry, regulators and health care professionals need to explore the many other aspects of non-adherence such as better education/training materials, more convenient dosing regimens, patient perceptions and behaviors.
- The rate of non-adherence is shockingly high, and we count the rate of errors [using devices] but we rarely discuss severity / consequences of errors.
- Devices used in clinical studies should be evaluated for patient-pertinent performance.
- Human factors analysis should be further integrated into risk management.
- Ratings are not helpful in human factor studies. Human factors is a game of words, not a game of numbers. If you can choose good responders, you could use fewer people to show effectiveness and have a more efficient study.
- Ease of use and user preference are not necessarily equal to optimal design.
- It would be to everyone's advantage to share information about user studies.
- Patients want medicine to fit into their life, not life fit their medicine and patient adherence is affected by their perception of their disease. Can we get to a point where medical device is seen as changing life for the better rather than marking a person appear as ill?
- Human Factors evaluations of device usability are gaining increased prominence in the regulatory review of medical devices and the need to conduct these specific studies, versus traditional analysis in clinical trials, is likely to begin to affect OIP development in the future.
- Marketing departments in other industries often makes better pictograms and better instructions for use than medical device and drug industry.
- We, physicians, need devices that report patient adherence to physician.
- The best inhaler is the one that's used. The most expensive inhaler is the one that the patient does not use.

Sue Holmes

GlaxoSmithKline,
Co-Chair, IPAC-RS
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Committee



Summaries of presentations:

Understanding and Addressing Patient Adherence and Overview of Workshop "Ensuring Patient Success: Improving Adherence Through Concordance"

Franklin Cerasoli, Jr., Ph.D., Senior Director, Allergy & Respiratory Team Leader, Pfizer, Inc.; Chair IPAC-RS Patient Adherence WG

Dr. Cerasoli emphasized the centrality of patient adherence to positive outcomes. He also discussed the consequences of non-adherence and barriers to adherence and described the vision for the patient workshop on Day three of the

conference, which was to acquire a better understanding of adherence and barriers to adherence from the perspectives of patients, health care professionals, and disease management and systems level.

The MDI – In Vitro Measures to Confirm Patient Perceptions: HFA vs. CFC

William H. Doub, Ph.D., Research Chemist/Division of Drug Analysis, OTR/OPS/CDER/FDA

Dr. Doub reviewed the issues associated with patient adherence from a regulatory point of view, explaining that while patient training and labeling is inadequate across the health industry, the statistics are especially poor for complex orally inhaled drugs (OIDs). He noted that the two key issues for patient adherence with orally inhaled and nasal drug products (OINDPs) are: synchronization of actuation/inhalation, and a lack of adequate shaking. Solutions he suggested included better training, better labeling, electronic measures, spacers or a valved holding chamber, and a better understanding of the factors influencing performance.

Lifting Medication Adherence: Lessons from Internet Connected Packaging

Joshua Wachman, President, Vitality, Inc.

The focus of Mr. Wachman's talk was on how well-designed technology can be utilized to improve medication adherence. He reviewed several examples of how packaging and technology can alter behavior (e.g., sensors and personalization) and presented a case study about the use of internet connected packaging for medications that provide feedback improved adherence.

Talking Packs: Making Packaging Part of the Treatment

Tim Chesworth, Device and Packaging Technology Team Manager, AstraZeneca

Mr. Chesworth provided an overview of how packaging can enhance patient adherence. He explained some of the key issues relating to patient adherence, such as remembering to take the medicine, having different sets of medicines, portability, aesthetics, and feedback between physicians and patients. His cross-functional team conducts efforts to address the patient's desire to have ownership of their treatment regime and feel in control.



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Attendees

Human Factors and the Design of Inhalation Devices

Stephen Eason, Director of Device Development, Vectura

Mr. Eason provided an overview of published literature on the use of inhalation devices and described how it could be used gain an understanding of approaches to human factors and how devices are used, as well as guidance on study design. Mr. Dixon considered best practices in inhalation device development with a focus on HE 75 and suggested that the existing human factors guidance is sufficient. They emphasized that industry is in the early phases of developing a consistent approach to human factors, and the need for conferences and dialogue to aid this process.

