U.S. FOOD & DRUG ADMINISTRATION

Reflections on the FDA Established Conditions Pilot

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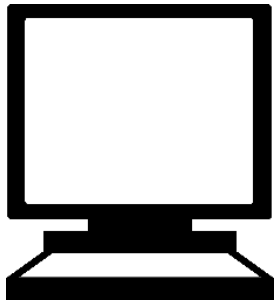
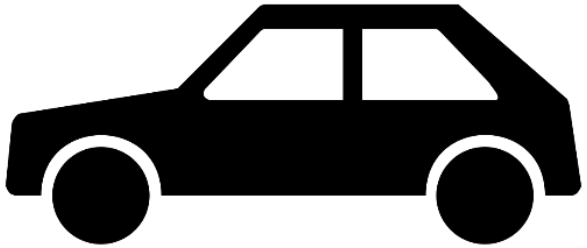
Pharmaceutical Quality

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





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

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.

FDA ECs 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 Program Context

- 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

Pilot Participant Summary

- Accepted 10 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 (Insulin)	Prior Approval Supplement	Approved
BLA	Prior Approval Supplement	Approved
NDA	Prior Approval Supplement	Approved
BLA	Prior Approval Supplement	Pending
BLA	Prior Approval Supplement	Pending
NDA	Prior Approval Supplement	Not Yet Submitted
ANDA	Prior Approval Supplement	Not Yet Submitted
NDA	Original Application	Approved

Four Key Themes from Pilot Experience

1. Applicants take different approaches:
   - Explicit designation of already-approved process parameters as ECs with reporting categories
   - New parameter-by-parameter assessment of EC/not-EC and reporting categories
   - Propose ECs, but not 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 might be more complex than examples in Q12*

