Quality by Design for Biotechnology Products: An FDA Perspective

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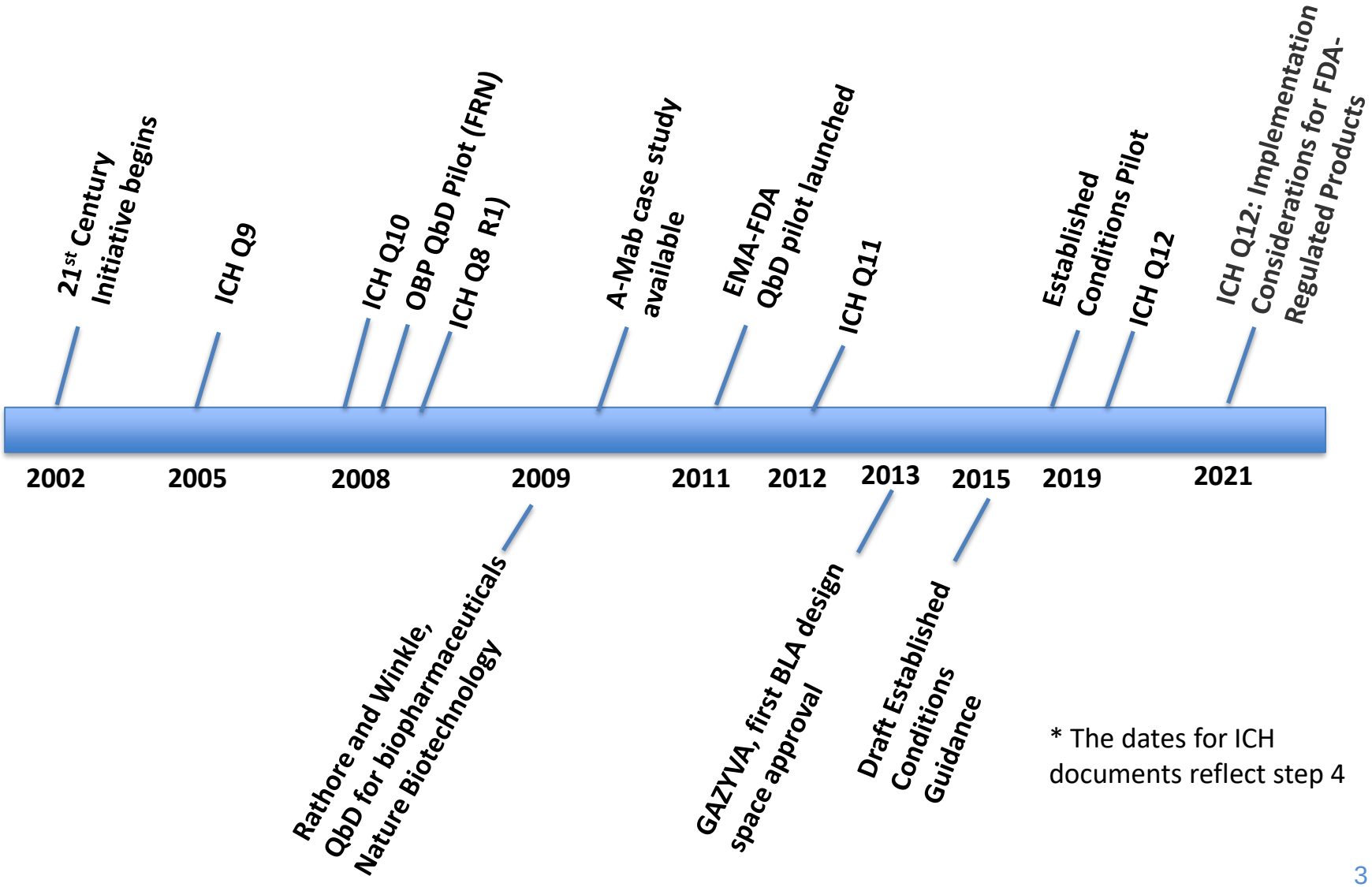
What is Pharmaceutical Quality?