Human Factors "Usability" in the Review of New Medical Devices at FDA's Center for Devices and Radiological Health (CDRH)

Ronald D. Kaye, Human Factors Specialist, Center for Devices and Radiological Health, Food & Drug Administration

Mr. Kaye discussed the criteria for the review of new medical devices at the CDRH, noting that user preference and the ease of use did not necessarily amount to optimum design. Evaluation of patient adherence issues have two aspects: anticipated issues, which are known problems from expert reviews, and unanticipated issues, which are identified by user-based reviews.

Martin
Shott,
Vectura
and
Mary
Ann
Smith,
Novartis



Regulatory Expectations for User Testing

Paul Lucas, Ph.D., Research Fellow, Pfizer Global Chemistry Manufacturing and Controls

Mr. Lucas' talk described current expectations for user testing in the United States and Europe and the increasing focus on human factors testing as part of risk management. He noted that OIPs present challenges common to other devices such as the ability of the user to operate the device but also have specific regulatory and scientific challenges, and also emphasized the importance of post-marketing surveillance because of the possibility that new issues could arise as larger populations use devices.



Jim Jamieson
and
Mary Devlin
Capizzi,
IPAC-RS
Secretariat
Sam Shum,
MannKind
Corporation

Day 2 Morning Focus: Product Quality

Session Chairs: Stefan Leiner (BI) and Julie Berry (Merck)

Key Messages and Recommendations

- FDA is updating the MDI/DPI 1998 guidance to reflect a Quality-by-Design (QbD) approach to drug product development [e.g., per the ICH Q8(R2) guideline]. In addition, the Agency is seeking an opportunity to better understand new test methodologies and approaches to data analysis proposed by industry.
- A QbD approach to analytical method development could allow a greater understanding of measurement uncertainty and, as a result, lead to better process control as well as to provide a mechanism for continuous improvements in methods/processes. It is particularly important to understand upfront the measurement uncertainty (method variability) and its contribution to the observed overall variability for process and product.
- The default version of the 2005 PTI-TOST proposed by FDA for control of delivered dose uniformity would lead to rejection of a substantial proportion of fit-for-purpose batches. Therefore, the test has not been used therefore for approved orally inhaled products. To enable the use of a parametric tolerance interval (PTI) approach, which in principle is welcome by the industry, the default has to be modified, or product-specific PTI tests/criteria should be allowed, or an aggregate (as opposed to isolated-batch) approach should be followed.
- Efficient Data Analysis (EDA) for control of aerodynamic particle size distribution was shown to be at least as sensitive to even small changes in MMAD, and has a lower rate of decision errors compared to the current metrics (stage groupings or fine particle dose).
- Dissolution testing of inhaled drug products appears to be most promising as a development tool, e.g., for evaluating particle engineering approaches or probing formulation characteristics. The clinical significance and interpretation of dissolution results is far from understood. The method itself is not standardized; several different implementations have been published in the literature. There is no established statistical method for comparing dissolution data.

Summaries of presentations:

FDA View On Assessing Quality Of Inhaled Products And Links To Efficacy And Safety

Prasad Peri, Ph.D., Acting Branch Chief, Division of Pre-Market Assessment, Office of New Drug Quality Assessment, Food and Drug Administration

Since the issuance of the 1998 draft FDA guidance on chemistry, manufacturing and controls (CMC) of metered dose inhalers (MDIs) and dry powder inhalers (DPIs), the Agency has developed and promoted such important initiatives as “Manufacturing for the 21st Century” and “Quality By Design”. Dr. Peri explained how these newer concepts could be integrated in the development of, and regulatory submission for an inhalation product as the FDA revises the MDI/DIP 1998 guidance. In particular, Dr. Peri noted that the QbD approach should streamline regulatory review of post approval changes. He mentioned that a less prescribed, more quality/risk-based approach to MDI and DPI development would include, for example, linking material attributes and process parameters to specific critical quality attributes; identifying risks based on knowledge of product and process; and estimating risk by determining the probability of occurrence and severity of harm.

