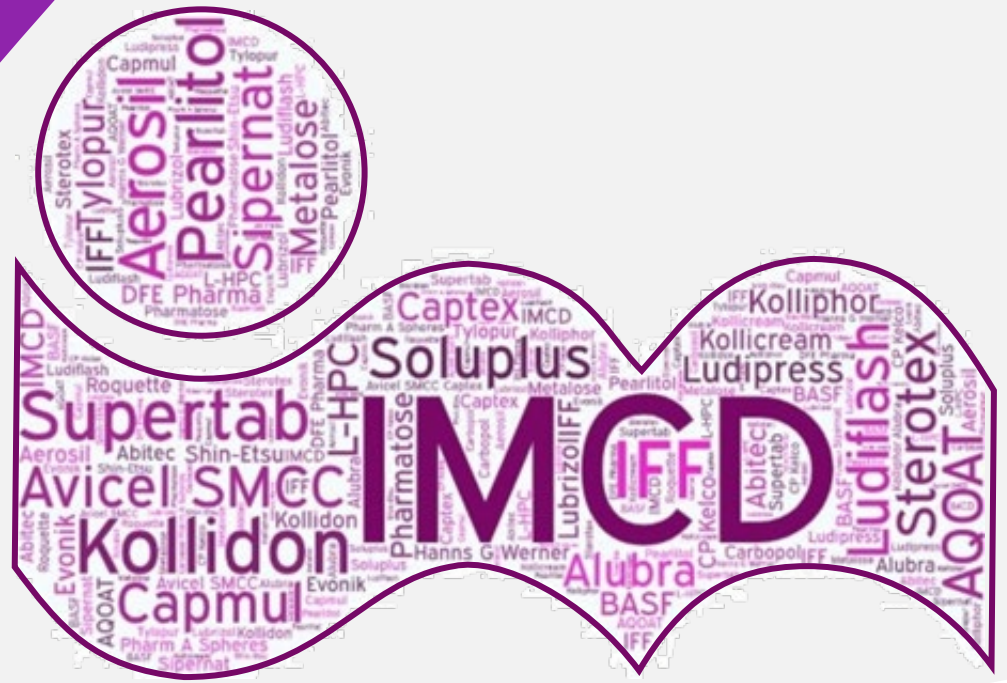
PQRI Workshop:
Managing Excipient and API Impact on Continuous Manufacturing
May 17 – 18, 2022

Beyond ICH Q13: Applicability & Use of Other ICH and IPEC Guides In Understanding Excipient Impact on Continuous Manufacturing Processes



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What is ICH?
Background

- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
  - Formed in 1990
    - 19 Members
    - 35 Observers
  - Foster the development and adoption of harmonized best practices in the development and manufacture of drug substances and drug products
  - https://www.ich.org/
  - https://www.ich.org/page/ich-guidelines

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Who is IPEC?
Background

- IPEC Federation
  https://ipec-federation.org/
  - Unified voice to promote the best use of excipients in medicines
- IPEC-Americas
  https://ipecamericas.org/
  - Brings together diverse stakeholders that share a common objective:
    - Safe and effective production and use of excipients
  - Mission: To advocate, educate, innovate and develop best practices for excipients, with a focus on patient safety.
  - Vision: IPEC-Americas will be the preeminent authority and resource on pharmaceutical excipients.

Understanding Excipient Impact on Continuous Manufacturing

Glossary Terms Common to Many ICH Guidelines

- **Pilot scale batch**
  - A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100,000 tablets or capsules, whichever is the larger.
- **Primary batch**
  - A batch of a drug substance or drug product used in a formal stability study, from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf life, respectively. A primary batch of a drug substance should be at least a pilot scale batch. For a drug product, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.
- **Production batch**
  - A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.
- The above terms do not apply to Continuous Manufacture in the same way as Batch Processing

Understanding Excipient Impact on Continuous Manufacturing

The ICH Q13 Guidance: Continuous Manufacturing of Drug Substances and Drug Products

