GLOBAL BIOANALYSIS CONSORTIUM

Regulated Bioanalysis
A Proposed Global Harmonization Process

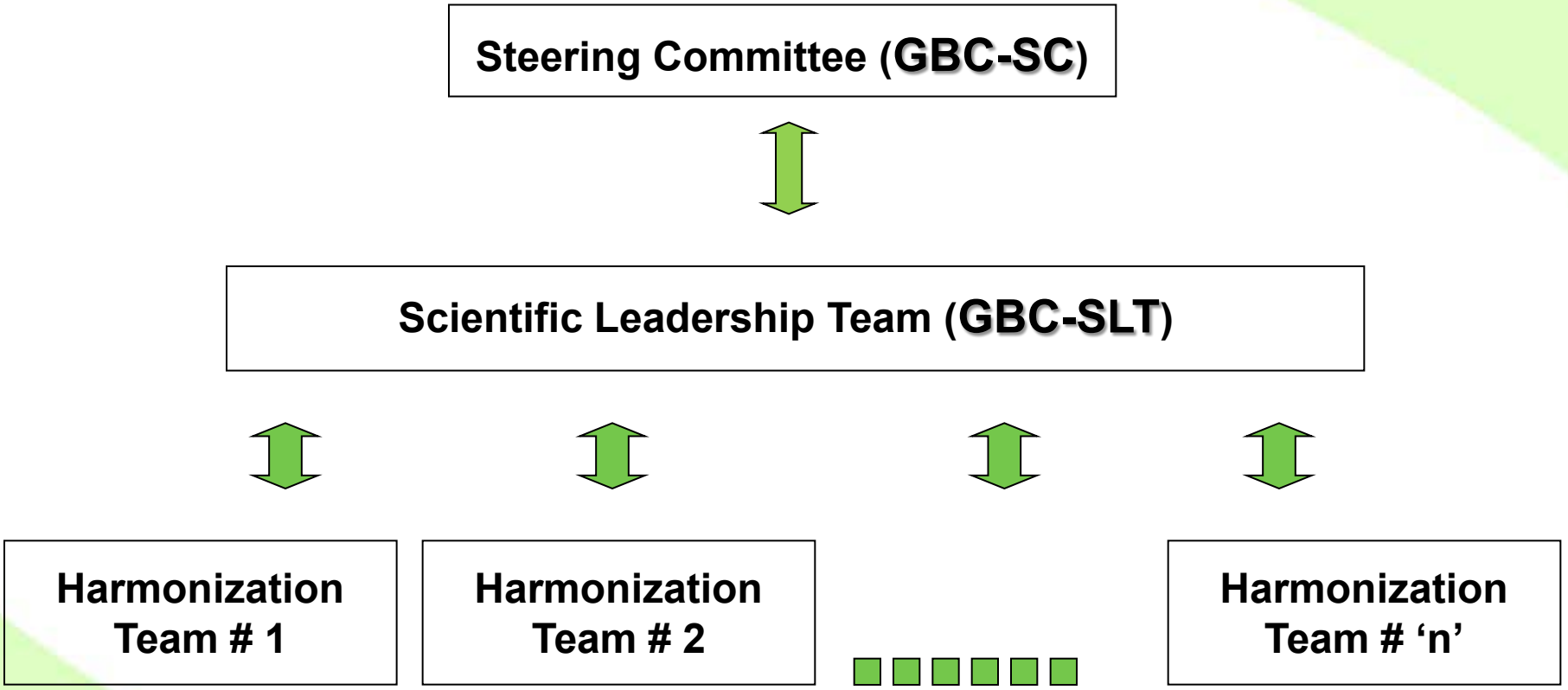
Mark Arnold for the GBC

APA-India February 2012

