Issues in Industry with Current Guidance

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on behalf of the EBF

Focus Workshop

(*In collaboration with the AAPS and JBF*)

Industry input into ICH M10: Experimental data as the cornerstone for a science driven bioanalytical guideline

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The problem statement today

- Multiple regions have issued their own bioanalytical method validation guidance
  - Guidance has morphed into regulatory expectation (exception ANVISA resolutions are law)
  - When guidance is not comprehensive, one region may add a new requirement to their own document
  - Draft guidance has been adopted and is being applied retrospectively
  - Impact: confusion, significant re-work and increased resources when filing in multiple countries
- Demand for bioanalysis support has increased
  - Multiple matrices, early stages of development, multiple analytes
- New technologies are being applied in PK bioanalysis
  - New molecule formats
  - Combination of chromatography and LBA methods
- Areas of ambiguity lead to risk aversion
  - Industry has a tendency to over regulate
  - Validation to standards beyond the intended use of the data ("BE standard")
  - CROs have many 'masters' and fear 483s
  - The definition of a pivotal study is not clear

So where have we been?

The initial cornerstone ....

New Zealand (1972), Denmark (1975), US FDA and OECD (1978)

Important first step

- 1990 - Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies meeting of industry and regulators
  - Became known as the first Crystal City meeting
  - BA method validation and performance mainly for HPLC and GC
  - Summarised by Shah (1992)
  - First set of expectations for PK methods adopted by regulators
  - Basis of guidance today
  - However, we are now suffering from "Copy, Paste, **Add**"

Bioanalytical guidance has evolved

1992 – HC BA and BE studies

1997 – FDA 21 CFR Part 11, Japan conduct of nonclinical studies

1998 – OECD for GLP

2000 – Crystal City II

2001 – FDA bioanalytical method validation guidance

2003 – FDA BA and BE studies, ANVISA bioanalytical method validation guidance

2005 – ANVISA regulation revision, India BA and BE guideline, ICH Q2(R1) validation of analytical techniques, CFDA BA and BE guideline

2006 – Crystal City III

2007 – Crystal City IV

2009 – WHO GCLP

2010 – EMA BE guideline

2011 – CFDA guidance on management of laboratory for clinical trial sample analysis, EMA guideline on bioanalytical method validation

2012 – ANVISA RDC 27 resolution, HC comparative BA studies, EMA GCLP reflection paper

2013 – MHLW bioanalytical method validation (chromatography), FDA draft guidance for bioanalytical method validation, Crystal City V

2014 – MHLW bioanalytical method validation (LBA)

2015 – EMA Triggers for audits of GLP studies, HC stability testing, CFDA bioanalytical method validation

Moving to now ....

- ICH has accepted the call for harmonisation

> ***"ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner" (www.ich.org)***

An example of misalignment

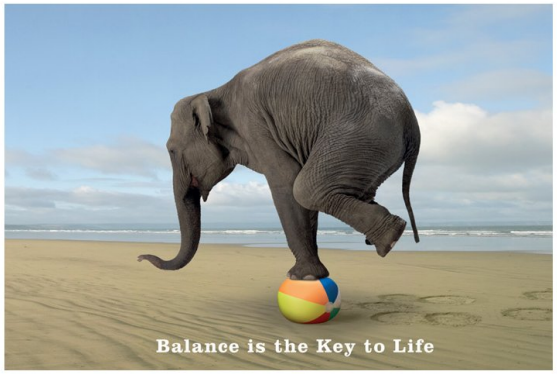
Description	EMA (2011)	FDA (2013)	MHLW (2013/14)
Studies	Clinical including BE studies Non-clinical TK	Clinical including BE studies Non-clinical TK Non-clinical PK	Clinical including BE studies Non-clinical TK
Methods	Chromatography LBA	Chromatography LBA Non-clinical PK Immunological and microbiology	Chromatography LBA
Analytes	Drugs Metabolites	Drugs Metabolites Endogenous compounds Biomarkers	Drugs Metabolites Includes biologics with same amino acid sequence by LBA Excludes endogenous compounds
Biological matrices	Blood, serum, plasma, urine, saliva	Blood, serum, plasma, urine, tissue, skin	Serum, plasma, urine

Definition of a pivotal study need to be clarified

More from Philip later ……

So what do we want from guidance for ICH M10 ....

