The regulatory landscape

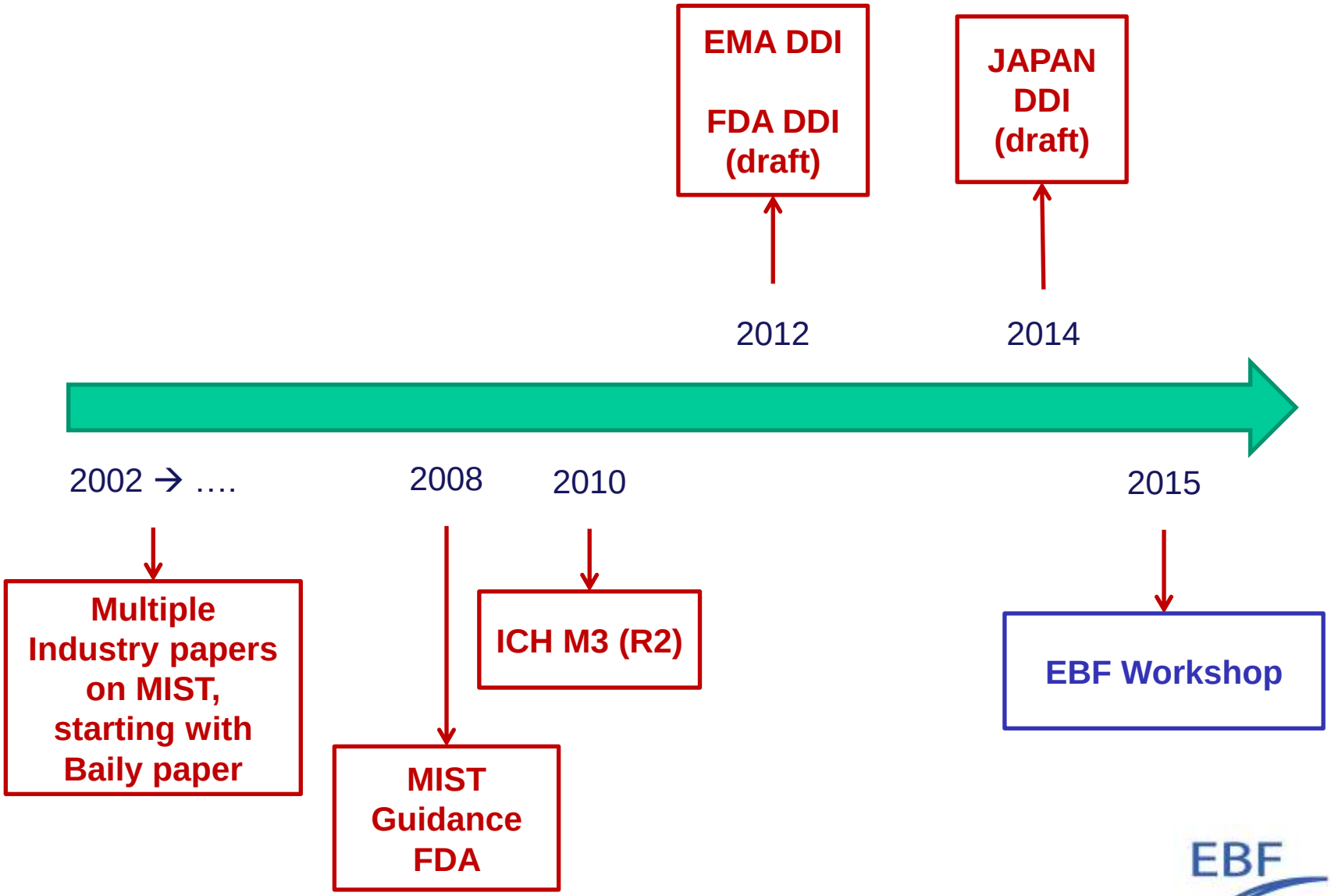
Stephen White
on behalf of the EBF

Overview

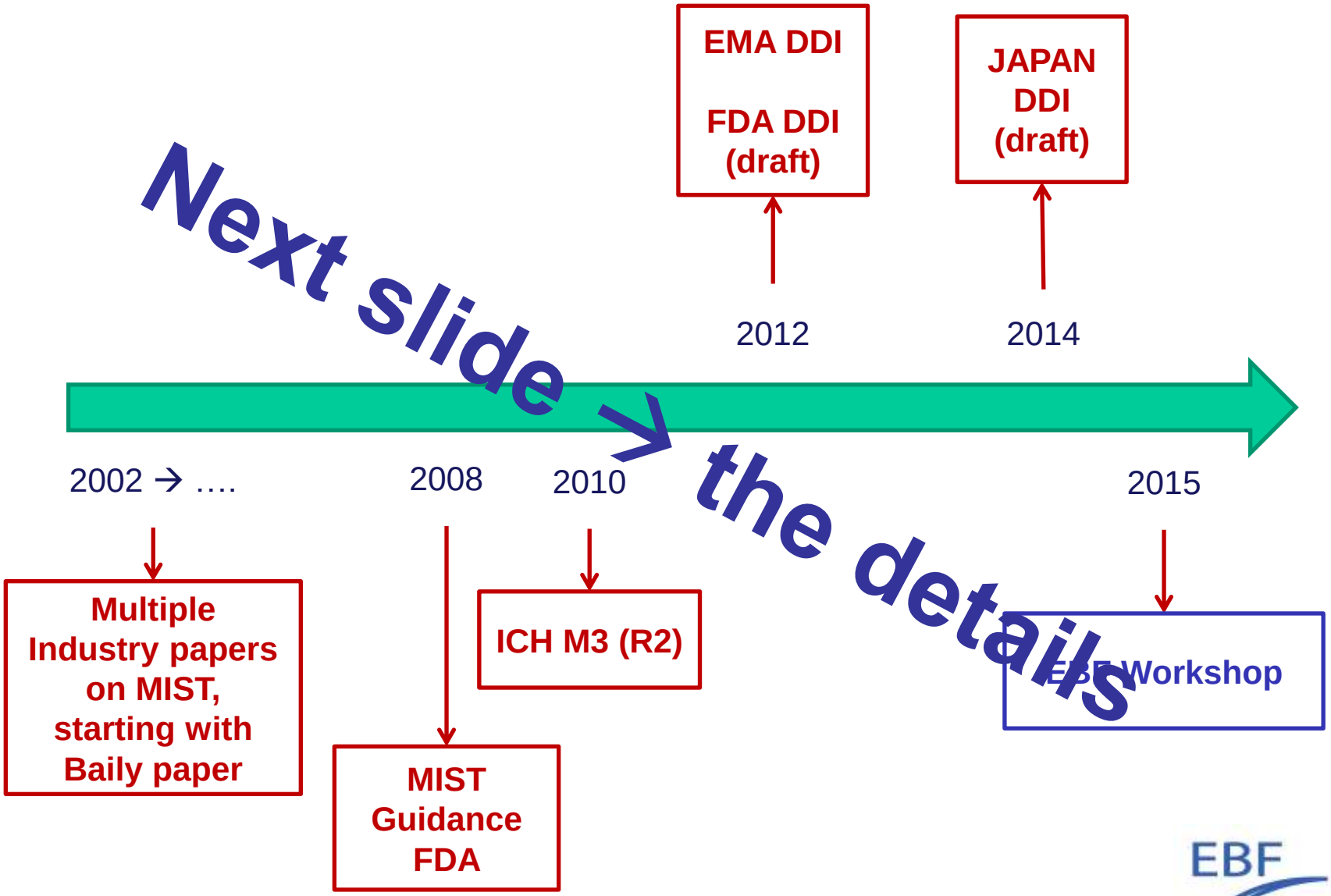
1. MIST and DDI Guideline
2. Regulatory landscape for BA
3. Tiered Approach on BA of metabolites
4. Conclusion

1. MIST and DDI Guidelines

MIST and DDI Guidelines – an overview



MIST and DDI Guidelines – an overview



Industry papers

- Drug Metabolites in Safety Testing, Toxicol. Appl Pharmacol, 182, 188-196., 2002
- Seeing through the mist: abundance versus percentage. Commentary on metabolites in safety testing. Drug Metab Dispos. ;33(10):1409-17, 2005
- Drug metabolites in safety testing. Toxicol. Appl. Pharmacol. 190, 91–92. (5), 2003
- Metabolites and safety: What are the concerns, and how should we address them? Chem. Res. Toxicol. 19, 1570–1579, 2006
- Which Human Metabolites Have We MIST? Retrospective Analysis, Practical Aspects, and Perspectives For Metabolite Identification and Quantification in Pharmaceutical DevelopmentChem. Res. Toxicol., 22 (2), pp 280–293, 2009

