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Determination of Acceptable Variability for Regulatory Flexibility

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Focus of the Presentation

- Objective
- Introduction
- Qualification of a CCS Based on Risk Assessment
- QbD for E/L

- Application of QbD to E/L

- Regulatory Flexibility
- Conclusion



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Objective

1. Discuss application of QbD concepts to determine acceptable *Material (or other) Variability*.
2. Identify the *focused testing* to seek the potential regulatory flexibility and acceptance



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Introduction

Acceptable Variations

- 🔔 Variability: Able or Apt to change
- 🔔 Accepted change – Scientifically justified
- 🔔 HOW? – Apply QbD; Relate to observable Quality:
 - ▶ Extractable profile (manufacturer of the component)
 - ▶ Leachable profile (DP manufacturer/sponsor)



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Introduction

Working Definitions for a New Paradigm

 Quality

 Quality by Design (QbD)

 Design Space (DS)

 Design of Experiment (DoE)

 Risk and Management of Risk



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Introduction

Working Definitions: ICH Guidelines

 "Risk based" concepts and principles of ICH:

- ▶ Q8 (knowledge transfer/science based)
- ▶ Q9 (opportunity to use structured thinking)
- ▶ Q10 (quality systems across product life cycle)



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Introduction
Working Definitions: QbD (ICH Q8)

Quality by Design (QbD):

 Design a quality product

 Quality should be built into the product

- ▶ * Knowledge
(ingredients/interactions/process/interactions)
- ▶ * Reduce variation of profile (E or L)




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Introduction
Working Definitions: DS (ICH Q8)

Design Space (DS):
multi-dimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality.

 DS in relation to E/L: Changes outside the DS have acceptable change to the E, L profile




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Qualification of a CCS Based on Risk Assessment

Why be Pro-active to Manage Quality?

 *Out of Crisis* by Edward Deming (1986)

 **(less re-work, fewer mistakes, fewer delays, less waste, improved productivity, capture market, stay in business, provide jobs)** (1950 in Japan: basis of all meetings)

 Renewed approach: QbD,
understood/improved/sustained quality = patient compliance, stay in business & more money



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Qualification of a CCS Based on Risk Assessment

Manage Quality: Assessment of Risk Factors

 Risk Factors must be:

- ▶ **Defined**
- ▶ **Estimated**
- ▶ **Evaluated**
- ▶ **Documented**

- A good DEED will lead to a logical decision
- Risk-based decisions can be easily re-visited when risk estimate changes or new risk factors become available



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Qualification of a CCS Based on Risk Assessment
Why assess Risk Factors?

-  Assess **Risk/Benefit data** related to drugs/CCS

-  Develop strategies to **manage the risks** and reduce harm


-  Manage **drug information** by developing and disseminating – encourage optimal use



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Qualification of a CCS Based on Risk Assessment
Risk/Benefit Assessment by the Regulator

-  Do the data support: the Drug's
 - ▶ Efficacy
 - ▶ Safety
 - ▶ Quality


- ▶ In relation to the proposed CCS?



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Qualification of a CCS Based on Risk Assessment
Regulation/mandate/administration Re. pharmaceutical products






-  Regulation - part of the pre-market evaluation/approval process
-  Mandate - *Canada's Food and Drugs Act and Regulations*
-  Administration - Therapeutic Products Directorate (TPD), Health Canada (comparable to CDER of US FDA)



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Qualification of a CCS Based on Risk Assessment
How Do We Manage Risk?

-  Establish facts about the disease being treated
-  The route of administration
-  Review scientific data (pre & post market)
-  Review of international experience
-  Implement risk reduction measures



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Qualification of a CCS Based on Risk Assessment Data for Review

 The Sponsor is responsible for the original data submitted; and data related to changes

 Data generated by:

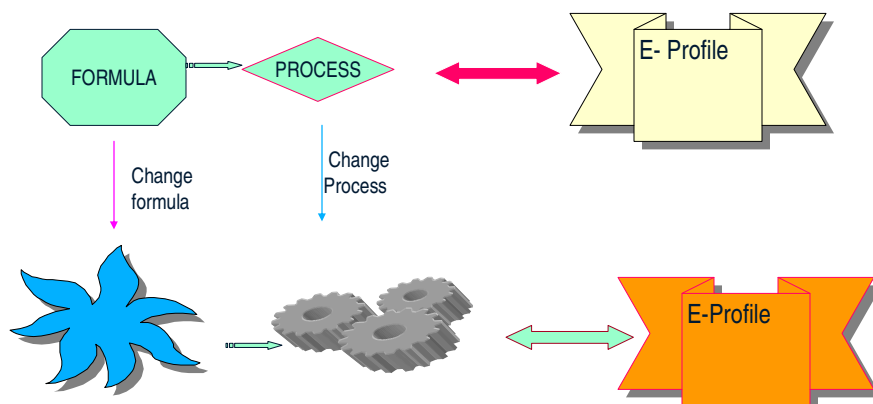
- ▶ the contract DP manufacturer?
- ▶ the component manufacturer (N-1)- Type II DMF
- ▶ those before N-1 – not regulated



