Establishing Clinically Relevant Drug Product Specifications: FDA Perspective

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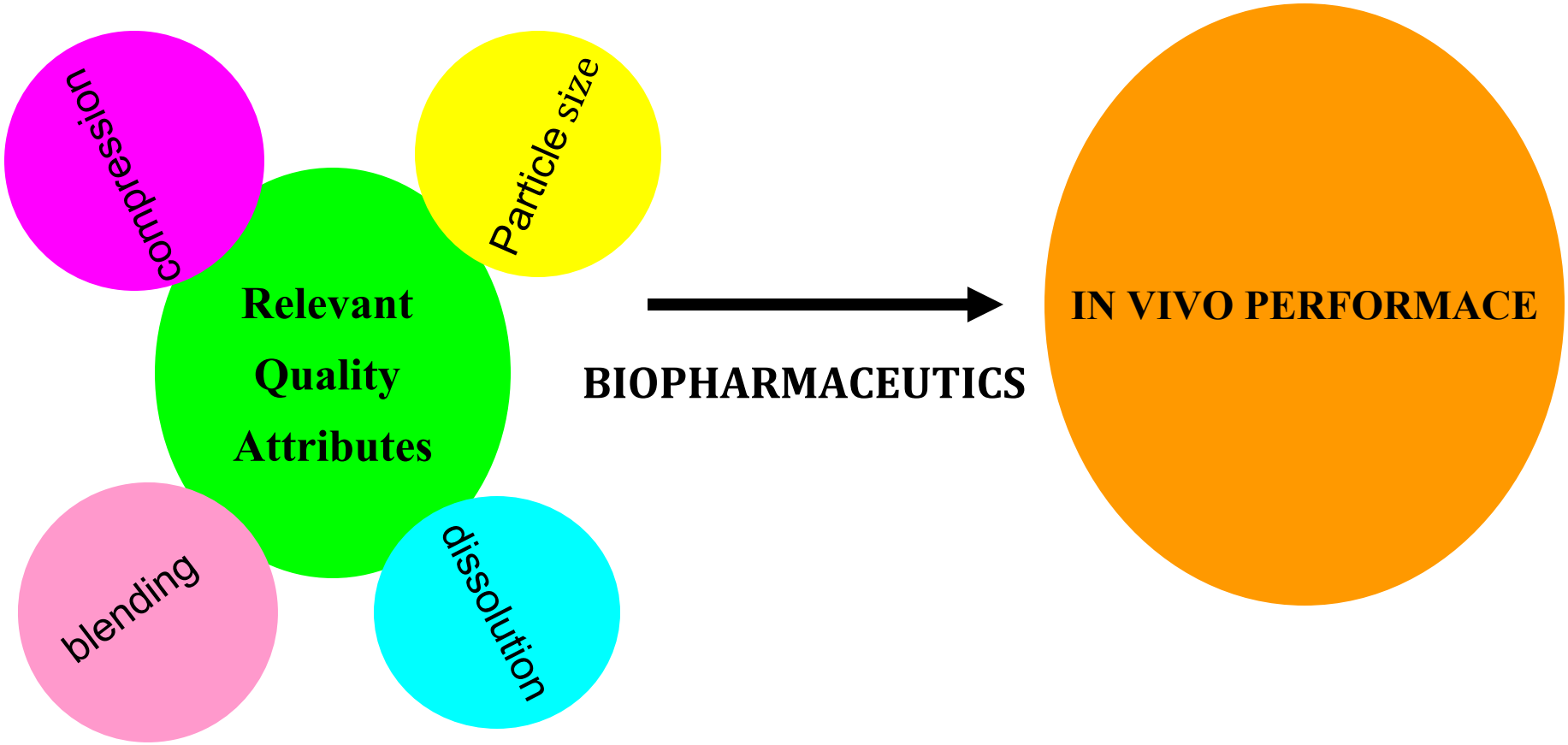
Outline

- Definition of Clinically Relevant Drug Product Specifications
- The Role of Biopharmaceutics
  - BA/BE Studies
  - Dissolution
- Approaches for Setting Clinically Relevant Drug Product Specifications
  - Approach 1
  - Approach 2
  - Approach 3
    - Case Study
  - Summary
  - Conclusions

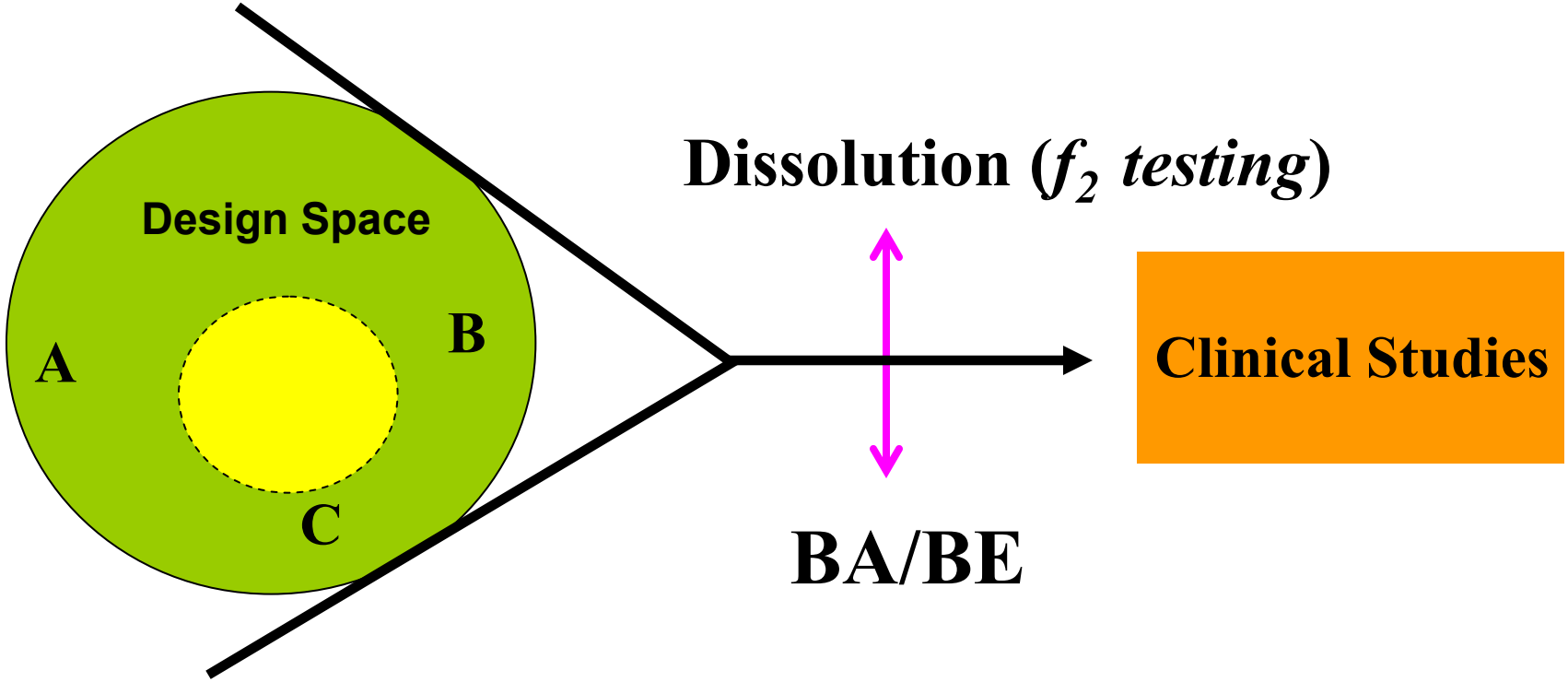
What Are Clinically Relevant Specifications (CRS)?

