The role of dissolution in development of very low and low risk compounds

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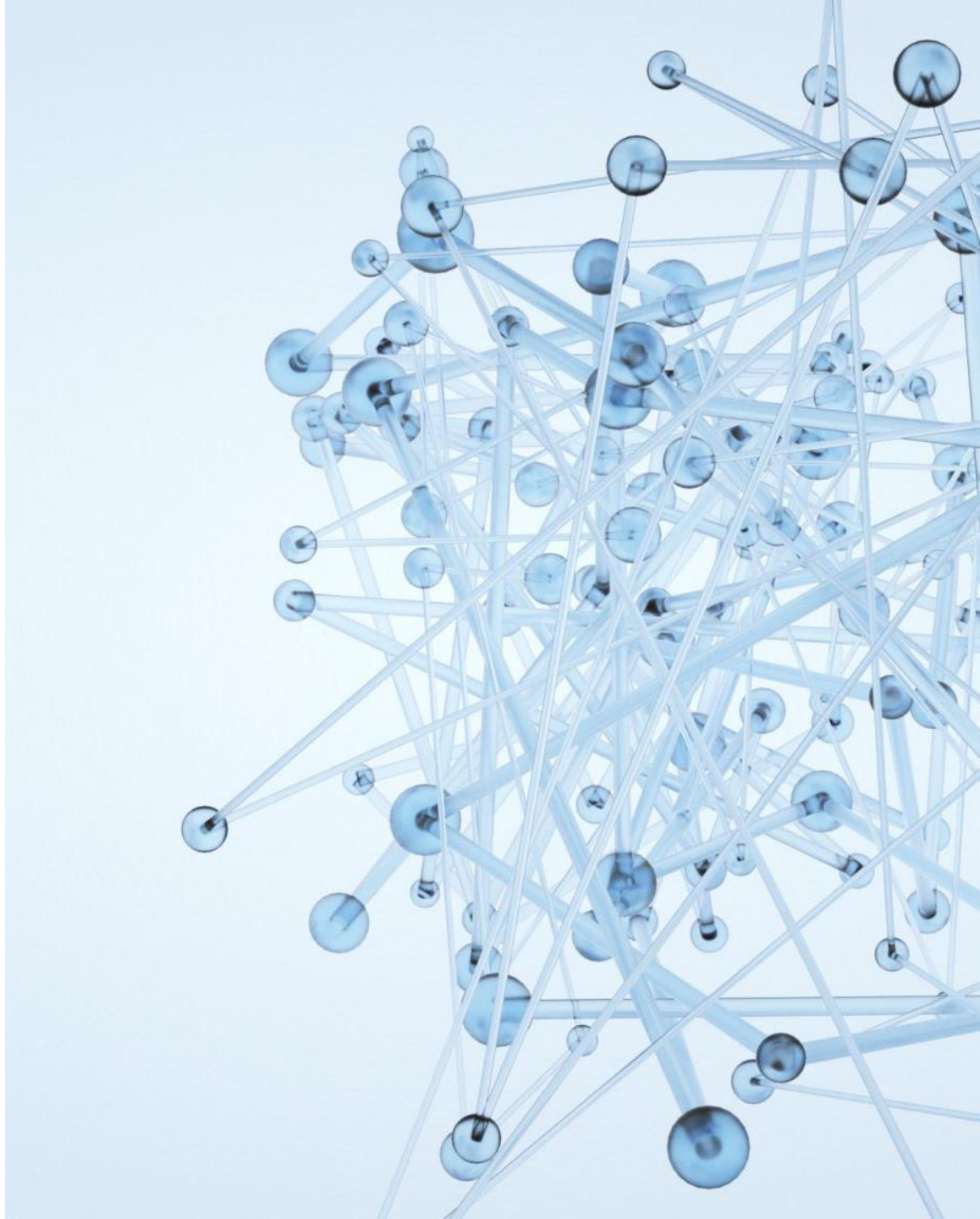
FDA/M-CERSI workshop on *The evolution of Biopharmaceutics: Risk assessment and Clinical Relevance*, Rockville, Md., April 30th to May 1st, 2026



