Post Market Quality Changes

Today, Tomorrow and Beyond

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Regulatory CMC Guidance in Canada

Today	Tomorrow	Beyond
"Dated" guidances	Updated to reflect current practice	Design Space (ICH Q8)
Small molecules-based	Updated to CTD format	Quality Risk Management (ICH Q9)
Lacking detail	Small molecules, biologics and radiopharmaceuticals considered separately	Quality Systems (ICH Q10)
Lack of harmonization across regions	Vastly increased detail	
	Harmonization increasing	

The Draft Post Notice of Compliance Changes Guidance

Favourable Changes – What we liked:

- One stop shopping
- Prescriptive – no “hidden” requirements?
- Organized according to the CTD – easily navigated
- Biological drug changes no longer force-fit into small molecules guidance
- Reduced real time stability at time of filing
- Level 4 is gone!
- Positive moves toward harmonization with other regions
- Has a risk-based approach – can be further refined through the current consultation with industry

The Draft Post Notice of Compliance Changes Guidance

Our comments/queries:

- Prescriptive – loss of scientific flexibility?
- Need to navigate carefully through the detail
- Changes are not exhaustive
  - To add or extrapolate….that is the question….
- Comparability protocols?
- No CTD Section A guidance

Clarity and Consistency: Points to Consider

- If it's not listed as required supportive data, it's not required?
  - Examples: validation summaries vs. protocols and reports, stability data
  - Understanding that Health Canada reserves the right to request additional information, the integrity of the "Supportive Data' section needs to be preserved.
    - **Guidance can't be "minimum acceptable requirements" one day and "just a suggestion" on another.**
  - Sponsors want to do it right the first time.
  - Some data cannot be *generated* when a clarifax is received, eg, stability.

Clarity and Consistency: Points to Consider

- If it's not a data requirement in an NDS should it be required in a change submission?
  - Examples:
    - Environmental monitoring data – trending/state of control is GMP
    - Laboratory qualification – GMP
    - Equipment qualification – not IQ or OQ

Clarity and Consistency: Points to Consider

- If it is assured through GMP audits is it necessary in a prior approval change submission?
  - Evidence of GMP compliance has to be meaningful.
  - We don’t submit water data, why would we submit EM data?
- Where do Yearly Biological Product Report submissions fit in with annual reporting requirements?

Clarity and Consistency: Points to Consider

- Categories with reduced filing/data requirements are not re-elevated on a case-by-case basis.
  - We are moving into an era of change categorization by risk assessment.
  - Need to not drift into elevated assessments or document requirements based on historical comfort level or scientific curiosity.

