M-CERSI DISSOLUTION SIMILARITY WORKSHOP

What Does it Mean to Demonstrate Dissolution Similarity?

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THE WORKSHOP

OBJECTIVES

- Clarify the regulatory application of dissolution similarity testing (when & how it can be used)
- Review how the standards for dissolution similarity were established & discuss the definition of similarity
- Delineate & contrast commonly used approaches to address dissolution similarity & to discuss novel methods
- Create a robust decision tree for dissolution similarity assessment
- Delineate the value of similarity testing in light of clinically relevant specifications & safe space
- Provide an opportunity for direct dialogue between Regulatory, Industry & Academic stakeholders to identify gaps in knowledge & potential paths forward (research opportunities in dissolution similarity assessment)

EXPECTED OUTCOMES

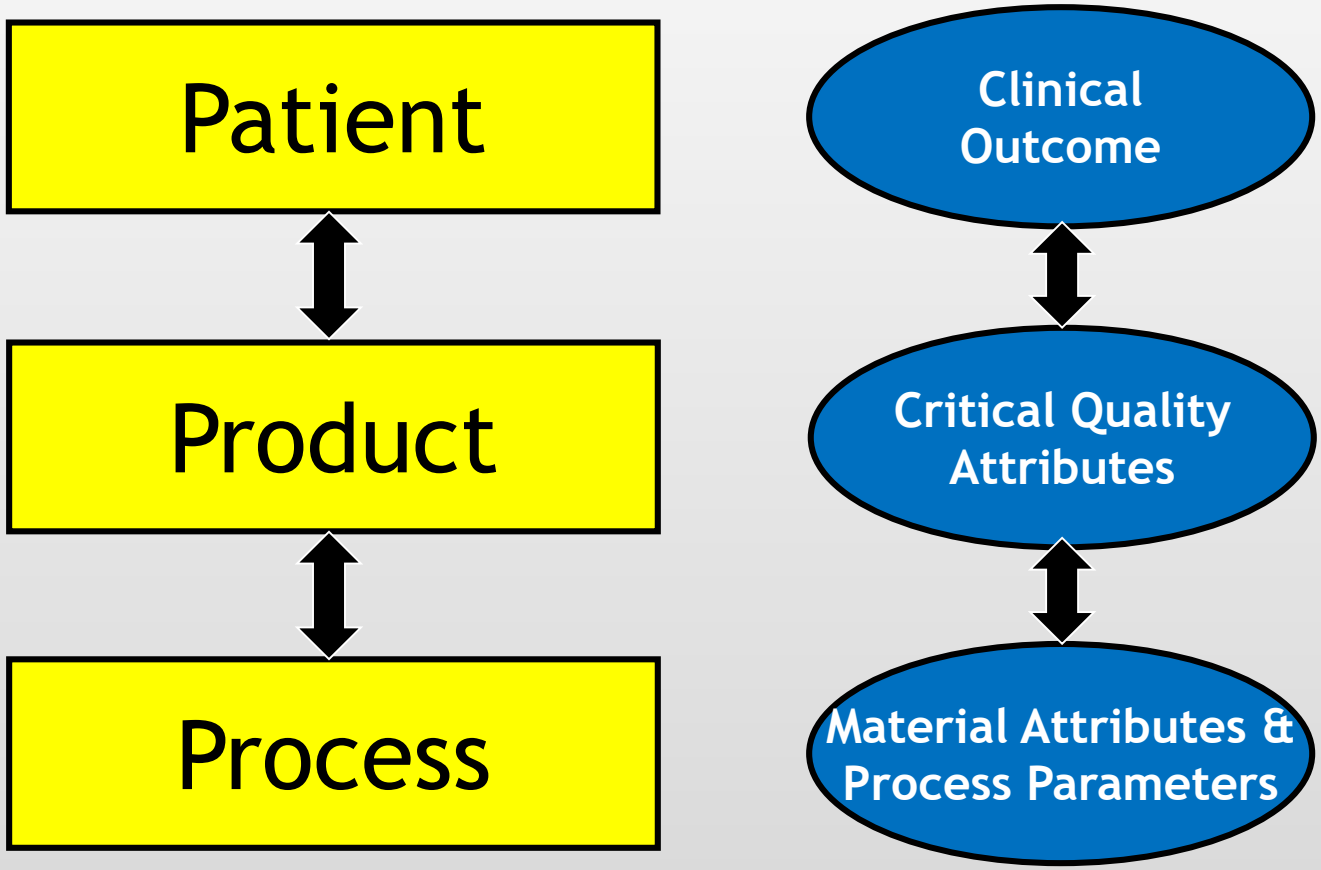
- Understand the meaning of "similarity" in the context of regulatory decision making
- Identify the reliability/predictive-ability of most commonly used mathematical approaches to assess similarity of dissolution profiles
- Identify scientific/regulatory/statistical best practices for the assessment of similarity in dissolution profiles
- Understand the role of similarity testing in consideration of safe-space/clinically-relevant dissolution specifications
- Propose a decision tree (s) on how/when to apply certain method(s) to assess for similarity testing.
- Develop manuscripts that summarize the workshop presentations & breakout session discussions.

