FDA's current practice and challenges in the evaluation of dissolution profile comparisons in support of minor/moderate product quality changes

Om Anand, Ph.D.
Division of Biopharmaceutics
Office of New Drug Products
Office of Pharmaceutical Quality
CDER, US-FDA

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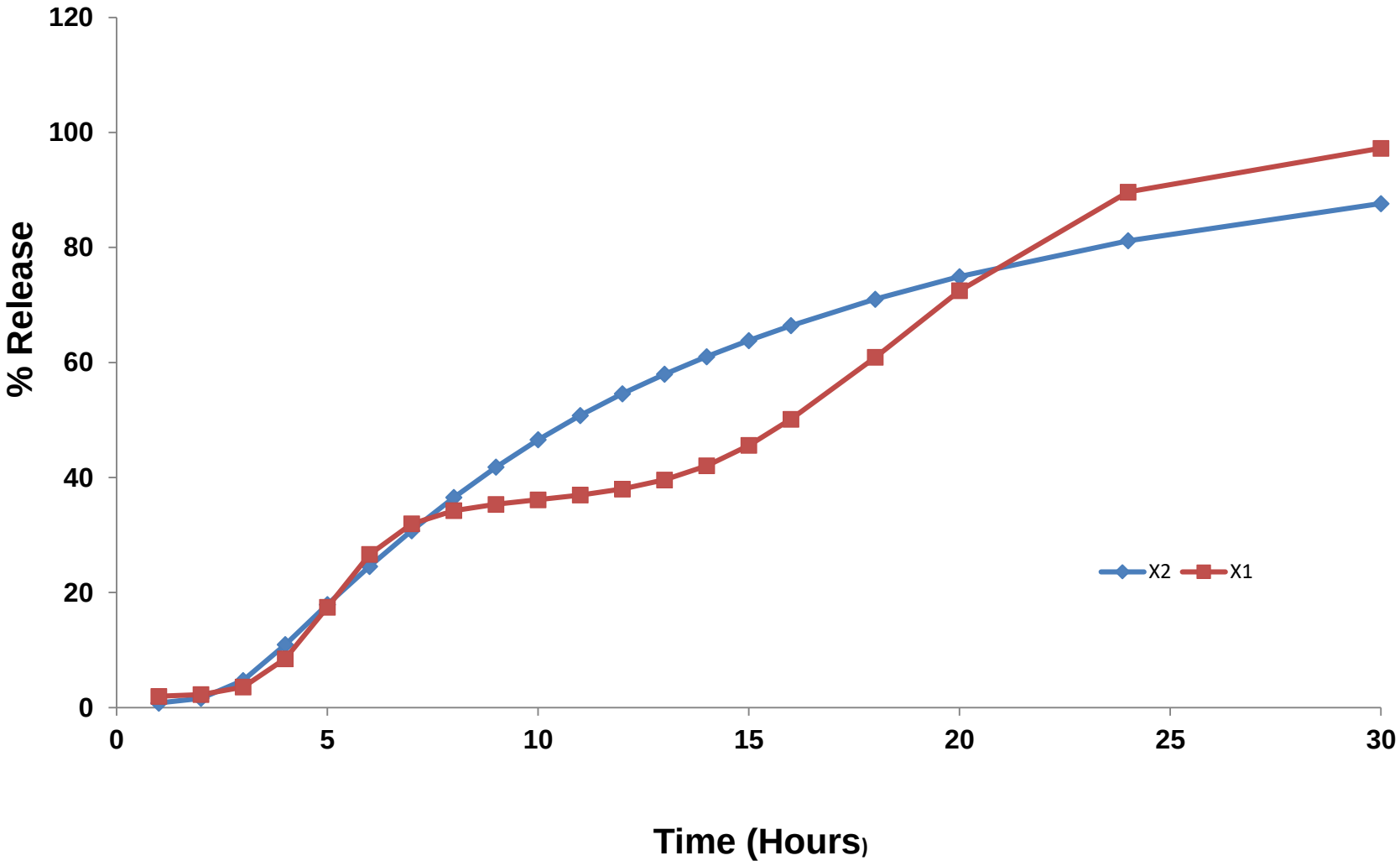
Are these profiles similar?



Dissolution Profile Comparisons

Dissolution profiles may be considered similar by virtue of (i) overall profile similarity and (ii) similarity at every dissolution sample time point.