Harmonization Opportunities

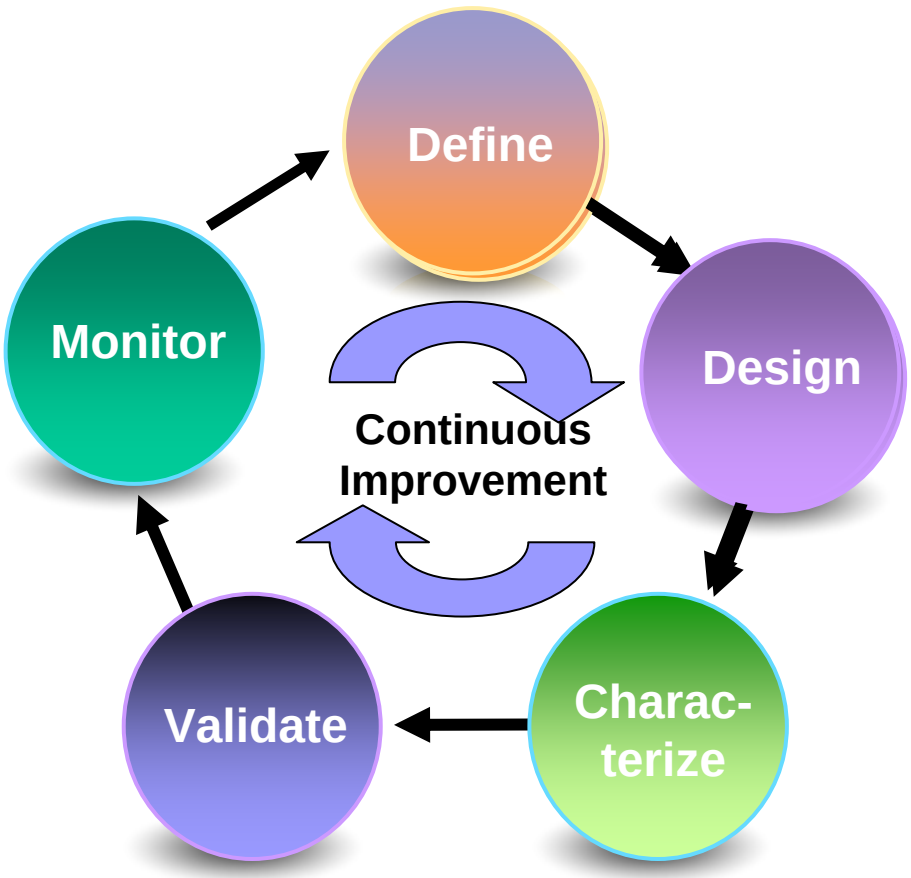
- Differences in post-market change assessment and filing requirements is a challenge for industry and regulators
- Unique opportunity: major regions are all currently relooking at post-market changes guidance
- A general trend toward risk-based methods of assessment and self-regulation
- This is the time to compare and contrast evolving guidance across regions – industry and regulators
- Explore opportunities for regulators to sit down together (with industry?) to look at proposed guidance across regions

