Dissolution Similarity Applications in New Drug Product Development – Issues and Challenges – Case Studies

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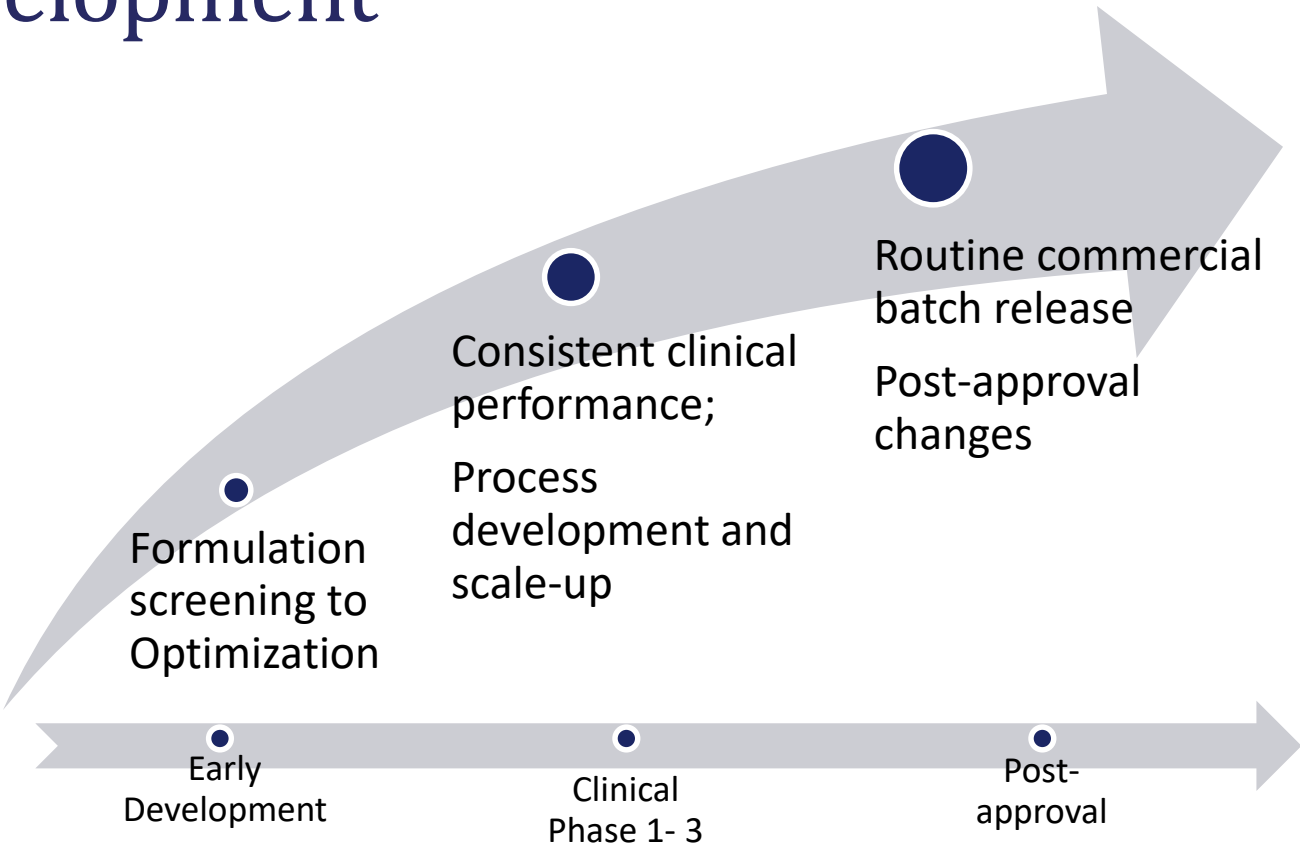
Outline

- Dissolution testing - an innovator company perspective:
  - Role of dissolution and similarity comparison
  - Dissolution similarity – challenges and issues
- Case studies to illustrate common challenges
- Conclusions