MIST

- US-FDA Guidelines: Guidance for Industry, Safety Testing of Drug Metabolites, (2008)
  - Metabolites with ≥10% of parent drug exposure (AUC) (inspired by EPA-1998)
  - Other metabolites also can elicit safety concern, (…) should be addressed on a case-by-case basis
  - Timing: toxicity assessment should be reported before beginning large-scale clinical trials.
  - No further testing required if human metabolite exposure is covered in toxicity assessment
- ICH Guidelines: included in ICH M3(R2), (2009) + Q&A (2012)
  - Metabolites with >10% of total drug-related exposure;
  - metabolites with an identified cause for concern (e.g., a unique human metabolite) should be considered on a case-by-case basis.
  - if dose/day <10 mg: greater fractions might be more appropriate triggers.
  - Waiver for phase-2 metabolites
  - Timing: to support phase 3 clinical trials

DDI (applies to small molecules only)

- EMA Guideline: Guideline on the Investigation of Drug Interactions (2012)
  - Phase I metabolites with both >25% of the AUC of parent drug and >10% of the drug-related exposure;
  - use unbound concentrations, if PPB data not available, use (bound + unbound)
  - Pharmacologically active metabolites based on AUC contributing *in vitro* activity ≥50% of the target activity identified
  - Formation and elimination pathways should be determined
- US-FDA: DDI studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (2012, draft)
  - DDI potential for metabolites ≥25% of parent drug (AUC) should be considered
  - both metabolism-based DDI and transport-based DDI
- MHLW (Japan): Drug interaction guideline for drug development and labeling recommendations (2014-draft)
  - Aligns with FDA / EMA

2. Regulatory landscape for BA

- Global BMV Guidances
  - Guidances and scope
- GLP
  - Guidances and scope

Global BMV Guidances

- FDA:
  - Guidance for Industry Bioanalytical Method Validation) May 2001
  - CC-III, CC-IV and CC-V conference reports
- EMA
  - EMEA/CHMP/EWP/192217/2009, Guideline on BMV http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf
- MHLW
  - Website: details on MHLW Guideline (Japan). http://bioanalysisforum.jp/images/T130918I0020.pdf#zoom=100
- Anvisa
  - Website: details on Anvisa Guideline (Brasil) http://bcn2012.europeanbioanalysisforum.eu/slides/day%203/7%20updates%20from%20the%20globe/3_tavares.pdf
- CFDA
  - Website: details on CFDA Guideline (China) http://knex2014.europeanbioanalysisforum.eu/site/ebf_knex2014/assets/slides/Dafang-Zhong--Guidelines-on-BMV-in-China.pdf

Scope of Guidance

draft FDA Guidance 2013:

- *"For pivotal studies that require regulatory action for approval or labeling, such as BE or PK studies, the bioanalytical methods should be fully validated. For exploratory methods used for the sponsor's internal decision making, less validation may be sufficient"*

In practice – scope of Guidance

non GLP

Screening

Or

Qualified Methods

Clinical, GLP and non GLP

Validated Methods

(non) rodent plasma (unchanged drug)
Other matrices - metabolites as appropriate

Human plasma
Other matrices - metabolites as appropriate

Additional preclinical species
Other matrices - metabolites as appropriate

Qualified Methods

- Samples from:
  - *In vitro* (e.g. PPB),
  - some mechanistic PK, PK/PD
  - most non standard matrices (e.g. tissues)
- Quantification of metabolites

Ref: Best practices in a tiered approach to metabolite quantification: views and recommendations of the European Bioanalysis Forum. Bioanalysis. 2010 Jul;2(7):1185-94.