The Importance of Participation

- Opportunities for improving guidance are infrequent.
- Sponsors have a responsibility to help get this right – your voice counts.

Don’t be a bystander!

Quality by Design (QbD)



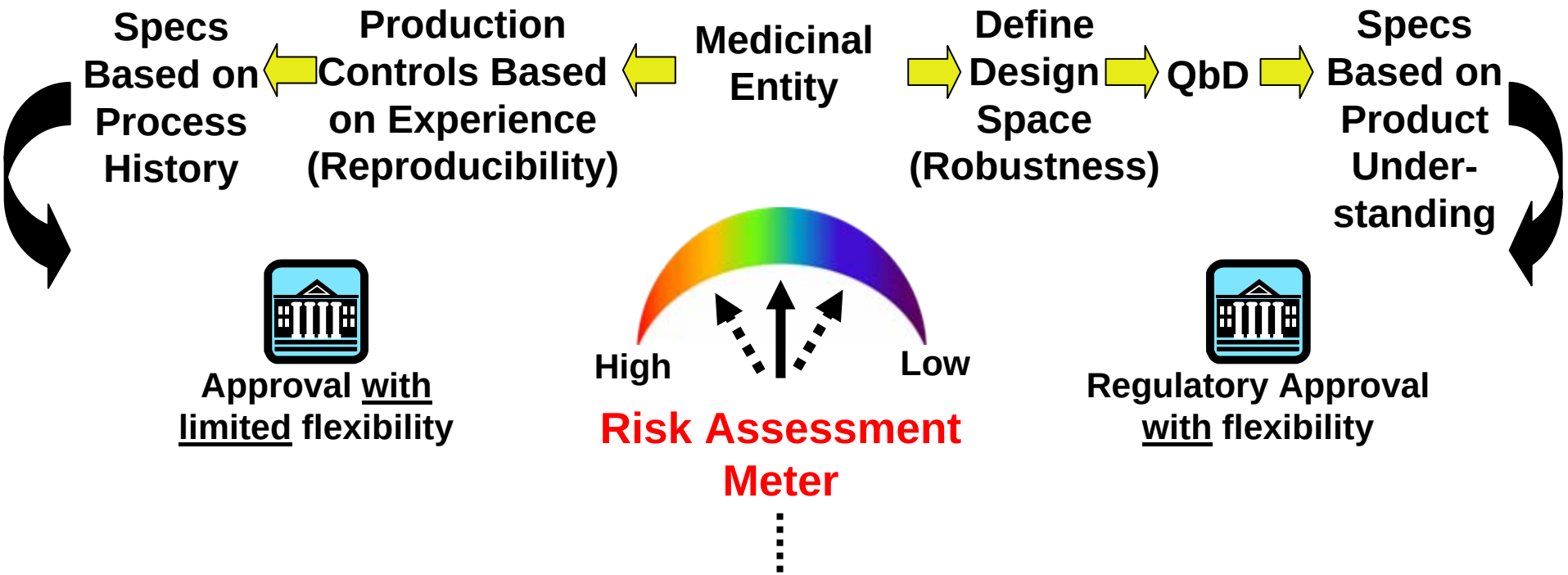
"*Quality by design* means designing and developing manufacturing processes *during the product development* stage to **consistently ensure a predefined quality** at the end of the manufacturing process…"