I HAVE A DREAM THAT . . .

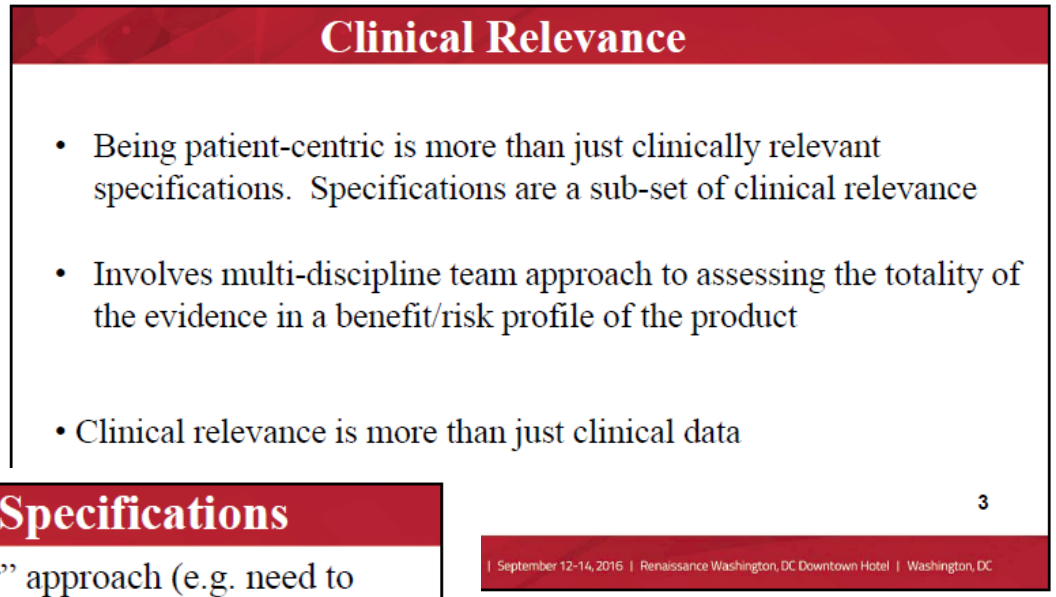
- *Patient variability can be effectively incorporated in IVIV product performance models*
- *IVIV models replace clinical studies to demonstrate bioequivalence*
- *A risk- based definition of similarity will harmonize regulatory expectations for demonstrating bioequivalence*
- *ICH M9 BCS Biowaivers will harmonize global regulatory expectations for bioequivalence*
- *Peak vessels are accepted to mitigate coning*

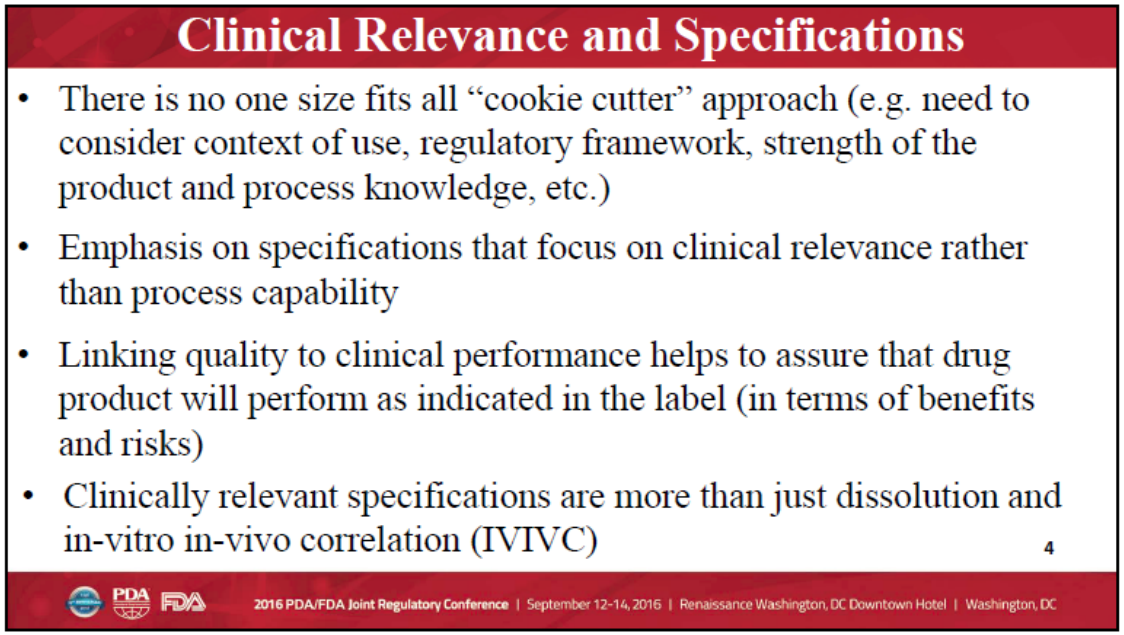
A clinically relevant specification is composed of critical quality attributes & acceptance criteria that predictably assure patient safety & efficacy.