GLP

OECD 1-15

- http://www.oecd.org/chemicalsafety/testing/goodlaboratorypracticeglp.htm

USA = 21CFR58

- http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=58

Fundamental aspects of GLP

GLP = non-clinical safety testing

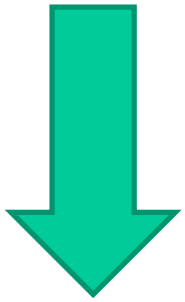
All GLP texts, whatever their origin, stress the importance of the following points :

1. Resources: organization, personnel, facilities and equipment.
2. Rules: protocols and written procedures (SOPs).
3. Characterization: test items and test systems.
4. Documentation: raw data, final report and archives.
5. Quality assurance unit.

But…..

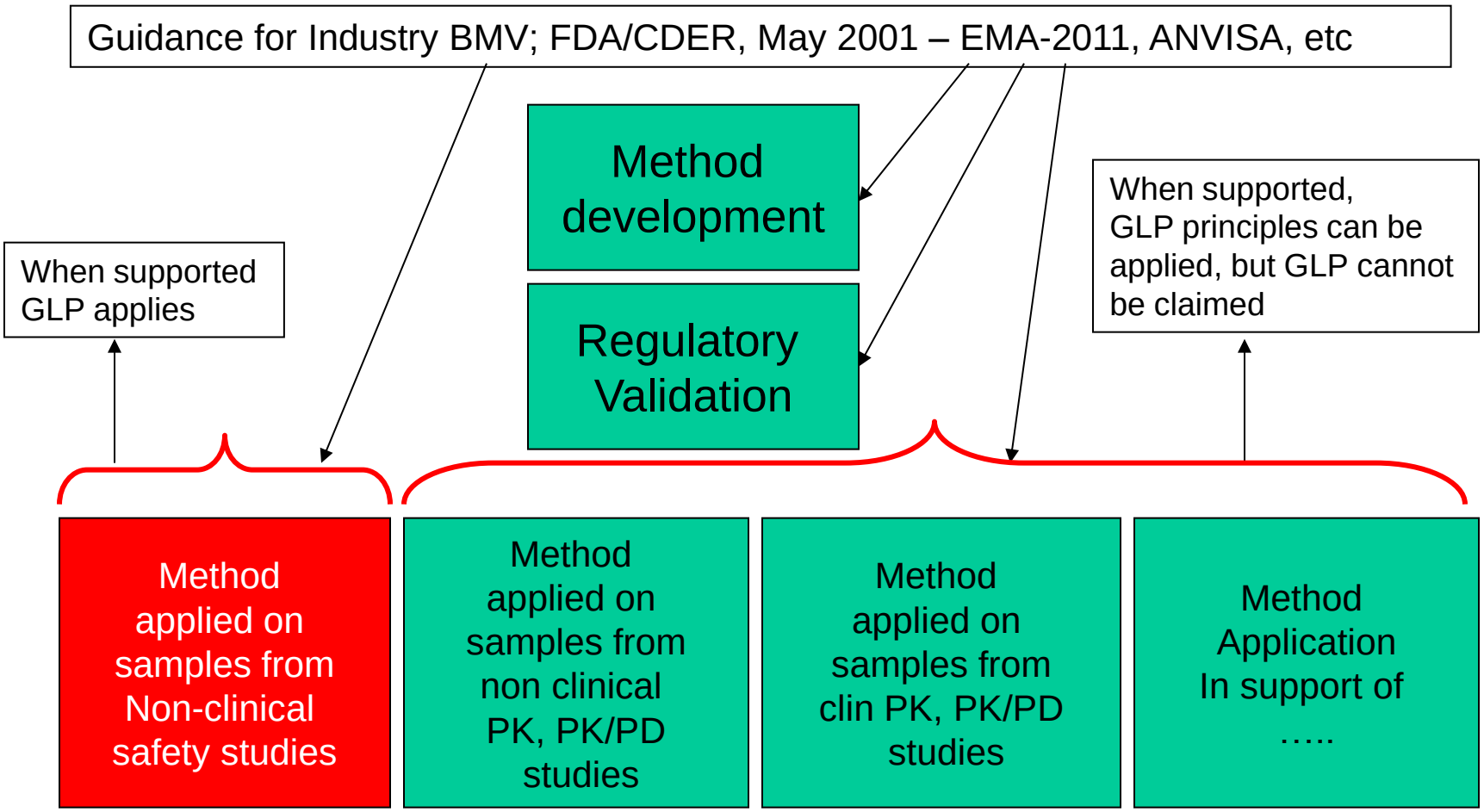
No reference to bioanalysis in GLP regulations :

