FDA/MCERSI

PHARMACOLOGY GUIDANCES ADVANCING DRUG DEVELOPMENT & REGULATORY ASSESSMENT: ROLE & OPPORTUNITIES

Do FDA Clinical Pharmacology Guidances Adequately Support Product Development & Lifecycle?

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White Oak, MD

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ABSTRACT

Demonstrating consistency and control for *in vivo* performance from late discovery through a product's development and lifecycle demands careful and concerted planning to effectively demonstrate seamless bioequivalence and avoid delays. Nearly all product development decisions, i.e., salt selection, establishing absolute bioavailability, dosage form & formulation selection, dissolution media/parameter selection criteria, manufacturing facility selection and scale-up, continuous improvement, etc., warrant demonstration of bioequivalence.

FDA guidances generally provide clear expectations with respect to demonstrating product performance control and consistency. Nevertheless, a measure of uncertainty remains when establishing definitive criteria for IVIVR modeling and simulations. Drug developers routinely agonize over appropriate change thresholds that may trigger the need for clinical BE studies especially where the regulatory expectations differ globally.

This presentation describes how decision-making, with respect to CMC changes, during development and through a product lifecycle, depends on appropriately assessing the impact on product performance (BE) in conjunction with relevant FDA guidances.

CONTENT

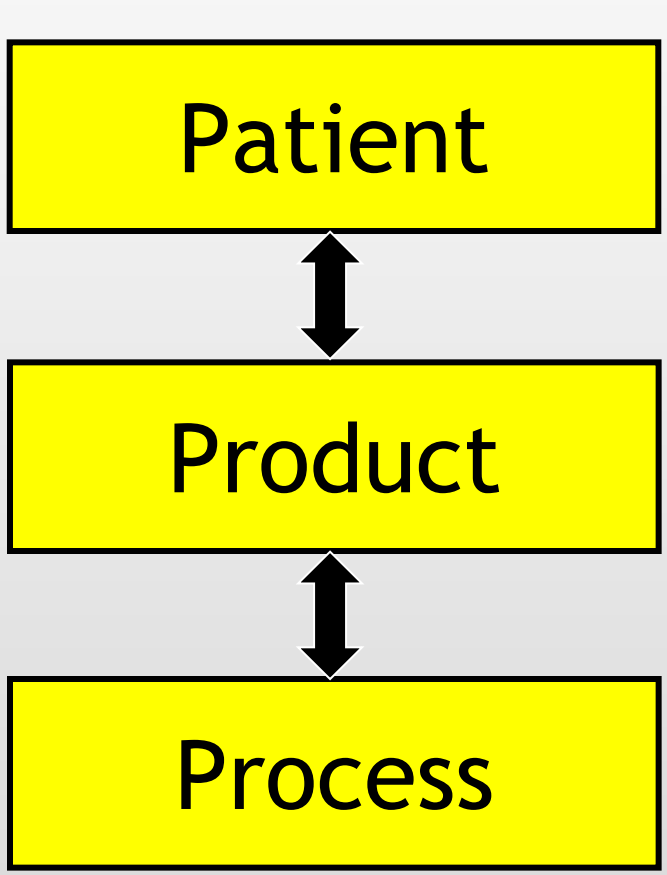
- Decision-Making During Product Development
  - Similarity
- Decision-Making Through Product Lifecycle
  - Continual Improvement (Post-Approval Optimization)
  - Alternative Dosage Forms & Administration, e.g., Pediatric

