

# Regulatory Requirements of Dissolution for Generic Drug Products

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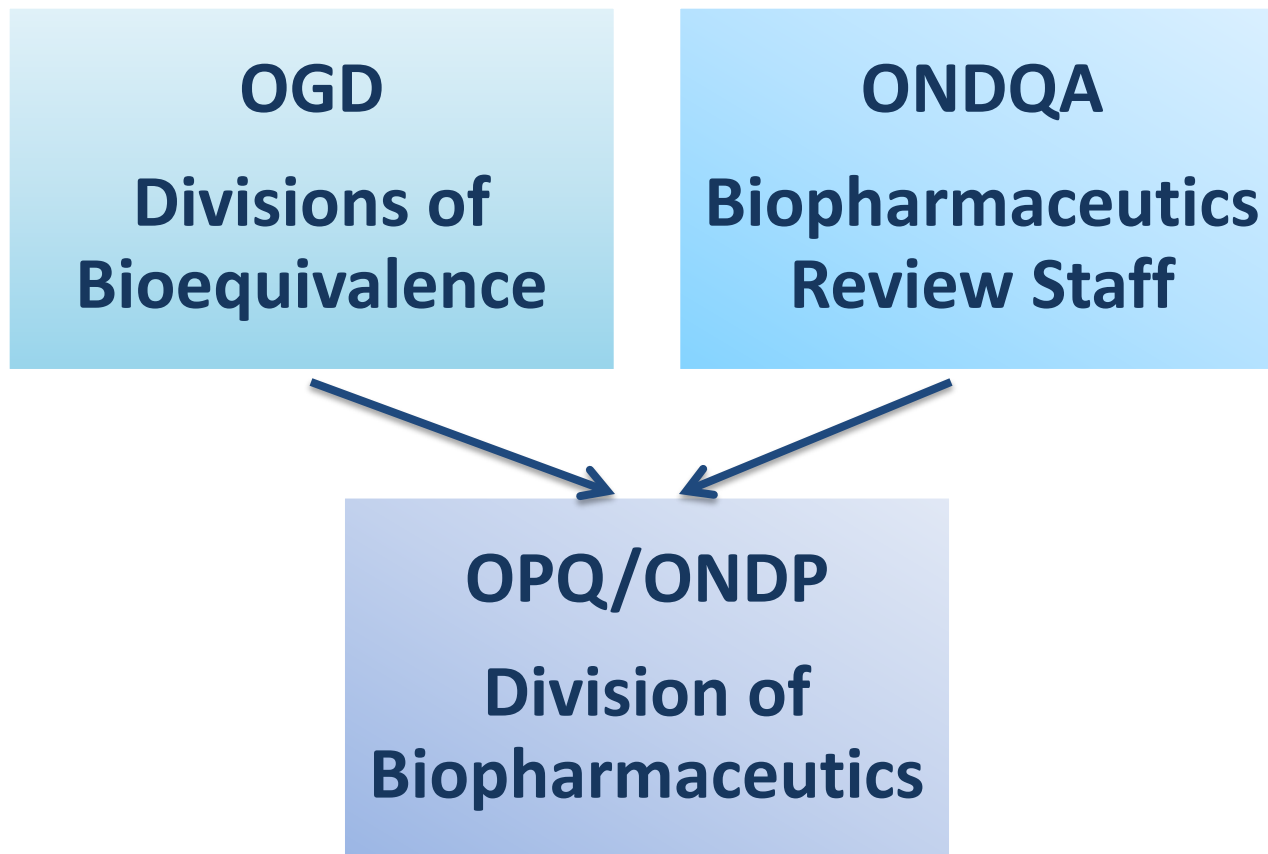
# Outline

- **Developing a dissolution test for generic products**
- **Historical perspective**
- **Current perspective**
- **Moving forward and future directions**
- **Conclusions**

