A "Compare and Contrast" of International Guidelines Impacting the Pharmaceutical and Clinical Development of New and Subsequent Market Entry OINDPs Part B: CMC

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INTRODUCTION

As noted in Part A, IPAC-RS has collaborated with EfPIA and other interested parties to provide a consolidated industry view and perspective during the discussion with the EMEA's QWP for the current Pharmaceutical Guideline for Orally Inhaled Products. Participation in these activities prompted IPAC-RS to prioritize the importance of maintaining an active international focus.

Other activities ongoing in the IICG are influencing and responding to current draft regulatory guidances while developing a comprehensive working tool (grid) describing the international regulatory landscape for OINDP. This poster is a small snapshot of the work product from the OINDP regulatory compendium, i.e. "grid".

DISCUSSION

The EMEA/Health Canada (2006) and FDA (draft 1998 (oral) and 2002 (nasal)) guidelines outline expectations for product characterization studies to be presented in marketing applications. These guidelines were developed before or in parallel with the ICH quality topics Q8, Q9, and Q10. As a result, the inhaled guidelines do not reflect fully the principles espoused in ICH Q8, Q9, and Q10. The characterization tests (Table 1), which may be linked to critical quality attributes, are not exhaustive. With focus on product knowledge, good science and enhanced process understanding, the characterization studies should support the establishment of the design space, specifications, and manufacturing controls. Hence, additional testing, based on product knowledge, may or may not be necessary.

Medicinal Product Guidelines.

In general, the OINDP CMC specific guidance documents apply to products intended for delivery of the active into the lungs, or to the nasal mucosa, with the purpose of evoking a local or systemic effect. Additionally, these guidelines, outline expected quality aspects of OINDP to be marketed, but the general principles should also be considered for products used in clinical trials. In the case of post approval modifications, the regulatory agencies have indicated that the general principles should also be considered.

Extensive characterization of the drug substance and drug product batches used in pivotal clinical trials has been defined as a necessity to qualify the product proposed for marketing, i.e. new marketing authorization applications and generic products.

These guidance documents have been developed for products containing drug substances of synthetic or semi-synthetic origin. However, the general principles described here should also be considered for other inhalation and nasal products, e.g. biotech, macromolecules.

Medical Device Requirements.

In the EU, the pulmonary inhaler may be considered a medical device governed under Directive 93/42/EEC, as amended by 2007/47/EC. Depending on the nature of the risk associated with the inhaler/delivery system and/or active being delivered, the inhaler is classified accordingly. The majority of MDIs and DPIs are Class I devices, although there are some instances of Class II.

Table 1. Comparison of FDA and EMEA/Health Canada Orally Inhaled Drug Product Performance Characterization Studies

Study	MDI	DPI		Nasal Spray	Inhalation Spray	Inhalation Soln/Suspn
		Device-Metered	Pre-Metered			
Relevant to Label/Instructions						
Stability	X, Z	X, Z	X, Z	X, Z	X, Z	X, Z
Priming/Re-priming	X, Z	X		X, Z	X, Z	
Shaking	X, Z			X		X, Z
Cleaning Requirements	X, Z	X, Z	X, Z	X, Z	X, Z	Z
Use/Misuse						
Temperature Cycling	X, Z			X	X	X (suspension)
Low Temperature Performance	Z					
Effect of Resting Time	X				X	
Dose Build-up and Flow Resistance		X	X			
Effect of Orientation	X, Z	X, Z	X, Z	X, Z	X, Z	Z
Effect of Patient Use		X	X			
Device Ruggedness/ Robustness	X, Z	X, Z	X, Z	X, Z	X, Z	
General Properties						
Delivery Device Development	X, Z	X, Z	X, Z	X, Z	X, Z	X, Z
Drug Deposition Mouthpiece/ Accessories	X, Z	X, Z	X, Z		X, Z	
Physical Characterization	Z	Z	Z	Z	Z	Z
Effect of Storage on PSD	X	X				X (suspension)
DDU and FPM thru Container Life	Z	Z	Z			
Profile/Actuations Near Exhaustion	X, Z	X, Z	Z	X	X	Z
FPM with Spacer Use	Z					
Single Dose FPM	Z	Z	Z			Z
Particle/droplet size distribution	X, Z	X, Z	X, Z	X, Z	X, Z	X, Z
Plume Geometry and Spray Pattern	X			X	X	
Microbial Challenge	X				X§	
In Vitro Dose Proportionality	X	X	X	X	X	
Effect of Varying Flow Rates*	X	X, Z	X, Z		X	
Leachables and Extractables (L&E)#	X, Z	X	X	X, Z	X, Z	X, Z
Effect of Moisture	X, Z	X, Z	X, Z			
Photostability		X	X	X	X	X
Fill Weight/Minimum Fill Justification	Z	X, Z	Z	X, Z	X, Z	X, Z
Preservative Effectiveness				X, Z	X, Z	X, Z
Compatibility	X	X	X	X, Z	X, Z	X, Z
Characterization of Nebulizer						X

