PQRI 2020 Webinar

Pre-Workshop Webinar

4th PQRI Workshop on ICH Q3D Elemental Impurities Requirements

Moderator: David Schoneker, Black Diamond Regulatory Consulting, LLC
Presenters: Douglas Muse, Eli Lilly and Company
           Donna Seibert, Ph.D., Perrigo Company
I. Introduction and Overview of PQRI and the PQRI EI Workshop
Moderator: David Schoneker

II. Current State of Implementation of ICH Q3D Globally
Speaker: Douglas Muse

III. PQRI Phase 2 Elemental Impurities Collaborative Study Results and Impact on Industry and Regulators
Speaker: Donna Seibert, Ph.D.

IV. Moderated Q&A Session with the speakers
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This webinar is being recorded.

The recording will be posted on the PQRI website at [www.pqri.org](http://www.pqri.org) after the webinar.

- **Your Participation**
  - If you have not done so already, please press #[Your Audio Pin]#
  - **Note:** Today’s presentation is being recorded.
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Questions

- Submit written questions using the Questions Panel.
- Raise your hand to be unmuted for verbal questions.

**Note**: Today’s presentation is being recorded.
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Handouts

- Click on the Handout Tab to download a copy of the Workshop Flyer. Please share with interested colleagues.
Mission:
PQRI is a non-profit consortium of organizations working together to generate and share timely, relevant, and impactful information that advances drug product quality, manufacturing, and regulation.
What Does PQRI Do?

• Unites thought leaders from regulatory agencies, standard setting bodies, industry and academia to conduct research and share knowledge on emerging scientific and regulatory quality challenges.

• Provides a unique, neutral forum to develop broad consensus among a diverse collection of industry organizations and regulatory bodies.

• Creates opportunities to accomplish mutual goals that cannot be achieved by individual organizations.

• Impacts global regulatory guidance and standards, bringing maximum value to members and patients.
PQRI Structure

- PQRI consists of two governing bodies – a Board of Directors and Steering Committee and three **Technical Committees**, 

- Technical Committees each have a broad disciplinary focus that collectively spans the drug product regulatory lifecycle. They establish and provide scientific guidance, direction and oversight to PQRI working groups and research projects.

- Current PQRI Technical Committees:
  - Biopharmaceutics Technical Committee (BTC)
  - Development Technical Committee (DTC)
  - Product Quality Technical Committee (PQTC)

- This webinar and the E1 Workshop are sponsored by the **PQTC**.

- You can find out more information about the TCs on the PQRI website: [https://pqri.org/about-pqri/](https://pqri.org/about-pqri/)
PQRI Webinars

2020 Webinars

- Regulatory Requirements and Scientific Considerations for Biosimilar Products (September 16, 2020)  
  Presenters: Stacey Ricci, M.Eng., Sc.D, FDA; Leah Christl, Amgen; Sundar Ramanan, Ph.D., MBA, BioCon
- BTC/PQTC Webinar Series: Excipient Considerations for Parenteral Drug Development (July 29, 2020)  
  Presenters: Janeen Skutnik-Wilkinson (Biogen) and Thomas Tice, Ph.D., Evonik
- The Challenge and the Promise: Developing Complex Drug Products (April 28, 2020)  
  Presenters: Wenlei Jiang, Ph.D., FDA and Adrian Goodey, Ph.D., Merck

2019 Webinars

- The Expanding IVIVC Toolbox to Enable Drug Product Quality and Clinical Pharmacology – Complementary Traditional and PBPK Based Approaches (June 7, 2019)  
  Presenters: Xianyuan (Susie) Zhang, Ph.D., FDA and Filippos Kesisoglou, Ph.D., Merck
- Holistic QbD to Enable Product Quality Webinar (October 10, 2019)  
  Presenters: Ajit Narang, Ph.D., Genentech; Rakhi Shah, Ph.D., FDA; Xavier Pepin, Pharm.D, Ph.D; Divyakant Desai, Ph.D., BMS; Xavier Pepin, Pharm.D, Ph.D., AstraZeneca

