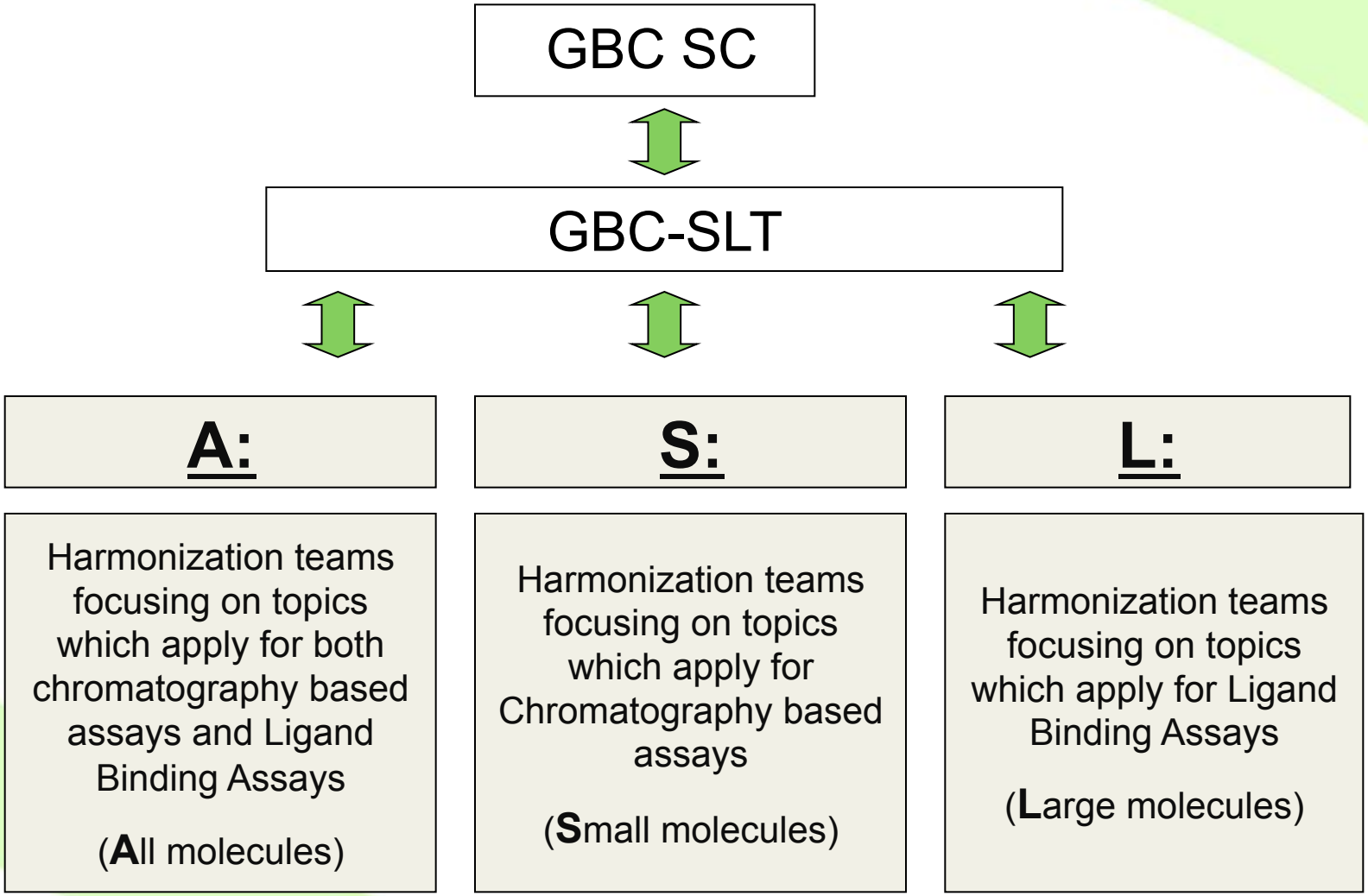
team Update Summaries
January 2012

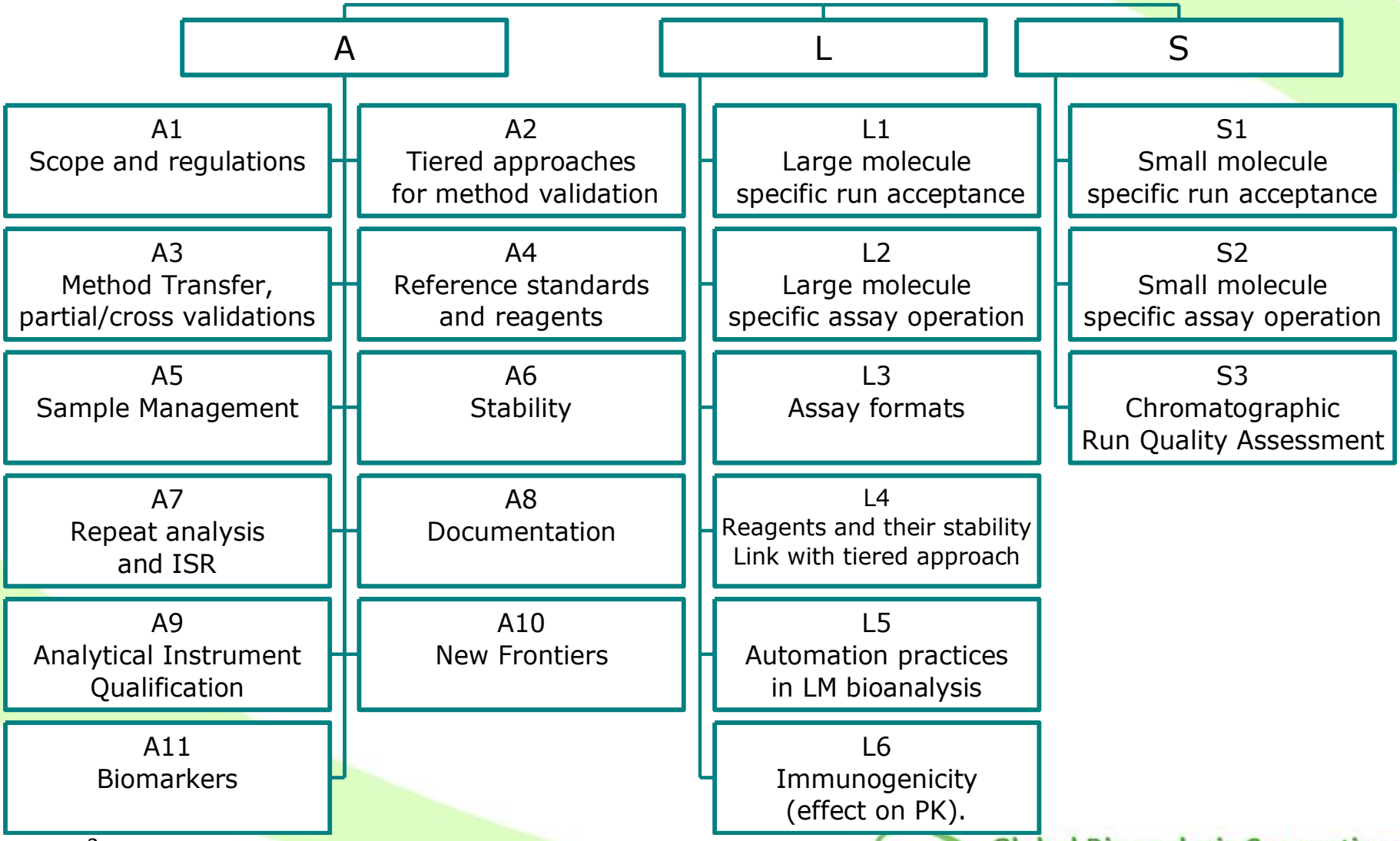
Global Bioanalysis Consortium
On harmonization of bioanalytical guidance

Which Harmonization Teams?

Overview



Which Harmonization Teams ?



Operating committees: HT-L

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: Russell Weiner

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

A1: Scope and Regulations

Team members:

Team lead

- Surendra Bansal NA

surendra.bansal@roche.com

Other members

- Dafong Zhong APAC
- Martin Ullmann NA
- Krzysztof Selinger NA
- Manish Yadav APAC
- Tomoko Arakawa APAC
- John Smeraglia EU
- Myriam Salvadori LA
- Jim Hulse NA

In scope

- Scope and regulations for bioanalytical method validation and samples analysis
- Extent of validation before analysis of samples
  - Consider Validation a continuum process
- Glossary

Interdependencies with other teams

- A2 Tiered approach for method validation
- All teams for glossary

Out of scope

- Biomarkers: Possibly include them as fit for purpose
- Immunogenicity within or out of scope?
  - Depends if large molecule HT is..

Current status

Drafted scope for performing bioanalytical work.

- Worked on the scope and regulations for bioanalytical method validation and samples analysis
- Considered Validation as a continuum process (need to interact with team A2 for tiered approach to include the tiered approach within the scope for bioanalytical work)