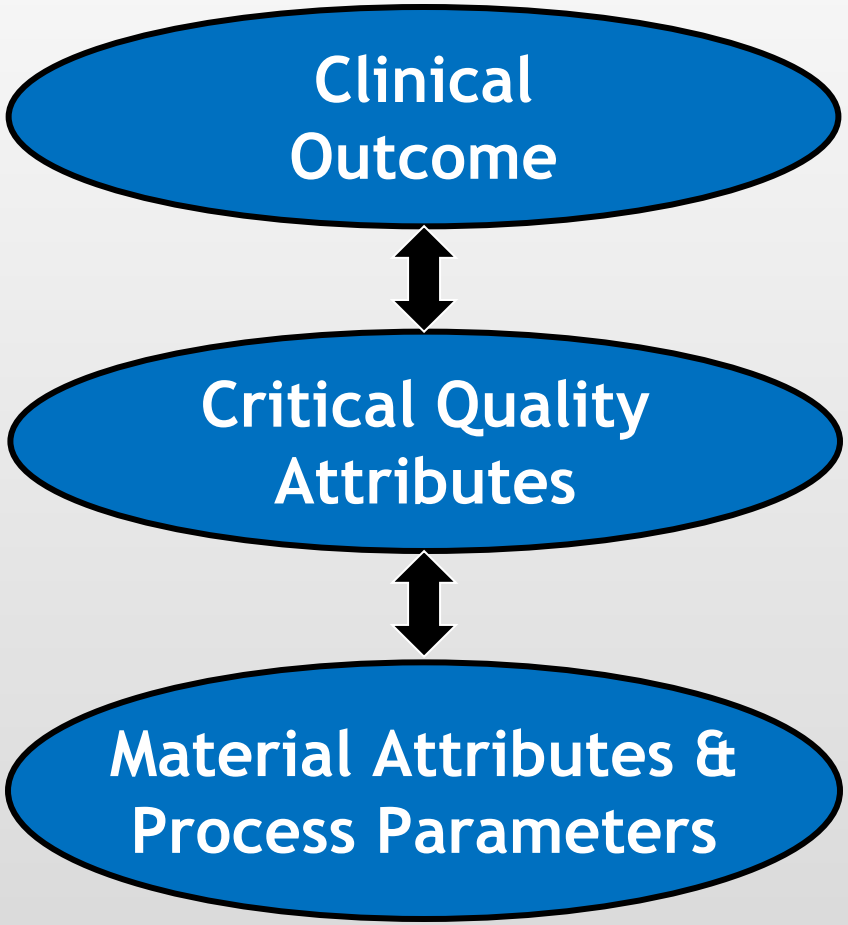
DECISION-MAKING DURING PRODUCT DEVELOPMENT

A large proportion of biopharmaceutics guidance focuses on demonstrating bioequivalence

- During early development criteria for demonstrating clinical relevance are established (Phase 1/2 Clinical Studies)
- During late development established criteria confirm & demonstrate bioequivalence for commercialization (Product & Process Commercialization)

LINKING PRODUCT QUALITY & PROCESS ROBUSTNESS TO THE PATIENT





John Jenkins, DIA, Washington, DC, 2010

DEMONSTRATING BIOAVAILABILITY

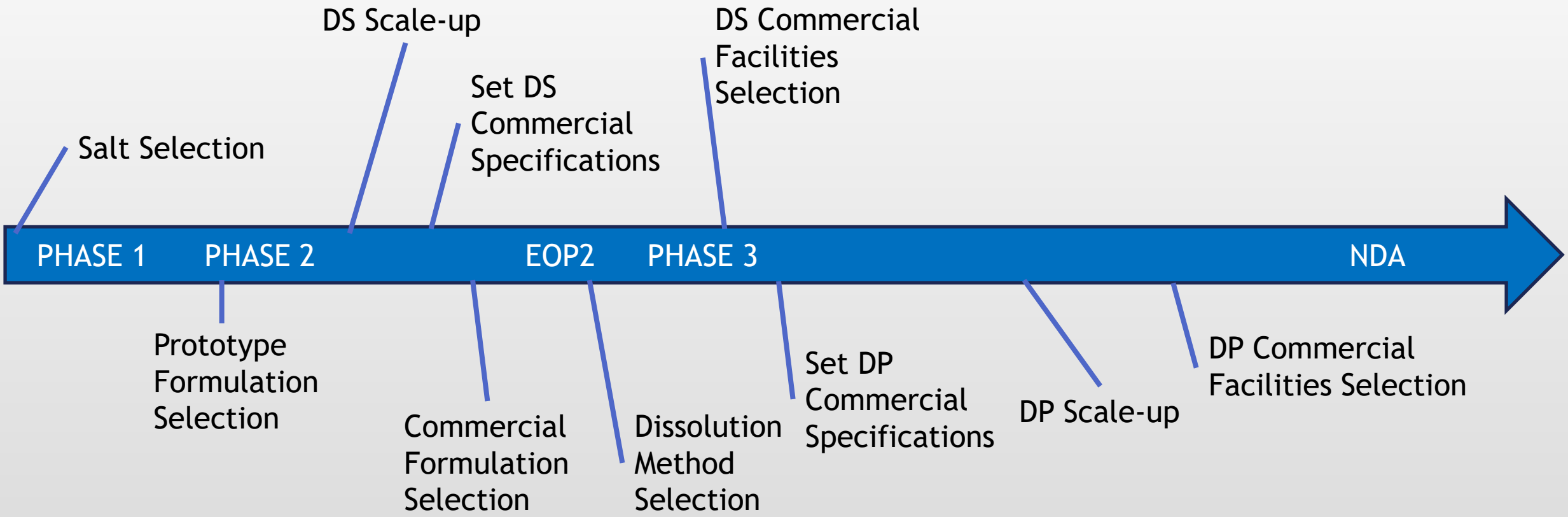
Bioavailability Studies Submitted in NDAs or INDs – General Considerations Guidance for Industry
April 2022

