Win, Lose or Draw

The ICH Q12 Experience from the Industry Perspective

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Disclaimer & Scope

This is based on our experiences so far. It is acknowledged that many Health Authorities have yet to fully implement Q12 and the legal frameworks are not updated yet to accommodate ICH Q12.

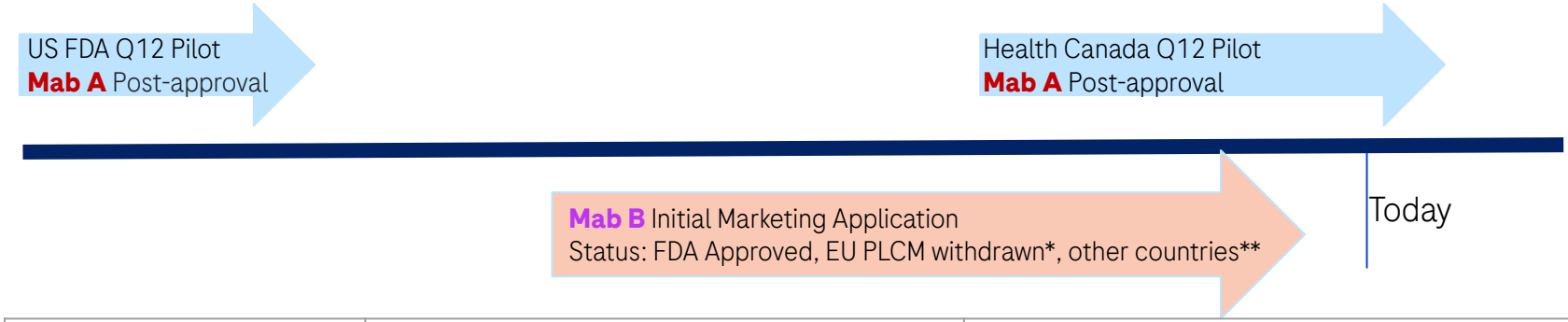
The focus of this discussion is mostly on Established Conditions and not the other elements of Q12.

Established Conditions and the PLCM

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

“The PLCM (Product Lifecycle Management) document outlines the specific plan for product lifecycle management that includes the ECs, reporting categories for changes to ECs, PACMPs (if used) and any post-approval CMC commitments. Its purpose is to encourage prospective lifecycle management planning by the MAH and to facilitate regulatory assessment and inspection. The PLCM document should be updated throughout the product lifecycle as needed.”

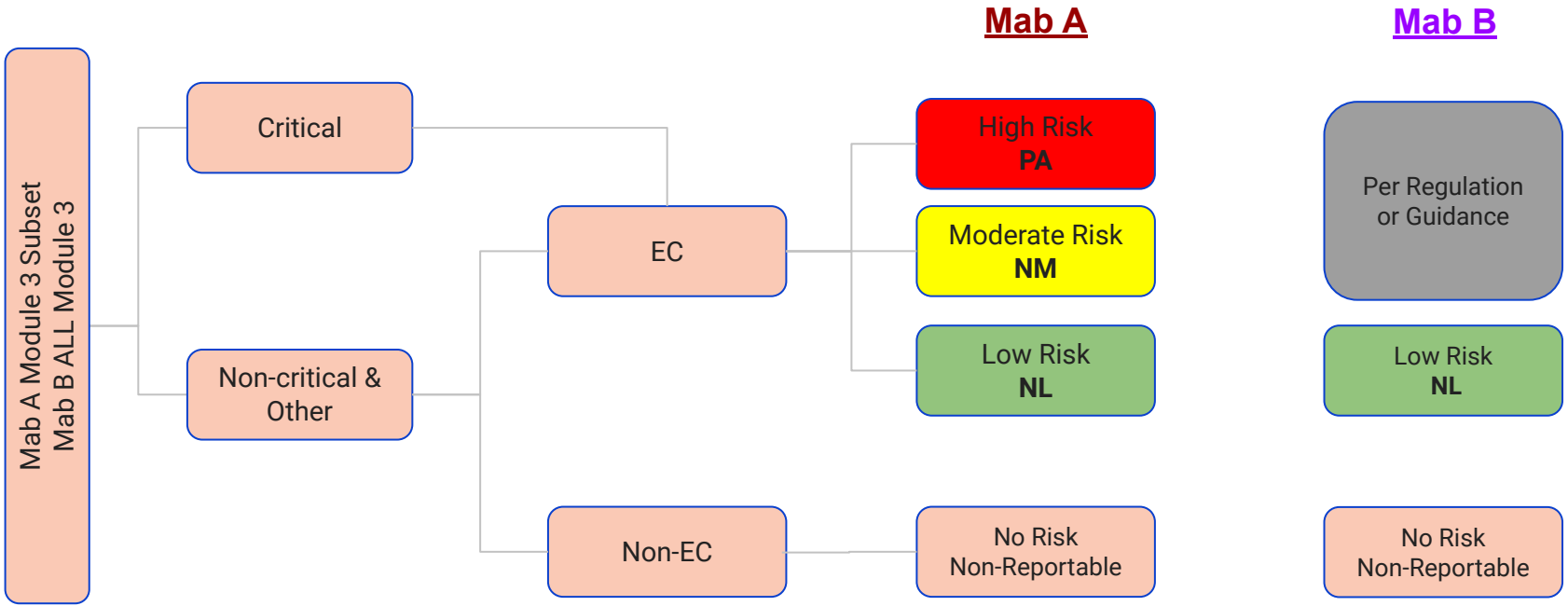
Two Product Experiences with ECs and PLCMs