- Drafted glossary from existing FDA and EMA documents. Additional terms to be added from other regulatory documents or from bioanalytical community, as necessary.

Next steps

- Interact with team A2 for tiered approach to include the tiered approach within the scope for bioanalytical work
- Send draft glossary to all HTs for their input
- Provide current summary to GBC HTs in March 2012 and take input
- Finalize by August 2012 to prepare for the GBC global meeting

A2 : Tiered Approaches To Method Validation

Team members:

Team lead

– Steve Lowes : NA

SLowes@advion.com

Other members

– Richard Hucker	EU
– Mohammed Jemal	NA
– Joe Marini	NA
– Vicinius Rezende	LA
– Ron Shoup	NA
– Puran Singhal	APAC
– Philip Timmerman	EU
– Naidong Weng	NA
– Tomoki Yoneyama	APAC
– Dieter Zimmer	EU

Interdependencies with other teams

- A1: Scope and Regulations
- A3: Method transfers, partial/cross validations
- A10: New Frontiers
- A11: Biomarkers
- S1: Small molecule specific run acceptance

In scope

- Definitions of screening, qualification in relation to validation, applicable for
  - Validation/qualification of assays for all matrices
  - Tiered approach for metabolites quantification
    - Relevance to MIST
  - Biomarker assay qualification/validation
- Stability assessment in tiered approach (blood, tissue, urine, metabolites, biomarkers – as applicable..)
- Applicability of Fit-for-Purpose
- Relevance to Phase of drug development