2018 Webinars

- A Science Based Approach to Simplifying the Regulatory Pathway for Topical Drugs (April 9, 2018)  
  Presenters: Vinod P. Shah, Ph.D., FAAPS, FFIP and Flavian Radulescu, Ph.D.
- Questions about the Proposed Topical Classification System (TCS) and What To Do With It (June 19, 2018)  
  Presenter: Sam Raney, Ph.D., FDA
- Performance Testing in Quality Control and Product Development, Where are We? (October 23, 2018)  
  Presenter: Raimar Löbenberg, Ph.D., University of Alberta
- Biowaiver Approaches for Solid Oral Dosage Forms in New Drug Applications (December 6, 2018)  
  Presenter: Poonam Delvadia, Ph.D., FDA

Posted at [https://www.gotostage.com/channel/pqriwebinars](https://www.gotostage.com/channel/pqriwebinars)
Pre-Workshop Event

• Pre-Workshop Survey
  • Obtain feedback from possible workshop attendees to understand the types of challenges they have experienced with their own organizations during the implementation of ICH Q3D. The results of the survey will be blinded, aggregated and shared during the November Workshop.
  • Click here to complete the survey.

4th PQRI Workshop on ICH Q3D Elemental Impurities Requirements
November 9-10, 2020

LIVE VIRTUAL EVENT

Click here for registration.

Please register for the workshop (even if you can’t attend it live); sessions will be recorded and made available to registered attendees.

See https://pqri.org/4th-pqri-ei-workshop/ for more information
Douglas G. Muse, Compendial Affairs Liaison, Global Quality Laboratories, Eli Lilly and Company
Muse_Douglas_G@Lilly.com

Mr. Muse is a compendial affairs liaison for the Global Quality Laboratories organization at Eli Lilly and Company. He currently serves on the IPEC-Americas Executive Committee as the Vice Chair of Compendial Harmonization and Monographs, and he is chair of the Compendial Review Committee. He has 29 years of pharmaceutical industry experience in Quality Control Laboratory testing. He participates in multiple pharmaceutical industry trade associations and Pharmacopoeial discussions groups. During his career he has held multiple Quality Control and QC Lab positions including supervision and management, subject matter expert, analytical technical steward, and consultant. He has experience in testing raw materials, excipients, bulk drug substances, and parenteral drug products. He earned a Bachelors of Science degree from Missouri Western State University in 1991.
Current State of Implementation of ICH Q3D Globally

PQRI Workshop Overview – Day 1
State of Global Implementation

• Overview of the Global Experience

• Results of PQRI Pre-Workshop Survey – Please Complete
  – Please complete the survey by October 2nd
    • Janeen Skutnik-Wilkinson, IPEC Americas, Biogen

• Implementation in Japan
  • Yoshiaki Ogasawara, IPEC Japan
Regulator Experience - Quality of Risk Assessments and Supporting Data

- Implementation in China
  - Lihe Liu, National Medical Products Administration (NMPA) **INVITED**

- Implementation in the US - FDA Perspective
  - Matthew Vera, OLDP/OPQ/FDA

- Implementation in Europe, EMA Perspective
  - Sophie Bertilsson, Swedish Medical Products Agency
State of Global Implementation

Industry Experience – Implementation Challenges

• Pharmaceutical Company Perspective
  • Mark Schweitzer, Novartis

• Excipient Company Experience
  • Priscilla Zawislak, DuPont Nutrition and Biosciences
Pharmacopeia Approaches to Element Specific Requirements in Monographs

Day 1 - Continued
Pharmacopeial Approaches

• An Update on USP Element Specific Chapters
  • Nancy Lewen, Consultant
• USP Update on the Draft Roadmap for Addressing Element-Specific Chapters and Tests in Excipient Monographs
  • Galina Holloway, USP
• European Pharmacopoeia Activities on Elemental Impurities – An Update
  • Ulrich Rose - EDQM
Pharmacopeial Approaches

Industry Perspectives and Consequences

• Excipient Company Perspective
  • Dale Carter, Evonik

• Industry Perspective on Managing Elemental Impurity Content in Monographs
  • Philip Travis, Merck
Break Out Session

Implementation Problems and Future Needs

• Participants will break out into small groups to discuss experiences with implementing the ICH Q3D requirements

• Moderators
  • Kathy Ulman, KLU Consulting
  • Doug Muse, Lilly
  • Janeen Skutnik-Wilkinson, Biogen
PQRI 2020 Webinar
Pre-Workshop Preview

