AAPS Views on Bioanalytical Method Validation Harmonization

(on Behalf of AAPS Bioanalytical Community)

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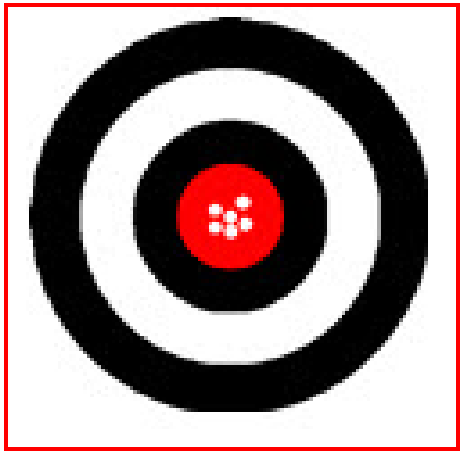
Background

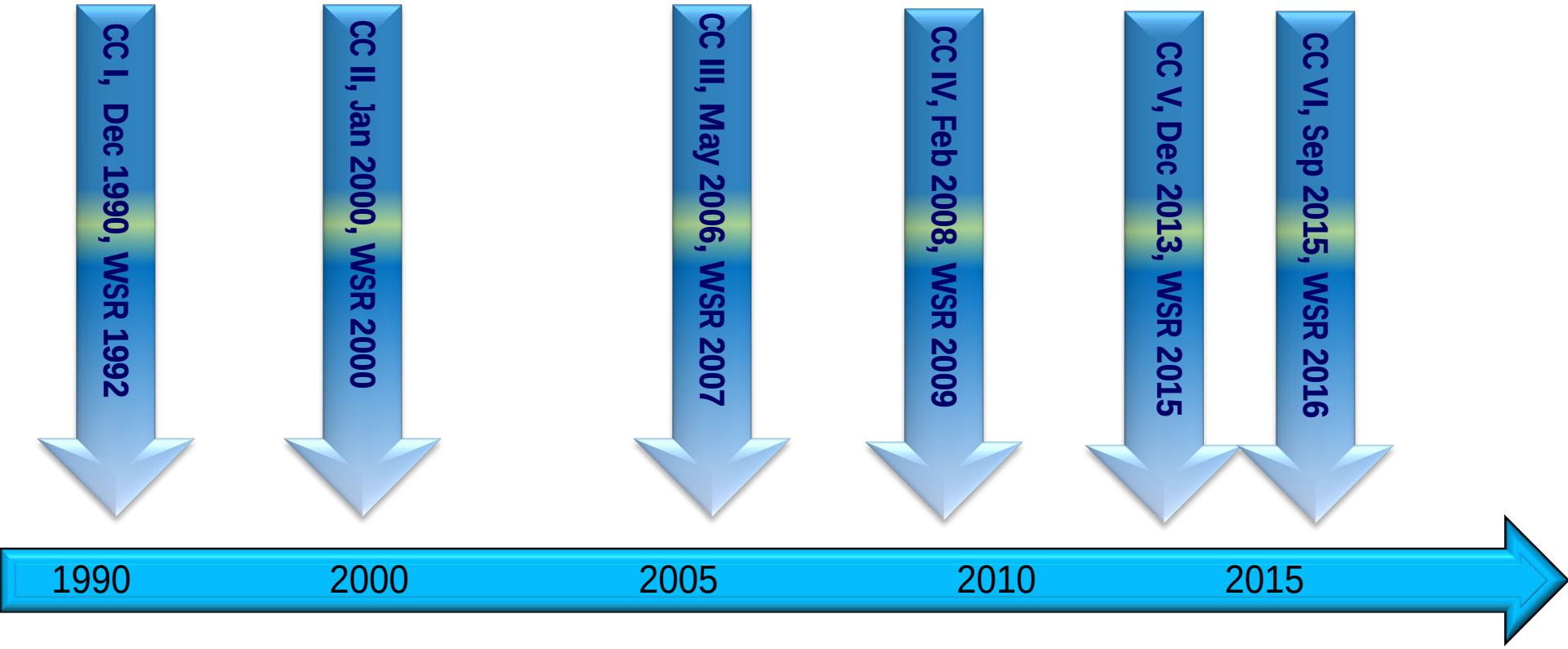
- AAPS has been actively involved for the last 3 decades in establishing and promoting the best practices in both bioanalytical science and bioanalytical method validation through:
    - Workshops famously known as Crystal City Meetings
    - Dedicated focus groups and their associated subteams
        - Bioanalytical and Ligand Binding Assay Bioanalytical
    - Annual and National Biotechnology meetings
    - Founding member of GBC
    - White Papers, Open Letters to regulatory authorities and the bioanalytical community

Purpose of Guidance

- Accurate and reproducible (reliable) bioanalytical data independent of the technology used



