ICH Q12 Update and Reflections on the USFDA Established Conditions Pilot Program

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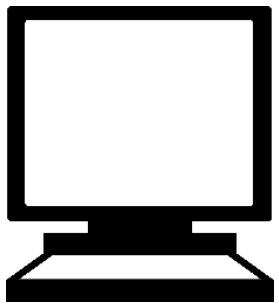
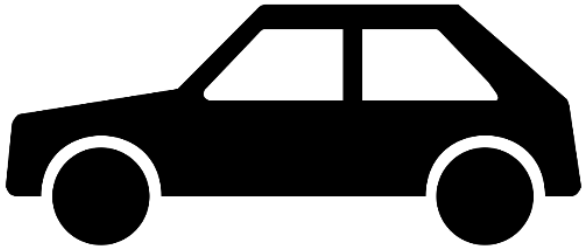
CASSS JAPAN Strategy Forum

Pharmaceutical Quality

A quality product of any kind consistently meets the expectations of the user.





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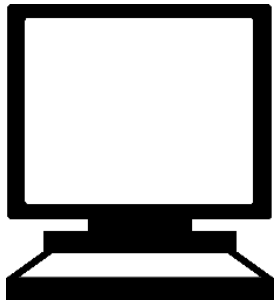
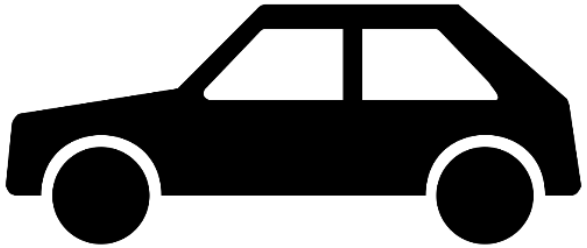



Drugs are no different.


Patients expect safe and effective
medicine with every dose they take.

Pharmaceutical quality is

consistently meeting standards that ensure every dose is safe and effective, free of contamination and defects.


It is what gives patients confidence
in their *next* dose of medicine.

ICH Q12

- Reached Step 4 in November 2019 (Singapore)
- Regions are beginning implementation
  - Regulatory Members of ICH are encouraged to provide publicly available information, preferably on their website, about the implementation of ICH Q12 in their region, especially with regard to regulatory considerations
- Formation of the Implementation Working Group (IWG)
  - Concept paper approved in March
  - IWG developing global training materials
  - ICH pilot with PIC/S to develop training materials for inspectorates

Q12 IWG

- Training materials
  - For ICH and non-ICH regions
  - Modules addressing each section of guideline
  - Case studies with additional examples and narrative text
- Ongoing regional implementation
  - Shared experiences and lessons learned from implementation - both regulators and industry
    - FDA Established Conditions pilot

ICH Q12 – FDA Implementation

- FDA adoption and publication in progress
  - Intended to replace 2015 draft guidance - Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products
- Draft guidance on considerations for ICH Q12 implementation in progress
  - Intended to clarify how to implement Q12 within FDA's regulatory system
- CDER MAPP on implementation of ICH Q12 by assessment teams in progress
- Significant training executed (2018-present)
  - Successful Q12 implementation hinges on regulator and industry readiness
  - Developed and initiated a multi-phase strategy to build awareness and capability within FDA staff

ICH Q12 – FDA Training

- Phase 1:
  - Created awareness and clarity on ICH Q12 (goals, content, scope, core elements)
  - Utilized theoretical examples to illustrate concepts and practice the identification of established conditions
- Phase 2:
  - Augmented understanding of pharmaceutical quality systems, CGMP, and their role in ICH Q12 implementation
- Phase 3:
  - Driven by assessment teams from the established conditions pilot
  - Utilized real world examples to demonstrate implementation
  - Teams shared their experiences assessing proposals and working with applicants
- Phase 4: To be implemented
  - ICH Q12 support team members to work with assessment teams to help answer questions, guide consistency, etc.

