
Evolution of Regulatory Paradigm for OINDP: Industry Perspective

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Overview

- Evolution of OINDPs
- OINDP Regulatory History
 - 1960s-1980s
 - 1990s
 - 21st Century & Beyond
- Conclusion

Evolution of OINDPs



"Take That! Oops sorry, that's my insulin inhaled!"

Modern Inhalation Drug Products



Asthmanex® Twisthaler®
(Schering-Plough)



Respimat® SMI
(Boehringer-Ingelheim)



Symbicort™ Turbuhaler™
(AstraZeneca)



Advair Diskus®
(GlaxoSmithKline)



Exubera®
(Pfizer)

Timeline



1940s	1950s	1960s	1970s	1980s	1990s	2000s
<p>1940s: Hand-bulb nebulizers used to deliver adrenaline for patients with asthma</p> <p>1956: First MDI developed; based on aerosol technology originally developed for military in World War II</p> <p>1960s: Hand-bulb nebulizers used to deliver cortisone for patients with asthma; Ultrasonic nebulizers introduced</p>			<p>1970s: Dry powder inhalers developed</p> <p>1970s: Spacers developed to combat problem of poor inhalation technique</p> <p>1987: CFCs subject to phase out under the Montreal Protocol; MDI granted exemption from immediate phase-out</p> <p>1980-90s: complex and time-consuming MDI reformulation efforts initiated</p>			<p>2000s: Seven HFA MDI products approved</p> <p>2006: First insulin inhaler approved in US</p> <p>2008: Albuterol CFC MDIs lose essential use status. Multiple Albuterol HFA MDIs available.</p>

OINDP Regulatory History

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Pulmonary: The Regulatory Challenge

1985: “Typical” OINDP NDA

- Chemistry, Manufacturing and Controls (CMC) section of NDA: **4 - 5 volumes**

1996: “Typical” OINDP NDA

- CMC section of NDA: **9 - 10 volumes**
- Response to “Approvable” Letter: **8 – 10 volumes**

What made the approval so difficult?

Early 1990s

- Unprecedented industry-wide product reformulation
 - For environmental reasons (Montreal Protocol), not necessarily due to safety or efficacy
- Reformulation effort was much more complex than anticipated — equivalent of development of a brand new drug product
 - Complexities of changing propellant
 - Complexities of changing components, e.g., valve
- OINDPs get notorious
 - Reformulation efforts trigger increase in FDA focus on OINDPs
 - FDA considers pulmonary route of administration as “highest risk”
 - OINDP regulation became progressively more prescriptive



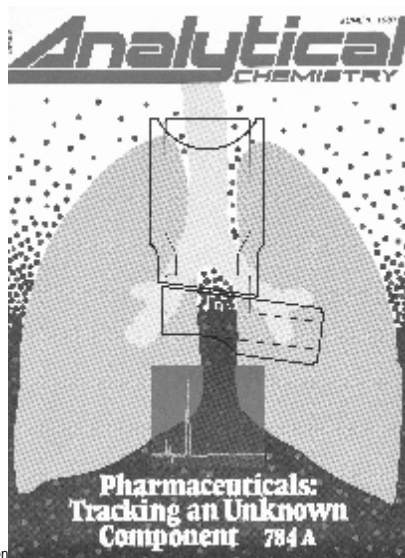
“...please identify the unknown peak at 4.2 minutes in the chromatogram on page.....”



These guys might have been smiling at the time, little did they know it was just the beginning...

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Metered Dose Inhaler Valve Components

