Global Bioanalysis Consortium: Update on Bioanalysis of Large Molecule Harmonization discussions

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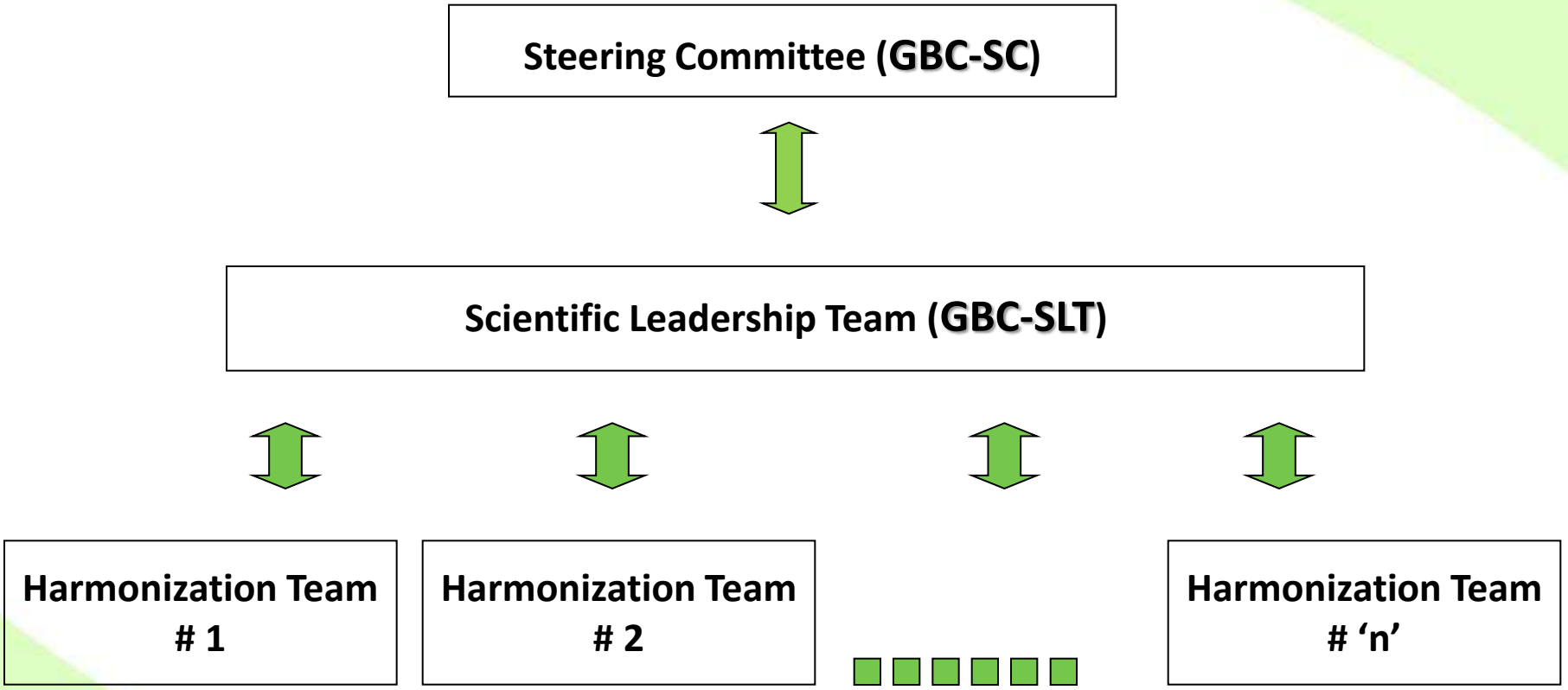
Global Bioanalysis Consortium
On harmonization of bioanalytical guidance

Organization Chart



GBC-Steering Committee

North America (US + Canada)

- Mark Arnold (AAPS)
- Binodh DeSilva (AAPS)
- Fabio Garofolo (CVG)