Out of scope

- Bioanalytical assays for non-regulatory data

Current status

1. Establishing Categories of Method "Validation": Terminology
   - Screening/ Research/Qualified and Validated
   - Fit for Purpose (FFP) vs. Tiered Approaches
     - FFP the domain of biomarker assays
     - Value in differentiation from FFP
   - Tiered Approaches : Small Molecule LC/MS vs. Large Molecule LBA (e.g. immunogenicity)
   - Alternate Terminology
     - Method Performance Characterization
     - Method Establishment

2. Establishing Framework to Accommodate Tiered Approaches
   - Use of Method Establishment Plans
   - Defining key elements of each category
   - Formulating decision tree(s) around multi-tier proposal
     - i.e. Help determine "When to use what tier"

3. Considerations of Implementation of Proposed Approaches
   - By Regulatory Authorities – Globally
   - By Bioanalytical Scientists
   - By Drug Development teams

Next steps

- Formulating communication of our progress
- Reaching out to other groups to test acceptance of where we are headed
- Touch base with key “opinion-leader” regulatory people to see if we are on right track.

A3: Method Transfer, partial and cross validation

Team members:

Team lead

- Ray Briggs EU
  raybriggs@tiscali.co.uk

Other members

- Richard Abbott EU
- Margarete Brudny-Kloeppel EU
- Patrick Duchene EU
- Jan Busch NA
- Bob Nicholson NA
- Naidong Weng NA
- Faye Vazaei NA
- Mahesh Kuma APAC
- Masanari Mabuchi APAC
- Paulo Galvinas LA
- Pei Hu APAC

In scope

- Life cycle of a method after first full validation or relation with other validated methods.
  - Partial validation
  - Method transfer
  - Cross validation
- Definitions of method transfer, partial and cross validations
- Recommendation on when to perform method transfer, partial and cross validations
- Specific requirements for the transfer, partial validation and cross validation of small and large molecules
- Recommendations of which experiments are desirable for each proposed steps after full validation
- Recommendations of acceptance criteria for cross validations and method transfers
- Use of quality control material and incurred samples for transfer, partial validation and cross validation
- Pre assessment activities in method transfer and their importance to successful transfer

Interdependencies with other teams

– L1, S1, A2, A6, A7

Out of scope

Scope will be limited to PK analyses only at this time

Current status

- Subteams have completed drafts of sections on Partial Validation, Cross Validation and Method Transfer
- These have bee individually reviewed by the team
- A consolidated single document has been prepare
- This is currently being reviewed to ensure consensus agreement and that it is consistent with current regulations in each region.

Next steps

- Complete review of Consolidated A3 document (Jan-Feb)
- Prepare slides sumarising current thinking for March Meeting and share with Team Sponsors and GBC SC (Feb-Mar)

A4: Reference standards and reagents

Team members:

Team lead

- Joseph Bower NA
  Joseph.Bower@covance.com

Other members

- Andrew Warren EU
- Carl Watson EU
- Jennifer McClung NA
- Kathy Wright NA
- Katia Pastre LA
- Mónica Cedrés Ercoli LA
- Takahiko Osumi APAC

In scope

- Recommendations for content in Certificate of Analysis (COA) or equivalent documentation to be included with material if COA is not available for:
  - Reference Standards
    - (small and large molecules)
    - Biomarkers
  - Metabolites
  - Internal Standards
- Recommendations for preparation of:
  - Calibration standards and QCs.
  - Stock solutions
  - Metabolites
  - Internal standards

Interdependencies with other teams

- L4 - Reagents and their stability – Lindsay King
- A11 – Biomarkers – Russ Weiner

Out of scope

- Positive controls for Immunogenicity Assays
- Bridging between lots of reference standards

Current status

- Reviewed all of the relevant regulatory guidance and industry white papers related to the content in the COA or equivalent documentation to be included for reference standards, metabolites and internal standards.
- Reviewed all of the relevant regulatory guidance and industry white papers related to the preparation of calibration standards and QCs, stock solutions, metabolites and internal standards
- From the above, our team has generated recommendations for each and has begun to circulate to colleagues to obtain feedback :
  - The content in the COA or appropriate documentation to be included for reference standards, metabolites and internal standards.
  - The preparation of calibration standards and QCs, stock solutions, metabolites and internal standards
- Next meeting is Jan 30th in which we will be reviewing all feedback on our recommendations.