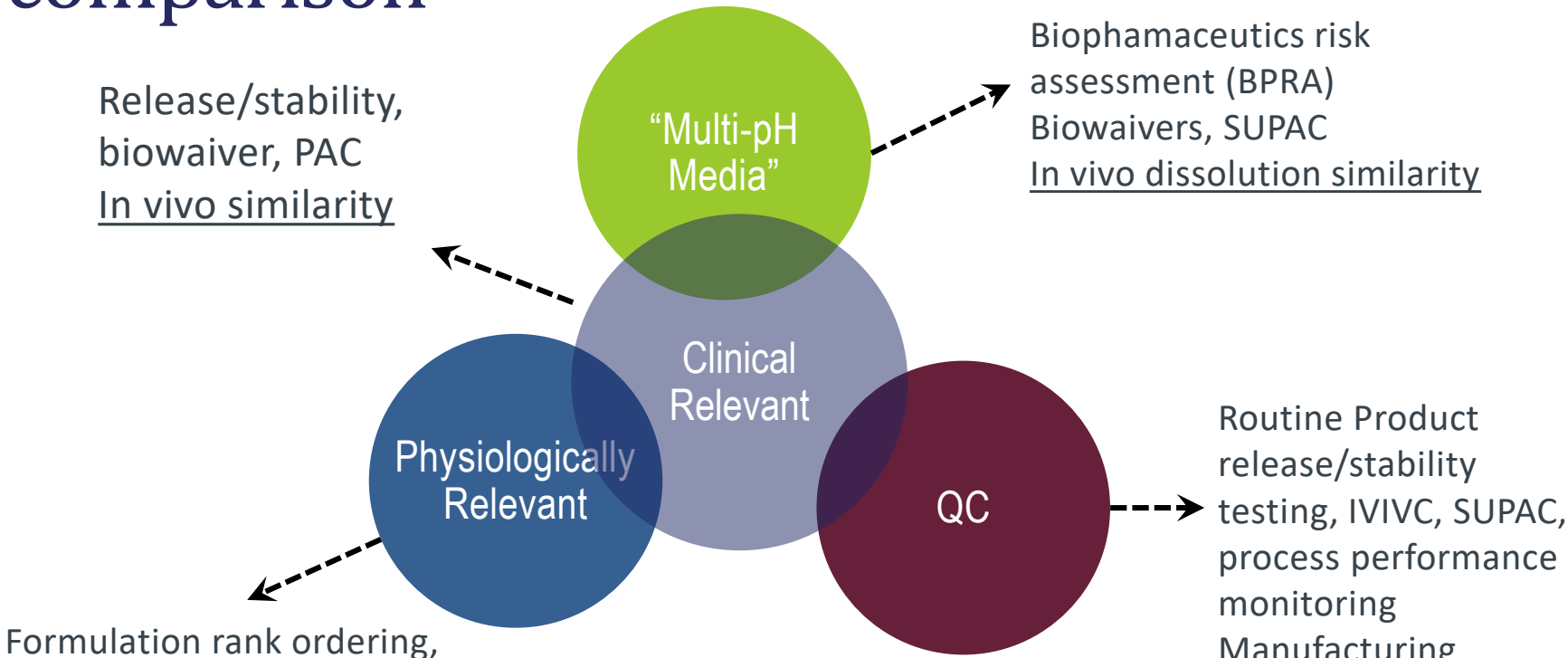
Dissolution in new drug product development



Dissolution similarity comparison

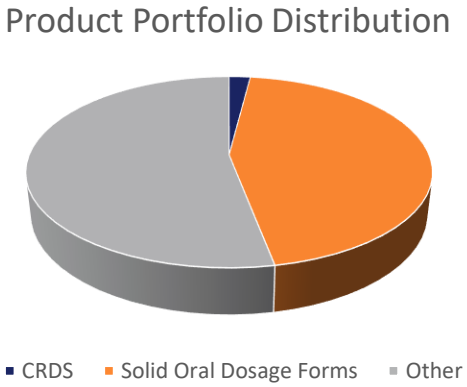
Qualitative → Quantitative

Common application of *in vitro* dissolution methodologies and role of similarity comparison



Dissolution similarity – practical challenges and issues

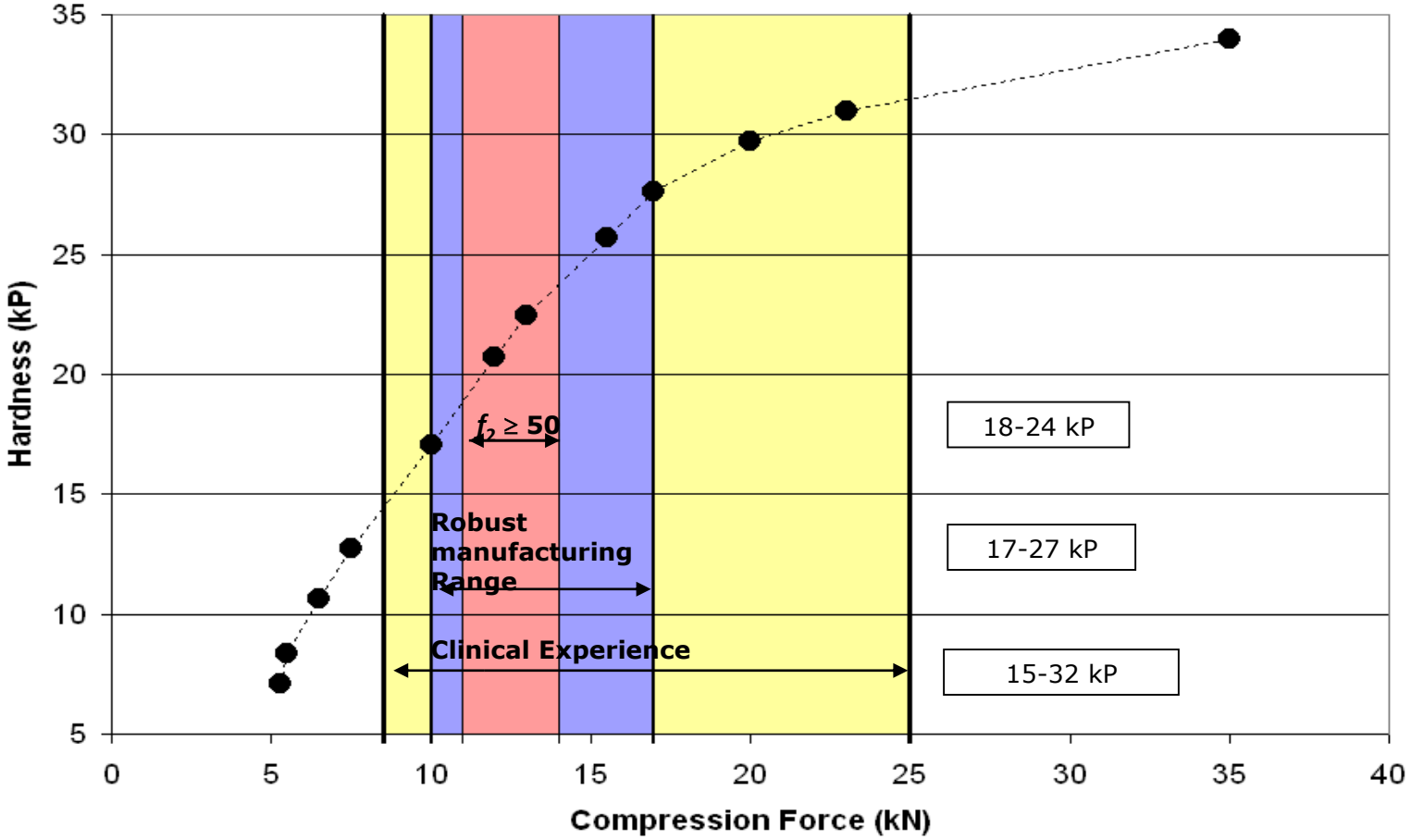
- Is the method aligned with the purpose of the dissolution test?
  - Process sensitivity versus **bioperformance**?
- Is *in vitro* dissolution always a measure of bioperformance?
  - For BCS 1 or III probably not!
- Discriminating Power of the Dissolution method:
  - Too sensitive <-> not sensitive enough?
- General lack of CRDS and general lack of global harmonization



