



QUALITY BY DESIGN (QbD) APPROACHES FOR ORALLY INHALED AND NASAL DRUG PRODUCTS (OINDPs) IN THE USA

Prasad Peri, Ph.D.

**Office of New Drug Quality Assessment
(ONDQA), OPS, CDER**

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Outline

- General QbD principles
 - What is QbD/Design Space
 - Why use QbD for OINDPs?
- QbD applied to OINDPs
 - Product Design
 - Formulation Design
 - Container Closure System Design
 - Process Design (e.g. micronization)
 - Design and Setting Specifications in the Future
- Blinded case studies where QbD could have helped shorten approval time

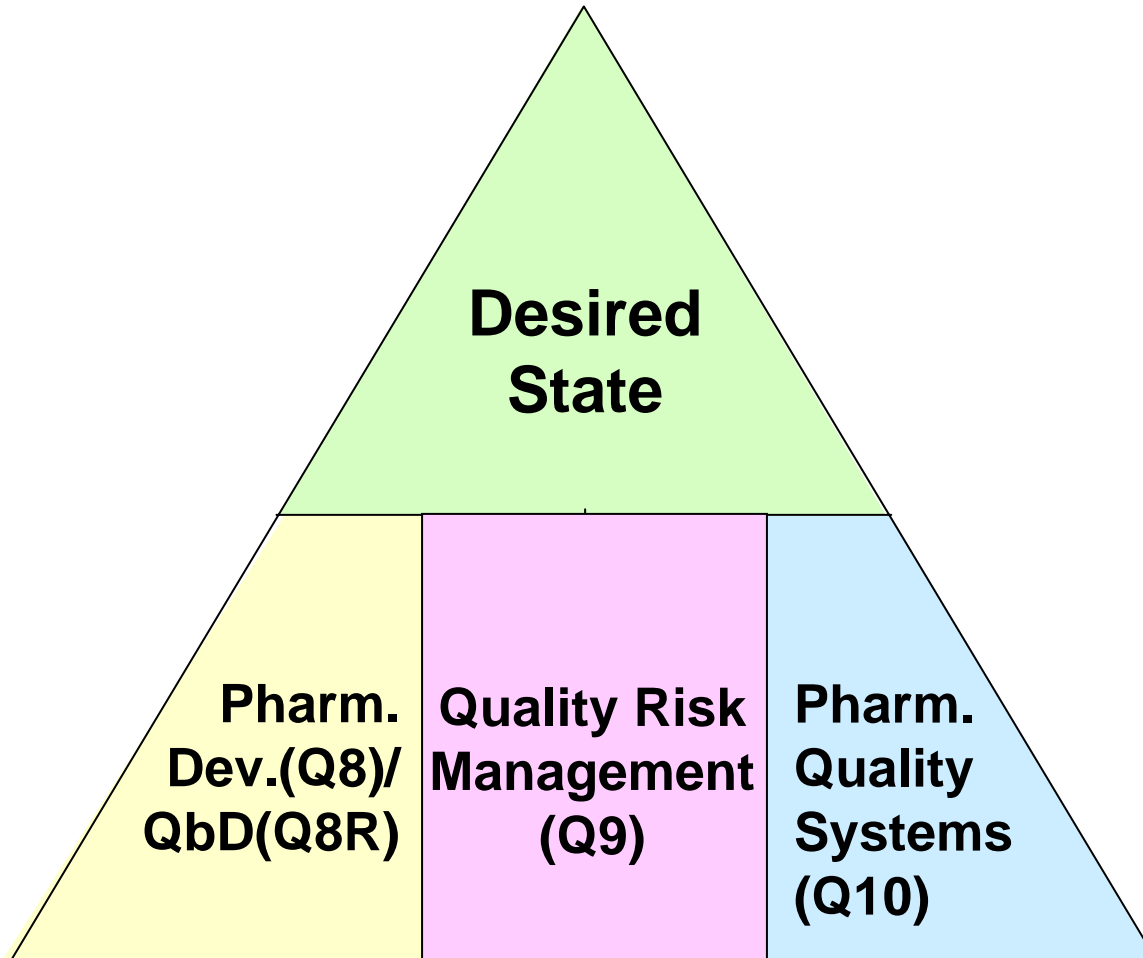


What is QbD?

