AAPS/PSCW 2010
APQ Open Forum

Harmonization of Global Bioanalytical Regulations – Scientific Perspective and Update on Developments

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Introduction

- From a bioanalytical scientists perspective, a few pivotal questions come to mind when we consider the development of bioanalytical regulations:
  - Are there lessons to learn from historical development of bioanalytical regulations?
  - Taking a critical look at status today – what are the top areas that we know need to be addressed?
  - What options as scientists do we have to contribute to the process improvement?
  - Thinking beyond the “now”, how can we accommodate the new challenges on the horizon?

- This presentation will step through these questions and concepts

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Background

- EMA draft Bioanalytical Method Validation (BMV) Guidance
  - Generated a significant scientific response
  - Clearly, scientific community understands the challenge and are willing to contribute to the process
- FDA Updated BMV Guidance
  - Projected for 2011
  - We can expect a similar lively debate and discussion
- Other Regional Developments
  - Expected but unspecific

Current Status

- Quote from APA meeting Sept 2010:

  "Bioanalysis is Stressful"

- Why?
  - Increasing regulatory pressures
  - Increased economic pressures
  - Job cuts and industry consolidation
- However
  - Exciting industry and technology developments coming along
    - Rise of biologics, DBS, HRMS, Biomarker assays
  - Proactive talk about regulatory harmonization and clarification of what is expected
    - Global Bioanalysis Consortium

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Current Status

- Global Bioanalysis Consortium (GBC)
  - Several North American presentations conducted
  - EU and ROW presentations gaining momentum
  - Initial steering committee identified
  - Missions and scope defined
  - Website launched
    - www.globalbioanalysisconsortium.org
  - Harmonization Team (HT) applicants subscribing
  - Harmonization Teams forming in Q1 2011
  - Forecasting Global Bioanalytical Conference in 2012

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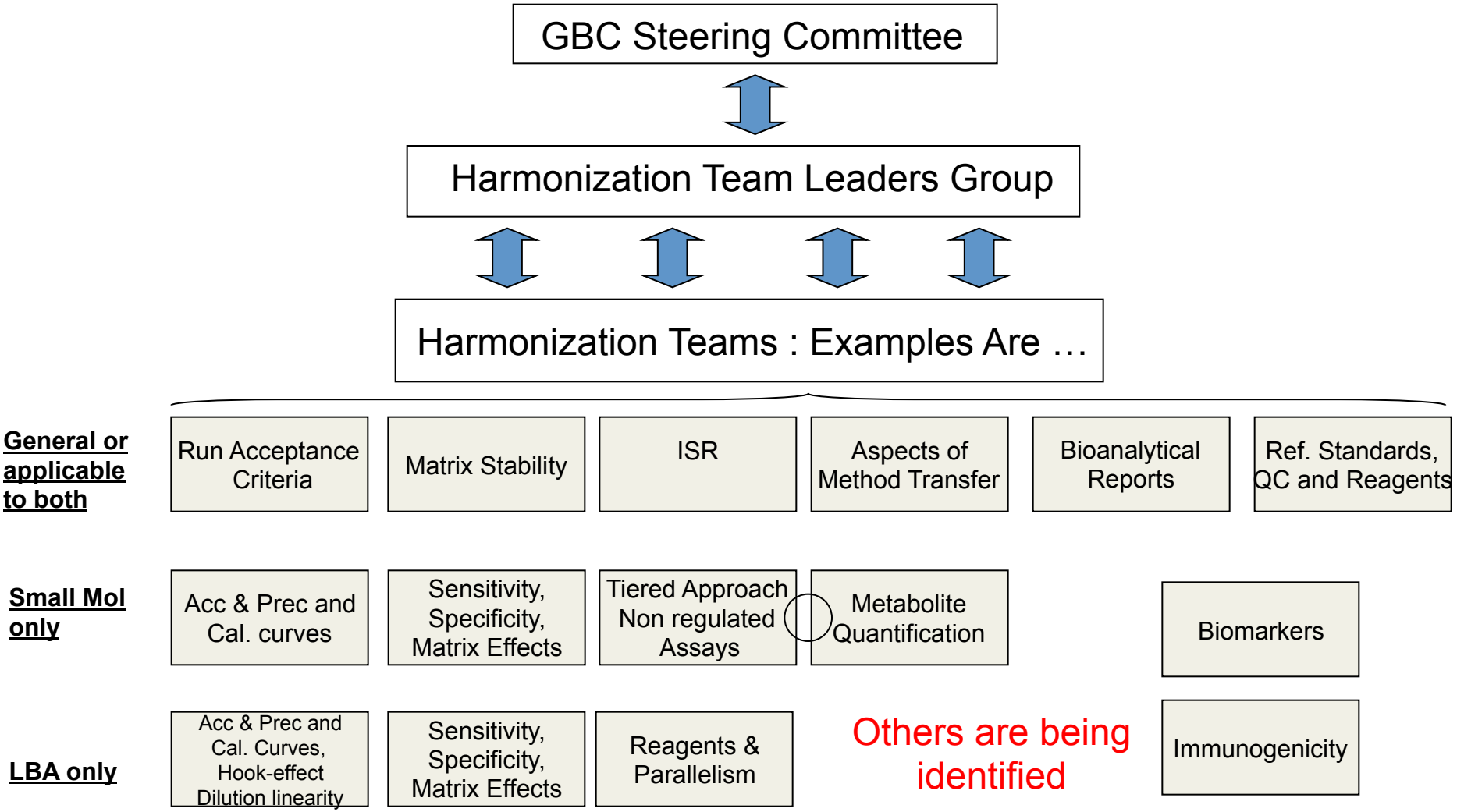
Current Status