Case study 1: Traditional f2 poses potential manufacturing challenges

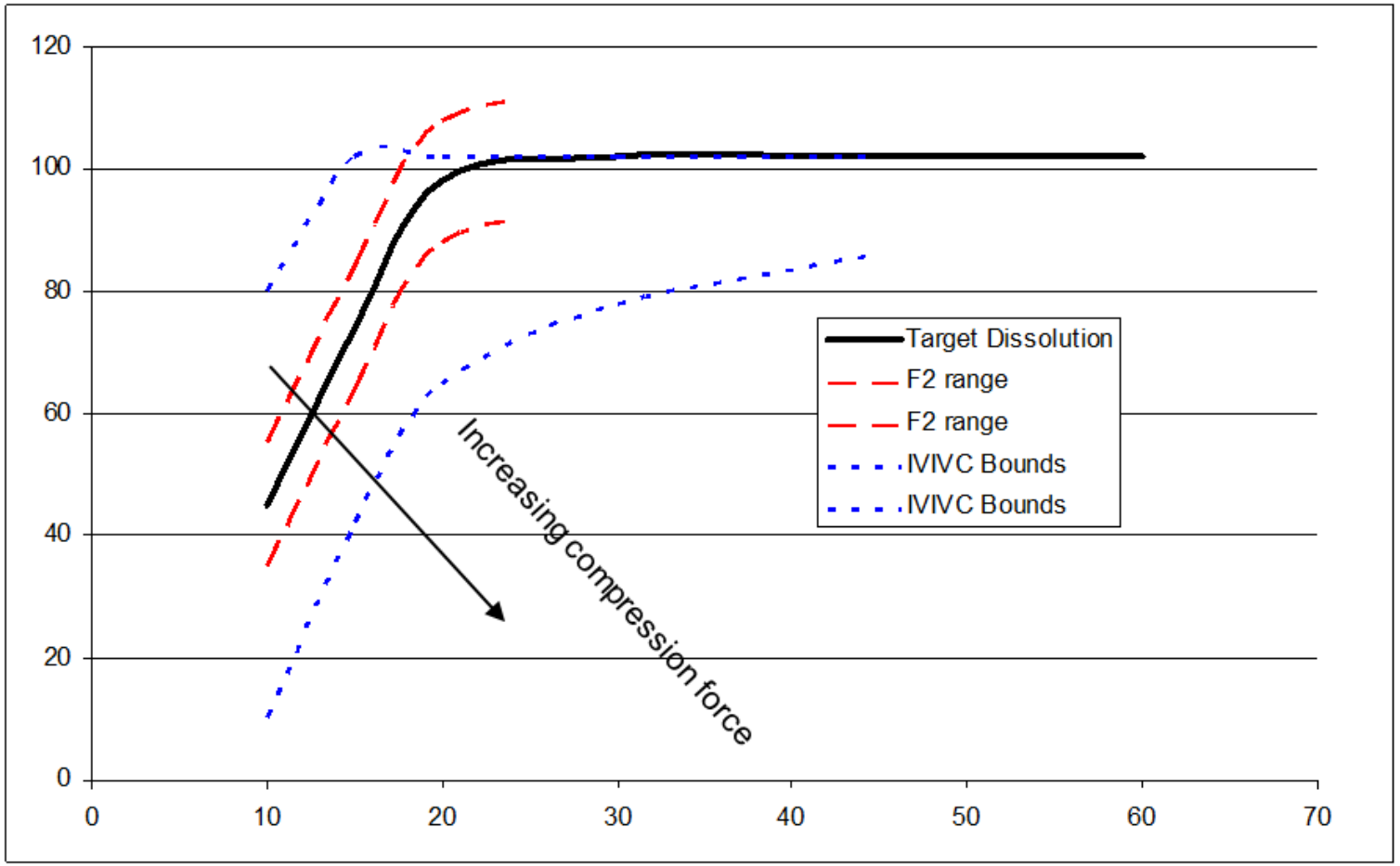
- BCS 2 compound using enabled technology (ASD)
- Method was developed within “global” regulatory framework:
  - Method requires surfactant to achieve sink and solution stability
  - Need to balance method conditions and “discriminating” power
- Tablet hardness very sensitive towards compression force
  - Dissolution profile is very sensitive to tablet hardness
  - Risk that the commercial process may be constricted by a narrow compression window