- OECD Principles on Good Laboratory Practice
- 21CFR58 Good Laboratory Practice For NonClinical Laboratory Studies



BMV does not equal GLP

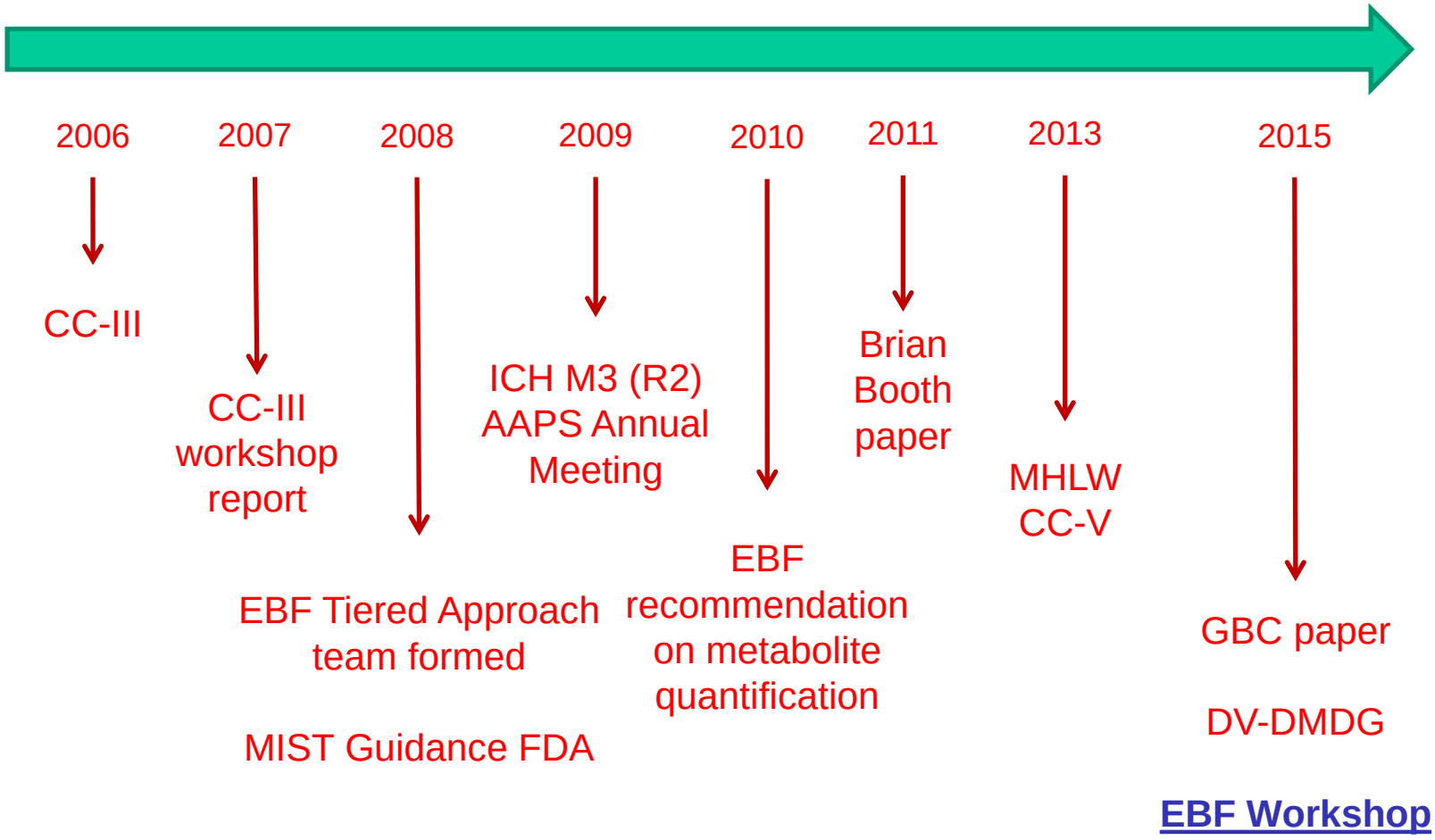