- CRS are those specifications that take into consideration the clinical impact of variations in the critical quality attributes (CQA) and process parameters assuring a consistent safety and efficacy profile

CRS Implies Establishing a Link



Why is the Use of Biopharmaceutics Relevant?



Why is it Important to Determine the in vivo Impact?

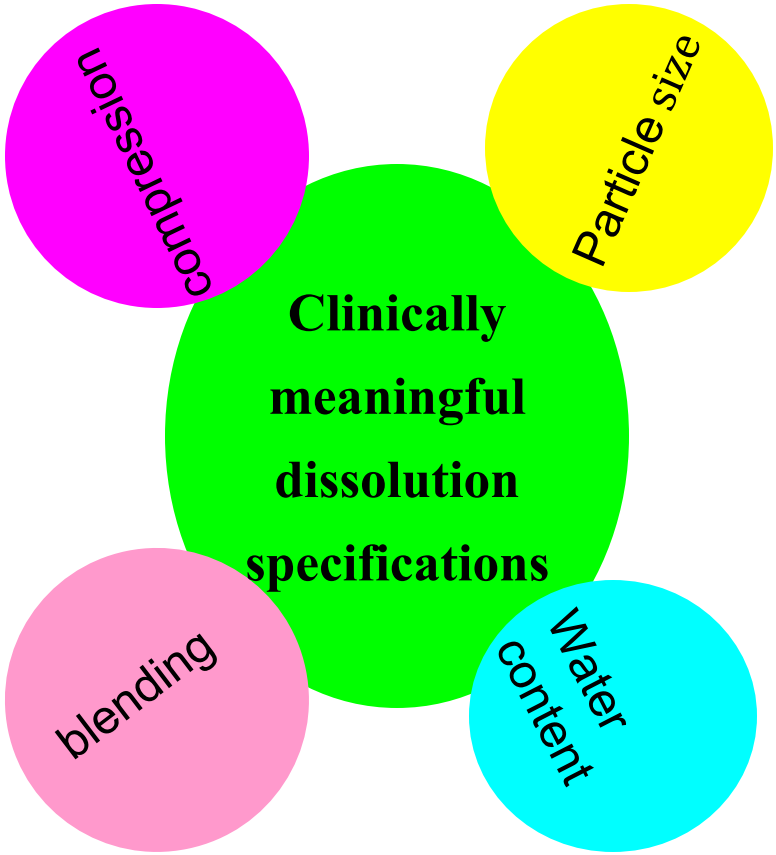
- When manufacturing changes are linked to ***meaningful in vitro tests***, it enables the development of science and risk based specifications

- Consistent in vivo product performance (safety and efficacy profiles) for the marketed product relative to the clinical trial formulation

The Relevance of Dissolution

- A quality control tool
  - Batch-to-batch consistency
  - Provide quality assurance
    - The only test that can monitor if the rate of drug solubilization is impacted by product storage conditions
- Guide formulation development
  - The only product test that truly measures the effect of formulation and physical properties of the API on the rate of drug solubilization
- Dissolution has being identified as a surrogate for bioavailability
  - Some manufacturing changes can be approved based only on the comparability of their dissolution profiles without having to conduct in vivo studies

The Relevance of Dissolution



How are clinically relevant drug product specifications established?

Approaches for Establishing CRS

- **Approach 1:**
  - Range established based on batches tested in pivotal phase 3 clinical trials
- **Approach 2:**
  - Range established based on a range of release characteristics resulting in bioequivalence
- **Approach 3:**
  - Range established based on predictive and robust in vivo in vitro correlations

Approach 1: Range established based on batches tested in pivotal phase 3 clinical trials

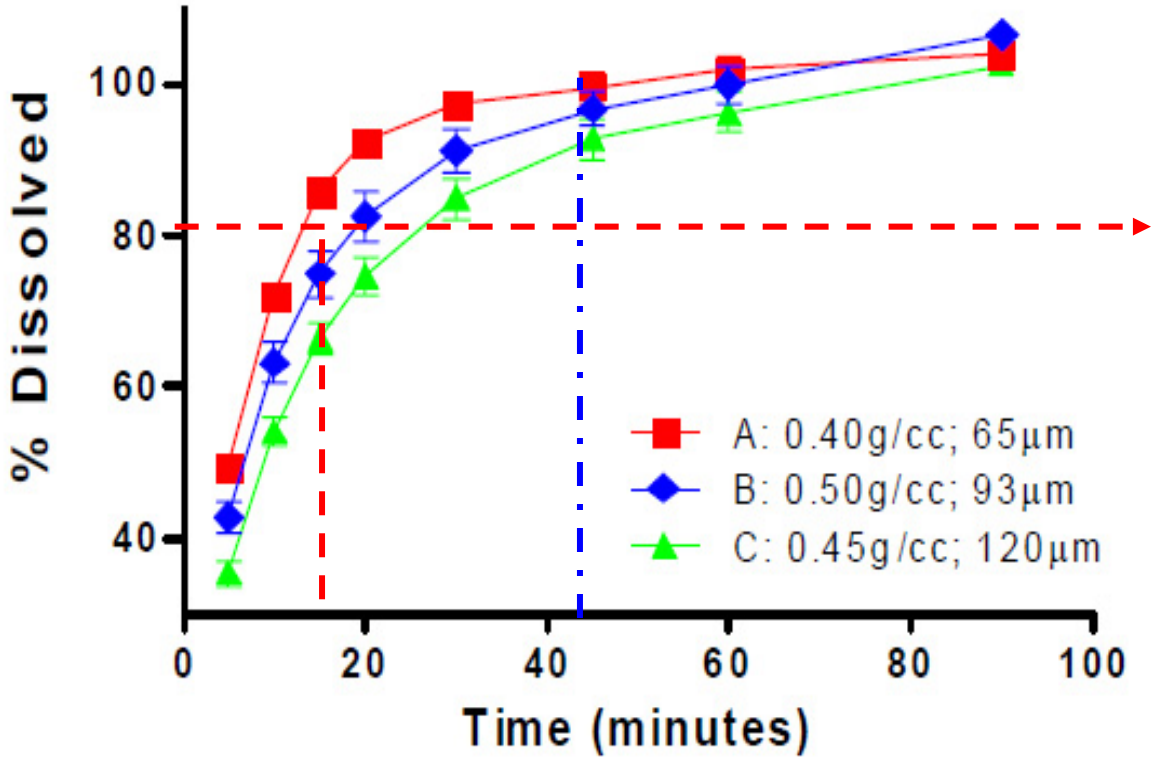
Approach 1

- Dissolution is a CQA
- No data linking formulation variants with different release characteristics to plasma levels
- Assume the use of a discriminating dissolution method and dissolution acceptance criterion
- Regulatory flexibility limited/determined by the dissolution acceptance criterion/ f_2 statistical test

What is a Discriminating Dissolution Method?

- A method that is able to differentiate drug products manufactured under target conditions vs. drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant manufacturing variables (e.g. drug substance particle size, compression force, tablet hardness, etc.)