- In general, this guidance is <u>comprehensive enough</u>
- Questions worth considering:
  - What are the development advantages of establishing absolute bioavailability?
  - Can bioavailability attributes of a product be integrated with concepts of *Quality by Design*?
  - What about patient variability?

DEMONSTRATING BE DURING DEVELOPMENT

- Industry relies on FDA guidances to establish boundaries prior to & during early development
- During late development, commercial needs drive decision-making
- Questions worth considering:
  - After/during pivotal clinical trials, how much change is acceptable w/o need for clinical BE study?
  - When are in vitro surrogate models acceptable for demonstrating BE?
  - Can a prospective understanding of process parameters & material attributes provide adequate confidence in demonstrating BE, i.e., mfg. scale up?

DECISIONS DURING DEVELOPMENT



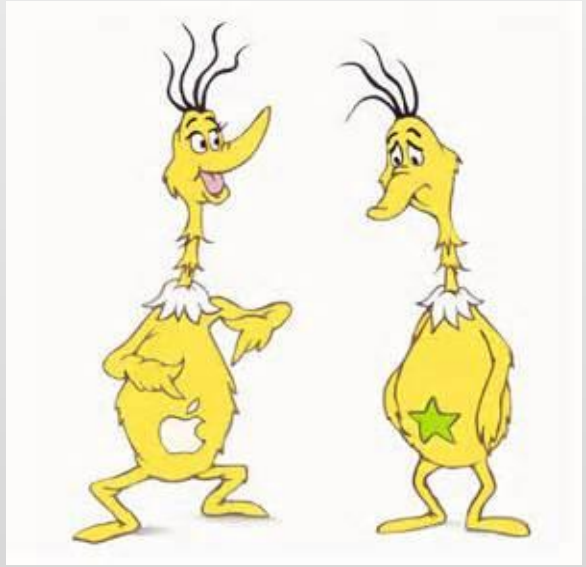
SIMILARITY IS A MEASURE OF PREDICATBILITY

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.

How much variability is acceptable?

- IVIVI Models account for product, process & analytical variability
- Patient - Epidemiology not always understood