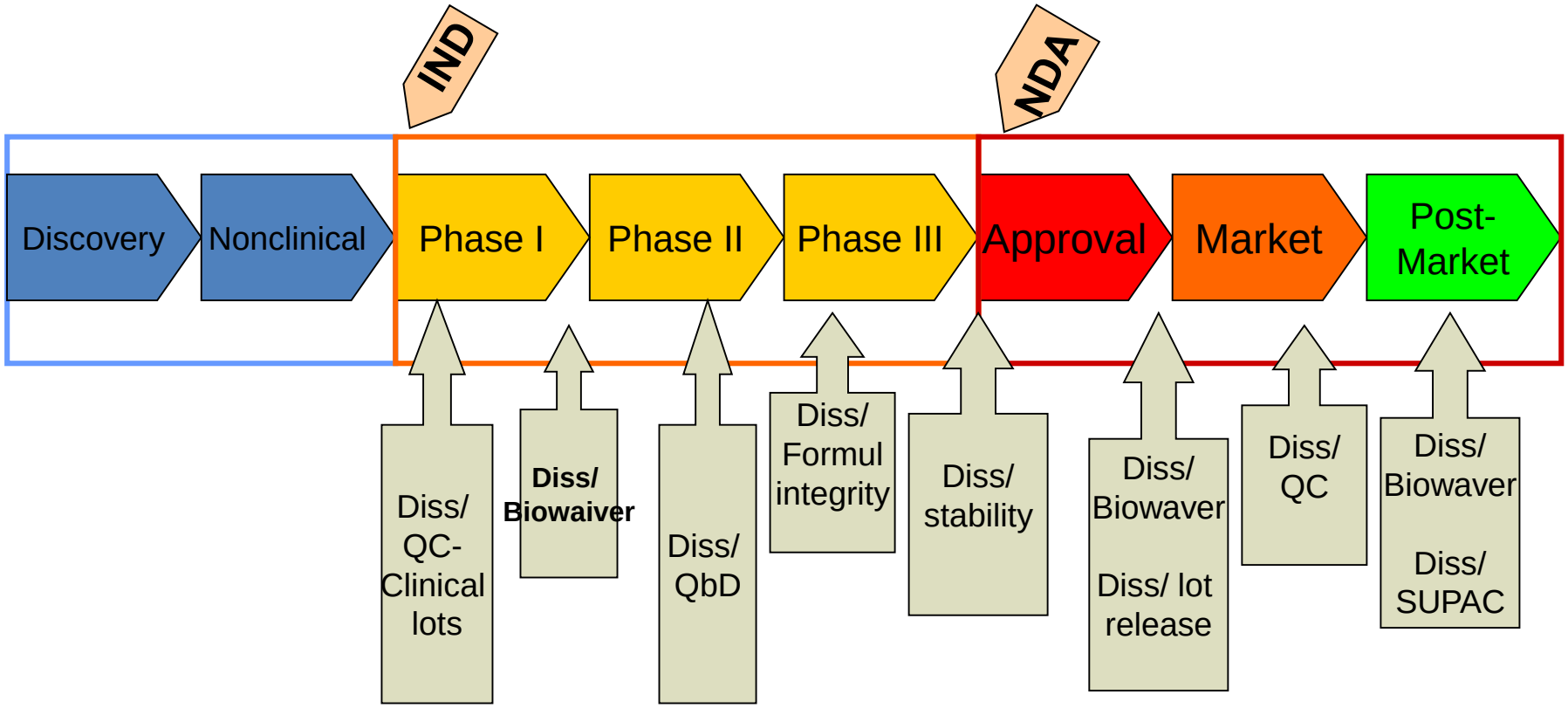
Two Approaches to demonstrate the similarity:

Model Independent Approach:

Similarity Factor (f_2)
Multivariate Confidence Region

Model Dependent Approaches

Regulatory Application of the Dissolution Profile Comparisons in the Life cycle of a Drug Product



Dissolution Profile Comparison

Model Independent Approach Using Similarity Factor (f_2)

$$f_2 = 50 \bullet \log \{[1 + (\frac{1}{n}\sum (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

n = number of time points
R(t) = mean % API dissolved of reference product at time point x
T(t) = mean % API dissolved of test product at time point x

Minimum of 3 time points (zero excluded)

12 units (each in own dissolution vessel) for each product

Only one measurement should be considered after 85% dissolution of both the products
%RSD at earlier time points (e.g., 15 minutes) ≤ 20%
%RSD at higher time points ≤ 10%

"f_2 values greater than 50 (50-100) ensure sameness of the two curves and, thus, of the performance of the test (post-change) and reference (pre-change) products."

Similarity Factor (f_2)- SUPAC MR Guidance

- **The average difference at any dissolution sampling time point should not be greater than 15% between the changed drug product and the bio-batch or marketed batch (unchanged drug product) dissolution profiles.**

Is f_2 Applicable to All Dosage Forms?

- **Oral simple dosage forms** → **f_2 applicable**
  - **Immediate release**
- **Oral complex dosage forms** → **f_2 applicable**
  - **Modified release (DR, ER)**
  - **Combination-IR/IR, IR/MR,MR/MR**
- **Non-oral dosage forms** → **f_2 applicable**
  - **Transdermal Drug Delivery Systems**
  - **Dug-Device Combination Products**
- **Other dosage forms** → **f_2 metric NOT applicable**
  - **For example topical etc.**

Cases When f_2 Cannot be Used

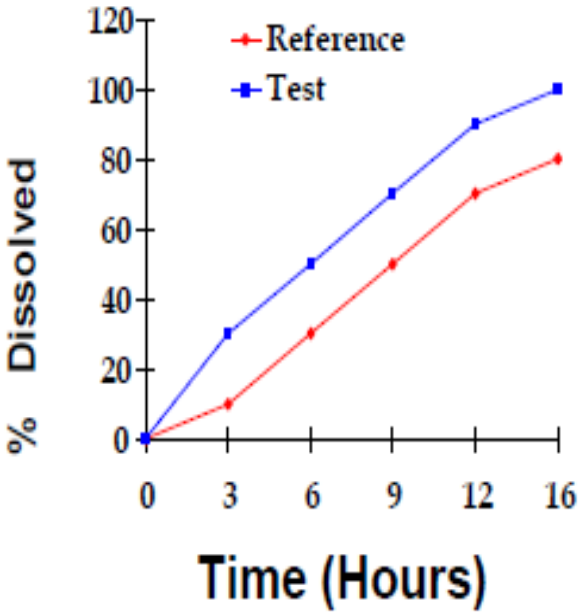
- When the percent coefficient of variation is higher than 20% requirement for earlier time points (i.e., 15 min) or higher than 10% for the other time points the f_2 test cannot be used.
  - Alternative methods to estimate profiles similarity should be used