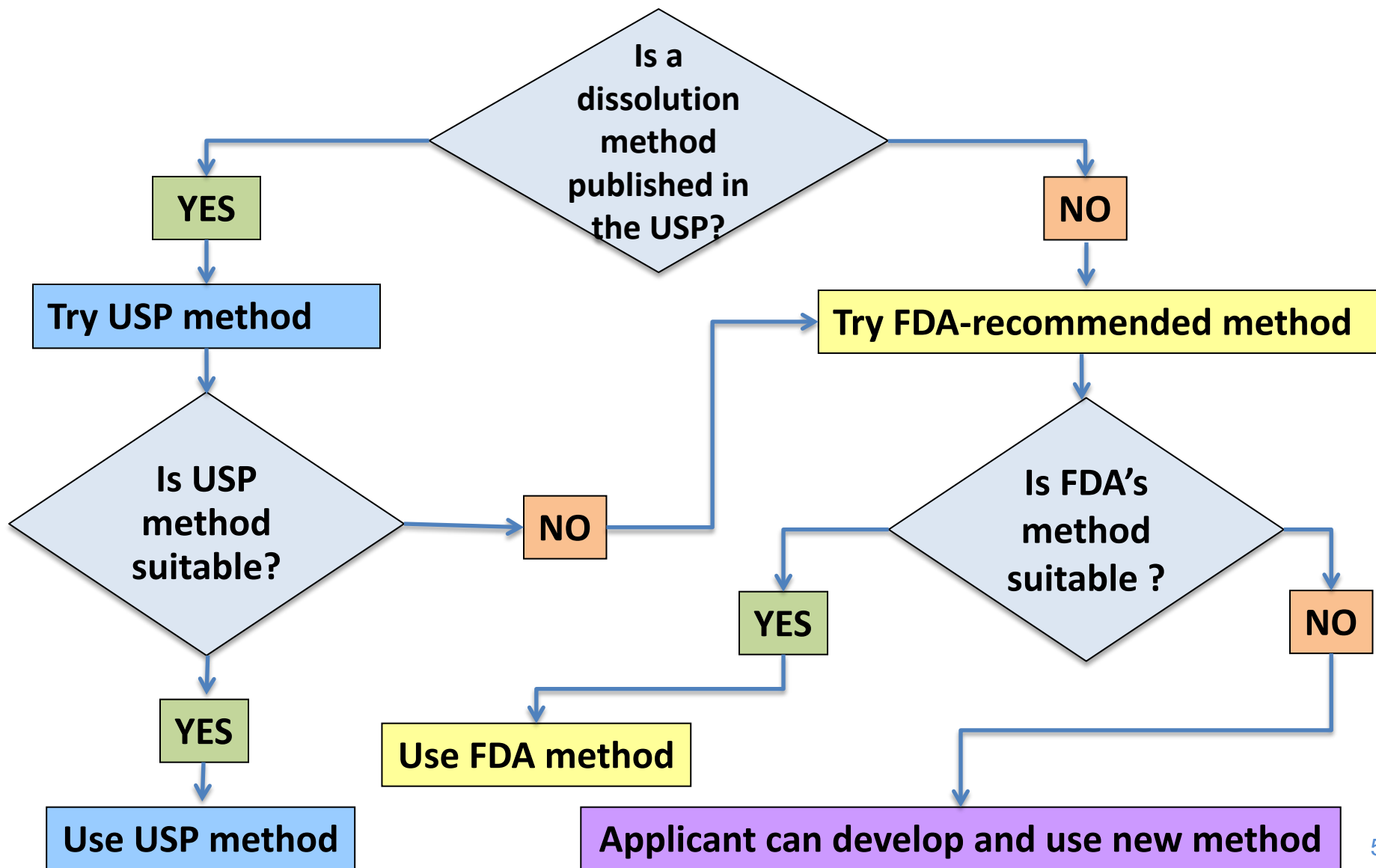
***Developing a dissolution test for a  
generic drug product***