Latin America (South America + Mexico)

- Rafael Barrientos (AcBio)

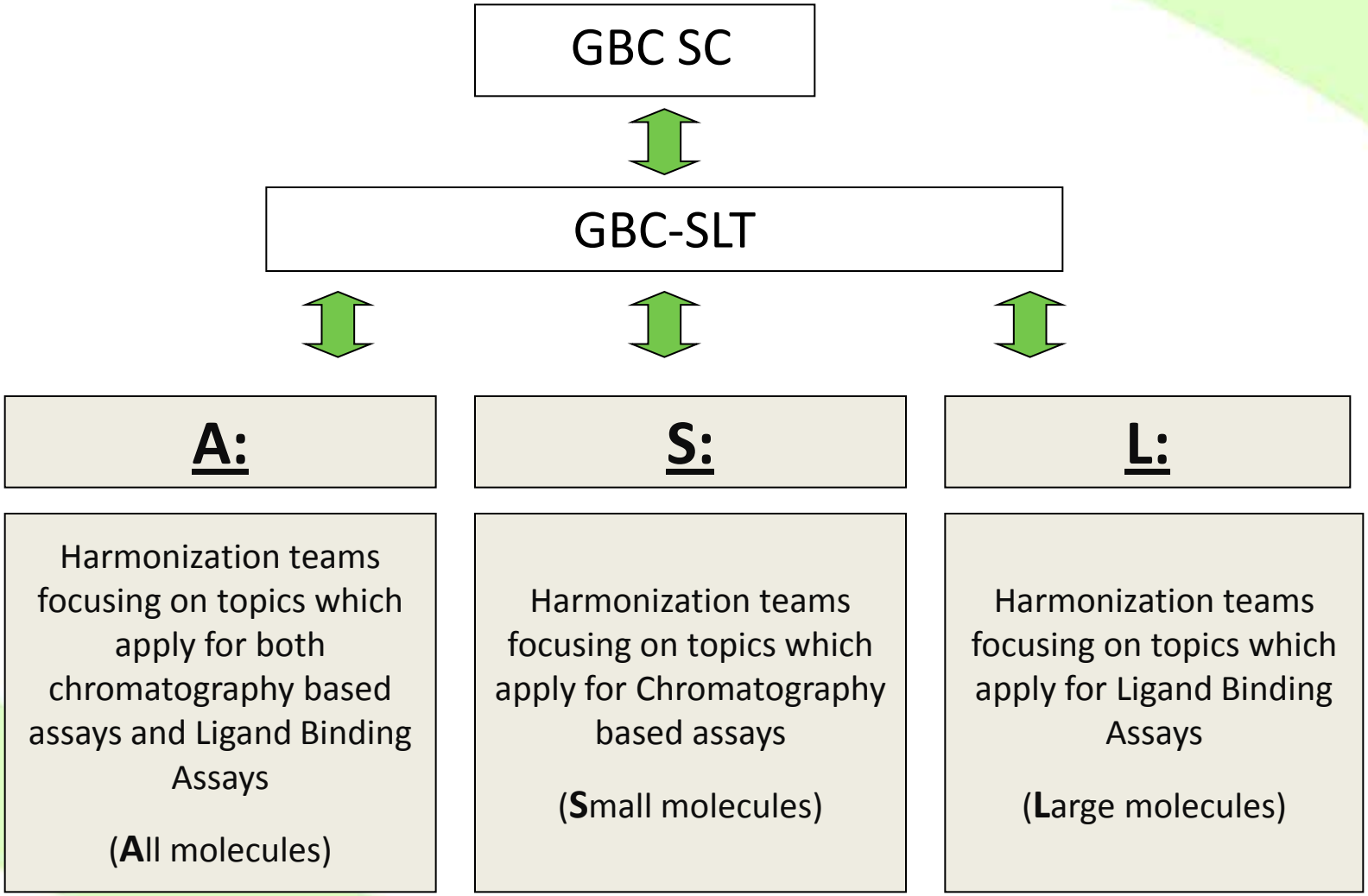
Asia Pacific (Asia + Pacific area)