- A quality product of any kind consistently meets the expectations of the user
  - Drugs are no different
- Patients expect safe and effective medicine with every dose they take
- Pharmaceutical quality is assuring every dose is safe and effective, free of contamination and defects
  - It is what gives patients confidence in their next dose of medicine




QbD Milestones for Biotechnology Products



* The dates for ICH documents reflect step 4

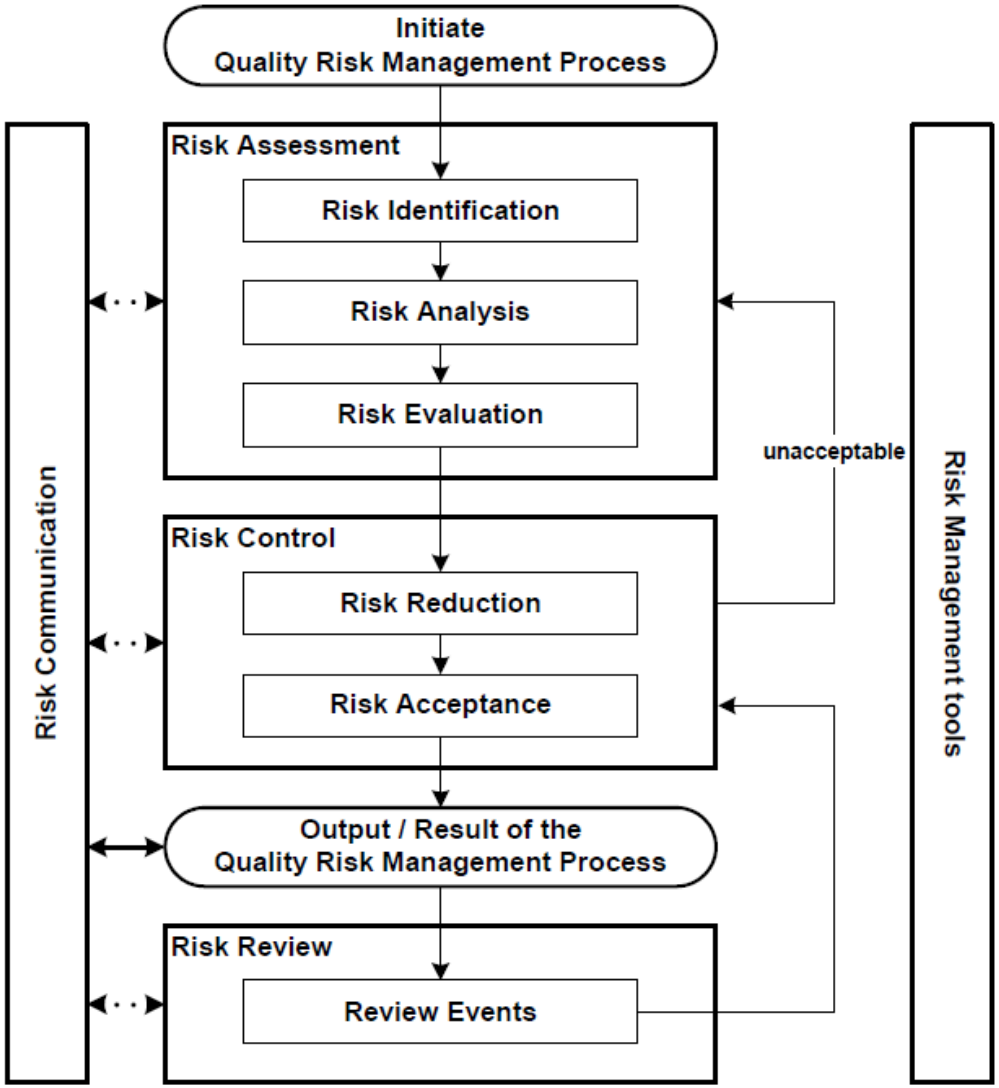
2002: Pharmaceutical Quality for the 21st Century – A Risked Based Approach