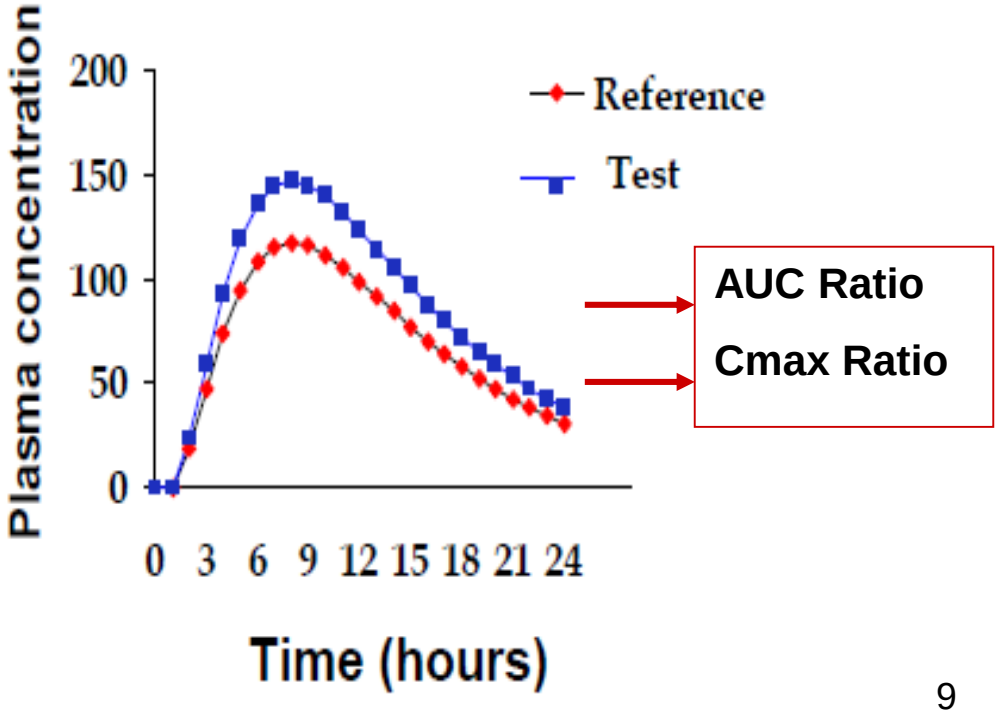
    ✓ **f_2 with Bootstrap method**

    ✓ **Multivariate approach**

Cases When f_2 may not be Used

- In general, the f_2 test should not be used when there is an IVIVC model available/ established ‘’safe space”
  - The IVIVC model must be used to estimate AUC and Cmax





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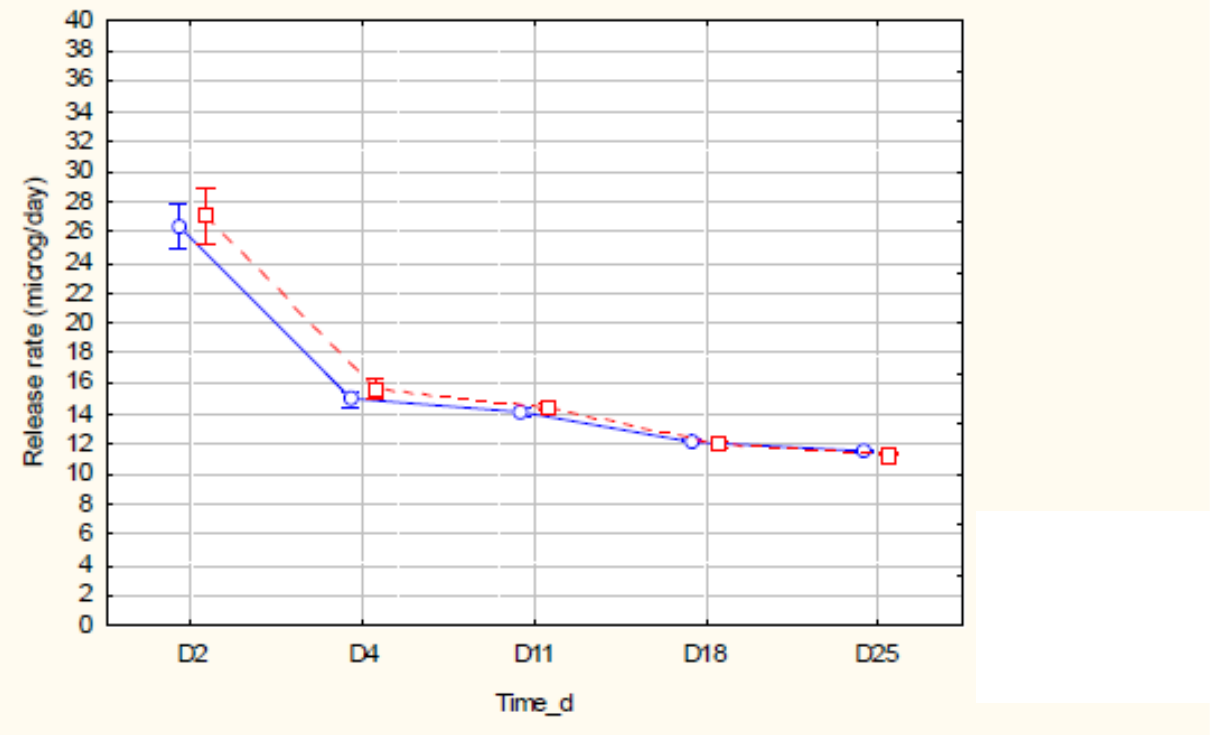
Cases When f_2 Cannot be Used cont..