Crystal City (CC) Meeting History



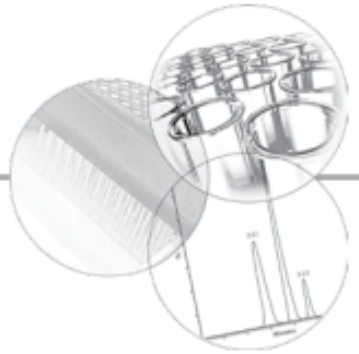
CCI - Workshop Report
CCII - Workshop Report
CCIII - Workshop Report

CCIV - Workshop Report
CCV - Workshop Report
CCVI - Workshop Report

Global Bioanalytical Consortium

- GBC was formed in 2010 as an industry response to different regional guidances – FDA (2001) and EMA (draft 2009) (Open Letter next page)
  - Differences and ambiguity in the guidelines gave rise to industry concern
  - GBC Mission: "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."
  - Science driven (Harmonization Team's recommendations have been published in *AAPJ)*
- Structure (global representation on all harmonization teams)
  - Buy-in from all regions (Asia Pacific, Europe, North America, Latin America
    - AAPS representing the USA industry

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

"[To] consider a collaboration and work towards a global harmonization of the guidelines on bioanalytical method validation and sample analysis for preclinical and clinical studies. Standardization and harmonization will largely contribute to the quality, transparency and efficiency of the data generated. These aspects are clearly of immediate benefit for the health authorities (ease of review of data) and laboratories (one set of standards), but eventually also for the patient and the community."

Philip Timmerman, MSc
www.europeanbioanalysisforum.eu/

EBF

Steve Lowes, PhD
www.aapspharmaceutica.com

aaps

Douglas M Fast, PhD
www.appliedpharmaceuticalanalysis.org

APPLIED PHARMACEUTICAL ANALYSIS

Fabio Garofolo, PhD
www.canadianlcmsgroup.com

CVG

Involvement in Other Global Activities

- Participation and representation at other meetings (e.g., JBF, EBF, APA India, etc.)
- Communication with regulatory agencies on behalf of the industry (e.g., Interaction with Health Canada on stability issue, provide industry comment on regulatory guidance, etc.)
- Open Forum on Harmonization of Bioanalytical Method validation (2014)
  - Speakers and panelists from AAPS, EBF, EMA, FDA
- Open Forum on Scientific Validation (2015)
  - Speakers and panelists from AAPS, EBF, JBF, FDA, NIHS)
- Drafting of an ICH concept paper (2016)
  - Representation from AAPS, EBF & JBF