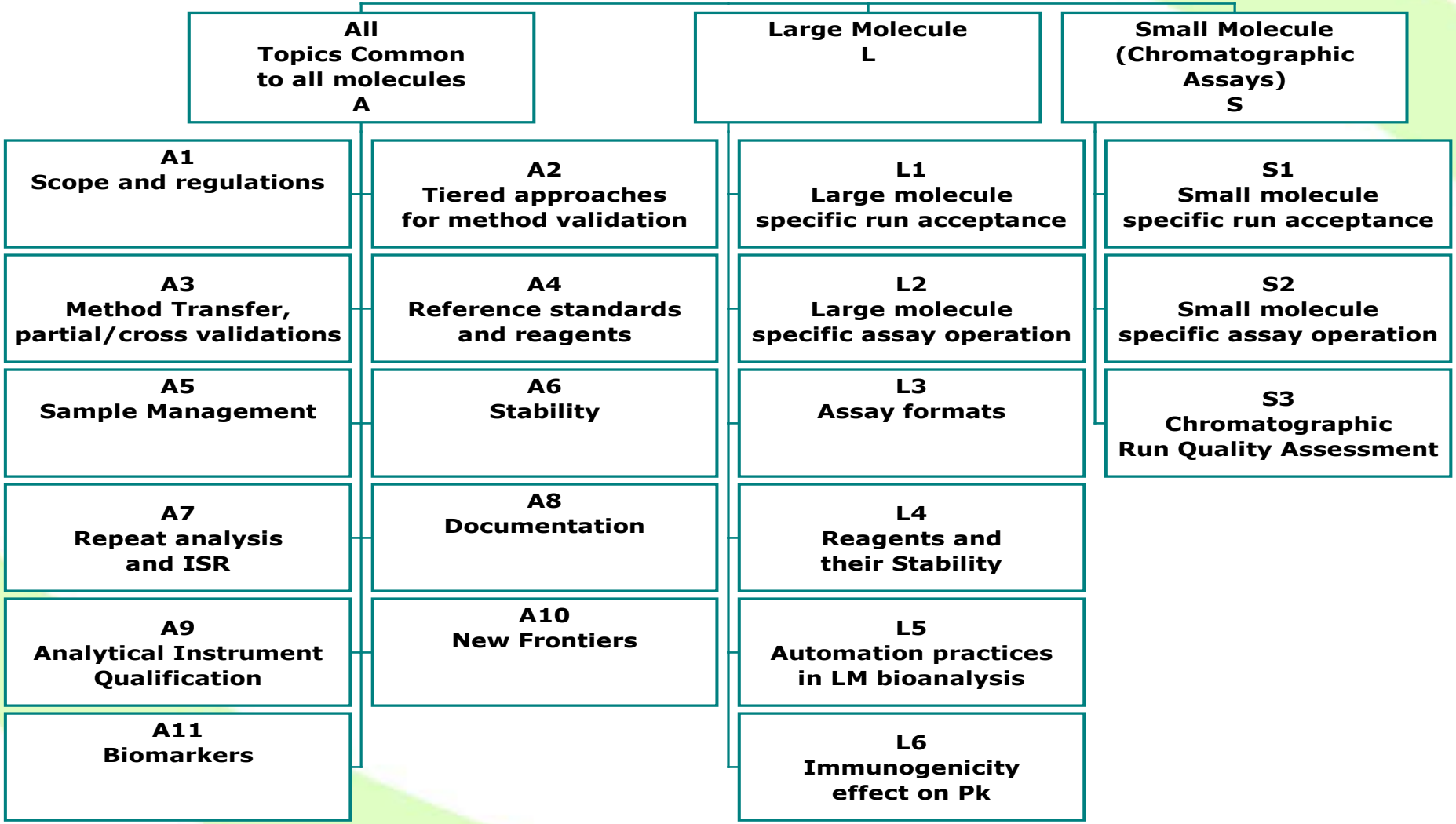
Agenda

- Review GBC structure
- Harmonization Teams' Activities
- Communications
- Details on some Harmonization Team Activities