- ICH Q13 written specifically to address continuous manufacturing
  https://database.ich.org/sites/default/files/ICH_Q13_Step2_DraftGuideline_%202021_0727.pdf
  - CM can be applied to some or all unit operations in a CM process
  - Control Strategy: the development of a successful control strategy for CM is enabled by a holistic approach…principles described in **ICH Q8 - Q11**
  - State of Control: A state of control (**ICH Q10**) is a condition that provides assurance of continued process performance and product quality
  - Material Characterisation and Control: …particle size, cohesiveness, hygroscopicity, or specific surface area of drug substances and **excipients**
  - Equipment Design and System Integration
    - Design and configuration of equipment
    - Connections between equipment
    - Locations of material diversion and sampling points

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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

CONTINUOUS MANUFACTURING OF DRUG SUBSTANCES AND DRUG PRODUCTS Q13

Draft version

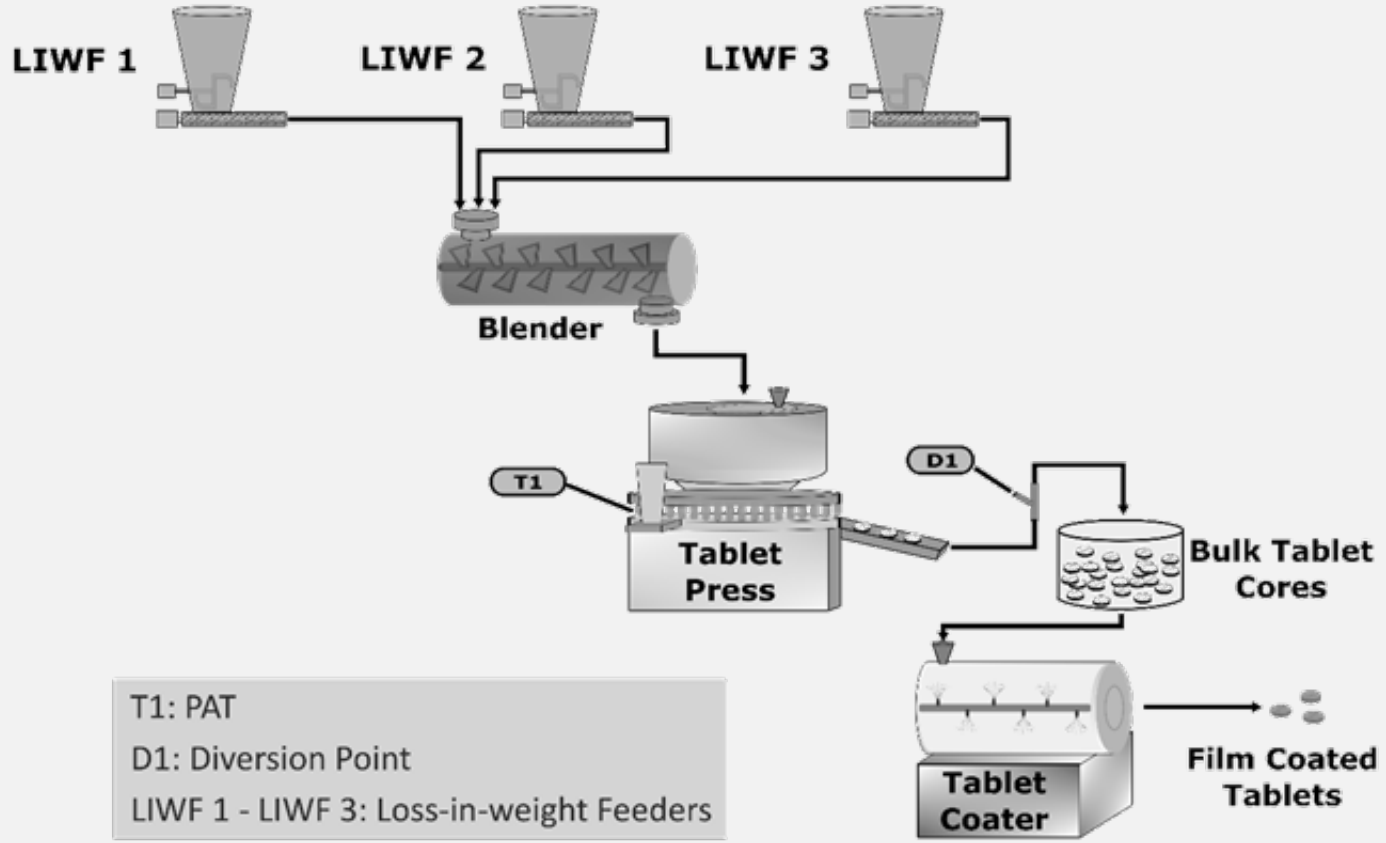
Endorsed on 27 July 2021

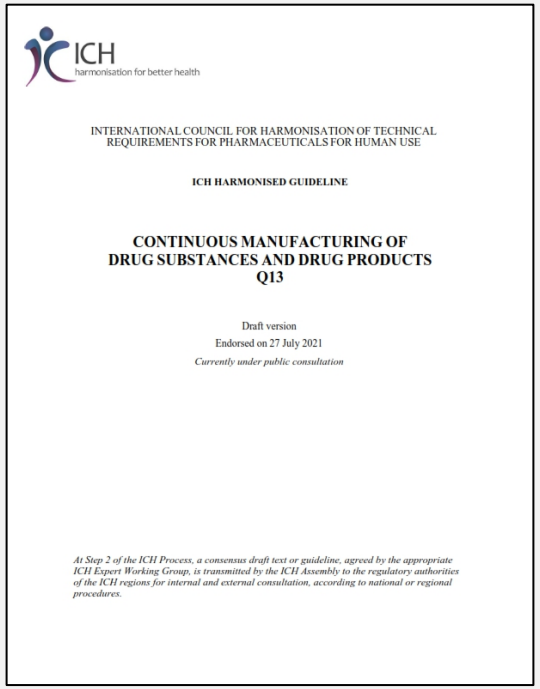
Currently under public consultation

At Step 2 of the ICH Process, a consensus draft text or guideline, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Assembly to the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures.

Understanding Excipient Impact on Continuous Manufacturing

The ICH Q13 Guidance: Continuous Manufacturing of Drug Substances and Drug Products





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Other ICH Guidelines

- ICH Q1A – Q1F: Stability
- ICH Q2: Analytical Validation
- ICH Q3A – Q3E: Impurities
- ICH Q4A – Q4B: Pharmacopeias
- ICH Q5A – Q5E: Quality of Biotech Products
- ICH Q6A – Q6B: Specifications
- ICH Q7: GMP
- ICH Q8: Pharmaceutical Development
- ICH Q9: Quality Risk Management
- ICH Q10: Pharmaceutical Quality System
- ICH Q11: Development and Manufacture of Drug Substances
- ICH Q12: Lifecycle Management

ICH guidelines are not applicable to excipients specifically or their manufacture
ICH guidelines are applicable to drug substance and drug product manufacture

Understanding Excipient Impact on Continuous Manufacturing

- ICH Q1A – Q1F: Stability
- ICH Q2: Analytical Validation
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- ICH Q11: Development and Manufacture of Drug Substances
