

OINDP case study: development of a novel DPI: Prohaler



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OINDP devices

- ü Nasal spray pumps
- ü Metering valves
- ü Dry powder devices
- ü Nebullizers



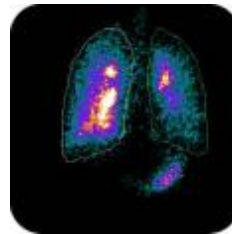
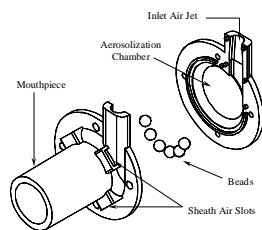
○ Often follow different development cycles (e.g. standard component vs. customized to a specific drug product)

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Prohaler history S2 engine license agreement

"...Valois has expanded its pulmonary franchise with the acquisition of intellectual property rights related to the "**bead inhaler**" from Quadrant Technologies Ltd. The technology is a novel multi-dose inhaler device under development based on a blister type powder storage system..."

Valois licenses in rights to S2 engine in August 2003 for multi-dose DPI.



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Prohaler key features

- **Multi-unit dose inhaler**
 - One months supply :30 dose
 - Foil laminate blister containing around 10 mg of powder blend
- **Effective deagglomeration of the powder**
 - Rapidly fluctuating airflow/shear within dispersion engine
- **Opening of the dose is Breath triggered**
 - Dose only opened whilst the patient is inhaling so:
 - No wasted doses
 - Prevention of multiple dosing
- **User-based design**
 - 3 step device- Open/Breath In/Close (OBIC™)
 - Audible and visual feedback (dose counter)

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Prohaler user interface

Open

Breath In

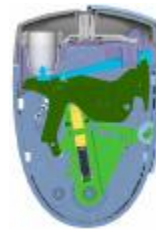
Close



Loaded



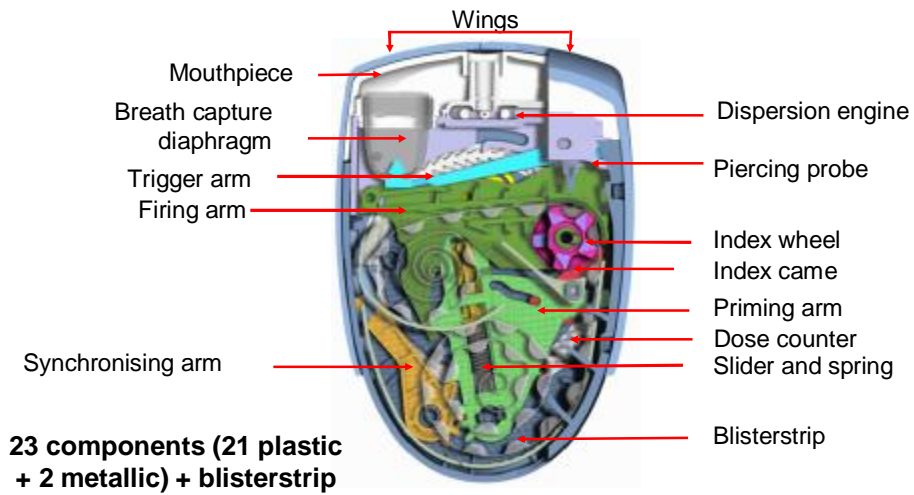
Triggered



Reset

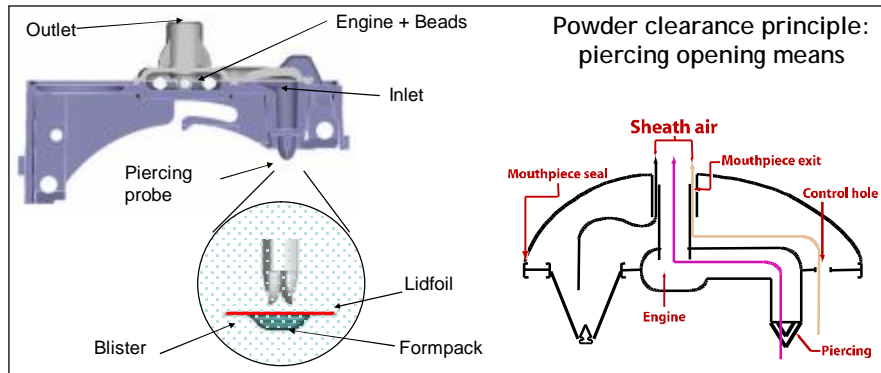
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Overall view of device



