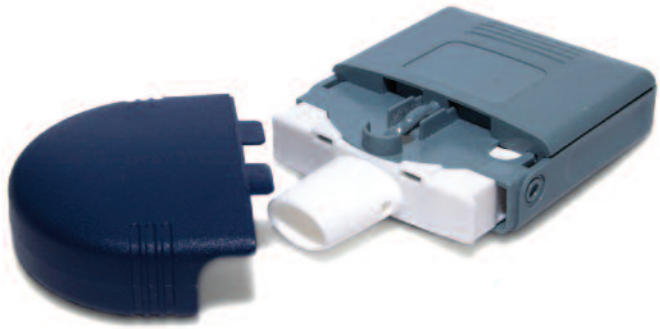
Risk management for combination products

The need for improved risk management practices for orally inhaled and nasal drug products



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Because the efficacy of orally inhaled and nasal drug products (OINDPs) depends on the interaction of the drug formulation and a delivery device, development of combination OINDPs presents significant challenges that often result in one or more changes to device designs prior to commercialization. As a result of the complexity of the process, development time for OINDP device-drug combination products generally takes from 5 to as many as 15 years, compared to typical 1-2 year development times for stand-alone devices [1].

The International Pharmaceutical Aerosols Consortium on Regulation and Science (IPAC-RS) conducted an interactive audience survey of current practices in device development during a 2008 conference. The survey revealed that nearly half of the audience had experience with non-trivial changes to devices between clinical phases II and III, typically extending the development timeline by more than a year. In addition, nearly half of the audience reported non-trivial changes to devices post-approval, with such changes typically requiring more than a year to justify and implement.

Currently, no harmonized guidelines for development of combination products exists; however, developing an early understanding of the relationships between a particular formulation and a particular device can minimize the need for changes or can streamline implementation of changes in late product development and post approval. In order to assist the industry in achieving these goals, a working group of IPAC-RS has studied the contrasting international approaches to regulation and design control for these types of products.

Reasons for and timing of changes

Of the 135 individuals who participated in the real-time survey, 65% worked in North America, 35% in Europe, and 1% in India. Approximately 70% worked in pharmaceutical companies; 11% worked in device or device component companies; 10% worked in the government; with the remainder from non-OINDP pharmaceutical companies, non-OINDP device companies, academia, consulting, or "other." Most of the audience had many years of experience with many types of OINDPs and had multiple job responsibilities.

Of those responding to the survey, 49% had experience with a significant change to a device for the following reasons:

- Mechanical reliability or robustness 42%
- External influences such as regulations, clinical trial results, market changes, supplier change 18%
- Manufacturability questions such as high-speed assembly issues 11%
- Changes to the drug product formulation 11%
- Complications during scale-up between phases II and III 9%
- Ergonomic changes 9%

Almost 60% of the respondents reported that a change in the device design extended the development timeline by more than a year, and 37% reported that a change required 3-12 months. Only 4% reported that cases resolved within 3 months.

Almost half (47%) of the audience had experience with non-trivial post-approval changes to an OINDP device for reasons such as:

- Changes in raw material suppliers 30%
- Changes with the supplier of device component(s) 17%
- Mechanical reliability or robustness of the device 15%
- Manufacturability 11%
- Changes in the supplier of formulation ingredients 11%
- Ergonomic improvements to the device 9%
- Changed market conditions 6%
- Retroactive changes of regulatory requirements 4%

Of those surveyed, 78% said it took over a year to conduct studies to justify the change, obtain regulatory approval and implement the change, and 17% reported that it took 3-12 months. Only 6 percent of cases resolved in under 3 months.

What takes so long?

The complex regulatory requirements for combination OINDPs regulated as drugs in the US mean that seemingly simple changes such as changing the type of plastic in the device can require 3-5 years for an inhalation product, as opposed to several months for a device alone. For stand-alone devices not subject to regulation as drugs, manufacturers have the freedom to make changes on their own, as long as they are certified to a recognized quality standard like ISO 13485. The manufacturer must notify the proper regulatory agency of the change but may implement the new material prior to regulatory review.

A change of plastic in a combination product regulated as a drug, however, requires not only time-consuming stability testing, it requires an update to the drug master file (DMF) and to the new drug application (NDA), new drug submission (NDS) or marketing authorization application (MAA), depending on the regional authority. Changes to the NDA, NDS, or MAA generally require regulatory approval prior to implementation, which can add considerable time to the process.

Heading off device design changes

Avoiding the need for changes to an OINDP device could save months or years on a development project, a savings that could translate to millions of dollars. Surprisingly, more than 40% of the survey respondents reported that failure mode and effects analysis (FMEA) is the predominant tool driving risk reduction during development, while guidance such as regulations and regulatory guidelines, ICH Q9 Quality Risk Management (applicable to drugs), ISO 14971 Quality Risk Management (applicable to devices), and other technical standards play a lesser role.

FMEA provides a tool for testing the reliability of design solutions in existing devices by examining robustness, workability, and the ability to detect any failures. Any change to the device would require a new FMEA. This technique questions the tolerability of a fault over time, taking into account other faults that could accumulate. FMEA, however, does not serve as a risk management tool in its own right.

An effective risk management program may include FMEA *after* the definition of the device concept but not before that point. Risk management for combination products should begin early in development and continue through design freeze/lock-in, production, marketing, and post-marketing, until the end of the product life-cycle. The ISO model, unlike the ICH Q9 approach for drugs, provides a method for product improvement based on market feedback, leading back to the risk analysis. Many medical device companies use this framework; but pharmaceutical companies develop most inhalation products, and they rarely employ this type of risk management strategy.

For effective risk management, device developers and formulation developers must exchange information and align strategies throughout development, preparation of regulatory submissions, and support of post-approval changes. Since little quantitative information currently exists about the ways that mechanical, chemical, and other *in vitro* characteristics relate to clinical outcomes, determining the acceptability of change between clinical phases can be difficult.

Integrating the drug and device development under the quality-by-design (QbD) paradigm and establishing subspaces for the device, the formulation, and the interaction of the device and formulation, may require more iterations than for the drug alone or the device alone. However, the benefits of this holistic approach for both the manufacturer of the combination product and for the patient will almost certainly justify the effort.

Considerations for OINDP design

The risk management process starts with the identification of qualitative and quantitative characteristics of the design attributable to both the device and the formulation (Table 1). Whether the device design for a combination product begins at a device company

Table 1

Key characteristics to be considered during device design

Aspect to consider	Characteristics to consider
Intended use	Indications, purpose Patient characterization Sequence of operation Reliability Environment Contraindications Disposal Stability Robustness
Intended users	Ergonomics Dexterity Handling training Age Disability Intellectual acumen Necessary accessories
Intended contact	Biological compatibility Durability Longevity Bioactivity Bioabsorbance
Materials of construction	Physico-chemical properties of materials Physical and chemical compatibility Structural integrity Packaging materials Cleaning, disinfection, sterilization Environmental compatibility
Energy/Active substances	Delivery or extraction Quality, quantity Control and duration Justification, optimization and dose

or at a pharmaceutical company, a thorough review of all of these wide-ranging factors necessitates interaction between scientists and engineers familiar with the various aspects of the project.

Reference

1. John L. Hart. Presentation at Management Forum conference New horizons in dry powder inhalers: The next generation DPIs. 2005, London, UK.

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