Dr. Peri also made the point that it would be beneficial to have a better understanding of what the target is, in terms of APSD, i.e. more specific clinical studies to look at how this could be utilized. He expressed Agency’s openness towards new technologies and approaches (e.g., AIM and EDA) and a desire to learn more about these opportunities.

Analytical Methods Quality by Design

Andy Rignall, Ph.D., Associate Director, Analytical Sciences, AstraZeneca, IPAC-RS QBD Analytical Methods WG

Quality-by-Design of pharmaceutical products involves not only understanding and building Design Spaces for the product performance and manufacturing parameters, but also understanding variabilities and capabilities of the analytical methods that are used to evaluate product performance and manufacturing processes. Using delivered dose uniformity (DDU) as a study case, Dr. Rignall illustrated the multitude of factors that can influence a DDU measurement from the “Method” perspective. He presented a prioritization matrix of most influential factors that was created by assigning a risk score (= Severity x Occurrence x Detectability) to each aspect of a DDU test method. Prior experience could be used to estimate severity, occurrence and detectability. Designed experiments could then be conducted to quantify major sources of variability. Control charts could be used to track performance over time.

For a comprehensive QBD approach, to error-proof and monitor the processes, method’s Design Space should be established. Moreover, QBD-type specifications would ideally be linked not to a prescriptive technique, but to an “Analytical Target Profile” that can ensure appropriate evaluation of the product performance using a range of possible analytical implementations. This strategy for developing a robust method highlights a broader way of thinking to implement new technologies and to incorporate prior learning.

So You Want to Use Parametric Tolerance Testing for Control of Delivered Dose Uniformity?

Greg Larner, Manager, Statistics, Pfizer, IPAC-RS DDU/PTIT WG

A consistent amount of the active pharmaceutical ingredient emitted by an inhalation product is one of the key quality attributes for such products. Traditionally, it has been controlled through a “delivered dose uniformity” (DDU) test. In 2001 IPAC-RS proposed an alternative, improved way for controlling DDU (see http://ipacrs.com/dose_uniformity.html for details), and in 2005, FDA proposed at an Advisory Committee a two one-sided test (TOST) using parametric tolerance interval (PTI) approach. Mr. Larner’s presentation explored the practical consequences of the FDA PTI-TOST and explained why this test has been difficult to use as a default quality standard. Overall, the PTI-TOST test set forth by FDA is viewed as less flexible than the counting test and imposes too high of a price for eliminating the zero-tolerance criteria of the current counting test.

Three potential solutions were presented: (1) changing the default PTI-TOST; (2) allowing modifications from the default as appropriate for individual products; (3) using aggregate approach as explained in existing consensus standards, rather than isolated-lot testing.

Additional considerations were presented in posters Influence of Stability Effects on Delivered Dose PTIT Acceptance Probabilities (by Hans-Joachim Delzeit and Stefan Leiner) and How PTI-TOST, Control Strategy Principles and Acceptance Sampling Consensus Standards can Work Together to Achieve an Appropriate Quality Assessment Strategy of Delivered Dose Uniformity of OIPs (by Helen Strickland, Lee Clewley and the IPAC-RS DDU/PTIT Working Group), which can be accessed at <http://ipacrs.com/posters2011.html>.

metrics, such as stage groupings in the US and fine particle dose in Europe. Dr. Tougas provided an overview of when to use EDA throughout a product life cycle. He then demonstrated that EDA is a robust and discriminating tool that can detect changes in particle size distributions at least as well as current metrics, and has lower probability of incorrect quality decisions. He introduced the concept of Operating Characteristic Curves (OCCs) in order to compare the utility of EDA and stage groupings which in simulation showed EDA metrics to be better suited for detecting differences in MMAD.