Next steps

- Review feedback and comments from our recommendations.
- Create a final draft version to be distributed to a wider audience.
- Compile preliminary slide deck for presentation in Mar
- Adjust slide deck following feedback
- Long term – discuss how best to present our recommendations in white paper for publication

A5: Sample management

Team members:

Team lead

- Mike Redrup EU
  mike.redrup@quotientbioresearch.com

Other members

- Harue Igarashi APAC
- Subramanium Ramachandran APAC
- Mohamed Ben Barak EU
- Vera Hillewaert EU
- Thales Cardoso LA
- Jenny Lin NA
- Jay Schaefgen NA
- Tanya Boutros-Brown NA

In scope

All aspects of sample management from collection to disposition

- Collection, handling and storage at clinical/ animal lab
- Storage and shipment from clinical/animal lab to CL or analytical lab
- Pre analysis storage at analytical lab
- Post analysis storage or shipment
- Disposal or archiving/banking
- Sample management using LIMS / sample management systems

Interdependencies with other teams

A6, A10, A11

Out of scope

TBD

Current status

- Team TC's ongoing (3 weekly intervals)
- Currently have only looked at 2/6 topics but will accelerate to at least touched each topic by San Antonio meeting in March
- Will need to re visit these topics over the next few months

Next steps

- Cover all topics by San Antonio meeting
- Prepare slides for San Antonio
- Will need to re visit all topics over the next few months before Autumn meeting. Topics will be shared by team members in sub groups.

A6: stability

Team members:

Team lead

- Nico van de Merbel – EU – merbelnicovande@praintl.com

Other members

- Julie Diancin NA
- Joleen White NA
- Natasha Savoie NA
- Maria Francesca Riccio LA
- Morten Kall EU
- Ronald de Vries EU
- Manish Yadav APAC
- Kelly Dong APAC
- Yoshiaki Ohtsu APAC

Interdependencies with other teams

- A3 (transfer of stability results)
- A4 (stability of reference standards)
- A7 (ISR and ISS)
- L1/L2 (fresh vs frozen standards)
- L4 (stability of reagents for macromolecules)
- S2 (reinjection and salt/counter-ion changes)

In scope

- Spiked samples (biological and surrogate) and extracts
- Incurred samples and extracts
- Normal matrices (blood, plasma/serum, urine, tissue)
- Special matrices (hemolyzed, lipidemic etc)
- Presence of co-formulated and co-administered drugs, metabolites
- Stock and standard solutions, reagents
- Stability during sample collection and transport
- Stability during extraction and analysis
- Definitions and nomenclature: -70 vs -80 °C, room temperature, degradation vs stability vs solubility loss vs absorptive loss, fresh vs stored
- Design: t=0 vs nominal, fresh vs frozen standards, number of replicates, concentrations and time-points, ultra-low temperature for reference, stability in whole blood, instrument response vs concentrations
- Criteria: fixed or statistical approach
- Transferability of results: between labs and between methods

Out of scope

- Stability assessment in tiered approach – A2
- Stability of reference standards – A4
- Stability of reagents for macromolecules – L4

Current status

- Stability requirements in relevant guidelines, white papers etc have been summarized and divided into issues of high, medium and low priority.
- Owners have been defined for each of the stability-related issues.
- Owners of (four) high-priority issues have drafted recommendations and lead the discussions, which are ongoing. The documents have been reviewed and discussed and will be finalized by end of January.
- Next, issues of medium priority will be addressed in the same way.

Next steps

- Each identified stability-related issue will be addressed in the same way as done so far:
- the owner will draft a text with (1) scientific background, (2) recommendations of the team and (3) where necessary a discussion of practical issues
- These will be reviewed by the entire team, discussed in one or more TCs and finalized
- Where applicable, discussions will be held with other teams to manage overlap and streamline the output of the teams
- Eventually, all texts will need to be combined into a single document, details still need to be clarified

A7: Repeat analysis and ISR

Team members:

Team lead

- Eric Fluhler NA

eric.fluhler@pfizer.com

Other members

- Ajai Chaudhary NA
- Bernard Jeanbaptiste EU
- Dafong Zhong APAC
- Faye Vazvaei NA
- Jignesh Bhatt APAC
- Puran Singhal APAC
- Theo de Boer EU
- Wenkui Li NA
- Oscar Alderetr LA
- Vinícius Rezende LA
- Masahiro Taniguchi APAC
- Petra Vinck EU

In scope

Repeat analysis:

- Repeats for analytical reasons
- PK repeats (Including pre-dose concentrations)
- Single analyte repeat in multi-analyte assays
- Reinjection <-> Reanalysis
- Decision trees
- Acceptance criteria
- Failure and Investigation

ISR:

- Multiple analytes & endogenous compounds
- Timing of ISR analyses
- Sample selection
- Number / percentage of ISR samples
- Types of studies
- Acceptance criteria
- Failure and Investigation
- Large molecule considerations

Interdependencies with other teams:

- Stability Team – Stability of incurred samples

Out of scope

- Run acceptance criteria, including IS response variability/ issues

Current status

- Sub-teams formed to address guidance around:
  1. Repeat analysis (RA)
  2. Incurred sample reanalysis (ISR)
  3. Failures and investigations
- Sub-teams 1 & 2 have been meeting throughout Q3-Q4 2011 and established recommended principles to be applied for their topics
- Sub-team 3 initiated activities in December 2011 and is working on establishing recommendations
- Full team has reviewed output from teams 1 & 2 and provided feedback to teams.
- Verbiage drafted for guidance around classical aspects of RA and ISR

Next steps

- Continue sub-team 3 efforts on “failure and investigations”
- Establish communication with Stability team (incurred sample stability)
- Prepare preliminary slide deck for March meeting
- Obtain SC feedback on positions
- Progress sub-team output to final draft for publication
- Prepare for global meeting overview

A8: Documentation

Team members:

Team lead

- Tom Verhaeghe EU
  tverhaeg@its.jnj.com

Other members

- Eric Woolf NA
- Hollie Barton NA
- Marian Kelley Mkelley NA
- Myriam Salvadori LA
- Richard Hucker EU
- Srinivasa Reddy APAC
- Hisanori Hara APAC/EU
- Franck Picard EU

Interdependencies with other teams

– A1: Scope and regulations for bioanalytical validation and sample analysis

In scope

– Definitions of different report types
– Method Validation reports
– Study protocol / plan
– Study reports
– Failure investigation and documentation
– Documentation at analytical site (including data generation, handling and reporting)
– Raw data definitions (electronic and paper) including chain of custody for samples and reference, standards, notebook records, instrument use, maintenance, system validation, freezer records etc
– Archiving and retrieval of data, storage period for data
– Bioanalytical summary documents ie CTD sections 2.7.1. and 2.6.5.
– Technology platforms for reports

Out of scope

- Clinical study reports
- Documentation of method development
- Harmonized template for validation and study reports

Current status

- Had six 1-hour meetings so far
- Almost done with the content of the bioanalytical study report
- Increase frequency of meetings to bi-weekly and duration to 1.5h

Next steps

- Tackle method validation report content

A9: Analytical Instrument Qualification

Team members:

Team lead

- Chad Briscoe – NA

briscoechad@praintl.com

Other members

• Hidehisa Tachiki	APAC
• Jianing Zeng	NA
• Manish Yadav	APAC
• Katia Pastre	LA
• Petra Struwe	EU
• Ron Shoup	NA
• Scott Davis	NA
• Michael Blackburn	EU
• Ping Du	APAC

In scope

- Equipment Software Validation
- Change control/Routine requalification
- Instruments/Equipment
- System Suitability
- Holistic Approach
- Regulatory/Audits
- Role of the Laboratory and IT in Lab Software Validation

Interdependencies with other teams

- A1 : Scope and regulations
- A8 : Documentation
- A10 : New Frontiers
- L5 : Automation practices
- S2: Assay Operation

Out of scope

- IT Infrastructure Qualification
- Design Qualification
- Stand-alone/non-instrument controlling software: spreadsheets, homegrown, COTS
- LIMS, ELN where not interfacing with instruments

Current status

- Completed detailed discussion of scope topics.
  - Developed 1-2 slides of detailed discussion on each in-scope topic.
- Identified that one of the biggest areas for harmonization is terminology rather than actual approach taken.
- Reached agreement that AIQ for Regulated Bioanalysis is not the same as for GMP and we need to be sure to keep this as a key output.

Next steps

- Clean up and agree on conclusions
- Compile critical messages from all topics
- Organize into a flexible presentation.
  - Flexible in the sense of being able to adjust it to meet the interests of multiple levels of AIQ knowledge

A10: New Frontiers

Team members:

Team lead

• Chad Ray Chad.A.Ray@pfizer.com	NA	LM
• Bob Bethem bob.bethem@vitaleascience.com	NA	AMS

Other members

• Steve Dueker	NA	AMS
• Mark Seymour	EU	AMS
• Greame Young	EU	AMS
• Philip Timmerman	EU	AMS/DBS
• Chris Evans	NA	DBS
• Keiko Nakai	APAC	DBS
• Qin Ji	NA	DBS/LM
• Leo Kirkovsky	EU	DBS/LM
• Jignesh Kotecha	APAC	DBS/LM
• John Smeraglia	EU	DBS/LM
• Hendrick Neubert	EU	LM
• Ronald de Vries	EU	LM
• Rick Steenwyk	NA	LM
• Monica Whitmore	NA	ICP/MS

Interdependencies with other teams

- A1, A2, A4, A5, A7, A8, A9, L4,L5

In scope

- Validation Figures of Merit for each technology, e.g., LOQ
- Fit for Purpose qualification/validation requirements for each technology
- Run acceptance criteria for each technology

Out of scope

- S - Small molecule specific run acceptance, assay operation and QCs
- L – Large molecule guidelines specific to LB

Current status

- Organized 3/4 sub-team with leaders
- Re-evaluating potential contributors to ICP/MS

Task	Lead	Status
AMS – Collecting definitions and White Paper Contributions from NA labs	Bob Bethem (NA)	Initiating
AMS – Definitions, best practices and White Paper Contributions from EU labs	Mark Seymour (EU)	Initiating
AMS – EBF Status and/or Guidelines in Development	Philip Timmerman (EU)	Initiating
Large Molecules – LM team organizing	Chad Ray (NA)	Initiating
Dried Blood Spots/Micro Sampling team organizing	Chris Evans (NA)	Initiating
ICP-MS team organizing	TBD	TBD

Next steps

AMS

- Survey existing White Papers and any existing precedent used by current labs, EBF etc.
- Definition of terms and validation figures of merit
- Determine Fit for Purpose validation requirements, e.g., TRA pK, absolute BA, met profiling/ fingerprinting
- Develop cross referenced table to determine area of general agreement and differences in validation and data acceptance approach

Large Molecules

- Survey of next generation technologies
- Evaluate how these technologies might be incorporated into regulatory environment
- Evaluation of gaps and opportunities
- Review existing documents relating to reagent life cycle management and qualification

ICP-MS

- Definition of terms and validation figures of merit
- Review recent White Paper relative to GBC objectives and other guidelines (EBF).