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Powder inhalation path description

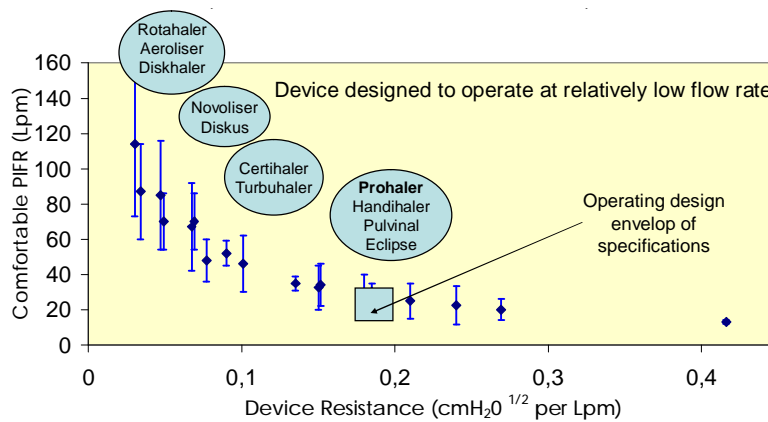


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Device resistance

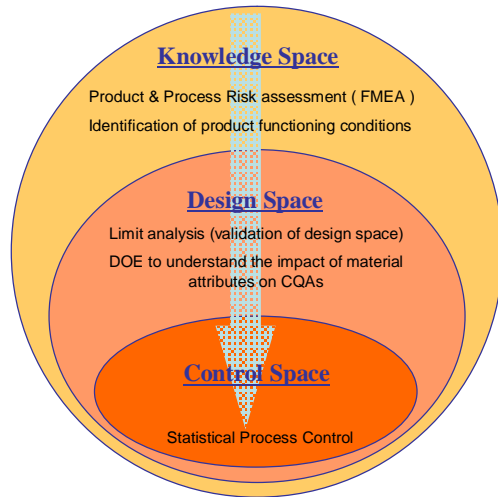
High resistance device to limit range of operational flow rate and reduce variation between users.

(datasets from Clark, DeBoer and Dura)



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QbD Methodology applied for Prohaler development



Define desired product perfs & product CQAs
(Critical Quality Attributes)



Understand impact of material attributes & process parameters



Identification & control sources of variability

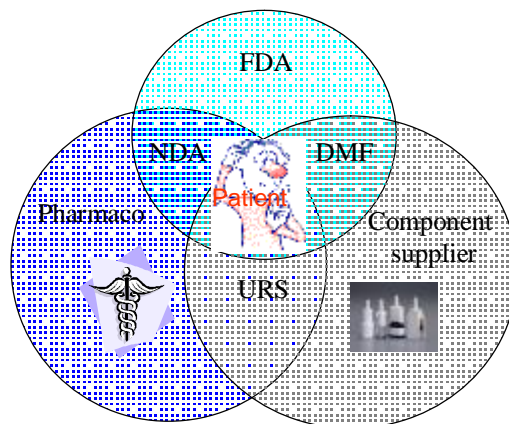


Monitoring of the process

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WHY use QbD APPROACH in device development?

- Ø Understand the impacts of product/process deviations on product final quality (CQAs)
- Ø Simplify the regulatory changes once product approved
- Ø Anticipate issues at critical interfaces (patient, pharmaco, FDA)



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Prohaler key critical functions

(performance, user interface)

- User interaction
- Powder dispersion engine
- Breath triggering mechanism
- Dose counter
- Powder protection & mobilisation

F Derived from initial product FMEA

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Breath triggering mechanism

Critical performance characteristics:

- Triggering sensitivity
- Patient interface

URS:

- Triggering point: 12-19 lpm, 4.1-14.1 mbar
- Understanding of potential for triggering upon drop, vibration, ageing, etc...