# A Historical Perspective

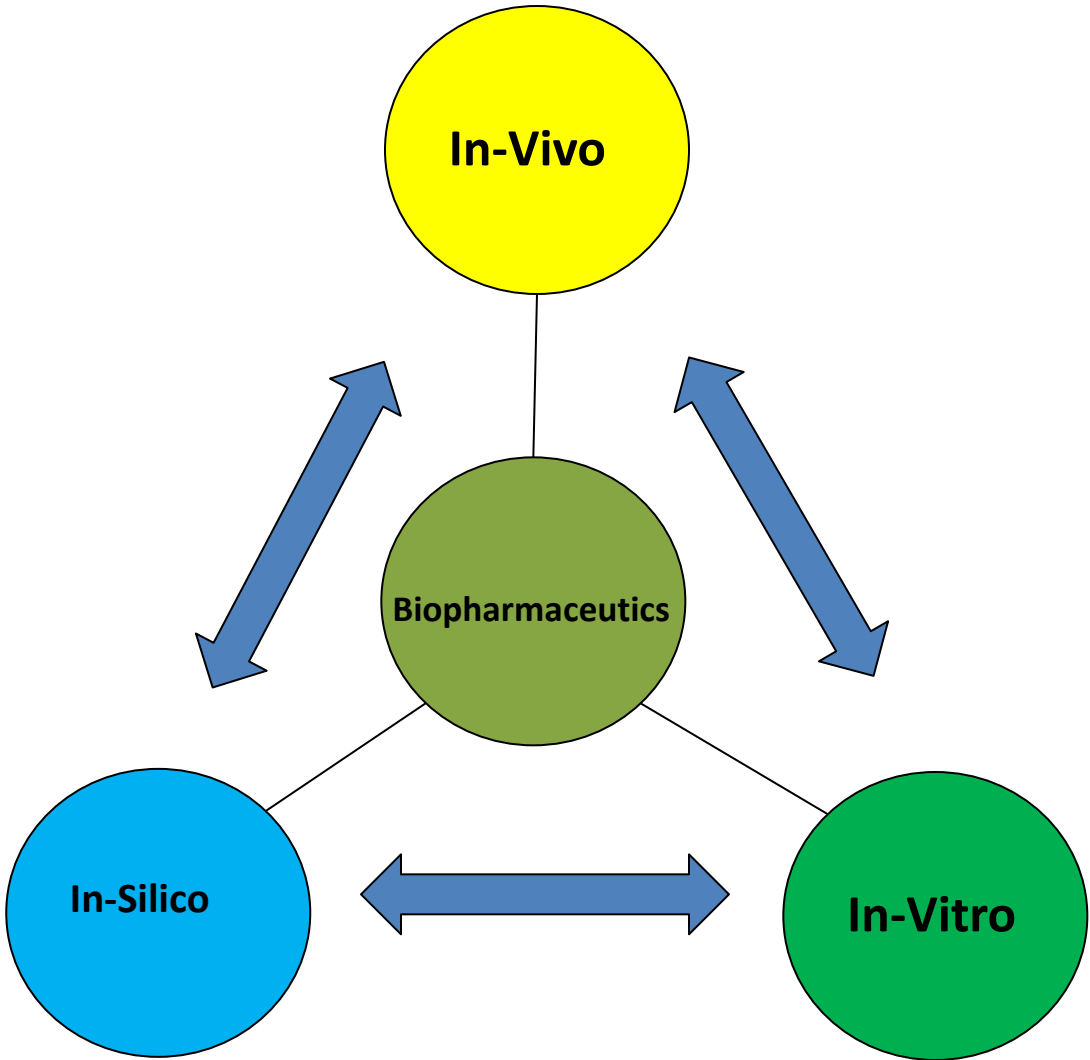
- **Biopharmaceutics discipline at FDA**



# Selecting dissolution methods for generic products: historical perspective



# Current Perspective Biopharmaceutics Approach





# Optimizing a dissolution method for generic drug products

- Applicants are recommended to develop product/formulation specific dissolution methods and provide a dissolution method development report
- Usually, either USP or FDA method may be suitable for a generic immediate-release (IR) products. Applicants are still encouraged to optimize the selected method with regard to their proposed formulation.
- MR product dissolution methods are generally developed case-by-case

# FDA requests use of USP apparatus in dissolution / drug release testing



USP Apparatus	Description
1	Basket
2	Paddle
3	Reciprocating Cylinder
4	Flow-through Cell
5	Paddle over Disk
6	Cylinder
7	Reciprocating Holder

However, to establish a discriminating dissolution method, changes [e.g. suspended baskets, peak vessels etc.] to the USP apparatus may be justified.