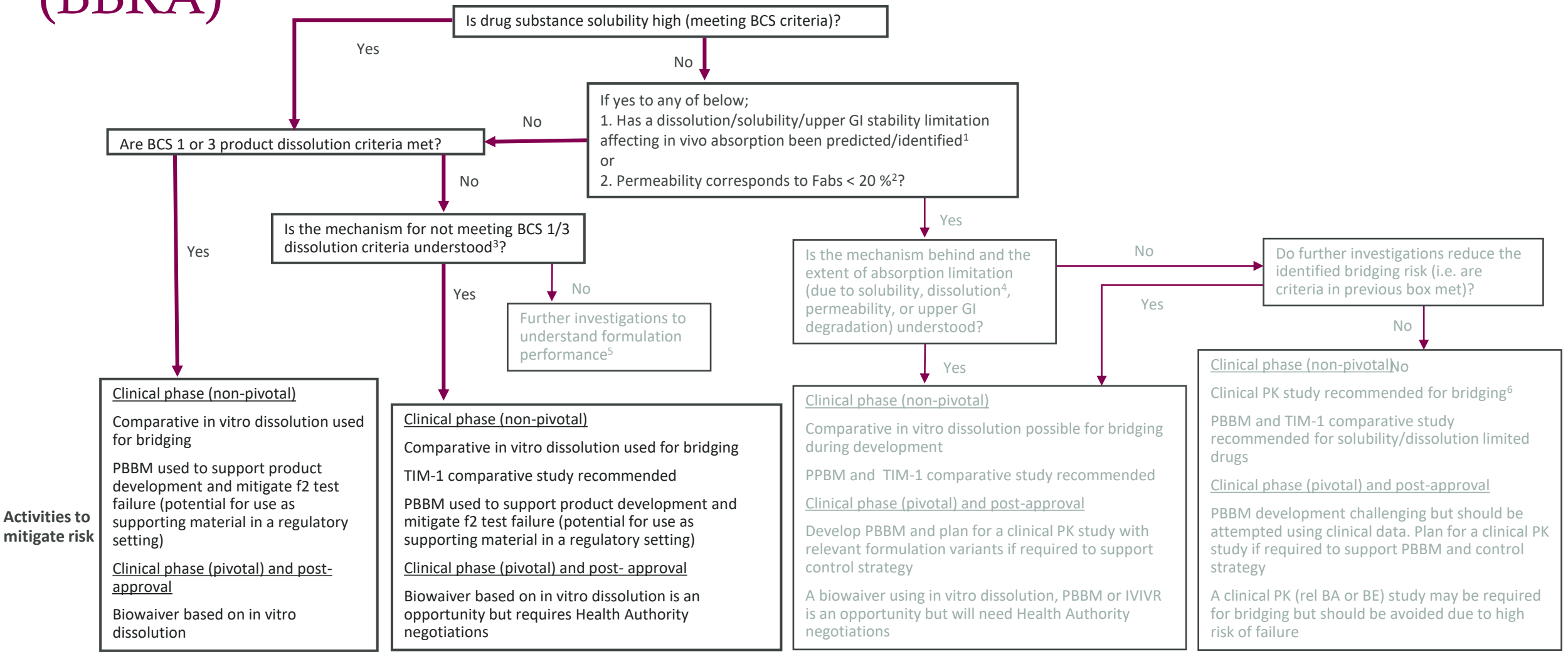
Purpose

- Present an AstraZeneca developed Biopharmaceutics bridging risk assessment tool
  - Opportunity to risk assess beyond BCS

- Present 4 case studies of low and very low risk compounds
  - Discuss dissolution assessment
  - Discuss use on disintegration for QC testing

- Show that BCS is overly conservative in risk assessment

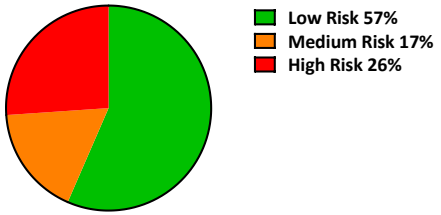
AstraZeneca decision tree for biopharm bridging risk assessment (BBRA)



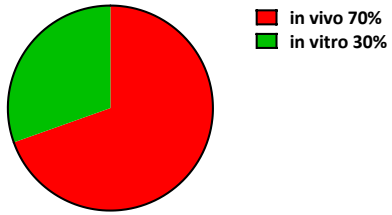
Ref. Mol. Pharmaceutics 2025, 22, 6203-6214.