Dr. Tougas explained that EDA uses two metrics – (1) the ratio of Large Particle Mass (LPM) to Small Particle Mass (SPM) and (2) the impactors sized mass (ISM). These metrics are independent of each other and together provide a superior quality control tool for aerodynamic particle size distributions. For maximum sensitivity to MMAD changes, the boundary between LPM and SPM should be placed near MMAD (so that the typical ratio is in the range of 0.3-3.0).

Additional information on EDA has been published in peer reviewed papers and presented at other meetings – see <http://ipacrs.com/PDFs/Presentations.pdf> for details.

Dissolution Testing For Inhaled Products

Trevor Riley, Ph.D., Manager, Inhaled Product & Device Technology, GlaxoSmithKline and J. David Christopher, Associate Director, Statistics, Merck Research Laboratories, IPAC-RS Dissolution WG

For inhalation drug products, dissolution has been used as an exploratory tool by pharmaceutical companies, and recently received much attention in the published literature from academic researchers. The Working Group could not find any published studies demonstrating a relationship between dissolution and PK or other in vivo effect.

In a joint presentation, Dr. Riley and Mr. Christopher reviewed the pros and cons of published techniques – both analytical and statistical. They concluded that the although dissolution may play a role in product development, especially in special situations such as screening modified-release formulations, this type of in vitro test is currently neither required nor ready for inclusion as a compendial test for inhalation aerosols. Instead, it appears to be most promising as a development tool, e.g. for evaluating particle engineering approaches or probing formulation characteristics.

Further details were presented in the IPAC-RS Dissolution Working Group’s poster Summary of Techniques for Measuring Dissolution of Orally Inhaled Products: Review of Published Applications (at <http://ipacrs.com/posters2011.html>).

Day 2 Panel



Overview of Efficient Data Analysis

Terrence P. Tougas, Ph.D., Highly Distinguished Research Fellow, Boehringer Ingelheim, IPAC-RS Cascade Impactor WG

The efficient data analysis (EDA) of pharmaceutical aerosols has been developed by an IPAC-RS Cascade Impaction Working Group as an alternative to current quality control

Day 2 Afternoon Focus: Product Quality (continued)

Session Chairs:
Cheryl Stults (Novartis) and
Lennart Brunberg (SHL Group)

Key Messages and Recommendations

- Ensuring quality in the supply chain requires constant communication and partnering with suppliers all along the supply chain, as well as with regulators.
- Partnering with suppliers should encourage robust exchange of meaningful information and implementation of risk based controls that would help support component quality as well as final drug product quality, e.g., technical information, composition information, quality agreements, effective change control.
- Quality and risk-based approaches should be implemented with the whole life-cycle of the product in mind.
- Outreach to suppliers world-wide, including (and especially) those in emerging markets will be important going forward.

Summaries of presentations:

Outreach to the Global Pharma and Supplier Industry to Enhance Product Quality

Barbara A. Falco, Consultant/Owner, Barbara Falco Pharma Consult, LLC, IPAC-RS Supplier QC WG

Ms. Falco provided an update on the work of the IPAC-RS Supplier Quality Working Group's activities, describing the Group's development of the IPAC-RS GMP guideline for OINDP container closure system component suppliers, its current efforts to incorporate the guideline into PS9000:2011 in collaboration with the Pharmaceutical Quality Group (based in the UK), and its on-going efforts to liaise with suppliers world-wide regarding GMP and quality issues. Ms. Falco noted that the guideline and subsequent IPAC-RS outreach and education efforts to suppliers, OINDP manufacturers, and regulators have been successful but that ensuring quality in the OINDP supply chain requires on-going vigilance and effort, especially due to the global nature and complexity of the supply chain.