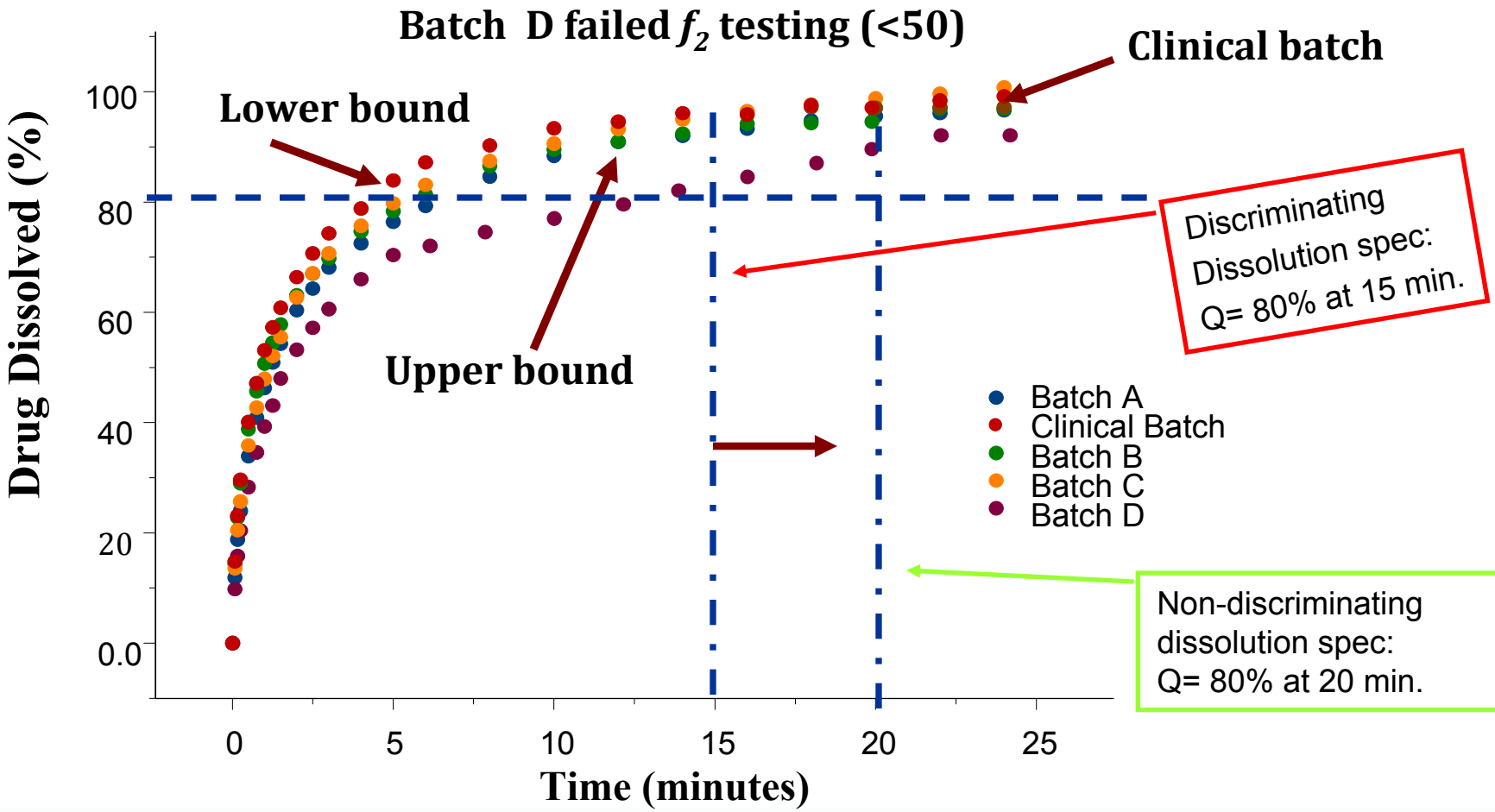
Dissolution Profiles of Tablets with Varying Bulk Density (BD) and Particle Size (PS)



A target profile
B: high BD
C: large PS

Discriminating ability is not only determined by the dissolution method conditions, but also by the timing of the acceptance criterion

Clinically Relevant Particle Size Ranges



What Are the Limitations of Approach 1?

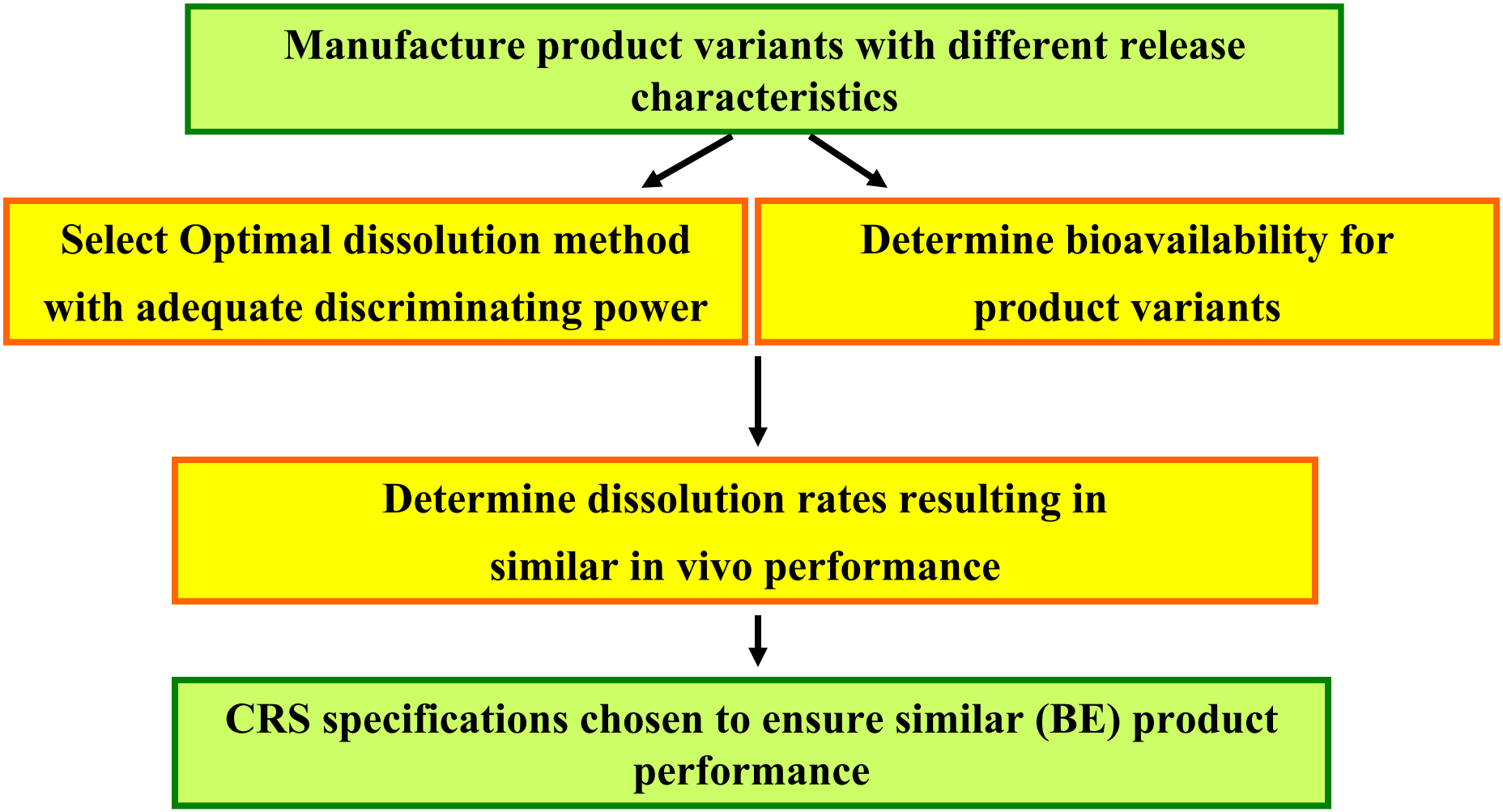
- Regulatory flexibility is limited and determined by the dissolution acceptance criterion and f_2 statistical test

- One cannot really determine if the dissolution method and acceptance criteria are under- or over-discriminating
  - No data available to determine if the method and acceptance criterion are able to reject for batches that are not BE

Clinical relevance may not always be assured

Approach 2: Established range of release characteristics resulting in bioequivalence