- Shinobu Kudoh (JBF) replacing Tatsuo Kurokawa
- Shrinivas Savale (APA-India)
- Daniel Tang (SBDG&BBDG)

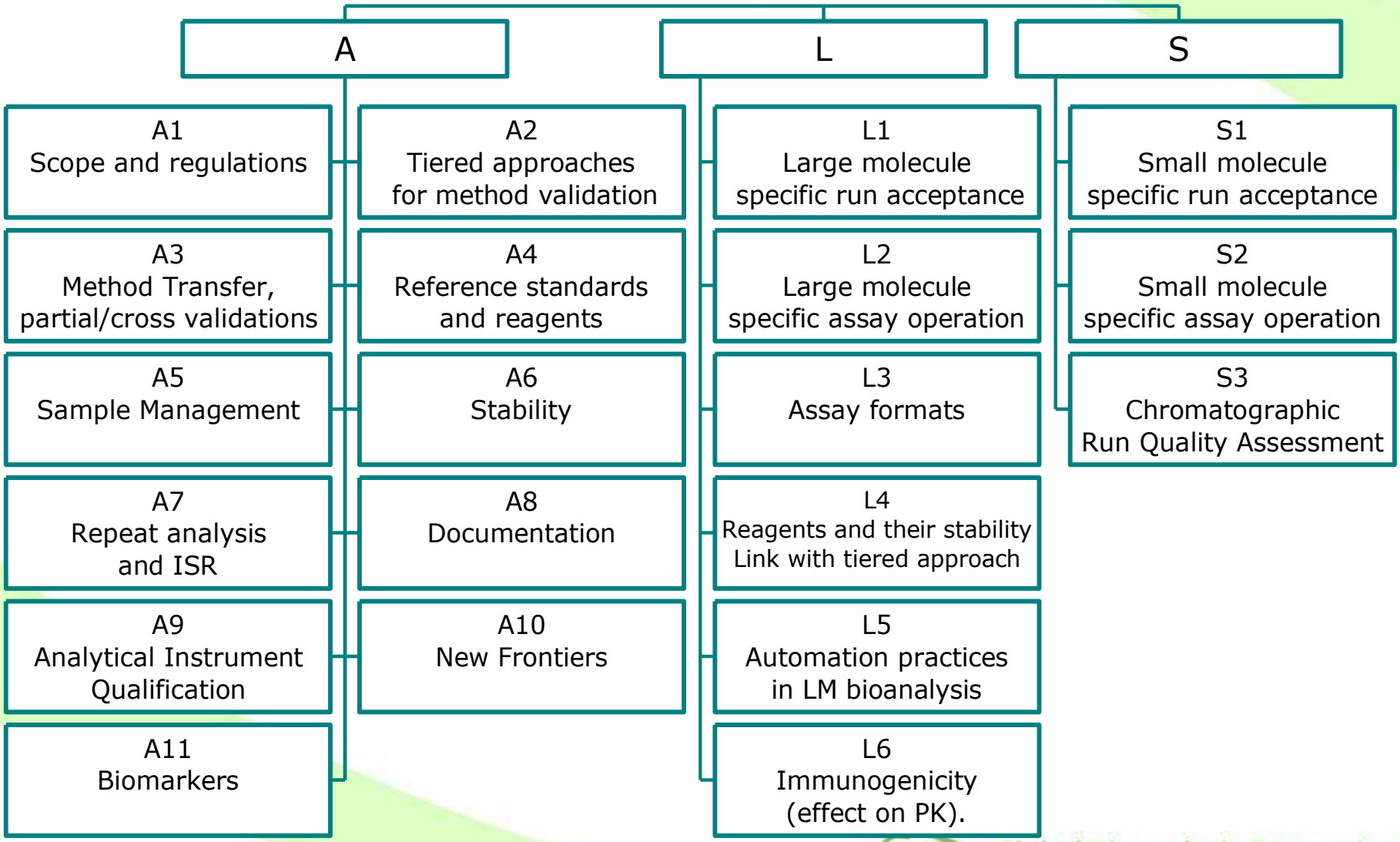
Europe (Europe + Africa/Middle East)

