



GLOBAL BIOANALYSIS CONSORTIUM

Regulated Bioanalysis A Proposed Global Harmonization Process

presented on behalf of GBC at
V AcBio São Paulo , Brasil





Mission Statement

Create an all inclusive **Global Bioanalysis Consortium** (GBC) consisting of represented **scientific associations** with world wide influence to merge existing or emerging bioanalytical guidance to create one, **unified consensus document** that can be presented to the regulatory bodies/health authorities in various countries.

History

2008-2009:

- Loose discussions in multiple BA communities contemplating on the need and added value of harmonized BA guidelines

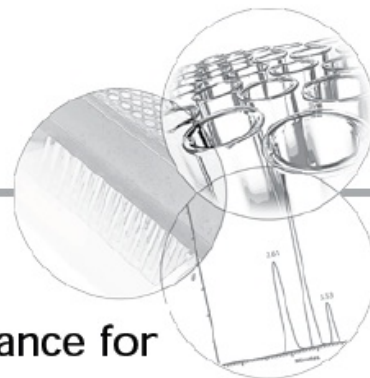
Dec. 2009 - EBF Conference (Barcelona, Spain)

- Formal request for harmonization from Bioanalytical community
- Acknowledgement by Regulatory Agencies present (FDA & EMA)
- Discussion among international pharmaceutical scientific organizations with a strong stake in bioanalysis: AAPS, APA, CVG and EBF
- Request Health Authorities to initiate a harmonization process
 - Offer support to Health Authorities for such a process
 - Letter sent to FDA and EMA in February 2010
- Publication as **Open letter** in April 2010 issue of *Bioanalysis*
- Entertain initial idea of forming a Global Bioanalysis Consortium

History

OPEN LETTER

Request for Global Harmonization of the Guidance for Bioanalytical Method Validation and Sample Analysis



Open letter to the bioanalytical community. Sent to the US FDA/European Medicines Agency in February 2010

The 2001 US FDA Bioanalytical Method Validation (BMV) guidance document has been widely accepted and adopted by the bioanalytical community worldwide. As such, it has become the cornerstone of regulated bioanalytical laboratory procedure. In recent years, clarifications to these FDA guidelines and subsequent enhancements were discussed at North American- and European-hosted meetings and conferences. The outcome of these meetings, published in White Papers, conference reports or recommendations, are currently being implemented in many bioanalytical laboratories around the world. Nevertheless, differences in expectations or interpretation of the guidelines from individual auditors/inspectors or regional health authorities are a growing concern for the bioanalytical community.

Further globalization of the pharmaceutical industry is also impacting the bioanalytical community. Bioanalytical labs are booming in regions outside the EU and North America, and regional authorities are looking to accommodate this growth or being confronted with the lack of guidance within their own regulations. Consequently, this creates a stimulus for these countries/regions to

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History

Apr. 2010 – 4th CVG Workshop (Montreal, Canada)

- Consensus reached among panelists, 5 regulatory agencies and international attendees on how to proceed with the Global Harmonization of Bioanalytical Guidances: institution of a **Global Bioanalysis Consortium**
- Agreement on the main characteristic of a **Global Bioanalytical Guidance**:
 - **Should be science driven**
 - **Should include rationale behind each requirement to prevent “box checking”**
 - **Should look at global picture, not local issues**
 - **Should NOT be a prescriptive guidance**
 - **Must get buy-in from all the countries**

GBC: Goals and Objectives

- To bring together stakeholders from the pharmaceutical industry, contract research organizations and academia to share **current understanding of bioanalysis guidelines**, identify differences in these guidelines or differences in the interpretation or application thereof to routine regulated bioanalysis.
- To come forward with **recommendations** to Health Authorities and regulatory bodies worldwide on globally agreed best practices for Bioanalytical Method Validation (BMV) and application of such methods/technologies to the analysis of drugs of all molecular sizes in support of clinical and nonclinical studies.