Pilot Program Context

- The case studies presented are based on submissions received under FDA's Established Condition (EC) Pilot Program
- Applicants followed the then-current version of ICH Q12 to prepare their submissions
- Certain administrative and technical elements were changed in reaching the final version of ICH Q12
- Please read the final version of ICH Q12 for current information
- Examples to follow are meant to illustrate themes and discussion points that arose
- Examples are altered to protect confidentiality and may be hypothetical

Stated Pilot Program Objectives

- 84 FR 4478, published on 2/15/2019
- To gain practical experience in:
  - Assessing proposed ECs;
  - Engaging with applicants during the review cycle to refine proposed ECs;
  - Ensuring assessment decisions are made without negatively impacting the ability to meet user fee timeframes; and
  - Identifying agreed-upon ECs at the time of approval.

Pilot Participant Summary

- Accepted requests submitted before May 30, 2019 from applicants intending to submit NDAs, ANDAs, or BLAs, either original applications or prior approval supplements, with proposed ECs

Application Type	Submission Type	Status
BLA	Prior Approval Supplement	Approved
NDA	Prior Approval Supplement	Approved
NDA	Prior Approval Supplement	Approved
BLA	Prior Approval Supplement	Approved
NDA	Prior Approval Supplement	Approved
BLA	Prior Approval Supplement	Withdrawn
BLA	Prior Approval Supplement	Approved
NDA	Prior Approval Supplement	Not Yet Submitted
ANDA	Prior Approval Supplement	Not Yet Submitted
NDA	Original Application	Approved

Key considerations from ICH Q12 for the manufacturing process

- Process parameters that need to be controlled to ensure a product of required quality should be considered ECs
- ECs identified through risk assessment and knowledge gained from studies, prior knowledge, and criticality assessment
- Criticality assessment that determines the level of impact that a process parameter could have on product quality. *Not new.*
- Critically and risk should be periodically assessed and the EC reporting category updated periodically, consistent with ICH Q10. *Not new.*

Key Process considerations from ICH Q12

- Details on ECs and reporting category will depend on the extent to which the company can apply knowledge from product and process understanding
- Use of Q12 should not lead to providing a less detailed description of the manufacturing process
  - **De-risks** providing detailed descriptions
  - Not all parameters in a CTD section containing ECs are necessarily ECs

Examples in Q12 annexes provide context

Terminology used in examples:

ICH Terminology	Regional Terminology
Prior Approval (PA)	PAS, Type II, PCA, etc.
Notification Moderate (NM)	CBE 30, Type IB, MCN, etc.
Notification Low (NL)	CBE 0, AR, Type IA, MCN, etc.
Not Reported (NR)	

Annex examples do not prescribe criticality or reporting categories for process parameter to be applied in all cases