- Peter van Amsterdam (EBF)
- Michaela Golob (EBF)
- Philip Timmerman (EBF)

Which Harmonization Teams? Overview



Which Harmonization Teams ?



Harmonization Team Leads

A1: Surendra Bansal
A2: Steve Lowes
A3: Ray Briggs
A4: Joseph Bower
A5: Mike Redrup
A6: Nico van den Merbel
A7: Eric Fluhler
A8: Tom Verhaeghe
A9: Chad Briscoe
A10: Bob Bethem
A11: Howard Hill

L1: Marian Kelley
L2: Lauren Stevenson
L3: Sherri Dudal
L4: Lindsay King
L5: Scott Davis
L6: Jeff Sailstad

S1: Douglas Fast
S2: Eric Woolf
S3: Stuart Mc Dougall

L1: Large molecule specific run acceptance

Team members:

Team lead

- Marian Kelley – NA – mmk48@comcast.net

Other members

- 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*

L2: Large molecule specific assay operation

Team members:

Team lead

- Lauren Stevenson, NA
  Lauren.Stevenson@biogenidec.com

Other members

- Marian Kelley, NA
- Mario Dominguez, LA
- Muruganandam Arumugam, APAC
- Karolina Oesterlund, EU
- Clare Kingsley, EU
- Maryam Monajati, NA
- Heather Myler, NA
- TBD , APAC

In scope:

- Testing of ruggedness and robustness
- Setting up a balanced validation design
- Dilution linearity
- Specificity testing
- Selectivity testing
- Parallelism
- Hook effect
- Long term stability in matrix

Interdependencies with other teams – if any

- L1 large molecule specific run acceptance

Out of scope

- TBD

L3: Assay formats

Team members:

Team lead

- Sherri Dudal – EU – sherri.dudal@novartis.com

Other members

- Daniel Baltrukonis– NA
- John Smeraglia – EU
- Karolina Osterlund – EU
- Katherine McKay – EU
- Mahesh Kumar – APAC
- Yoshitaka Taniguchi – APAC

In scope:

- Possible assay platforms for LBAs – Gyros, Biacore, ELISA (96, 384 etc), MSD
- Acceptance criteria for these methods
- How to set up the assays – placement of standards and QCs in these new formats
- Pros and cons of using these formats
- Stability of any new reagents for these methods
- Determination of interaction of ADA in new assay format

Interdependencies with other teams

- A10 New Frontiers:
  - determine acceptance criteria for new methods Assay format is set-up in function of new technologies used.
- L1 Large molecule specific run acceptance:
  - acceptance criteria for new methods versus ELISA 96 well plate

Out of scope:

- L2: set-up of a balanced design for 96 well ELISA
- L4: stability of classical reagents used in ELISA formats

L4: Reagents and their stability - Link with tiered approach

Team members:

Team lead

- Lindsay King – NA – lindsay.king@pfizer.com

Other members

- Susanne Phil, EU
- Mark Ma, NA
- Esme Farley, NA
- Priya Sriraman, NA
- Masood Khan, NA
- Chun Hua (Sherry) Cai, NA
- Jeannine Keefe, NA
- Mami Imazato, APAC

In scope: LBA Critical Reagents

- What are the critical reagents
  - Ab, peptides proteins, conjugates, Drug as reagent, ADA reagents including positive and negative control.
- Reagent testing
  - Specificity testing
  - What to do when you change critical reagents
  - Batch to batch testing
- Stability of reagents
  - Testing
  - Reagent formulation
- In-house vs. commercial reagents pros and cons
- Reagents and assay transfer

