CROSS-INDUSTRY Organizations

IPAC-RS: 15 years of research, advocacy and consensus building

Susan Holmes, MS; Mary Devlin Capizzi, JD; Lee Nagao, PhD and Svetlana Lyapustina, PhD
GSK and Drinker, Biddle and Reath, LLP

2016 will mark the fifteenth anniversary of the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS), which is an association of companies that manufacture and develop orally inhaled and nasal drug products (OINDPs). But the Consortium's history started in the twentieth century.

In response to FDA draft guidances

In October 1998, the US Food and Drug Administration (FDA) published a draft guidance titled "Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls [CMC] Documentation."[1] Companies developing MDIs and DPIs applauded the fact that FDA had described, in a public guidance, its CMC expectations for inhalation products. However, companies also found many of the requirements in the draft guidance unjustifiably stringent and incommensurate with the diversity of products on the market and especially in development. That diversity was due, in part, to a circumstance outside of industry's control: in the 1990s, industry had to reduce reliance on chlorofluorocarbons (CFCs) as MDI propellants in compliance with the international environmental treaty called the Montreal Protocol. A large number of new products entered the pipeline using replacement propellants or novel delivery systems without propellants.

A few months after publication of the above-mentioned CMC draft guidance, FDA published the draft guidance "Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action,"[2] which also caused concerns in the industry. At the time, however, there was no organization focusing exclusively on the regulatory issues of the OINDP industry. An ad hoc regulatory guidance commenting group was convened within the International Pharmaceutical Aerosol Consortium (IPAC), which generally addressed the legal and technical issues related to the Montreal Protocol. The only other OINDP-focused forum was the Inhalation Technology Focus Group (ITFG) of the American Association of Pharmaceutical Scientists (AAPS), which represented individual scientists rather than companies, and included academicians, students and clinicians in addition to industry experts, meeting once or twice per year to discuss technological, scientific and other relevant news.

An initial collaboration

During a June 1999 public workshop co-sponsored by the FDA, USP and AAPS, titled "Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery," an IPAC industry representative proposed a collaborative initiative to gather data and prepare a collective industry response to the guidances. A senior FDA representative supported this proposal. Later that year, IPAC and ITFG met to consider how an industry collaboration could be established and effectively managed, in order to deliver the data-based responses to the draft guidances before their finalization. By 2000, an ITFG/IPAC Collaboration was formed.

Several Technical Teams were established by the IPAC/ITFG Steering Committee: CMC Specifications (with Subgroups for Delivered Dose Uniformity and Particle Size Distribution); CMC Leachables and Extractables; CMC Tests and Methods; Supplier Quality Control; and Bioequivalence and Bioavailability. The Collaboration also hired a third-party Secretariat, which provided legal, scientific, project management, administrative and other services, and served as a neutral party enabling confidential surveys and database collections. By 2001, the Collaboration submitted several technical reports to the FDA and presented at FDA Advisory Committee meetings, thereby completing its initial remit limited to the 1998-1999 draft guidances. However, the companies were interested not only in addressing certain requirements in the draft guidances, but also in developing improved methods for controlling OINDP quality and demonstrating bioequivalence. The IPAC-RS consortium was formed to work on these issues.

The IPAC-RS Organization

From the beginning, IPAC-RS was organized as an association of companies (rather than individuals), with a focus on practical advancements in OINDP regulatory science. At the same time, IPAC-RS stayed true to its collaborative nature and, where appropriate, actively engaged with the USP Aerosol Expert Committee and its European counterpart Inhalanda, the FDA, the Product Quality Research Institute (PQRI), the European Pharmaceutical Aerosol Group (EPAG), the International Society for Aerosols in Medicine (ISAM) and other stakeholders. The number of companies involved in IPAC-RS has varied over the years, and is currently

at 16. In addition, suppliers of OINDP devices and device components participate in pertinent working groups as associate members of IPAC-RS, with four such members active currently.

IPAC-RS output

Many of the final deliverables from IPAC-RS have been published in peer-reviewed journals (Table 1), presented at scientific meetings (including RDD and DDL) and discussed in meetings with regulators (e.g., FDA, European Medicines Agency, Health Canada, Brazilian ANVISA, and China Food and Drug Administration). Several handbooks and comprehensive guides have also been produced, such as a handbook covering best cascade impaction practices, abbreviated impactor measurements (AIM) and efficient data analysis (EDA), which is now being translated into Chinese; a Leachables and Extractables handbook, already available in a Chinese translation; and a GMP guideline for manufacturers of OINDP container closure system components, in collaboration with the UK-based Pharmaceutical Quality Group (PQG). The latter GMP guideline is considered by industry, suppliers and regulators as a go-to source for GMP compliance and best practices with respect to container closure systems/packaging. IPAC-RS has also organized several public conferences and training courses (Table 2) to share and discuss results of its work with the broader community.