Four Key Themes from Pilot Experience

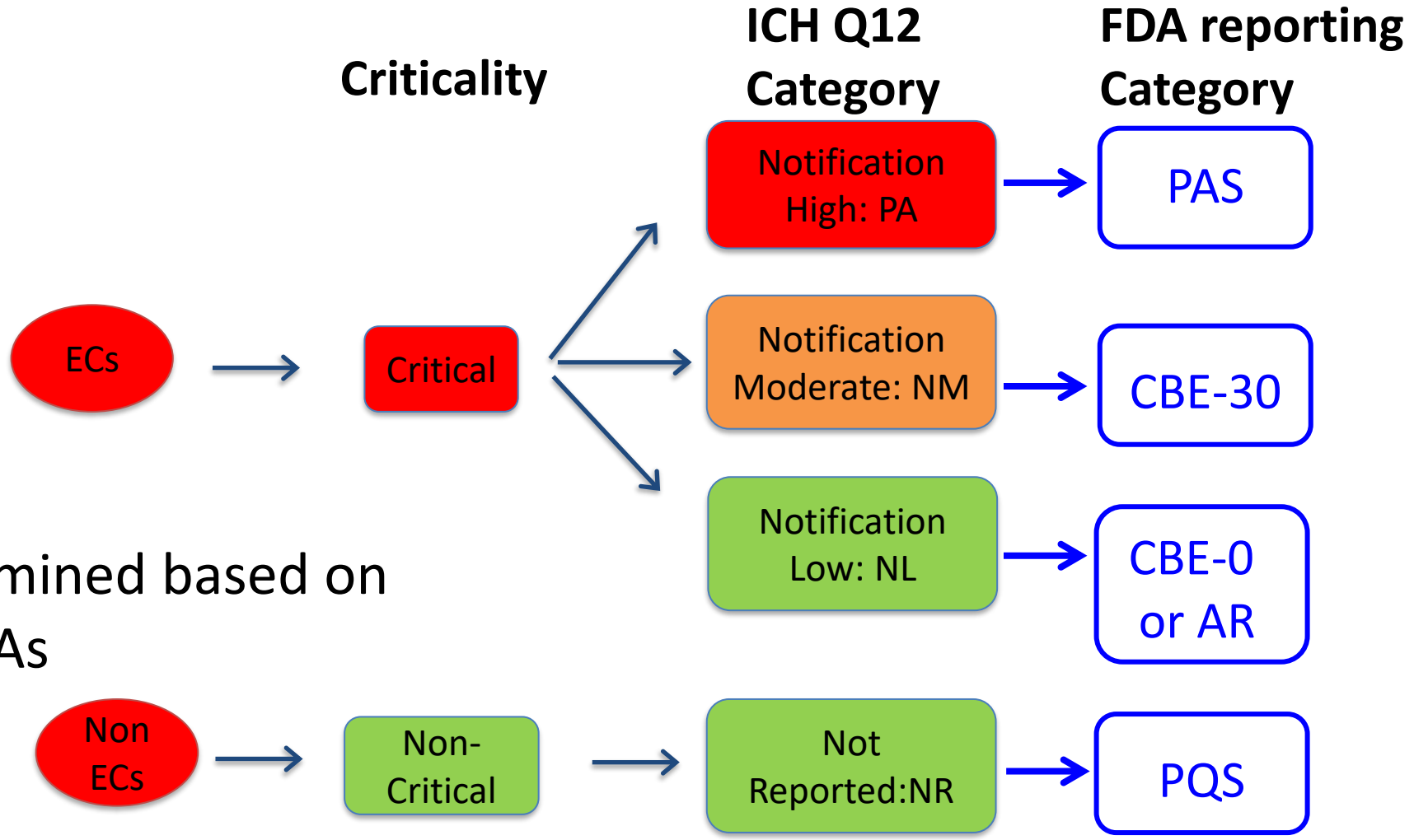
1. Applicants take different approaches:
   - Explicit designation of approved process parameters as ECs with reporting categories
   - New parameter-by-parameter assessment of EC/not-EC and reporting categories
   - Propose ECs, but no reporting categories
   - ICH Q12 principles may not be applied to all sections (e.g., only specified for one unit operation or method)
   - *Applicant's proposals may be more complex than examples in Q12*

Four Key Themes from Pilot Experience

2. Established Conditions need to be sufficiently detailed and clear to have intent understood
3. Criticality assessments become more consequential even if ECs are not proposed
4. EC proposals do not supersede scientific understanding and importance of understanding risk