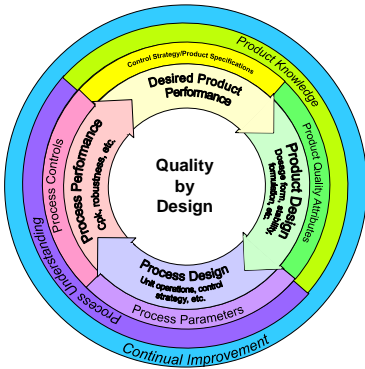
- Quality by Design is:
 - Scientific, risk-based, holistic and proactive approach to pharmaceutical development
 - Deliberate design effort from product conception through commercialization
 - Full understanding of how product attributes and process relate to product performance

QbD information and conclusions should be shared with FDA

ICH Quality Roadmap



QbD System



Product & process design and development

Define desired product performance upfront; identify product CQAs

Design formulation and process to meet product CQAs

Continually monitor and update process to assure consistent quality

Identify and control sources of variability in material and process

Understand impact of material attributes and process parameters on product CQAs

Risk assessment and risk control

ICH Q8 – Design Space

■ Definition

- The *multidimensional combination and interaction* of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality
 - *Traditional one dimensional process range doesn't meet Q8 definition and will not lead to "regulatory flexibility"*

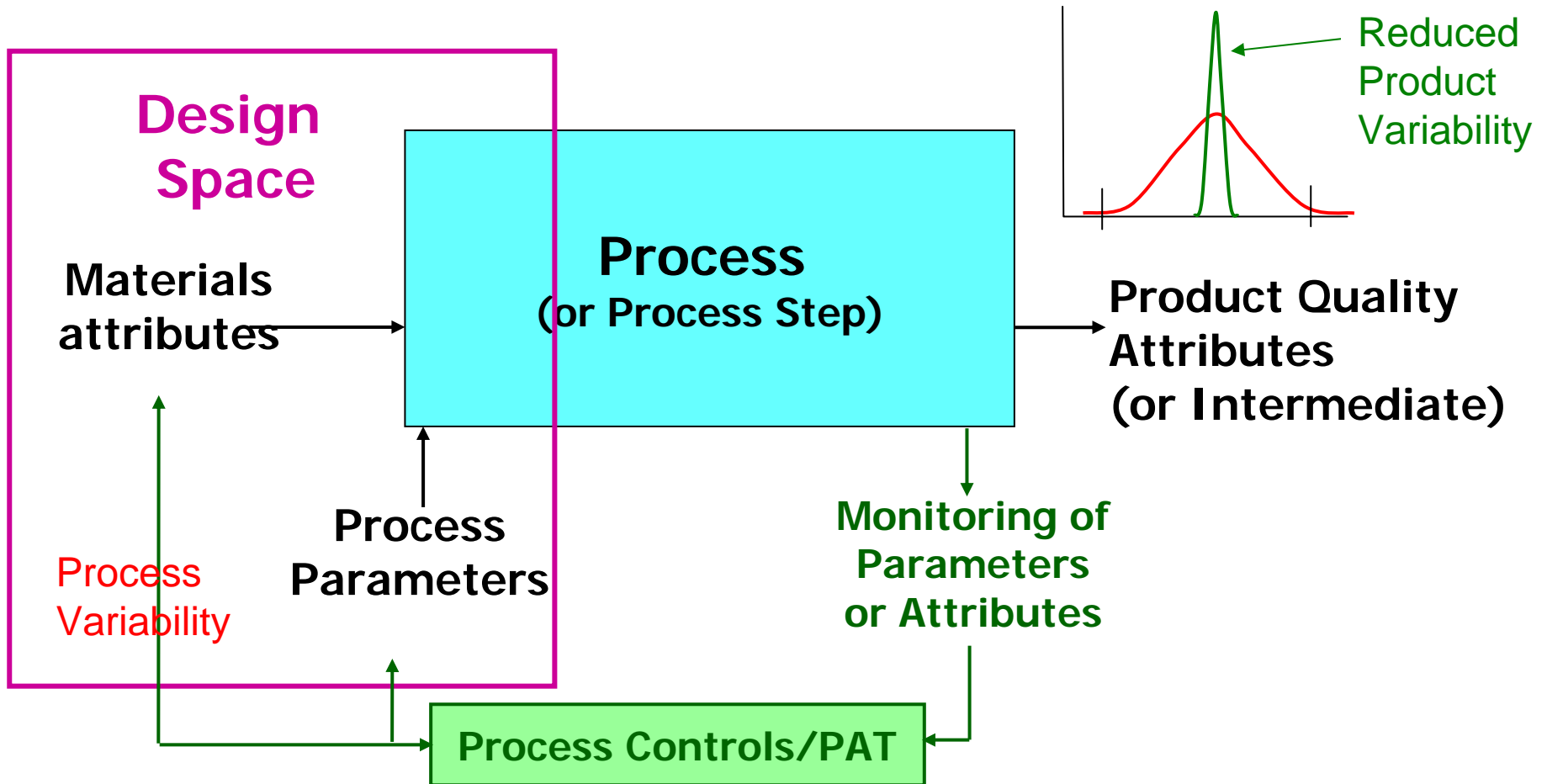
■ Regulatory Flexibility

- Working within the design space is not considered a change

■ Important to Notice

- Design space is proposed by the applicant and is subject to regulatory assessment and approval

Reducing Product Variability



Why Use QbD for OINDPs?

- CQAs for materials, products, and process parameters (CPPs) are better understood
- Controls are rationally designed to fit end-use performance criteria in light of CQAs and CPPs
- The entire manufacturing system is more flexible; accounting for and responding to variability in materials, environment, and process, within a known design space