# Dissolution or drug release testing for complicated dosage forms



Dosage form	Considerations in developing a dissolution or drug release test
Oral suspension	Start with Apparatus 2, 25 rpm
Transdermal	Apparatus 5, 6, 7
Beads/Pellets	Apparatus 3
Chewing gum	Try European Pharmacopeia mechanical chewing apparatus
Lipophilic drug in oil-filled capsule	Quantify capsule rupture rate in medium containing surfactant
Semisolid preparations (e.g., creams, gels, lotions, and ointments)*	Diffusion cell system such as a Franz cell system

**\* Mostly, only for Scale-Up and Postapproval Changes**

# FDA's on-line dissolution methods database:

<http://www.accessdata.fda.gov/scripts/cder/dissolution/index.cfm>

## Example entries

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Abacavir Sulfate	Tablet	II (Paddle)	75	0.1 N HCl	900	5, 10, 15, and 30	03/22/2006
Cefprozil Monohydrate	Suspension	II (Paddle)	25	Water	900	5, 10, 15 and 30	01/21/2004
Rivastigmine	Film, Transdermal	VI (cylinder)	50	0.9 % NaCl at 32° C	500	1, 2, 4, 7, 9 and 12 hours	06/10/2009

The dissolution methods referenced in the database are recommended methods, and are nonbinding recommendations that do not establish legally enforceable responsibilities.

These methods may serve as starting points for the dissolution method development for the generic drug product.



# Product specific dissolution method development

**Users are encouraged to develop a product specific discriminating dissolution/drug release method.**

**It is recommended that the critical material attributes (CMA) and critical process parameters (CPP) affecting the dissolution/drug release be identified and the discriminating ability with regard to those CMAs and CPPs which affect dissolution/drug release be established.**

**Users may also consider developing an appropriate in silico/modeling approach to further justify/support a newly proposed dissolution/drug release method.**

# Product specific dissolution method development cont'd

## Three Components:

- **Evaluation of the dissolution method**
- **Discriminating ability of the dissolution method [with regard to relevant CMAs and CPPs]**
- **The Acceptance criterion/criteria**

# Evaluation of the dissolution method



**Drug substance solubility profile**

**Sink condition [are recommended, NOT necessary]**

**Justification and data to support selection of surfactant [type, concentration]**

**Dissolution data in different pH media [ for example., pH 1.0, 4.5, 6.8 etc.] without and with [if needed] surfactant**

**Selection of an appropriate apparatus/rotation speed.**

**Selection of in vitro dissolution/release medium/media**

**Selection of an appropriate analytical method**

# **Discriminating ability of the dissolution method**

**Discriminates drug products manufactured under target conditions vs. formulations with meaningful variations [variant formulations] for the most relevant manufacturing variables (i.e.,  $\pm 10-20\%$  change to the specification-ranges of these variables)**

**If available, submit the data showing that the selected dissolution method is able to reject batches that are not bioequivalent.**



# The acceptance criterion/criteria

**Acceptance criterion/criteria are established to ensure batch-to-batch consistency and to signal potential problems with in-vivo bioavailability**

**Acceptance criterion/criteria should be based on the performance of acceptable bioequivalence batches of the drug product**

# The acceptance criterion/criteria cont'd.



For IR products: At least 85% of the drug is dissolved or where plateau of drug dissolved is reached. The selection of time point should be where Q=80% of drug dissolved.

Examples: 80 % (Q) in 15 minutes  
80 % (Q) in 30 minutes

Two-point acceptance criteria :

Example: NMT 30 % in 30 minutes and NLT 80 % in 120 minutes

(e.g., slow dissolving or poorly water soluble drug products)

For ER products: selection of time points justified, acceptance criteria ranges based on mean target value  $\pm 10\%$  and NLT 80% for the last specification time-point