Vision

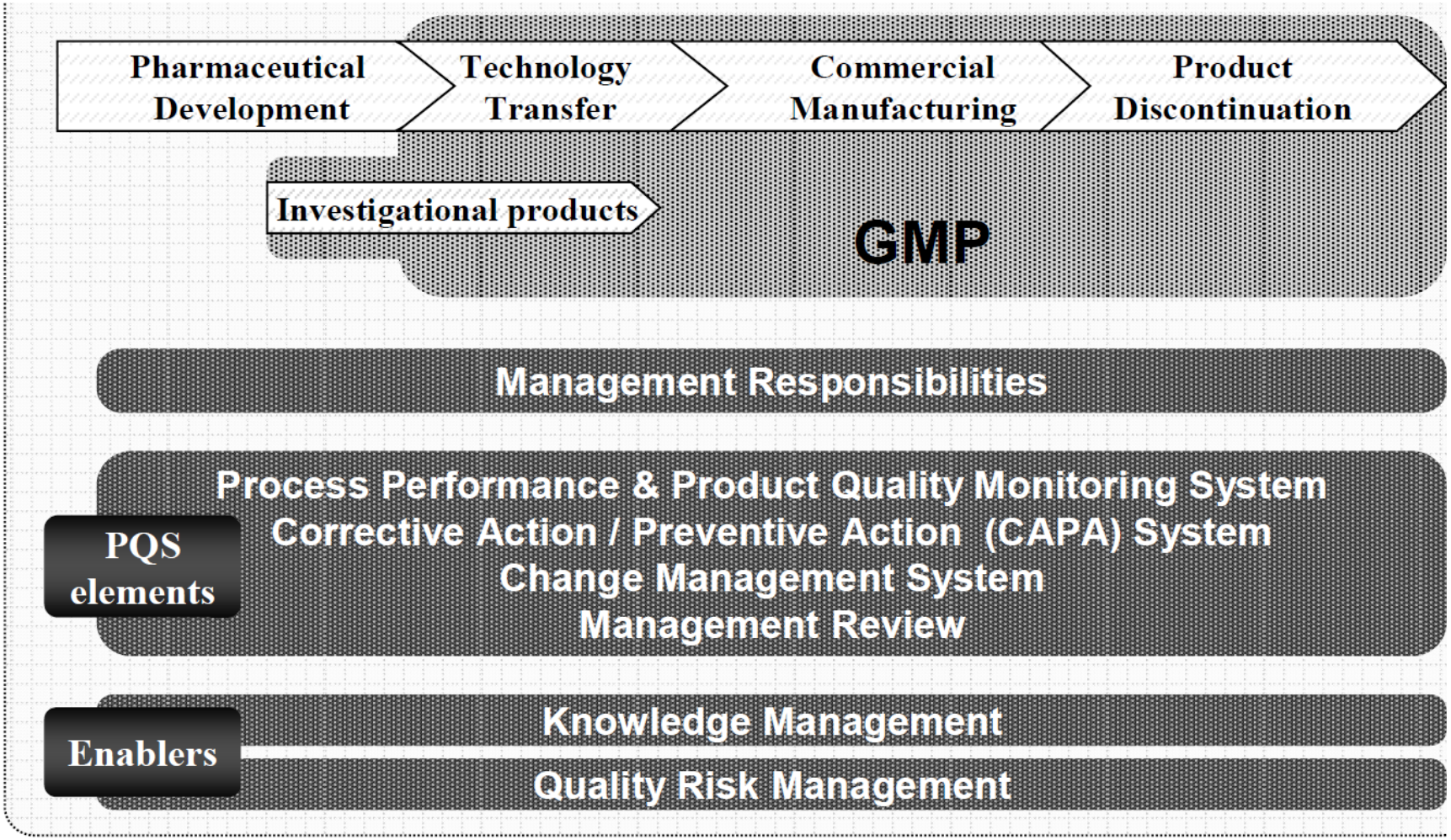
"A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight"