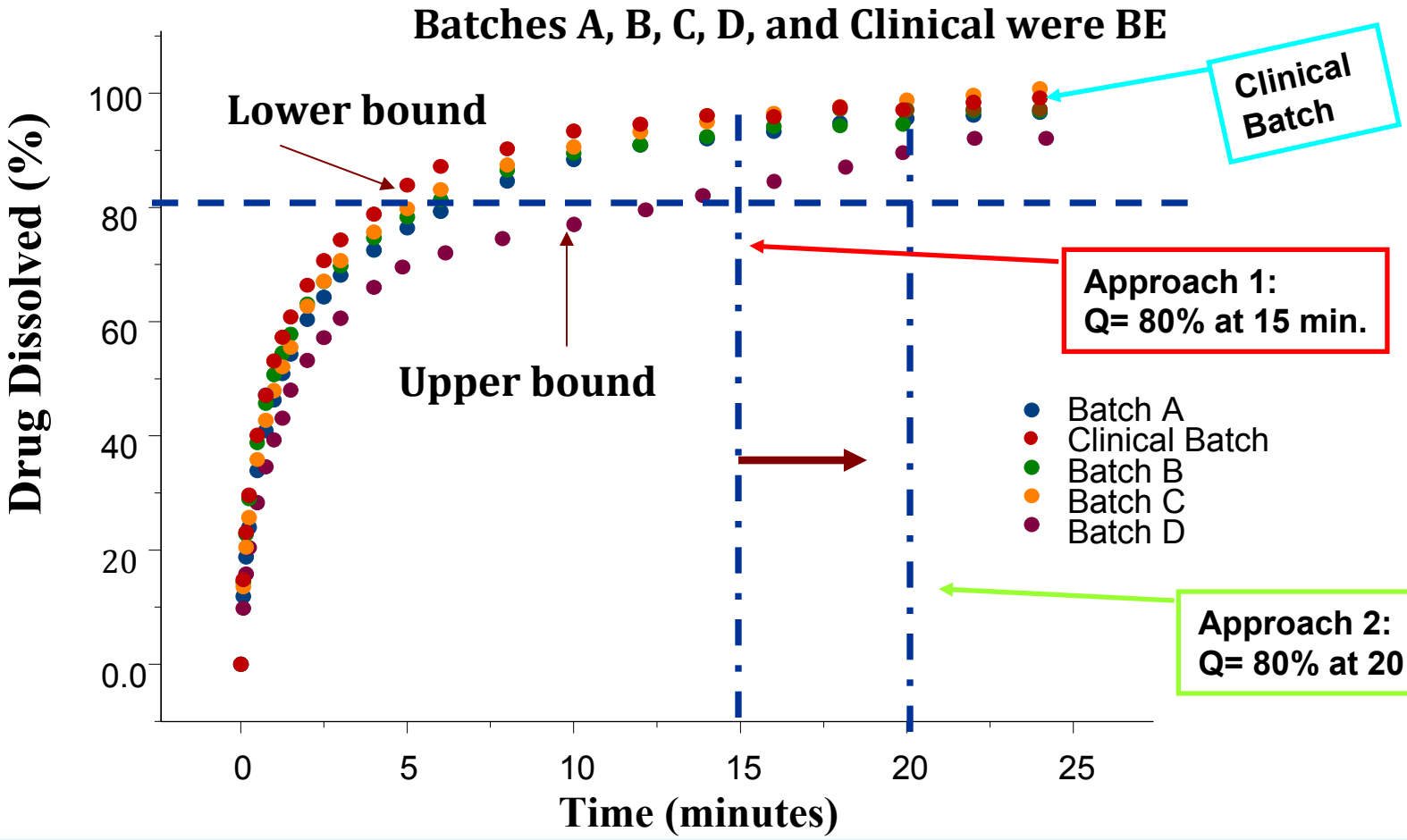
Approach 2


Manufacture product variants with different release characteristics
Select Optimal dissolution method with adequate discriminating power
Determine bioavailability for product variants
Determine dissolution rates resulting in similar in vivo performance
CRS specifications chosen to ensure similar (BE) product performance

What are the Advantages of Approach 2?

- Assures the establishment of clinically relevant dissolution method and acceptance criterion
  - Direct link to in vivo performance
- An in vivo performance similar to the target profile is always assured within the ranges tested
- Regulatory flexibility resulting in wider specifications

Illustration of the Advantages

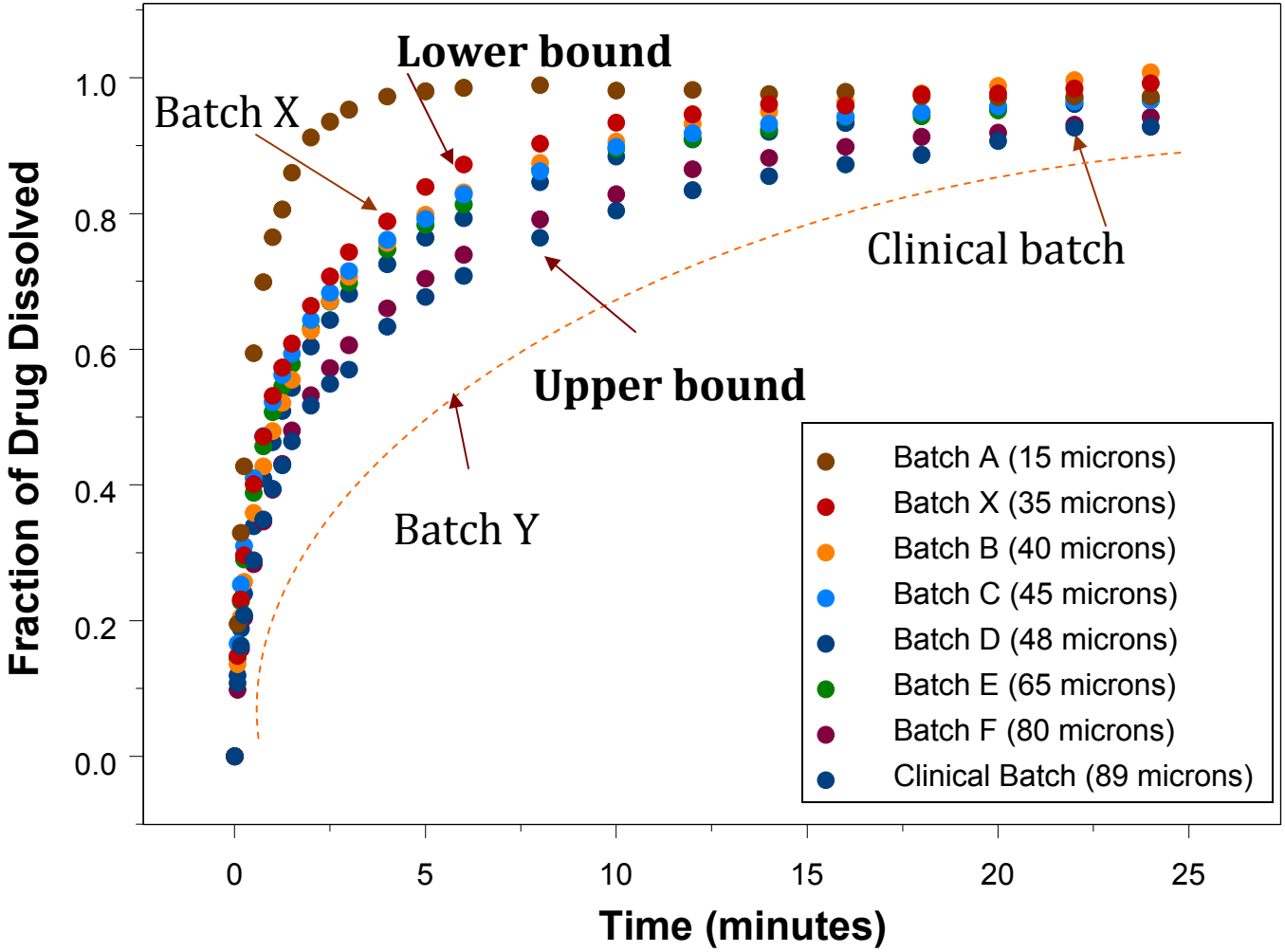


What Are the Limitations of Approach 2?

