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BIOPHARMACEUTIC RISK ASSESSMENT OF A NEUTRAL BCS CLASS IV DRUG: A GENERIC INDUSTRY PERSPECTIVE

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The Evolution Of Biopharmaceutics: Risk Assessment And Clinical Relevance
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Outline

- Risk Classification & Complexity Scale
- Overview of Biopharmaceutics Risk Assessment (BRA) Cycle in Generic Development
- Role of Innovator Product Understanding
- Dissolution considerations
- Case study – BCS IV neutral in IR formulation

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Biopharmaceutics Risk Classification – general principles

Low/Very Low Risk

Dissolution unlikely rate limiting

- BCS1/ BCS3 in IR dosage form with rapid dissolution
- BCS2a in IR dosage form with rapid release in pH 4.5 and 6.8

Medium Risk

Dissolution may be rate limiting

- Drug substance properties control the dissolution of the API
- low soluble API in simple IR formulation

High/Very High Risk

Dissolution is rate limiting

- Formulation/process modifies the dissolution of the API
  - IR enabled formulations (e.g. *ASD, lipid-based, nano-systems, surfactants)*
  - MR formulations

BCS class	IR simple	IR enabling	MR
Class 1	Very Low risk	-	High risk
Class 2	Medium risk	High risk	Very High risk
Class 3	Low risk	-	High risk
Class 4	Medium risk	High risk	Very High risk

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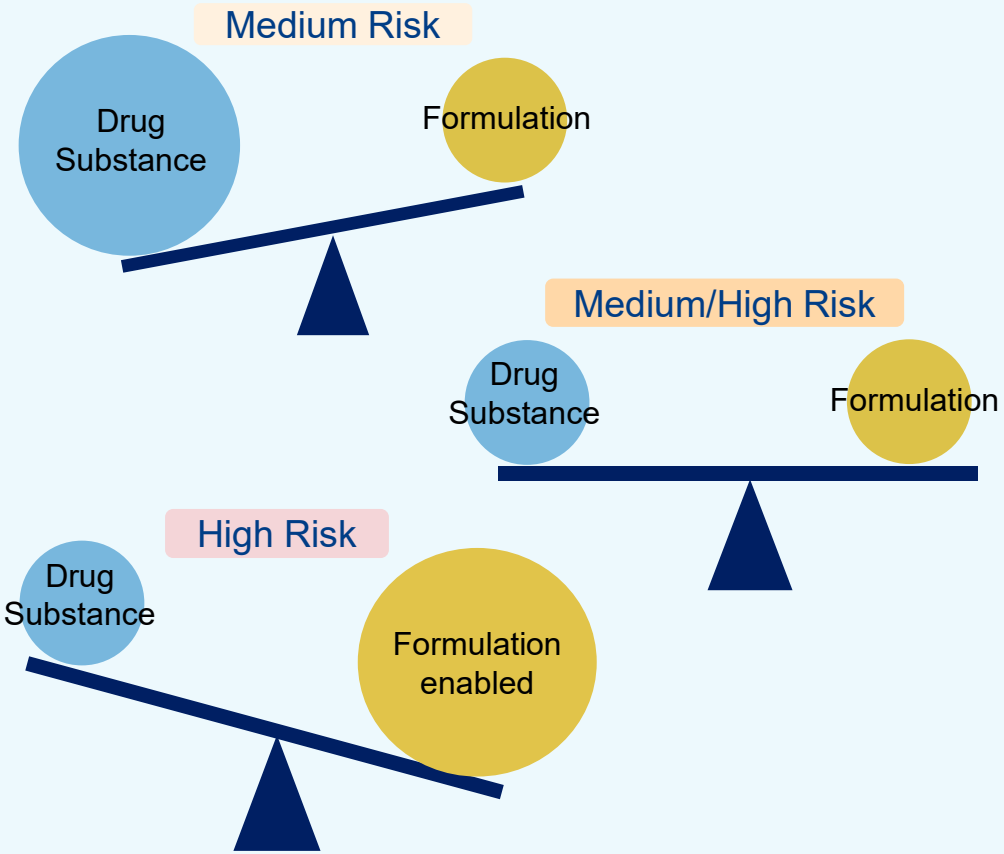
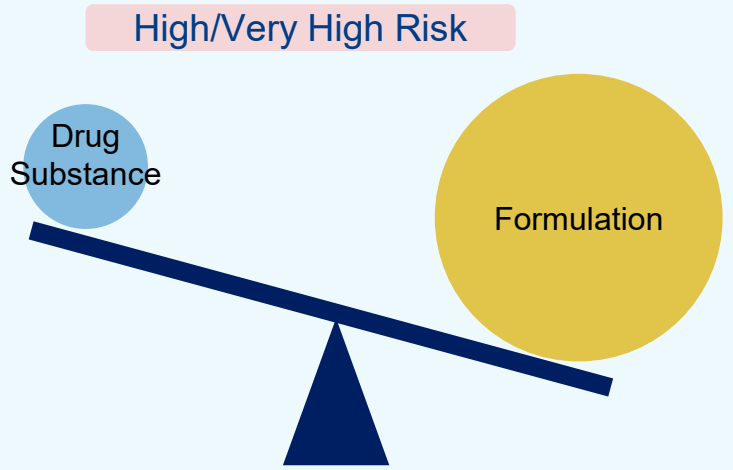
Complexity “scale”