- FDA Draft Guidance, Sept. 2004

QbD A new paradigm for management of product quality

Historic Approach
Quality by Testing and Inspection

Future Approach
Quality Designed into Product



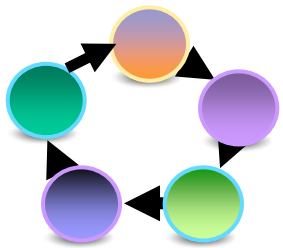
Views on CMC

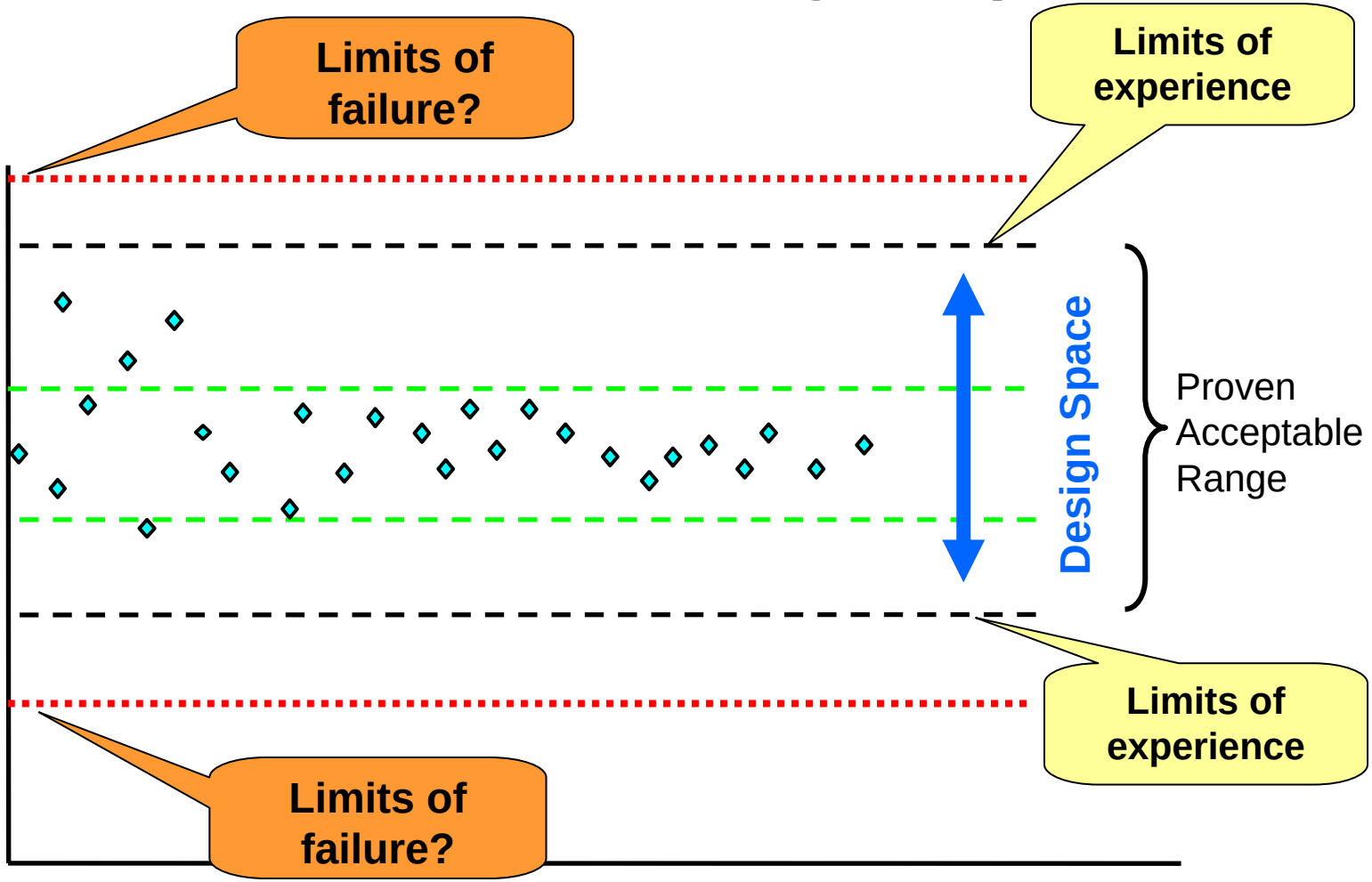
Traditional View	Vision Going Forward
■Document what *can* be measured	■Document what *should* be measured - clearly identify and justify critical controls
■CMC written to summarize *experience* instead of *capabilities* to set controls and specs	■Set controls and specs based on knowledge of justified operating boundaries
■Focus on process validation (reproducibility)	■Focus on process understanding and design for robustness
■Submissions define rigid boundaries for operating – “continuous improvement” is burdensome	■Proactive identification of latitude for changes – Design Space ■Regulatory mechanisms to facilitate continuous improvement