PQRI Phase 2 Elemental Impurities Collaborative Study Results and Impact on Industry and Regulators

Presenter: Donna Seibert, Ph.D., Senior Manager, Perrigo Company
Today’s Presenters

Donna Seibert, Ph.D., Senior Manager
Perrigo Company
Donna.Seibert@perrigo.com

Donna S. Seibert, PhD is Sr. Manager in Analytical Research and Development in Consumer Self Care at Perrigo Company, a leading global healthcare supplier that develops, manufactures and distributes OTC and generic prescription pharmaceuticals, infant formulas, self-care, and nutritional products. Seibert has over 18 years of pharmaceutical R&D experience spanning branded, generic prescription, and generic OTC product lines. In her current role, Seibert’s responsibilities include new product development, raw material change management, as well as both organic and elemental impurity aspects of the USP monograph modernization initiative. She also serves on the USP OTC Methods and Approaches Expert Committee. Seibert holds a BA in Chemistry from Transylvania University and a Ph.D. in Analytical Chemistry from Wayne State University.
I. Welcome and Overview of Day 1  
   David Schoneker

II. Ongoing ICH Q3D Activities—Update on Transdermal Limits  
    Andrew Teasdale, Astra Zeneca

III. Lhasa Database Update  
     Laurence Harris, Pfizer

IV. PQRI Phase 2 Elemental Impurities Collaborative Study Results and Impact on Industry and Regulators  
    Donna Seibert, Perrigo  
    James Harrington and Stephen Erickson, RTI International  
    Denise McClenathan, Proctor & Gamble  
    Thanh Nguyen and Glenn Williams, Rigaku  
    Francine Walker, SGS Chemical Solutions Ltd.  
    Xiaoyi Gong, Merck

PQRI Webinar  
September 2020
Break Out Session

Explore the Impact of the Phase 2 Study on Industry and Regulators

• Participants will break out into small groups to discuss the impact of the PQRI Collaborative Phase 2 Study on Industry and Regulators

• Moderators
  Donna Seibert, Perrigo
  James Harrington, RTI International
  Denise McClenathan, Proctor & Gamble
Disclaimer

• Any images of or references to specific commercial products, processes, or services does not constitute an endorsement or recommendation by PQRI, the TAC team, or Interlaboratory study organizers.

• The views and opinions of authors expressed herein do not necessarily state or reflect those of PQRI, and shall not be used for advertising or product endorsement purposes.
Inter-laboratory Study Objectives

Objectives

• Address some key technical challenges faced by industry in preparation for compliance to ICH Q3D and USP <232>/<233>

• Provide a data-driven way to discuss technical aspects and expected variation of ICP-MS analysis of elemental impurities

• More specific objectives:
  – Inter-laboratory data comparison for standardized samples
  – Inter-laboratory evaluation of effectiveness of microwave digestion
  – Comparison of acid leach/extraction techniques to total metal extraction
  – Examination of the correlation (good or bad) between the analysis of individual components (summation) vs. the formulated tablet analysis
  – Comparison of ICP-MS and alternative techniques (ICP-OES and XRF)
Uniform Sample Preparation

- Specify parameters such as sample size, sampling technique, replicates, acid mixtures, and digestion temperature/pressure
- Document type of digestion vessels and microwave model used
  - IPV vs. SRC
Uniform Analysis

- Define isotopes used for quantitation
- Define procedures around units, LOQs, calibration, system suitability and data reporting
- Document interference management (reaction/collision gases, correction equations, etc.), internal standards, and any additional isotopes monitored
- Document instrument type
  - Single Quad vs. Triple Quad vs. High resolution systems
Second Round Evaluation Samples

**Liquid Sample**
- Added to assess instrumental variation independent of sample preparation

**Solid Samples**
- Tableting is preferred to preserve homogeneity
- Material combination must have favorable mixing & flow properties, and must be compressible
- Multiple tableted evaluation samples targeting three different levels
- EI source from pharma materials wherever possible
- EI source from materials that are not easily solubilized
# Formulation Design