In Vitro Metric Evaluated - Drug Release Rate (mcg/day)



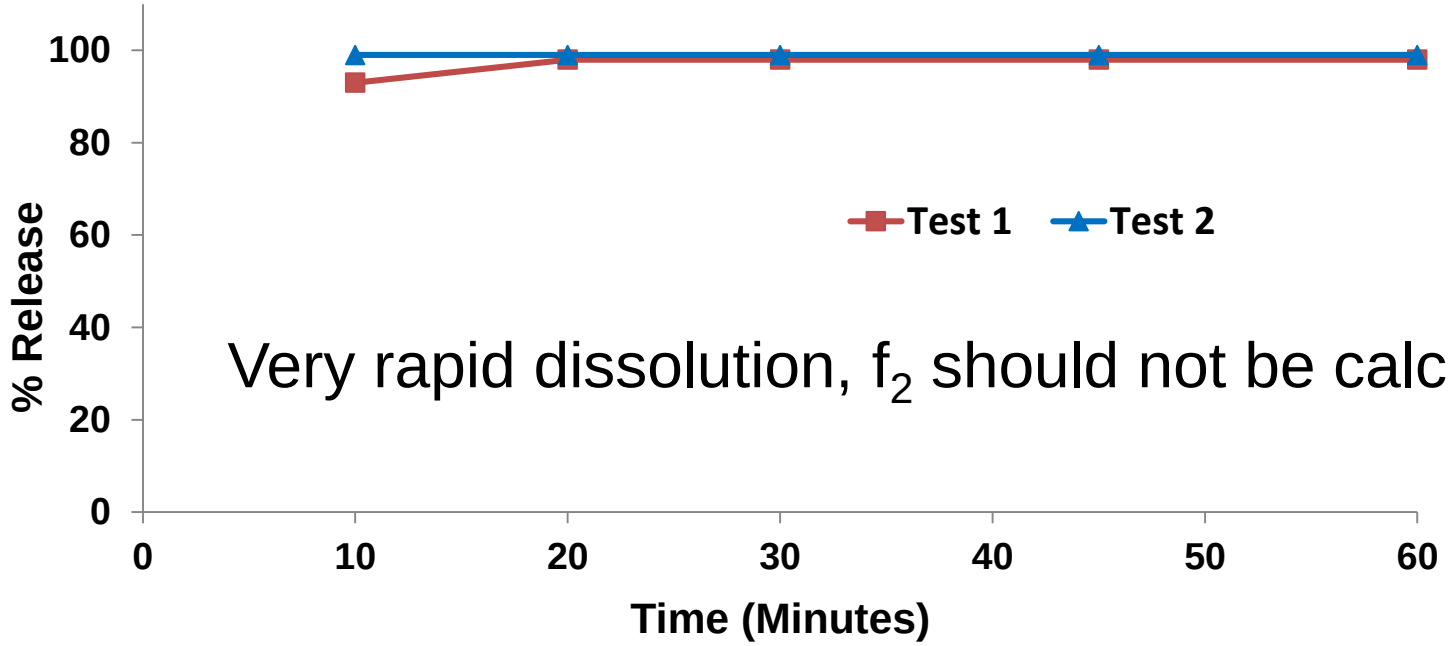
f_2 metric cannot be used to estimate the similarity of drug release rate data (mg/day etc.).

Case Studies

Case study 1: Discriminating method

BCS class 2 drug product

$f_2 = 76^*$



Method not discriminating/ drug particle size

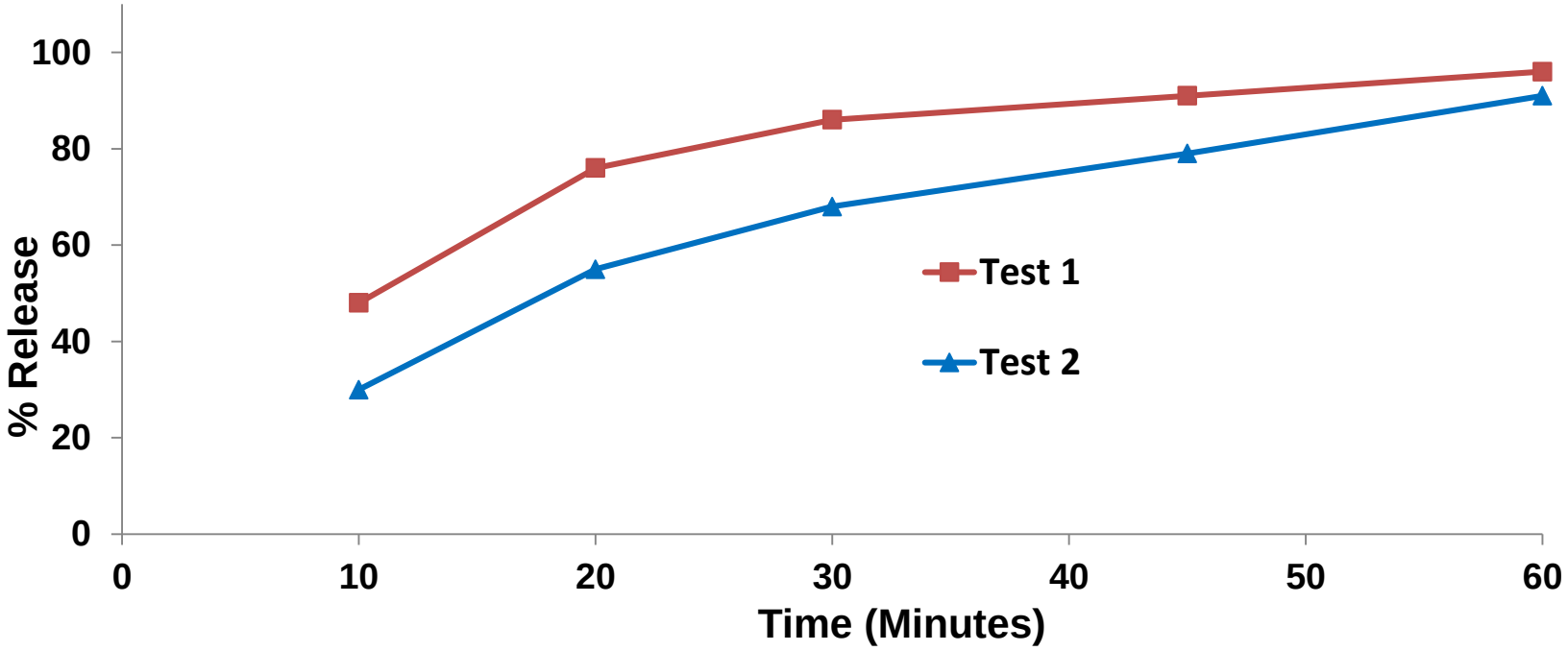
In an in vivo study Test 1 and Test 2 were found not bio-equivalent

*Applicant calculated

Case study 1: Discriminating method..

