

Application of Quality Tolerance Limits Within the Pharmaceutical Industry: Results of an Industry Survey

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Introduction

Predefined Quality Tolerance Limits (QTLs), a key element of ICH GCP E6 (R2)¹, are used to identify systemic issues that could impact the safety of participants and/or the reliability of study results early enough during trial conduct so that corrective action may be taken.

The PHUSE RBM QTL team conducted an industry-wide survey of stakeholders to assess the current state application of QTLs in the industry.

Methods

The survey instrument was developed via Google Forms to gather data directly from colleagues working in the Risk-Based Quality Management (RBQM) space in the pharma industry.

Respondents answered according to the current state of QTLs application in their organization. The survey contained 30 questions; 12 contained subparts in tabular format.

Demographic information (e.g., type of company, size) was captured, as well as information on how QTL's fit into an organization's implementation of RBQM.

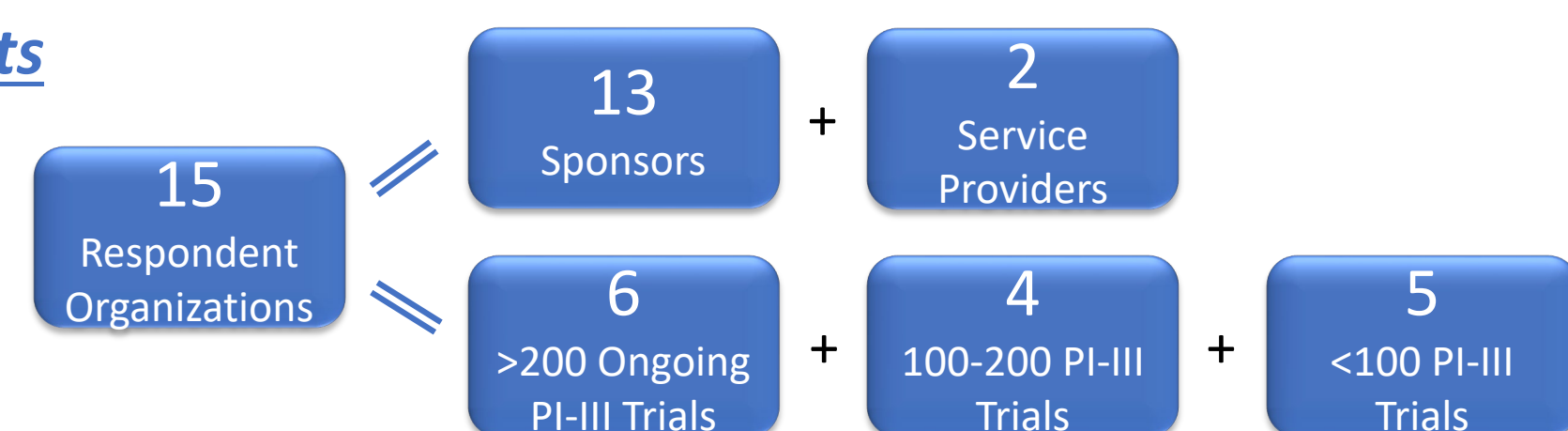
Acknowledgments

The following QTL Team members contributed significantly to the work shared in this poster:

- Chris Wells (Roche) QTL Team Co-Lead;
- Mireille Lovejoy (GE HealthCare);
- Nathalie van Borrendam (Johnson & Johnson);
- Jennifer Krohn (PPD)
- Madalina-Daniela Spiridon (Roche)

Highlighted Results*

Survey Respondents



Risk-based Approaches Differ by Trial Type (Figures 1 and 2)

There appears to be more consistent use of risk-based efforts to phase II and III trials than other trial types. There is a mixed response with regards to early phase, complex designs, post marketing approvals or non-interventional trials.