GBC: Goals and Objectives

- To invite relevant stakeholders, from industry, academia, Health Authorities and regulatory bodies, to jointly discuss the GBC recommendations at a **global conference(s)** in order to achieve globally agreed guidelines on bioanalysis.
- Going forward, to serve as a **pivot point** on the continued harmonized interpretation and/or updates of globally agreed guidelines.

Organization Chart

Steering Committee (GBC-SC)



Scientific Leadership Team (GBC-SLT)



**Harmonization
Team # 1**

**Harmonization
Team # 2**



**Harmonization
Team # 'n'**

Operating committees: Summary - membership

GBC Steering Committee (GBC-SC)

- Participation with balanced representation from all (4) regions
- Members from organizations which represent the regional BA community
- Balanced membership to cover LBA and chromatographic assays

GBC Scientific Leadership Team (GBC-SLT)

- Participation based on scientific expertise and contribution
- Members = SC + FM + HL-L

Steering Committee, Founding members (FM) and Harmonization Team Leads (HT-L)

Harmonization teams (HT)

- Participation based on scientific expertise and contribution
- HT = HT-lead + HT-members

Operating committees:

Summary - roles

GBC Steering Committee (GBC-SC)

- Build/coordinate GBC as organization
- Facilitates and coordinates
- Represent GBC in outside world

GBC Scientific Leadership Team (GBC-SLT)

- Coordinate HT interactions and provide input as needed
- Provide scientific leadership to facilitate progress
- Ensure HTs work in concert and don't derail

Harmonization teams (HT)

- Prepare proposals, blending (emerging) science, existing and emerging guidelines, on a harmonized way forward on all topic assigned to the team
- Propose draft harmonized proposals to GBC-SLT
- Present harmonized proposal at the GBC conference

Operating committees: details

1. GBC SC

Roles and Responsibilities of the GBC-SC

- **Coordinate** the GBC process of a global BMV harmonization strategy.
- **Organize** and register GBC as an independent entity unless association with reputed existing organization is in the best interest of GBC
- **Financial** responsibility for overseeing finances and filings
- **Oversight** and co-ordinate the GBC-SLT and facilitate conflict resolution
- **Communicate** or facilitate communication of the GBC progress to global community
- **Represent** or facilitate representation of GBC at international and regional meetings.
- **Dialogue** with Health Authorities/regulatory agencies on behalf of GBC
- **Organize** international meetings/conferences for harmonization / globalization
- **Interact** with and appraise other interested BA and related groups having interest in GBC
- **Report back** to GBC-Scientific Leadership Team
- **Sponsor** of selection of HT teams

Operating committees: details

1. GBC SC (cntd)

Notes:

- SC membership aims at balanced representation from all identified regions
- Size of SC will be kept small
- Regions to manage representation in GBC in line with regional expectations
- Currently **4 regions** are identified:
 - North America (NA = US and Canada)
 - Latin America (LA = South America + Mexico)
 - EU (Europe + Africa)
 - Asia-Pacific (APAC)

Operating committees: GBC-SC

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)

- Tatsuo Kurokawa (JBDG)
- Shrinivas Savale (APA-India)
- Daniel Tang (SBDG&BBDG)

Europe (Europe + Africa/Middle East)

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

Operating committees: details

2. GBC - Scientific Leadership Team (GBC-SLT)

Roles and Responsibilities of GBC-SLT

- **Participation:** The GBC-SLT consists of recognized BA experts who can contribute significantly to the long-term mission of GBC and are committed to devote time and energy in GBC activities
- **Harmonization:** GBC-SLT members should
 - Develop/support harmonization activities in their regional meetings and organizations, speak with one voice and report back to GBC-SC
 - Connect and support the harmonization teams (HT) (via HT lead)
 - Interact with BA community and regulators to achieve GBC mission. However, GBC-SLT members should be mindful of communication to regulators from GBC that should be limited to the SC members.
- **Ensure:**
 - Ensure GBC activities are all inclusive, both on regions and experts
 - Harmonization-blending of HT outcome to ensure consistency and continuity
 - Representation of biologics and small molecule analytical in HT