- Clinical performance can be assured for the following CMC changes:
  - Those evaluated in the bioequivalence study
  - Those changes whose dissolution profiles fall within the extremes of dissolution profiles for batches that were BE
  - Other changes typically evaluated by f_2 statistical test

Illustration of the Limitation

- Batches B through F were BE to clinical Batch
- Batch X not part of BE study. However, f_2 value is > 50
- f_2 value for batch Y is < 50



Do the CMC Changes to Batch Y Have an Impact on the Efficacy and Safety of the Drug?

How Can we Answer this Question?

The Role of Models in Setting Clinically Relevant Specifications

- Validated models (e.g., IVIVC) can provide the means for predicting/determining the clinical impact of CMC changes without the need for additional in vivo studies

Approach 3: Predictive and robust in vivo in vitro correlations

The Purpose of IVIVC

- Reduction of regulatory burden: IVIVC in lieu of required *in vivo* studies, leading to:
  - Time/Cost savings during product development
    - Less testing in humans
- Permits setting wider than standard (±10%) *in vitro* release acceptance criteria
- Permits the setting of specifications based on targeted clinically relevant plasma concentrations
- If available, could support the approval of a design space
  - Prediction/determination of the clinical impact of “movements” within the design space without the need for additional *in vivo* studies
  - Regulatory flexibility resulting in wider specifications

Case Study

Establishment of an IVIVC Model to Support Design Space Development

Drug Product A

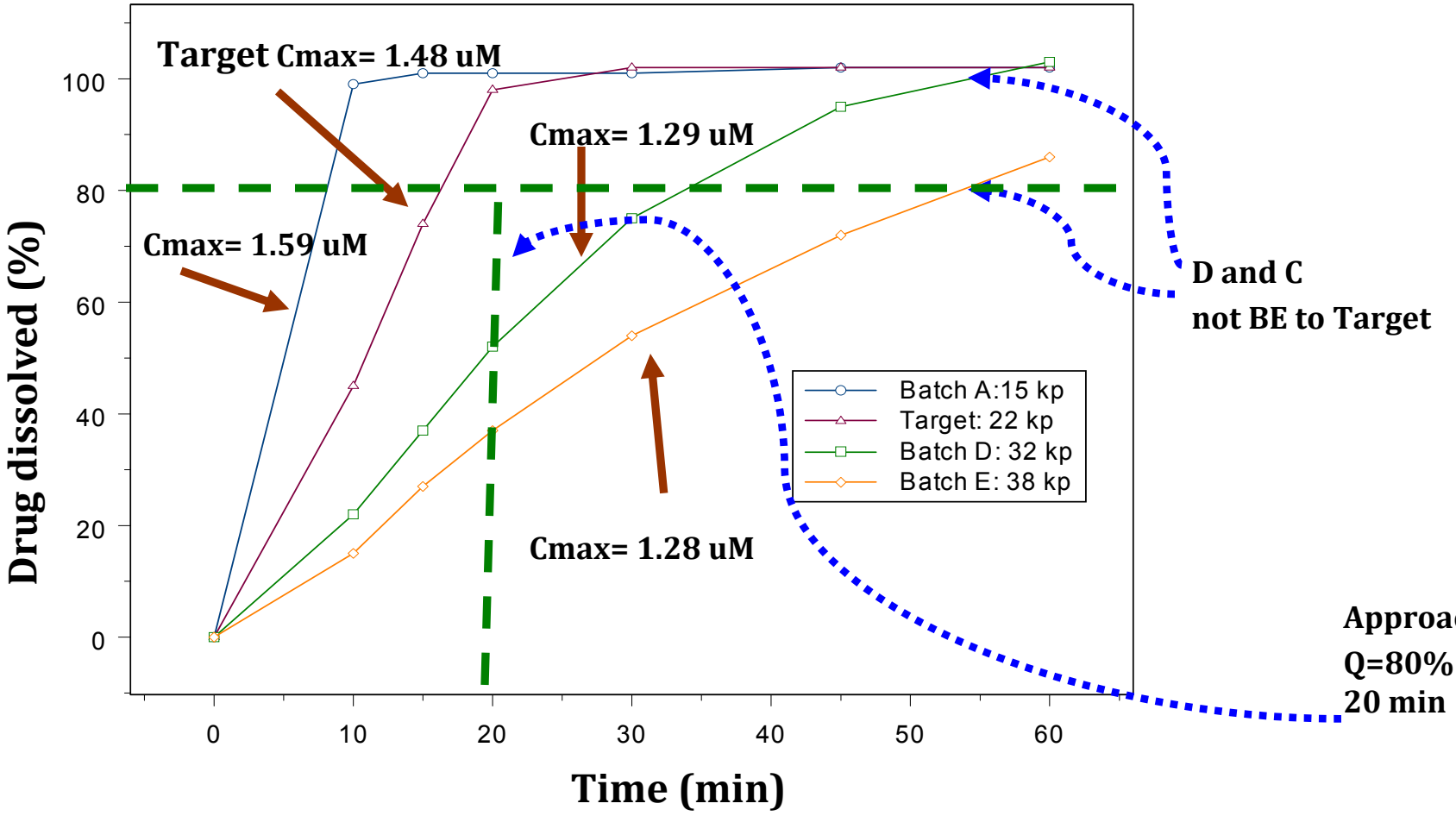
- BCS 2 Drug Substance
- Immediate Release Tablet
- Several strengths

Data Used for the Construction of the IVIVC Model

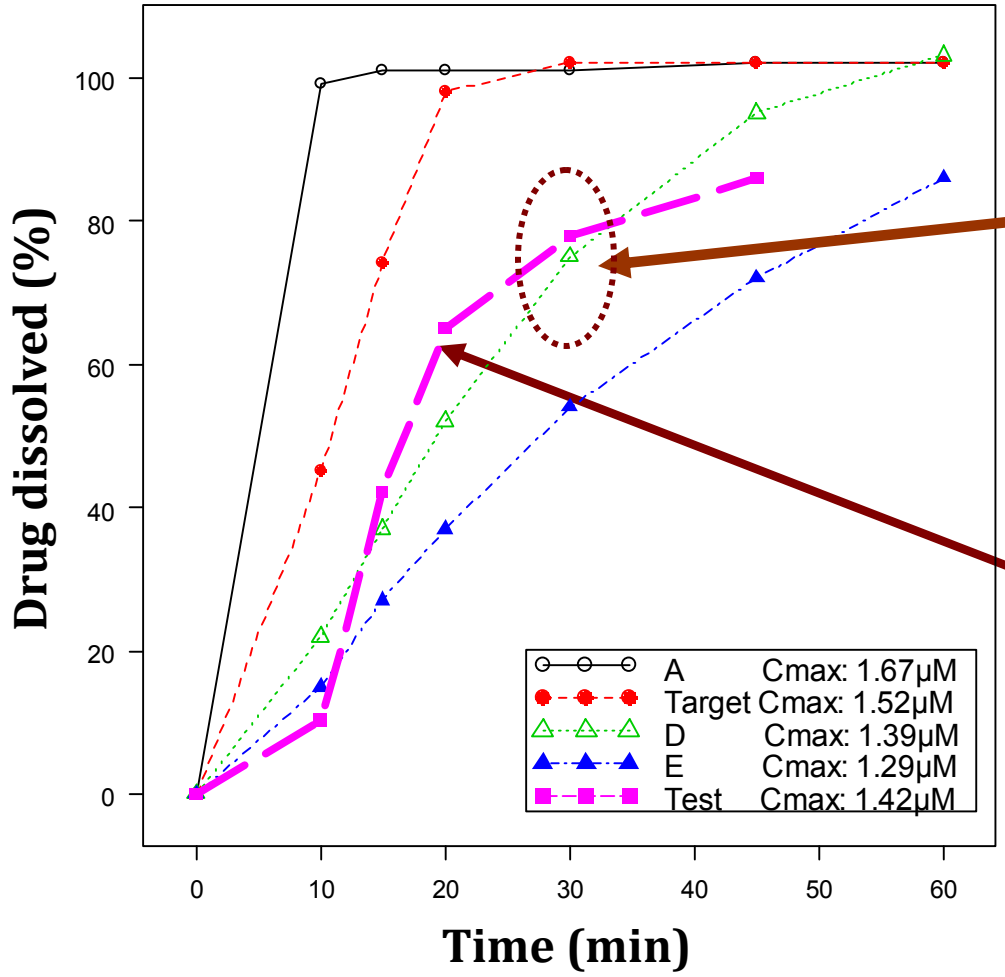
- Dedicated PK study to determine the effect of hardness on Bioavailability
  - Four batches with different hardness values
  - Targeted value (clinical batch) included