Justification of a wider processing space



Hermans A, Abend A, Kesisoglou F, Flanagan T, Cohen MJ, Diaz DA, et al. Approaches for Establishing Clinically Relevant Dissolution Specifications during Drug Development. AAPS J. 2017;19(6):1537-49.

Level C IVIVC provides a safe space for dissolution -> process space!



Case study 2: Clinically Relevant Specifications in early product development

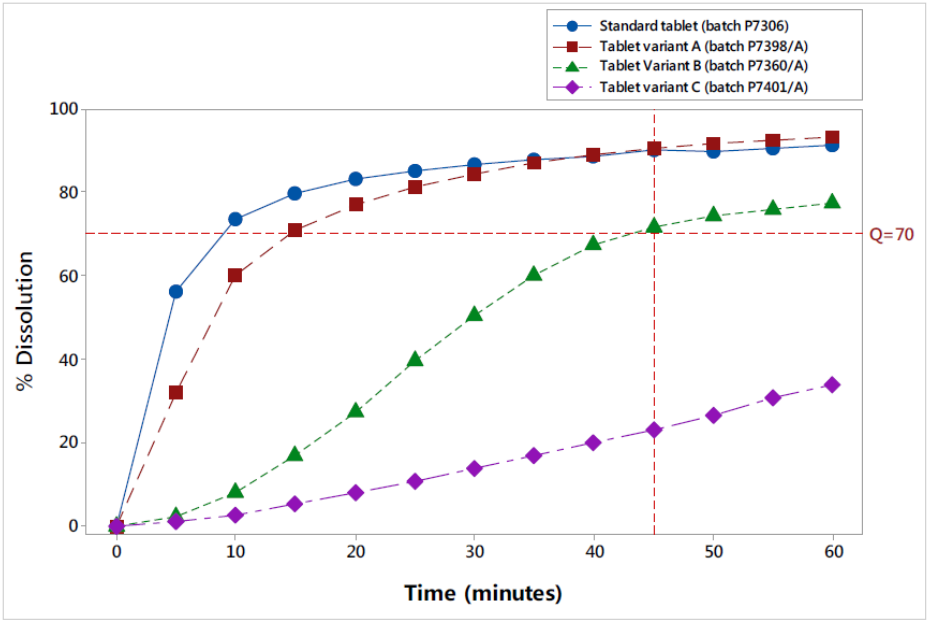
Establishing a link between *in vitro* dissolution performance and *in vivo* PK to enable formulation and process development and justification of the approved dissolution specification ("QC method").

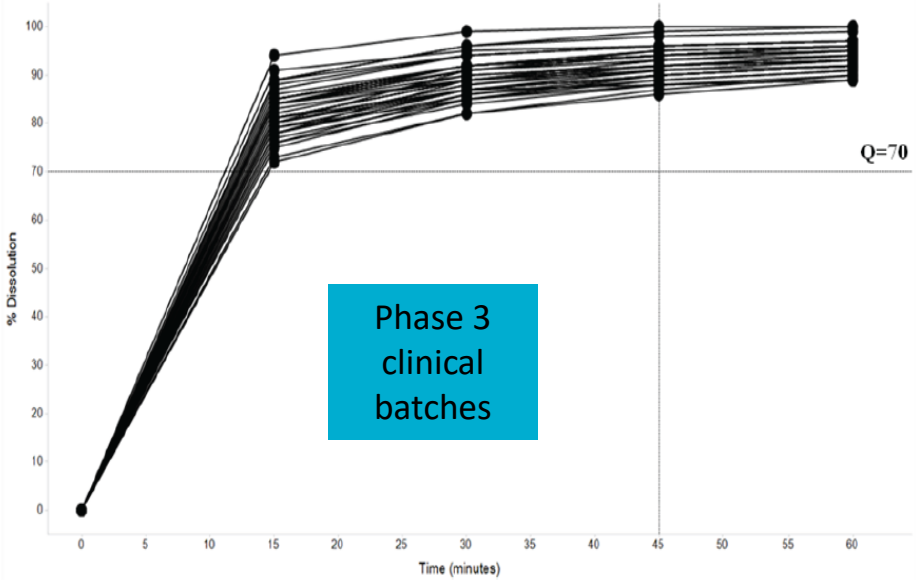
	Description – *In Vitro In Vivo* Study
Standard tablet	tablet batch with a typical *in vitro* dissolution profile
Tablet Variant A	**Process variant :** Over granulated and over-compressed
Tablet Variant B	**Process variant :** Over granulated (extreme) and over-compressed, only large (>1 mm) particles used for compression
Tablet Variant C	**Formulation variant :** Double the amount of binder and no disintegrant

Dissolution specification justification

• The specification limit has been established on the basis of an evaluation batches dosed in pivotal clinical Phase 3 studies, and the results of the *in vivo* study.