Operating committees:

3. Harmonization Team Leads (HT-L)

Roles and Responsibilities of HT-L

- **Leads** the a specific HT
- **Identifies** team members for his/her team (preferably from multiple regions and recruited via application forms)
- **Responsible** for organizing regular HT meetings (agenda/timing) and ensuring meeting minutes are available.
- **Connects** with GBC-SLT to report back on progress or get input.
- **Connects** with other HT leads in case of overlapping discussions

Operating committees: details

Objective of the HT Lead

Objective of HT-L

- Remove concepts of company or region from thinking - you're leading a global effort
- Facilitate discussion, don't push 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.
- Recognize that some governments 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 e.g. 80% may already have industry-regulatory consensus

Operating committees: details

Role of HT-L

Select team members

- from application list
- from different regions
- look for thought leaders; people who have published, spoken or previously been involved in topic at workshops

Evaluate Scope with team

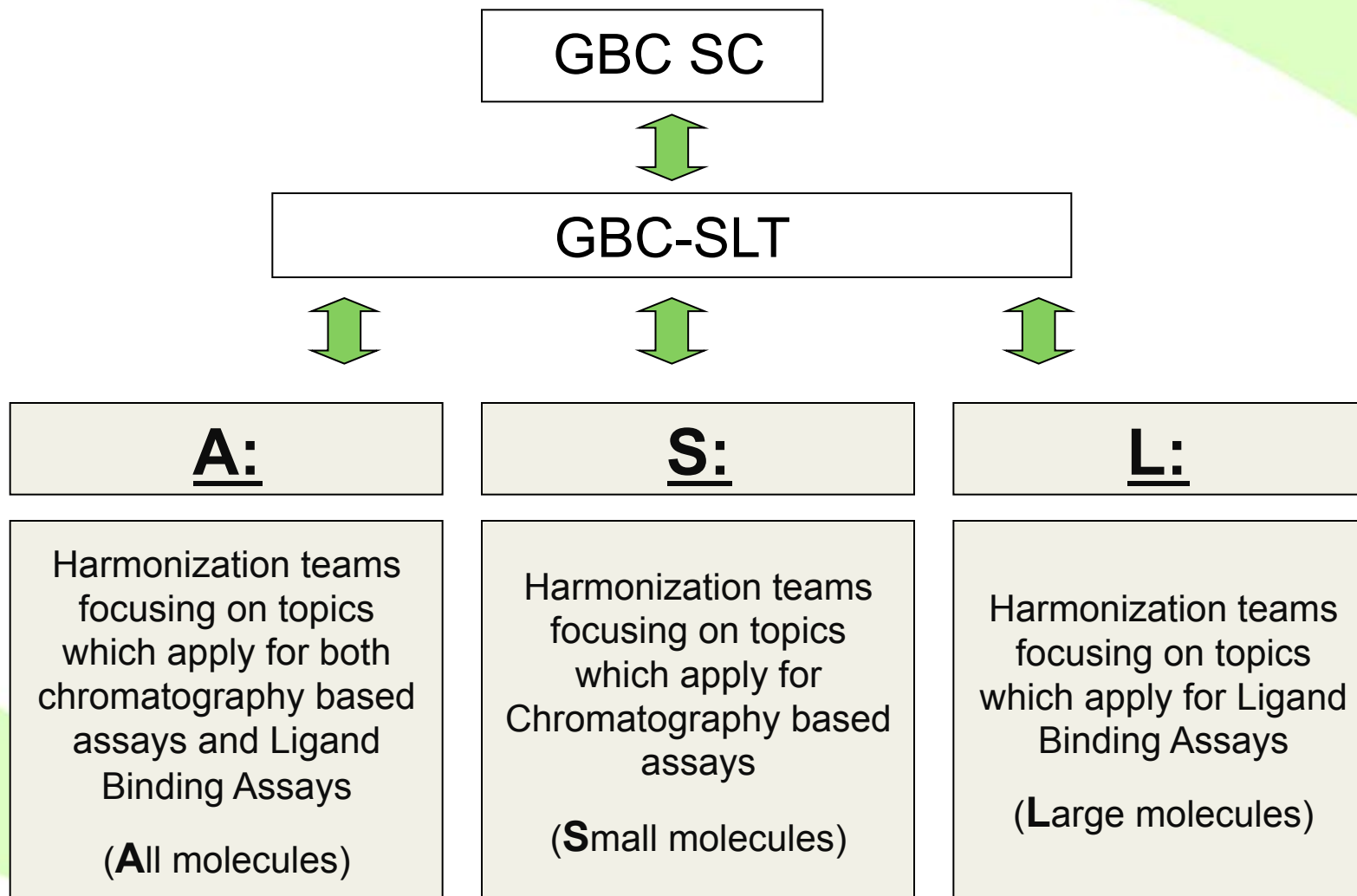
- Is everything presented appropriate to team?
- Is anything missing?
- Ensure there is clarity within team on Scope
- Finalize Scope and meet with GBC SC and other team leaders to review and evaluate overlap or points of contact for resolution of individual team