Anticipating a productive fifteenth year

IPAC-RS is entering its fifteenth year with a full portfolio of active projects, as well as educational activities promoting best practices and recommendations developed over the previous years. The current work is carried out via four workstreams: Delivery Systems; CMC and Product Development Tests; Bioequivalence and IVIVC; and General Outreach (see http://ipacrs.org). The newer Working Groups formed to address recent regulatory challenges include Combination Products, Human Factors, Instructions for Use and others. In April 2016, IPAC-RS will hold a coordinated symposium with RDD to debate new regulatory approaches in the US and other world regions, review the global regulatory environment for OINDPs, showcase a number of industry case studies, and highlight best practices for OINDP device design and patient-centric product development. In addition, plans are forming for future workshops beyond 2016 to ensure opportunities for ongoing scientific discourse on topics of interest to OINDP industry and regulators.

Remembering Gordon Hansen

This article is dedicated to the memory of our dear colleague and friend, Gordon Hansen, who passed away in 2015 after a valiant battle with cancer. Gordon Hansen was one of the "founding fathers" of IPAC-RS. He played a crucial role in envisioning a collaborative effort that would benefit industry, the wider scientific and regulatory community, and patients. He served as the first Chair of the IPAC-RS Board of Directors and held numerous other leadership positions in the Consortium over the years. Gordon's scientific expertise, integrity, deep knowledge of both industry and the regulatory environment, and an unparalleled skill at consensus-building even on controversial topics, allowed this industry to come together and advance common causes in effective and constructive ways.

References

1. 1998 FDA Draft CMC Guidance is available at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070573.pdf

2. 1999 FDA Draft BA/BE Guidance is available at http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3609b1l.pdf

Susan Holmes, MS (of GSK) is current Chair of the IPAC-RS Board of Directors. Mary Devlin Capizzi, JD serves as Legal Counsel, and Lee Nagao, PhD and Svetlana Lyapustina, PhD as Science Advisors for the IPAC-RS Secretariat. The Pharmaceutical Practice Group of Drinker, Biddle and Reath, LLP (DBR) provides legal counsel and secretariat services to IPAC-RS and other industry consortia. Corresponding author: Svetlana Lyapustina, PhD, 1500 K Street NW, Washington, DC, 20005, US, Tel: +1 202 230-5607, Svetlana.Lyaustina@dbr.com. Website: www.ipacrs.org.

Table 1

Key IPAC-RS Publications

Year	Title	Publication and Link
2016	Risk Management for Materials and Components Used in Orally Inhaled and Nasal Drug Products	Pharmaceutical Research. 2016; 33(1):1-17. (Link)
2015	Current Scientific and Regulatory Approaches for Development of Orally Inhaled and Nasal Drug Products: Overview of the IPAC-RS/University of Florida Orlando Inhalation Conference	AAPS Journal. Themed Issue. 2015. (Link)
	A Risk Based Approach to Management of Leachables Using Statistical Analysis of Extractables	AAPS PharmSciTech. 2015; 16(2):315-326. (Link)
2014	Gaps in Statistical Approaches to Control of Delivered Dose Uniformity throughout Product Lifecycle	Inhalation Magazine. 2014. (Link)
2013	Good Cascade Impactor Practices, AIM and EDA for Orally Inhaled Products	Book published by Springer. 2013. (Link)
2012	Challenges with Developing *In Vitro* Dissolution Tests for Orally Inhaled Products (OIPs)	AAPS PharmSciTech; 2012; 13(3):978-989. DOI: 10.1208/s12249-012-9822-3. (Link)
	Leachables and Extractables Handbook: Safety Evaluation, Qualification, and Best Practices Applied to Inhalation Drug Products	Book published by Wiley. 2012. (Link)
	Equivalence Considerations for Orally Inhaled Products for Local Action - ISAM/IPAC-RS European Workshop Report	J. Aerosol Med Pulm Drug Delivery; 2012; 25(3):117-139. DOI: 10.1089/jamp.2011.0968. (Link)
2011	Challenges and Opportunities in Implementing the FDA Default Parametric Tolerance Interval Two One-Sided Test for Delivered Dose Uniformity of Orally Inhaled Products	AAPS PharmSciTech; 2011; 12(4):1144-1156. DOI: 10.1208/s12249-011-9683-1. (Link)
2010	Advancing Quality of Materials Through Collaboration with the Supply Chain: The Work of the IPAC-RS OINDP Materials Working Group	Proceedings Extractables and Leachables for Pharmaceutical Products; 2010; RAPRA; September 2010.
2009	Use of Polymeric Materials in Orally Inhaled and Nasal Drug Products	European Medical Device Technology; 2009; 20(2):32-38. (Link)
	A Two One-Sided Parametric Tolerance Interval Test for Control of Delivered Dose Uniformity Part 1 –Characterization of FDA Proposed Test	Part 1: AAPS PharmSciTech; 2009; 10(3):820-828. DOI: 10.1208/s12249-009-9270-x. (Link)
	Part 2 – Effect of Changing Parameters	Part 2: AAPS PharmSciTech; 2009; 10(3):841-849. DOI: 10.1208/s12249-009-9269-3. (Link)
	Part 3 – Investigation of Robustness to Deviations from Normality	Part 3: AAPS PharmSciTech; 2009; 10(3):829-840. DOI: 10.1208/s12249-009-9271-9. (Link)
	Device Development and Design Control for Combination Products: Standards, Regulations and Current Practices for Orally Inhaled and Nasal Drug Products	IPAC-RS. 2009. (Link)
2008	Quality By Design for Analytical Methods Intended for Use With Orally Inhaled and Nasal Drug Products (OINDPs)	PharmTech Europe; 2008; 20(10) and PharmTech Asia Pacific; 2008; 2(4).