DBS

- Generate survey of applications and evaluate longer term harmonization needs

General

- Review interdependencies with other teams where appropriate.
- Compile preliminary slide deck for presentation in March

A11: Biomarkers

Team members:

Team lead

- Russell Weiner NA
  russell.weiner@merck.com

Other members

- Jean Lee NA
- Mohammed Jemal NA
- Ajai Chaudhary NA
- Ray Briggs EU
- Birgit Jaitner EU
- Yuichi Yamamoto APAC
- Dongbei Li APAC
- Invited NA
- Invited EU
- Invited APAC

In scope

To be confirmed once team is formed

- Fit-for-purpose assay development and validation
- Exploratory data used for internal decision making and not to be submitted to regulatory agencies versus data to be used for making dosing decisions that will be part of the filing (e.g. modeling PK/PD data to justify dose)
- When to use GLP versus non-GLP validation
- GLP versus CAP/CLIA for assays performed in-house, in a clinical lab or in a clinical lab when assay has regulatory approval (510K, PMA, CE marked, etc) and/or assay is well established

Interdependencies with other teams

- A2:Tiered approach to method Validation
- A4: Reference standards and reagents
- A5: Sample management
- L4: Reagents and their stability

Out of scope

- TBD once team is formed

Current status

- Team invitations sent 13-Jan-12
- Awaiting RSVP from 3 team members

Next steps

- Finalize team members
- Once team membership is locked-in determine what is in scope/out of scope via e-mail
- Schedule monthly telecons

L1: Run Acceptance

Team members:

Team lead

Marian Kelley mmk48@comcast.net	NA

Other members

• Paula Kaminski	NA
• Katsuhiko Yamamoto	APAC
• Daniela Stoellner	EU
• Ross Bamford	EU
• Arumugam Muruganandam (Anand)	APAC
• Ravi Trivedi	APAC
• Samantha Little	EU
• Lauren Stevenson	NA
• Dongbei Li	APAC
• Chris Beaver	NA

In scope

- Non-linearity of standard curve
- Accuracy, precision and total error
- Fresh or Frozen QCs/Standards during validation
- Identify the parameters to be used for monitoring validity of the data
- Curve editing

Interdependencies with other teams

- L2: Assay Specific Operation
- A3: Method Transfer
- L3: Assay Formats
- S1: Small Molecule Run Acceptance

Out of scope

- Stability of QC long term during sample analysis:

Current status

The team has a discussed:

- Non-linearity of the curve
- Total Error
- Use of Fresh/Frozen calibrators and QCs
- Curve Editing

Next steps

The team still needs to discuss:

- Accuracy and Precision acceptance during validation and during sample analysis
- Which parameters are most important for accepting a method or considering a run valid

L2: Large Molecule Specific Assay Operation

Team members:

Team lead

- Lauren Stevenson NA
  lauren.stevenson@biogenide.com

Other members

- Clare Kinglsey EU
- Karolina Oesterlund EU
- Marian Kelley NA
- Heather Myler NA
- Boris Gorovits NA
- Yoshiyuki Minamide APAC
- Arumugam Muruganandam APAC
- Mario Dominguez LA

In scope

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

Interdependencies with other teams

- L1 – Assay Acceptance
- A6 – Stability

Out of scope

- Cross validation (A3)
- Approach for spiking QCs for validation (L1)
- Use of drug product, drug substance or reference standard as the entity used in validation/sample analysis (A4)

Current status

- All in-scope topics have been discussed in some detail and broad agreement has been achieved
- Ongoing team and consultant discussions occurring monthly or more frequently to refine consensus
- Consensus refined and language being drafted for:
  - Robustness and ruggedness
  - Balanced validation design
- Continuing to refine consensus for:
  - Dilution linearity
  - Specificity testing
  - Selectivity testing
  - Parallelism
  - Hook effect

Next steps

- Work through details on topics requiring further discussion and complete draft language for all topics
- Goal – draft language on most if not all topics in time for 6th WRIB (March)

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
- Alison Joyce NA
- Rebecca Crisino NA
- Jihong Yang NA
- Jaya Goyal NA

In scope

- Assay platforms for LBAs – Gyros, MSD, Biacore, AlphaLISA, Delfia, Singulex, Luminex, Immuno-PCR, ELISA (384), Cell-based assays, RIA
- Acceptance criteria for these methods for both validation and sample analysis
- How to set up the assays – placement of standards and QCs in these new formats
- Pros and cons of using these formats
- Multiplexing with these formats and criteria required

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/platforms versus ELISA 96 well plate

Out of scope

- L2: set-up of a balanced design for 96 well ELISA
- L4: stability of critical reagents
- L5: any automation activities linked to the platform

Current status

In January, each work group will present their assay platform for discussion in a larger team session:

- Each team has been formed to ease time differences and is grouped according to expertise with a particular platform.
- It is expected that once the platform issues, criteria and pros and cons are presented and discussed within the team, these will be presented to colleagues at the workplace and in forum discussion groups to obtain more feedback.
- The following organization is in place for January:

Platform	Leader	Team member	Team member	Team presentation
Gyros	Karolina (EU)	Sherri (EU)	Alison (NA-E)	**January 16th**
Cell-based assays	Daniel (NA-E)	Yoshitaka (APAC-Japan)	Jaya (NA-E)	**January 30th**
RIA	Mahesh (APAC-India)	Daniel (NA-E)		**January 16th**
384-well format	John (EU)	Karolina (EU)		**January 9th**
Alpha-ELISA/Delfia	**Rebecca (NA-E)**	Jaya (NA-E)	John (EU)	**January 9th**
Singulex	Alison (NA-E)	Rebecca (NA-E)	Mahesh (APAC-India)	**January 16th**
Biacore	Sherri (EU)	Jihong (NA-W)	Alison (NA-E)	**January 23rd**
MSD multiplex	Katherine (EU)	Yoshitaka (APAC-Japan)	Karolina (EU)	**January *30th***
Luminex multiplex	Jihong (NA-W)	Katherine (EU)	Jaya (NA-E)	**January 23rd**
Immuno-PCR	Jaya (NA-E)	Jihong (NA-W)		**January 23rd**

Next steps

Once each assay platform has been presented and discussed:

- A preliminary slide deck will be compiled for presentation in the various conferences of 2012 and adjusted throughout the year according to feedback.
- After each presentation, a GBC L3 team session will be organized to present the discussion points to the team.
- September goal: to publish results from assay platforms in a journal to capture the L3 team contribution.
- Long-term goal: discuss incorporation of assay platform criteria into regulatory guidelines and how this can be done through GBC. Possibly a white paper publication.

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
- Jeannine Keefe NA
- Mami Imazato APAC
- Mario Richter EU

Past Member; First line external contact

- Chun Hua (Sherry) NA

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 – if any

A3: Method Transfer

A4: Reference Standards and Reagents

A6: Stability

L2: Large molecule specific assay operation

A8: Team Documentation

Out of scope:

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

Current status-

Sub-teams are generating Draft overviews of each sections in context of identified regulatory guidance, white papers and literature to indentify gaps, areas of ambiguity/debate and potential best practices

Critical Reagents Outline and Sub-team Responsibilities

- Introduction
- What are the critical reagents: (Jeannine)
  - Antibodies, peptides, proteins, conjugates, Drug as reagent, ADA reagents including positive and negative control. (hybridization assays reagents)
- Documentation (SOP and COA); (Jeannine);
- Regulatory Landscape (Susanne, Priya, and Lindsay)
- Reagent testing (Esme and Mario)
  - Specificity testing
  - What to do when you change critical reagents
  - Batch to batch testing
- Stability of reagents (Mark and Lindsay)
  - Testing
  - Reagent formulation
- In-house vs. commercial reagents pros and cons (Masood and Mami)
- Reagents and assay transfer (Lindsay)

Next steps

- Team meetings; Feb 1, Feb 22 and March 14th
  - Subteams to meet offline as needed.
- Sub Team section first draft/outlines must be complete with comments from full team by March 4
- Each sub team will then draft 2-3 slide max as high level overview of sections with any content gaps identified for review by March 13th
- At March 14th Team meeting these slide will be reviewed by full team
- Target March 21 for San Antonio meeting Slide Set
  - Anticipate that this Slide set will have gaps in that will need to be addressed. These will be identified in the slide we present in San Antonio with a mid May target for completion
- March-Sept 2012: Incorporate feedback from global community. Solicit as widely as possible. Draft Final Slide set for Fall 2012 Read out.
- Draft white paper for Dec 2012

L5: Automation practices in LM bioanalysis

Team members:

Team lead

- Scott A. Davis NA
  Scott.Davis@ppdi.com

Other members

- Ago Ahene NA
- Claudio Calonder EU
- Joseph Kowalchick NA
- Takahiro Nakamura APAC
- Nouri Parya NA
- Igor Vostiar EU
- Jin Wang NA
- Yang Wang APAC

In scope

- Operational

  Includes procedural concerns.
- Electronic

  Includes concerns with electronic data and compliance.
- Instrument

  Includes concerns with instrument hardware.
- Assay

  Includes concerns with assay validation and/or verification.

Interdependencies with other teams

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

Out of scope

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

Current status

An outline of our main topic headings that are being discussed.

Operational

- Automation Instrument & Software Validation
- System Documentation
- User Training
- Automation Issue Reporting
- Configuration Management
- Scripts
- Maintenance
- Decommissioning
- Periodic Review

Electronic

- User Access
- eData Security
- Compliance With Appropriate Guidance Documents
- Business Continuity

Instrument

- Instrument Maintenance Including Calibration/Verification
- Risk Assessment
- Validation of Interfaces

Assay

- Assay Accuracy & Precision Testing
- Gold Standard for Assay Performance: Automation vs Manual
- Instrument /Script Qualification for Validated Analytical Methods

Next steps

Our main discussions are complete and we are presently fine tuning our notes. A completed document including specific guidance will definitely be ready by March 2012.

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) WNAtner NA
- Lakshmi Amaravadi NA
- Lei Tang NA
- Renuka Pillutla NA
- Shobha Purushothama NA
- Joleen White NA
- Vikram Kansra NA
- Madhan Kumar Rose APAC
- K. Sonehara APAC
- Monique Putman EU

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.