Inform GBC SC and other Team leads of progress

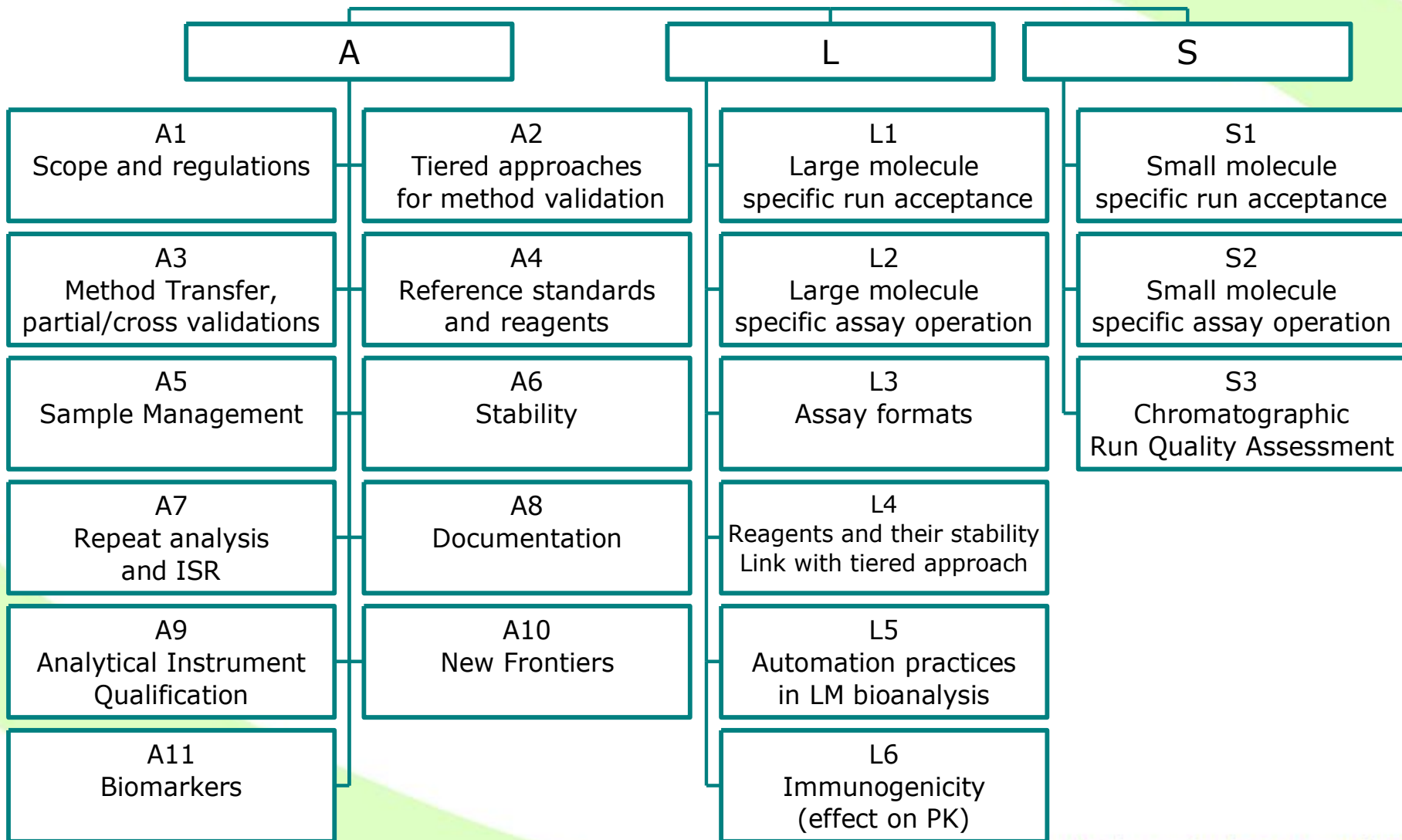
- seek counsel and input as needed

Which Harmonization Teams?

Overview



Which Harmonization Teams ?



Operating committees: HT-L

A1: Surendra Bansal

A2: Steve Lowes

A3: David Muirhead

A4: Joseph Bower

A5: Mike Redrup

A6: Nico van den Merbel

A7: Eric Fluhler

A8: Tom Verhaeghe

A9: Chad Brisco

A10: Bob Bethem

A11: Jean Lee

L1: Marian Kelley

L2: Lauren Stevenson

L3: Sherri Dudal

L4: Lindsay King

L5: Han Gunn

L6: Jeff Sailstad

S1: Douglas Fast

S2: Eric Woolf

S3: Stuart Mc Dougall

Operating committees: details

Harmonization teams (HT) - cntd

HT composition - Profile of HT members

- Team consists of a **team lead** and **subject matter experts**, preferably from multiple regions and recruited via application forms
 - Individual membership to more than 1 team can be beneficial and is endorsed, but for practical reasons membership is limited to 3 teams
 - Team members **are committed to attend HT-meetings** (via TC). The team is mindful of time zone challenges, 'difficult hours' rotate equally amongst the team members
 - **No region should be excluded**, unless the regional SC member confirms lack of expertise, the subject is out of scope or insufficient experts volunteer
 - **No region should have >50%** of team members.
 - Size of teams can vary (advice: 5-10 members, depending on the topic)
- Will include all technologies during assessment, but may defer some in favor of earlier enacted recommendations for those more broadly used

Operating committees: details