Views on CMC (cont'd)

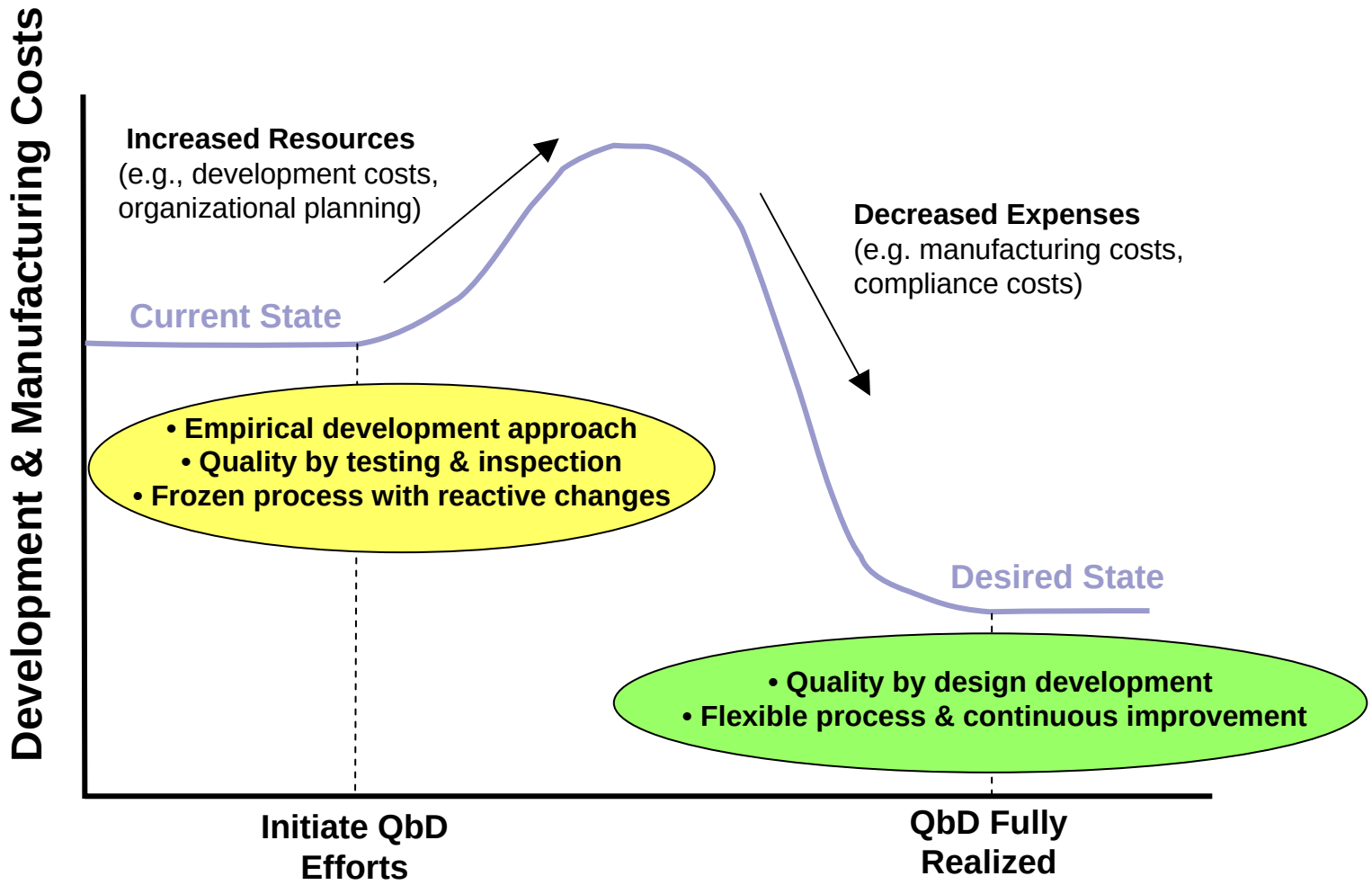
Traditional View	Vision Going Forward
■Extensive post-market change submissions – "everything *might* be critical"	■Reduction of unnecessary submissions for movement in the Design Space
■Speed to market influences scope of pharmaceutical development knowledge	■Planning target product profile as part of development ■Prioritize knowledge-gathering by risk level ■Platform approaches
■Resource burden of post-market changes	■Offset through more effective resource allocation in the design and development stages

Movement in the design space





Cost and Benefit of QbD



Moheb M. Nasr, Ph.D. CDER, FDA, 2006 PhRMA API WORKSHOP Denver, Colorado, September 28, 2006

QbD – Implementation Issues

"Design Space is proposed by the applicant, and is subject to regulatory assessment and approval."

- Supporting data: "Pharmaceutical development data to support the establishment of the design space."
- Regulators and sponsors do not yet have experience with QbD submissions.
- What elements of Quality by Design ***must*** be in the original submission?
- What ***may be*** provided to agencies above the baseline volume of data?
- Need to consider how Design Space can be established for legacy dossiers.

QbD – Global

- A globalized approach is vital – to ensure a single, harmonized QbD program is suitable to all regulators
- ICH Q8 describes the suggested content for 3.2.P.2. Pharmaceutical Development
  - Design Space is introduced but requirements are not detailed
- There are already differing views on interpreting movement within the design space:
  - ICH Q8 “Working within the design space is not considered as a change.”
  - Cdn draft post NOC changes guidance: “Working within the design space is not considered as a change that would require prior approval and should be described in the next *Annual Notification*.”
- FDA is developing a Design Space guidance and has ONDQA* Pilot Program to gain experience.

** Office of New Drugs Quality Assessment*

In Summary

- Moving from a diverse collection of “top line” guidances to a single, more prescriptive guidance
- Health Canada has invested tremendous efforts into this initiative – now it’s our turn to provide valuable input
- The future vision of CMC will further the risk-based approach, designing in quality, robustness and regulatory flexibility