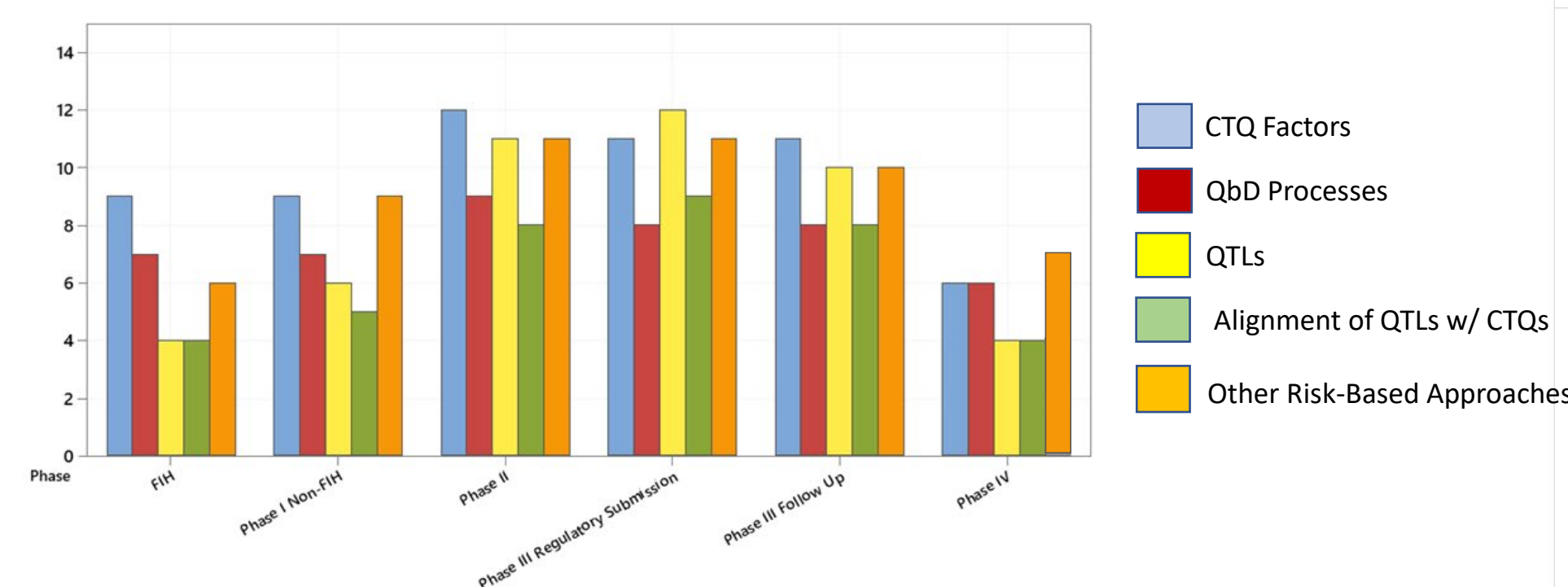


Figure 1: Risk Based Approaches to Quality organizations apply by trial type

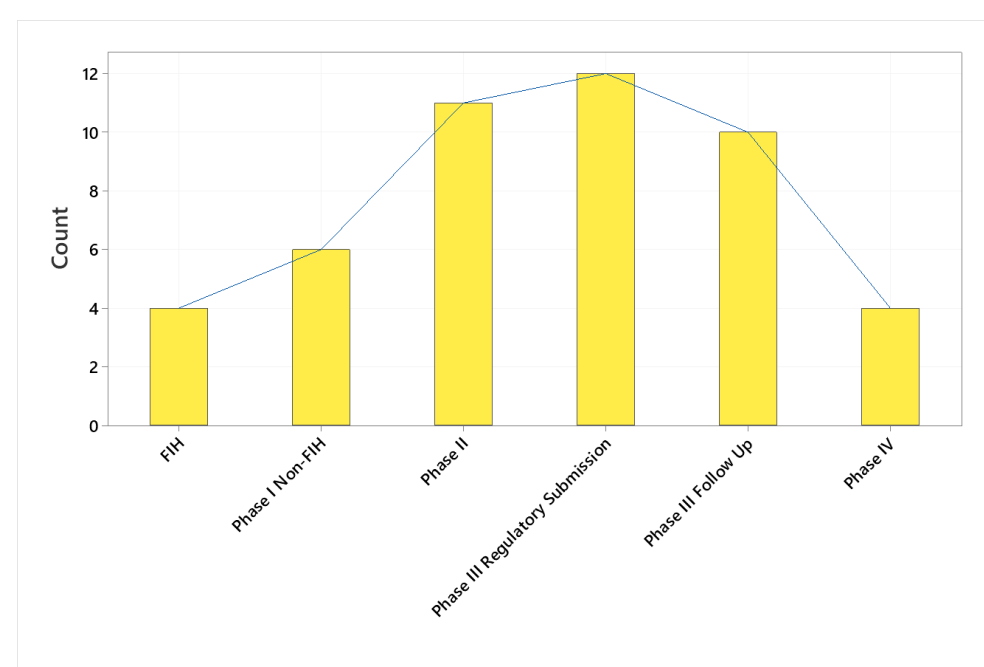


Figure 2: Use of QTLs by Trial Type

QTL Implementation is mainstream and tied to study-specific Critical-to-Quality factors (Figures 3 and 4)

87% of respondent organizations have applied QTLs.