Organization Chart



Active Harmonization Teams



SC Sponsorship of Harmonization Teams

Team Leaders	SC Sponsor
A1: Surendra Bansal	Philip Timmerman
A2: Steve Lowes	Daniel Tang
A4: Joseph Bower	Shinobu Kudoh
A6: Nico van den Merbel	
A11: Russ Weiner	

Team Leaders	SC Sponsor
L1: Marian Kelley	Michaela Golob
L2: Lauren Stevenson	Fabio Garofolo
L3: Sherri Dudal	Binodh DeSilva
L4: Lindsay King	
L5: Scott Davis	
L6: Jeff Sailstad	

Team Leaders	SC Sponsor
A3: Ray Briggs	Peter van Amsterdam
A5: Mike Redrup	Shrinivas Savale
A7: Eric Fluhler	
A8: Tom Verhaeghe	

Team Leaders	SC Sponsor
A9: Chad Briscoe	Rafael Barrientos
A10: Bob Bethem/ Chad Ray	Mark Arnold
S1: Douglas Fast	
S2: Eric Woolf	
S3: Stuart McDougall	

Harmonization Team Objectives

HT Leaders Objectives

- Remove concepts of company or region from your thinking - you're leading a global effort.
- Facilitate discussion, don't push your personal agenda

Teams are to develop science-based best practices

- Recognize that consensus may not be possible. People with different views will spark vigorous discussion.
- Prevent bullying by the loudest voice. Allow and stimulate less extrovert people to share their opinion and experience
- Recognize that some governments /regions may have regulations that are outdated or inconsistent with a science-based approach. Be prepared to defend proposals that conflict with existing regulations.

80:20 Rule

- Not all items within the Scope of the Team need to be redone, in fact 80% may already have industry-regulatory consensus

HT activities

Compile regional information on regulations and practices related to the Team's scope

- Share regulations with other Team
- A lot of prework has been done

Evaluate scope list to categorize those that:

- Are fully agreed to
- Are generally agreed to
- Have no agreement

HT activities

- For those that are **agreed to** write science-based language as proposed position

- For those that are **generally agreed to**, discuss differences and develop science-based position, write science-based language as proposed position

- For those that are **not generally agreed to**, prioritize the list to enable discussion on those with the greatest impact to the bioanalytical community
  - Have internal team discussions and where possible, develop recommendations
  - Where no consensus is achieved, provide arguments on both sides
  - Utilize GBC SC and other HT leaders for input

Team members should reach back to regional organizations for input

- Query regional organization membership on positions on a topic(s)
- Coordinate across Teams. Regional memberships will lose interest if frequently bombarded with requests.

HT activities

Proposals and outcome

- Write proposals in a clear and concise manner that are suitable for publication, include references to existing literature and regulations
  - As noted above, where proposal conflicts with existing regulations, additional details and discussion may be needed

- Create slide deck for communication of proposals that go into greater depth and may contain data. This will be foundation of
  - Presentations at regional meetings
  - Presentation at international meeting
  - Publications in international journals
  - Note: timing of publications in relation to international meeting
    - ***Targeting International meeting in last week of Sept 2012 – venue selection in EU is ongoing***
- Where no consensus is achieved, provide arguments on both sides

New insights developed at GBC-SC meetings

Feedback indicates a desire for increased engagement, input and contribution from the different regions

- The current team dynamics and composition may not sufficiently engage the broader scientific community
- Open discussion

Desire to provide opportunity for regular updates on GBC progress in an open format

- The current process may lead to a significant period of ‘radio silence’
- Prevent all GBC-proposals coming as one avalanche at the global meeting, which may be too much to manage if not previewed
- Provide regulators a chance to get better understanding of activities of GBC

How will these concerns be addressed

Move GBC Global meeting from Q2 to Q3 2012.

Inform scientific, QA and regulatory community via discussions at appropriate 2011-2012 regional meetings in all 4 regions to give a flavor of the progress we are making.