Interdependencies with other teams

- A3 Method Transfer
- A4 Reference Standards and Reagents
- A6 Stability
- L2 Large molecule specific assay operation:

Out of scope:

- Reference Standards
- Internal Standards
- Cell Based PK assays
- Matrix

L5: Automation practices in LM bioanalysis

Team members:

Team lead

- Scott Davis, NA
  scott.davis@ppdi.com

Other members

- Jin Wang, NA
- Joseph Kowalchick, NA
- Ago Ahene, NA
- Claudio Calonder, EU
- Igor Vostiar, EU
- Yan Wang, APAC
- Nouri Parya, EU

Interdependencies with other teams

- A3 Assay Transfer
- A7 Repeat Analysis and ISR
- A9 Analytical Instrument Qualification

In scope

- Operational
  - Automation instrument & software validation (Fit-for-Bioanalysis-purpose)
  - Minimal guidelines for software validation
  - User training
  - Automation issue reporting, CAPA
  - Change control process
  - Documentation requirement for automation application
  - Safety Concerns
- Electronic
  - User access
  - eData security
  - Compliance with Appropriate Guidance Documents
- Instrument
  - Instrument maintenance including calibration/verification
  - Risk Assessment
  - Validation of interfaces (robot/samples, robot/reading device, reading device/LIMS)
- Assay
  - Assay accuracy & precision testing: include automation with manual comparison
  - Gold standard for assay performance: automation vs manual
  - Instrument / script qualification for validated analytical methods
  - Optimization of assay performance using automation (DOE)

Out of scope

- LIMS
- Automation application for non-regulated activities
- Large Molecule analysis using LC/MS
- Sample Preparation

L6: Anti-drug antibody (ADA) Interference of PK Assessments

Team members:

Team lead

- Jeff Sailstad, NA Sailstad@aol.com

Other members

- Adrienne Clement Egan, NA
- Boris Gorovits, NA
- Heather Myler, NA
- Jason (Jay) Wustner, NA
- Lakshmi Amaravadi , NA
- Lei Tang, NA
- Renuka Pillutla, NA
- Shobha Purushothama, NA
- Joleen White, NA
- Madhan Kumar Rose, APAC (invited)
- Sonehara from SCAS, APAC (to be invited)

Interdependencies with other teams

– Link with tiered approach

Scope

ADA can alter the pharmacokinetics of a therapeutic as well as interfere with the analytical methods or assays used to determine the pharmacokinetics. Since the primary expertise within our group is bioanalytical we will be discerning ways to separate true alterations of pharmacokinetics from artificial changes by interference in the analytical method. Consideration will be provided on various assay formats and relative susceptibility to ADA interference. Much of the discussion will be based upon case studies where analytical interference was suspected, either confirmed or shown not to be an issue.

Where analytical interference was confirmed, examples will be given of the actions taken to address the impact on PK assessments. Once analytical interference is ruled out we will provide guidance on factors to consider in assessing the magnitude in changes to PK assessments. This will also be done using case studies where a change in pharmacokinetics can have no effect to profound changes in the pharmacodynamics and possible safety of a therapeutic.