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QbD for E/L Determination of Acceptable Variations by CM



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QbD for E/L Who Should Monitor the Outcome of Variations?

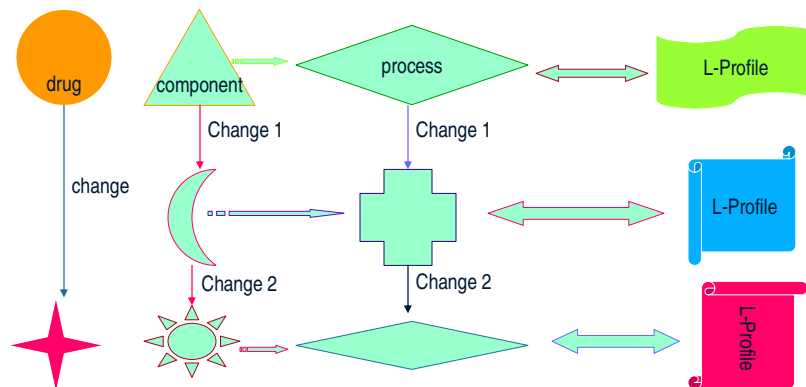
-  The component manufacturer
-  The Contract DP manufacturer
-  The DP manufacturer/sponsor



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QbD for E/L Determination of Acceptable Variations (DPM)






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QbD to E/L

Who Should Monitor the Outcome of Variations?

-  The Contract DP manufacturer
-  The DP manufacturer/sponsor

-  The ultimate responsibility of the DP quality: The sponsor; in Canada

-  The DP manufacturer:
 - ▶ In Canada
 - ▶ In any other country

Consequences of not reporting variations !




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Application of QbD to E/L

Purpose

-  Eliminate unknowns by:
 - ▶ Systematic Experiments (risk based evaluation, Critical Parameters)

 - ▶ Understand parameters (potential impact on E/L, safety & efficacy)


 - ▶ Design experiments (monitor/control parameters, achieve desired & sustainable profile)



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Application of QbD to E/L
Reasons to Eliminate Unknowns

-  Removes Quality Concerns:
 - ▶ Proprietary information
 - ▶ E profile/Leachables by DP manufacturer
 - ▶ Specific Analytical methods
 - ▶ Second/Third Party involvement (ingredients, manufacturer, supply chain etc.)



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Application of QbD to E/L
preamble

 What?

 When?

 Why?

 Who?

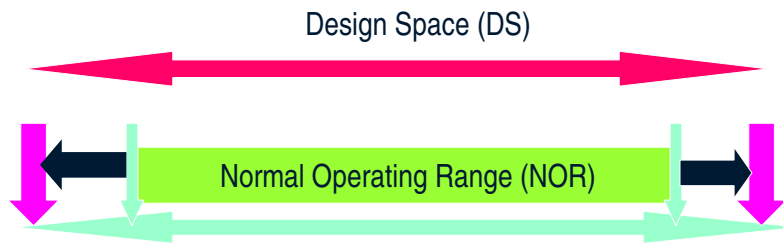


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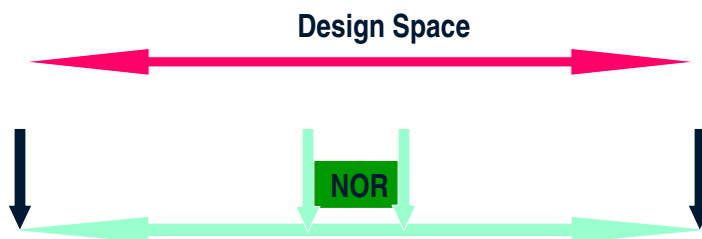
Application of QbD on E/L
Working definition: Process Parameters

- 1. Critical Process Parameters (CPPs):
Direct impact on one or more Critical Quality Attributes (CQA)