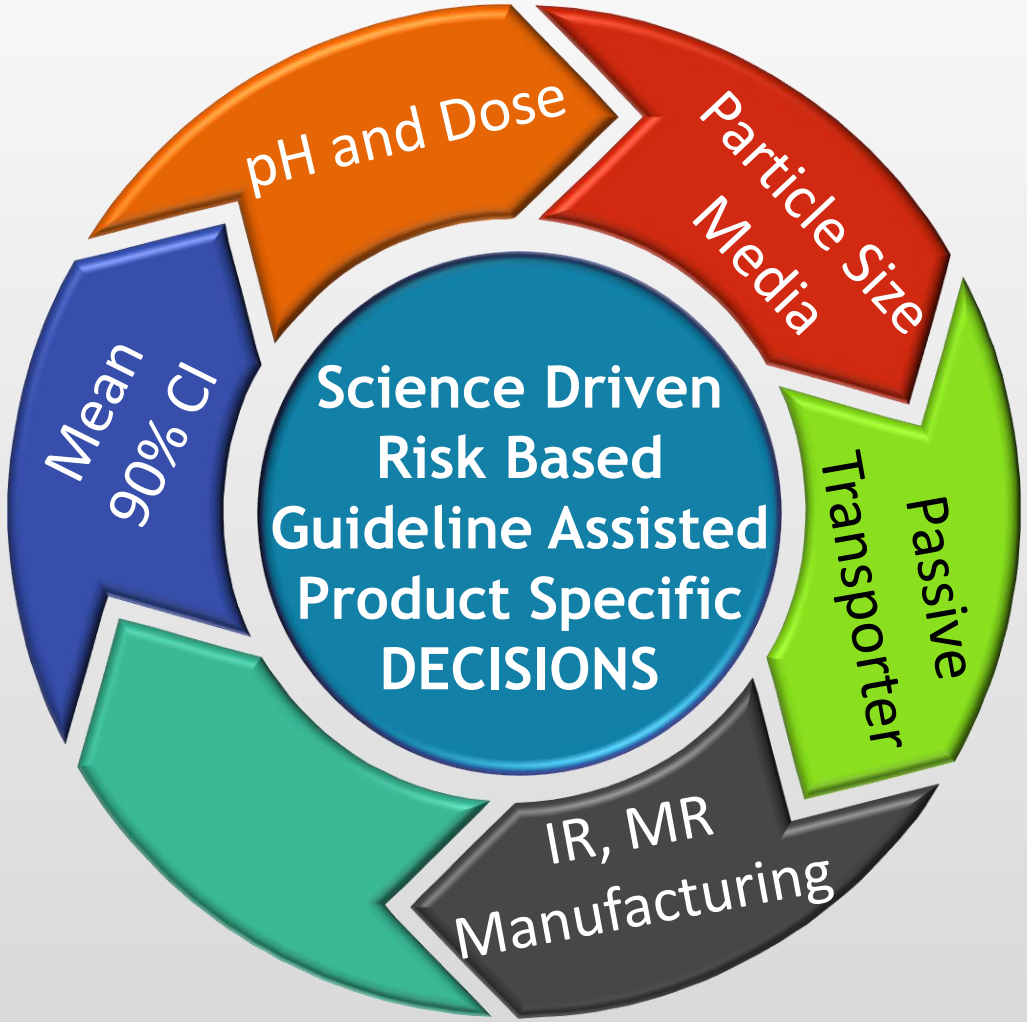


MODELS CAN COMPRESS PRECLINICAL DEVELOPMENT TIME

- Several *Approved*, in vitro pharmacology models, PK/PD, demonstrate more robust human *in vivo* predictability relative to surrogate animal models
- Gastroplus™ demonstrates surrogate GI Transit performance
- In silico DEREK Nexus®/SARAH/TOPKAT computational models provide robust comparability of SAR for toxicology thresholds
- Predictive permeability assays, i.e., CACO-2 measure drug absorption