Harmonization teams (HT)

Roles and Responsibilities of HT

- **Engage on discussing** different harmonization topics in preparation of harmonization meeting(s)
 - Discuss - share experience in support of harmonization and best practice.
 - Prepare proposals, blend (emerging) science, existing and emerging guidelines into a harmonized way forward on a specific harmonization topic assigned to the team - propose draft proposals to GBC-SLT
 - By focusing on content in detail, come forward with a **recommendation**, reached by consensus, to be presented at Global Harmonization meeting(s).
 - Present HT subject content at Global Harmonization meeting
 - Each team focuses on the their **defined topics**, but is mindful of potential **overlaps** and will discuss these with HT-L and/or SLT
- **Interact** (via HT-L) with GBC-SC (each HT has SC sponsors as first point of contact) and SLT on a regular basis to ensure progress, potential roadblocks or overlap and consistency

Harmonization Team activities - 1/3

Keep minutes

- utilize a team member to record minutes
- distribute and permit team to comment
- ensure agreement prior to finalizing

Compile regional information on regulations and practices related to the Teams scope

- Share regulations with other Team leaders/Teams

Harmonization Team activities - 2/3

Based on commonality, filter scope list to those that are fully agreed to, generally agreed to, and those with no agreement. The GBC SC believes that for many, if not all, topics, 80% of the items will be generally agreed to with only 20% in the latter two categories.