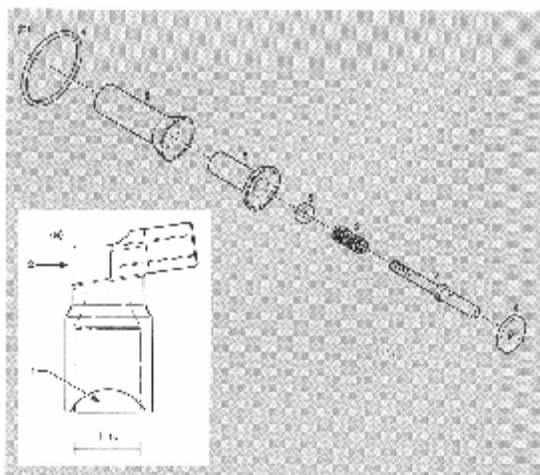
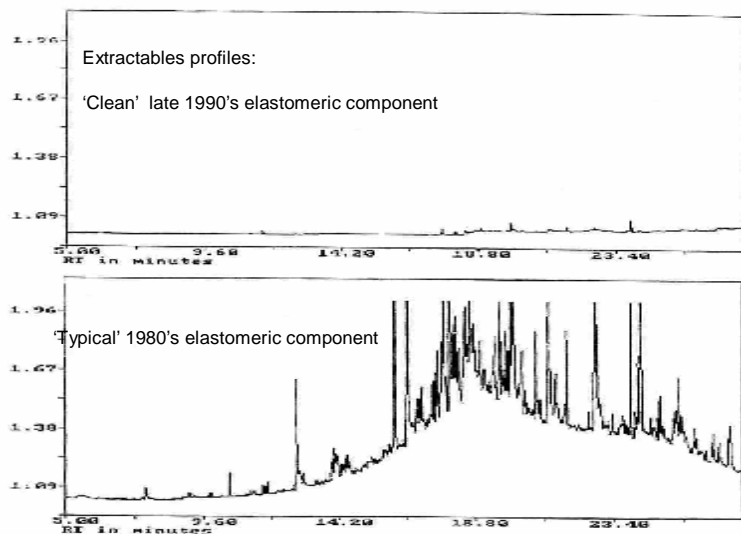
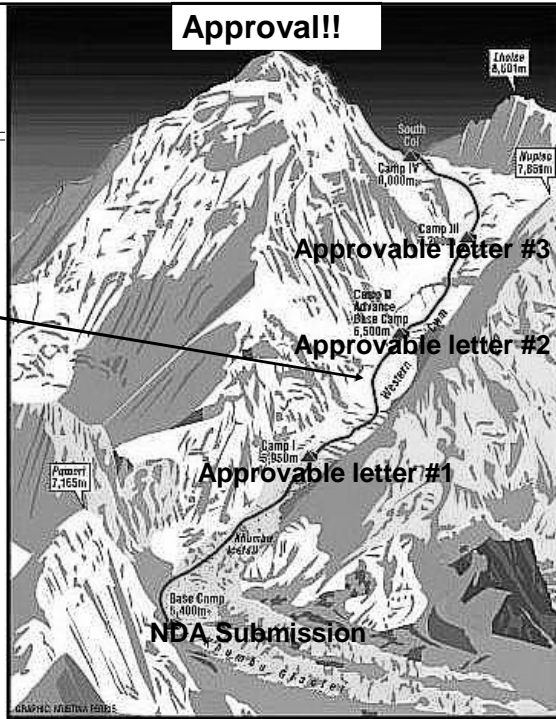


Figure 2. Metered Dose Inhaler Valve (MDI).
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Agency concerns led to improved component designs



The Route to Pulmonary Approval



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FDA Drug Approval Times 1995 - 2002



- Agency-wide approval times:
 - **More than 60% NDAs approved in less than 1 year**
 - Less than 10% NDAs take longer than 2 years
 - Average 2.4 approvals per division per year
 - Mean approval times
 - CDER = 11.2 months
 - CDRH = 9.6 months
- Inhalation Products
 - **Mean approval times for Metered Dose Inhalers 34 months**
 - Average 1.1 approvals per year

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• Sources: FDA webpages, public presentations

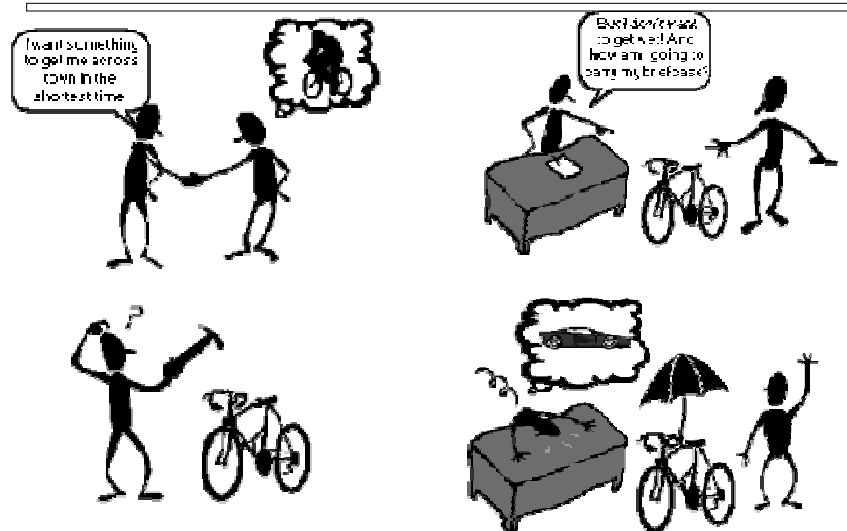
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Late 1990s