IVIV MODELS INTEGRATE KEY CRITERIA

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



IVIVC/IVIVR COMPARATIVE MODELS

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

DECISION-MAKING THROUGH PRODUCT LIFECYCLE

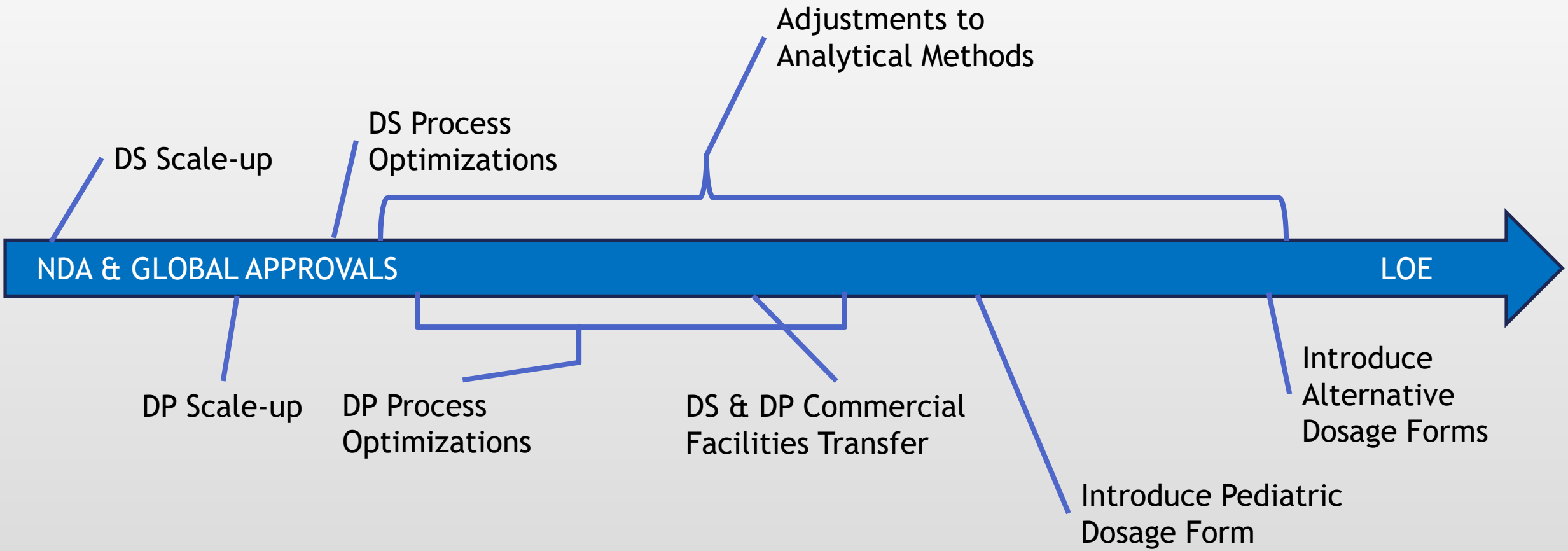
- During commercial lifecycle process & product improvements must demonstrate *equivalent* product performance
  - Continual Improvement to increase productivity, improve quality assurance & reduce costs
  - Introduce alternative dosage forms & improve administration for patient compliance

DEMONSTRATING BE THROUGH PRODUCT LIFECYCLE