- QC Dissolution Method

Dissolution Profiles of Batches Used in the Construction of a Multiple Level C IVIVC



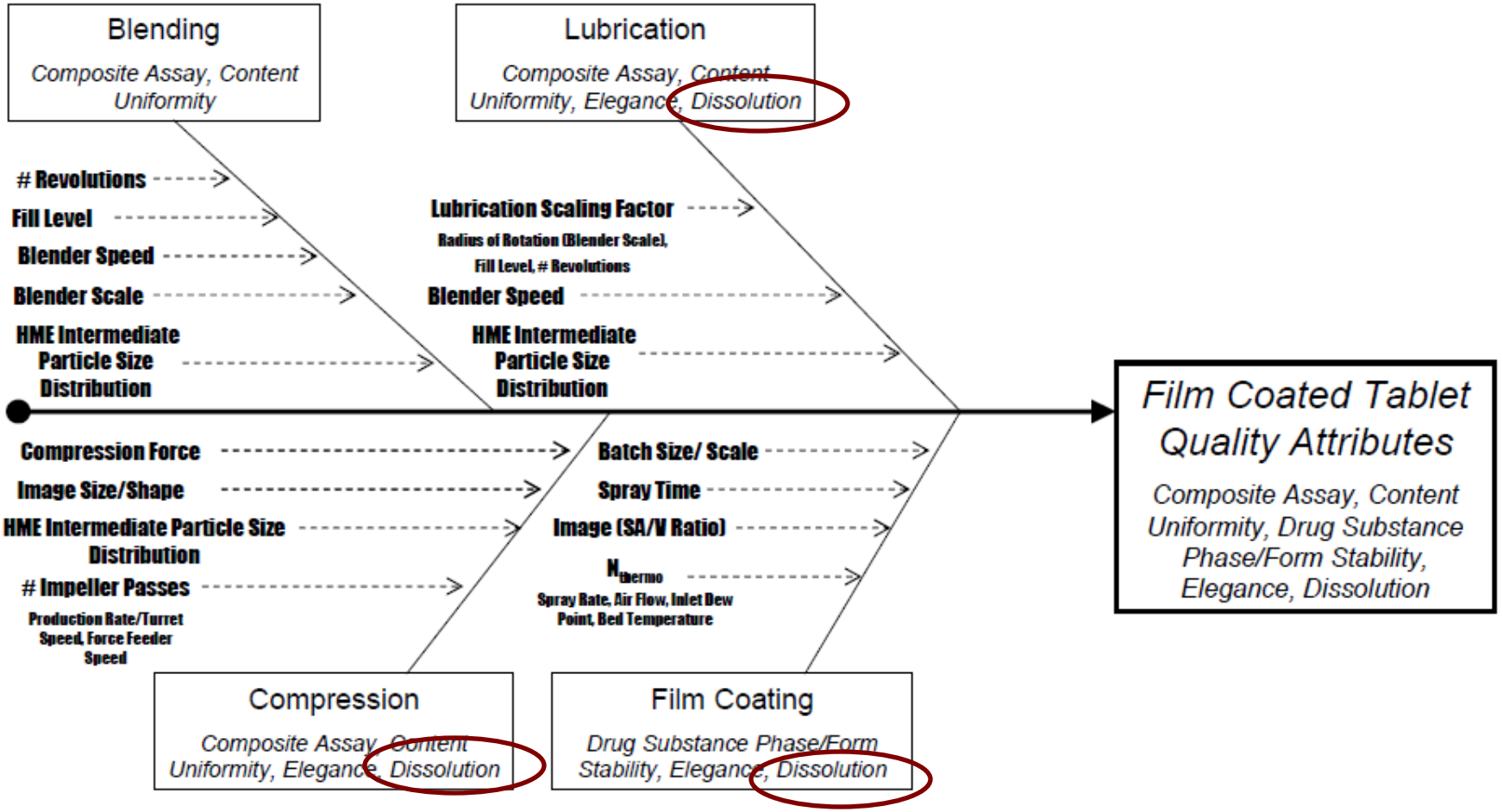
IVIVC Predicted Borderline for BE to the Target Formulation