	Mab A	Mab B
Development Type / Control Strategy	Enhanced process development Leveraging prior knowledge Platform process	Enhanced process development Leveraging prior knowledge Platform process
EC/Non-EC Identification Scope	Process parameters, in-process controls, reference standards, stability	All CMC, including materials and analytical procedures
Reporting Categories	Defined for all ECs: Prior Approval, Notification Moderate and Low (NL)	Defined only NL ECs Other ECs default to “Per Regs”

* PLCM not allowed within the legal framework, **Submitted but final acceptance is TBD.

Established Conditions Definition & Reporting Categories Approach



MabA: Subset of M3 assessed. Reporting categories and justification provided for all ECs identified.
MabB: All of M3 assessed. Reporting categories only identified for low risk changes (i.e AR). All M3 sections assessed.

General Principles of ECs in PLCM

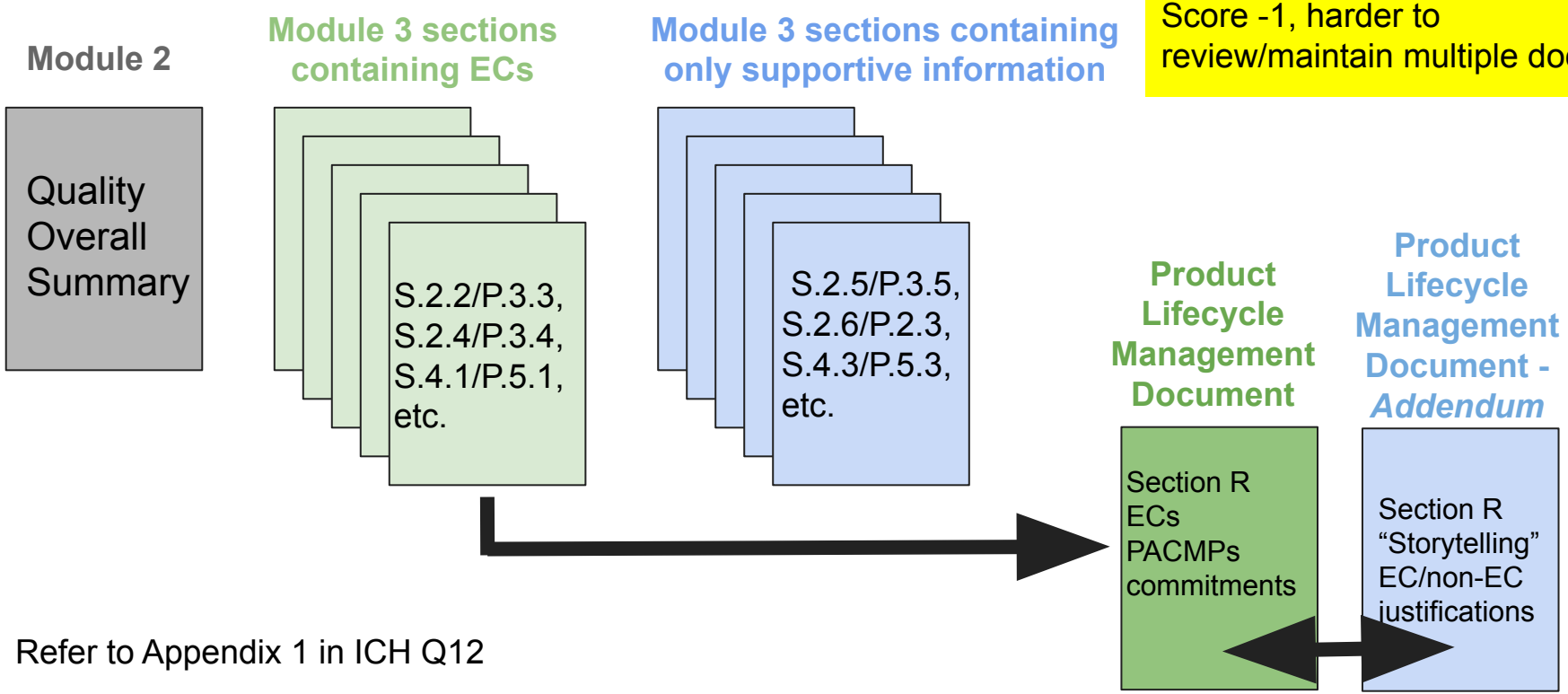
Score +1, evaluation and reporting of changes is more clear