SUPAC IR November 1995 *& SUPAC MR* September 1997

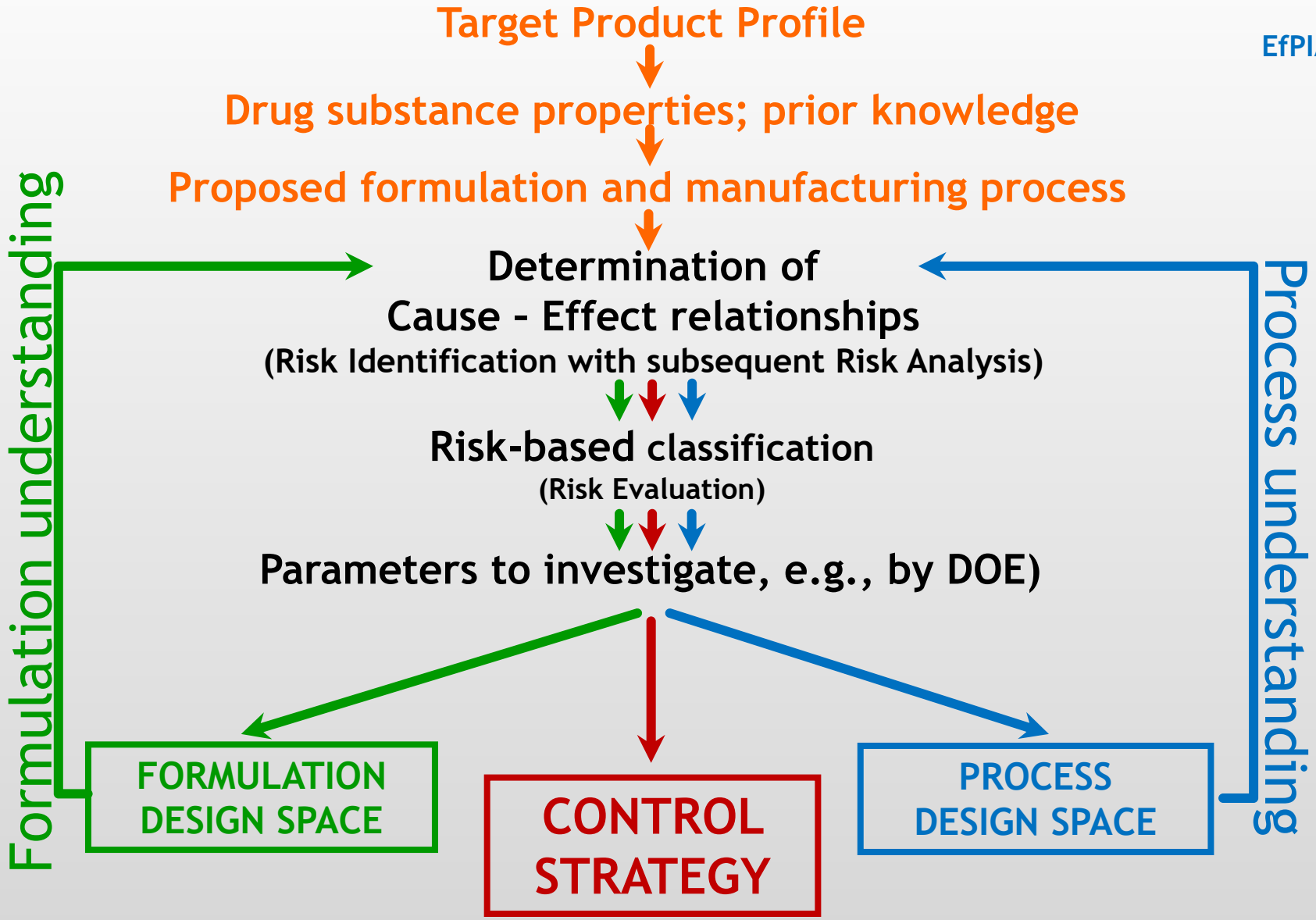
- SUPAC guidances have been exceptionally useful during development
- Questions worth considering:
  - Can FDA introduce risk-based approaches to revisions of the SUPAC guidances?
    - ✓Can FDA update SUPAC to incorporate concepts from *Quality by Design*?
    - ✓Can the Target Product Profile that identifies Critical Quality Attributes of the drug product be leveraged to increase in vitro BE options?
    - ✓How does a robust control strategy translate to risk-based flexible approaches for demonstrating BE?