BCS class 2 drug product- New method

$f_2 = 40$



Method discriminating/ drug particle size

Case study 1: Discriminating method…

f_2 limitations: f_2 has no application for very rapid dissolution.

The outcome of f_2 test is uncertain if the method is not discriminating.

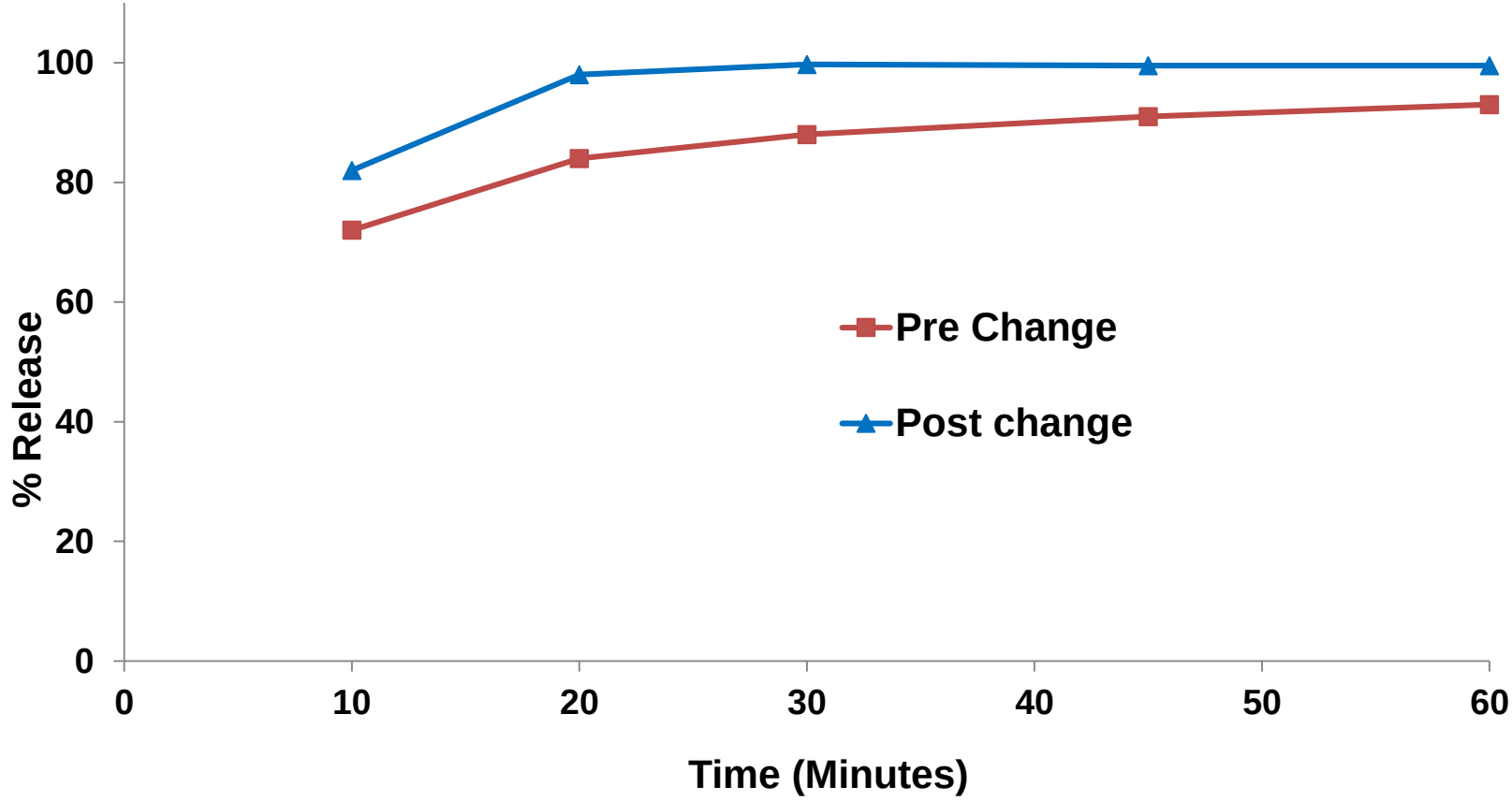
Lesson learnt: For a meaningful/reliable calculation of f_2, the dissolution method should be discriminating/meaningful.

Case study 2: site change

Alternate Manufacturing Site

Low solubility drug

$f_2 = 46$



Case study 2: site change…

f_2 < 50, was justified and found acceptable

- Previously, a PK study showed no difference in BA between a tablet vs. suspension formulations of the same drug. Plasma levels peaks in approximately four hours.

- The dissolution profile of the post-change batch was within those observed for the tablet and suspension.

- Slightly faster dissolution and the lower value of f_2 should not have affect on the efficacy/safety of the drug product.

- Based on totality of information provided, the change in the site was accepted even though the dissolution was faster and the f_2 was slightly lower than 50.