<table>
<thead>
<tr>
<th>Raw Material</th>
<th>Tablet Level 1 (30% J, µg/g)</th>
<th>Tablet Level 2 (100% J, µg/g)</th>
<th>Tablet Level 3 (300% J, µg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microcrystalline Cellulose</td>
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<td>0.150</td>
<td>0.150</td>
</tr>
<tr>
<td>Magnesium Aluminum Silicate Clay, USP/NF</td>
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<td>0.100</td>
<td>0.100</td>
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<tr>
<td>Lactose monohydrate, NF</td>
<td>0.5305</td>
<td>0.465</td>
<td>0.478</td>
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<tr>
<td>Pregelatinized Starch</td>
<td>0.200</td>
<td>0.200</td>
<td>0.200</td>
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<tr>
<td>Stearic Acid</td>
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<td>0.012</td>
<td>0.012</td>
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<td>Ferric Oxide Red, BC</td>
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<td>Silicon Dioxide Standard (Cd, Ni, Pb)</td>
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<td><strong>1.00</strong></td>
<td><strong>1.00</strong></td>
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<td></td>
<td>Material</td>
<td>Expected concentration (ug/g)</td>
<td>Measured Concentration (ug/g)</td>
</tr>
<tr>
<td>---</td>
<td>----------</td>
<td>-------------------------------</td>
<td>-------------------------------</td>
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<td>6.05</td>
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<td>17.9</td>
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<td>Level 3</td>
<td>49.2</td>
<td>43.6</td>
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<td>Level 3</td>
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<td>13.5</td>
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<td>Level 1</td>
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<td>Level 2</td>
<td>19.45</td>
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<td>Level 3</td>
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<td>Level 3</td>
<td>17.35</td>
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## Reference values

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<td>8.63</td>
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<td>91.3</td>
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<tr>
<td>V</td>
<td>22.25</td>
<td>22.7</td>
<td>0.9</td>
</tr>
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<td></td>
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</tr>
<tr>
<td></td>
<td>102</td>
<td>105</td>
<td>146</td>
</tr>
</tbody>
</table>
Exhaustive Extraction vs Total Digestion

• Exhaustive extraction
  – Nitric acid microwave extraction
  – Mass 1 tablet (or specified mass of RM), crush tablet
  – Add 10 mL HNO₃ and 50 µL Au standard
  – Microwave digestion
    • Ramp to 175 °C for 10 min
    • Hold at 175 °C for 10 min
    • Cool to RT
  – Dilute 50-fold to ~2% HNO₃, 2% HCl

• Total Digestion
  – HNO₃, HCl, H₃PO₄, and HBF₄ microwave extraction
  – Synthesize HBF₄ from HF and H₃BO₃
  – Mass 1 tablet (or specified mass of RM), crush tablet
  – Add 2.5 mL HNO₃, 0.5 mL HCl, 0.5 mL H₃PO₄, and 1.0 mL HBF₄
  – Microwave digestion
    • Ramp to max safe temp for 25 min
    • Hold at max safe temp for 20 min
    • Cool to RT
  – Dilute 50-fold to 2% HNO₃, 2% HCl, 0.2% HF
Exhaustive Extraction vs Total Digestion

Percent Recovery (Measured vs Measured)

Total Digestion
Exhaustive Extraction

PQRI Webinar
September 2020
Initial results – ICP-MS

- Final tally of responding labs
  - Reproducibility analysis and comparison to reference data:
    - Microwave type analysis:
      - SRC Microwave: 14 labs
      - IPV Microwave: 8 labs
    - Digestion method analysis:
      - Exhaustive Extraction: 19 labs
      - Total Digestion: 7 labs
**Key takeaways:**

**Analysis of tablets by ICP-MS**
- Consistent results WITHIN labs, but higher variability between labs
  - Specific elements - **Hg, V**

**Raw material analysis**
- Consistent for elements present at high concentrations
  - Low concentrations exhibited some variability (e.g., Smectite clay)
- False positives in raw materials were generally not an issue
  - V exhibited high false positive rate; potentially due to interference correction strategies

**Exhaustive extraction vs Total Digestion**
- No significant difference for tablets
Key takeaways:

**SRC vs IPV**
- Most elements in Raw Materials > LOQ were consistent
- Hg, Pb: SRC concentrations > IPV concentrations
  - Potential volatility for Hg?