IR products



API and/or Formulation drive the complexity/risk

MR products



Formulation drives the complexity

Excludes low risk

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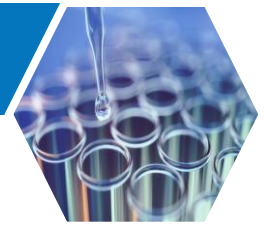
Overview of BRA cycle in Generic Product Development



Biopharmaceutics risk assessment is a continuous process

Complexity & Risk based determination/decision

Evaluation of the RLD

- Biopharmaceutics understanding and risk level
- Initial **BRA:**
  - *Identify potential CBA*
  - *Identify in-vitro dissolution media to guide formulation development*
- Preliminary IVIVR
- Assign complexity level

Development

- Prototype formulations (typically 2 variants)
- **BRA** before pilot
- Pilot BE for PK confirmation
- **BRA** after pilot:
  - *confirm the bioindicative media*
  - *refine the model & propose target profile for pivotal or return to development*

Pivotal batches

- Optimize the formulation
- **BRA** before pivotal
- Pivotal BE
- IVIVR/IVIVC
  - *BE safe space*
  - *CRDS*
  - *Biowaiver support*
  - *Specification support*
- Filing and approval

Lifecycle management

- **BRA** for biowaiver of the post approval changes supported with IVIVR/IVIVC

CRDS - Clinically Relevant Dissolution Specification;
CBA –Critical Bioavailability Attributes

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What is a Generic Drug Product ?

A generic drug is a medication created to be the same as an already marketed brand-name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.

These similarities help to demonstrate bioequivalence, which means that a **generic medicine works in the same way and provides the same clinical benefit as the brand-name medicine**.

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First things First…

- **Understand the target - Innovator's product**

Drug Substance
+
Drug Product
+
Pharmacokinetics

⟺

Literature evaluation
+
In vitro characterization

- Identify the CBAs for the innovator's product
- Determine the **complexity**
- Determine the **initial biopharmaceutics risk**
- **Establish dissolution condition (s) that correlate with in vivo (to be used in the development)**