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Understanding Excipient Impact on Continuous Manufacturing

ICH Q8: Pharmaceutical Development

- ICH Q8 speaks to Quality by Design (QbD) approach to product design and manufacture and PAT
  - Systematic approach to product and process design
    - DOE (Design of Experiments) will likely have added variables in CM
  - Helps capture the interactions among the variables – materials and process
  - PAT used to demonstrate control/make adjustments
    - This is particularly important to CM
- Why is ICH Q8 important to continuous manufacture
  - There is a significant difference when shifting from batch to continuous manufacture
    - Critical Material Attributes (CMA) can be (often are) different
      - Powder flow for example
    - Some Critical Process Parameters (CPP) will be different
    - Critical Quality Attributes remain unchanged
- The established design space can be (and likely will be) quite different, batch to CM
  - Design space provides understanding of various interactions and helps establish manufacturing flexibility – creates knowledge
  - In CM, the design space defines all manufacturing "scales"
    - "Scale" does not change – the process "cross-section" remains the same throughout manufacture

Understanding Excipient Impact on Continuous Manufacturing

ICH Q8: Pharmaceutical Development

- Excipients (Section 2.1.2 Excipients)
  - Excipients can influence the drug product performance or manufacturability
    - Type, concentration/use level, and physicochemical characteristics
    - Functional characteristics – CM suitability
  - Excipient-excipient / excipient-API compatibility should be established.
  - Ability to provide intended function, performing throughout drug product shelf life, should also be demonstrated
    - Performance/intended use can/should be used to justify the choice and quality
- Process development (Section 2.3 Manufacturing Process Development)
  - Critical formulation attributes are important to consider
    - Manufacturing process options should be understood
      - Equipment used should be appropriate for the intended task
    - Component selection needs to be appropriate for CM
  - Product and process development studies should capture other additional information
    - Process improvement, process validation, continuous process verification, process control requirements.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL DEVELOPMENT
Q8(R2)