Example: NMT 20 % in 1 hour

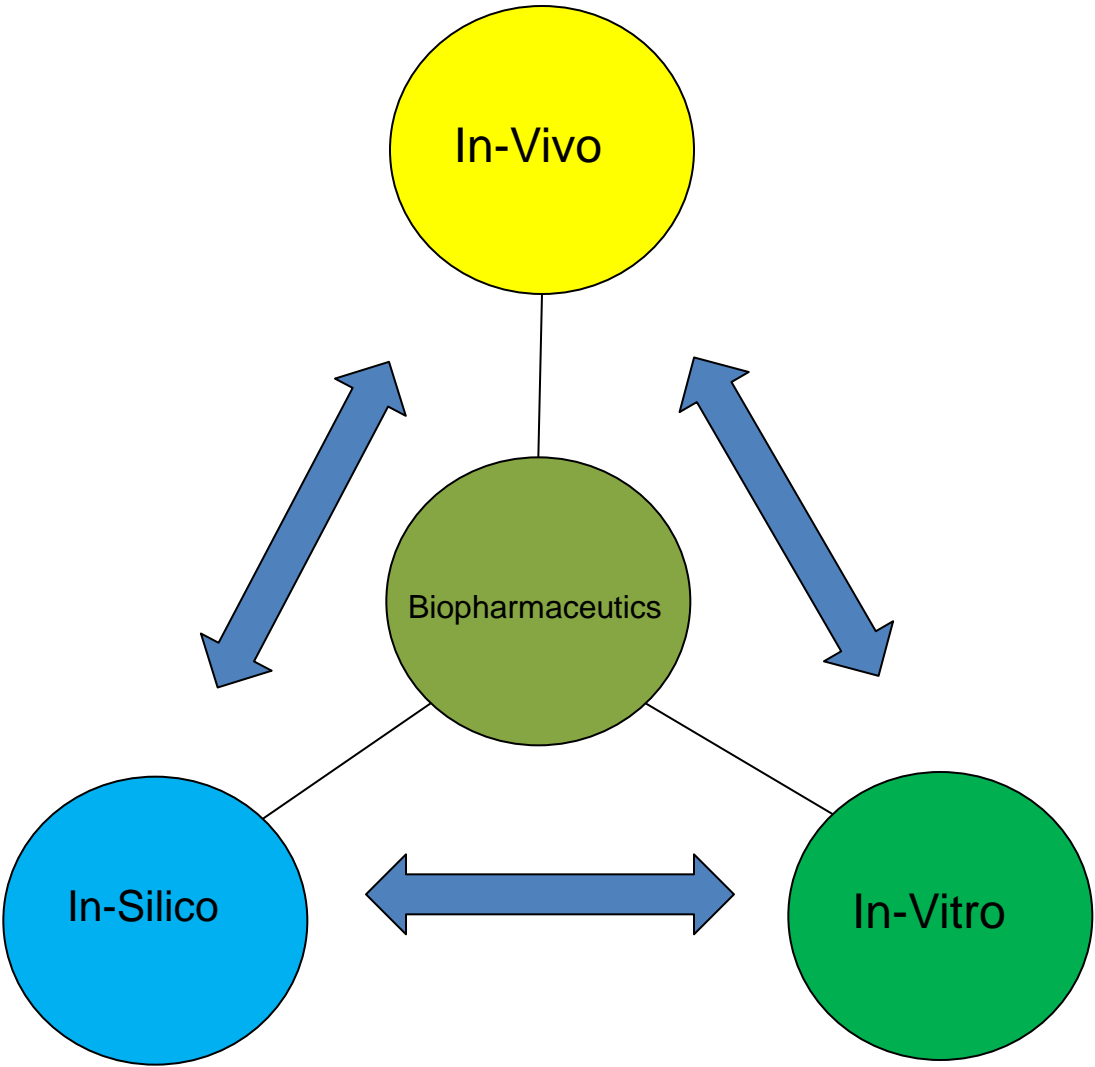
30-50 % in 4 hours