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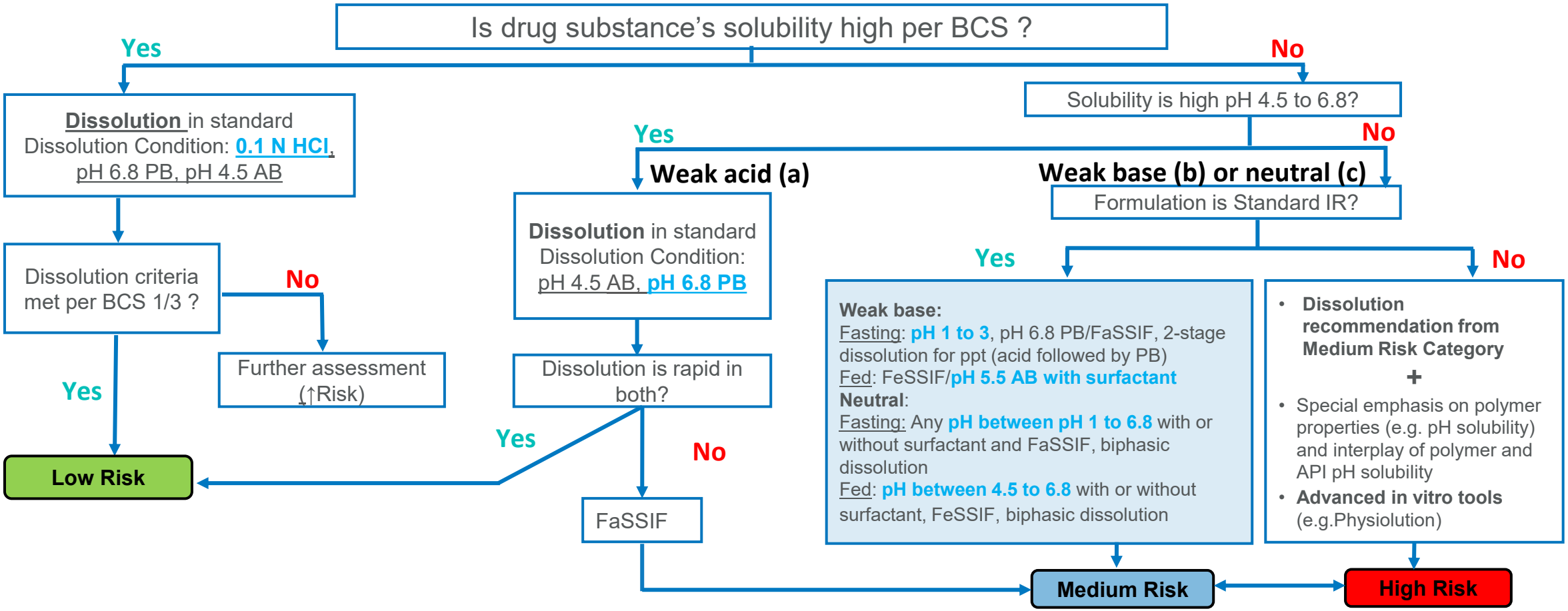
Dissolution considerations (IR)

Select **meaningful dissolution condition** considering:

- **Formulation attributes** – **Drug Substance** and **formulation performance** across GIT environment
- **GIT** - site of release, pH



**Blue font – potential QC*

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Case study – medium risk

IR product
BCS4c (neutral)
Simple formulation and process

Literature evaluation

RLD facts

- BCS4 neutral compound & simple formulation
- Moderate In vitro (Caco-2) permeability
- Tmax ~2h
- Absolute BA ~40%
- Hepatic metabolism and elimination
- T/2 moderate ~7h
- Food effect - minor ↑AUC, no effect on Cmax
- Crushed tab *vs.* whole tab are BE
- Low PK variability both Cmax and AUC

RLD understanding

- Moderate in vivo dissolution
- Moderate permeability/absorption
- Not sensitive to in vivo tablet disintegration / formulation variables
- API properties likely most critical for solubility/bioavailability

In vitro characterization

DS solubility | **Physical characterization** | **In vitro dissolution**

Complexity, potential CBA

Initial Risk – **Medium**, potential CBA – **API Particle size** (variants to study)