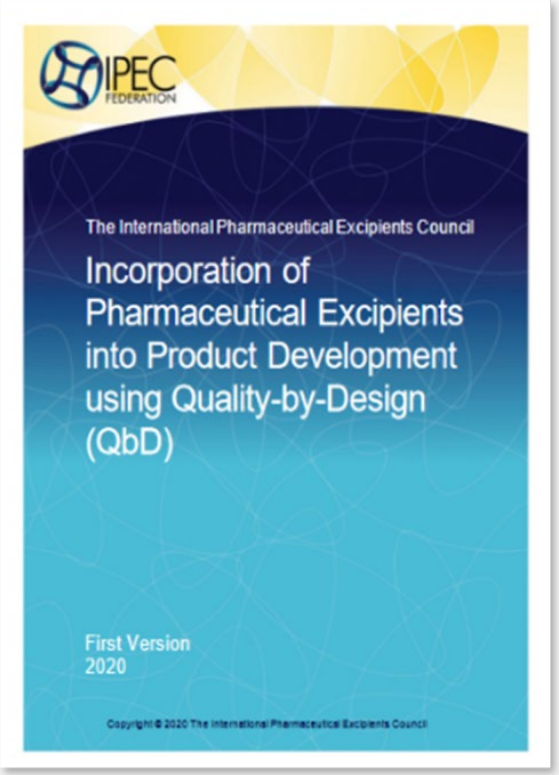
Current *Step 4* version
dated August 2009

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Understanding Excipient Impact on Continuous Manufacturing

IPEC Guide: Incorporation of Pharmaceutical Excipients into Product Development using Quality-by-Design (QbD)

- IPEC Quality by Design (QbD) Guide
  https://ipecamericas.org/filedepot?fid=1527
  - Introduce QbD & formulation development concepts
  - How QbD impacts excipient manufacturers and users.
  - Guide excipient manufacturers on customer requirements for QbD.
  - Manage user/regulator expectations on incorporating excipient variability into QbD formulation projects.
  - Impact of excipient variability on finished product quality in development and control strategy



Understanding Excipient Impact on Continuous Manufacturing

IPEC Guide: Incorporation of Pharmaceutical Excipients into Product Development using Quality-by-Design (QbD)

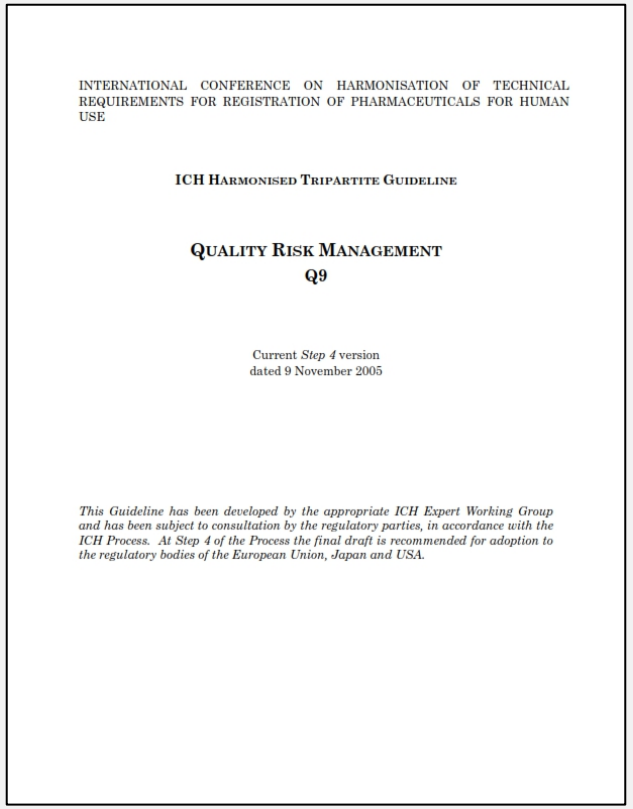
- What impacts of excipient variability?
  - Supplier-to supplier
  - Batch-to-batch
  - Package-to-package
- What other variables beyond the specification/acceptance criteria?
  - Performance expectations
- Special Cause Variation due to excipient and finished-product complexity?
- How to factor excipient variability into Design of Experiments, Control Strategy, and Lifecycle Management
- Alignment of supplier, user, and regulator expectations
- Increase Product Robustness