• The single-point specification of Q=70% at 45 minutes is well within the range where bioequivalence has been demonstrated, and provides assurance of batch-to-batch consistency in dissolution performance





Product variant and dissolution performance assessment to establish CRDS

Geomean plasma concentrations over 72 hours following administration of standard Phase 3/commercial ticagrelor tablet, tablet variants and oral solution (PK analysis set)

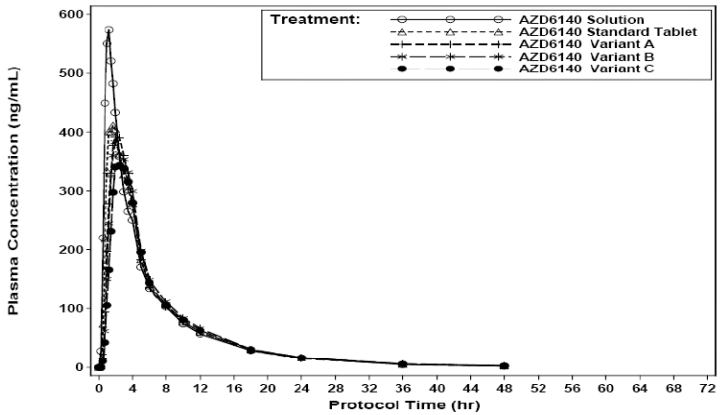


Table 1 Comparisons of exposures from Study 55 versus standard tablet according to bioequivalence criteria (n=24)

Treatment	AUC (ng.h/mL)		Cmax (ng/mL)	
	GLS mean	GLS mean ratio (90% CI)	GLS mean	GLS mean ratio (90% CI)
Standard tablet	2887.0	-	491.3	-
Tablet variant A	2781.7	0.97 (0.90, 1.06)	512.0	1.05 (0.95, 1.16)
Tablet variant B	2925.8	1.02 (0.94, 1.10)	514.0	1.04 (0.94, 1.15)
Tablet variant C	2703.6	0.97 (0.89, 1.05)	440.8	0.91 (0.82, 1.00)

AUC Area under the plasma concentration-time curve from zero to infinity.
C_{max} Maximum plasma (peak) drug concentration after single dose administration.
GLS Geometric least squares
CI Confidence interval.

Passed standard bioequivalence criteria 0.80 to 1.25

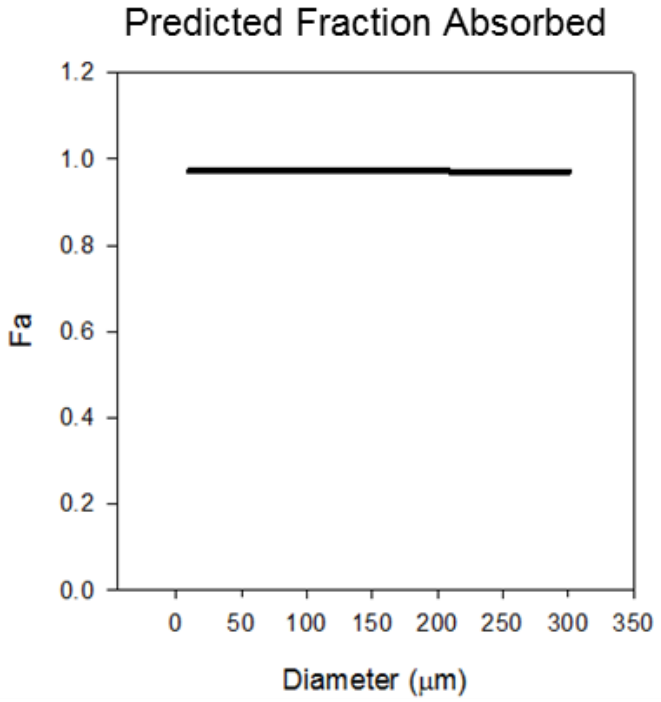
Conclusions

- All of the slowly dissolving tablet variants dosed gave *bioequivalent* exposures to the standard tablets dosed in pivotal clinical Phase 3 studies.