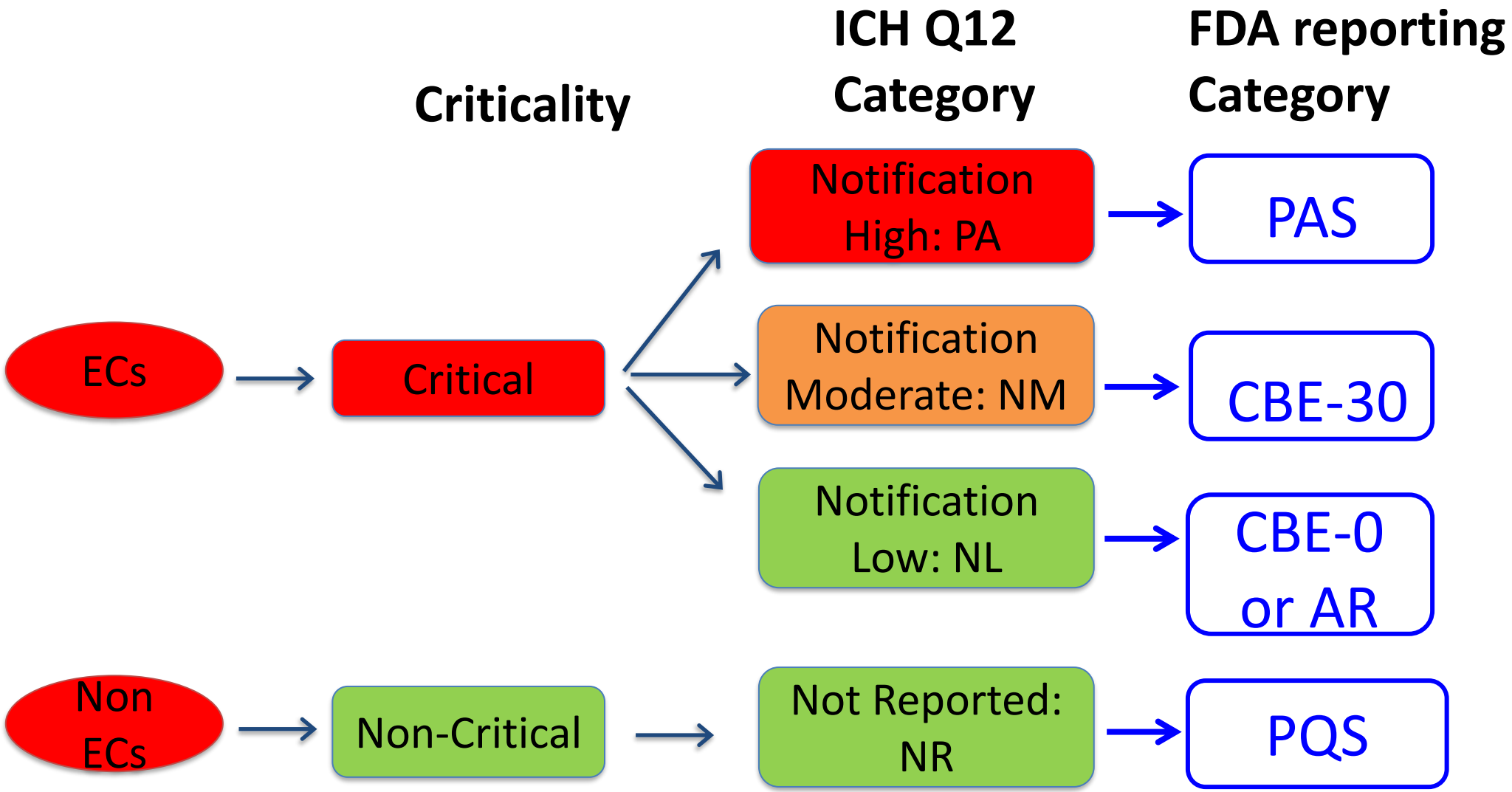
Four Key Themes from Pilot Experience

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

Criticality Assessment and ECs

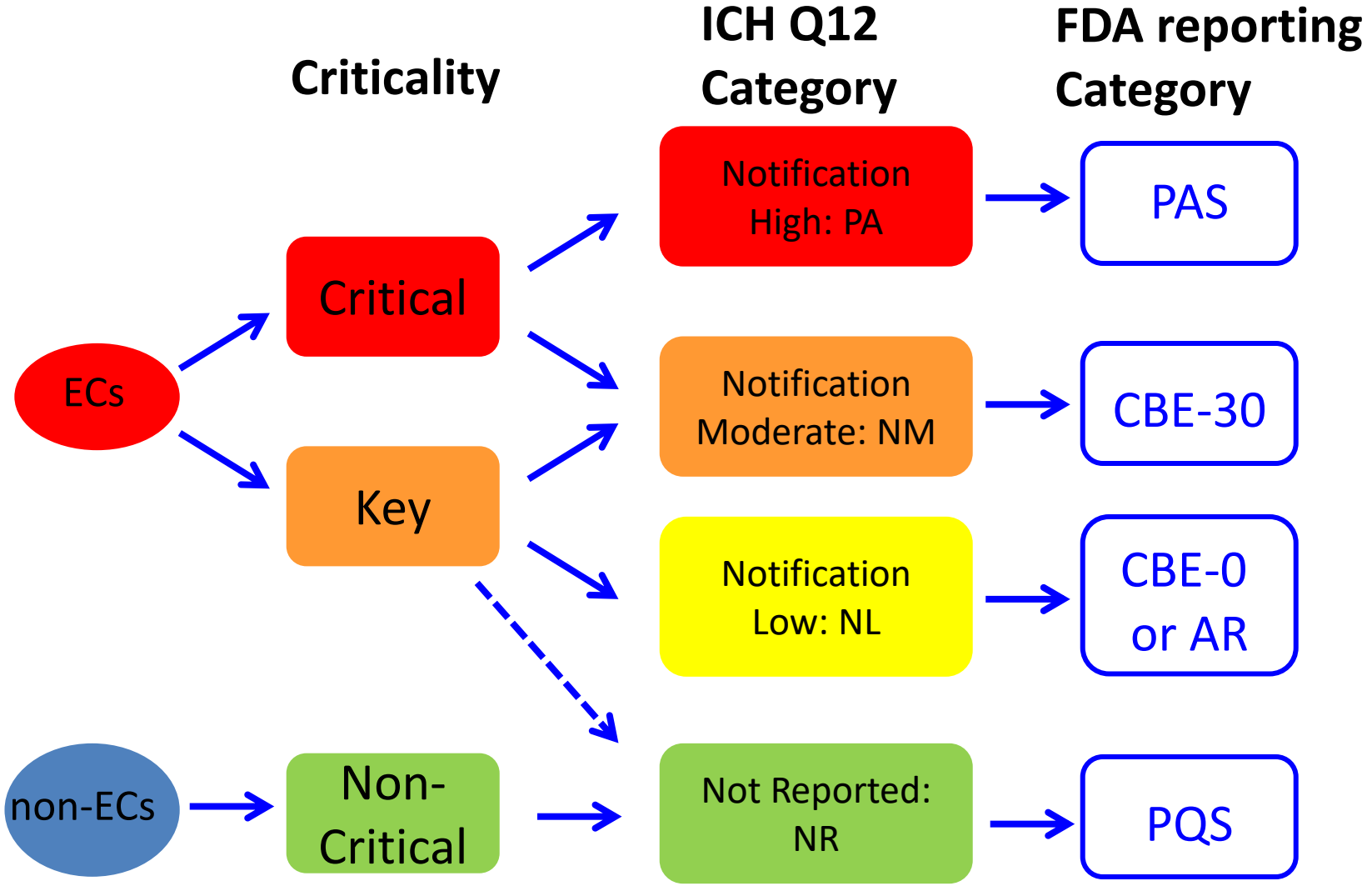
- Criticality should reflect:
  - Severity of harm
  - Whether range studied accounts for expected variability in the EC
- Critical parameters are those that need to be controlled to assure quality
- Reporting category for critical parameters is determined by risk
  - Critical parameter does not necessarily mean Prior Approval reporting
- Non-critical parameters where impact cannot be impact cannot be reasonably excluded may also be ECs

Criticality and FDA notification categories



Example 1: Proposed ECs based on pre-Q12 criticality assessment

- *Critical and Key parameters proposed as ECs*
- ECs not necessarily an explicit consideration at the time of original marketing application
- ECs proposed within existing criticality framework



Example 2: ECs proposed for certain 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 impacts risk assessment

Example 3 – Description is not detailed enough to be interpretable

Proposed EC	Proposed Reporting Category for Change
Equipment used in manufacturing process	Annual Report

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

Based on risk, some equipment changes could be prior approval, others non-ECs/PQS

Example 4 – Site-Specific ECs

CTD module	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 – EC supported by other commitments or protocols

Proposed EC	Proposed Reporting Category for Change
Column resin cycles <50	Change in accordance with concurrent at-scale validation protocol: Annual report Change beyond small scale characterization and protocol: PAS

- Relies on the protocol being included in the application
- Is the protocol supporting information? A regulatory commitment? An EC?

Example 6 – Impact of characterization data

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

- *Are CQAs insensitive to elution pH? Or was process always run at set point?*
- Little data: cannot exclude impact from change, potentially upgrade reporting category
- More extensive characterization assessing impact over broader range and/or multivariate studies 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 7 – Where is the supporting information?

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

- Cannot effectively assess the EC proposal if:
  - Study ABC never submitted
  - Assessor cannot find Study ABC in the historical dossier
  - Assessor cannot find or unclear where the relevant data are within Study ABC
- Recommend use of hyperlinks or references to specific submissions, and page numbers as applicable

Example 8 – 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 understanding that MAH will revise ECs/reporting categories if additional process knowledge and experience alter the understanding of 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 regulatory burden
  - Not all information in a CTD section containing ECs are necessarily ECs

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