- More flexible regulatory framework which relies on the demonstration and use of knowledge
- May reduce overall approval time (time to approval + launch)
- May reduce product failures after approval associated with variability in ingredients and process that would not otherwise have been considered

Desired Product Performance

- Utilize early phase data such as
 - Optimum dose or dose range
 - Therapeutic index
 - PK / PD profile where applicable
 - Site of activity (local) / absorption (systemic)
 - If local, rescue versus chronic
 - Physicochemical properties prior knowledge
 - CCS (compositions, extractable profile etc.)
- To define desired product characteristics and performance (CQAs) such as
 - Delivered Dose Uniformity (DDU)
 - Aerodynamic Particle Size Distribution (APSD)
 - Product stability
 - Drug/device combination issues

Formulation/Product Design



- Drug Substance (DS)
 - Identify Critical Quality attributes (CQAs) such as moisture content, polymorph form, surface morphology, PSD which affect downstream drug product performance of DDU, APSD, etc.
- Delivery Platform
 - MDI, DPI, Nasal Spray, Inhalation Spray, etc.
- Formulation/device subtype
 - e.g., suspension versus solution MDI
 - e.g., device metered versus pre-metered DPI
- Limited excipient choices in all cases
 - Limited by pharmacology/toxicology concerns

Identify CQAs of Excipients

- Propellant(s) and Ethanol
 - Water content
 - Impurities
- Surfactants
 - Compositional profile, surface active properties
- Lactose
 - Hydrate form, amorphous content
 - Surface morphology
 - Water content
 - PSD
- Magnesium stearate
 - Compositional profile
 - PSD
- Leucine, DPPC, water, buffers, salts, preservatives, etc.