Figure 3: Protocol objectives are the top driver for choosing QTL parameters. In contrast, ease of use and standard parameters were not reported as key drivers.

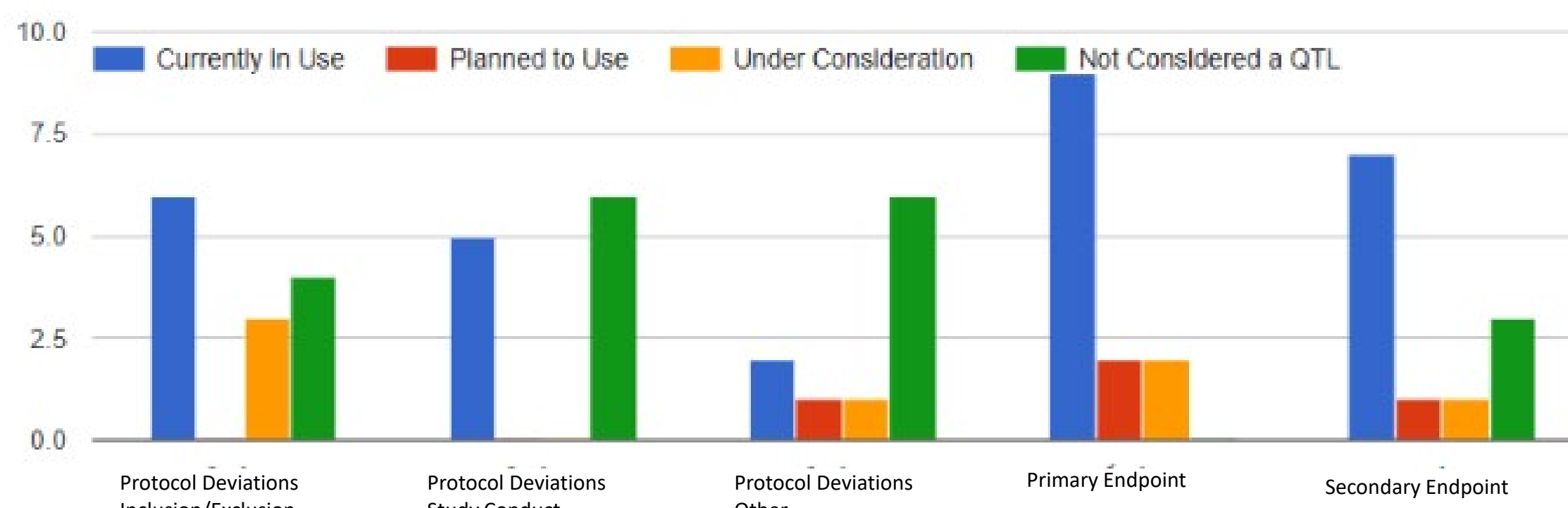


Figure 4: Primary endpoints are the most used parameter, whereas protocol deviations are not necessarily considered as a QTL parameter by the majority of organizations that responded.

Feedback loops are being put in place to ensure learnings from trial to trial

73% of respondent organizations have put a process in place for a feedback loop.

Assessing breaches for importance is gaining traction and most often results in changes to the protocol or monitoring strategy. Changes to the QTL parameter itself were reported less often/not used (Figure 5)

67% of respondent organizations assess breaches for importance. Of those that assess, 42% report that the process is consistently applied. Of those that are not assessing, most (80%) are considering this process for the future.