-Dr. Janet Woodcock

2005: ICH Q9 Quality Risk Management



2008: ICH Q10 Pharmaceutical Quality System



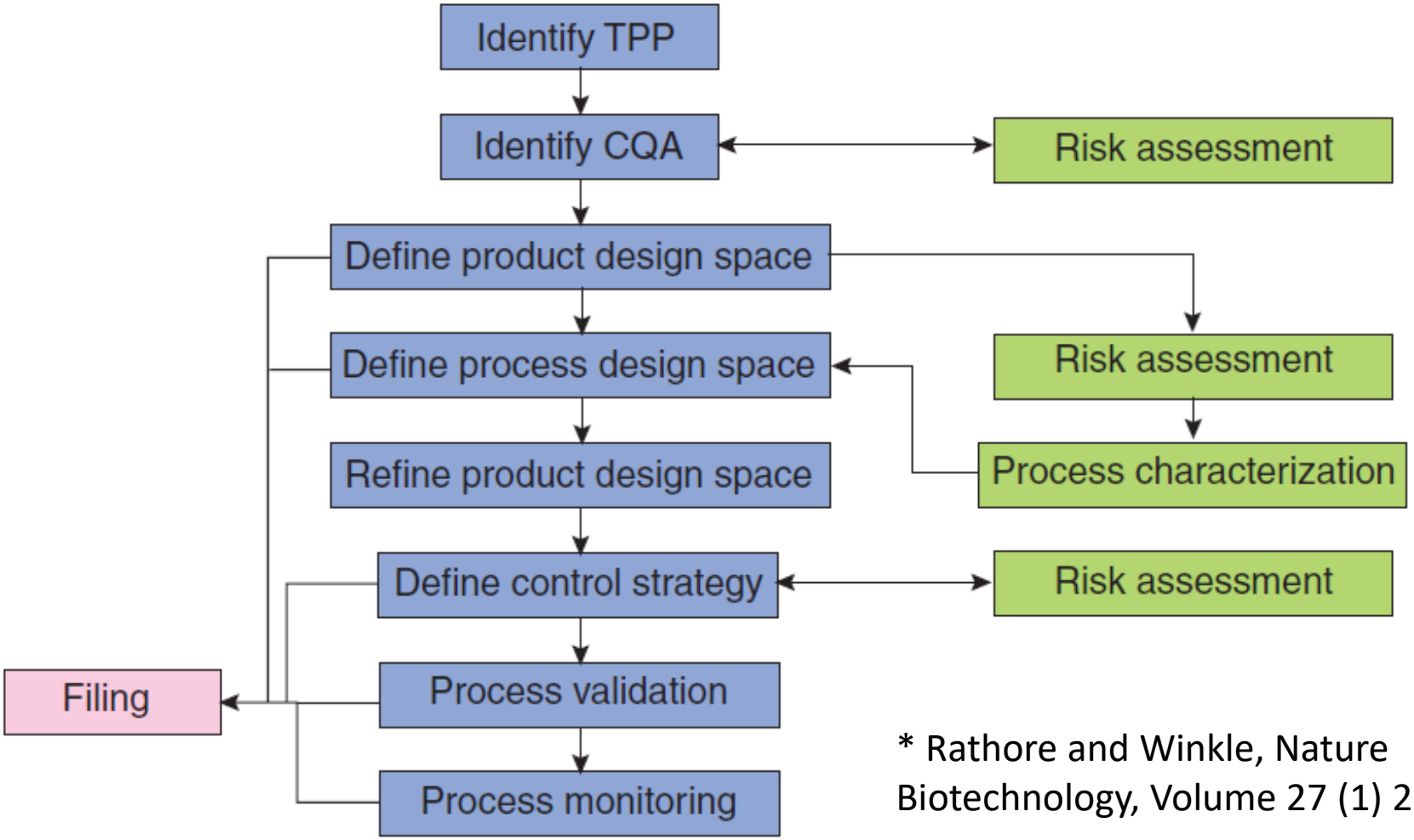
2008: Annex to ICH Q8 Pharmaceutical Development

1) Describes the principles of QbD

- Quality Target Product Profile
- CQAs
- Risk Assessments: Linking Material Attributes and Process Parameters to CQAs
- Design Space
- Control Strategy
- Product Lifecycle and Continual Improvement

2) Describes Minimal and Enhanced Pharmaceutical Development Activities

Key Steps of QbD Implementation for Biotechnology Products (2009)