X = US/FDA; Z = EU/EMEA and Canada/HC, DDU = Delivered Dose Uniformity; FPM = Fine Particle Mass

***Also known as "over patient flow rate range**

§ device-metered, aqueous- based

 # While not specifically referenced in the Product Characterization section of the FDA Guidances, L&E studies as discussed in the Container Closure section of the Guidance are included in this table because they are a key study related to product performance.

Based on FDA Draft MDI/DPI Guidance (available at http://www.fda.gov/cder/guidance/2180dft.pdf) and Nasal Spray and Inhalation Solution, Suspension, and Drug Products Guidance (available at http://www.fda.gov/cder/guidance/4234fnl.pdf). Only studies relevant to the drug product performance (formulation, container closure system, and device if included) have been included.
From Joint EMEA/Health Canada Guidance for Industry on Pharmaceutical Quality of Inhalation and Nasal Products. Available at http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/chem/inhalationnas_e.html#3.

Representative OINDP Specific CMC Guidelines.

Canada

Pharmaceutical Quality of Inhalation and Nasal Products.(2006)
http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/inhalationnas_e.pdf

EMEA/Europe

Recommendation on the need for revision of (CHMP) Points to consider on the requirements for clinical documentation for orally inhaled products (OIP) (CPMP/EWP/4151/00) (2007)
http://www.emea.europa.eu/pdfs/human/ewp/4423807en.pdf

Ph. Eur. Inhalanda Monograph 0671, Preparations for Inhalation (2003)

Ph. Eur. Nasalia Monograph 0676 Nasal Preparations, in European Pharmacopoeia 1997, 3rd ed. (Council of Europe, Strasbourg, 1996, ISBN 92-871-2991-6), 1763-1765 (1997).

Medical Device Directive 93/42/EEC, as amended

EUDRALEX Volume 4 - Medicinal Products for Human and Veterinary Use : Good Manufacturing Practice: Annex 10, Manufacture of Pressurised Metered Dose Aerosol Preparations for Inhalation
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-4/pdfs-en/anx10en.pdf

US

Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products - Chemistry, Manufacturing, & Controls Documentation. (2002)
http://www.fda.gov/cder/guidance/4234fnl.pdf

Draft Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, & Controls Documentation. (1998)
http://www.fda.gov/cder/guidance/2180dft.pdf .

USP. Chapter <601> Aerosols, Nasal Sprays, Metered Dose Inhalers, and Dry Powder Inhalers (in-process revision), Pharmacopeial Forum 29(4) 1176 (2003).

International

ISO 20072: Aerosol Drug Delivery Device Design Verification – Requirements and Test Methods (not final, under review with stakeholders)

ISO Standards.

Through the active participation in the work of ISO Technical Committee 84/Working Group 4, IPAC-RS has helped to develop draft ISO standard 20072 "Aerosol Drug Delivery Device Design Verification – Requirements and Methods". In this process, the goal of IPAC-RS has been to ensure that the standard is aligned with the most current regulatory framework for OINDP and risk-management approaches. The resulting ISO document, which "applies to the design, labeling, instructions for use and testing requirements for hand-held single- and multi-use aerosol drug delivery devices (ADDDs)" [from: DIS 20072.2 - Scope] is scheduled to be finalized and published as an official ISO standard in 2009.