- All technical changes are evaluated per PQS (ICH Q10), regardless of EC/non-EC status
- All changes that impact ECs will be reported according to the risk-levels and reporting categories as defined in the PLCM. ***Tightening of acceptable limits or ranges will be reported*** based on the level of potential impact.
  - ***Applicant may choose to operate within tighter ranges than approved limits; this can be managed within PQS provided this is not being done to address a product quality issue***
- The reporting categories in the PLCM are intended as default reporting categories. At the time of change if the risk is assessed to be higher, the change will be reported in a high submission category
- Changes to supportive information (non-EC) will be managed within the Applicant's PQS and not reported to the Health Authority
- Any change to pre-defined risk categorization and reporting categories of ECs and scientific justification thereof will be reported to to the Agency, and the PLCM (and Addendum) will be updated commensurate with the risk level, ***minimally CBE-0***

Bold items were adjusted during review

Where do ECs go?

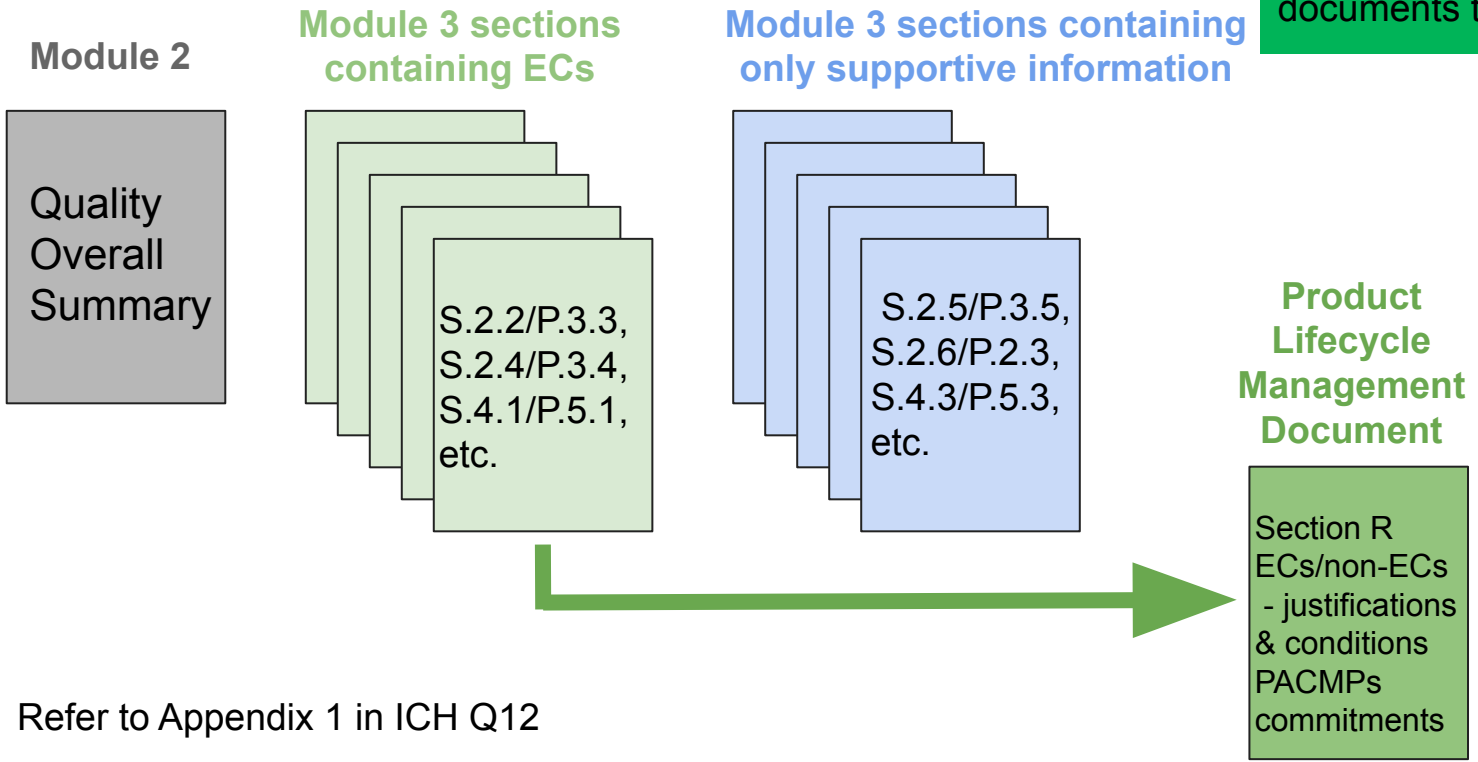
Score +1, location of binding information is more clear.
Score -1, some of the justifications became binding
Score -1, harder to review/maintain multiple docs