Understanding Excipient Impact on Continuous Manufacturing

ICH Q9: Quality Risk Management

https://database.ich.org/sites/default/files/Q9%20Guideline.pdf

- ICH Q9 outlines all topics related to risk assessment
- Two primary principles of quality risk management are:
  - The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient
  - The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk.



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ICH HARMONISED TRIPARTITE GUIDELINE

QUALITY RISK MANAGEMENT
Q9

Current *Step 4* version
dated 9 November 2005

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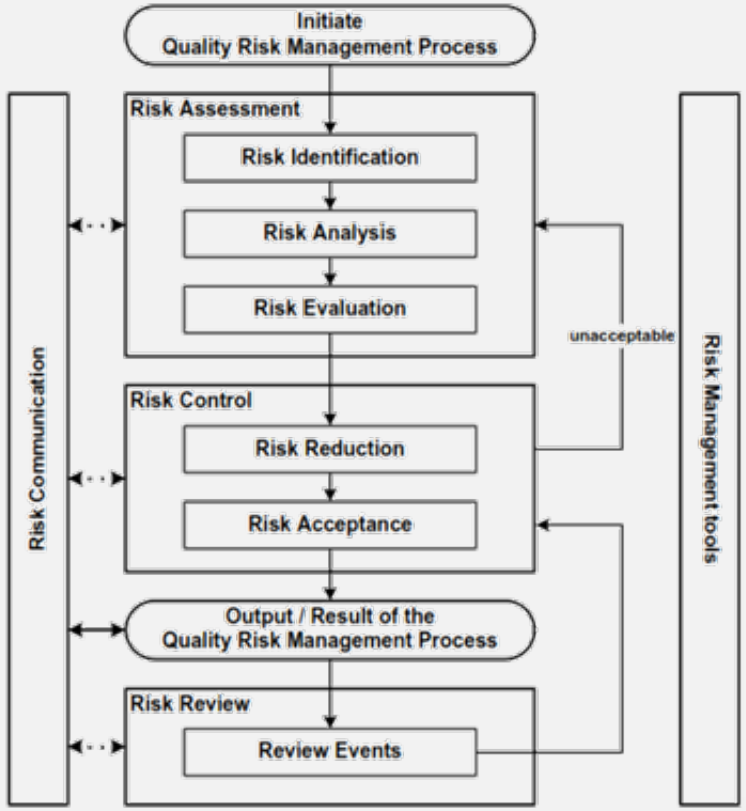
ICH Q9: Quality Risk Management

https://database.ich.org/sites/default/files/Q9%20Guideline.pdf

- Section 4.3 Risk Assessment
  - What might go wrong?
  - What is the likelihood (probability) it will go wrong?
  - What are the consequences (severity)?
- Section 4.4 Risk Control
  - Is the risk above an acceptable level?
  - What can be done to reduce or eliminate risks?
  - What is the appropriate balance among benefits, risks and resources?
  - Are new risks introduced as a result of the identified risks being controlled?
- Section 5 Risk Management Methodology