Case study 2: site change…

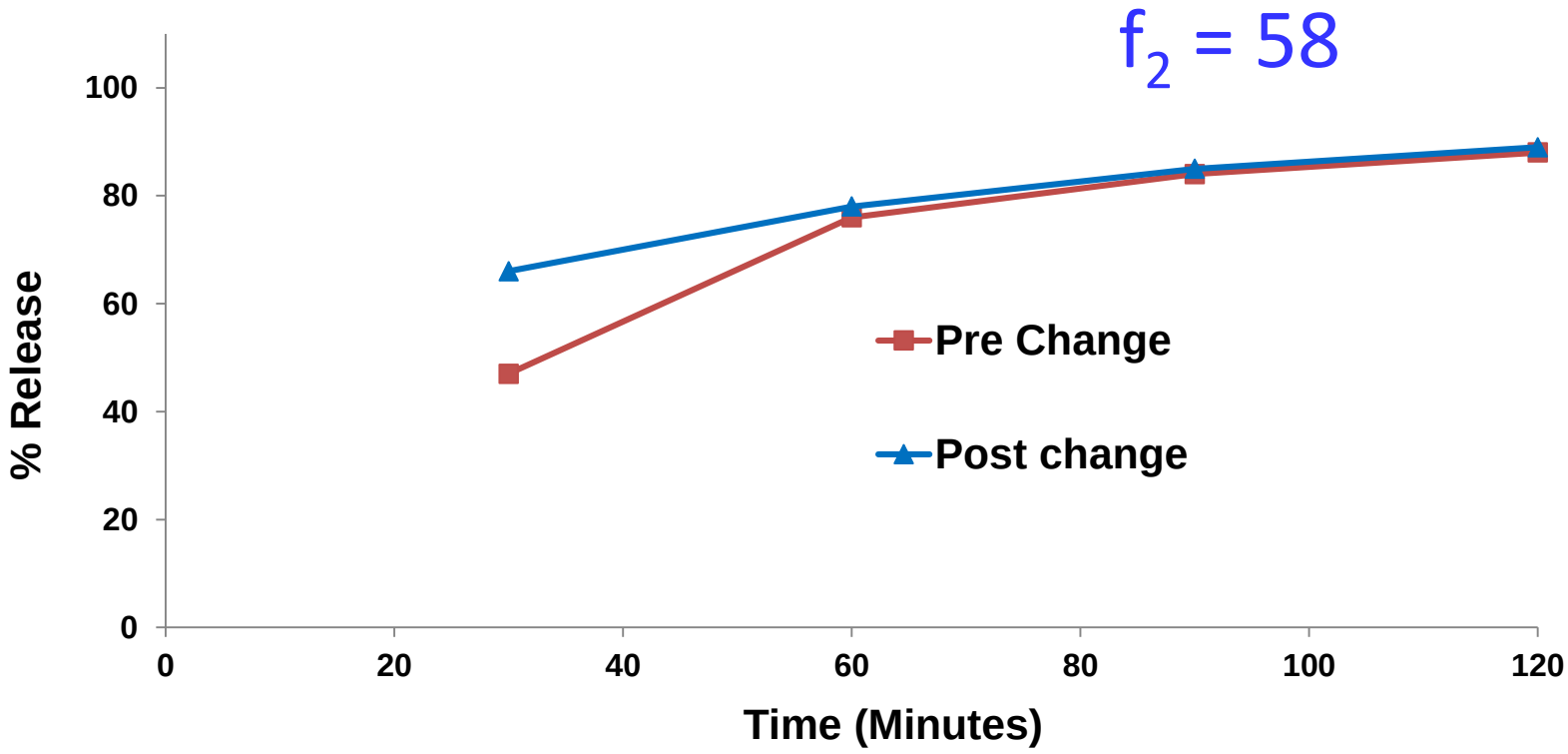
f_2 limitations: f_2 similarity may have limited application for very rapid dissolving products.

Lesson learnt: An f_2 value less than 50 does not necessarily indicate lack of similarity. Risk-based assessment on the potential effect of the proposed change(s) on bioavailability should be conducted.

Case study 3: Multiple process changes

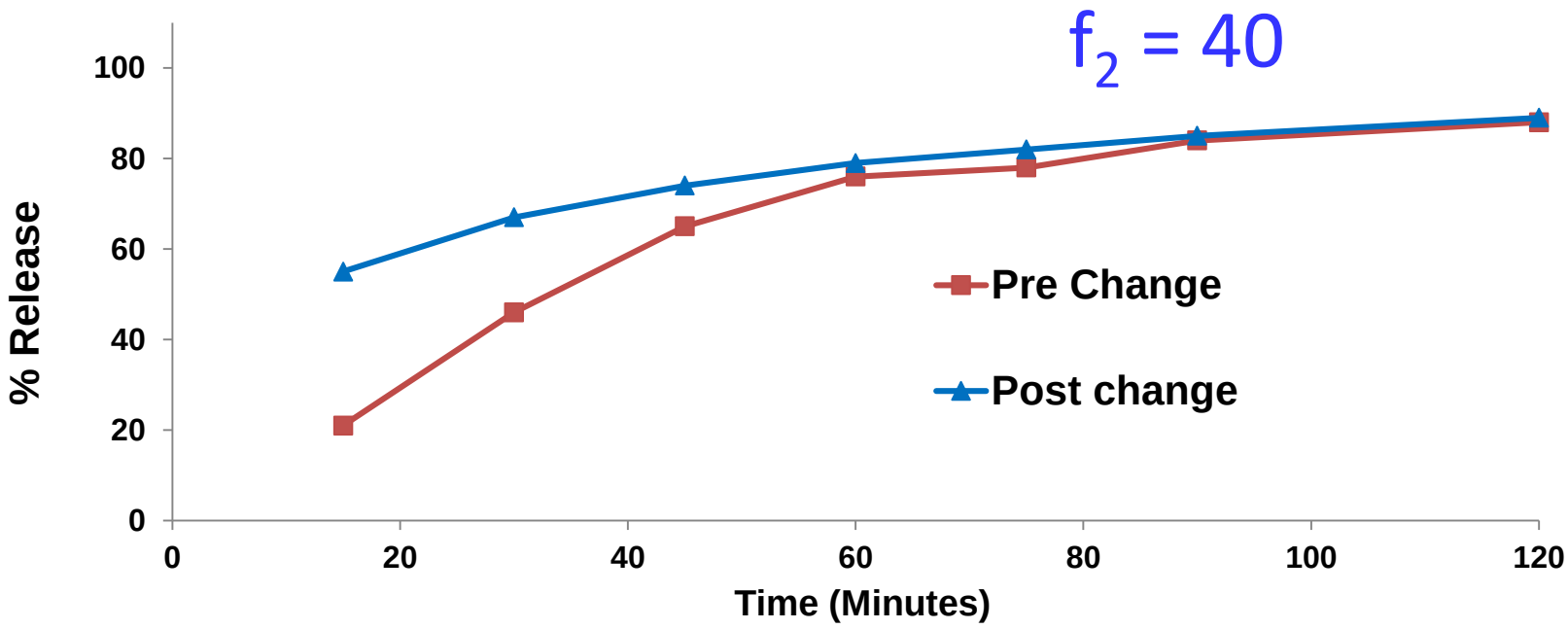
Post approval, multiple, Level 1 changes in the process to improve the stability of the drug product