Refer to Appendix 1 in ICH Q12

Where do ECs go? - A future direction

Score +1, location of binding information is more clear.
Score +1, single location for binding information, fewer documents to maintain.



Refer to Appendix 1 in ICH Q12

Harmonized Approach Still Requires Regional Customization

Score 0, no single document
Score 0, neither product specific or HA alignment.

- Want to use ICH Q12 terms as much as possible and avoid HA-specific terms so that the same PLCM can be used globally.
- Mapping of Q12 terms to multiple categories makes this challenging. HAs may still require country-specific designations and designations might not map directly to the Q12 terms.

ICH Q12 Term	Canada	US
Prior Approval	Level 1, Level 2	PAS
Notification Moderate	Level 2 (default)	CBE-30
	Level 3 Immediate (under negotiation)	
Notification Low	Level 3 Immediate	CBE-0
	Level 3 Annual	AR (default)

- Each HA might start with their own guidance and seek specific justifications for downgrades.
- We also still have the “PLCM-like” documents like M1 (Japan) and CPID (Canada)

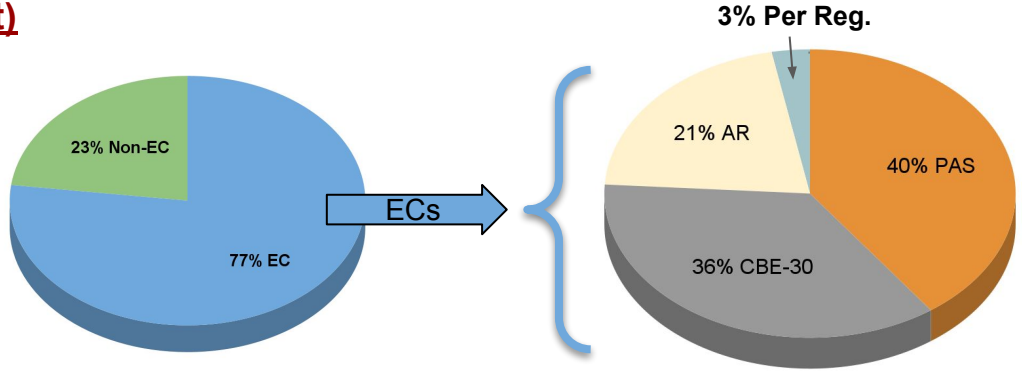
More ECs, More “low-risk ECs”

Score -1, more ECs than anticipated, even if low-risk. (after a lot of effort)

Mab A (Post-approval, FDA pilot)