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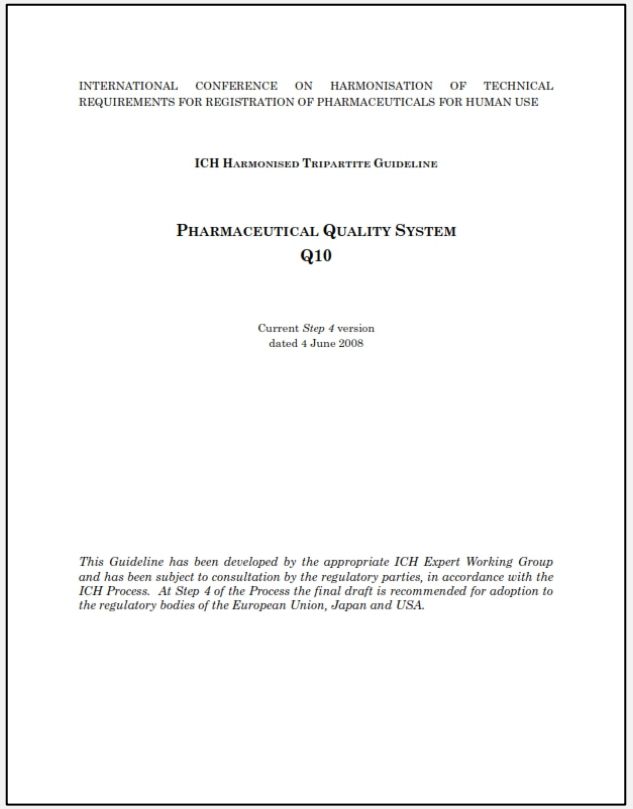
ICH Q10: Pharmaceutical Quality System

https://database.ich.org/sites/default/files/Q10%20Guideline.pdf

- ICH Q10 outlines all topics related to quality systems
- Q10 implementation should result with three objectives in coordination with local GMP
  - Achieve Product Realisation
  - Establish and Maintain a State of Control
  - Facilitate Continual Improvement



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ICH HARMONISED TRIPARTITE GUIDELINE

PHARMACEUTICAL QUALITY SYSTEM
Q10

Current *Step 4* version
dated 4 June 2008

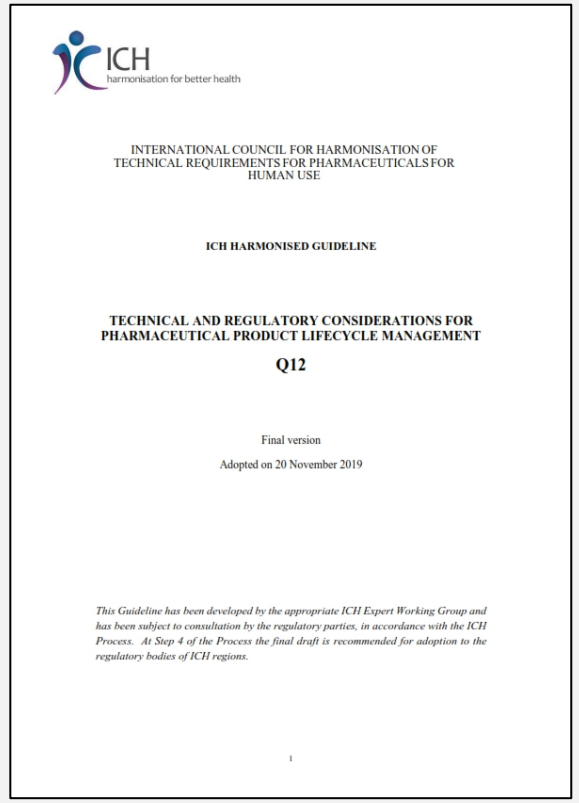
This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Understanding Excipient Impact on Continuous Manufacturing

ICH Q12: Technical And Regulatory Considerations for Pharmaceutical Product Lifecycle Management

https://database.ich.org/sites/default/files/Q12_Guideline_Step4_2019_1119.pdf

- ICH Q12 provides a framework to facilitate the management of post-approval changes
- What changes are being considered?
  - Composition
  - Process
  - Combination of composition and process
- How does an excipient change impact process?
  - Process feed
  - Residence time distribution
  - Drug product quality and performance
- Does a process change drive the need for a compositional review/change?
- What/How should changes be reported?



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INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

TECHNICAL AND REGULATORY CONSIDERATIONS FOR PHARMACEUTICAL PRODUCT LIFECYCLE MANAGEMENT

Q12

Final version

Adopted on 20 November 2019

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of ICH regions.