**XRF analysis**
- Consistent within-lab variability, higher between-lab variability
- As, Cd: ICP-MS < XRF
## Summary of ICP-MS results by analyte

<table>
<thead>
<tr>
<th></th>
<th>Strong Equivalence</th>
<th>Moderate Equivalence</th>
<th>Weak Equivalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reproducibility</strong></td>
<td>As, Co, Ni</td>
<td>Cd, Hg, Pb</td>
<td>V</td>
</tr>
<tr>
<td>How variable is an element between labs and within labs (Strong = low variability; weak = higher variability)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exhaustive vs Total</strong></td>
<td>Cd</td>
<td>As, Co, Hg, Ni, Pb</td>
<td>V</td>
</tr>
<tr>
<td>Compares exhaustive vs total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Microwave types (SRC vs IPV)</strong></td>
<td>Cd, Ni</td>
<td>As, Co, V</td>
<td>Hg, Pb</td>
</tr>
<tr>
<td>Compares SRC vs IPV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Summation Approach</strong></td>
<td>Ni</td>
<td>As, Co, Pb</td>
<td>Cd, Hg, V</td>
</tr>
<tr>
<td>Compares summation of RM’s vs finished product analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comparison to Reference</strong></td>
<td>Pb</td>
<td>As, Cd, Co, Ni</td>
<td>Hg, V</td>
</tr>
<tr>
<td>Compares all lab results to Reference lab results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Overall ICP-MS</strong></td>
<td>Ni</td>
<td>As, Cd, Co, Pb</td>
<td>Hg, V</td>
</tr>
<tr>
<td>Summarizes overall element performance</td>
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<td></td>
<td></td>
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Note: Similar analysis performed for raw materials.
### Summary of XRF results by analyte

<table>
<thead>
<tr>
<th><strong>Reproducibility</strong></th>
<th><strong>Strong Equivalence</strong></th>
<th><strong>Moderate Equivalence</strong></th>
<th><strong>Weak Equivalence</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>How variable is an element between labs and within labs (Strong = low variability; weak = higher variability)</td>
<td>As</td>
<td>Hg</td>
<td>Cd, Co, Ni, Pb, V</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>XRF vs ICP-MS (all)</strong></th>
<th><strong>Strong Equivalence</strong></th>
<th><strong>Moderate Equivalence</strong></th>
<th><strong>Weak Equivalence</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compares XRF lab results to all ICP-MS laboratory results</td>
<td>Pb, V</td>
<td>Co, Hg, Ni</td>
<td>As, Cd</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>XRF vs ICP-MS (exhaustive)</strong></th>
<th><strong>Strong Equivalence</strong></th>
<th><strong>Moderate Equivalence</strong></th>
<th><strong>Weak Equivalence</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Compares XRF lab results to ICP-MS laboratory results for exhaustive extraction</td>
<td></td>
<td>Co, Hg, Ni, Pb, V</td>
<td>As, Cd</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>XRF vs ICP-MS (total)</strong></th>
<th><strong>Strong Equivalence</strong></th>
<th><strong>Moderate Equivalence</strong></th>
<th><strong>Weak Equivalence</strong></th>
</tr>
</thead>
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<tr>
<td>Compares XRF lab results to ICP-MS laboratory results for total digestion</td>
<td>Co, Pb</td>
<td>Hg, V</td>
<td>As, Cd, Ni</td>
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<th><strong>Comparison to Reference</strong></th>
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<th><strong>Overall XRF</strong></th>
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<th><strong>Moderate Equivalence</strong></th>
<th><strong>Weak Equivalence</strong></th>
</tr>
</thead>
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<tr>
<td>Summarizes overall element performance</td>
<td>Pb</td>
<td>Co, Ni, V, Hg</td>
<td>As, Cd</td>
</tr>
</tbody>
</table>

*Note: XRF analysis only performed for Tablet materials.*
Key questions

• What level of error or uncertainty would represent a compelling indicator for adjusting analytical methods?
• What strategies are labs taking with respect to total digestion/exhaustive extraction considering the extensive infrastructure and safety considerations for total digestion?
• Are comparable levels of analytical uncertainty and variability of results acceptable for risk assessment purposes as for routine release testing of products?
• What role do statisticians and analytical experts play in the development of risk assessments to account for potential uncertainties?
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- Gary Hayes, Colorcon
- TAC Team members
- All participating labs
Polling Questions
Q&A Session

• Submit written questions using the Questions box in your control panel
• Raise your hand to be unmuted for verbal questions.
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