



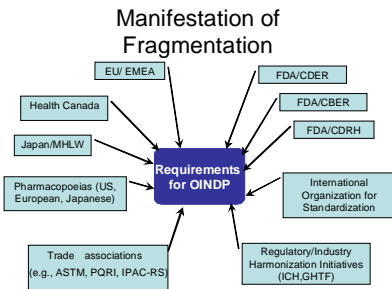
Rationalized Approach to Chemistry, Manufacturing & Control (CMC) Requirements For Orally Inhaled and Nasal Drug Products (OINDPs) Based on Risk Management

IPAC-RS Risk Management Working Group: Steve Horhota[†], Stefan Leiner, Robert Berger, Ann Purrington, Sebastian Kaerger, Svetlana Lyapustina, Noel Butterworth, Rajni Patel, Barbara Davidson, Eric Johansson, Andrew Grant, Mary Ann Smith

STATEMENT OF PROBLEM

From the international perspective, Chemistry, Manufacturing, and Controls (CMC) requirements for Orally Inhaled Nasal and Drug Products (OINDPs) have grown into a complex and fragmented set of guidelines, rules and standards that confront both developers and regulators.

A compilation of all international standards, guidelines, guidances, etc. that would apply in some form to inhalation/nasal delivery was recently performed by the International Industry Coordination Group of IPAC-RS. This survey revealed that over 100 separate documents contain a requirement to be fulfilled to realize a global submission for marketing approval.

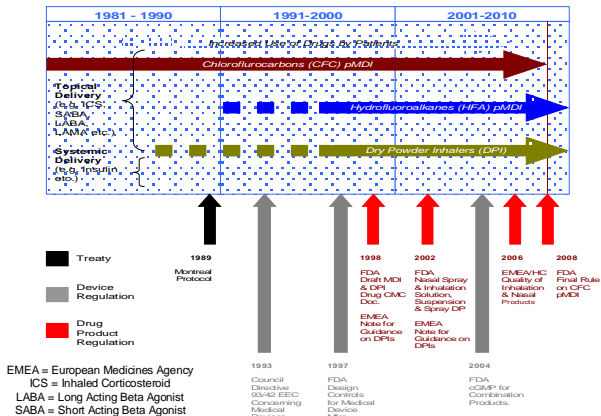


- ASTM = American Society for Testing and Materials
- CDER = Center for Drug Evaluation and Research
- CDRH = Center for Drug Evaluation and Research
- CDRH = Center for Devices and Radiological Health
- EMEA = European Medicines Agency
- FDA = U.S. Food and Drug Administration
- GHTF = Global Harmonization Task Force
- ICH = International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
- IPAC-RS = International Pharmaceutical Aerosol Consortium on Regulation and Science
- MHLW = Ministry of Health, Labor and Welfare
- PQRI = Product Quality Research Institute

HOW DID THIS COME ABOUT?

- The legacy originating from the early dominance of pressurized metered dose inhalers (pMDIs) and their regulation as traditional drug products** pMDIs were, from their first appearance in the 1950's, nearly universally classified as pharmaceutical products despite the complexity of device technology embedded in their function. Medical device regulation was still immature in the late 1950's and early 1960's making it more logical to fit pMDIs into already existing regulatory schemes for approval and marketing authorizations of pharmaceutical items.
- An increase in the size of the overall OINDP patient population** The rising incidence of respiratory diseases worldwide and greater access to therapies have increased the number of patients using OINDPs. Assuming the core frequency or percentage of product quality failures remained at a constant level, the absolute number of complaints or adverse event reports would nonetheless increase. This alters perceptions about the frequency and severity of risks connected to the use of these products and the degree of control afforded by existing regulations and guidelines.
- Consequences of Montreal Protocol** The challenges of reformulating products required considerable basic and applied research to identify and implement solutions. The new information challenged many long held assumptions about performance and relevance of in vitro test criteria. It also accelerated innovation and renewed interest in alternative and novel inhalation delivery systems such as DPI's, SMI's.
- Growing use of OINDP for systemic drug delivery**
- Divergent regional views on how to manage the integration of drug product and device requirements**

United States: classification based on which element, drug or device, was the principal contributor to the treatment effect with review then assigned to the respective Agency Center (CDER, CDRH). If classified as a combination product, responsibilities can be split. EU: when drug and device elements are separable, the Medical Device Directives are relied upon for assessing conformity of the delivery mechanism whereas relevant pharmacopoeial and/or medicines standards are used for review of the drug containing portion. Device elements not separable – only pharmacopoeial and/or medicines standards are followed.



Quality Risk Management is a Means to Focus Development and Harmonize CMC Regulation

BUT

Defining an OINDP is Necessary in Order to Apply Risk Management Concepts

OINDP's have 3 essential elements:

1. A delivery system containing a substance, or mixture of substances intended to furnish a pharmacological action or other direct physiological effect in humans;
2. A defined amount of the substance(s) is (are) dispersed into an aerosol form^a by the system;
3. The aerosolized form is available for transport to the lower respiratory tract^b, nasal cavity, or nasal sinuses.

^a A gas borne suspension of solid or liquid particles

^b Trachea, bronchi, bronchioles, alveolar ducts and alveoli

With this Definition, OINDP Performance Targets Can Be Identified

- Achieving reliable and consistent aerosolization, delivery and deposition of the intended agent;
- Excluding unintended materials (e.g., foreign particulates, leachables, microbiological material, infectious and/or sensitizing agents or impurities) from an OINDP;
- Encouraging proper use; and minimizing chances of misuse of an OINDP;
- Reducing the likelihood of unintended effects.

Categorizing OINDP Risk Areas Affecting Performance Outcomes

- Device elements, including primary and secondary packaging, or integrated dose counting mechanism;
- Formulation elements;
- Interaction of device and formulation;
- Patient factors

CONCLUSIONS

Consistent identification and application of safety and performance principles to an OINDP offers significant benefits to patients, manufacturers, as well as regulatory authorities.

- It will provide a common framework for developers to design, manufacture and demonstrate that a particular product is suitable for its intended use.
- It will facilitate regulatory review thus allowing patients earlier access to new technologies and treatments.
- It offers the potential to eliminate differences between jurisdictions thereby decreasing the redundancy of regulatory requirements.
- It will help to ensure that products have more predictable registration pathways, sustainability in the market place, and compatibility with Quality by Design (QbD) principles.

A risk based approach further offers the opportunity to effectively organize and consolidate the diffuse set of OINDP requirements into a logical scheme. Such simplification will promote further innovation in the area of pulmonary delivery and streamline the pathway to market approval. The realization that most of the existing regulations have the same underlying intent entices the hope that an internationally harmonized regulatory framework for OINDPs can be adopted to the benefit of patients, developers, and regulators

YOU CAN CONTRIBUTE!!

Stop at the neighboring display. What do you feel are significant OINDP Risks? Post your thoughts in the Risk Factor/Performance Target Matrix

ACKNOWLEDGEMENTS

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[†]Corresponding Author (shorhota@rdg.boehringer-ingenheim.com)

Affiliations: Steve Horhota (Boehringer Ingelheim), Stefan Leiner (Boehringer Ingelheim), Robert Berger (Schering-Plough), Ann Purrington (3M), Sebastian Kaerger (Novartis), Svetlana Lyapustina (DBR), Noel Butterworth (Novartis), Rajni Patel (Boehringer Ingelheim), Barbara Davidson (3M), Eric Johansson (Aradigm), Andrew Grant (GSK), Mary Ann Smith (Nektar)