- If the regional meeting can accommodate, include a GBC session in those meetings to provide update and allow input
- Invite 4-5 topic HT-L (or a regional representative from those teams) to present the progress of their teams and to share.
- Stimulate HT-SC(s) to present high level progress on other topics, with input from other HT
- Engage with meeting organizers how to optimize GBC visibility during the meeting
- Publish outcome as a rapid communication to ensure all regions connect (GBC website or “Bioanalysis”)
- Inviting organizations to provide travel assistance for speakers

Potential win-win

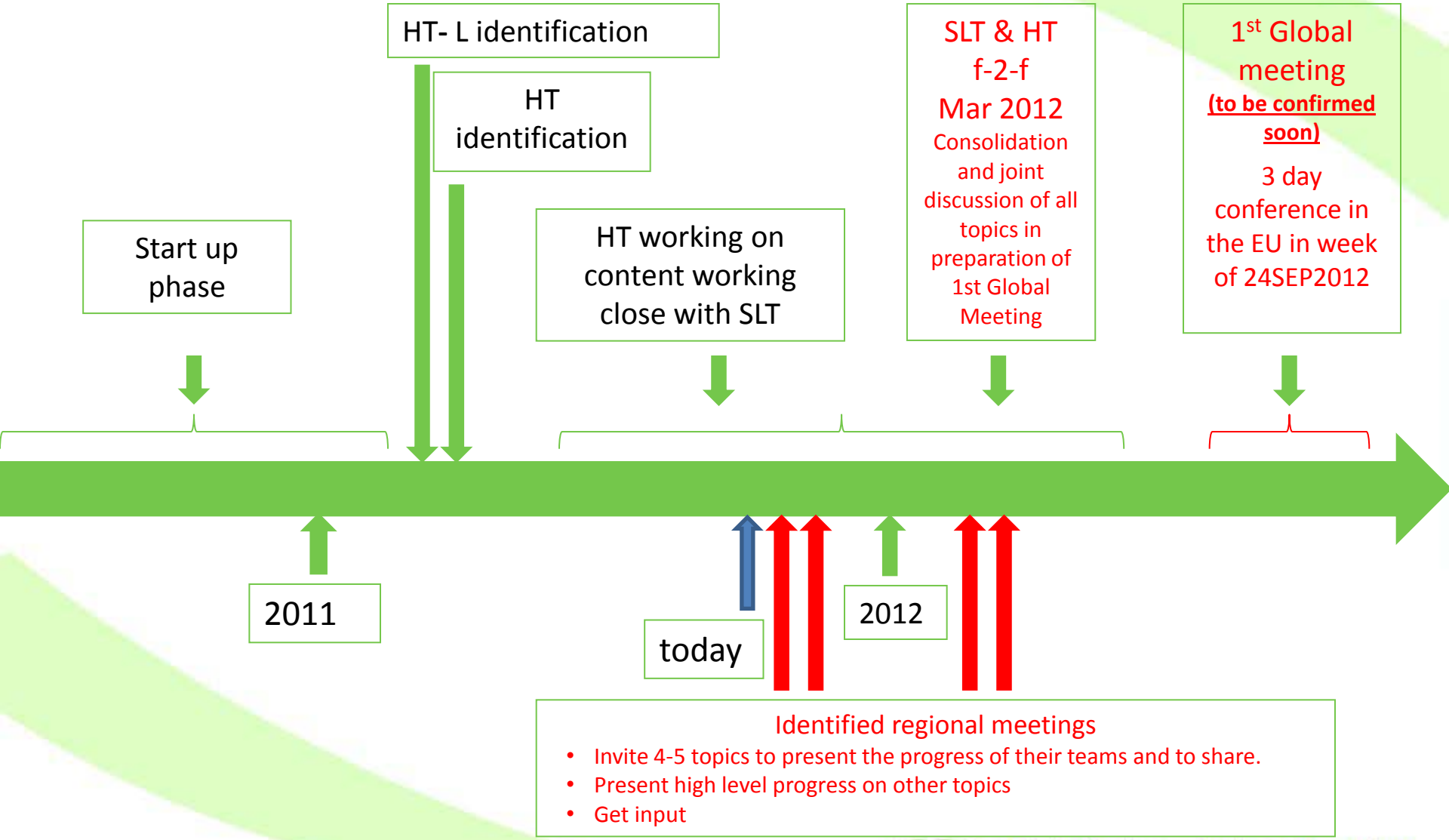
- Connect GBC better with the regions
  - Reconnection with supporting organizations as our day to day supporters
  - All regions get expanded opportunity to be involved
- Engage and inform a broader scientific community in advance of the global meeting
  - Allow BA community to comment within the comfort zone of their region
  - Allow BA community to comment to their regional organizations
- Provide the opportunity to publish a summary of thinking in advance of the global meeting
  - Allow global community of practice to know what's coming
  - Be more engaged in the global meeting and not be caught by surprise
- Create visibility, recognition and connectivity in regions
  - for HT-L and HT members
  - for SC members
- Create flexibility to present on topics in need of influencing current thinking of regulators or on emerging guidelines