DECISIONS THROUGH PRODUCT LIFECYCLE

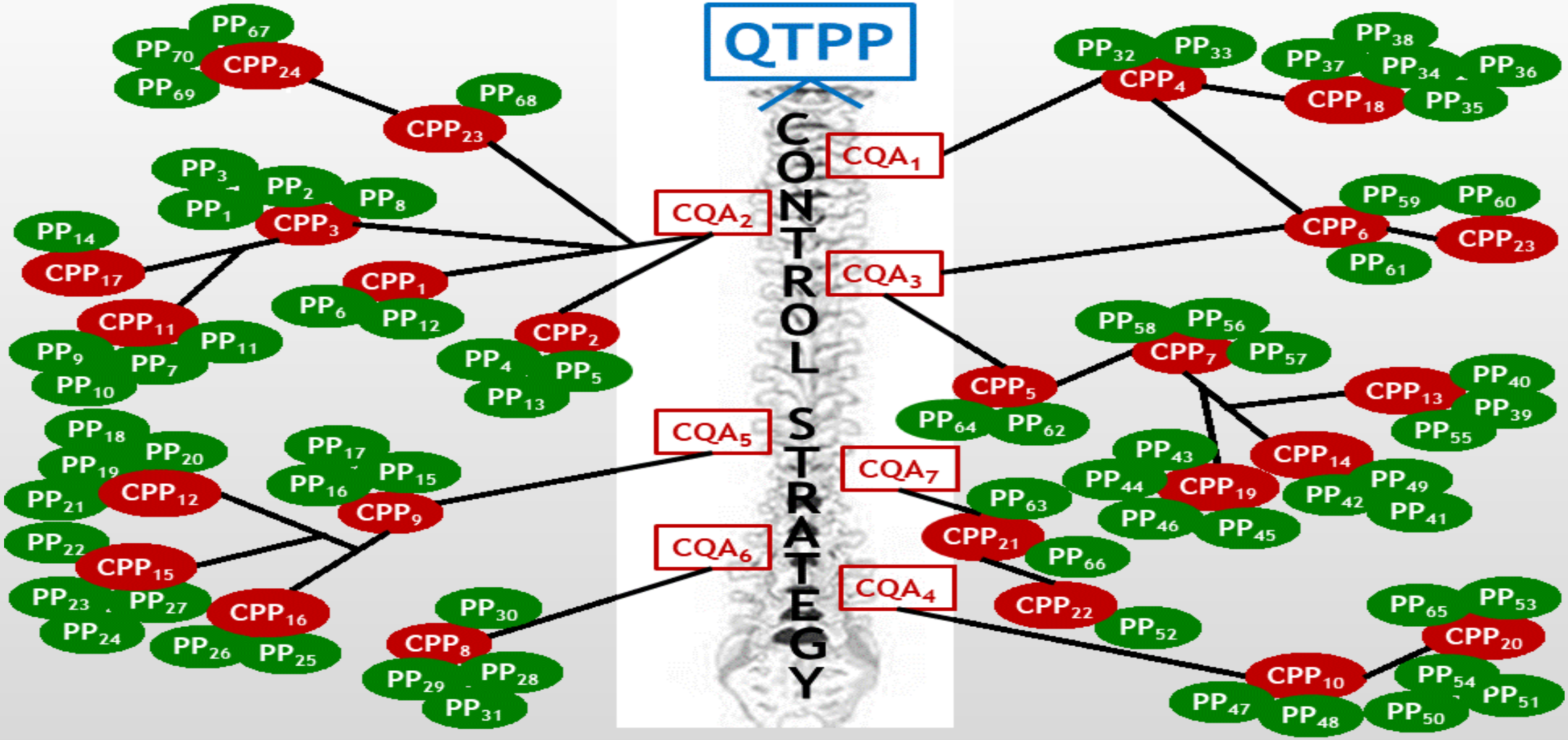


A PROSPECTIVE APPROACH TO DEVELOPMENT

EfPIA Working Group, 2005



FUNCTIONAL RELATIONSHIPS



FUNCTIONAL RELATIONSHIPS → CONTROL STRATEGY

Risk Assessment

KQA1 associated with KPP1,n
KQA2 associated with KPP1,n
KQA3 associated with KPP1,n
KQA4 associated with KPP1,n
KQA5 associated with KPP1,n

Plan Execution (DOE, Models,SOS)

$KQA_1 = f\ (KPP_2, KPP_3, KPP_6)$
$KQA_2 = f\ (KPP_4)$
$KQA_3 = f\ (KPP_1, KPP_4, KPP_5)$
$KQA_4 = f\ (KPP_1, KPP_3, KPP_4, KPP_6)$
$KQA_5 = f\ (KPP_2, KPP_5)$

Work Process

CDT Prep Process

CONTROL STRATEGY

$CQA_1 = f\ (KPP_1, CPP_4, KPP_5)$

$CQA_2 = f\ (CPP_2, KPP_5)$

Describe in CTD S.2.6 & P.2

$KQA_3 \rightarrow CQA_1$

$KQA_5 \rightarrow CQA_2$

$KQA_1 = f\ (KPP_2, KPP_3, KPP_6)$
$KQA_2 = f\ (KPP_4)$
$CQA_1 = f\ (KPP_1, CPP_4, KPP_5)$
$KQA_4 = f\ (KPP_1, KPP_3, KPP_4, KPP_6)$
$CQA_2 = f\ (CPP_2, KPP_5)$

Consider severity of impact, probability of deviation & detectability of KPP relative to each CQA