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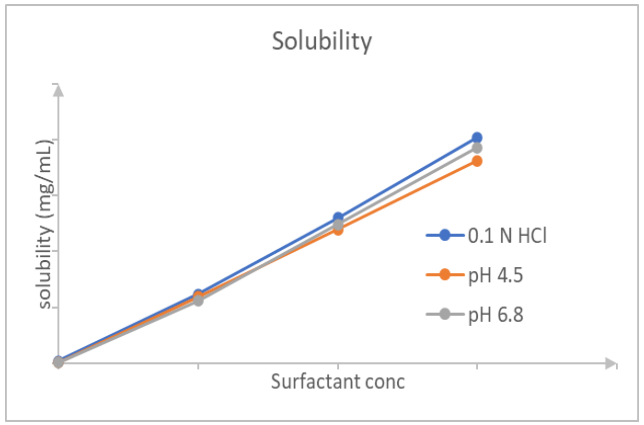
Case study (ctn'd)

DS solubility

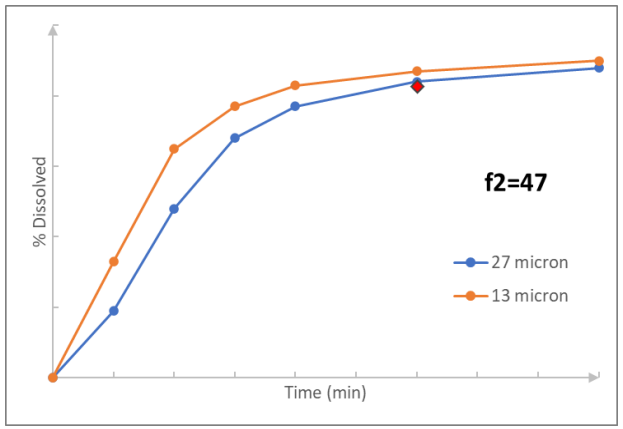
BCS4c (neutral)
pH independent
Very low solubility w/o surfactant
Moderate in biorelevant
(D/V<1000ml)



In vitro dissolution

Dissolution condition selection:
- Dissolution pH independent
- Surfactant required

Dissolution condition optimization:
- DoE 2^2
- Factors: **surfactant conc** & **agitation**
- Assess discrimination toward **API PS** (+CFV,CPP)



Variants

CBA – API PS range to be studied ~10-30μm

	API PS (D90)	T/R Cmax FA	T/R AUCt FA
Variant 1	13 μm	90	97
Variant 2	27 μm	81	93
PS spec (3 tier)	**D90 NMT 18 μm**		

- Dissolution condition is discriminatory to API PS
- API PS is controlled with tighter limits

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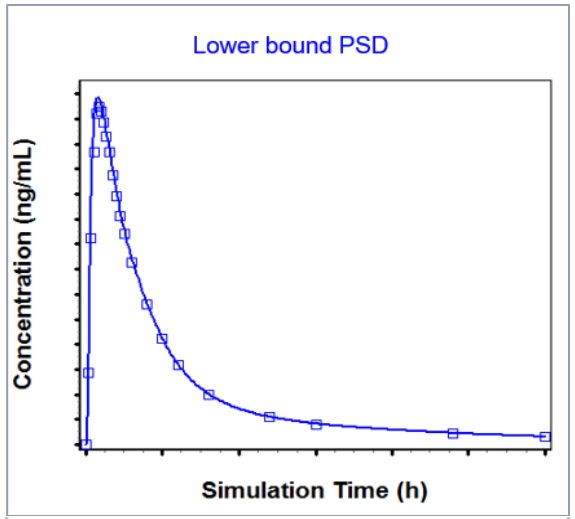
Case study (ctn'd)