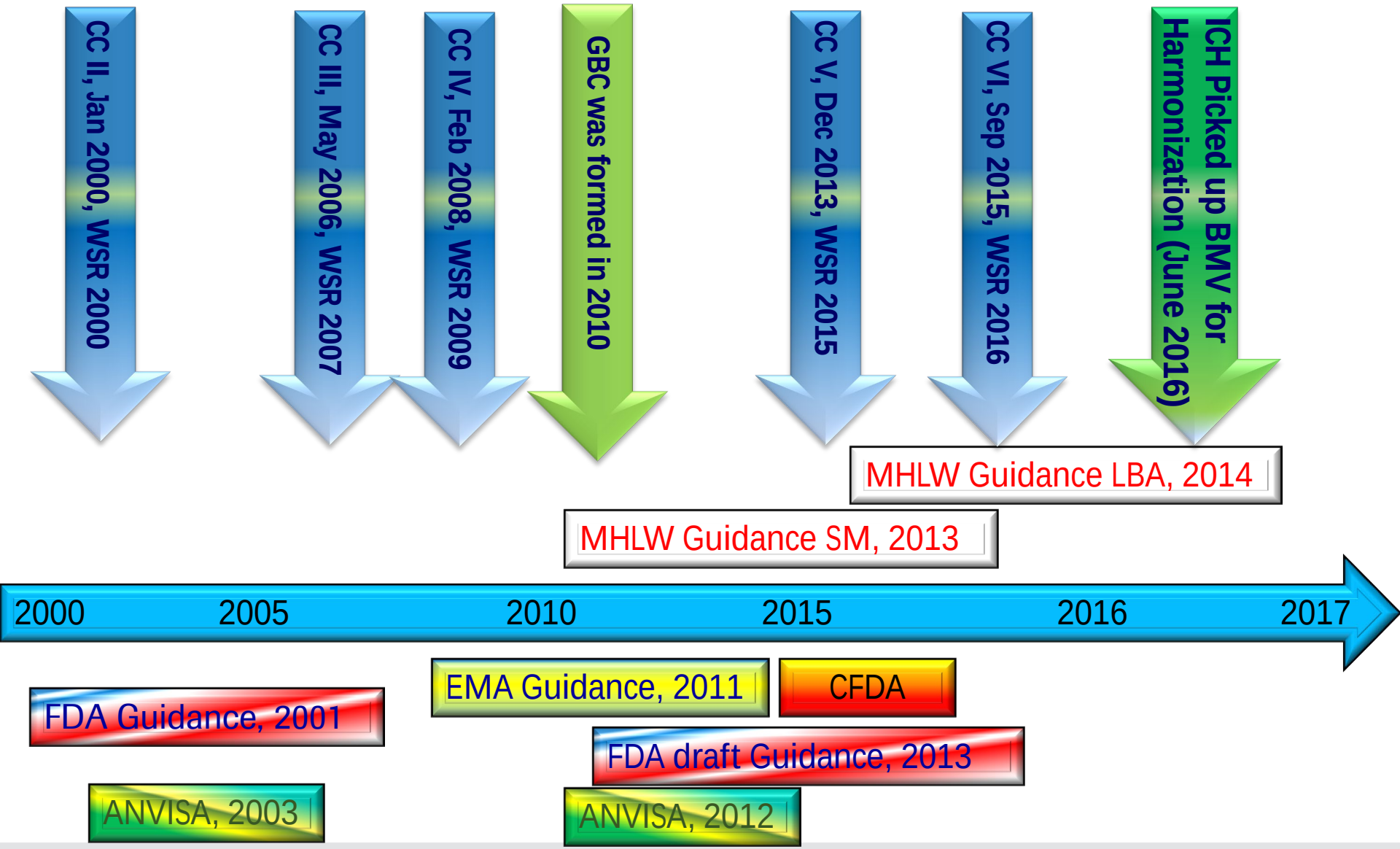
Regulations vs. Guidance

- What would constitute an ideal harmonized guidance
  - Science is universal--scientific based approach
  - Regulations are not universal (goal: provide reliable data)
  - Regulations are binding
  - Guidance: Provides guidelines on a specific subject (not binding)
    - Important: Alternative approaches may be used but you have to justify why the recommendations were not used
    - Equally important: Allows scientific interpretation/judgment

Bioanalytical Landscape

- Bioanalysts need guidance to help them understand and comply with regulatory expectations
  - A challenging task in today's global bioanalytical arena with multiple guidance
    - Studies are conducted globally and submitted to different regulatory bodies
    - Reviewed by multiple regulatory agencies leading to questions / inspections (which guidance should be followed?)
    - Good news: for the most part there is agreement in the requirements
    - However, there is ambiguity in some areas and even a lack of harmonization between some aspects
  - Even more challenging when the guidance is lacking or vague in new areas or in the new application of science & technology (hybrid methods, micro-sampling, other emerging technologies

Bioanalytical Regulatory Landscape



ICH

- BMV was picked up by ICH for harmonization in June 2016 based on a proposal from MHLW/PMDA (ICH M10)
- Timely and welcomed by the bioanalytical community

Differences and Opportunities

- Philosophical differences which lie within the scope of the guidance
- Opportunities for expansion
  - Scientific validation
  - New technologies (hybrid assays, micro-sampling)
- Procedural differences

I will highlight a few differences that are important to the AAPS community in the next few slides.

Scope

US FDA draft	EMA	MHLW
For investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), biologic license applications (BLAs), and supplements in developing bioanalytical method validation information used in human clinical pharmacology, bioavailability (BA), and bioequivalence (BE) studies that require pharmacokinetic (PK) or biomarker concentration evaluation. This guidance also applies to bioanalytical methods used for nonclinical pharmacology/toxicology studies. Full Validation is required for pivotal studies. Less validation for exploratory studies for internal decision making.	For Bioanalytical methods applied to measure drug concentrations in biological matrices obtained in animal toxicokinetic studies and all phases of clinical trials.	Applicable to validation of analytical methods applied to measure concentrations of drugs and their metabolites in biological samples obtained in toxicokinetic studies and clinical trials, as well as to the analyses of study samples using such methods (for both chromatographic and LBA)

GBC Recommendation

- Bioanalytical method is used to analyze samples at various stages after its development
    - Samples from discovery studies are generally analyzed using a generic or quickly developed method.
    - As development of the drug candidate continues, and one prepares for regulated studies, samples are analyzed using fit for purpose qualified methods.
    - Validation experiments must be completed before analyzing samples from regulatory studies where pharmacokinetics is a primary endpoint.
- Clarify (remove) validation requirement for non-clinical pharmacology studies
- Further clarification is recommended/essential for validation requirements for non-clinical vs. clinical studies (e.g., do we need all experiments that are required for a BE or a pivotal clinical study for a tox study?)