LINKING PRODUCT QUALITY & PROCESS ROBUSTNESS TO THE PATIENT



PERSPECTIVE FROM FDA POLICY OFFICE





Laurie Graham, PDA, 2016

REGULATORY QUERIES

"The acceptance criteria applied in the specification of the finished product has been set without taking clinical qualification into account and are in many cases considerably less stringent compared to the clinical batches. The applicant should clinically justify the limits or tighten the acceptance criteria."

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

"We do not agree with the approach to establish acceptance criteria based exclusively on manufacturing capability. Your proposed limits and justification should reflect the impact of each individual critical quality attribute on product performance and where possible, actual clinical experience."

FDA U.S. FOOD & DRUG ADMINISTRATION

Pfizer

COMPARATIVE PERSPECTIVES

CLINICAL

- Without IVIVC & PK/PD correlation, most clinical studies are not sensitive enough to detect quality deviations
- At best, for efficacy, an IVIVC/IVIVR must include dose-response context to ensure assay sensitivity
- Epidemiological studies & spontaneous reports are not necessarily definitive indicators of quality differences

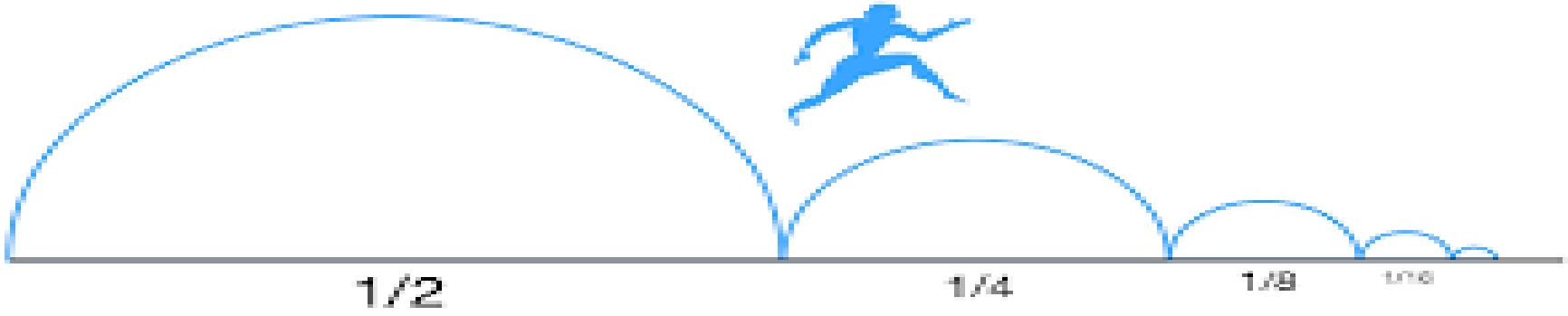
  Exceptions: Heparin & Procrit

QUALITY

- IVIVC
  - Primary bridge to clinical environment
  - Identify ADME characteristics where IVIVC is unlikely to be developed
- Industry Experience
  - Generally confined to IR → MR switch
  - Route of administration may determine viability
  - ***One size does not fit all -*** inconsistent criteria & regulatory acceptance
  - Reset approved commercial product specifications – retrospective IVIVC often non-robust