In practice

Identified meetings qualifying for inclusion GBC session

- Fit with respect to timing
- Fit with respect to willingness of organizers to include GBC session
- Meetings potentially qualifying – further discussion with meeting organizers needed
  - NA:
    - Oct 2011: AAPS Washington USA ***+ Meet & Greet HTLs and SC***
    - March 2012: 6th WRIB-CVG – San Antonio – USA **+ SC and HTLs f-2-f working session**
    - May 21-23, 2012: National Biotech Conference, San Diego USA ***– session planned***
    - May 2012: ASMS Vancouver Canada ***– presentation planned***
    - July 2012: Land O'Lakes Wisconsin USA
    - Sept 2012 APA Boston- USA
    - Other regional meetings (e.g., DVDMG)
  - EU:
    - Nov 2011: EBF - ***Full session on GBC progress and team presentations + Meet & Greet HTLs and SC***
    - June 12-13, 2012 EBF Focus meeting - Brussels - ***1/2 day session on GBC progress and team presentations***
    - Other regional meetings (e.g., Fabian, French GLP,..)
  - APAC:
    - Feb 2012: APA India
    - Mar 2012: JBF Japan
    - April 2012: CPSA Shanghai, China ***– presentation on GBC progress***
    - Nov 2012:- 2nd APBC-CVG China
    - Other regional meetings
  - LA:
    - ACBio will be planned, targeted in May2012
    - Other regional meetings

Proposed way forward - *Updated*



HT in action

Challenges seen with HT process

- Gathering all team members for meetings across the various time zones
- Engaging all team members in the discussions

L1: Large molecule specific run acceptance

Team members:

Team lead

- Marian Kelley – NA

Other members & region

- Paula Kaminski, NA
- Daniella Stollner, EU
- Ross Bamford, EU
- Muruganandam Arumugam, APAC
- Ravi Trivedi, APAC
- Samantha Little, EU
- Lauren Stevenson, NA
- Dongbei Li ,APAC
- Chris Beaver, NA

In scope:

- Non-Linearity, of standard curve
- Makeup of standard curve
- Standard Curve editing
- Selection of "best" curve fit
- Quality Controls
- Assay range definition
- Accuracy, precision, total error
- Individual runs and overall run acceptance during validation
- Individual runs acceptance during samples analysis

Inter-dependencies with other teams

- S1 Small Molecule Run Acceptance
- L2 Specific LBA Operation

Out of scope:

- Stability of QCs long term during sample analysis: If it fails what do you compare to? Nominal, fresh? Two fold question: technical vs. stability. *Will be addressed in L2 team*

S1: Small molecule – Specific run Acceptance

Team members:

Team lead

- Douglas Fast, NA

Other members & region

- Maristela Andraus, LA
- Matt Barfield, EU
- Michael Blackburn, EU
- Ben Gordon, EU
- David Hoffman, NA
- Noriko Inoue, APAC
- Amy LaPaglia, NA
- Richard LeLacheur, NA
- Gabriel Marcelin Jimenez, LA
- Scott Reuschel, NA
- Ravi Sankar, APAC