Biopharmaceutics Strategy – based on portfolio learning, key contributor to achieve Lead Time Reduction & Productivity Goals

2021: Evaluation of 23 bridging cases & outcomes with acceptable clinical performance



Biopharmaceutics Developability Risk



Bridging Approach

74% Low-Medium Biopharmaceutics Risk…

…still in vivo bridging studies in **70%** of the cases, but…

0% in vivo study failures

- Strong rationale for reducing number of in vivo bridging studies without increasing risk
- Triggered initiation of new risk assessment in 2022

2025: Portfolio impact of implementing new bridging risk assessment

- Decision tree defining Bridging Risk & guiding Project Bridging Strategy
- Maximizes use of in vitro disso, PBBM & AiV as rel BA study surrogates
- Combined late IVIVR study & PBBM used to reduce/remove BE failure risks

60-70% Estimated reduction in RelBA studies based on 2022 strategy

16 Bridging cases in 2025

80% of 16 bridging cases based on in vitro, AiV and PBBM

- Productivity gains 2023: 49 months lead time reduction.

Characteristics of very low and low risk compounds

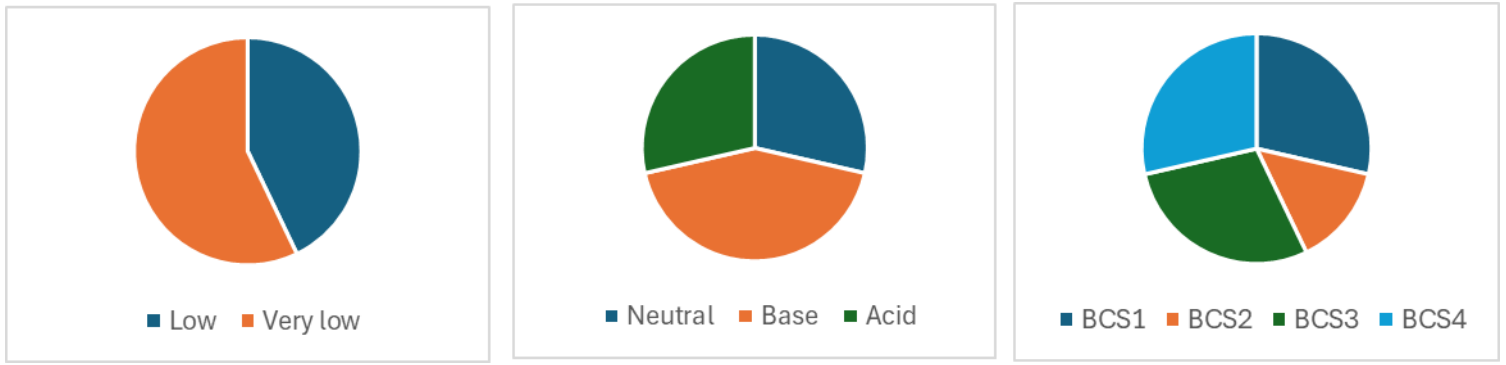
Very Low Risk

- Fulfills BCS class 1 or 3 criteria according to ICH M9.
- Bridging can be done using comparative, standard in vitro dissolution only and has a very low risk of failing to show similarity.

Low Risk

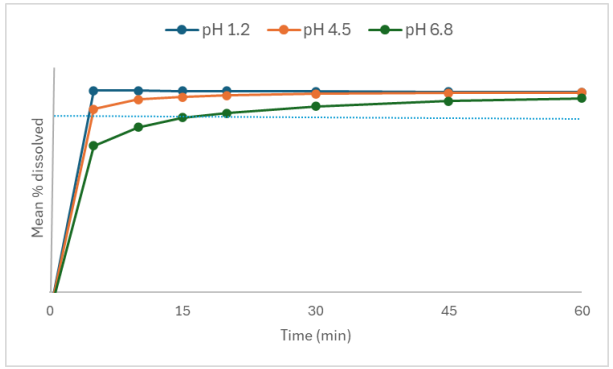
- Substances that do not fulfill strict BCS class 1 or 3 criteria according to ICH M9 but demonstrate BCS class 1 or 3 characteristics
- Absorption is not limited by formulation performance, as assessed by means of PBBM, clinical PK, and/or solubility/dissolution data.