Interdependencies with other teams

– Link with tiered approach

Out of scope

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

Current status

- We are currently working with a “trail balloon” outline for a white paper.

- This outline is helping the team channel our thoughts, eventually leading to a paper but at this point more importantly directing the team to area of more discussion and where additional case studies can be invoked.

Next steps

- Continue with Monthly Telecoms –
- Subdivide sections for initial draft of paper
- Outreach, starting at WRIB and continuing at NBC share high level outline and direction committee is going for input from a larger community
- Targeting having paper ready for submission approximately November 2012.

S1: Small molecule – Specific run acceptance

Team members:

Team lead

- Douglas Fast NA
  Douglas.Fast@covance.com

Other members

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

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 and overall acceptance
  - Validation of plasma blank samples
  - Cross validation of anticoagulants and 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

Interdependencies with other teams:

- A2, A7, A8, A9, L1, S2, S3

Out of scope:

Current status

- Meeting biweekly from September through December
- Meeting weekly from January 2012
- 14 Topics identified for discussion (as shown on Slide 1)
- We in general favor less-prescriptive language, are in agreement with the bulk of the regulations (FDA/EMA at least), but have specific comments on almost all topics
- Have completed 8 of the 14 topics
- Have identified 3 topics encompassing system suitability and matrix conditioning that require input from or coordination with other HTs (A9, L1, S2, S3)
- Presented on progress at EBF Barcelona

Next steps

- Complete topic reviews and discussion
- Assemble draft document with recommendations
- Present at GBC HT-L meeting in San Antonio (March)
- Identify regional meetings for presentations prior to global conference and team members to attend and present

S2: Small molecule specific assay operation

Team members:

Team lead

- Eric Woolf NA

woolf@merck.com

Other members

- 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 APAC
- Steve White EU

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

Interdependencies with other teams:

Sample reinjection – Team A6 (re: stability)

API Salt / Counter-ion changes – Team A6 (re: stability)

System Equilibration – Team A9 (re: system suitability)

Out of scope

- stability criteria

Current status

Where are we now:

1. Scope fully flushed out and aligned with current regulatory requirements
2. Points of agreement and points of discussion for in-scope topics determined
3. Currently working through points of discussion

   -complete for 2 of 11 topics as of 9 January

Next steps

Continue working through topics with a goal to have completed the bulk of them by the time of the CVG meeting

Begin drafting text.

S3: Chromatographic Run Quality Assessment

Team members:

Team lead

- Stuart McDougall EU

stuart.mcdougall@covance.com

Other members

- Ravi Kumar Trivedi APAC
- Ravi Sankar APAC
- Chris Holliman NA
- Hollie Barton NA
- John Dunn NA
- Ray Farmen NA
- Katja Heinig EU
- Liz Thomas EU
- Maria Francesca Riccio LA
- Junji Komaba APAC

Interdependencies with other teams

- S1 Small molecule specific run acceptance (Run acceptance, IS acceptance criteria & SST)
- S2 Small molecule specific assay operation (sensitivity, specificity and selectivity)
- A9 - Analytical instrument qualification (calibration and maintenance)
- A1 - Scope and regulations (21CFR11, audit trail, glossary of terms)

In scope

- All analytes giving a quantitative chromatographic response
- Chromatographic approaches (primarily LC)
- Chromatographic detection (primarily MS)
- Calibration and maintenance of chromatographic systems
- Signal to Noise
- Resolution & selectivity
- Peak shape
- SST
- Data sampling
- Peak smoothing & peak filtering
- Internal Standard response criteria
- General integration parameters (not vendor specific)
- Integration process (automated, semi-automated, manual)
- Reintegration (post regression)
- Chromatographic data review
- Audit trail (integration & reintegration)

Out of scope

- Specific integration parameters (vendor)
- Regression slope
- Instrument qualification

Current status

- Team members have delegated subtask assigned and provides summary document (regulatory position, scientific literature, recommendation) to team in advance of regular (two-week) teleconference and WebEx meeting.
- Meeting agenda and meeting minutes distributed
- All TC's organized until end Mar

Task	Lead	Status
Calibration and maintenance of chromatographic systems	Chris (NA)	Active
Signal to noise	Junji (APAC)	Active
Peak shape, resolution and selectivity	Stu (EU)	Active
SST	On hold	In S1
Data smoothing and peak filtering	Francesca (LA)	Complete
Internal standard response criteria	Ravi T (APAC)	Pending (also in S1)
General Integration parameters	Hollie (NA)	Active
Integration process (automated, semi-automated, manual)	John (NA)	Active
Reintegration (post regression)	Ravi S (APAC)	Active
Chromatographic data review	All	On hold (last task)
Audit Trail	Hollie (NA)	Complete

Next steps

- Complete, agree and issue recommendation for each subtask
- Obtain ‘key’ vendor input where available
- Team completes ‘Chromatographic data review’ task
- Check interdependencies with other ‘S’ teams
- Compile preliminary slidedeck for presentation in Mar
- Solicit feedback from wider audience (e-survey or similar)
- Adjust slidedeck following feedback