

Quality Risk Management and Design Space in Device Development

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Overview

- Quality Risk Management
- Design Space
- OINDP: Unique and Complex
- Quality Risk Management and Design Space concepts
- Case Study
- Information in a submission
- Issues for further consideration
- Conclusion

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Design Space

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality.

– *ICH Q8, Pharmaceutical Development (2005)*

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Quality Risk Management

A systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle

– *ICH Q9, Quality Risk Management (2005)*

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OINDP are Unique

- OINDP include
 - Metered Dose Inhalers (MDIs)
 - Dry Powder Inhalers (DPIs)
 - Inhalation Solutions, Suspensions and Sprays
 - Nasal Solutions, Suspensions and Sprays
- OINDP comprised of formulation *and* Container Closure System (CCS)/device
- OINDP generally have complex CCS and Devices. Components include:
 - Valves, mouthpiece, electronics, dose counters, different pack configurations, etc

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OINDP are Unique

- OINDP as a whole system must fit the patient's needs:
 - Easy to use
 - Robust
 - Provide appropriate performance with use
 - Ensure delivery of correct amount of medication
- Container closure system and device must
 - Be safe to use
 - Be compatible with formulation
 - Protect the formulation
 - Deliver correct dose consistently through life

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OINDP are Unique

- The Drug product (formulation/CCS/device) acts as a "patient interface" between active drug and patient
 - Human interaction with drug product is critical in the assessment of risks and design space considerations
 - Makes OINDP unique from many other drug dosage forms
 - Potentially adds complexity to application of quality by design and risk management concepts

Risk Management and Design Space for Device and Formulation

Common Risk Analysis Techniques

- ICH 9 lists some of the tools in Annex I:
 - Failure Mode and Effects Analysis (FMEA)
 - Failure Mode and Effects Criticality Analysis (FMECA)
 - Fault Tree Analysis (FTA)
 - Hazard Analysis and Critical Control Points (HACCP)
 - Hazard Operability Analysis (HAZOP)
 - Preliminary Hazard analysis (PHA)
 - Risk ranking and filtering
 - Supporting statistical tools

Potential applications for Quality Risk management

- ICH 9 lists some of the applications in Annex II:
 - Quality Risk management:
 - as part of Integrated Quality Management
 - as part of Regulatory Operations
 - as part of development
 - for facilities, equipment and utilities design of facility/equipment
 - as part of materials management
 - as part of production
 - as part of laboratory control and stability studies
 - as part of packaging and labeling

Potential applications for Quality Risk management

- ICH 9 lists some of the applications in Annex II:
 - Quality Risk management:
 - as part of Integrated Quality Management
 - as part of Regulatory Operations
 - as part of development

ICH 9 states in Annex II.3

"To make use of the design space concept"

Active Risk Management as a Requirement of Development

- CCS/Device and formulation are inseparable. Global implications of CCS/device on drug product must be well understood. Risk management must include close collaboration among:
 - Formulators
 - Analysts
 - Product design engineers
 - Manufacturing engineers
 - Industrial designers
- Human factors (use-related hazards) should be incorporated into risk management strategy

Active Risk Management as a Requirement of Development

- When conducted early it allows for improvements when sponsor has most flexibility to change designs/plans
- From an identified set of user needs, it drives and guides design control:
 - Used to identify areas of potential risk, gives focus to the testing required to evaluate those risks, and decide if risks are relevant. Relevant risks may be “designed out” of the device
 - Used to select, develop and refine the testing program for device development

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Active Risk Management as a Requirement of Development

- It is recommended that Quality Risk Management be applied *throughout* the development process
 - Device design and conceptualization
 - Pilot scale creation of device
 - Scale-up and manufacture of device
 - Use of device with formulation (as a drug product)