Application of QbD to E/L
Working definition: Process Parameters

- 2. Key Process Parameters (KPPs):
potential impact on CQAs, lower risk



Application of QbD to E/L
Desired State

 Pro active versus Reactive

 Target CQA in the Drug Product = Purity
(other)

 Ultimate Aim: Patient Safety



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Application of QbD to E/L
The Outcome Due to Variations




 MINIMUM Changes to the **E-**
Profile/ L-Profile



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Focused Testing for Qualification


-  Biocompatibility as per USP <87>, <88>
-  Systematic approach to determine an extractables profile and compare to that approved
-  Systematic testing to determine a Leachable profile and compare to that approved



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Lifecycle Management

-  Continue life-cycle management
 - ▶ Continuous monitor/evaluate/report
 - ▶ Assess challenges to sustain/enhance quality
 - ▶ Assess impact on ultimate QA- E Profile



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ICH Q8, Q9 & Q10 & Related Opportunities

 *Quality Implementation Working Group on Q8, Q9 and Q10: Questions and Answers; March 11, 2009*

 Q10:

- ▶ Comply with GMP- potential changes if quality systems are in place?
- ▶ Facilitate science/risk based pharmaceutical quality assessment
- ▶ Enable innovative approaches to process validation
- ▶ Establish real time release mechanisms
- ▶ Etc.



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Application of QbD to E/L **Advantages/Disadvantages**

 Advantages

 Reputation: Assured Quality

 Major market share: 'ready for change'

 Higher level of knowledge: Future prospects for innovations

 Disadvantages

 Cost/resources/time

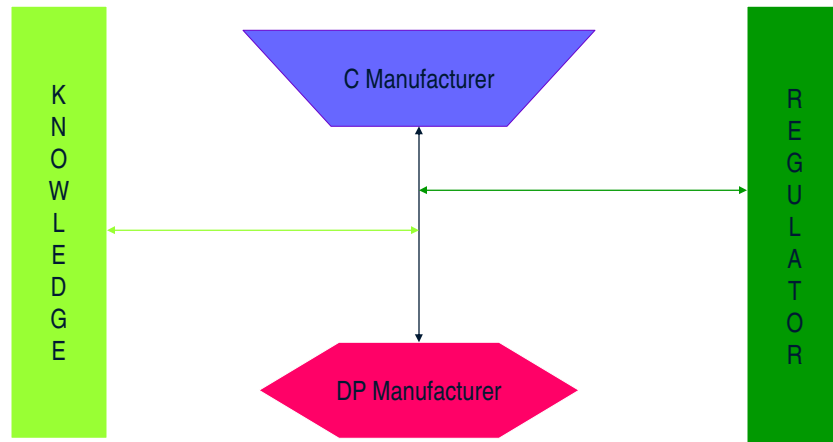
 Proprietary information: share/not share







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Application of QbD to E/L Knowledge Transfer – CM/DPM/R



Regulatory Flexibility The strategies to Integrate Applicable Data

-  Demonstrate Process understanding: effects on CCS– critical steps/ in-process controls, process validation
-  Demonstrate product specific suitability – leaching (eliminate post market out of specifications / market withdrawal)
-  Prepare an effective summary- use of QOS-CE
-  Demonstrate the connection between data, eliminate the 'disconnect'

Regulatory Flexibility Roles & Responsibilities

Manufacturer:

- ▶ Extensive knowledge-CQAs & CPPs
- ▶ Strive for continuous improvement
- ▶ Communicate/educate regulator
- ▶ Effective data presentation
- ▶ Effective summary
- ▶ Identify QbD in CPID-CE
- ▶ Compliant tracking system?
- ▶ Partnership with involved parties?



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Regulatory Flexibility Roles & Responsibility

Regulator

Extensive knowledge-CQAs & CPPs

Initial verification, subsequent audit, create environment conducive to innovation and continuous improvement

Effective internal, international cooperation



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Conclusion

- 🔔 Maintaining quality standards and product safety - price versus implicit risk to health, and scientifically justify any variations
- 🔔 The goal of the drug review process in Canada is to provide safe and efficacious drugs to all Canadians
- 🔔 The regulatory flexibility by application of QbD concepts
- 🔔 Who would benefit? *Ingredient supplier, component manufacturer, DS manufacturer, excipient supplier, DP manufacturer, shipper, re-packer, the physician/nurse and the pharmaceutical regulator*



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Thank you

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