AZ compounds evaluated in vivo with successful bridging



Case study 1: BCS1/Very low risk compound

Buffer	Dose/solubility ratio (<1)
pH 1.2	<0.0001
pH 4.5	0.007
pH 6.8	0.04



Is drug substance solubility high (meeting BCS criteria)?

Yes: Solubilty high across pH range

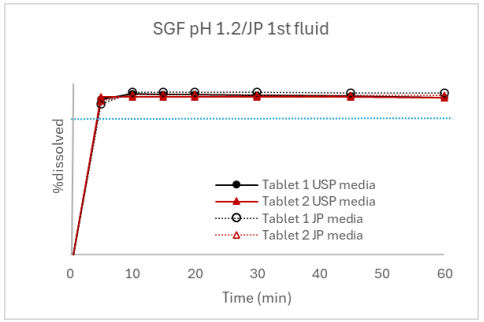
Abs BA>85%

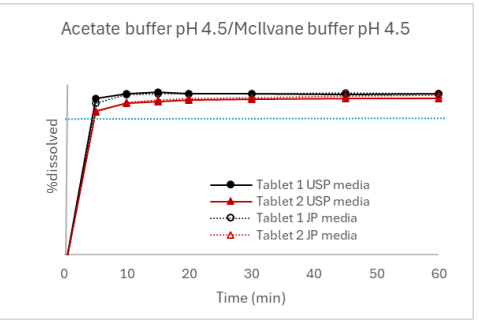
Are BCS 1 or 3 product dissolution criteria met?

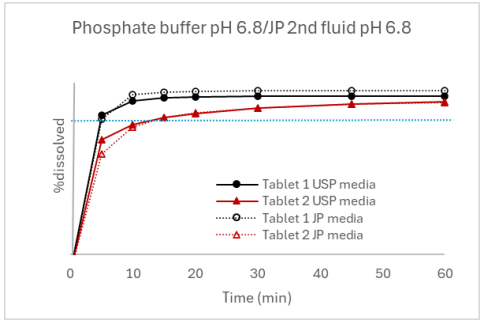
Yes
> 85% in 15 min, pH 1.2-6.8

Very low

Biowaiver based on in vitro dissolution

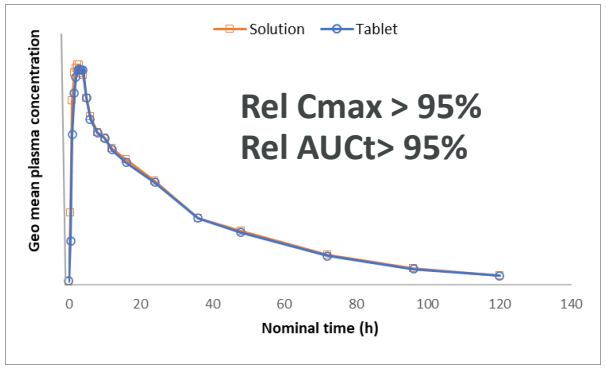






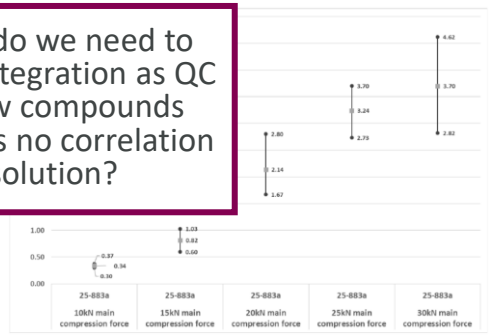
Topic for discussion:
Could dissolution package be reduced for highly soluble compounds?

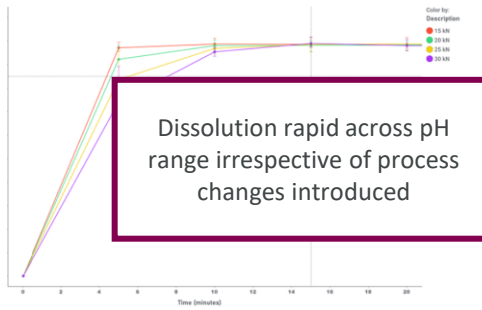
In vivo data validating very low risk:



Disintegration as QC

What data do we need to support disintegration as QC for very low compounds when there is no correlation to dissolution?