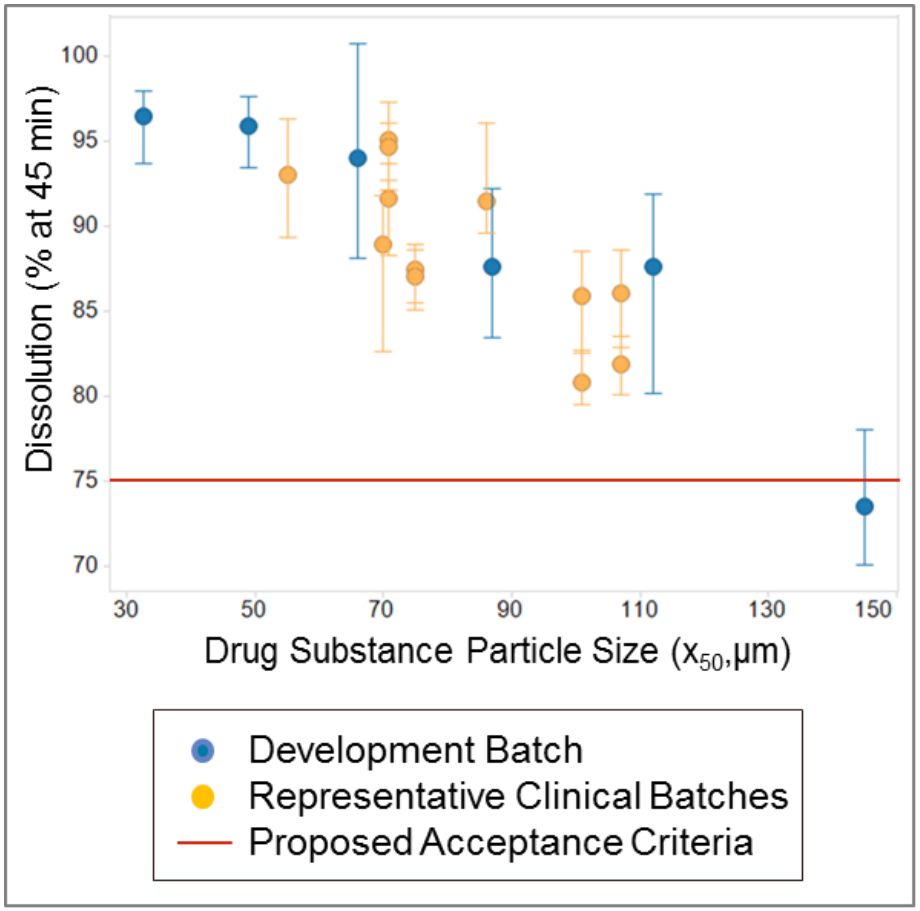
- The study data demonstrate that commercial dissolution method is significantly over-discriminatory with respect to *in vivo performance*

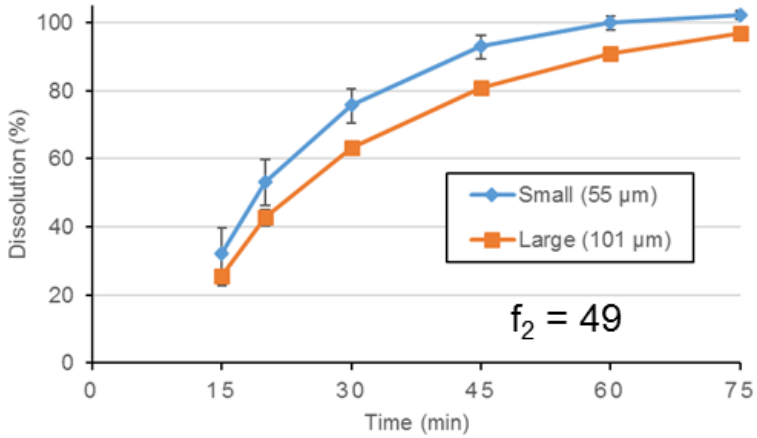
Case study 3: Background

- Highly soluble, slowly dissolving drug substance, blended capsule formulation.
- Appearance in plasma is slow due to holding compartment kinetics and saturation (dissolution is not rate limiting).
- Dissolution method is highly discriminating for particle size.
- PBPK absorption model predicts no impact to absorption or exposure across a wide particle size range.
- Model predictions are supported by in vivo data on a range of formulations and particle size, showing no significant impact to exposure.



Development and Clinical Experience



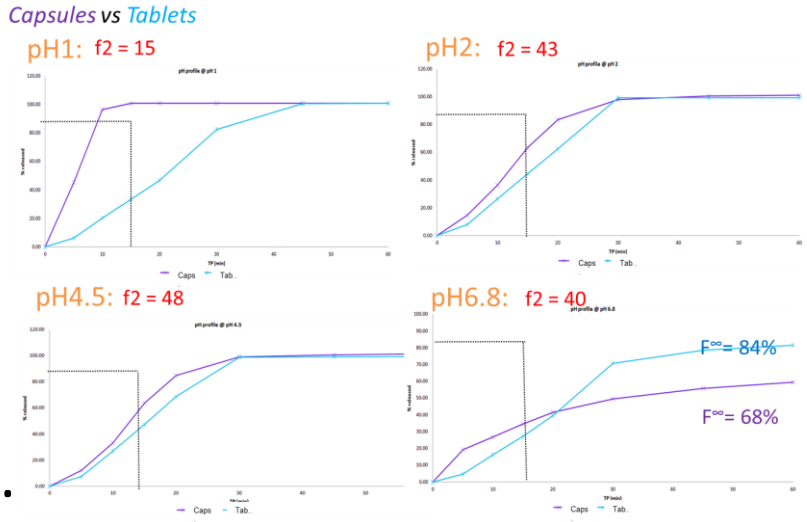


Fastest and slowest representative clinical batches do not meet f_2 criteria.

Risk that future SUPAC type changes may not meet f_2 criteria, despite meeting the dissolution acceptance criteria, and despite the lack of impact to in vivo exposure.