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- FDA issues two OINDP Draft Guidances for Industry
 - Public Comments
 - Over 600 pages of comments from more than 25 entities
 - Commended FDA for outlining requirements
 - Expressed concerns regarding certain approaches
 - ignore USP, ICH standards
 - overly prescriptive
 - require testing that is excessive, redundant and irrelevant
 - Initiated robust scientific dialogue among industry and regulators in multiple forums:
 - RDD
 - IPAC-RS
 - PQRI
 - Others

OINDP Regulation: The 21st Century & Beyond

Known Requirements, Emerging Requirements: Know thy Product, Build in Quality Up-Front



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2002



- FDA Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century
- Objectives:
 - Enhance and modernize regulation of pharmaceutical manufacturing and product quality
 - Modernize FDA's regulation of pharmaceutical quality
 - Encourage early adoption of new technological advances
 - Facilitate industry application of modern quality management techniques
 - Encourage implementation of risk-based approaches
 - Ensure that regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science
 - Enhance the consistency and coordination of FDA's drug quality regulatory programs

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2003 - 2004

- FDA's implementation of CGMP plan
 - Assessed existing CGMP programs
 - current practices
 - available new tools of enhancing manufacturing science
 - Created a new framework for regulatory oversight of manufacturing quality based on quality systems and risk management approaches
- Guiding principles:
 - Risk-based orientation
 - Science-based policies and standards
 - Integrated quality systems orientation
 - International cooperation
 - Strong public health protection
 - Implementation of the envisioned new framework

Sounds Good... But What Does it Mean?



Where We Are in 2006

- Much good thinking has occurred
- Many public discussions have taken place
- Countless conferences and workshops are happening
- Thoughtful publications are appearing



"Death of Socrates" Jacques-Louis David (1787)

- The thinking, discussions and publications, however, have been primarily high-level and philosophical
 - What does it all mean for OINDPs?*

Moving from the Abstract to the Concrete



Where We Need to Go

- Step 1: Take the FDA's guiding principles
- Step 2: Translate principles into concrete framework
- Step 3: Develop and register new products

How do we get there?

- In many respects the OINDP industry is already using QbD principles!
 - Design of critical components
 - Designing a valve to have minimum L/E
 - Working with suppliers to employ raw materials in finished components that have low L/E content
 - Building quality into the product
 - Looking at risk-based approaches
- History Lessons
 - Reformulation efforts were often very complicated and frustrating
 - Initial product designs were undertaken under old regulatory paradigms
 - Heightened regulatory barriers in the early 1990s made it very difficult for reformulated products to meet the standards
 - Companies that built in quality as part of development experienced had less difficulty meeting the standards
- The Challenge:
 - How do we apply QbD more generally into the whole OINDP development process?

Conclusion

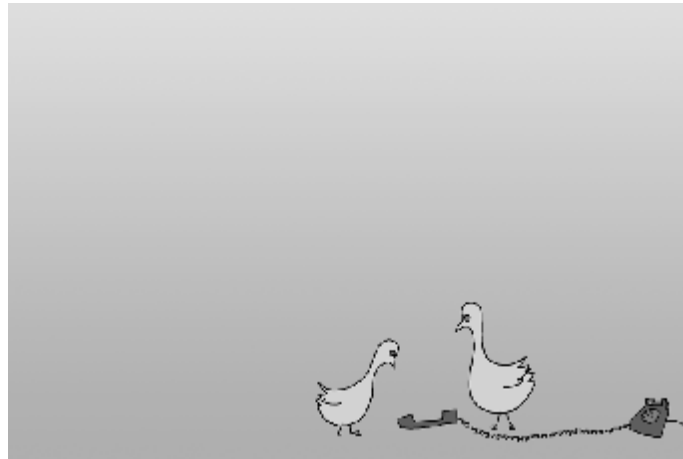
Conclusions

- The OINDP industry wants to understand **HOW** to work within the new regulatory paradigm
- No one wants to return to the mid 1990s and the lack of a clear regulatory pathway
- The paradigm is moving away from prescriptive guidances, which is a constructive move
- While increased flexibility is good, all parties need a clear understanding of the expectations

Conclusions

- The 2006 IPAC-RS Conference is intended to serve as a first step forward in helping all participants, from representatives of OINDP manufacturers and component suppliers, to regulators from the US, EU and Canada, to work together to gain a better understanding of how OINDPs fit within the new paradigm
- Once we figure out the **HOW**, the OINDP industry can serve as a leader for other manufacturers of novel dosage forms that are struggling to apply the new paradigm to fit specific drug products

We All Need to Keep Talking



Thank you.