2008	Minimizing Variability of Cascade Impaction Measurements in Inhalers and Nebulizers	AAPS PharmSciTech; 2008; DOI: 10.1208/s12249-008-9045-9. (Link)
2007	Best Practices for Managing Quality and Safety of Foreign Particles in Orally Inhaled and Nasal Drug Products, and an Evaluation of Clinical Relevance	Pharmaceutical Research; 2007; 24(3). (Link)
	Comparison of Two Approaches for Treating Cascade Impaction Mass Balance Measurements	J. Aerosol Med; 2007; 20(3):236-256. (Link) Correction: J. Aerosol Medicine and Pulmonary Drug Delivery. 2008; 21(1):155-156. (Link)
	Product Quality Research Institute Evaluation of Cascade Impactor Profiles of Pharmaceutical Aerosols Part 1: Background for a Statistical Method	Part 1: AAPS Pharm Sci Tech. 2007; 8(1):E32-E37. DOI: 10.1208/pt0801004. (Link)
	Part 2: Evaluation of a Method for Determining Equivalence	Part 2: AAPS PharmSciTech. 2007; 8(1):E39-E48 DOI: 10.1208/pt0801005. (Link)
	Part 3: Final Report on a Statistical Procedure for Determining Equivalence	Part 3: AAPS PharmSciTech. 2007; 8(4):65-74 DOI: 10.1208/pt0804090.(Link)
	In Vitro/In Vivo Comparisons in Pulmonary Drug Delivery	J. Aerosol Med. 2007; 20(2):211.
2006	GMP Guideline for Suppliers of OINDP Device Components	IPAC-RS. 2006. (Link)
	Safety Thresholds and Best Practices For Extractables and Leachables In Orally Inhaled and Nasal Drug Products	Submitted to FDA. 2006.
	Zero-Tolerance Criteria Do Not Assure Product Quality	Pharm.Tech; 2006; 30(1):52-60.
2005	Microbial Testing for Orally Inhaled and Nasal Drug Products	USP Pharmacopeial Forum; 2005; 31(4):1258-1262.
2004	Foreign Particles Testing in Orally Inhaled and Nasal Drug Products	Pharmaceutical Research; 2004; 21(12).
	Debating the Parametric Operating Curves for DDU Tests on Marketed Inhalers	Respiratory Drug Delivery IX; (VCU/DHI, ISBN 1-930114-63-X) 2004; I:135-141.
2003	Considerations for the Development and Practice of Cascade Impaction Testing Including a Mass Balance Failure Investigation Tree	J. Aer Med; 2003; 16(3):235-247. (Link)
2002	Recommendations to the Food and Drug Administration: Metered Dose Inhaler Tests and Methods in the Chemistry, Manufacturing, and Controls Draft Guidances for Metered Dose Inhalers and Dry Powder Inhalers	Drug Information Journal; 2002; 36(3):549-556.
2001	A Parametric Tolerance Interval Test for Improved Control of Delivered Dose Uniformity of Orally Inhaled and Nasal Drug Products	Submitted to FDA. 2001.
	Leachables and Extractables Testing: Points to Consider	Submitted to FDA. 2001.
	Recommendations for Tests and Methods	Submitted to FDA. 2001.
2000	Initial Assessment of the ITFG/IPAC Dose Content Uniformity Database by the CMC Specifications Technical Team of the ITFG/IPAC Collaboration	Submitted to FDA. 2000. (Link)
	Initial Assessment of the ITFG/IPAC Aerodynamic Particle Size Distribution Database by the CMC Specifications Technical Team of the ITFG/IPAC Collaboration	Submitted to FDA. 2000. (Link)

Table 2

Key IPAC-RS Conferences and Training Courses

Year	Title
2015	ISAM/IPAC-RS Device Design Workshop (Munich, Germany)
2014	University of Florida/IPAC-RS Bioequivalence Conference (Orlando, FL, US)
2011	IPAC-RS Conference (North Bethesda, MD, US)
2010	Materials Forum (Philadelphia, US and Barcelona, Spain)
2010	ISAM/IPAC-RS Bioequivalence Workshop (Frankfurt, Germany)
2008	IPAC-RS Conference (Rockville, MD, US)
2006	PQRI Leachables and Extractables Recommendations for OINDP Workshops (led by IPAC-RS)