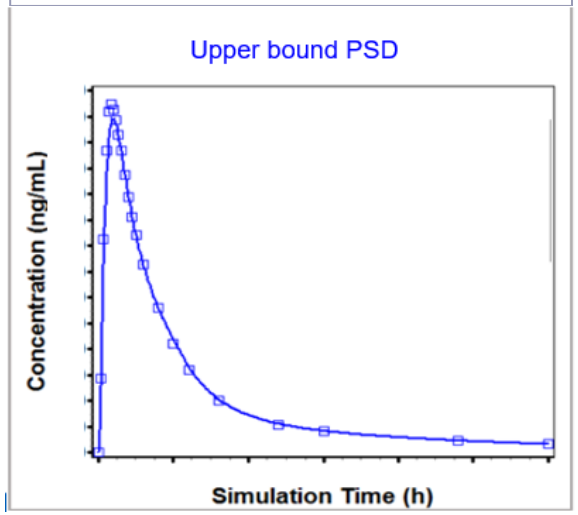
Agency's ask - API PS specification to be supported with:
- in vivo/in vitro results and their correlation
- Comparative dissolution of batch at high end of spec with f2<50

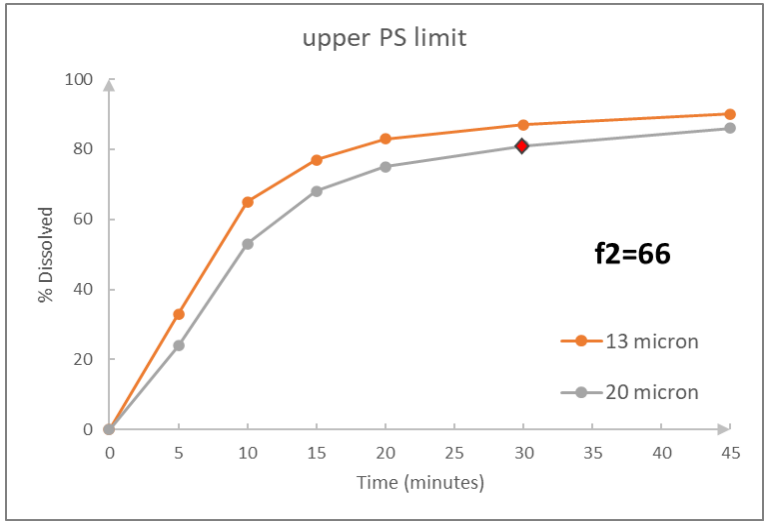
Model development (Johnson)
- IV profile literature
- BE batch

Model validation
- Non-BE batch

Model application: - simulate PSD impact on PK
- Virtual Lower bound PS
- Virtual Upper bound PS







PK Parameter	Bio Batch vs Lower Bound PSD spec	Bio Batch vs Upper Bound PSD spec
Cmax	103%	95%
AUCt	101%	98%

- Dissolution is bio indicative
- API PS specification supported by PBBM
- Totality of evidence used for biopharmaceutics risk mitigation

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Case study - overview

Biopharmaceutics risk assessment - mitigation

Development

Initial stage: Identify Initial Critical Bioavailability Attributes (iCBA)

- Knowledge base
- Complexity factors identified
- Similarity of approach

Confirm the iCBA

- In vitro studies
- In vivo pilot studies
- In silico studies

Control Strategy

- Determined acceptable ranges for CBA
- *Control strategy based on dissolution and API PS specification*

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Summary

BRA in generic development

- Understand the **innovator (target)** and key pCBA
- Identify pCBA for the **generic product** (API, formulation)
- Continuously refine **biopharmaceutics risk** (literature, in vitro, pilot BE)
- Dissolution should reflect the **physiological relevance**
- Integrate **multiple evidence streams**:
  - Combine dissolution, additional controls on CBA, in vivo data, in silico
- **Control strategy** should be risk-driven and clinically relevant
- **Dissolution is one tool – not the entire control strategy**

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