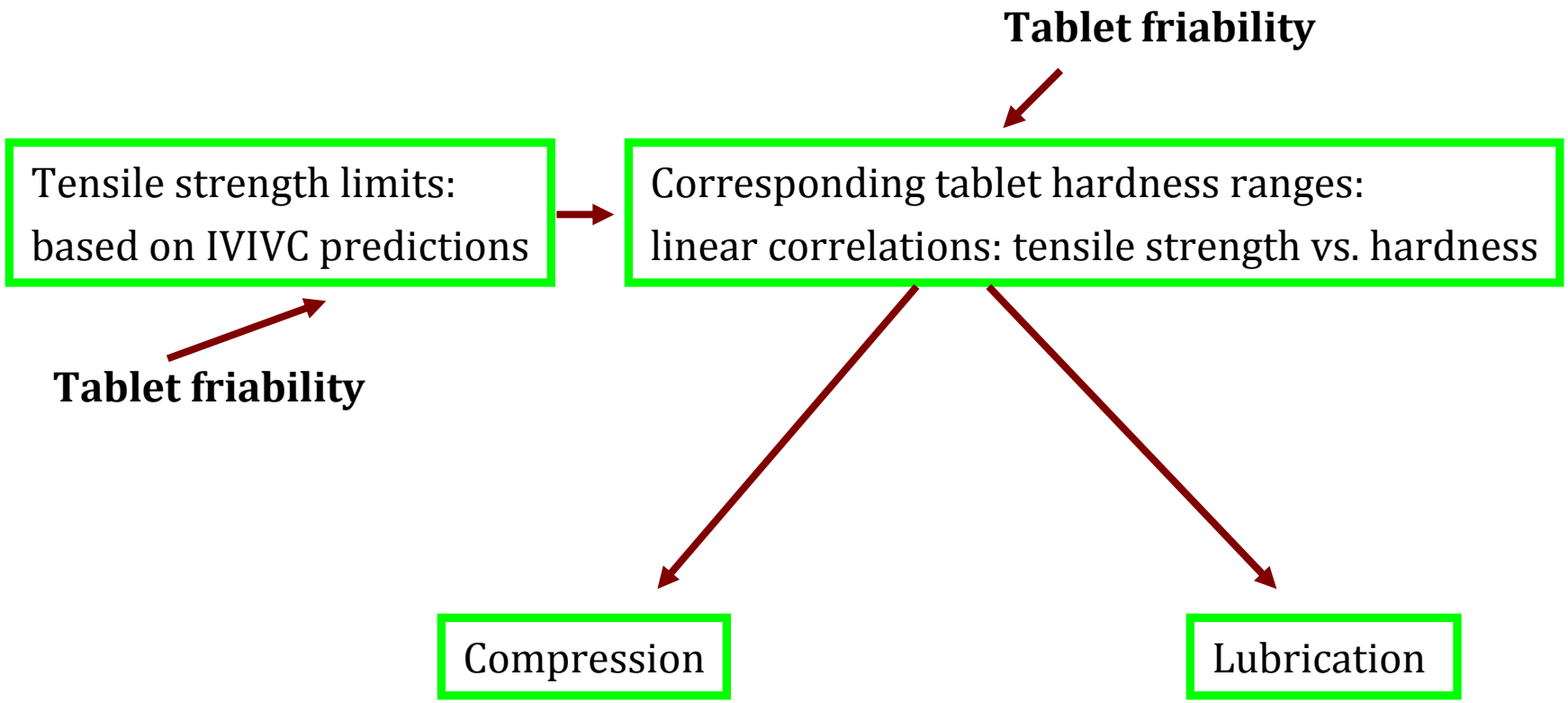
Approach 3: Q=75% at 30 min

Predicted borderline profile

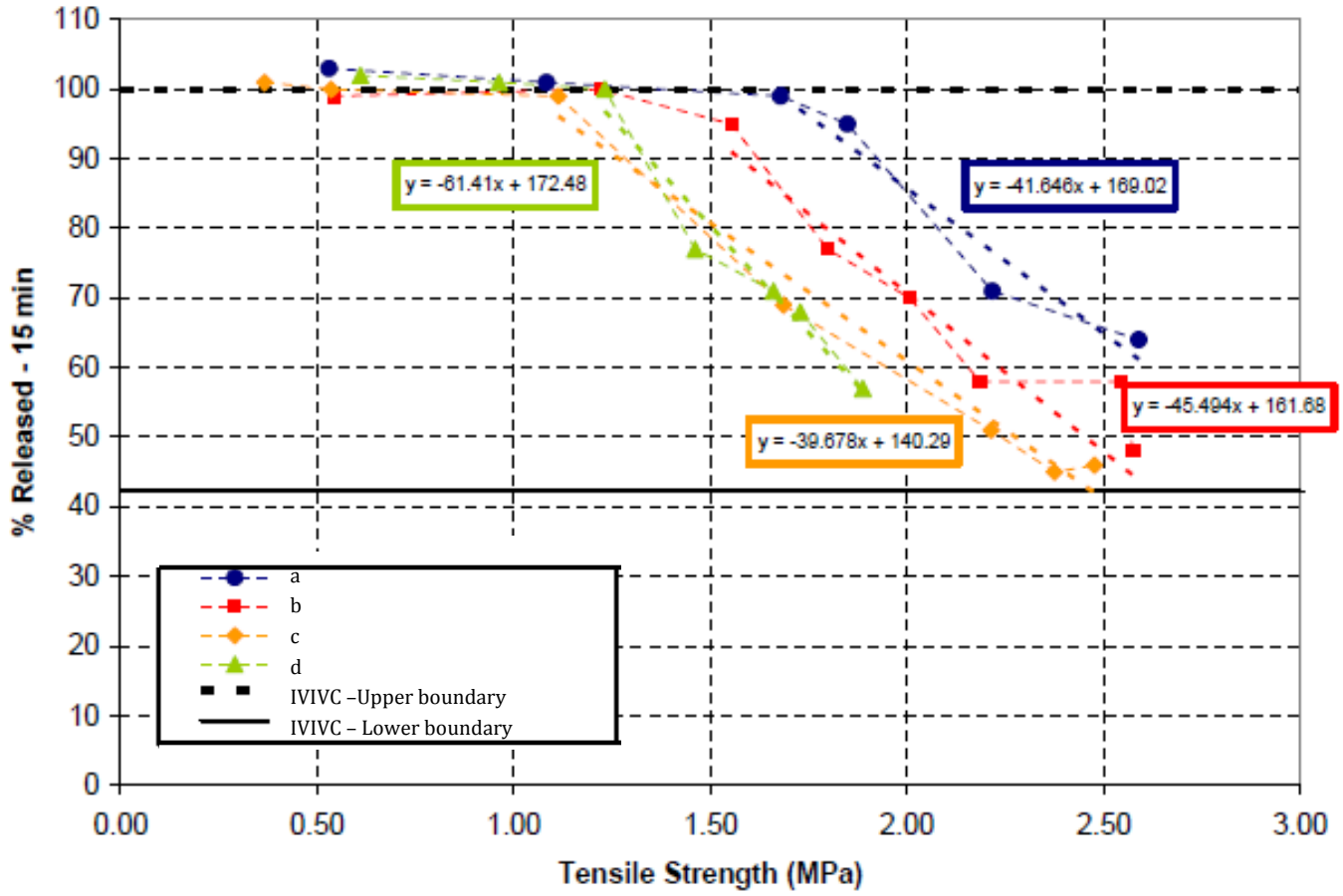
Fishbone Diagram for "Drug Product A" (Downstream Process)



Design Space (DS) for Down Stream Process



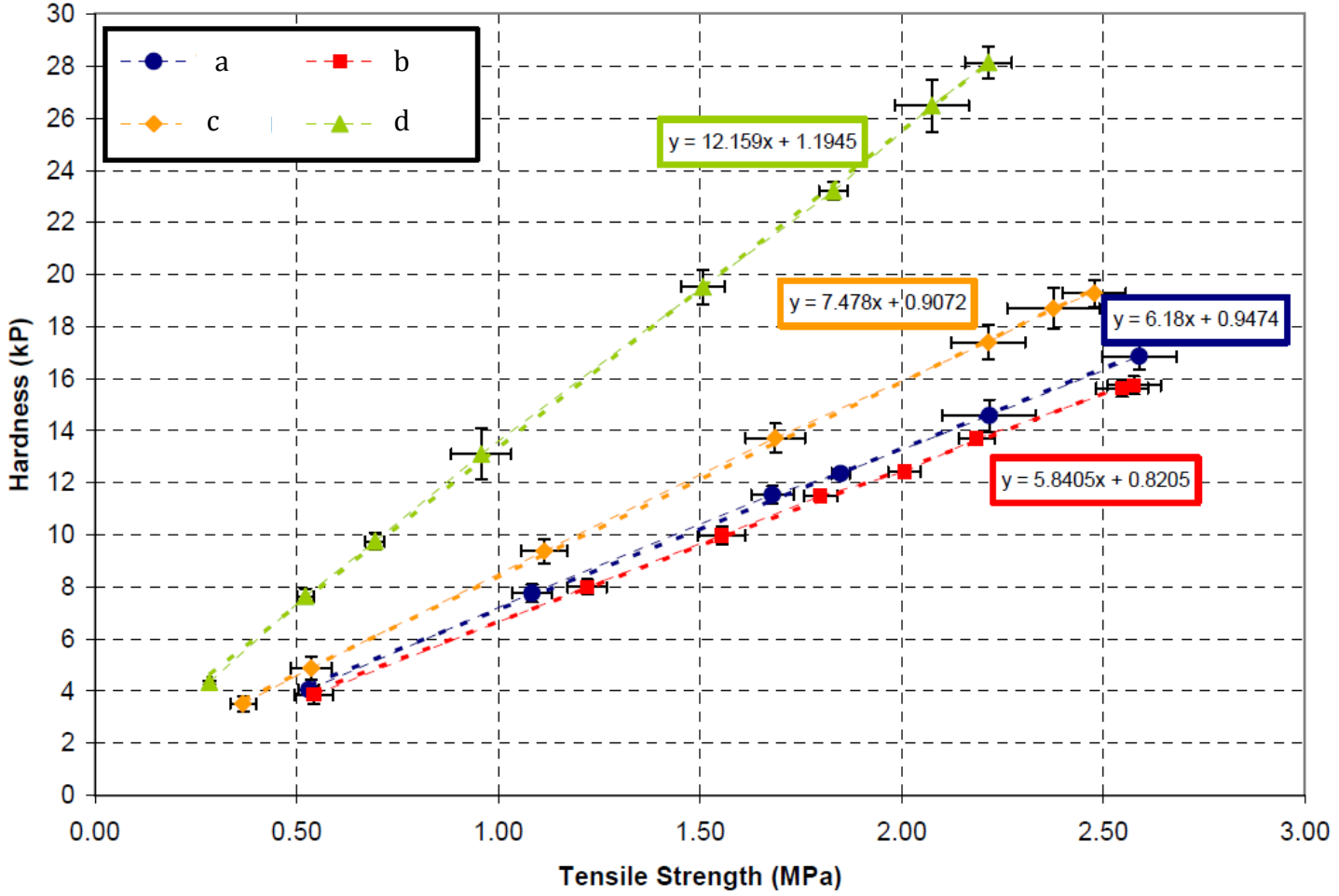
Percent Dissolved at 15 minutes Versus Tablet Tensile Strength for all Drug A Images