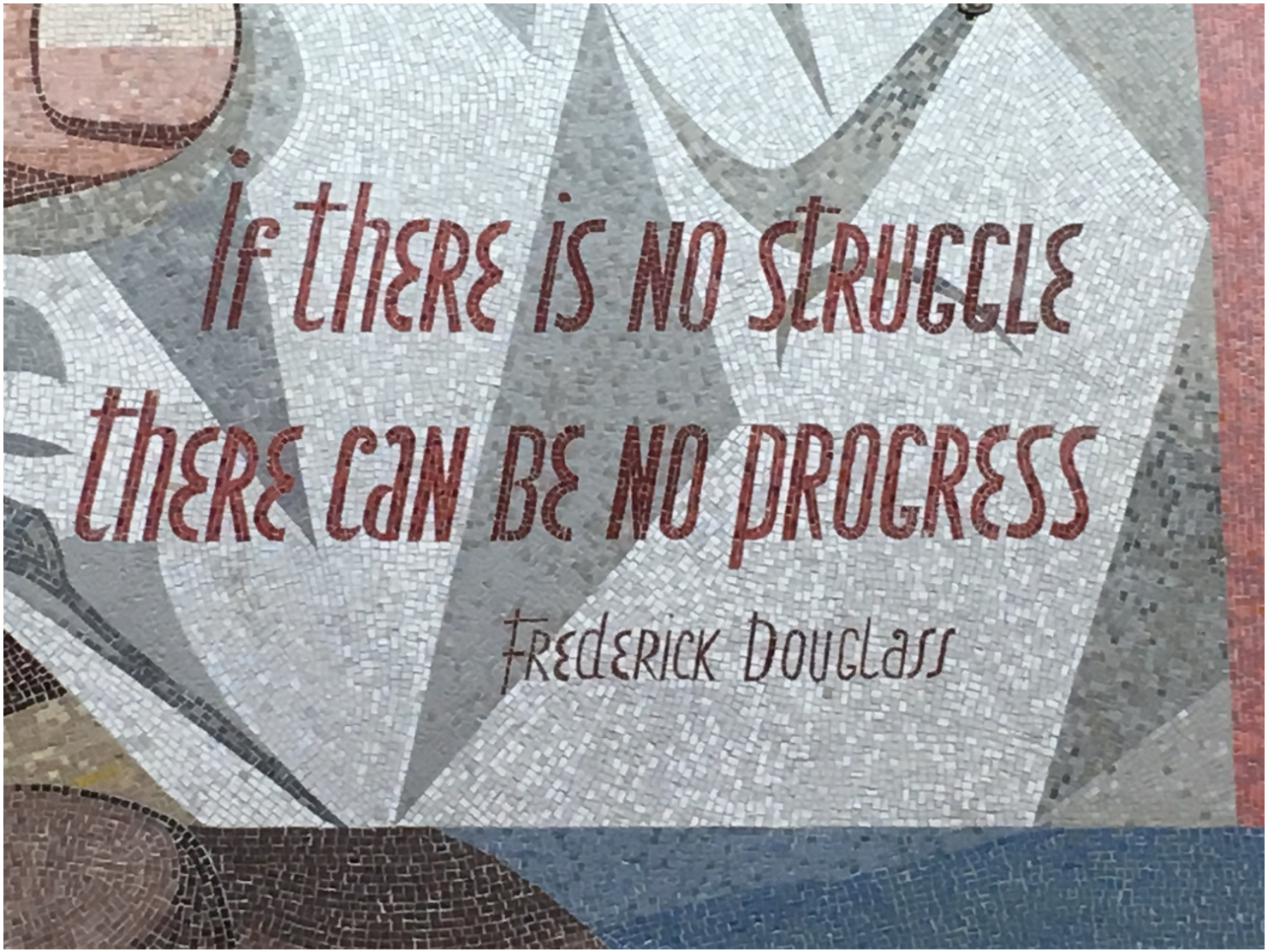
- Adoption from the agencies and industry
- Removal of ambiguity and confusion
  - Same interpretation from industry and regulators
  - Avoid unnecessary citations
  - Simple and easy to follow
- Minimise unneeded work, cost and resources
- Recommendation: that it is not an entirely prescriptive guidance (unless the scope is narrow)
  - Allowance for science and flexibility
  - Should not cover every eventuality
  - Absolute requirements and not something that includes every best practice
  - However, there is a risk of “copy, paste, add” if it is not comprehensive enough
- Recommendation: clearer LBA sections
  - Chromatography has been used as the framework for LBA
  - Removal of any “creep”



What would guidance look like if we started with a blank page today?

Summary and key messages

- Regulated bioanalysis has evolved with guidance from multiple regions that are not always aligned
- Unnecessary work and resources are expended to reconcile differences
- Ambiguity exists and industry takes a conservative approach
- Consider what the data are being used for rather than applying a BE approach for everything
- ICH M10 is a **unique opportunity** for this (and the next) generation of bioanalysts to create guidance that reflects our needs and allows the most resource efficient practices
- The new guidance should focus on the minimum requirements
  - However, there is a risk that if guidance is not comprehensive or specific then other regions will add to their own guidance
  - Same interpretation from both industry and regulators
  - Avoid unnecessary citations from regulators
- **Remember patients are waiting for safe and effective medicines**


If there is no struggle
there can be no progress
Frederick Douglass

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