

Industry Perspectives on OINDP Regulatory Challenges in Global Environment

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Overview

- Introduction
- OINDP and Guidelines
- OINDP and QbD
- Challenges and Opportunities
- Conclusions

Introduction

- Previously, heard about:
 - Public collaboration between Canada and Europe to produce a joint guideline on OINDP.
 - New regulatory initiatives and how these impact OINDPs.
- This presentation will focus on:
 - The challenges and opportunities ahead for OINDP manufacturers in preparing global submissions.

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OINDP and Guidelines

OINDP Quality Guidelines

- All the ICH quality guidelines apply to OINDP.
- Devices guidance, ISO standards, CFR, pharmacopoeias, national guidances, etc.
- Specific OINDP guidance:
 - Pharmaceutical Quality of Inhalation and Nasal Products (Health Canada and EU, Final 2006).
 - Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products (FDA, Final 2002).
 - Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products (FDA, Draft 1998).
- No Japan OINDP specific guidance.

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OINDP-Specific Guidelines

- Outline expectations for various sections of the application, notably:
 - Pharmaceutical Development
 - Product characterization
 - Labelling support
 - Product Specifications
 - Tests to be considered.
 - Reflect pre-QbD approach.
- Scope for further guideline revision or harmonisation, beyond that started by Europe and Canada.
 - But OINDP-specific guidelines don't stand alone.

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OINDP and QbD

Quality by Design

- 'It is important to recognize that quality cannot be tested into products; i.e., **quality** should be built in **by design**.' (ICH Q8)
- QbD builds on existing expectations.
 - EU regulatory systems required information on the pharmaceutical development of the medicinal product.
- More focus on product knowledge and enhanced process understanding:
 - Impact of raw materials and process parameters on product quality.
 - Identify and control sources of process variability.
 - Appropriate control strategies!
 - Less emphasis on end-product testing.
 - More reliance on process control and in-process monitoring.

ICH Guidelines

- Guidelines simplifying regulatory implementation of the cGMPs for the 21st Century initiative:
 - ICH Q8 Pharmaceutical Development
 - ICH Q9 Quality Risk Management
 - ICH Q10 Pharmaceutical Quality Systems
 - Guidances for a global environment that encourage development of science based and risk based approaches to quality.
- ICH Q6A and OINDP guidelines:
 - Don't reflect current QbD approach.
 - But quality targets based on safety and efficacy.

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OINDP and QbD

- ICH Q8 :
 - 'At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified.'
- OINDP are combination products of drug formulation and device.
 - Drug(s)
 - Excipient(s)
 - Container Closure System
- OINDPs ideal candidates for QbD approach.

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What does it all mean for Industry?

- Paradigm shift
 - From:
 - “Confirm the proposed product and processes are suitable for manufacture.”
 - To:
 - “What suite of studies, DoE, multivariate analyses, etc, is needed to establish product understanding, design space, etc?”
- Benefits include better product and process understanding, leading to more predictable approvals and greater regulatory flexibility.

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One Successful Science and Risk Based Approach

- Leachables and extractables for p-MDIs.
 - Subject has progressed to the benefit of Industry and Regulators.
 - IPAC-RS has dedicated much time working with OINDP suppliers to better understand extractables and their potential to become leachables.
 - Through the Product Quality Research Institute (PQRI), IPAC-RS, OINDP Suppliers, FDA, and other industry groups have worked together to successfully advance the idea of safety threshold levels for leachables.
 - The idea of control on extractables at the component level rather than on leachables at the product level is well accepted.

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Challenges and Opportunities

Challenges

- Changing mindset:
 - 'That's not how we did it with the ark?'
 - Data ≠ knowledge or understanding.
- Move away from yesterday's thinking on specifications.
 - Non-prescriptive, fit for purpose 'specifications.'
 - Science and patient based control strategies.
 - Focus on what is critical to safety and efficacy.
 - **Critical not Nice to Have** Quality Attributes!
- Demonstrating comprehensive understanding of the product and manufacturing process in the original marketing application comes at a considerable cost for Industry.

Opportunities

- From enhanced product knowledge and process understanding.
 - “Real time” quality assurance with less dependence on end-product testing.
 - Facilitation of innovation and continuous improvement throughout product life cycle.
 - Increased manufacturing efficiency
 - Waste minimisation.
 - Less product recalls and batch failures.
 - Increased post-approval regulatory flexibility.
 - Proposed by applicant, approved by regulator.
 - Fewer post-approval submissions.
- Applicant decides when to invest!!

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Global Scene

- It's not an homogeneous regulatory landscape.
 - ICH is not the world.
 - ICH vs nonICH vs ASEAN vs SADC etc
 - Mechanisms for post-approval change.
- Requirements are not harmonised.
 - QbD to be worked into Regional guidances as overarching philosophy.
 - Challenge - need to develop products via QbD but recognise that concepts not fully assimilated in some countries.

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Further Harmonization?

- Further harmonization and updating of CMC requirements may be required.
 - Updating OINDP specific guidelines and other regional guidelines to incorporate ICH Q8, Q9 and Q10 principles.
 - Update ICH Q6 with key aspects of QbD, e.g. PAT.
- Benefits of any harmonization may be:
 - More economical use of resources for industry and regulators.
 - More streamlined development process and more predictable approvals for industry.
 - Elimination of unnecessary delay in the global development and availability of new medicines to patients.

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Conclusions

Conclusions

- Most OINDP producers seek to operate in more than one region
 - Global acceptance of QbD concepts will facilitate global developments.
- Through QbD:
 - Emphasis on enhanced product and process understanding
 - Control strategies based on understanding.
 - Less emphasis on end-product testing.
 - More reliance on process control and in-process monitoring.

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Conclusions (Cont'd)

- At this time, the potential benefits of QbD to Industry are unproven for OINDP
 - Challenges should also be seen as opportunities for industry.
 - Application of QbD in the development of OINDP will help set a sound scientific basis for controls, based on greater understanding.
- Industry and Regulators can collaborate to achieve a win-win situation
 - L/E work is an excellent example.
- Need for open and sharing applicant/regulator interactions.

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