Container Closure System (CCS)



- CCS or device components are part of the drug delivery system, which is an integral part of the drug product.
- CCS design has always been critical to OINDPs
- Dose Counter recommended
- The sharing of knowledge between the drug product manufacturer and the CCS designer/ manufacturer would facilitate 1st cycle approval and flexible risk-based regulatory decisions.



CCS Performance Goals

- The following are desired throughout the shelf life
 - Reliable and accurate dose delivery
 - Stable and dimensionally consistent
 - Mechanically robust
 - Protection of the formulation
- Readily manufacturable
- User friendly characteristics (ruggedness to variability in patient use)



CCS Development in QbD

- Gather knowledge early in partnership with CCS component manufacturers/supplier(s)
- Material choice for the CCS components of the OINDP will be driven by the desired performance parameter outcomes and formulation compatibility considerations

This includes:

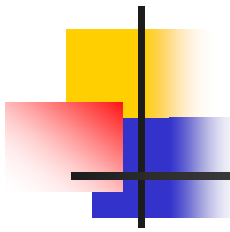
- Metals
- Plastics
- Elastomers
- Fabrication methodology for each component
- Additives in plastics and elastomers
- Processing aids used in forming, cleaning, and assembly

CCS Development in QbD



- Understand sources of variability for each material, component, and processing used in the CCS for your drug product
- Evaluate the impact of this variability on CCS performance as it pertains to your drug product.
 - Rational Design of Experiments (DOE)
 - Determine who (NDA applicant or supplier) will do them
- Work with your supplier(s) to ensure appropriate in-process controls for your CCS components
- Collaboration with your CCS supplier(s) to maximize the chances for success as part of a rational risk assessment program

Manufacturing Process Understanding

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- For each unit operation
 - Understand how process parameters affect CQAs
 - Conduct risk analysis/assessment to:
 - Identify critical process parameters and materials attributes
 - Develop risk reduction strategies
 - Establish appropriate control strategy to minimize effects of variability on CQAs
 - Evaluate risk in terms of severity, likelihood, and detectability

Manufacturing Process Understanding



As an example, consider DS micronization

- Current recipe approach
 - Time, temp, humidity set at predefined ranges
 - Fixed process; almost any change requires Agency approval
 - This approach is controlled but not robust
 - Tight controls over incoming non-micronized DS are usually necessary
 - Problematic with planned site, equipment, and scale, changes
 - Sensitive to variability without being responsive to it
 - Data laden, but knowledge poor, system