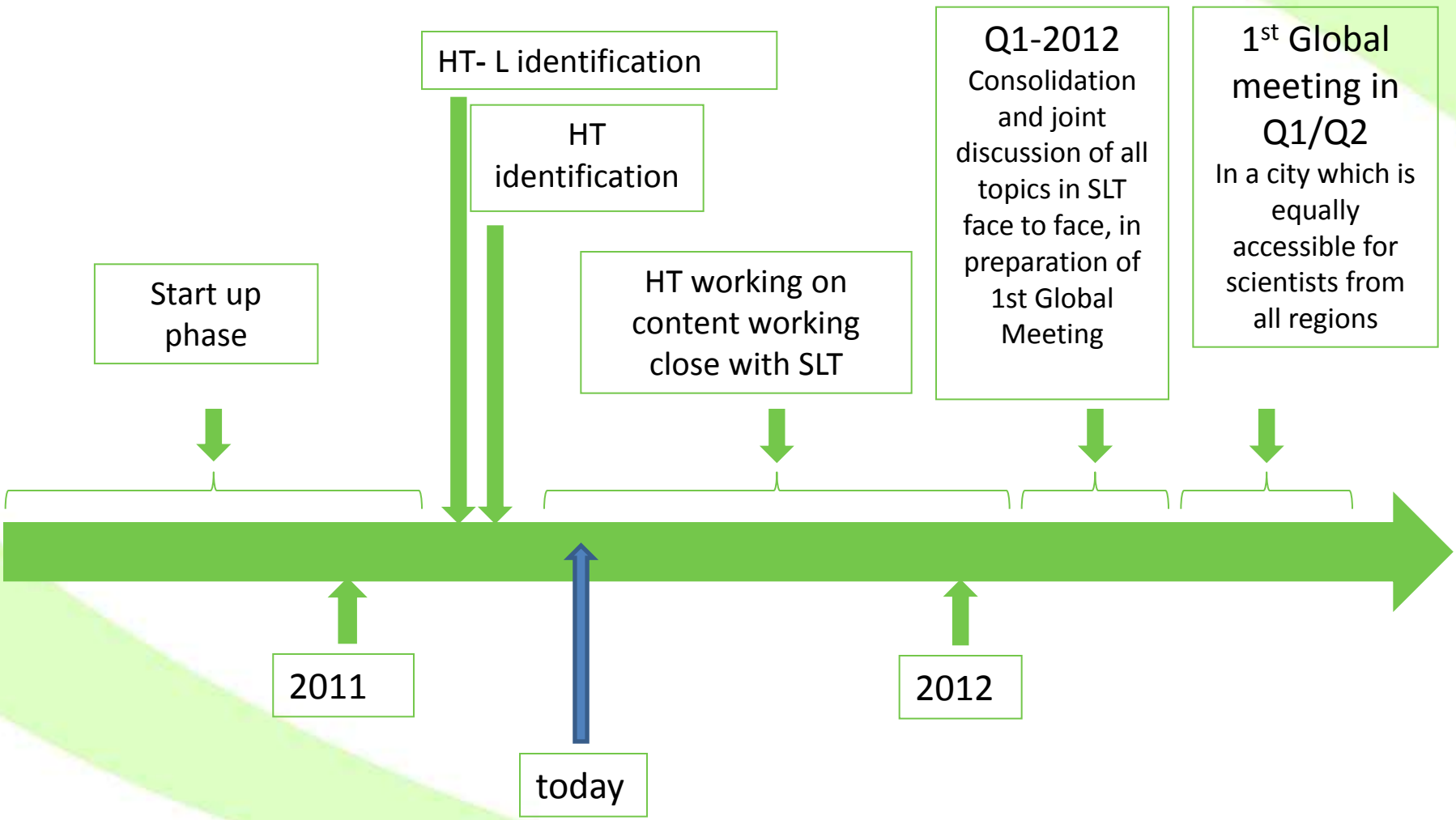
We hope to provide guidance on the factors to consider in assigning the magnitude of ADA impact on pharmacokinetics. Based on the collective experience of the team members we attempt to rank those factors.

ADA interference can impact the interpretation PK data throughout a development program therefore our scope will include pre-clinical and clinical applications.