50-70 % in 8 hours

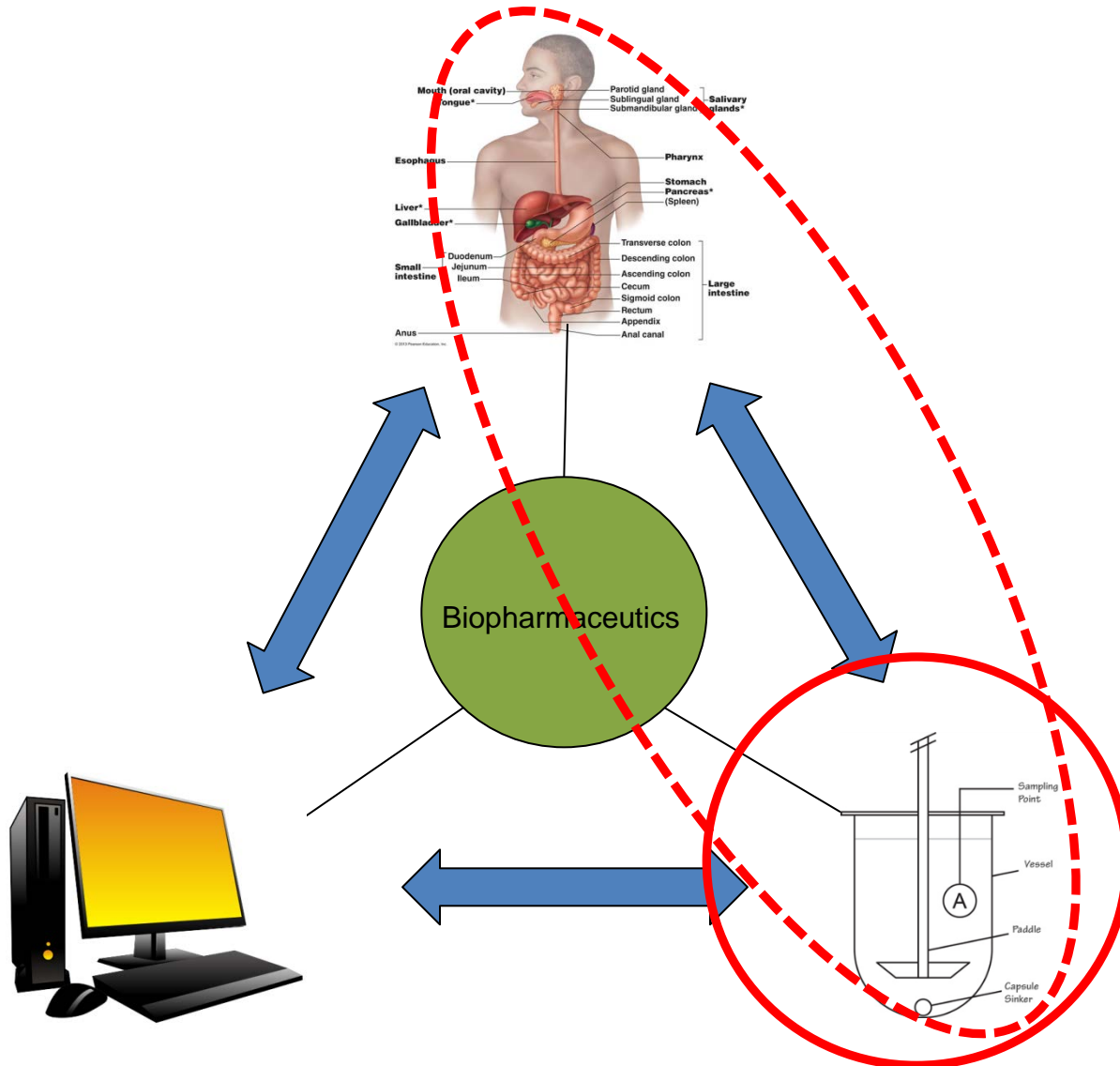
NLT 80 % in 12 hours