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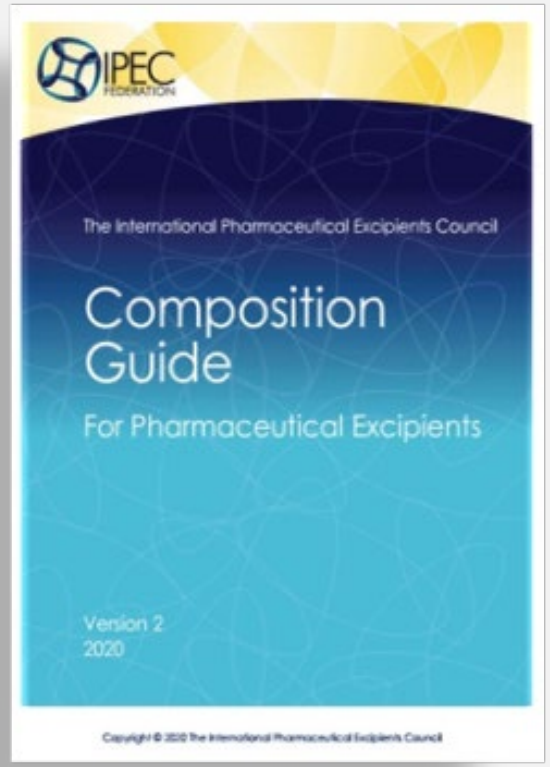
Understanding Excipient Impact on Continuous Manufacturing

IPEC Guide: Composition Guide for Pharmaceutical Excipients

- IPEC Composition Guide
  https://ipecamericas.org/filedepot?fid=1229
  - The Composition Guide provides an approach for excipient manufacturers to establish excipient composition profiles
    - Profiles may be used for:
      - Regulatory purposes
      - Assessing quality consistency
      - Manufacturing process monitoring and change control
      - Establishing product specifications
      - Evaluating excipient safety
  - The Composition Guide provides excipient users information related to excipient complexity
    - Concomitant components
    - Additives
    - Processing aids



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IPEC Guide: Composition Guide for Pharmaceutical Excipients

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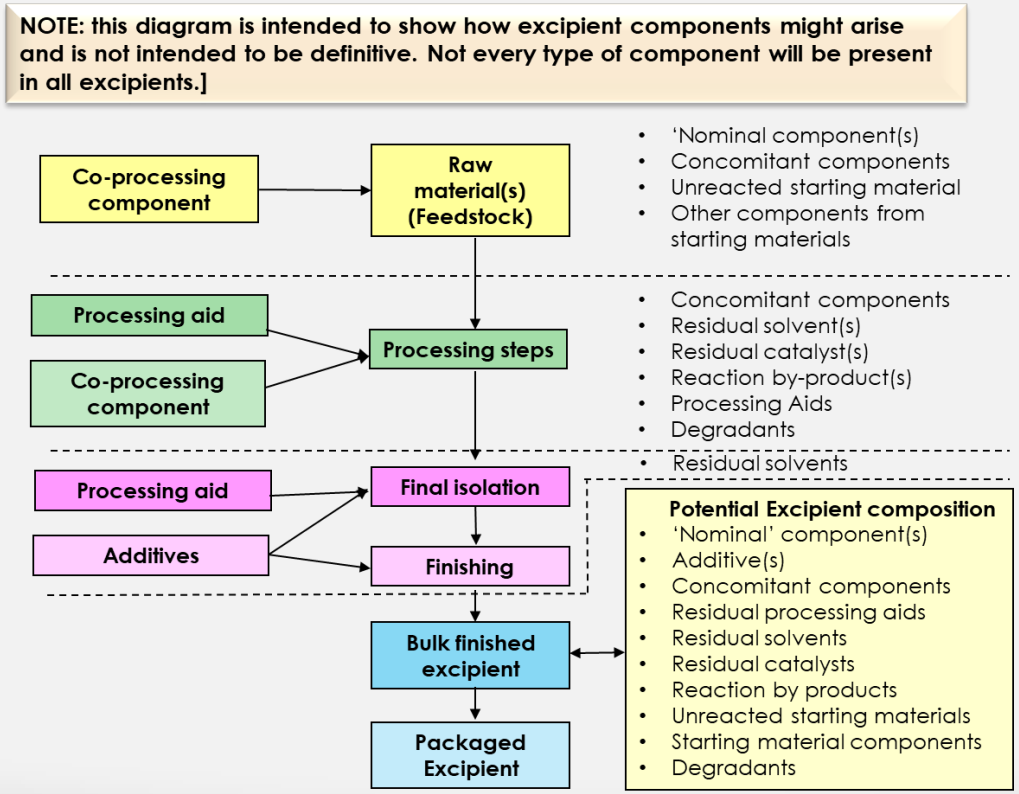