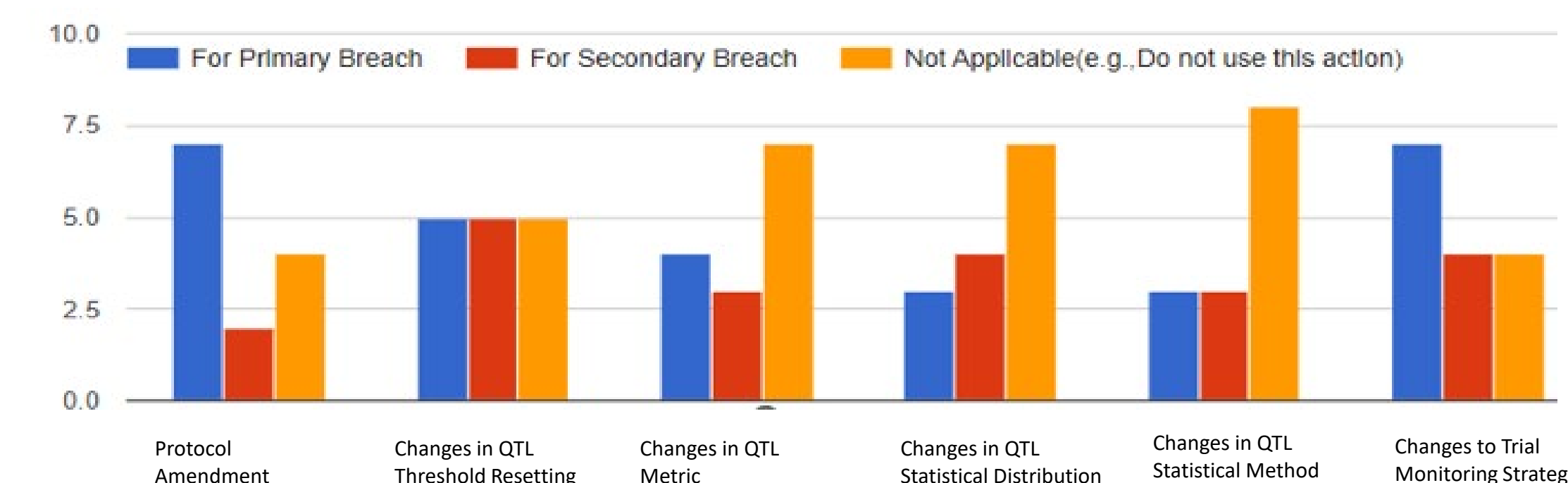


Figure 5: Important breaches are resulting in changes to the protocol or monitoring strategy. Since most organizations also have a feedback loop in place, this could result in better written protocols and monitoring strategies in the future.

Discussion

Overall

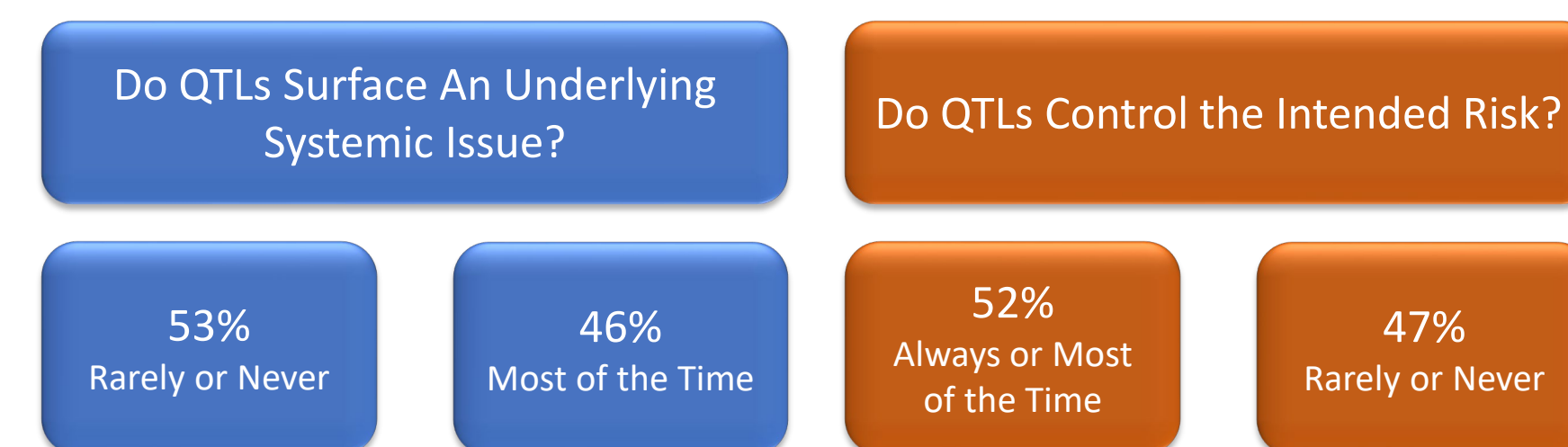
- Respondents provided valuable insights into the implementation and impact of QTLs at their respective organizations.
- QTLs are implemented across organizations of all sizes.
- Implementation is most prevalent in Phase II and III trials, whereas Phase I, IV and more complicated designs had mixed implementation. This was not surprising as there are known challenges with setting parameters and thresholds for these types of trials.

QTLs are integrated into the RBQM approach

Organizations are generally aligning QTLs with Critical-to-Quality Factors and Quality-by-Design as a part of a Risk-Based approach, as evidenced by the trend of implementing and finding the most value in study-specific parameters. This means that effort is directed where it matters most areas that could impact patient safety and/or the reliability of study results.