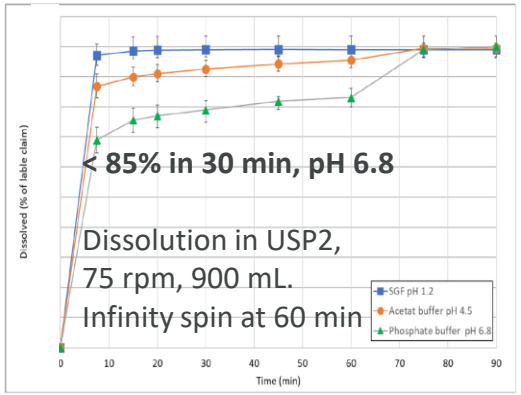




Dissolution rapid across pH range irrespective of process changes introduced

Case study 2: Low risk basic compound not fulfilling BCS1/3 criteria for bridging wrt dissolution

Buffer	Dose/solubility ratio (<1)
pH 1.2	<0.01
pH 4.5	<0.08
pH 6.8	0.14



< 85% in 30 min, pH 6.8

Dissolution in USP2,
75 rpm, 900 mL.
Infinity spin at 60 min

Is drug substance solubility high (meeting BCS criteria)?

Yes: Solubilty high across pH range

Permeability high
(Mass balance study –> Fabs=91%, Caco-2 BCS = High)

Are BCS 1 or 3 product dissolution criteria met?

No

Is the mechanism for not meeting BCS 1/3 dissolution criteria understood[3]?

Yes

>85% in 30 min after removal of coning as in vitro artefact

Low

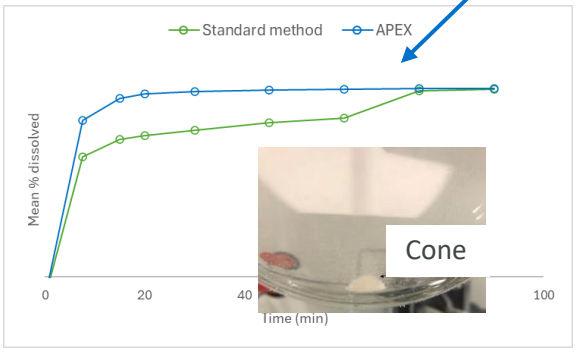
Disintegration as QC

Potential for disintegration as QC test?

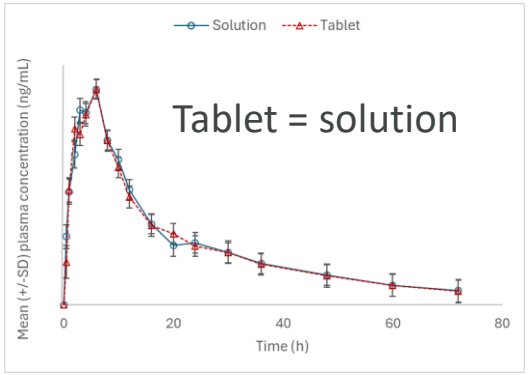
"> 80% in 15 minutes at pH 1.2, 4.0 and 6.8 is not considered fulfilled as standard conditions should be used to show rapid dissolution."

Topic for discussion:

APEX vessel or alternative methods acceptable to show rapid dissolution for formulations with excipients that are prone to cone?

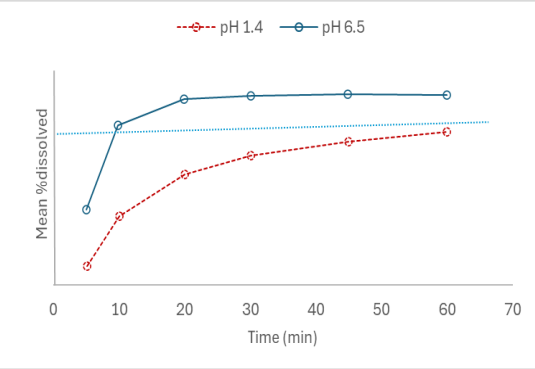


In vivo data validating low risk:



Case study 3: Low risk acidic compound not fulfilling BCS1/3 criteria for bridging wrt solubility and dissolution

Buffer	Dose/solubility ratio (<1)
pH 2	1.1
pH 4.5	1.4
pH 6.8	0.14



Dissolution in USP2, 75 rpm, 900 mL

Is drug substance solubility high (meeting BCS criteria)?