Adapted from Peter Honig, DIA, 2010, ICDD 2015 & 2018/James McLeod, DIA, 2010

IVIV MODELS & PATIENT VARIABILITY



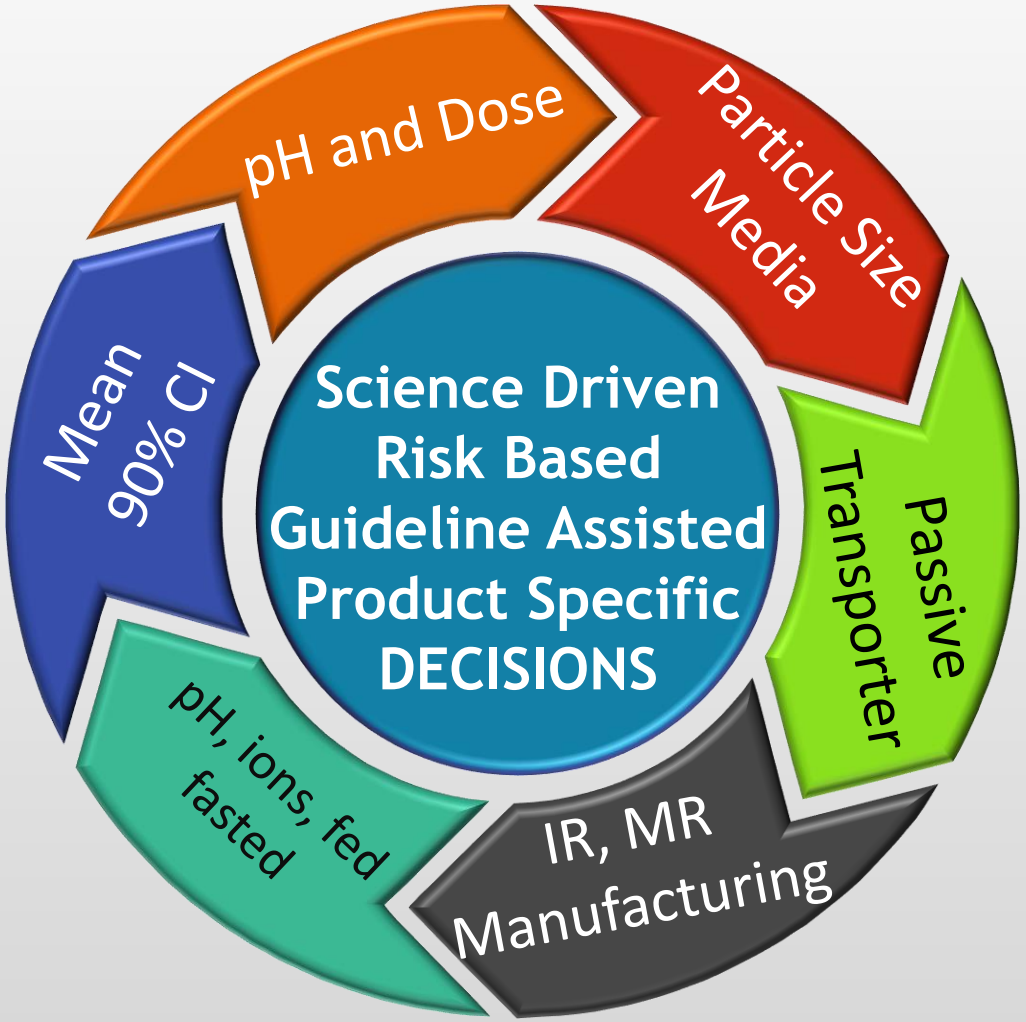
- Patient Variability
  - Epidemiology not always understood
- IVIV Models
  - Account for patient variability
  - Introduce product & process variability

IVIV MODELS LEVERAGE *IN VIVO* DATA

- Mechanism of Action - Biomarkers
- PK – Absorption & Metabolism
- Phenotype/Genotype
- GI Transit
- Toxicology
- Transgenic Mice PK
- Animal Models