Applicants may use different nomenclature than Q12

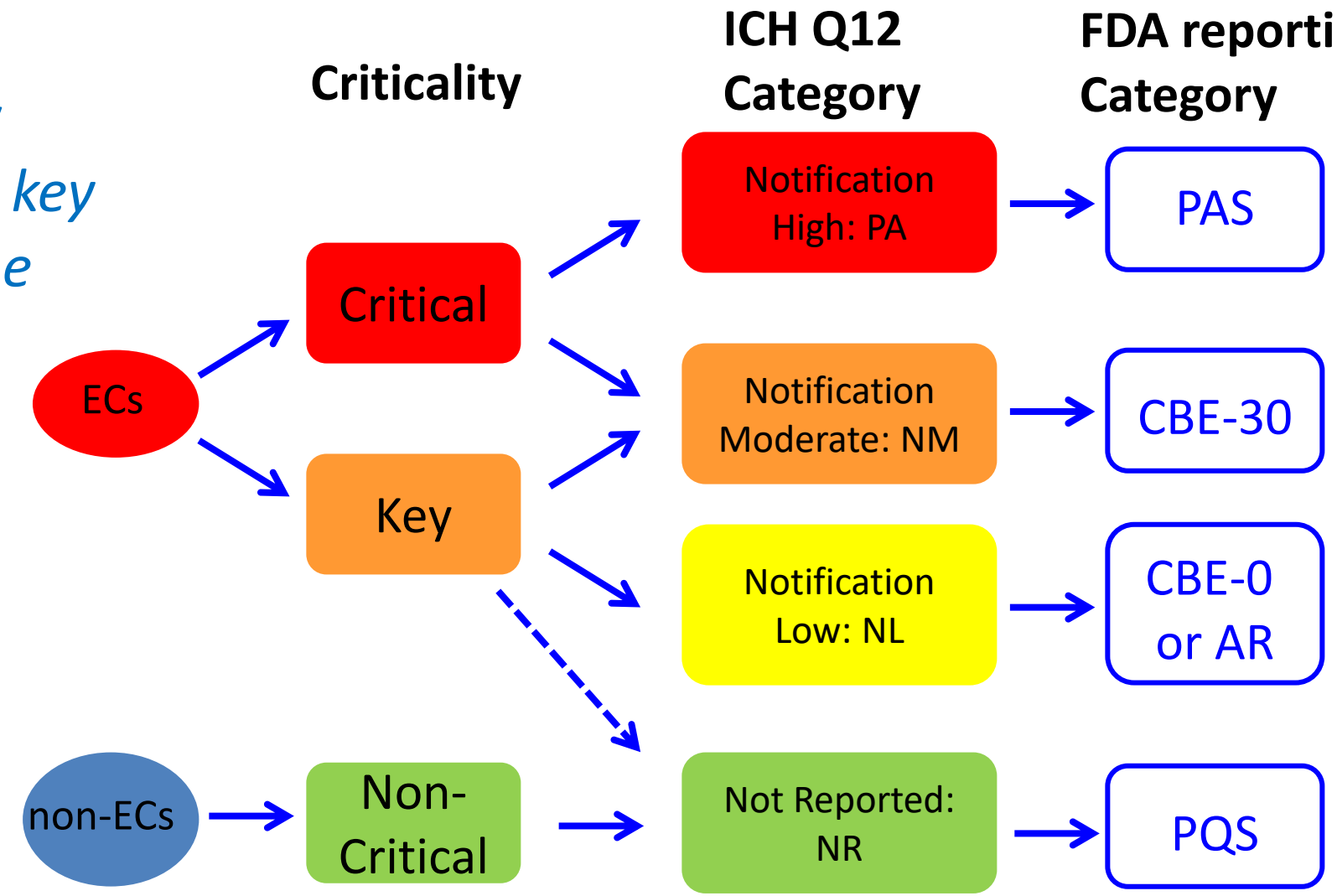
Critical/non-critical: All parameters that impact CQAs, or impact cannot be excluded, are critical and ECs



Criticality is determined based on impact on the CQAs

Example of alternate nomenclature

3-Tiered Criticality assessment: some key parameters may be ECs



"Key" parameters that are ECs: impact on product quality not reasonably excluded.

Reminder: The USFDA EC Pilot was based on the draft ICH Q12 document from Step 2b.

Example 1: Applicant proposes ECs and reporting categories derived from previous criticality assessment

Process parameters and acceptable ranges for a chromatographic purification step

Parameter	Acceptable Range	EC (reporting category)	Parameter Type
Bed height	AA – BB cm	EC (Notification Moderate)	KPP
Process temperature	CC°C – DD°C	EC (Notification Moderate)	KPP
Flow rate	EE – FF cm/h	EC (Prior approval)	CPP
Equilibration buffer volume	≥G Column Volumes	EC (Notification Low)	KPP
Load density	HH – II g/L resin	EC (Prior Approval)	CPP
Elution volume	Volume as required to elute	Non-EC	PP

ECs may not have been an explicit consideration at the time of original marketing application review and approval

ECs proposed within existing criticality framework

Reminder: The USFDA EC Pilot was based on the draft ICH Q12 document from Step 2b.