- 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 team leaders for input
- Team members should reach back to regional organizations for input
 - Query regional organization membership on positions on a topic(s), use surveys if time permits. Coordinate across Teams, regional memberships will lose interest if frequently bombarded with requests.

Harmonization Team activities - 3/3

Proposals

- 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 presentation at international meeting*
- Where no consensus is achieved, provide arguments on both sides

Examples of Consensus Topics

Basic 6 principles of Method Validation

- Accuracy, Precision, Sensitivity, Selectivity, Stability and Reproducibility (ISR)
 - Overall design of the validation experiments
 - Run acceptance criteria: 4/6/15(20) or 4/6/20(25) Rules

Principles of Incurred sample reanalysis (ISR)

Fundamentals of what goes into a bioanalytical report

- For MV or sample analysis
- Recent debate around the report generation process and finalization

Topics Requiring Consensus Building

Examples

Within current Method Validation guidance

- Tiered approaches to metabolites
- Statistical approaches vs. fixed number (e.g. 4/6/15 rule)
- Analyte stability experiments
- Scientific investigations
- Method transfer and cross-validations
- Internal standard criteria

Other developments

- Challenge of LBA vs. chromatographic assays
- Will regulatory language accommodate emerging technologies? – chromatographic and LBA
- Accommodating biomarker assays
- New technologies or other evolving issues

Harmonization team activities?

An example: Harmonization team A6 - Stability

Scope:

- Reference standards and reagent stability
- Process stability established during validation
- Stability in matrix
- Co-formulated and co-administered drugs
- Whole blood and tissue stability
- Stability at the sample collection time
- Degradation vs. stability vs. solubility loss vs. absorptive loss

Moving forward:

- Team to have regular TCs
- Team to give feedback to SLT at regular intervals or BA community as appropriate
- Team to present outcome at GBC conference

Proposed discussion points:

- Understand and discuss areas of difference in interpretation – provide clarification
- Understand current (global) regulatory environment on assigned topic
 - Consider both Existing guidelines and anticipated or emerging guidelines
 - Acknowledge consensus (**probably 80%**)
 - Focus on missing, unclear or conflicting guidelines (**maybe 20%**)

A6: Stability

Team members:

Team lead

- Nico van de Merbel - EU

Other members

- Name – region – e-mail
- Name – region – e-mail
- Name – region – e-mail
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In scope

- Stability in relation to validated methods
- Reference standards and reagent stability
- Process stability established during validation
- Stability in matrix
- Co-formulated drugs, co-administered drugs
- Whole blood and tissue stability for validated methods
- Stability at the sample collection - A6
- Degradation vs. stability vs. solubility loss vs. absorptive loss

Interdependencies with other teams – if any

- A2
- A3
- A5

Out of scope

- Stability assessment in tiered approach (blood, tissue, urine, metabolites, biomarkers – as applicable..) – A2