Manufacturing Process Understanding



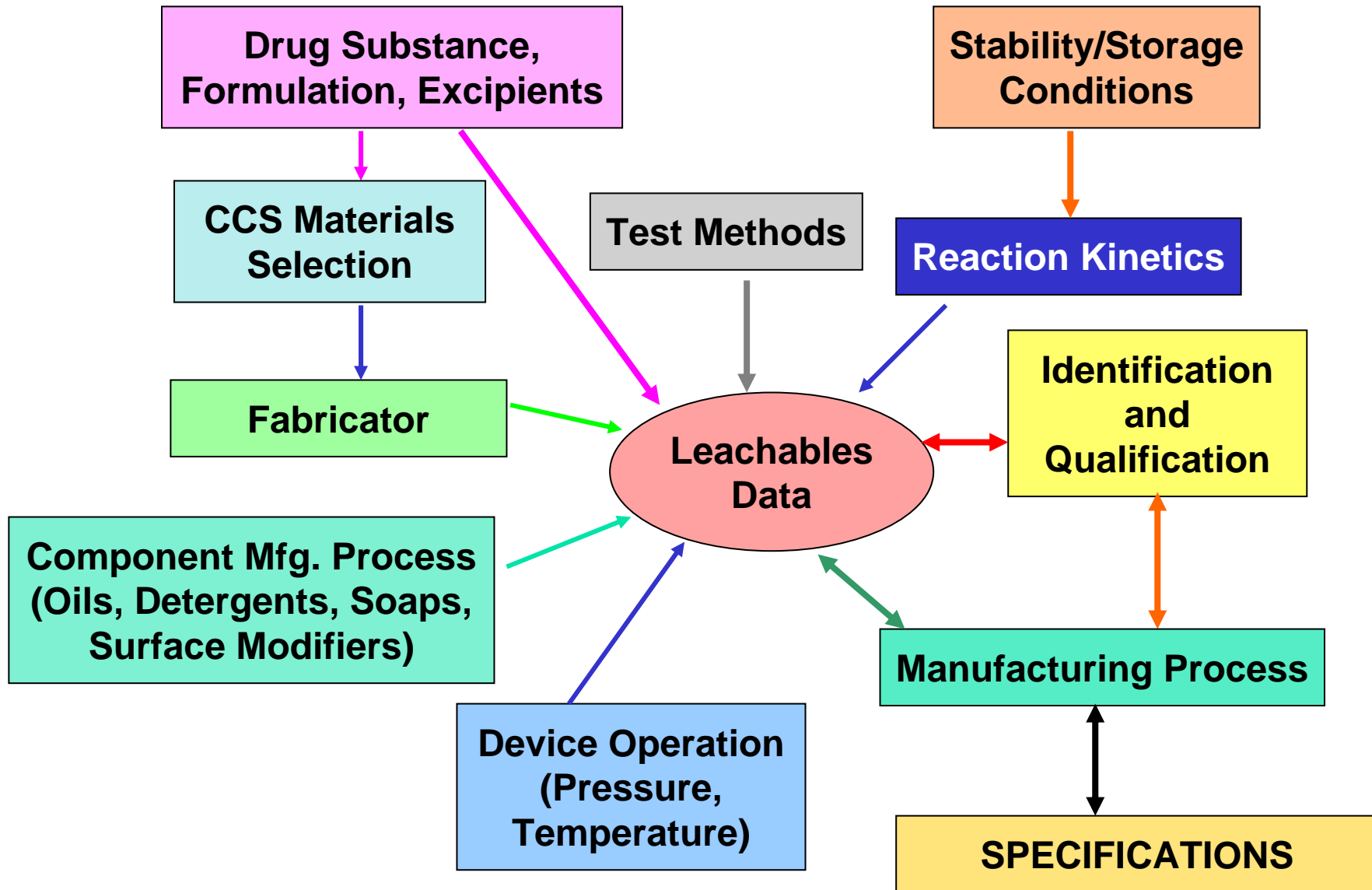
- Alternatively, for a QbD approach
 - Combination and interaction effects of time, temp, and humidity on DS CQAs are studied and understood, and design space established
 - Process is adjustable within design space without regulatory oversight
 - A QbD approach controls the DS to desired endpoints (PSD, polymorph limits, surface morphology, etc.) and is more robust



Designing/Setting specifications in the Future

- Clinical Relevance
- Science and risk based
- Part of quality control strategy
- Alternative approaches (e.g., statistical approaches/PTIT for DCU) may be considered

Leachables Specifications



Case Study 1: Metastable Reversion of Micronized DS Used in an MDI

- During early development the applicant discovers that there is a drop in drug product fine particle mass (FPM) as collected on stages 3-5 of ACI associated with micronized DS physical instability
 - 20% drop over several weeks at 40°C/75%RH
 - Same drop over several months at 25°C/60%RH
 - This initial trend is problematic. In both cases above, there is very little drop in FPM afterwards
- The firm is considering to address the problem for subsequent studies by storing the finished MDI for several weeks at 40°C ambient RH before release testing