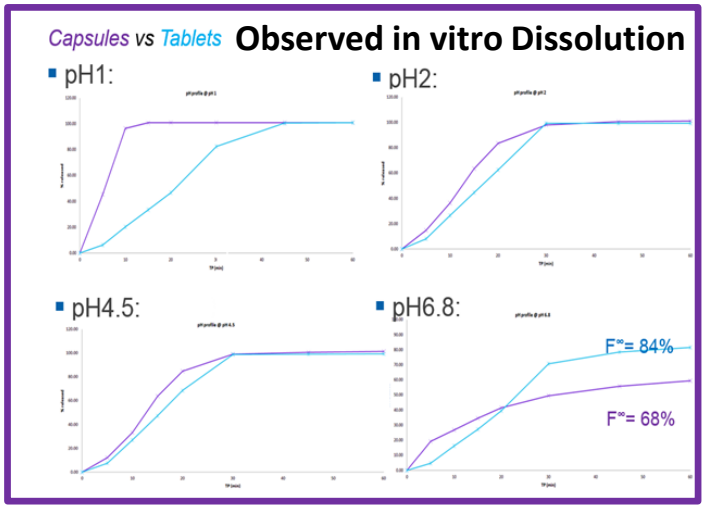
Case study 4: Background

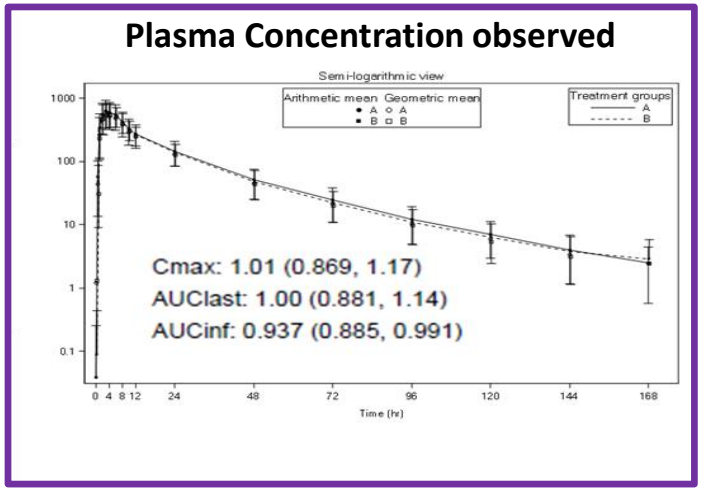
- A capsule formulation used in clinical development is compared with a film-coated tablet formulation which is used as commercial formulation
- compound is BCS category 3, does not fulfill the dissolution criterion of very rapidly dissolving
- the f2 similarity approach failed
- a BE study showed perfect bio-equivalence for both formulations.



- A PBPK absorption modeling approach demonstrated a permeability controlled absorption -> small differences in dissolution performance are not biopredictive