Operating committees details

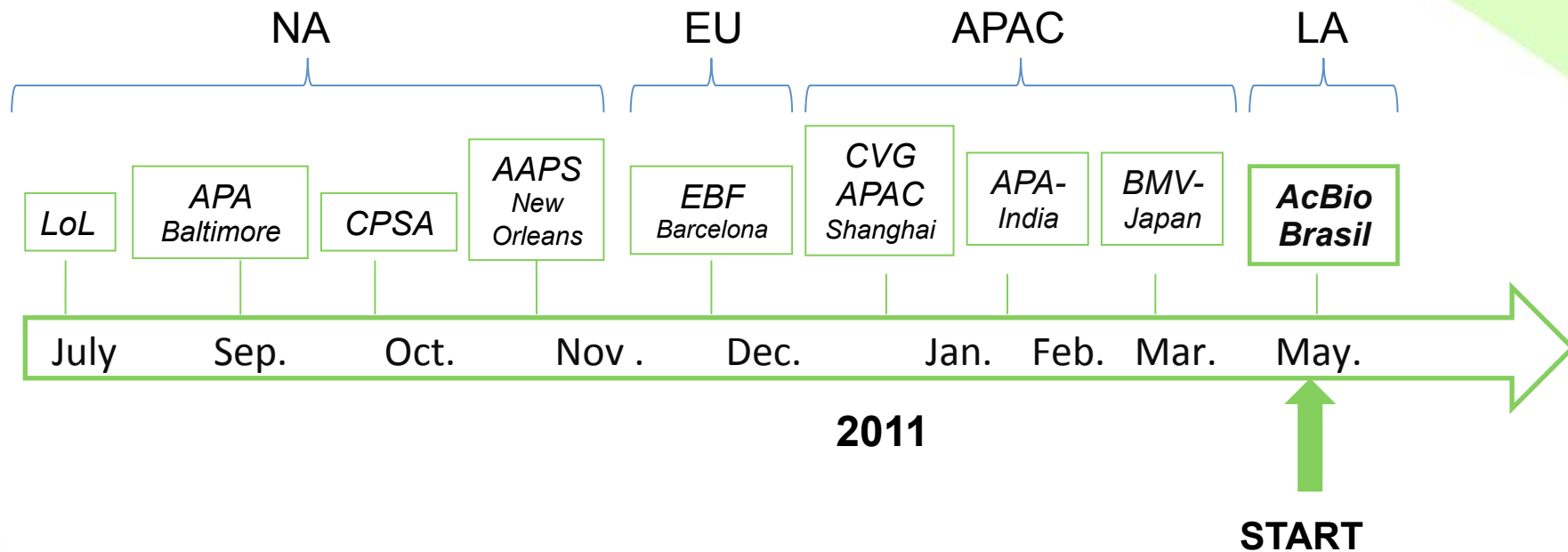
Dynamics of SC – SLT – HT-L interactions

Dynamics of SC – SLT – HT-L interactions

- HT-L feedback and interaction through in SC-sponsorship:
 - Each HT has a SC sponsor as first point of contact
 - Each HT will provide monthly executive summaries (via HT-L, in agreed template format) to facilitate feedback from HT to SC and across teams.
 - Essential part of this feedback is on progress and hurdles identified by the HT.
 - All summaries are shared with full SLT for information purposes
 - Difficult to resolve hurdles are escalate to SC prior to escalation to SLT
- In order to make sure SLT does not become a virtual team, quarterly TCs should be planned. Logistics to be determined
- GBC-SC is planning for a SLT face-to-face in Q1 2012 for consolidation and joint discussion of all topics, in preparation of 1st Global Meeting

Where are we now?

- Created **awareness and get input** at international Bioanalysis meetings in all regions