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Breath triggering mechanism

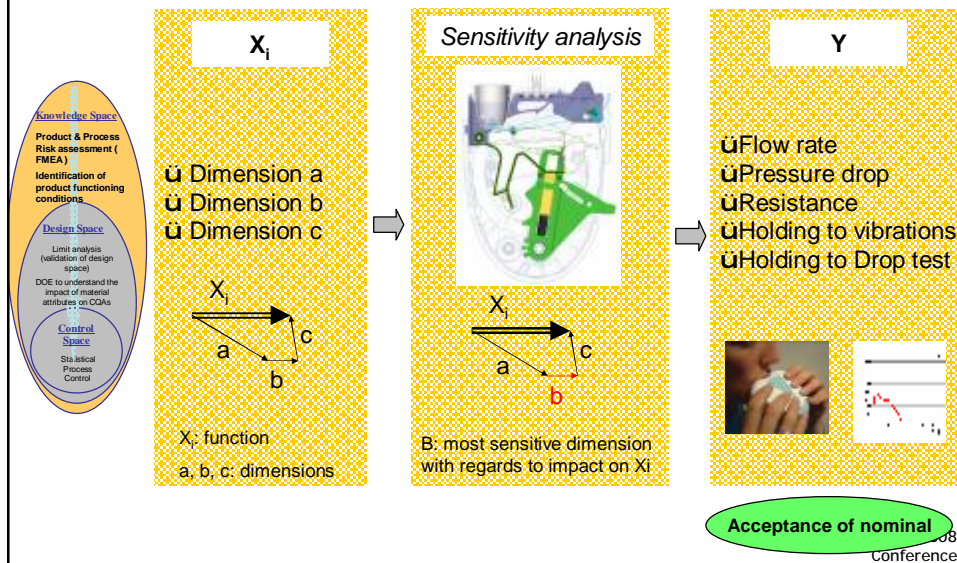
Development/validation tools used:

- ⊖ Statistical tolerancing
- ⊖ Edge of tolerance studies
- ⊖ In vitro testing
- ⊖ In vivo studies (with healthy volunteers & Asthma/COPD patients)
- ⊖ Robustness & misuse testing

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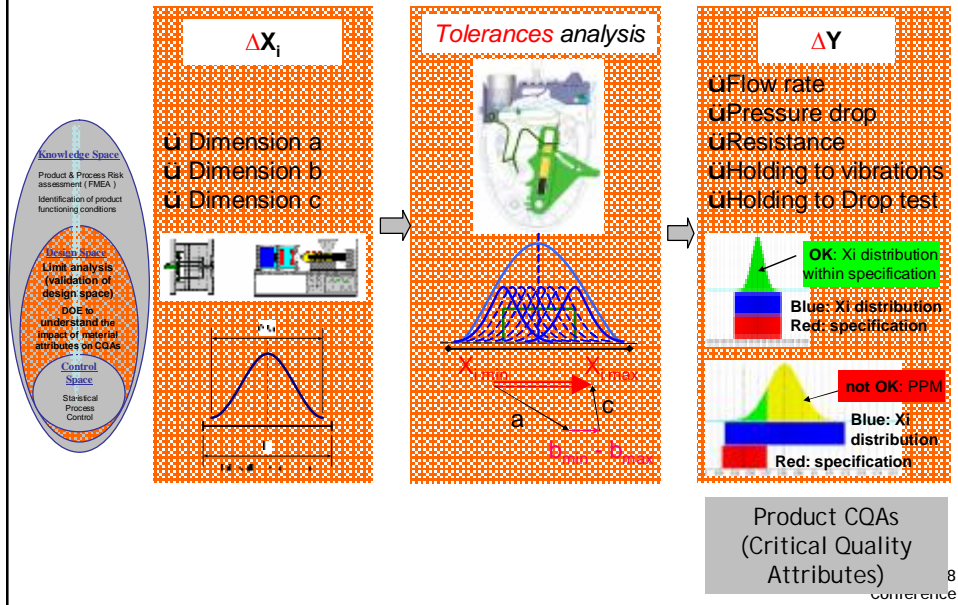
Tolerancing studies

Identification of key parameters (dimension, force or fluidic parameter)