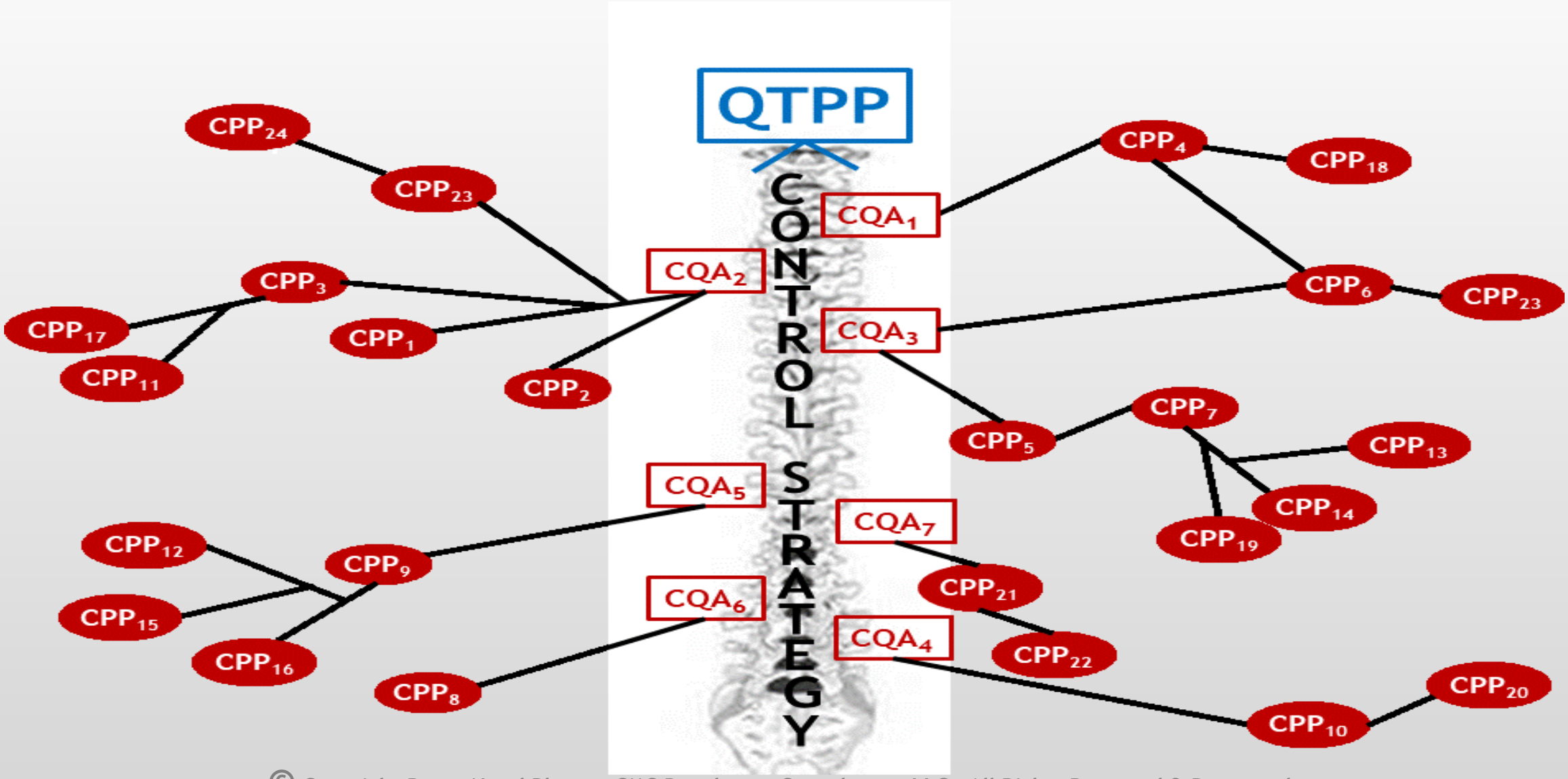
Regulatory Alignment

$KPP_1 \overset{?}{\rightarrow} CPP_1$
$KPP_4 \overset{?}{\rightarrow} CPP_4$
$KPP_2 \overset{?}{\rightarrow} CPP_2$

$KQA_1 = f\ (KPP_2, KPP_3, KPP_6)$
$KQA_2 = f\ (KPP_4)$
$CQA_1 = f\ (KPP_1, KPP_4, KPP_5)$
$KQA_4 = f\ (KPP_1, KPP_3, KPP_4, KPP_6)$
$CQA_2 = f\ (KPP_2, KPP_5)$

Drug Product CQAs generally serve as the drug product specification

CQA = fCPP$_n$



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**

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 in in vitro dissolution*

RELEVANT GUIDANCE

- Bioavailability Studies Submitted in NDAs or INDs – General Considerations | FDA
- Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations | FDA
- Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications Guidance for Industry | FDA
- M9 Biopharmaceutics Classification System-Based Biowaivers | FDA
- SUPAC-IR: Immediate-Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation | FDA
- SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation | FDA
- M10 BIOANALYTICAL METHOD VALIDATION | FDA
- Model-Informed Drug Development Paired Meeting Program | FDA