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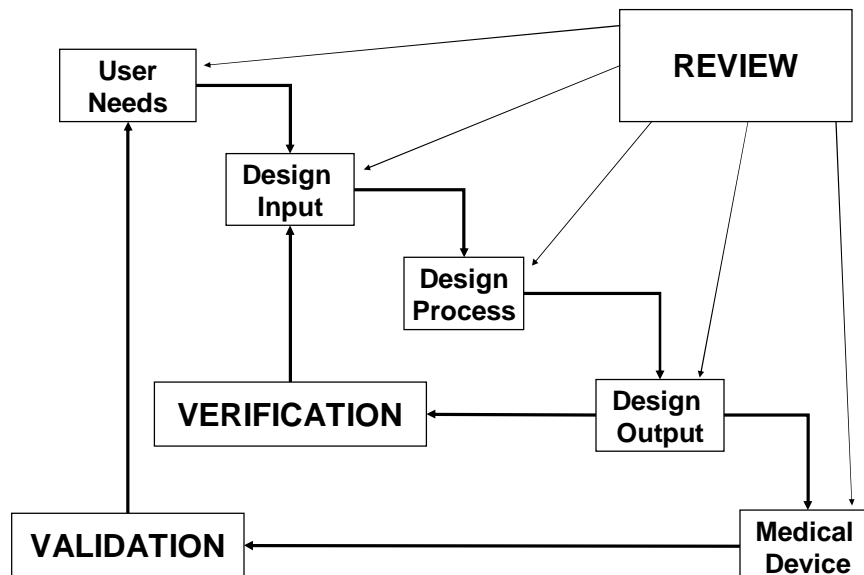
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Active Risk Management as a Requirement of Development

- An iterative process of continuous risk assessment and mitigation is possible
- For example.....

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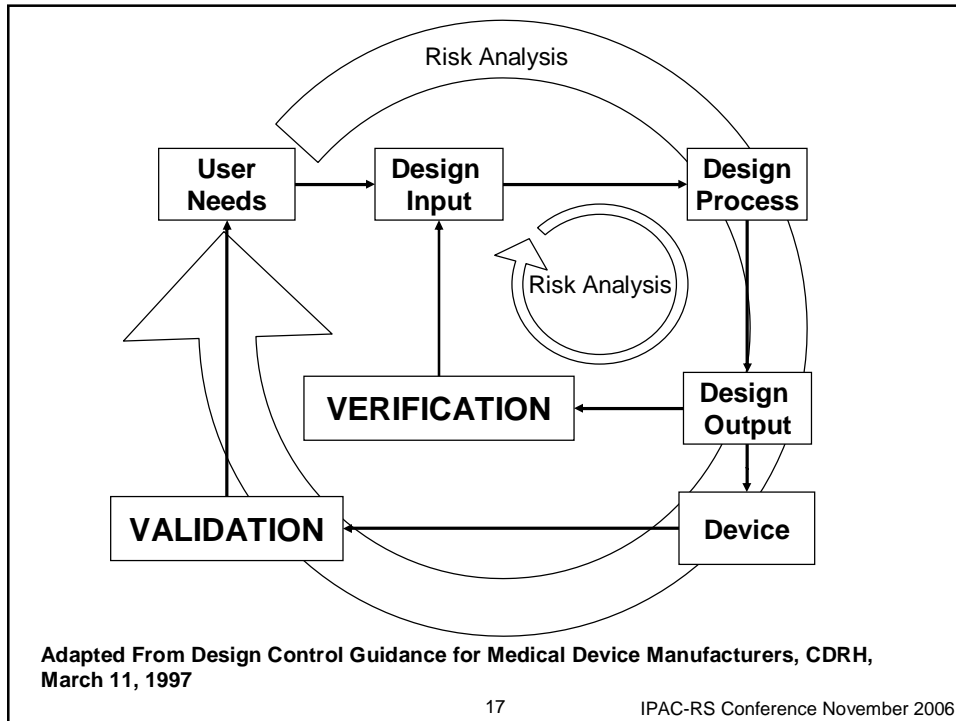
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From Design Control Guidance for Medical Device Manufacturers, CDRH, March 11, 1997

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Active Risk Management as a Requirement of Development

- The risk management framework should guide the sponsor in
 - Designing quality into the device and
 - Developing a design space for the device, which will
 - Ensure that the device meets the user needs and formulation requirements
 - Ensure sound manufacture of device and drug product
 - Ensure a sound control strategy for the drug product

Case Study

Case Study

- By way of example, let us consider the FDA Guidance:

Guidance for Industry, Integration of Dose counting mechanisms into MDI Drug products.