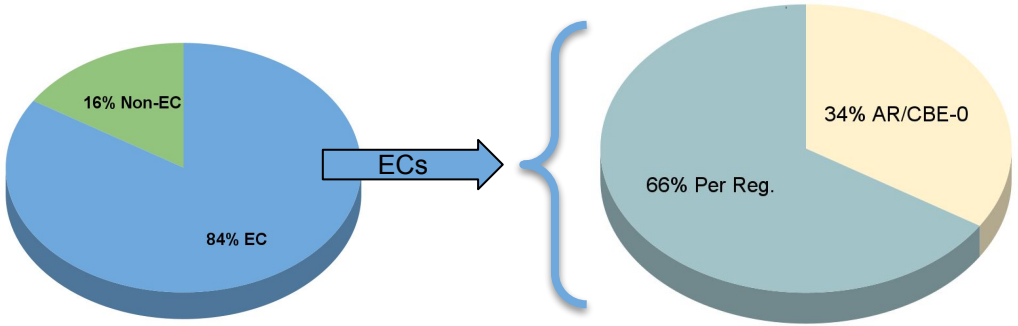
PLCM = 37 pages
PLCM addendum = 84 pages
FDA questions = 26

% are for the sections in scope, not all sections were in scope



Mab B (Initial Marketing application)

PLCM = 53 pages
PLCM addendum = 106 pages
FDA questions = 52

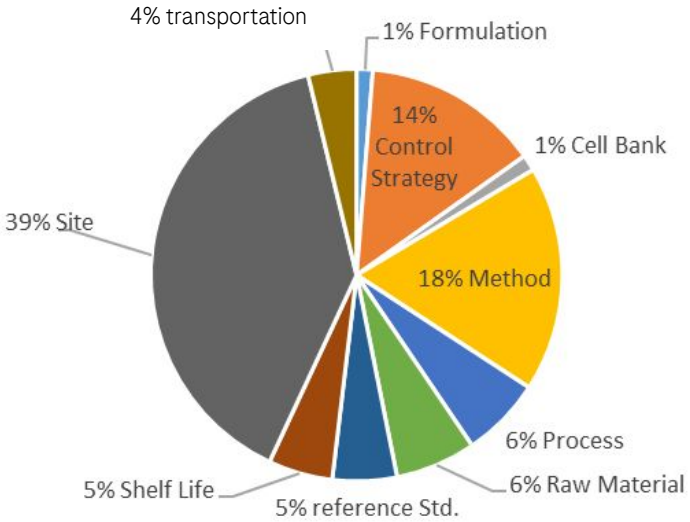


Post-Approval Changes

Score 0, yet to utilize some of the downgraded categories

- Most common changes are:
  - Site transfers
  - Analytical changes
- Standalone process changes are less common

Consider focusing Q12 efforts on more common changes, leveraging PACMPs to downgrade high-risk changes



Additional observations

- The line between ECs and variation guideline/PACMP is sometimes blurred.
  - Justifications for lower reporting categories became part of the main PLCM. These turned into “Conditions to be met” and/or “mini-protocols” before a NL reporting category could be applied.
  - Common changes (i.e. resin reuse extensions, cell bank and ref standard replacement)
    - are they PACMPs or mini-protocols?
    - Can they be simply described in M3 documents or treated as regulatory commitments
    - Is there a better path, given some HAs don’t accept PACMPs yet
- Be prepared to answer questions about the PQS.

Win, Lose or Draw - Scoring the Game

Game Modification - Industry "winning" does not necessarily mean Health Authorities "losing" or vice versa!

1 point	*"Management of cmc changes in a more predictable and efficient manner"*
1 point	*"Harmonized approach"*
1 point	*"Ability to manage many CMC changes effectively under the company's Pharmaceutical Quality System (PQS) with less need for extensive regulatory oversight prior to implementation"*
5 points (bonus)	*"incentivize continual improvement by providing an opportunity for greater flexibility in making post-approval changes"*

Score card so far, can we still win?

Benefit	Score	Challenges / Opportunities
Predictability	+2	Increased clarity in what is binding, overall change assessment process.
Efficiency	-2	Harder to maintain additional documents.
Harmonization	0	Still challenges with differences in risk ranking of changes and mapping of reporting categories. Implementation by HA still pending.
Less Need for Regulatory Oversight	-1	More ECs than anticipated. Can we increase score by focusing efforts on common changes?
Incentivized Continuous Improvement	TBD	Yet to utilize some downgraded items. Can we do more with PACMPs and/or structured approaches?

It's still early in the game, but we need to adjust our strategies along the way.

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....and many others

Doing now what patients need next