- Scientific Feedback to GBC
  - Make sure there's enough large molecule representation
  - General support from US presentations
  - Strong support for defendable scientific rationale to drive the discussions
  - Excellent response to call for HT members
- Regulatory Feedback to GBC
  - Encouraging feedback so far

Which Harmonization Teams?



Consensus Topics

- **Basic 6 principles of Method Validation**
  - Accuracy, Precision, Sensitivity, Selectivity, Stability and Reproducibility (ISR)
  - Basic conduct of the experiments
  - 4/6/15(20) or 4/6/20(25) Rules
- **Incurred sample reanalysis (2/3rd within 20% of the mean)**
  - At least in the US
- **Fundamentals of what goes into a bioanalytical report (MV or sample analysis)**
  - Recent debate around the report generation process and finalization

Topics Requiring Consensus Building

- Challenge of LBA Vrs chromatographic assays
- Accommodating biomarker assays
- Tiered approaches to metabolites
- Will regulatory language accommodate emerging technologies? – chromatographic and LBA
- Statistical approaches V fixed number (e.g. 4/6/15 rule)
- Analyte stability experiments
- Scientific investigations
- Method transfer and cross-validations
- Internal standard criteria
- Other evolving issues

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Emerging Challenges

- FDA Regulatory Process
  - The FDA regulatory process has helped the evolution of our discipline as well as its governance.
  - Has also fostered global consistency
    - Look at the basis of other emerging regulatory language
  - The Form 483 has been an influential part of this.
    - E.g's from ISR to chromatographic peak integration
  - However, on a global stage we are now running into problems
    - Confusion in our community over 483s issued
    - Poor visibility to context of some 483s and what should be inferred
    - Resistance outside of US to comply/adopt some developments that deserve scientific debate first
    - Divergence in emerging global regulatory language specifics

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Emerging Challenges

- Accommodating technology advancements which improve quality, decrease timelines and add value
  - Electronic Laboratory Notebooks (ELN)
  - Microsampling – Dried blood spots
  - Tag-free LBA technologies
  - High Resolution Mass Spectrometry
  - Combination LBA/LC-MS assays
  - Accelerator Mass Spectrometry (AMS)
  - ICP/MS etc

- How can/will global regulatory language accommodate the worthwhile advances?

Conclusions

- Clearly we have much for discussion
- Lessons from the past should not be overlooked
- Possibly 80% of what we do today is in consensus
- The no-consensus issues warrant a global harmonization response. Their resolution will define our rate of progress and extent of improvement.
- There are many more challenges coming over the horizon.
- Regulated bioanalysis may be stressful today but does it need to be tomorrow?

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