No: Solubilty borderline at low pH

If yes to any of below;
1. Has a dissolution/solubility/upper GI stability limitation affecting in vivo absorption been predicted/identified[1]
or
2. Permeability corresponds to Fabs < 20 %[2]?

No: Caco-2 BCS High
Dose proportional exposure
PBBM Predicted Fabs=100%
Solution vs tablet: Rel BA > 90%

Are BCS 1 or 3 product dissolution criteria met?

No: < 85% in 30 min, pH 1.4

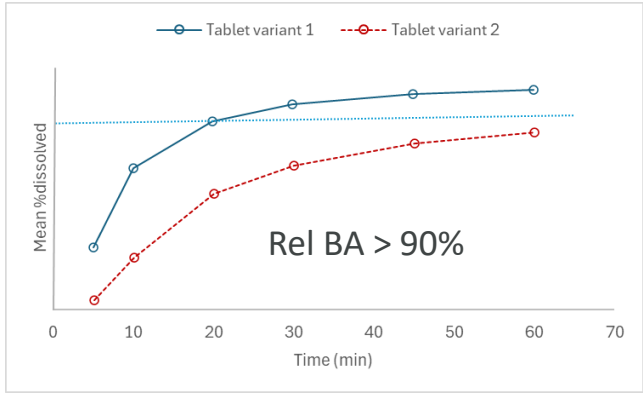
Is the mechanism for not meeting BCS 1/3 dissolution criteria understood[3]?

Yes
PBBM: Slow dissolution due to low solubility

Low

In vivo data validating low risk:

Fast vs slow releasing tablet variants BE



Dissolution in USP2, 75 rpm

Totality of data support BCS1 like performance in vivo

Case study 4: BCS4 Low risk compound (base)

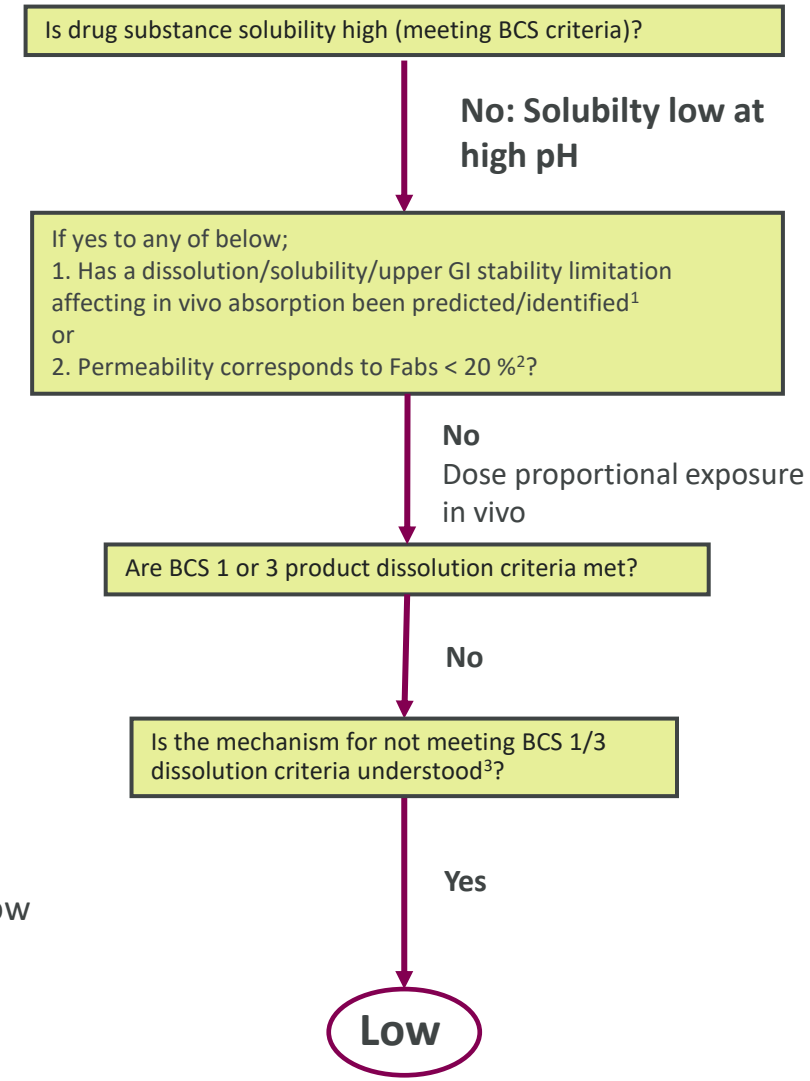
Buffer	Dose/solubility ratio (<1)
pH 2	0.025
pH 4.5	7.8
pH 6.8	8.4