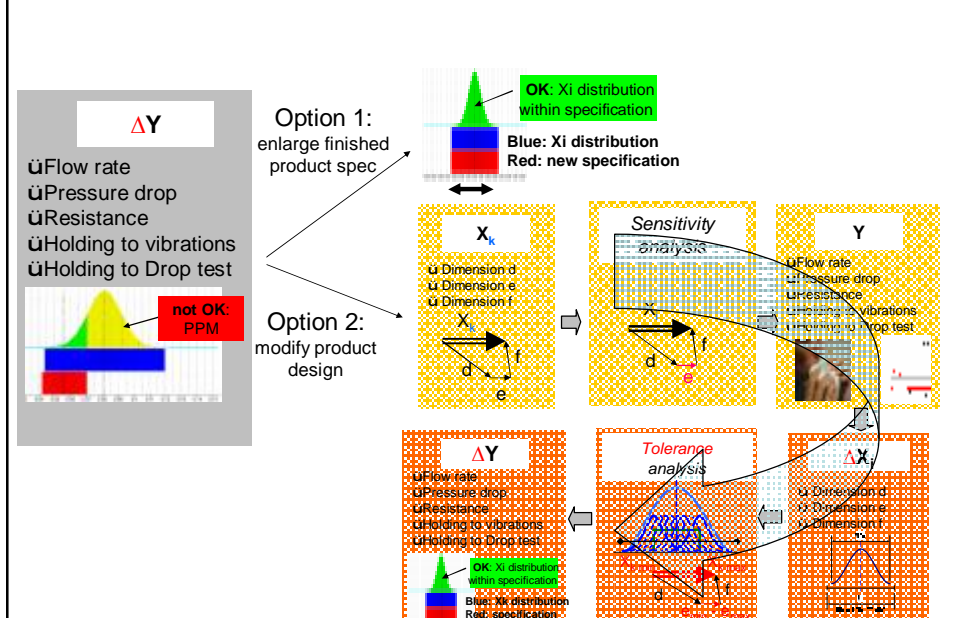


Tolerancing studies

Simulation of industrial variability



Design loop in case of no compliant CQA



Example of in vivo Asthma & COPD patients breath profile study

Study launched in Tours Hospital (France), on 40 COPD & Asthmatic patients

Objectives:

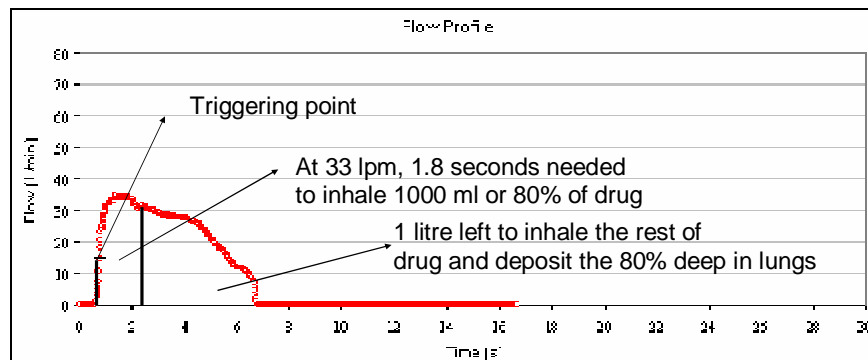
- Confirm ability of COPD & Asthma patients to trigger the Prohaler
- Accommodate breathing with high resistance device
- Verify patient ability to inhale sufficient volume of air to get the right amount of medication
- Gather additional comment on ease of use / compliance / comfort

Expected completion: 3rd Q 2008

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Example of breath profile generated through Prohaler

Confrontation to patient inhalation profiles



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Robustness & Misuse studies

Verification program:

- Simulated misuse studies (low & high actuation speed, exhalation into device, no mouthpiece cleaning...)
- Evaluation of Prohaler performance with various drug formulations:
 - Ø Variation of inhaled volume
 - Ø Variation of air flow and pressure drop
 - Ø Variation of air flow ramp up
 - Ø Vibration & drop testing
 - Ø Ageing & environmental studies
 - Ø Intentional powder pollution on defined area...

} Addresses potential concerns on breath triggering feature

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Summary & conclusion

1. Devices are designed to be used by patients together with drug formulations. **Final product quality** should be used as a reference.
2. QbD tools help to anticipate the device & drug industrialization difficulties (e.g. variability associated with used of **multi-cavity moulds**) and should be used as early as possible in the development process.

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