Scope of GLP for Analytical support



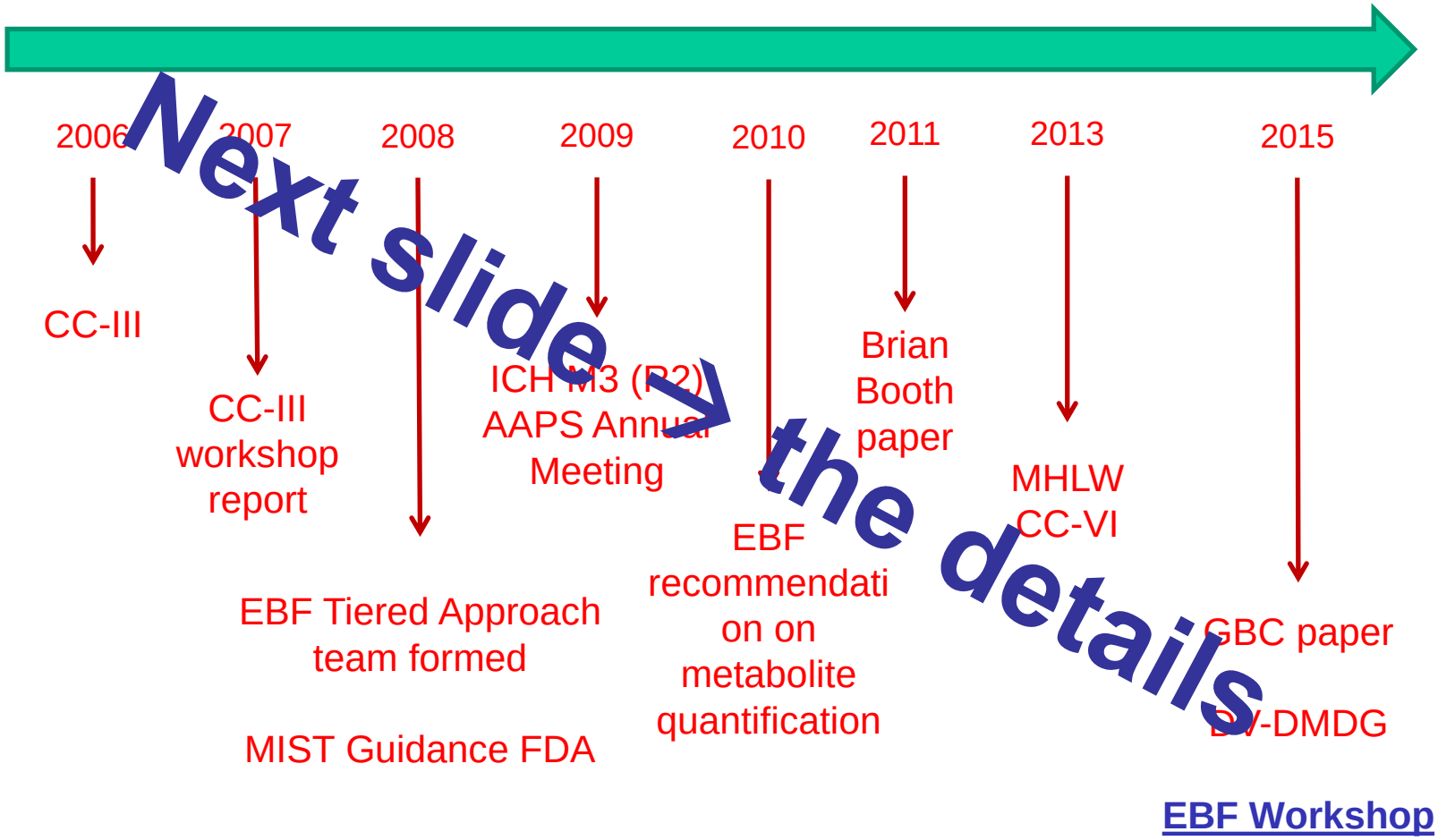
Both from a BMV Guidance as from GLP regulatory perspective we have room to optimize the bioanalytical support