IVIV MODELS INTEGRATE KEY CRITERIA

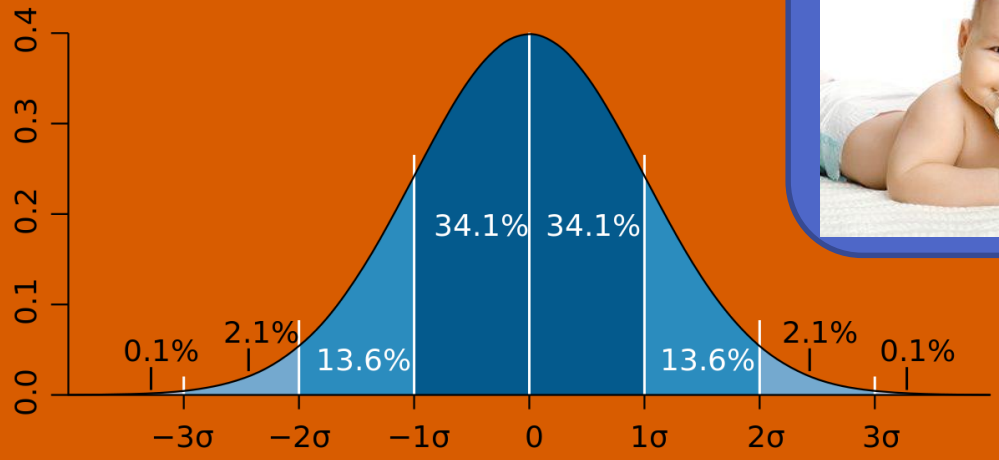
- **Solubility**
- Dissolution
- Permeability
- Solid Oral
- GI Physiology
- C_{max}, AUC
- Clinical Relevance



HOW PRECISE DOES DEMONSTRATION OF SIMILARITY HAVE TO BE?

WHAT IS SIMILARITY?

Mean +/- 3σ?



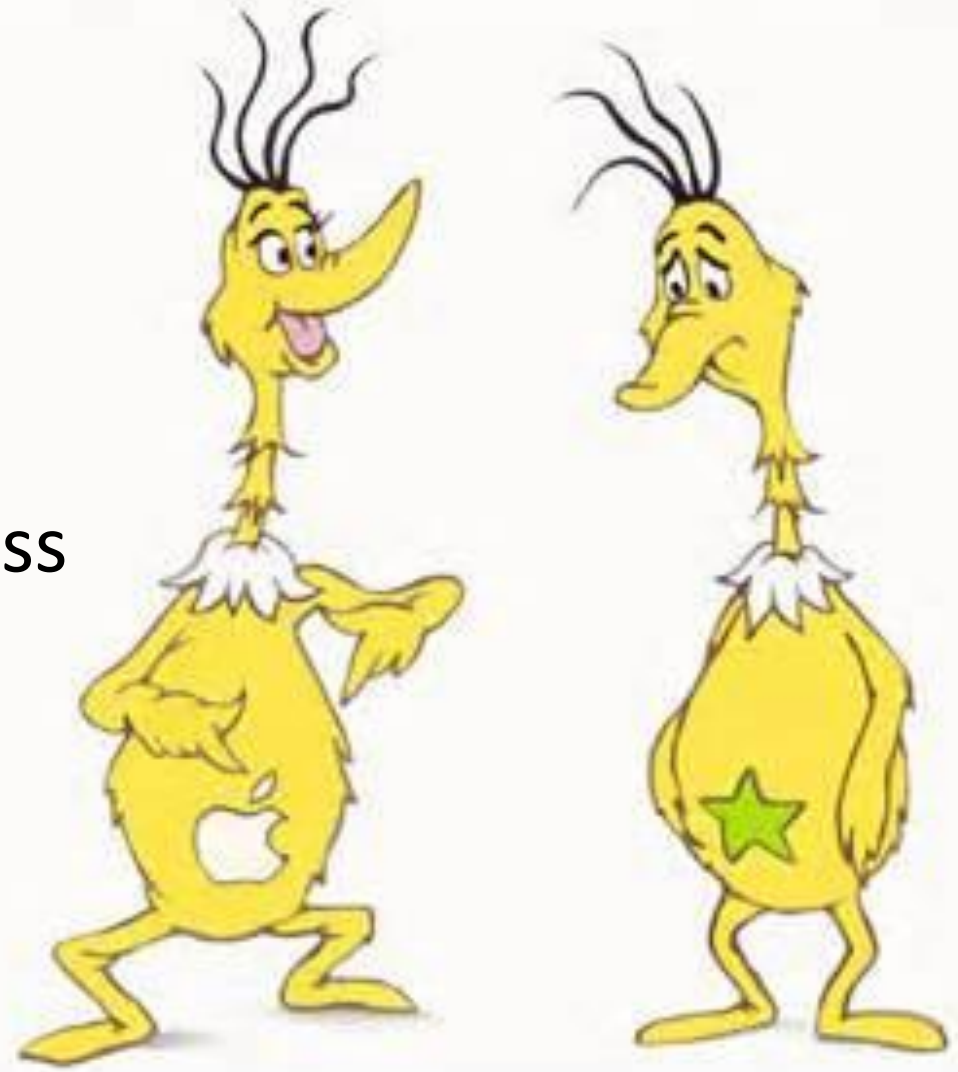
Identical?