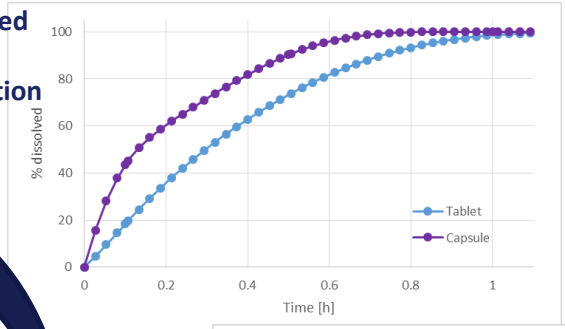
BE Study and PBPK based modeling



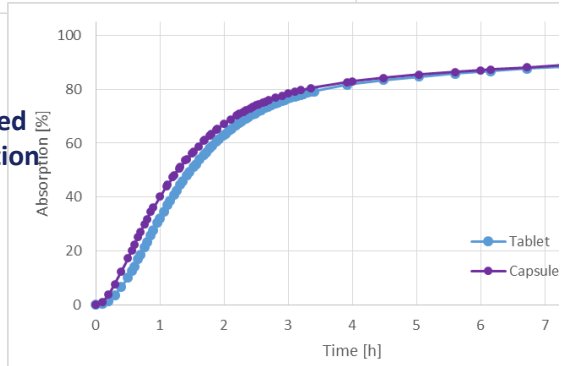


PBPK modeling

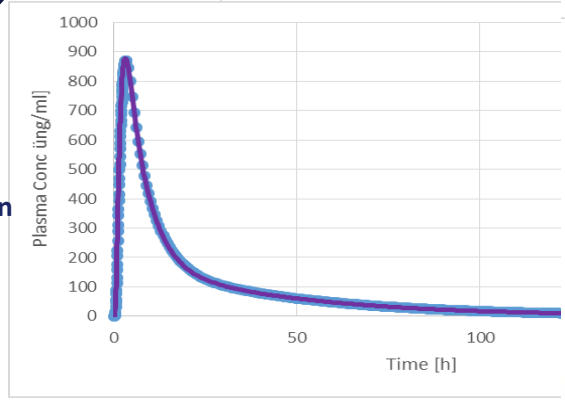
Simulated in vivo Dissolution



Simulated Absorption



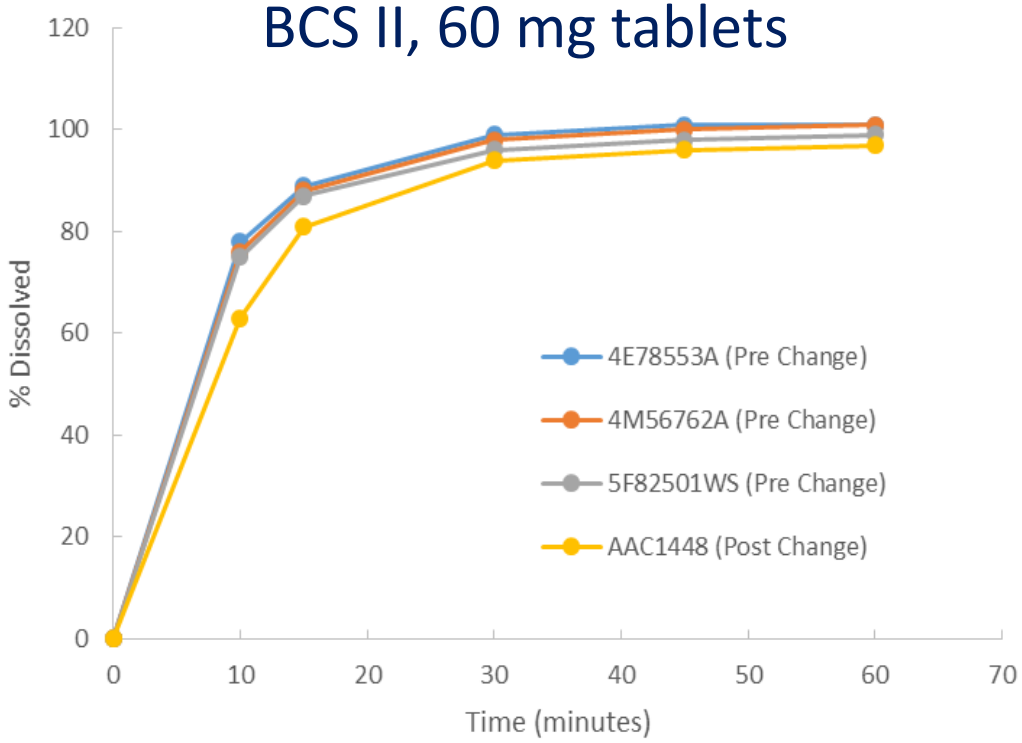
Simulated Plasma Concentration



Case study 5: Post approval changes

- Regulatory filing requirement: comparative dissolution of post change batch(es) to pre-change batch(es) in the application medium
- Slight difference in country requirement.
  - Australia: three pre-change batches and one post change batch
  - EU: no requirement on dissolution profile comparison
  - US: Level 3 change. Dissolution in QC medium, one batch each
  - Taiwan: in three compendia media (pH 1.2, 4.5 and 6.8), one batch each

Manufacture Site Change
BCS II, 60 mg tablets

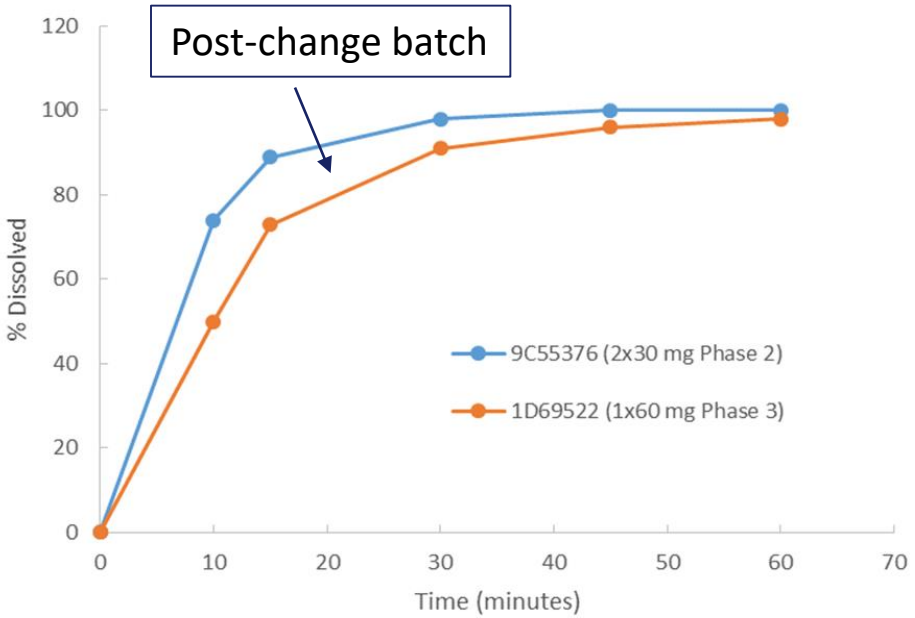


Data did not meet f_2 criteria for pre-change and post-change batches

Justification of manufacture site changes

- A BE study was previously conducted on Ph 2 and Ph 3 formulations which have very different dissolution profiles (f2 can't be used due to too few data points < 85% for Ph 2 formulation).
- The BE study shows perfect bioequivalence between these two formulations despite dissolution difference.
- The dissolution profile for post-change batch meets dissolution specification and falls between the Ph 2 and Ph 3 profiles, thus, the site change was justified.

Ph 2 (2x30 mg) vs Ph 3 (60 mg):



Ph 2 vs Ph 3 formulation:

- Similar excipients
- Different drug load
- Bioequivalent
- Different disso profile

Conclusion

- Regulatory decisions based on dissolution profile comparisons are unlikely going away soon
  - Dissolution as a surrogate of bioperformance is deeply rooted in regulatory guidance practiced globally
  - Most practical option for lifecycle management of commercial products
- Ambiguity of the dissolution method in the absence of an established link to *in vivo* performance is the weakness in *any* decision based on the test!
  - It is the responsibility of the Industry to establish this link
  - Highly desirable for global alignment to accept CRDS
- In the absence of clinically relevant dissolution specifications, dissolution similarity as acceptance criteria maybe appropriate

$50 < F2 < 50$

Thank You!
Q&A