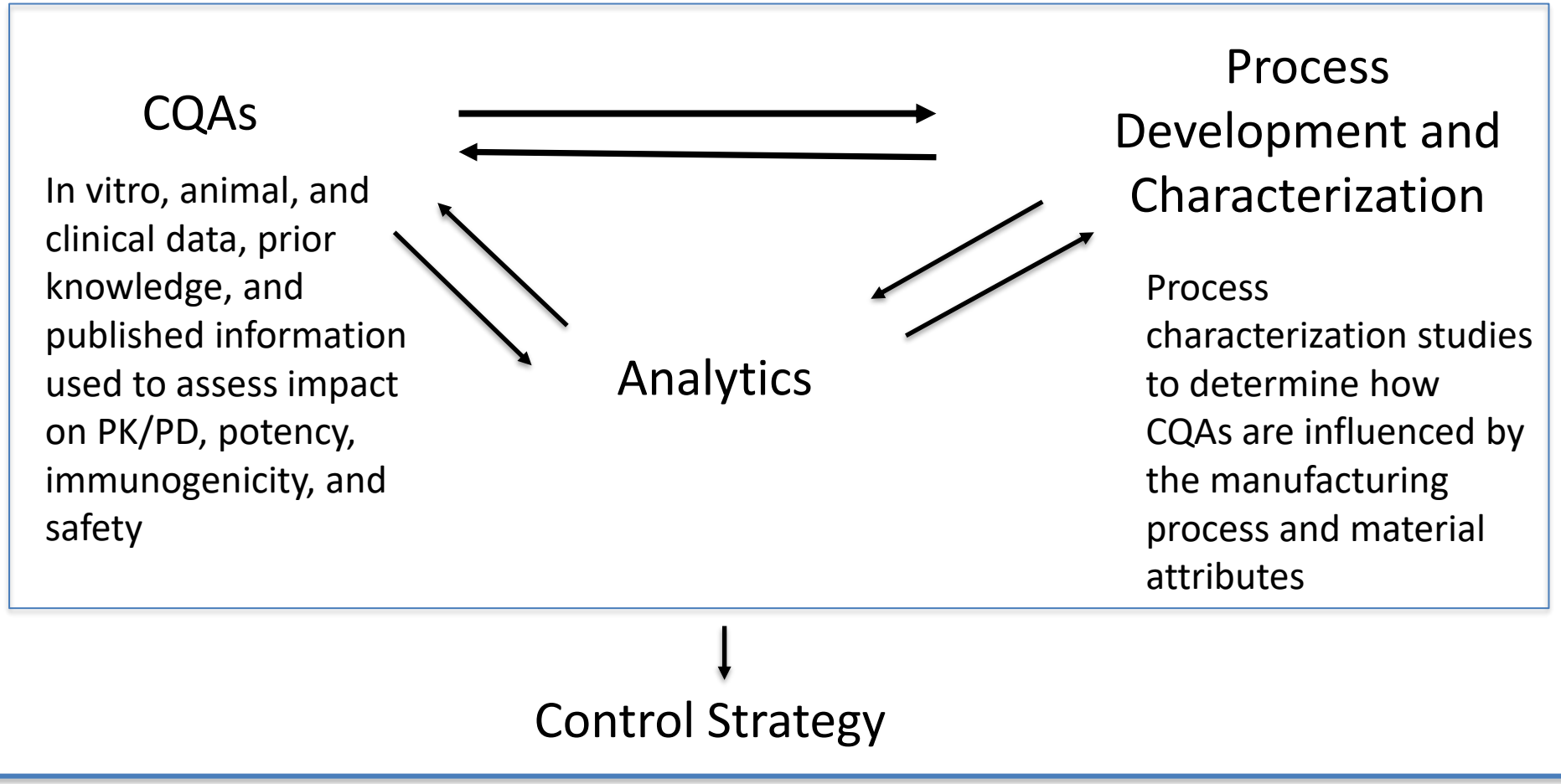


* Rathore and Winkle, Nature Biotechnology, Volume 27 (1) 26-34

2012: ICH Q11 Development and Manufacture of Drug Substances

Provides further clarification on the principles and concepts described in ICH Guidelines on Pharmaceutical Development (Q8), Quality Risk Management (Q9) and Pharmaceutical Quality System (Q10) as they pertain to the development and manufacture of drug substance.