Case Study 1 Issues

- Many uncertainties persist
 - Reliability and predictability are unknown
 - Gaps in knowledge are not filled in
 - The material attributes and/or process parameters that cause (or mitigate) the FPM drop have not been elucidated
 - The role of moisture the FPM drop is unclear
 - Other changes that several weeks at 40°C may induce in the CCS and formulation are not yet known
 - Valve function changes in response to elastomer aging
 - Leachables may increase in response to the proposed operation

Case Study 1 Resolution



- Conduct lab scale studies
- DOE
- Possible outcomes
 - The proposed operation may be supported by thorough knowledge
 - The need for (and effects of) several weeks of “hot storage” may be eliminated
 - Control of material CQAs (e.g., water content, feed PSD, etc.)
 - Control of micronization CPPs

Case Study 2: Optimization of Device/Formulation

- DPI change after Phase 2 studies. Design of device was “optimized” and the new device operated in the same general manner
- Formulation was changed to add certain excipients claiming the drug product was easy to manufacture
- In vitro comparative data for several dose strengths were compared to previous version
- A substantial change that was deemed medically relevant in the FPM (>20%) was noted
- No scientific justification as to what caused the change in FPM

Case Study 2: Resolution

- Sponsor asked to perform clinical studies to re-characterize the drug product performance in clinical trials. Development timelines extended.
- A QbD approach would have characterized the dependence of FPM on APSD properties (e.g., airflow within the device, device resistance, impact of formulation change, moisture content) prior to instituting the change.
- A design of experiments approach to evaluate the impact of these variables on FPM and total emitted dose would have indicated possible developmental hurdles.

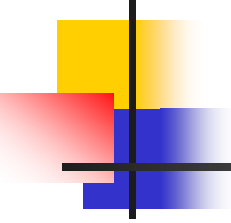
Case Study 3: MDI Valve Sticking

- During Phase 3 development of an MDI, the applicant realized that the metering valve did not behave as it did in phase 2 trials while incorporating a dose counter.
- Modification of the actuator, necessary for incorporating the dose counter led to a condition where the valve return and the release of the drug was impaired.
- Dimensional incompatibility and or/patient handling were thought to play a role in causing valve sticking and extensive variable dose delivery.

Case Study 3: Resolution

- The sponsor proposed to include specific labeling instructions for patient usage of the modified device.
- However since the root cause of the valve sticking problem was never clearly identified, a “quick-fix” approach with labeling modifications was unlikely to resolve the issues.
- Recommendations were made to redesign the components and evaluate the modification made to the actuator as a result of incorporating the dose counter, and perform a patient use study with the device extending the development time.

Case Study 4: DPI Device Failures

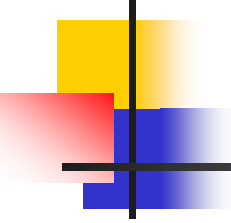
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- During Phase 3 development of a device metered DPI, the sponsor submitted reports of device failures during patient use.
 - Emitted dose significantly different than specified.
 - More critical for device metered DPIs
 - Therapeutic index for the active relatively low.



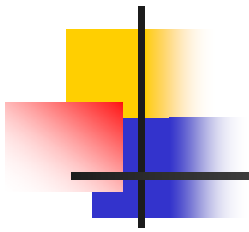
Case Study 4: Resolution

- Sponsor was asked to address this problem of device failures
- Sponsor modified the device based on engineering and mechanistic concepts and responded to the Agency with a series of design changes
- These design modifications appeared to reduce the likelihood of these problems recurring
- Under a QbD process, these issues hopefully would have been identified early on in development to minimize the development times

Concluding Remarks

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- QbD approach is recognized as the desired state for drug development, more so for OINDPs due to their complex nature
 - Proactive thought process should be involved in assessing the CPAs and CPPs that define the product
 - Specifications only part of quality control strategy
 - Culture change is necessary for implementing this sort of development both by the applicants and regulators
 - Ultimate goal is to make a quality product available to the consumer with less regulatory oversight

Acknowledgements

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