Interdependencies with other teams:

- **A2, A7, A8, L1**

In scope:

- During validation
  - Linearity, accuracy, precision
  - Calibration curve range and QC placement
  - Selection of regression analysis model (linear, quadratic, weighting)
  - Criteria for individual runs & overall acceptance
  - Validation of plasma blank samples
  - Cross validation of anticoagulants & counterions
- During samples analysis
  - Individual run acceptance
  - Internal standard criteria
  - Carryover
  - Positive control or predose samples
  - Anomalous sample results on run acceptance
  - System suitability testing
  - Sample and run reinjection
  - System conditioning

Out of scope:

S2: Small molecule specific assay operation

Team members:

Team lead

- Eric Woolf – NA

Other members & region

- Abhishek Sharma– APAC
- Barbara Duncan – NA
- Berthold Lausecker– EU
- Gabriel Marcelín – LA
- Kazutaka Togashi– APAC
- Miguel Vago- LA
- Pat Bennett– NA
- Ravi Kumar Trivedi – APAC
- Roger Hayes– NA
- Steve White- EU

Interdependencies with other teams:

Team A6 (re: stability)

- Sample reinjection
- API Salt / Counter-ion changes

Team A9 (re: system suitability)

- System Equilibration –

In scope

- Carryover and contamination
  - methodology to assess
  - acceptance criteria
  - impact of sample analysis sequence
- Sensitivity
  - "One off" std. curve range changes
- Specificity - selectivity
  - impact of co. meds/metabolites
- Matrix Effects
  - assessment methodology
  - effect of hemolyzed/hyperlipidemic plasma
- Recovery
  - assessment methodology & acceptance criteria
- IS evaluation
  - addition methodology
  - response variability assessment & acceptance criteria
- System equilibration
  - use of study samples
- Sample reinjections
- Reporting of failed runs
- Impact of salt form/counter ion changes of analyte
- Preparation of calibrators – organic solvent content

Out of scope

- stability criteria

L2: Large Molecule – Specific Assay Operations

- Recommendations generated for:
  - Selectivity
    - Best approach(es) for conducting selectivity testing when endogenous analyte is present in matrix
  - Parallelism
    - When best to incorporate parallelism testing
    - Include when performing ISR for a given method
  - Long term stability samples
    - Should we include a high concentration sample in LTS testing to represent in-study Cmax samples?
  - Hook effect
    - How to approach testing of high concentration samples when/if some degree of hook effect is observed in validation?

L5: Automation Practices in LM Bioanalysis

Developed recommendations for the method validation of automated sample preparation systems (automation or robotics)

- As follow-on to fully validated manual method
- With no previously validated manually method
- Combined validation of manual procedure and its automated counterpart
- Includes recommendations for validations after modifications to the automated method script

Alignment will be needed with A9: Instrument Qualification

A6: Stability

Incurred sample stability

Scientifically, it is a potentially important issue, which may influence reliability of results, when not properly controlled

Practically, it has many difficult aspects, with respect to timing (difficult to perform prior to clinical phase), availability and ownership of samples, etc.

Stability in presence of co-administered or co-formulated drugs

Scientifically questionable, how can the presence of another drug induce instability of an otherwise stable compound?

Practically, it has many difficult aspects, with respect to timing (difficult to perform prior to clinical phase), availability and ownership of samples, etc.