ICH Q8, 9, 10, 11
Enhanced approaches



PQS

OBP QbD Pilot Program

FR Notice July 2, 2008

- To define clinically relevant attributes for protein products (regulated by OBP) and link them to manufacturing processes
- To consider quality-by-design (QbD) approaches to unit operations in supplements (10) as well as original applications (5)
- To explore the use of comparability protocols submitted under 21 CFR 314.70(e) and 601.12(e))

OBP QbD Pilot Program

- Applications Accepted in QbD Pilot
  - 24 Meetings have been held for the six applications

  - 6 Original Applications
    - 5 Monoclonal Antibodies and 1 Fc Fusion Protein
    - 1 QbD original submission BLA received in 2012

  - 4 Post-approval Supplements
    - 2 with site transfers
    - 1 post-approval supplement with CP (approved in 2010) (multi-product, multi-site)

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Examples of Lessons Learned* and Recommendations

- Adhere closely to definitions and concepts outlined in ICH. Deviations from ICH definitions and recommendations will need to be robustly justified

- The submission should contain detailed explanations of all risk assessment tools used and links to individual reports. There should be justifications for the scoring systems and cut-offs used.

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* Lessons learned applies to QbD in general

Examples of Lessons Learned and Recommendations on CQAs

- The structural and functional complexity of biotechnology proteins makes identification of a product's critical quality attributes very challenging.
  - Large number of quality attributes need to be assessed for patient impact. Potential for attributes to interact and/or impact stability (e.g., oxidation and free thiols contributing to the formation of aggregates).
  - Many attributes are present at levels near or below the limit of detection. Issues arise on how these attributes should be evaluated and controlled.
  - There is a need to communicate a large database of information that was used in the CQA risk assessment

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Examples of Lessons Learned and Recommendations for CQAs

- For each attribute, it is recommended that a detailed summary narrative be provided of the risk assessment that was performed. Include a summary of the data used to assess criticality along with links to both the literature cited and the relevant sections of the submission.
- Reach agreement with the Agency on all relevant mechanisms of action of the product that need to be considered.
- CQAs risk assessment tools should not include process capability
- Need to include information/discussion on attribute interactions.

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Examples of Lessons Learned for Process Characterization

- Lack of information to justify CPP vs. non-CPP classification
  - Lack of sufficient information to justify which parameters were included/excluded from the process characterization studies
  - Lack of sufficient information to support process parameter ranges used in characterization studies. Process parameter ranges should be broad enough to assure that CQA impact would be identified.
  - Justifying statistically significant vs. clinically meaningful changes in CQAs in process characterization studies

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Examples of Lessons Learned Examples for Process Characterization

- Lack of sufficient information on how material attributes were considered in the characterization studies.
- Addressing the residual risk associated with the use of small-scale models that are not fully representative of the full-scale process. This is particularly problematic for bioreactors.

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Examples of Process Characterization Recommendations

- For process wide knowledge: it is recommended that, for each CQA, a systematic summary of process impact (i.e., the impact of each unit operation, hold step, stability study, linkage study, etc.) be provided.
- A justification for the statistical analysis should be provided. Need to provide an explanation of how a statistically significant change to a CQA is discriminated from and one that is 'practically' meaningful.
- For non-CPPs: it is recommended that the submission contain a justification for the non-CPP classification, the limits of the process at which a parameter is a non-CPP, summaries of any risk assessments, additional data and/or studies demonstrating that the parameter does not affect CQAs

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Examples of Process Characterization Recommendations

- Provide summary information on preliminary risk assessments performed to determine which parameters to include/exclude from the process characterization studies.
- Provide a justification for the process parameter ranges used in the characterization studies determined
- Provide information on how material attributes were considered in characterization studies.
- Clearly describe how residual risks from small scale models were addressed

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Lessons Learned for Control Strategies (CQA Acceptance Criteria)

- Cumulative effects of attributes should be considered in establishing acceptance criteria.
- Increased quality attribute knowledge and risk assessments can be used to broaden the acceptable range for some attributes so that they outside of manufacturing and clinical experience.
  - The acceptability of this approach will consider how process consistency is addressed. This can include, for example, information on the strength of the pharmaceutical quality system to monitor and trend quality attributes.