NEW PARADIGM CONSIDERATIONS

Product quality must be maintained throughout shelf life and patient use. Standard tests (e.g. assay, related substances) are augmented by specific tests such as delivered dose/delivered dose uniformity and aerodynamic particle size distribution. Additional attributes such as microscopic evaluation, spray pattern and plume geometry are required currently by the FDA.

Aerosol Quality Attributes.

There is shared agreement across the three regions that suitable control over the drug delivered per dose and the aerodynamic particle size distribution (APSD) are considered critical quality attributes of the finished drug product. Under the new paradigm, there is the opportunity to propose alternative approaches to quality control based on increased product knowledge, good science and enhanced process understanding.

Delivered Dose/Delivered Dose Uniformity

Inter and intra device delivered dose uniformity is assessed in all regions. Application of the test to individual data is not consistent. Delivered dose uniformity assessment is expressed as variation around the label claim (FDA/HC) or the mean (EMEA). The data distribution criteria are also not uniform across the three regions.

Aerodynamic Particle Size Distribution/Fine Particle Dose/Mass

All three regions require full aerodynamic particle size distribution data generated using a multi-stage cascade impactor for product (clinical, stability, commercial) to be presented in the marketing application as part of product characterization. These individual stage data will be used to set appropriate product acceptance criteria for APSD with particular emphasis on the clinical batches. EMEA/HC recommends setting an upper and lower limit for the 'fine particle mass' consisting of particles less than 5µm. Impactor stages may also be pooled to more fully control the particle size distribution of the therapeutic dose and this practice is an FDA requirement where the particle size range 1-5µm is considered the most important.

Safety Attributes.

Extractables and Leachables

Sponsors provide extractables/leachables data generated by validated analytical methods in their applications to ensure that product quality and safety are maintained. Detailed information on container closure system (CCS) components are typically referenced in drug master files (DMFs), which may be cross-referenced in the US and Canada using a letter of authorization.

Elsewhere, many countries do not have a DMF system in place or have DMFs limited to drug substance information, e.g., the EU ASMF. The current DMF systems provide for a repository where suppliers may place proprietary information not shared with their customers, but where an assessor may obtain these proprietary technical data. In Europe, the applicant also depends upon the supplier to provide information, but as there is no DMF system for components, the regulatory mechanism differs. The system relies upon the supplier to either provide certification to the authorities and the applicant that its material complies with applicable compendia and/or is safe for contact with foodstuffs (in accord with Directive 2002/72/EC, as amended) , or to provide confidential material composition directly to the health authority.

Quality by Design.

QbD creates an opportunity to design, develop and commercialize OINDP that have more scientifically defined quality and safety attributes which are controlled by robust fully understood processes. While movement in this direction is progressing, there clearly need to be ameliorations in existing regulatory frameworks to account for the new development and reporting dialogues. Additionally, as noted with the IPAC-RS Supplier Working group, there equally exists opportunity for a pro-active partnership between the supplier and the OINDP developer. This opportunity could allow for the conveyance of broader product knowledge/understanding while opening the prospect for minimizing post approval submission requirements.

NEXT STEPS

Next steps for the IICG efforts include:

- Influencing the direction of guideline development in emerging markets, e.g. China, Brazil etc.
- Continue to facilitate discussion amongst industry and regulatory agencies
- Further develop the regulatory "grid" and expand to include member company experiences regarding general OINDP development matters
- Consider and define how the implementation of ISO 20072 for Aerosol Drug Delivery Devices will impact registrations worldwide
- Develop a better understanding for biotech or macromolecule requirements for OINDP.
- Consider how to proactively include references to the PQRI Leachables and Extractables recommendations in relevant OINDP international guidelines
- Help to progress the IPAC-RS plans to further our understanding of the relationship between quality attributes, e.g. particle size and clinical outcomes (Quality/Clinical Correlations Working Group).

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