Example 2: Applicant proposes ECs for "Non-critical" parameters

Process parameters and acceptable ranges for a chromatographic purification step

Parameter	Acceptable Range	EC (reporting category)	Parameter Type
Bed height	AA – BB cm	Change to the lower limit: EC (CBE-30)	Non-CPP
		Change to the upper limit: EC (AR)	
Process temperature	CC°C – DD°C	EC (CBE-30)	Non-CPP
Flow rate	EE – FF cm/h	EC (PAS)	Non-CPP
Equilibration buffer volume	≥G Column Volumes	EC (AR)	Non-CPP
Load density	HH – II g/L resin	Change to the lower limit: EC (AR)	Non-CPP
		Change to the upper limit: EC (CBE-30)	
Elution volume	Volume as required to elute	Non-EC	----

Multivariate studies characterized impacts over wide operating ranges

Proposed reporting categories are for changes beyond studied range

Direction of change can impact risk

Example 3 – Description is not detailed enough to be interpretable

Proposed EC	Proposed Reporting Category for Change
Equipment used in manufacturing process	Notification – Low

What is the intended scope of a change to "equipment?"

Based on risk, some equipment changes should be PA, others PQS

Example 4 – Site Specific ECs

3.2.S.2 – Alderan Manufacturing Facility	ECs and reporting categories for DS upstream and downstream manufacture
3.2.S.2 – Middle Earth Manufacturing Facility	No explicit ECs proposed

- *Acceptable to have different ECs for different sites*
- *Needs to be clear which ECs apply where*
- *ECs applying to multiple sites may need to have additional details for clarity*
- *Request for addition of new site in future would need to be explicit about which ECs apply*

Example 5 – Limited characterization data

Proposed EC	Proposed Reporting Category	Justification for category
Elution pH 4.8 – 5.2	Notification – Low	No impact to CQA over 4.8 – 5.2 range

- Cannot distinguish whether CQAs are insensitive to elution pH or if process was just always run at the set point
  - Higher risk of impact from change, potentially upgrade reporting category
- More extensive characterization assessing impact over broader range could support that:
  - the relationship between the parameter and CQAs is well understood
  - tools are in place to detect and assess impacts
  - reduced reporting category is justified

Example 6 – Where is the supporting information?

Proposed EC	Proposed Reporting Category	Justification for category
Elution flow rate 100 – 200 cm/h	Notification – Low	Study XYZ demonstrated that flow rate does not impact yield or clearance of HCPs for our platform

- If reviewer cannot find Study XYZ, or the relevant data within Study XYZ, it might as well not exist
- Use hyperlinks or references to specific submissions and page numbers

Example 7 – What happens if a parameter we currently believe is non-critical turns out to be important later?

- Agreement on ECs and reporting categories allows for transparency and predictability between FDA and MAH for managing changes to ECs
- Success relies on **trust** that MAH will revise ECs if process knowledge and experience gained in the future alter the risk profile!!

Challenges and opportunities for applying Q12 to existing products

- ECs may not have been an explicit consideration at the time of process development and regulatory approval
- Developing and evaluating EC proposals for products developed pre-ICH Q8 (i.e. without formal criticality assessments for process parameters)
- Capturing and communicating manufacturing experience in support of EC proposals.
  - There may be data from dozens or hundreds of commercial batches in addition to formal development studies

Lessons Learned from the Pilot Program

- Applicants use diverse approaches for criticality assessment and EC development
- A shared understanding of applicant's intent, scope, and nomenclature is essential
- Extent of regulatory relief from ECs depends on extent of understanding of the process and of risk
  - (*and how effectively that understanding is communicated)*
- Opportunity for increased transparency in submissions with decreased risk of increased regulatory burden

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