Close Enough?

Similarity = 1/Variability?

HOW MUCH VARIABILITY IS ACCEPTABLE?

- Patient
- Product
- Manufacturing Process
- Analytical Methods



IS THE DEFINITION OF SIMILARITY A MEASURE OF PREDICTABILITY?

Variability → Predictability

Similarity is a comparison that accounts for all sources of variability that may have an impact on *in vivo* product performance, reliably demonstrates the risk of that impact is adequately controlled & consistently predicts appropriate *in vivo* product performance.

ALTERNATIVE PERSPECTIVE OF SIMILARITY - DISCRIMINATION

- *A method that is able to differentiate products manufactured under target conditions vs. drug products that are intentionally manufactured with meaningful variations, i.e., aberrant formulations & manufacturing conditions, for the most relevant critical variables, i.e., drug substance particle size distribution, tablet compression force or hardness*
- *A method that is able to reject batches that are not bioequivalent*

DISSOLUTION CONTINUUM

Uncertain or high risk that variability may impact in vivo product performance & Low degree of predictability

- IR SOD
- Non-narrow therapeutic index drug
- Not a titrated drug
- BCS Class I or III
- No steep dose – response curve
- Does not require therapeutic monitors
- T_{max} not critical - no claim of rapid onset
- Standard conditions for BCS-I & III

Very low risk that variability impacts in vivo product performance & High degree of predictability

DISSOLUTION SIMILARITY

QC **Discrimination** **IVIVR** **BCS Biowaiver** **IVIVC**

ICH M9 HARMONIZATION WILL . . .

- Create a common understanding of the applicability of BCS-based biowaivers & standard criteria for waiver justification
- Reduce unnecessary human/patient exposure
- Reduce costs/time to conduct in vivo studies
- Simplify regulatory requirements & expedite post approval changes

BASED ON SIMILARITY

ICH M9 BCS BIOWAIVERS

Scope

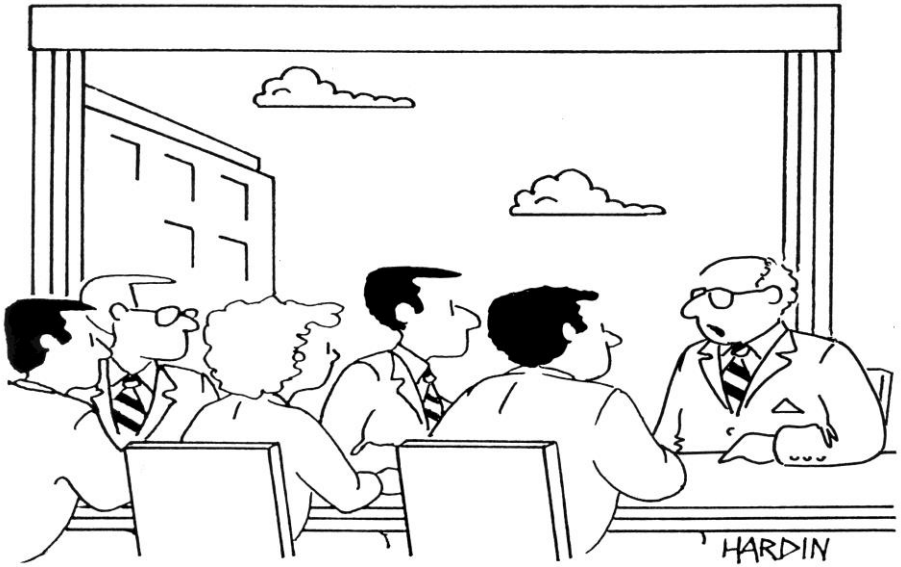
This guideline will provide recommendations to support the criteria for biopharmaceutics classification of medicinal products & for the waiver of bioequivalence studies.

Objectives:

- Harmonization of regional guidelines to streamline global drug development
- Harmonization of data needed for classification of drugs into BCS I or III - Solubility & Permeability
- Harmonization of data needed for a waiver of *in vivo* BE - Dissolution & formulations/excipient comparability

BASED ON SIMILARITY

FUTURE TANGIBLE REGULATORY OPPORTUNITIES



"We've considered every potential risk except the risks of avoiding all risks."

RISK MANAGEMENT