Low solubility drug



Case study 3: Multiple process changes..

The Applicant was asked to provide dissolution data with additional time points at early phase



Based on the totality of the information and potential effect of the manufacturing changes on the bioavailability, the Application was asked to conduct a BE study.

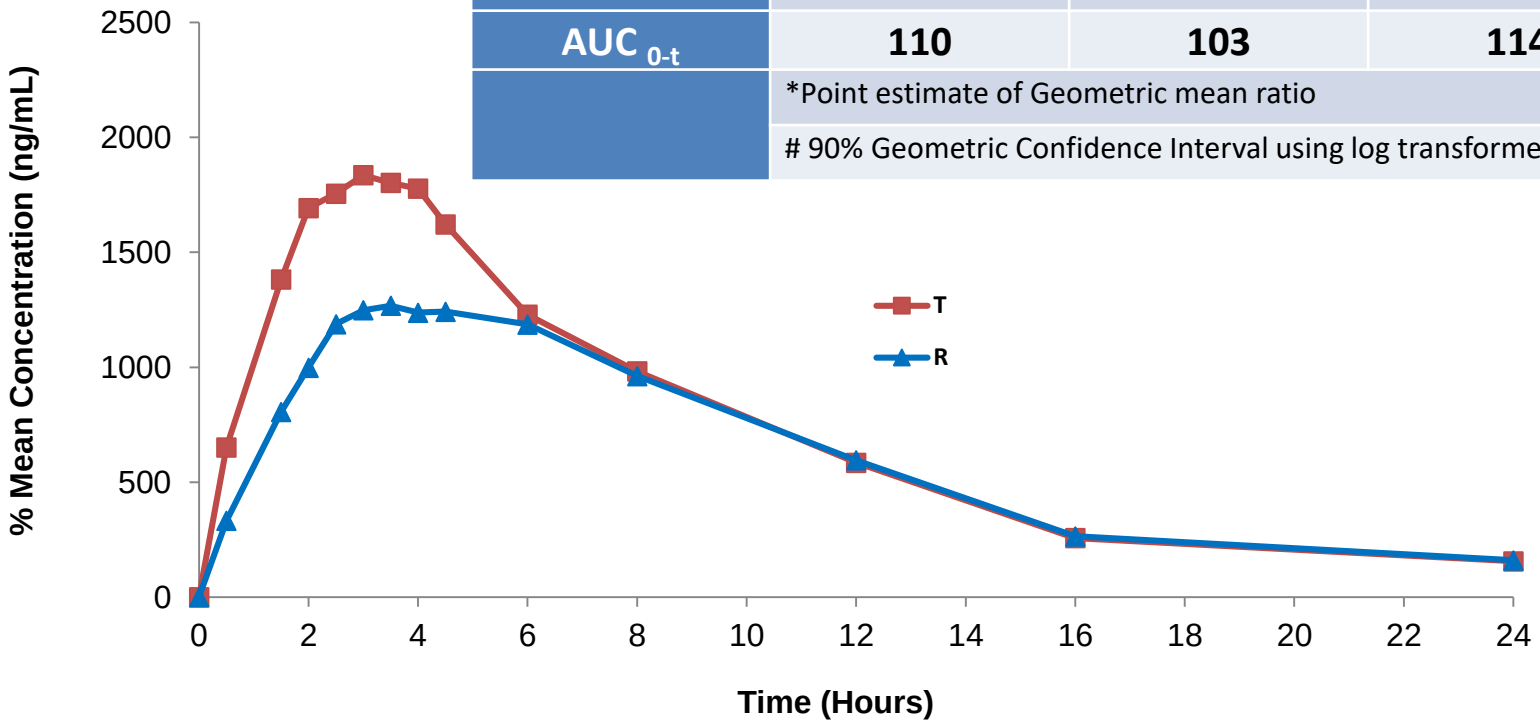
Case study 3: Multiple process changes …