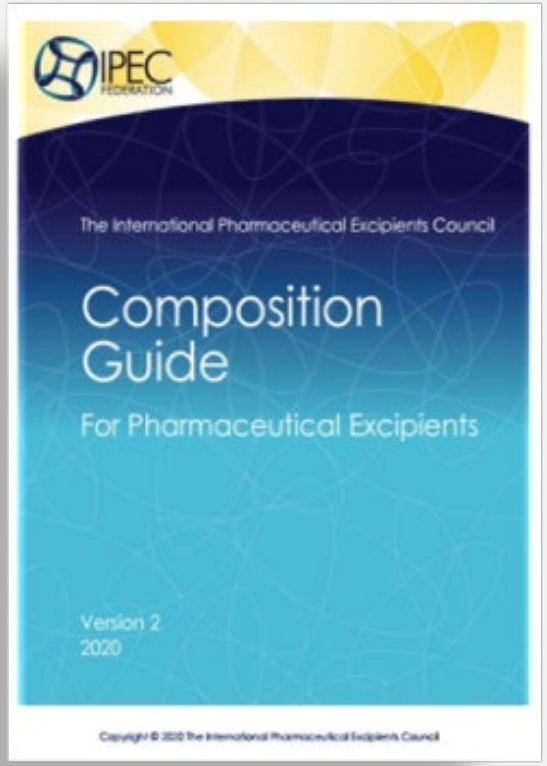

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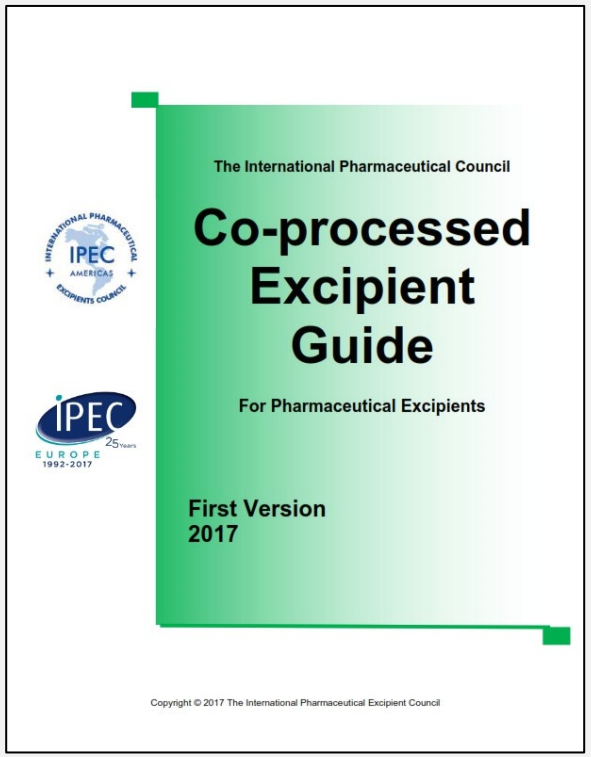
IPEC Guide: Co-processed Excipient Guide for Pharmaceutical Excipients



- IPEC Co-processed Excipient Guide
  https://ipecamericas.org/filedepot?fid=599
  - Defines what a co-processed excipient (CPE) is
  - Discusses the difference between co-processed excipients and simple blends
  - CPE Development
  - Composition and specification
  - Analytical method development

- Why are CPEs important?
  - Can provide a highly functional/multi-functional excipient option to replace multiple ingredients
    - Limited process feeds make this an important consideration/option

Summary

- ICH Q13: uniquely focused on continuous manufacture
  - Other ICH documents as applicable to batch manufacture as to CM
- Other ICH guidelines important to CM design, development, and control
  - ICH Q8 – Q10, ICH Q12
    - ICH Q8: Pharmaceutical Development – QbD and PAT
    - ICH Q9: Quality Risk Management – assessing, avoiding, and mitigating things that go wrong
    - ICH Q10: Pharmaceutical Quality System – documentation, documentation, documentation
    - ICH Q12: Lifecycle Management – system/formulation changes
- IPEC Guides – provide insights from excipient perspective
  - QbD Guide
  - Composition Guide
  - Co-processed Excipients Guide
  - Others may be of benefit as well
- Many other references available

Thank you

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