Collaborating with the Global Supply Chain on Materials Requirements and a Rationalized Testing Paradigm

James Mullis, Principal Scientist, Boehringer Ingelheim, IPAC-RS OINDP Materials WG

Mr. Mullis explained that the Materials Working Group held a number of substantive discussion forums with N-1, N-2 and N-3 suppliers to help suppliers and OINDP manufacturers understand the need for quality testing and technical information exchange among the supply chain and drug product manufacturers. In response to input from these forums, the Group articulated a vision

for changing the paradigm for testing and technical information exchange in line with quality by design approaches, and also developed a document explaining the baseline requirements for evaluation of quality in materials used for OINDP container closure systems. Mr. Mullis described feedback from suppliers on what suppliers are willing to do and what they need from OINDP manufacturers, the proposed new testing paradigm, and details of the baseline requirements.

During the panel discussion, an attendee asked why industry shouldn't consider working towards the use of common ingredients in materials and share information on these ingredients. Panelists noted that the Extractables and Leachables Information Exchange is working towards sharing safety information on individual extractables/leachables and extractables profiles from commonly used materials.

Supply Chain Approaches to Ensuring Component Quality

Ken Chesney, Global RA/QA/Quality Engineering, Flextronics

Mr. Chesney used Flextronics as an example of how a supplier might set up its internal quality management systems and communications platforms to meet the global requirements of their customers (with respect to global regulatory requirements). He explained how his company has also provided input to Global Harmonization Task Force documents addressing medical devices.



Cheryl Stults

Novartis,
Co-Chair, IPAC-RS
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Regulatory Perspectives on Supply Chain Quality and Security

Vibhakar Shah, Ph.D., Senior Policy Advisor, Division of Manufacturing and Product Quality, Office of Compliance, Food and Drug Administration

Dr. Shah provided perspectives from the Office of Compliance, Division of Manufacturing and Product Quality. He presented compiled examples of post-market problems/complaints from patients linked to quality/performance of products. He noted that ICH Q9 on risk management is a useful tool for managing the supply chain, that continuous improvement should be an expectation for the supply chain as well as management of the supply chain, that supplier management is part of the lifecycle approach to products, and noted that quality by design approaches such as continuous process verification and PAT would ideally be adopted within the supply chain (e.g., FDA is interested in suppliers looking at process validation guidelines). He noted supply chain security as an issue.

Dr. Shah noted during the panel discussion that one of the biggest issues in understanding and managing quality and safety of materials is the lack of knowledge of those materials due to trade secrets.

Posters

Throughout both days of the main conference, attendees were given the opportunity to view more than 30 posters and select the top three. Some of the posters supplemented information discussed from the podium, while many others presented new aspects or new topics pertinent to the OINDP development, quality, patient interface, and regulatory trends.

The top three posters voted “Best” by the attendees were:

1st Prize

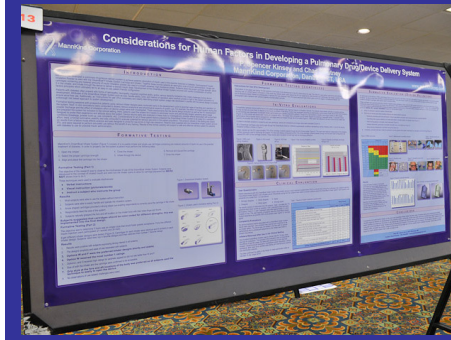
Considerations For Human Factors In Developing A Pulmonary Drug/Device Delivery System (by P. Spencer Kinsey and Chad Smutney)

2nd Prize

Design of Experiments to Optimize an In Vitro Nasal Cast to Predict Human Nasal Drug Deposition (by Samir Shah, Chris George, Walter Horodnik, Joel Sequeira, David Monteith, Colin Dickens, Anna Banaszek, David Ward)