There appears to be an opportunity to broaden the practice of assessing the importance of primary breaches based on the root cause, to determine appropriate mitigation actions and reportability.

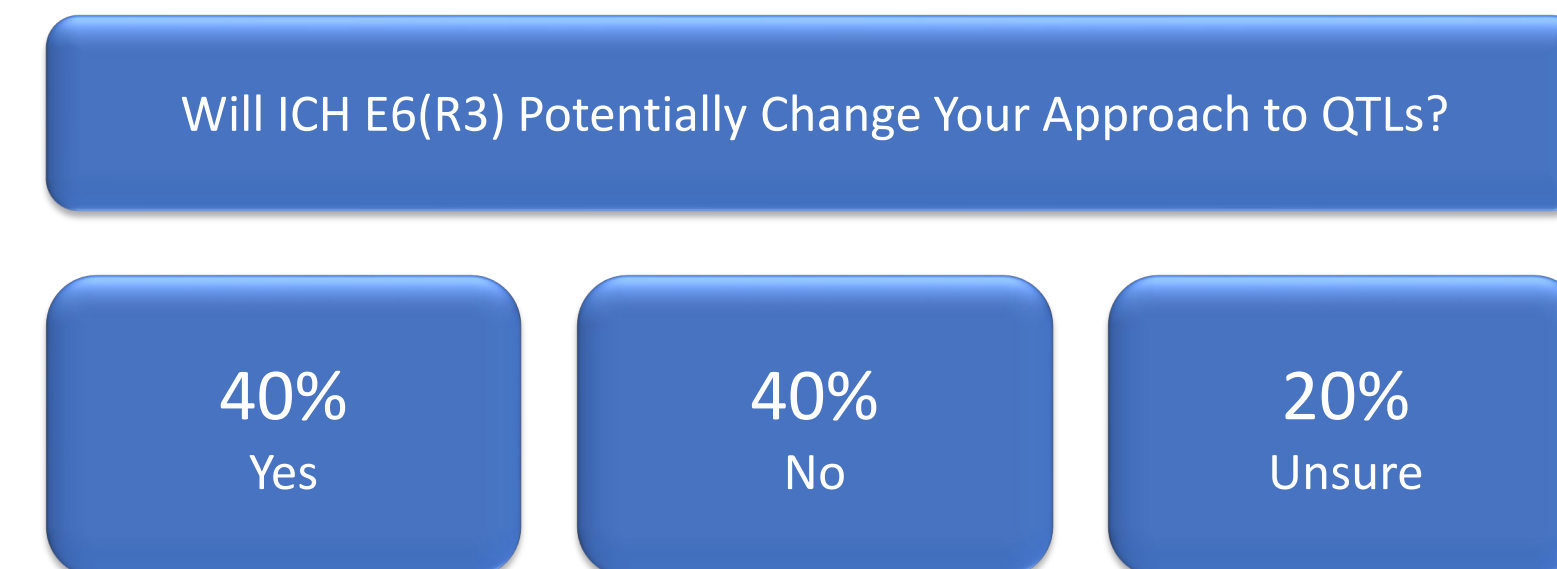
Are QTLs effective?



This suggests there are opportunities to evaluate how to choose the most impactful parameters linking to critical to quality factors. It also may indicate that QTLs must work in tandem with other mitigation strategies (e.g., robust Root Cause Analysis) as part of an overarching RBQM framework. Possibly relating the QTL to the Estimand² Framework may make it easier to identify the most meaningful parameters.

Thoughts about the draft changes in ICH E6 (R3)

ICH E6 (R3)³ will potentially replace QTL terminology with “Acceptable Ranges” and remove the language requiring them to be pre-defined.



Considering that defining a QTL is setting a threshold for a parameter (metric) and identifying breaches to an acceptable range, QTLs can clearly be seen as acceptable ranges. The change in language suggests ranges can be set using a sophisticated statistical model or setting a simpler acceptable range and manually tracking. When thought about in this way, the change in wording appears to broaden the ability of organizations to set meaningful ranges on more types of trials.

*Note Due to space limitations only selected results from the survey are presented here.

¹ ICH Good Clinical Practice E6(R2). www.ich.org.

² ICH Good Clinical Practice E9(R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials. www.ich.org

³ At the time of the PHUSE/FDA CSS, ICH E6(R3) was in Step 3 (Public Consultation). Thus, the final language in the guidance (and the opinions expressed here) are subject to change.