Tablet Tensile Strength Limits for all Drug Product A Images as Established by IVIVC Boundaries

Drug Product A Image	Lower Tensile Strength Limit (MPa)	Upper Tensile Strength Limit (MPa)
a	1.4	3.05
b	1.4	2.63
c	1.4	2.47
d	1.4	2.12

Tablet Hardness versus Tablet Tensile Strength for All Drug A Images

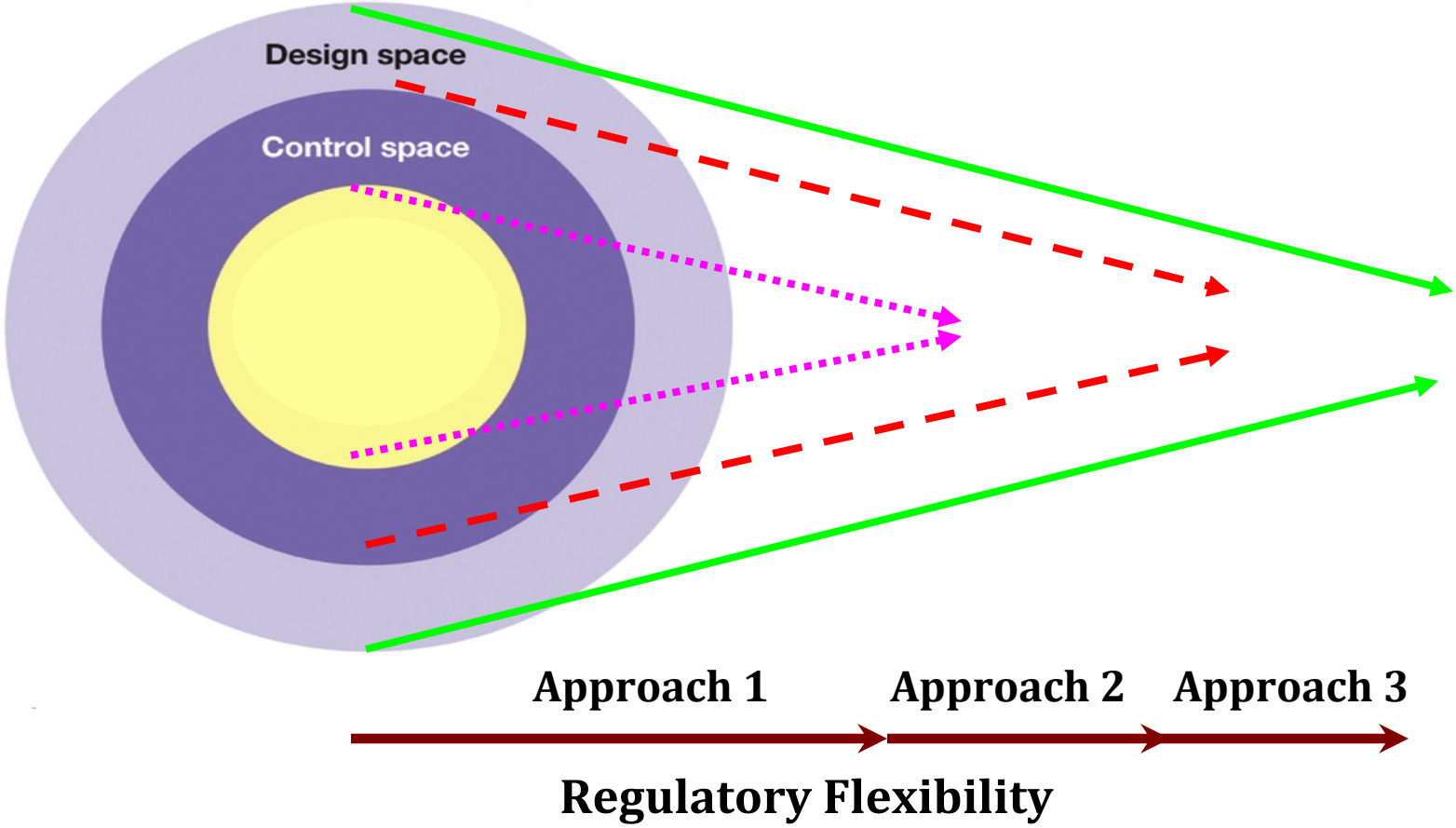


Tablet Hardness Limits for all Drug Product A Images as Established by IVIVC Boundaries

Drug Product A Image	Hardness Limit (kp)	Hardness Limit (kp)
a	11	20
b	8.5	16.5
c	8.5	19.5
d	15	27.5

Approach 2: hardness= 22 Kp

Regulatory Flexibility



Summary

- Setting clinically relevant specifications starts with the development of a clinically relevant (predictive) dissolution method and dissolution acceptance criterion
  - Setting clinically relevant dissolution specifications → clinically relevant drug product specifications

- Three approaches for setting clinically relevant dissolution specifications
  - **Approach 1:**
    - Less desirable approach
    - Discriminating ability is crucial
    - There is no relationship established between in vitro release and plasma levels
    - Clinical relevance not always assured
    - Limited regulatory flexibility
      - Determined by the dissolution acceptance criterion/ f_2, statistical test

Summary, cont.

- **Approach 2:**
  - There is a relationship between in vitro release and plasma levels
  - Clinical relevancy is assured
    - Those manufacturing changes resulting in dissolution profiles that fall within the extremes of dissolution profiles for batches that were BE
  - Regulatory flexibility

- **Approach 3:**
  - Most desirable approach
  - There is a correlation between in vitro release and plasma levels
  - Clinical relevance is assured
  - Regulatory flexibility resulting in wider specifications

- The ultimate goal is to assure consistent in vivo product performance (safety and efficacy) for the marketed product relative to the clinical trial formulation

Conclusions

- FDA encourages the conduct of dedicated BA/BE studies during product development to establish the relationship between drug products variants with different release characteristics and plasma levels:
  - Mechanistic understanding of the critical manufacturing variables
  - Establishment of clinically relevant drug product specifications
  - Potential for developing IVIVC models
  - Potential for wider drug product specifications
  - Stronger link between *in vivo* and *in vitro* performance as compared to using $f_{2,}$ statistical test
  - Regulatory flexibility within the QbD frame-work

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