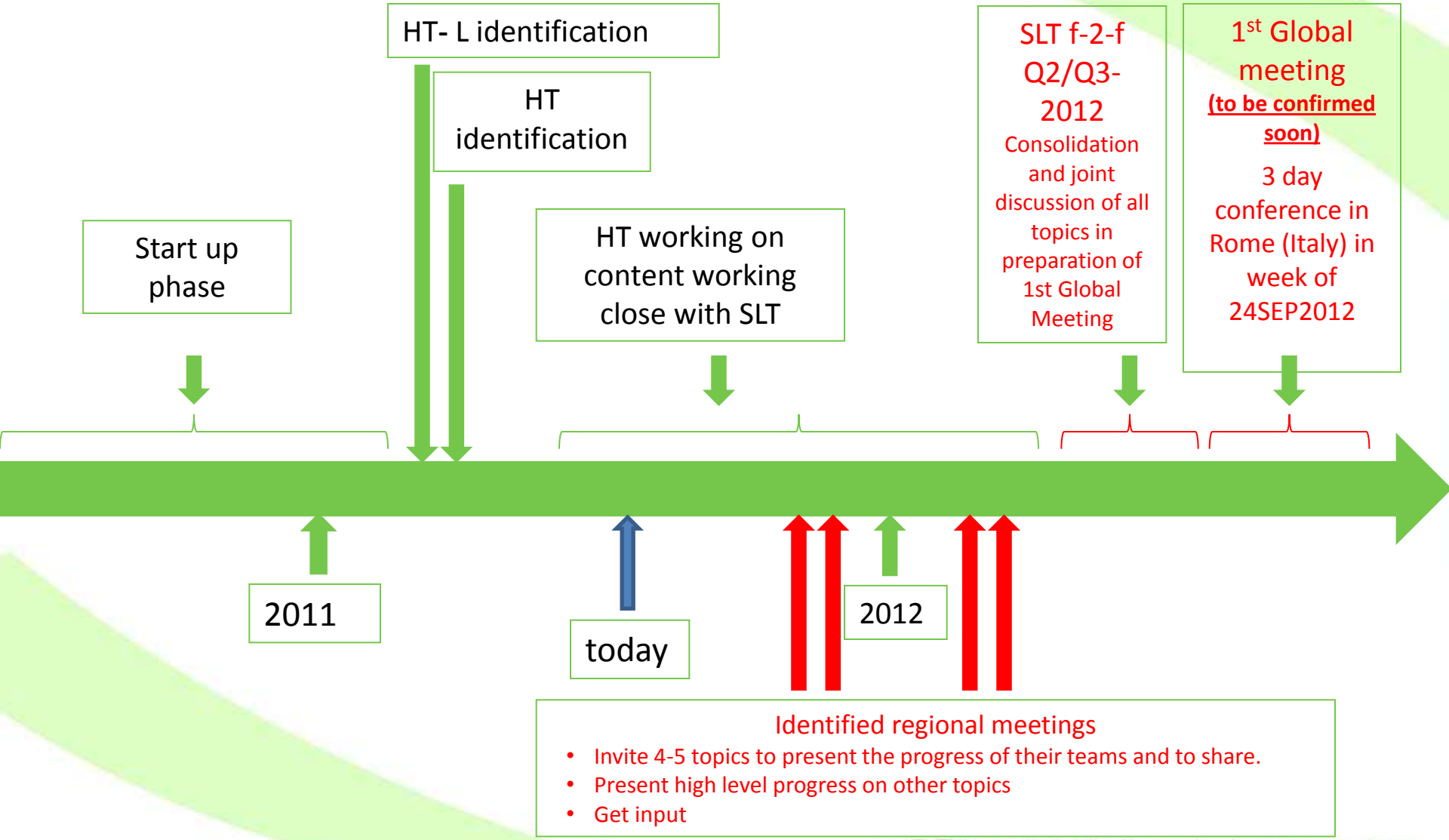
Out of scope

– Immunogenicity Assessment
– Cut point analysis
– Screening assay
– Confirmatory assay
– Nab assay

Proposed way forward - OLD



Proposed way forward - NEW



Acknowledgements

- The GBC Founding Members
- The GBC Steering Committee
- The Large molecule Harmonization Team leads
- Large molecule bioanalytical community for volunteering to be part of this consortium