

Feedback from AAPS Open Forum on: “Next Steps Towards International Harmonization of Bioanalytical Guidance”

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(Merck Serono, on behalf of EBF)

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“Next Steps Towards International Harmonization of Bioanalytical Guidance”

AAPS Open Forum November 4th, 2014

Moderator: Eric Fluhler

Speakers: Mark Arnold (representing SM)

Lakshmi Amaravadi (representing LM)

Michaela Golob (representing EU /LM)

Panel: Steve Lowes

Jan Welink (EMA)

Brian Booth (FDA)

Mark Arnold (AAPS)

“Regulatory Harmonization:

Current and Future Perspectives on
Chromatographic Assays”

- Harmonization inhibitors
 - Protective commercial regulations (certified in-country facilities/ restrictive shipping regulations)
 - Differences in regulation
 - Technology evolution & fear of findings/ 483

- Industry perspective?
 - => different local guidelines and nuances require changes in practice

- Industry response? => local collaborations & GBC

- Science based regulations

	HPLC UV or FI	LC-MS				LBA			PCR			?		
Small molecules	3	6	9	12	15	18	21	24	27	30	33	36	2 to 1	
Peptides	0	2	5	8	11	14	17	20	23	26	29	32	35	2 to 1
Proteins	0	1	4	7	10	13	16	19	22	25	28	31	34	2 to 1
ADCs	0	1	4	7	10	13	16	19	22	25	28	31	34	2 to 1
Milla molecules		1st 12				2nd 12			3rd 12					
Oligonucleotides		1 to 18		EVEN		◇		◇		ODD		19 to 36		
<i>Biomarkers</i>		1 to 18		EVEN		◇		◇		ODD		19 to 36		

Support Harmonisation

➤ Scientific community

- Must explore the strengths and weaknesses of new technology to
 - o demonstrate adequate for intended use
 - o customize validation

➤ Regulatory community

- Learn the strengths and weaknesses of a technology
- Evaluate the validations and study data in light of the science and intended use
- Avoid blindly applying existing regulations

To achieve harmonisation we need continued dialogue with individual country and regional health authorities

Lakshmi Amaravadi (AAPS)

“Regulatory Harmonization:

Current and Future Perspectives on
Ligand Binding Assays”

Summary

- Topics with strong alignment
 - Across Guidances (EMA, FDA, MHLW, Japan, CFDA)
 - Agreement between Industry and Regulators

- Topics with incomplete alignment

- Future Perspectives

Note: with respect to FDA, alignment presented herein is reflective of outcomes from CCV (conference report in final review) which may differ from text in the Draft Guidance. Health Canada adapted EMA recommendations; ANVISA does not provide LBA specific guidance

Topics with Alignment

- Standard/Calibration Curve
- Accuracy and Precision, including total error
- Analytical Run and Acceptance Criteria
- Specificity – structurally similar molecules; potentially interfering substances
- Selectivity – normal and disease matrix
- Dilutional linearity and hook effect
- Reanalysis of study samples
- ISR - general approach and acceptance criteria
- Stability
- Documentation (Method Development Summary in VR)
- *Japanese Guidance- almost complete alignment*

Topics with Incomplete Alignment

- Selectivity
 - Routine testing of lipemic and hemolyzed samples
- Specificity
 - Routine testing of concomitant medications (potentially including small molecules)
 - QC concentration levels to be tested
- Routine Parallelism Assessments
- Criteria for ULOQ
- ISR sample numbers
- Inclusion of Biomarker Assays in BMV Guidance

Towards Global Harmonization

- Are the differences big enough?
- Flexibility, scientific judgment vs precise and restrictive language - walking on thin ice
- How will a harmonized document be used in the context of local regulatory guidance documents?
- ICH, USP, WHO and other

Michaela Golob (EBF)

„The Path to Harmonization,
a European Perspective “

How it all started?

- EBF OS (2009)

in 2010:

- Open letter to the agencies
(EBF, AAPS, APA-BSAT & CVG)
- WRIB
- GBC founded

GBC: Goals and Objectives

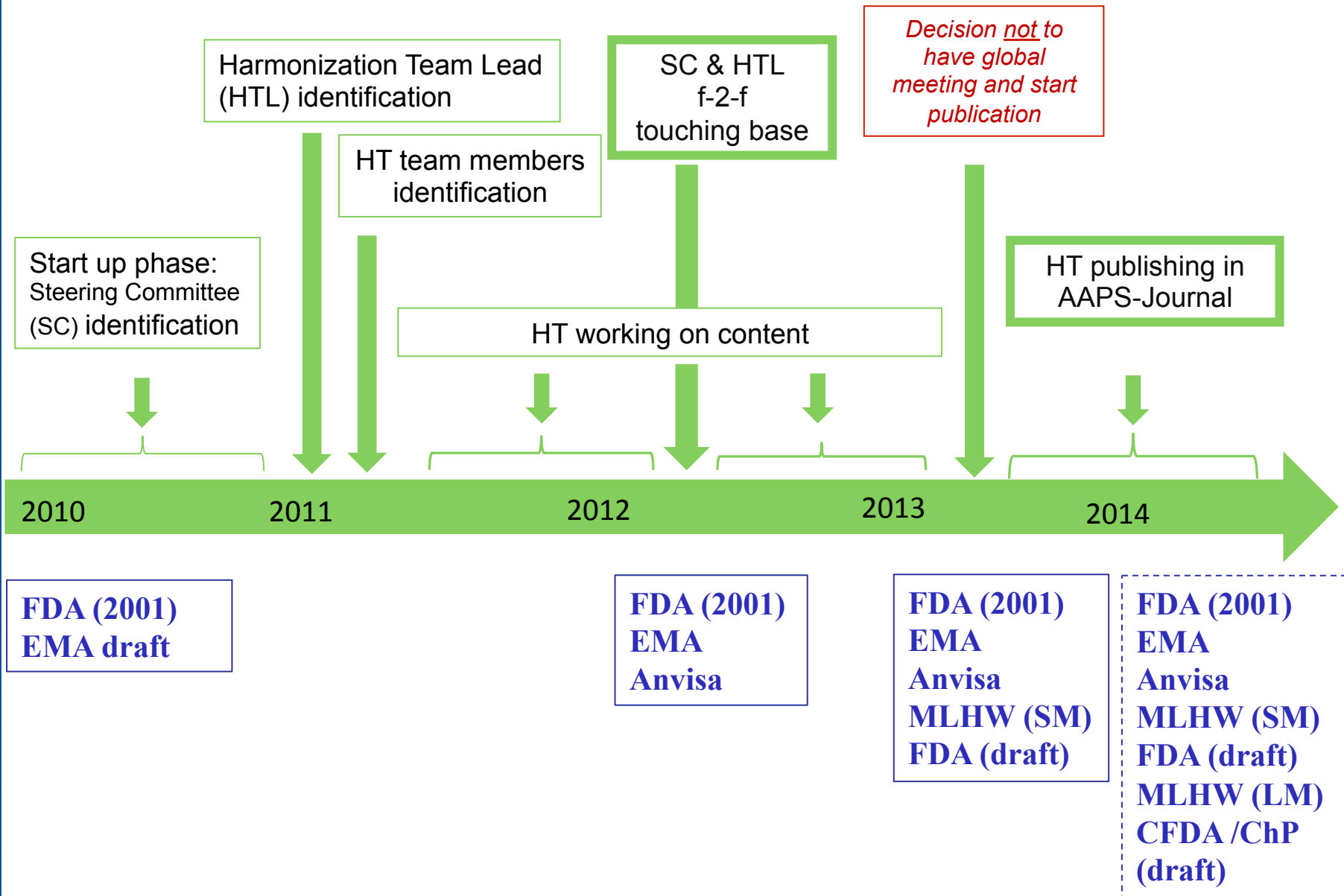
- To bring together stakeholders from the pharmaceutical industry, contract research organizations and academia to share **current understanding of bioanalysis guidelines**, identify differences in these guidelines or differences in the interpretation or application thereof to routine regulated bioanalysis.
- 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.
- 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.



Global Bioanalysis Consortium

On harmonization of bioanalytical guidance

GBC activities & Applicable Guideline till 2014



What did we achieve with GBC?

GBC build bridges



- GBC brought together a global community of bioanalytical scientist and stimulate regional & global discussions on bioanalytical best practice
- Visualizing the challenges of different global guidance's
- Highlight the need/desire for a harmonized view on bioanalytical regulations based on scientific best practice

ICH?

With many guidelines showing small differences / ambiguities should we stimulate a harmonized ICH guideline?

- GBC-SC is currently considering potential consequences of promoting an ICH guideline i.e.
 - Harmonize regional differences; propose best global practices
 - Clarify the scope of regulations (e.g. when is a validated assay required and when can other criteria be applied)
- GBC-SC is aware ICH doesn't represent all regions/countries, but ICH Guidance is often used as reference in industry or Regulatory Authorities in non-ICH countries

Next proposed actions within GBC:

- Encourage strong discussion in BA community prior to stepping to ICH
- Philip Timmerman assigned within GBC to coordinate with Harmonization Team leaders (and if needed other interested parties) the preparation of an ICH guideline development conversation



Open Forum Discussion

- General recognition of what GBC has achieved
 - productive international dialogue
 - both regulatory representatives congratulated to all the achievements reached by the industry harmonisation process
- General agreement that 80-90% of content guidelines are equivalent.
- Guidelines are equally needed for industry **& regulators** (training/education of the regulators around the rapidly evolving aspects of Bioanalysis is challenging)
- Consensus on tiered approach: clear definition around what is required for BE studies vs what is really needed for nonclinical & other clinical studies.

Open Forum Discussion: ICH

The audience was unfamiliar with ICH process
Agreement on GBC-SC plan to get more clarity about the ICH
process (Philip coordination lead)

To be considered:

- Possible consequences?
 - implications in non-ICH regions ?
 - consequence for regional guidelines?

- Long Term Process

- Harmonization at this level is extremely challenging
(EU has already 28 member countries to be harmonized.)