March 2003

Case Study

- The guidance explains that currently

"...patients must guess how many doses are left in their MDIs and have two practical options:

1) throw away an MDI that may still contain acceptable metered-doses

or

2) use a product when it may be beyond the recommended number of doses and risk not receiving the correct drug dose."

In the form of an FMEA

- From a user perspective and taking (2) as being the higher risk scenario:

- *Failure mode:* User receives incorrect dose
- *Cause:* MDI has been actuated beyond label claim
- *Effect:* User suffers asthma attack
- *Severity:* Score ?
- *Occurrence:* Score ?
- *Detection:* Score ?
- *Action:* Provide means to indicate to the user that the MDI has reached label claim

Case Study

- The guidance goes on to explain

"should be engineered to reliably track actuations and should be designed to be as close to 100 percent reliable as possible. However, if some low frequency of error is unavoidable, the device should be designed to specifically avoid undercounting (i.e. the MDI sprays, but the counter does not advance). Undercounting could result in patients assuming they have medication left in their MDI when they do not, a circumstance that is potentially dangerous."

In the form of an FMEA

- From a Design perspective:
 - **Failure mode:** MDI becomes empty before the counting means reaches the label claim (undercounting)
 - **Cause:** User is able to actuate the MDI and receive dose without counting means registering an actuation
 - **Effect:** User suffers asthma attack
 - **Severity:** Score ?
 - **Occurrence:** Score ?
 - **Detection:** Score ?
 - **Action:** Ensure counting means registers an actuation each time the MDI sprays

Case Study

- "Ensure counting means registers an actuation each time the MDI sprays"
 - A solution to achieve this would be to ensure that the counting means always registers an actuation before or at the same time as the MDI sprays

Case Study

- Need to consider design space of the counting means and its relative position to the design space of the MDI spray mechanism to predict the likelihood of undercounting: Design FMEA
- Need to adjust design tolerances accordingly and understand how tolerances are affected by manufacturing process: Process FMEA
- Design and Process FMEA define Design Space
- Need to control tolerances in manufacturing process accordingly: Control Strategy
- Select tolerances via Design and Process FMEA

Information in Submissions

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Design Information in Submissions

- Quality by design paradigms may require different information on Container Closure System and device part of OINDP than historically required

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Information in Submissions

- Describe the CCS and device in general terms
- Describe user needs and formulation requirements and how device meets those needs and requirements
- Describe the development of the testing program for the device, and justify the selection of tests. This may be achieved by a presentation of a Risk analysis.
- Describe considerations used for verification and validation of the design and results of design validation studies (i.e., user studies)

Information in Submissions

- Describe how design space is established for the device and its relationship to the design space for the formulation
- Describe the manufacturing process that is able to manufacture with in the established design space
- Describe the control strategy required to ensure that the manufactured product remains within the established design space.
- Describe how the design space, product performance specification and clinical performance relate to each other

Information in Submissions

- Describe control strategy for the device during its manufacture. If manufactured by a supplier, then give appropriate reference to the supplier DMF for the device

Issues for further consideration

Linking establishment of Design Space to the Clinical Program

- Product design space may need to be correlated with clinical results
 - Through direct comparison with clinical trials
 - Through comparison with surrogate in-vitro tests
- Consider Usability Testing earlier in development process to better understand potential hazards
- How can design space studies be effectively incorporated into the clinical program?

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How to achieve regulatory body buy-in?

- The development strategy for risk management and design space establishment could be shared with regulatory body prior to clinical trials to ensure early buy-in.
 - Develop plan for comparing clinical trial results with design space elements, which can be shared with regulatory body.
- Use of existing formal meetings with regulatory body that could be used to present such plans e.g. for FDA, pre-IND and End of Phase II meetings.
- Other types of regulatory body-sponsor meetings may need to be formalized under new paradigm?

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Conclusion

- Risk analysis is a significant tool to not only justify decisions in the establishment of the design space but also to proactively direct product development
- Implementation of Risk management may be appreciated but some questions particularly regarding establishment of design space and the link to clinical performance still remain

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Thank you
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