Slow dissolution at pH 6.8 (85% >30 min) in standard method.

But

>85%@30 min in FaSSIF, peak vessel, 50 rpm

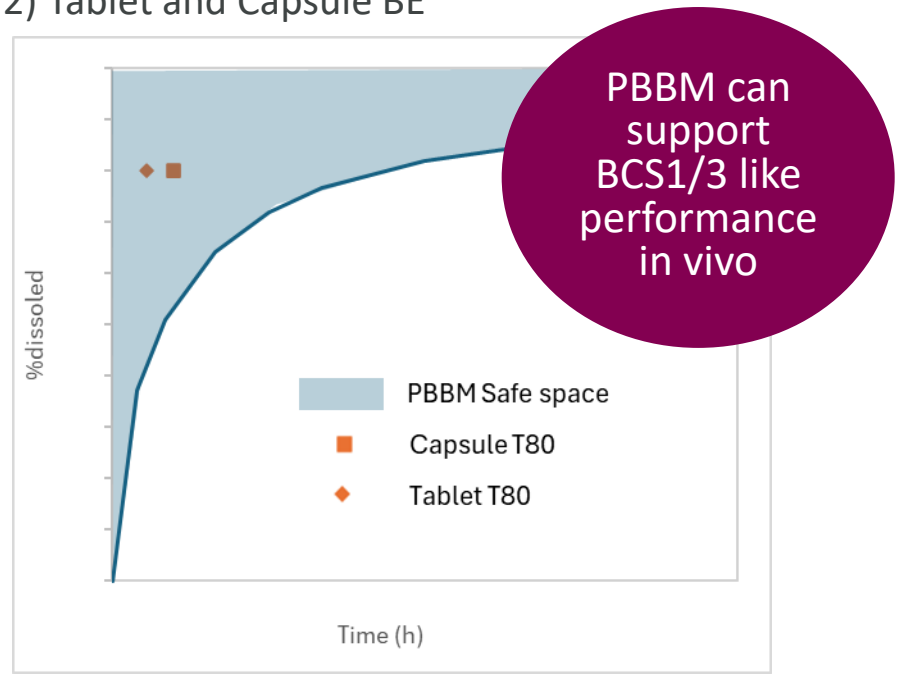
-> Slow dissolution due to low solubility and coning



In vivo data validating low risk:

Tablet and capsule dissolve within PBBM predicted safe space in vitro

In vivo:
1) Solution and tablet BE
2) Tablet and Capsule BE



Conclusions

- BCS overly conservative as basis for biowaivers. Instead, risk assessment should be based on state-of-the-art science (incl PBBM).
- Risk assessment tools expands biowaiver opportunities beyond BCS1/3 through use of PBBM (and Advanced in vitro tools)
- Discussion topics:
  - Can the in vitro dissolution package for bridging be reduced for very low risk drugs?
  - What data are needed to support disintegration as QC method?
    - Very low risk: Dissolution/disintegration required at all?
  - What´s the view of apex vessel to remove coning as in vitro artefact and support rapid dissolution in context of biowaivers?
  - What is the requirements for use of PBBM to support low risk?

Acknowledgements

AstraZeneca colleagues in Global Product Development with special thanks to:

- Bertil Abrahamsson
- Christer Tannergren
- Donal Murphy
- Fredrik Winge
- Helena Engman
- James Mann
- Maria Hammarberg
- Staffan Berg

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