3rd Prize

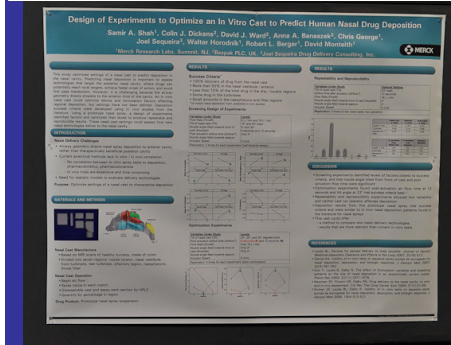
Pressure Profiling In Development of a Dry Powder Delivery System (by Chad Smutney, Benoit Adamo, John Polidoro, Brendan Laurenzi, Carl Sahi)



1st Prize

Considerations For Human Factors In Developing A Pulmonary Drug/ Device Delivery System

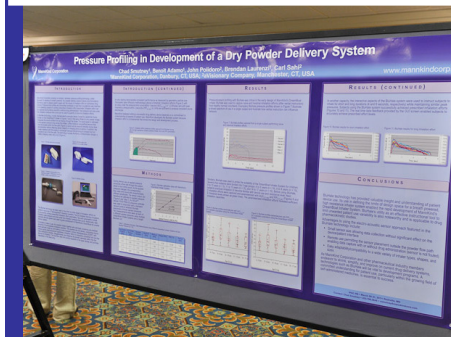
<http://ipacrs.com/PDFs/IPAC-RS%202011%20Conference/Posters/13-MannKind.pdf>



2nd Prize

Design of Experiments to Optimize an In Vitro Nasal Cast to Predict Human Nasal Drug Deposition

<http://ipacrs.com/PDFs/IPAC-RS%202011%20Conference/Posters/8-Shah.pdf>



3rd Prize

Pressure Profiling In Development of a Dry Powder Delivery System

<http://ipacrs.com/PDFs/IPAC-RS%202011%20Conference/Posters/12-MannKind.pdf>

Further information about the poster session is available at <http://ipacrs.com/posters2011.html>.



Poster Winners: (L) to (R) Chad Smutney, Benoit Adamo and Spencer Kinsey (MannKind Corporation), Samir Shah (Merck) and Jackie Schumacher, IPAC-RS Chair (Pfizer), Stefan Leiner, IPAC-RS Vice Chair (Boehringer Ingelheim)

Workshop #1: Leachables & Extractables

Presenters:

Cheryl L.M. Stults, Ph.D., Senior Fellow, Novartis
Daniel L. Norwood, Ph.D., Distinguished Research Fellow, Boehringer Ingelheim
Guirag Poochikian, Ph.D., Consultant, Poochikian Pharma Consulting
Thomas N. Feinberg, Ph.D., Director of Structural Chemistry, Catalent Pharma Solutions
William P. Beierschmitt, Ph.D., DABT, Regulatory Strategy Lead, Pfizer
Andrea Mieth, Ph.D., Analytical Expert, Sandoz
Jason Creasy, Manager E&L Team, GlaxoSmithKline
Kumudini Nicholas, B.Sc., M.Sc., Advisor/Team Leader, Generic Drugs Quality Division II, Health Canada

This Workshop addressed questions and experiences to date that companies have had with the PQRI Recommendations for L&E in OINDP. The Workshop provided an overview of the Recommendations; a look back at the history of how L&E became an issue of concern for FDA (including case studies); case studies from industry discussing application of and challenges related to the Recommendations; and open discussion among the participants and panelists. The open discussion included discussion from regulators (FDA and Health Canada) and industry experts on questions such as:

- How can routine testing for materials be incorporated into risk management approaches, especially for DPIs?
- How does one set specifications on incoming material for routine testing (taking into consideration L&E correlations)? Is the acceptance criterion set at maximum observed concentration levels? Is it appropriate to create an artificial range? Would Mean plus 3 Standard Deviations be advisable?
- What is the role of biocompatibility testing in the safety qualification process? Are there any thoughts regarding whether these tests might be replaced by other more current tests?