Tiered Approach on bioanalysis of metabolites

3. Tiered Approach on BA of metabolites



3. Tiered Approach on BA of metabolites



EBF Workshop

Crystal City III

- FDA/AAPS meeting on interpretation and refinement of bioanalytical Guidance
- 2007 - Meeting report --> paragraph on tiered approach

"DETERMINATION OF METABOLITES DURING DRUG DEVELOPMENT"

……..Characterization of UMMs should proceed using a flexible, " tiered " approach to bioanalytical methods validation. This tiered approach would allow metabolite screening studies to be performed in early drug development using bioanalytical methods with limited validation, with validation criteria increasing as a product moves into clinical trials. A tiered validation approach to metabolite determination would defer bioanalytical resource allocation to later in the drug development timeline when there is a greater likelihood of drug success. As a minimum, the specifics of this tiered validation process should be driven by scientifically appropriate criteria, established a priori…..

Ref: Workshop/Conference Report — Quantitative Bioanalytical Methods Validation and Implementation: Best Practices for Chromatographic and Ligand Binding Assays The AAPS Journal 2007; 9 (1) Article 4

ICH M3 and EBF Tiered approach team

ICH M3(R2)

- 2009: Guidance on what to measure

EBF

- 2008: EBF Tiered approach team formed
- 2010: After discussing internally for 1.5 y, and building on above and ICH M3 (R2), EBF issued their first recommendation paper* on metabolite quantification → Recommendation on How to measure and When to measure

**Reference: Best practices in a tiered approach to metabolite quantification: views and recommendations of the European Bioanalysis Forum, Bioanalysis (2010) 2(7), 1185–1194*

"FDA" and Tiered approach

- 2011: the principles of the EBF and CC-III paper were acknowledged by Brian Booth (FDA) in his 2011 manuscript*

"The EBF has developed a paradigm for addressing this issue [1]. ……The European Bioanalytical Forum scheme makes very reasonable sense and may be a very valuable tool for industry."

"In summary, the fit-for-purpose paradigm is applicable to several different analytical questions. The general rule that can be applied is that if the data generated will support regulatory action, such as assessing safety and/or efficacy, or supporting labeled-dosing instructions or patient treatment, then the data must be reliable and the analytical assays should be fully validated. In other cases, where the sponsor will use the data internally to make decisions about candidate selection, or continuing product development, the sponsor can use as much analytical method validation as it deems appropriate to make these decisions"

*Reference: in "When do you need a validated assay?" Bioanalysis (2011) 3(24)

FDA and Tiered approach, cntd

- 2013:…and reconfirmed by the FDA. FDA Draft BA BMV Guidance states….

"If a unique or disproportionately high concentration of a metabolite is discovered in human studies, a fully validated assay may need to be developed for the metabolite, depending upon its activity (refer to the FDA guidance for industry Safety Testing of Drug Metabolites)."

"For pivotal studies that require regulatory action for approval or labeling, such as BE or PK studies, the bioanalytical methods should be fully validated. For exploratory methods used for the sponsor's internal decision making, less validation may be sufficient."

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm368107.pdf

Other Guidance or industry reports

- 2013 → MHLW (Japan) refers to CC-III conference report and EBF 2010 Recommendation paper to support tiered approach

- 2012-2015: GBC (Global Bioanalysis Consortium) developed further details on tiered approach, incl. where again metabolites in early development

  Ref.: Tiered Approaches to Chromatographic Bioanalytical Method Performance Evaluation: Recommendation for Best Practices and Harmonization from the Global Bioanalysis Consortium Harmonization Team. The AAPS Journal January 2015, Volume 17, Issue 1, pp 17-23

- 2015: DV-DMDG/EBF meeting in US, included a vivid discussion and challenge on the metabolite quantification / validation practices in early development, a discussion contributing to the initiative to have today's meeting.

  Ref. : Scientific or regulated validation: a tiered approach? Meeting report from a joint EBF/DVDMDG workshop. Bioanalysis 7:14, 1703-1710.

4. Conclusion

- MIST, DDI and bioanalytical Guidance allows a focus on science
- Industry should take the responsibility and opportunity to agree on best practices to integrate best scientific practices with regulations
- This workshop can contribute to bringing this goal into day-to-day practice