Inclusion of Biomarker and Immunogenicity Assays

- Feedback from CC VI workshop on Biomarkers:
  - “Biomarker assays are not PK assays” and it was requested that they should be removed from the FDA draft guidance
  - They should not be included in the harmonized guidance
- Immunogenicity: Harmonization is ideal but not within the PK guidance (separate guidance)

Scope -- Legal Basis

US FDA draft	EMA	MHLW
The analytical laboratory conducting nonclinical pharmacology/toxicology studies for regulatory submissions should adhere to the FDA's Good Laboratory Practices (GLPs) requirements7 (21 CFR Part 58). The bioanalytical method for human BA, BE, PK, and drug interaction studies must meet the criteria specified in 21 CFR 320.29.Analytical laboratories should have written standard operating procedures (SOPs) to ensure a complete system of quality control and assurance.	The validation of bioanalytical methods and the analysis of study samples for clinical trials in humans should be performed following the principles of Good Clinical Practice (GCP). Normally, the validation of bioanalytical methods used in non-clinical pharmacotoxicological studies that are carried out in conformity with the provisions related to Good Laboratory Practice should be performed following the Principles of Good Laboratory Practice. Aspects of method validation not performed according to GLP should be clearly identified and their potential impact on the validation status of the method indicated.	No specific requirement provided for GXP validation

Follow GBC Recommendations on Scope -- Legal Basis

- Regardless of GxP, the regulated bioanalysis is considered to include:
  - Adherence to regulatory bioanalytical guidance
  - Use of validated assays for samples analysis
  - Independent Quality Assurance
  - Qualified personnel and training
  - Instrument qualification (calibration and maintenance as part of performance qualification)
  - Use of Certified Reference standards
  - Sample tracking, chain of custody
  - Full documentation
    - SOPs, Study plan, protocol
    - Reports
  - Archiving (documents and data)

- Validation: Follow regulated bioanalysis
- Clinical and non-clinical studies: Follow regulated bioanalysis and appropriate regulations

Opportunities--Scientific Validation / Tiered Approach

- The concept of scientific validation has been discussed for many years. It was first introduced at the CC III meeting.
- The 2015 AAPS Open Forum (joint meeting with EBF and JBF) focused on the industry views on application of scientific validation
  - Most participants felt it should be applied during early development phase
  - However, the participants cautioned against including specific requirements for scientific validation within the guidance. The majority view was to clarify the scope of the guidance to only include studies for which full validation according to BMV is required

Cross Validation

US FDA draft	EMA	MHLW
When two or more bioanalytical methods are used to generate data within the same study or across different studies. Within a single study at more than one site or more than one laboratory Cross-validation should also be considered. When data generated using different analytical techniques (e.g., LC-MS/MS vs. ELISA) in different studies are included in a regulatory submission.	Where data are obtained from different methods within and across studies. When data are obtained within a study from different laboratories, applying the same method, comparison of those data is needed.	When data are generated in multiple laboratories within a study or when comparing analytical methods used in different studies, after a full or partial validation.

The use of spiked samples or incurred samples as well as the procedure and acceptance criteria should be harmonized.

GBC Recommendation

- Where the same analytical methodology is being used in at least two different laboratories to compare data from within the same study, it is acceptable to use spiked QC samples to make the comparison
- Where different analytical methodologies are being used, both spiked QC samples and incurred samples should be used to make the comparison

Opportunities—New Technologies

- Science moves forward at a fast pace
- We need to keep up with new technologies and use new tools to advance our mission (improving patients lives)
- Hybrid LC-MS/MS is now routinely used for many applications
  - Including this technology in the harmonized guidance would be helpful to the industry
- Other technologies used for PK assays (qPCR)?
  - Fit for purpose/Scientific Validation?

Additional Validation Parameters for Harmonization

- MRD - No added value during validation. Determine during method development
- Parallelism - should not be mandatory during validation for PK samples. Can be used as a investigative tool if problems are encountered during sample analysis
- Matrix effect (procedure—for LC-MS/MS assays, do we need 6 lots if SIL IS is used?)
- Requirements for number of QC levels (3 or 4?) and stability samples (the number of replicates)

Summary

- The harmonization of the BMV is highly welcomed
- Science is paramount—while some of the philosophical issues are a higher priority for clarification, others may need a quick consensus to determine the most common sense approach
- The majority of the requirements are already aligned
- The scope needs to be harmonized/clarified but it shouldn't be too prescriptive
- GBC whitepapers provide industry consensus views on various harmonization team discussions and can be a great source of reference
- The BA community should take this unique opportunity to engage in the harmonization discussions and feedback in the available forums

Acknowledgement

- AAPS bioanalytical community
  - BFG and LBA BFG SC and topic teams members
- AAPS staff
- GBC Teams
- EBF Community
- JBF Community
- Regulatory community engaged in discussions with the BA community at large

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Thank you!