Workshop #2: AIM/EDA – Implementing a New Best Practice for OIP Aerosol Particle Size Analysis

Presenters:

Lana Lyapustina, Ph.D., Senior Science Advisor, Drinker Biddle & Reath
Terrence P. Tougas, Ph.D., Highly Distinguished Research Fellow, Boehringer Ingelheim
Rajni Patel, Ph.D., Director, Pharmaceutical Analytical Development, Boehringer Ingelheim
Jolyon P. Mitchell, Ph.D., Scientific Director, Trudell Medical International
J. David Christopher, Associate Director - Statistics, Merck
Helen Strickland, Statistical Consultant, Global Manufacturing and Supply, GlaxoSmithKline
Adrian Goodey, Ph.D., Senior Scientist, Merck

During this workshop, members of the IPAC-RS CI Working Group presented for their colleagues from industry, FDA, EMA and US pharmacopeia the justification, technical details, and regulatory considerations for efficient data analysis (EDA) and abbreviated impactor measurements (AIM) of aerodynamic particle size distributions (APSDs). An APSD has been recognized as one of the critical quality attributes of inhalation aerosols, although direct in-vitro in-vivo correlations that could assist in establishing clinically-based quality requirements, have been elusive. Due to its importance, an inhaled product's APSD is (1) thoroughly tested during development; (2) carefully controlled for quality during commercial phase; and (3) used as one of in-vitro tests of equivalence for follow-on products or when changes to the original product is introduced.

The EDA concept has been developed specifically for the quality-control purposes (item 2 above) as an alternative to current quality

- Quite vigorous extraction techniques are described in the Recommendations. How can you mitigate the extraction to make sure that the extraction process is not creating altered material?
 - What is the next "hot" topic for L&E?
- The discussions on these questions will be summarized in an upcoming separate report on the L&E Workshop.

Key Messages and Recommendations:

- The PQRI Recommendations for OINDP have been very useful for companies. However some key challenges exist, e.g., how to develop a reasonable AET for low dose, high volume inhalation products (same issue as is being worked out for Large Volume Parenterals in the PQRI PODP).
- The PQRI Recommendations are comprehensive but are not meant to be prescriptive. As such, they can work in concert with companies' risk-based approaches to developing extractables and leachables programs for their specific products. The Recommendations should not simply be followed "blindly." Perhaps this needs to be discussed through future IPAC-RS workshops, case studies, papers, etc.
- The quality of OINDP depends on controls for leachables and extractables being established throughout the supply chain. It is important for cross-disciplinary teams within Pharma and their suppliers to work together to establish such controls and minimize the impact of materials or processes on OINDP safety and quality.
- IPAC-RS should consider and identify specific issues that still need to be addressed for leachables/extractables in OINDP

control metrics (stage groupings in the US and fine particle dose in Europe). EDA can be used either with full-resolution impactor data or with AIM, which offers additional efficiencies.

The "What? Why? and How?" of AIM and EDA were addressed in the following presentations:

- Lifecycle Strategies for Using EDA, AIM and Full Resolution Impactor – Terry Tougas
- Control Strategies for APSD – Rajni Patel
- Equipment Options for AIM and Beyond – Jolyon Mitchell
- Precision and Accuracy of AIM – Dave Christopher and Rajni Patel
- Considerations for Applying EDA to an Existing Product - Helen Strickland
- Road to Adopting AIM/EDA as a Standard – Adrian Goodey

Additional information on EDA has been published in peer reviewed papers and presented at other meetings – see <http://ipacrs.com/PDFs/Presentations.pdf> for details.

Key Messages and Recommendations:

- AIM and EDA are different concepts. AIM is about equipment. EDA is about data analysis (which can be used either with AIM or a full-resolution impactor).
- EDA has a sound basis and worked-up examples. There is interest from industry, regulatory agencies and pharmacopeias.
- More specific data and information on AIM and EDA should be made available (see <http://ipacrs.com/PDFs/Presentations.pdf> for published data).