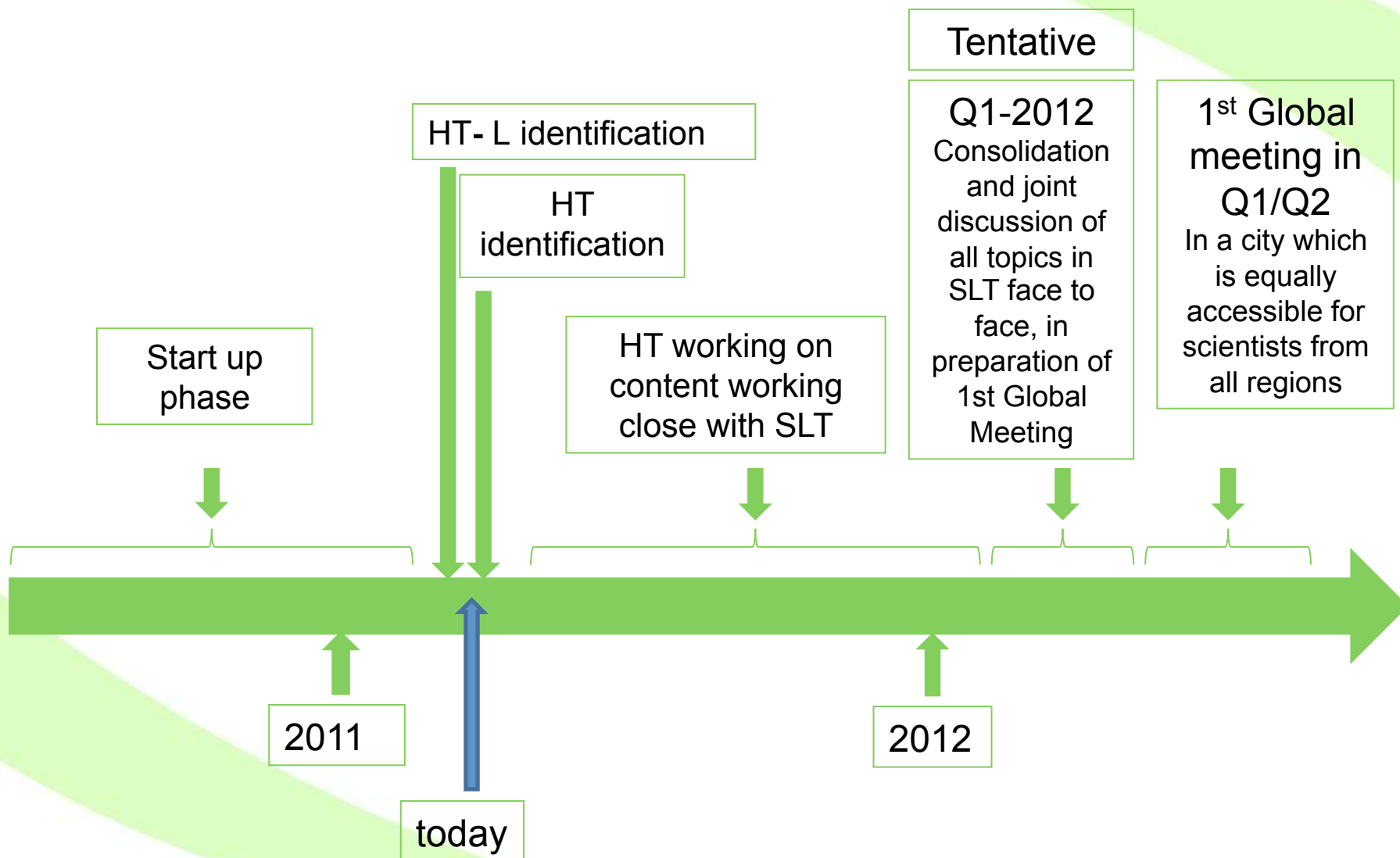


- Engaged **270+ experts** from industry, with participation from all regions
- From these 270+ experts, SC identified **20 Harmonization Team leaders (HT-L)**
- HT-L are currently composing their teams
- Within a few weeks, all harmonization teams will be up and running

What took us so long?

- We made sure **SC was composed with all regions included**
 - With GBC process starting in EU-NA, APAC took a bit longer to identify SC members
 - Consider industry feedback on initial low representation of LBA expertise in SC
- We made sure **all regions were informed**
 - GBC was depending on global meeting calendars
 - With calendars favorable for NA + EU, APAC + LA took longer to engage
 - Make sure all regions had the time to absorb information and mission
 - Allow time for experts from all regions to enroll based on the same information and at their own pace
- **Managed the enrolment of 270+ experts** from industry
- Carefully identified **20 Harmonization Team leaders (HT-L)**

Proposed way forward



Acknowledgment

Founding members and Steering Committee members:

The GBC Steering Committee:

- Mark Arnold (AAPS)
- Rafael Barrientos (AcBio)
- Daniel Tang (SBDG&BBDG)
- Shrinivas Savale (APA-India)
- Tatsuo Kurokawa (Japan)
- Peter van Amsterdam (EBF)
- Philip Timmerman (EBF)
- Michaela Golob (EBF)
- Binodh DeSilva (AAPS)
- Fabio Garofolo (CVG)

and

- Surendra Bansal (AAPS)
- Douglas Fast (BSAT)
- Steve Lowes (AAPS)
- Eric Woolf (BSAT)