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Lessons Learned for Control Strategies

For each CQA, it is helpful to provide a summary paragraph/table/diagram of the control strategy (i.e., release, in-process, monitoring, comparability, no testing) that pools together all of the available information (e.g., CQA risk, process characterization studies, linking studies, stability studies, material attributes, an assessment of the strengths/weaknesses of the analytics).

From 2013 L. Graham presentations

2013: FDA approval of GAZYVA and first design space for a BLA

Most sponsors, however, moved away from claiming a design space, and towards utilizing elements of QbD to achieve a more flexible control strategy as well as regulatory flexibility , such as:

- Wider parameter ranges based on process characterization studies
- More focused testing strategies based on process characterization and product understanding
- Wider CQA acceptance criteria based on clinical relevance

Next evolution: QbD and ICH Q12

ICH Q12 Objectives

ICH Q12 Objectives* include:

- …**Harmonize change management**…in a more transparent and efficient manner…across ICH regions
- …Facilitate **risk-based regulatory oversight**…
- Emphasize…**control strategy** as a key component of the…dossier
- Support **continual improvement** and facilitate introduction of **innovation**
- Enhance use of regulatory tools for **prospective change management**…enabling **strategic management of post-approval changes**…

*From the ICH Q12 concept paper

ICH Q12 Tools

- Established Conditions
- Post-Approval Change Management Protocols
- Product Lifecycle Management Document
- Structured Approaches to Frequent CMC Post-Approval Changes

Established Conditions (ECs)

ECs = legally binding information considered necessary to assure product quality. As a consequence, any change to ECs necessitates a submission to the regulatory authority.

Established Conditions (ECs)

- Can rely upon the risk-based paradigm set forth in the regulations and the recommendations in these associated guidance documents (i.e., typical ECs)

Or

- Can propose ECs in the original application or supplement, for the entire CMC section of a BLA, or limited subset, that differ from the typical

Proposing Established Conditions (ECs)

If proposing ECs: There are multiple opportunities for flexibility, considering product, process and analytical knowledge, along with associated risk assessments, such as:

- Whether a parameter/attribute is an EC or not (if not, manage changes under the PQS)
- For parameters, the ranges (or design space) within which changes can be made without reporting
- For those parameters/attributes that are ECs, lower reporting categories can be proposed (e.g., CBE-30 vs. PAS)

Post-Approval Change Management Protocols

- Refers to comparability protocols submitted under 21 CFR 314.70(e) and 601.12(e))
- Follow FDA guidance on Comparability Protocols

Product Lifecycle Management Document

- The PLCM document should include proposed ECs, reporting categories for making changes to approved ECs, a list of comparability protocols (if submitted), and postapproval CMC commitments, if applicable.
- Applicants should provide an updated PLCM document with each supplement or annual report that reports changes to approved ECs. If no specific ECs are proposed, submission of a PLCM document is not necessary.
- The PLCM should indicate the manufacturing sites (preferably by facility establishment identifier (FEI) number) where an EC will be implemented.

ICH Q12 Pharmaceutical Quality System

- An effective PQS is critical to support the use of the tools in ICH Q12
- FDA will assess the effectiveness of a firm's PQS, which generally will be informed by routine inspections conducted by FDA and capable foreign regulators, and other available information
- When introducing a new manufacturing site, the applicant should
  - Reassess the relevant ECs considering the capability of the new site's PQS
  - Provide a justification for the changes in ECs based on this assessment

Conclusions
QbD for Biotechnology Products

- Significant progress has been made in the use of Modern Pharmaceutical Principles, including implementing QbD elements, for biotechnology products
- The use of QbD does result in a significant increase in product and process understanding, which can enable increased regulatory flexibility, continuous improvement, and innovation (e.g., ICH Q12 implementation, advanced manufacturing)


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