Transferability of stability results

Scientifically, (in)stability is determined by physico-chemical parameters (temperature, time, matrix composition, exposure to light)

Results are universally valid if storage conditions can be reproduced

Practically, it has a relatively large impact if stability has to be re-assessed at all bioanalytical labs involved; especially for long-term stability

S1: Validation Run Acceptance

1. Linearity, Accuracy, Precision
2. Appropriate calibration curve range and QC placement across range for certain study types
   - ➢ Considerations for ascending dose/FIH studies
     - When, How to change calibration range
     - How to address sample results in limited/low portion of range only (linearity issues, number of calibrant points, QC placement)
   - ➢ Other study designs: repeat dose (steady-state results vs. PK results), high dose tox, etc.
3. Criteria on selection of regression analysis model (linear, quadratic, weighting)
4. Criteria for individual runs and overall acceptance during validation
   - ➢ IS response acceptance criteria, variability permitted (individual samples or groups of samples)
   - ➢ Minimum levels of IS response needed
     - S2 team interaction
   - ➢ How to address, report failed validation runs
     - Inclusion, exclusion from summary and statistics
5. Validation of plasma blank samples
   - ➢ Stability of blank samples
   - ➢ Use of predose samples for calibrators and controls from subjects
     - How long can they be used?
6. Cross validation of anticoagulants and counterions: requirements to perform, acceptance criteria when performed

S1: Sample Analysis Run Acceptance

1. Individual run acceptance during sample analysis
   - Single analyte vs. Multiple analyte with mixed pass/fail outcomes
2. Internal standard criteria: acceptance criteria, variability permitted
   - Minimum levels of IS response needed
   - Decisions on anomalous IS response: anomaly in individual sample or between groups of samples (i.e., QCs/Calibrants vs. dosed samples)
3. Carryover: acceptance criteria, role of standard (double) blank and standard zero
   - Determination of and criteria for contamination vs. carryover
   - Carryover decisions based on sample-to-sample results rather than just carryover samples
   - Interaction with S2 Team
4. Implications of positive control or predose samples
   - Limits for acceptance of sample results and entire run results
   - Impact on carryover/contamination considerations
   - Guidance on actions/remediation to be taken
5. Implications of anomalous sample results on run acceptance (contamination, sample switch issue?)
6. System suitability testing
   - Purpose of and criteria for suitability testing (approve or not approve a run start or entire run itself)
   - Consider multiple plates and unattended operation: suitability review done at run start or after run completion
   - Is suitability testing only considered at run start or also during run?
7. Sample and run reinjection: when, how to perform reinjection; how to address results
8. System conditioning with matrix samples: guidance on when required, how to perform

S1: Additional Topics Considered

1. Is S1 Team about molecule size (“small molecule) or detection technique?
   - Inclusion of all analytes determined by LC/MS techniques: antibodies, proteins, oligos, small molecules
   - Use of small molecule criteria for all LC-MS determinations?
2. Metabolite screening: flexible acceptance criteria, fit for purpose criteria
   - Addressed by A2 Team?
3. Determination of dosed endogenous materials (e.g. steroids)
   - Role of small molecule criteria, biomarker criteria
4. ISR Guidance
   - Actions if ISR fails: implications for entire analytical run
   - Discussion for A7 team?

S1: Small Molecule – Specific Run Acceptance

Multi-analyte methods - Proposed text:

For validation of an assay with multiple analytes, it is recommended that at least one accuracy and precision run be acceptable for all analytes in the same run; however, exceptions to this recommendation may be allowed based on the number of analytes in the method and/or the degree of complexity required to analyze all analytes (e.g. separate elution steps, separate LC/MS injection parameters, etc.) from a single sample aliquot.

Acceptance criteria should be 15% (20% LLOQ) for the primary analyte(s) intended for "regulated" bioanalysis; however, acceptance criteria for non-primary analytes may be expanded depending on the nature of the analysis (i.e., fit-for-purpose) and should be based upon the performance of the analytes during validation.

Other Requirements:

- No requirements that differ from existing guidance were determined (e.g., minimum of 6 concs).

Recommendations:

- 8 point calibration curve, preferred both at beginning and end of analytical run (especially with analogue IS).
- Concentrations at LLOQ, 2-3x LLOQ, about 0.8x ULOQ, and ULOQ. Remaining points not defined, but distributed across range.
- Blanks included to assess contamination and carryover, with minimum per guidance documents.

Acknowledgements

- The GBC Founding Members
- The GBC Steering Committee
- The Harmonization Team leaders and members