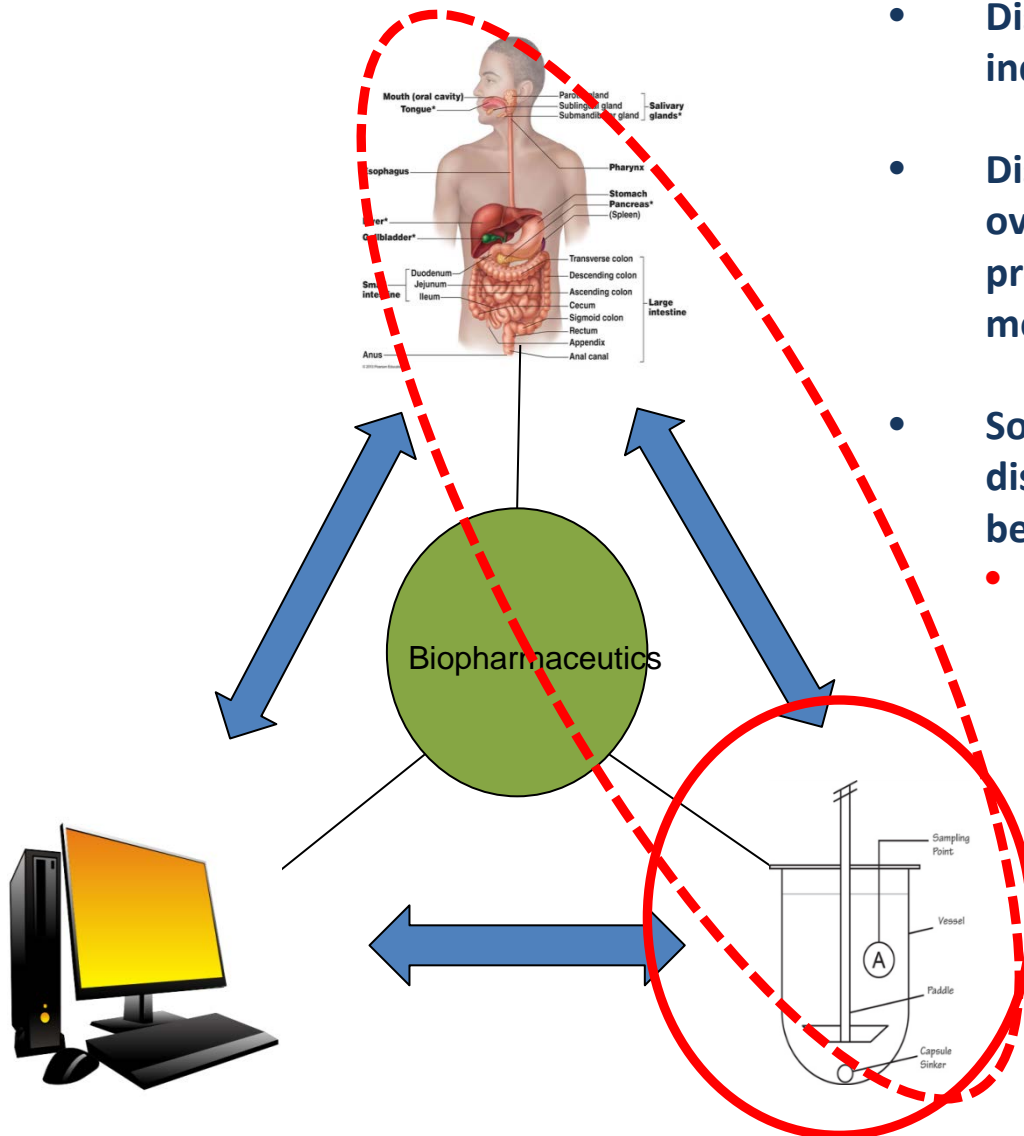
# Current perspective Biopharmaceutics Approach