Workshop #3: Ensuring Patient Success: Improving Adherence Through Concordance

Presenters:

Franklin Cerasoli, Jr., Ph.D., Senior Director, Allergy & Respiratory Team Leader, Pfizer
Nancy Sander, President & Founder, Allergy & Asthma Network - Mothers of Asthmatics
Sandra Fusco-Walker, Director of Patient Advocacy, Allergy & Asthma Network - Mothers of Asthmatics
John W. Walsh, President & CEO, Alpha-1 Foundation
Barbara Yawn, M.D., FAAFP, Director of Research, Olmsted Medical Center
Suzanne Lareau, RD, MS, FAAN, Senior Instructor, College of Nursing, University of Colorado
Leonard Fromer, M.D., FAAFP, Executive Medical Director, Group Practice Forum
Peter F. Hayes, Principal, Healthcare Solutions
Jake Flaitz, Director - Benefits & Human Capital, Paychex, Inc.

The Ensuring Patient Success workshop highlighted key challenges to adherence and methods to improve adherence through presentations by patient advocates, health care professionals, and disease management professionals and breakout discussions. Key messages from the workshop were that there is a need for a better understanding of challenges from different perspectives and increased education and communication between all involved in treatment.

Perspectives on Adherence:

- For patients (as presented by Ms. Sander and Ms. Fusco-Walker) there are numerous challenges to medication adherence and there can be important consequences including unplanned doctors visits and in some cases visits to the emergency room. Tools such as asthma action plans as well as continued communication between health care professionals, care providers, the patient and other stakeholders is key; there are also policy issues that are relevant to patients.
- For health care professionals, (as presented by Dr. Barbara Yawn and Ms. Lareau), there are important distinctions between compliance, adherence, and concordance; the patient has an increasingly active role in each, as does communication. COPD and asthma patients face some of the same challenges, although there are some challenges unique to each, including cognitive issues in many COPD patients. Different types of non-adherence (erratic, unwitting and intelligent) exist, and it is important that HCPs and patients are intentional about exploring non-compliance because non-adherence results in sub-optimal treatment.

- Recognizing the fullness of the patient experience, including time spent within and outside the doctors office as well as support from the practice and family is important from the payer/healthcare purchaser perspective. There are several essential attributes of patient care experiences in primary care, including trust, access, continuity, and others, which should be considered. Critical elements of success include leadership, measurement, system-level changes, and public reporting as well as health literacy and collaborative care.

Key Messages and Recommendations:

Participants in the Health Care Professional Breakout sections agreed that education of health care professionals and patients, reimbursement of physician and asthma instructors for patient education, clear instructions for use, and training tools, regular adherence assessments, evaluation of tool effectiveness, and evaluation of regional differences are needed to resolve adherence problems. They also discussed the imperative for consumer-friendly instructions. For Patient breakout session participants agreed on the need for clear definitions and understanding, the need to engage patients through active listening and feedback as well as intention to improve adherence. Participants in the Disease Management Breakout session agreed that there was a need for: a trusted third party to provide information on disease management; to reward value delivery and outcomes; for employers and providers to jointly discuss insurance options with providers; to reward long-term results; and to develop a concept of balance between standardized and personalized medicine.

Slides from the workshop are available here:
<http://www.ipacrs.com/2011%20Conference.html>.



Workshop #3

General Information about IPAC-RS

IPAC-RS is an international consortium of companies that develop, manufacture or market orally inhaled or nasal drug products (OINDPs).

IPAC-RS is committed to advancing consensus-based, scientifically driven standards and regulations for these products, with the purpose of facilitating the availability of high-quality, safe, and efficacious drug products to patients.

Current IPAC-RS Members are 3M, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, MannKind Corporation, Merck, Novartis, Pfizer, Teva, Vectura Ltd.
Associate members are Aptar Pharma, Rexam, SHL Group and West.

Visit the IPAC-RS website at www.ipacrs.com