# Current State



# Current State → Moving Forward



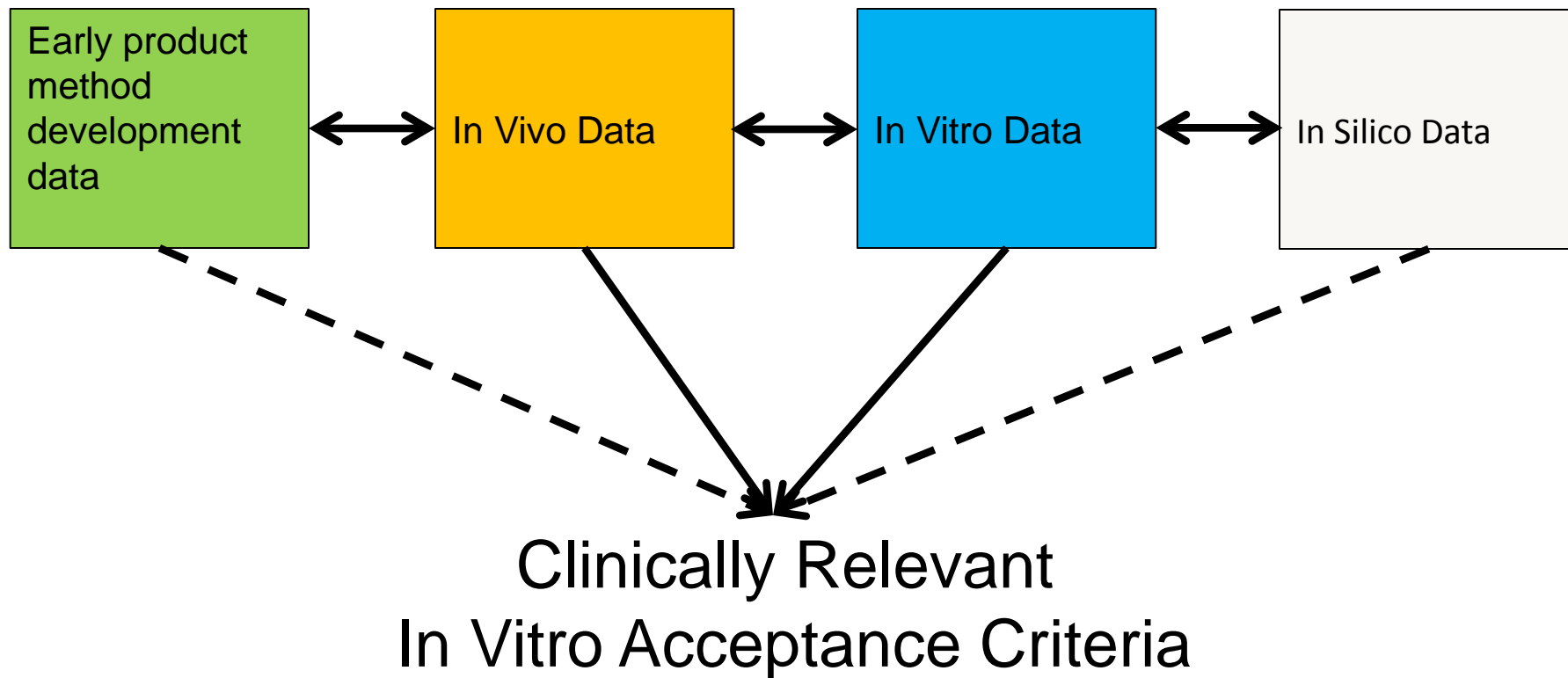
- Dissolution assessment often independent of in vivo assessment
- Dissolution methodology sometimes oversimplified for higher risk products (e.g. apparatus selection, media, etc.)
- Sometimes methodology is over-discriminating as in vivo results can be “less sensitive”
  - **CRS via IVIVC or in silico supported can lead to wider specifications**

# Additional Considerations

- **Open to different dissolution apparatuses with justification**
- **“Bio-Relevant Dissolution”**
  - **Apparatus?**
  - **Media?**
  - **In-Vivo Correlated?**

**From QC perspective, could be none or all of these.  
Application/Product specific.**
- **Various apparatuses often explored in development phase but not seen as “viable” as QC.**
  - **Could still have relevance in modeling**
- **In Silico Modeling and Analysis**

# Future Directions—Clinical Relevance(A/NDA)



# Conclusions

- **Historically, FDA tried to achieve consistency in selecting dissolution methods for generic products. ER product dissolution methods have been generally developed case-by-case bases.**
- **Currently FDA recommends a biopharmaceutics approach towards developing product specific dissolution methods/in vitro release tests for the ANDAs as well as the NDAs**
- **More early development data should be submitted in support of QC in vitro release tests**
  - **Computational modeling can be a useful tool with larger data pool**
- **Additional tools {e.g. PBPK} can be used to support clinically relevant specifications**

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