BE study results

	Ratio*	90 % CI#	
Cmax	146	135	156
AUC $_{0-t}$	110	103	114

*Point estimate of Geometric mean ratio

90% Geometric Confidence Interval using log transformed data



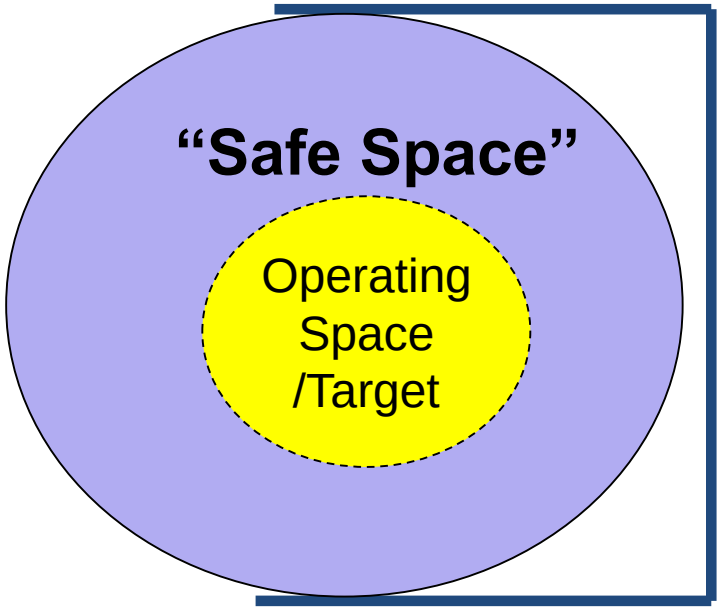
Based on the BE study results, the Applicant withdrew the supplement

Case study 3: Multiple process changes..

f_2 limitations: the selection of sampling time points (both number and sampling time distribution) are critical for a robust conclusion on the similarity results.

Lesson learnt: To evaluate the similarity of the drug product performance, it is important to assess the totality of the information. f_2 values are only one part of the total information.

The use of f_2 in "Safe Space"



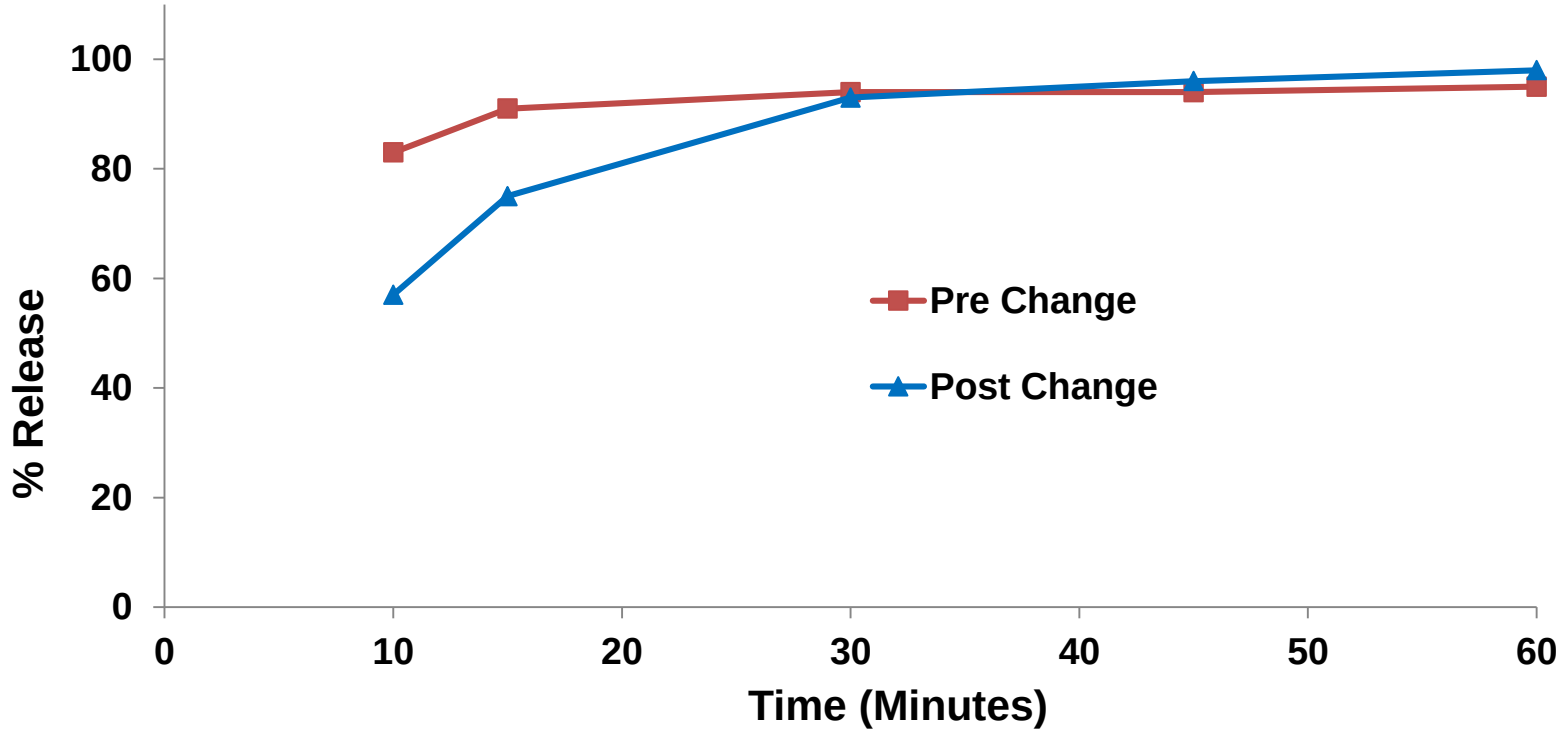
If **"Safe Space**" [all batches are assumed to be bioequivalent] is established, through IVIVC, BE studies, IVIVR, virtual BE studies etc.

Similarity in the dissolution profiles is not needed, if the dissolution profiles are with in the "safe space".

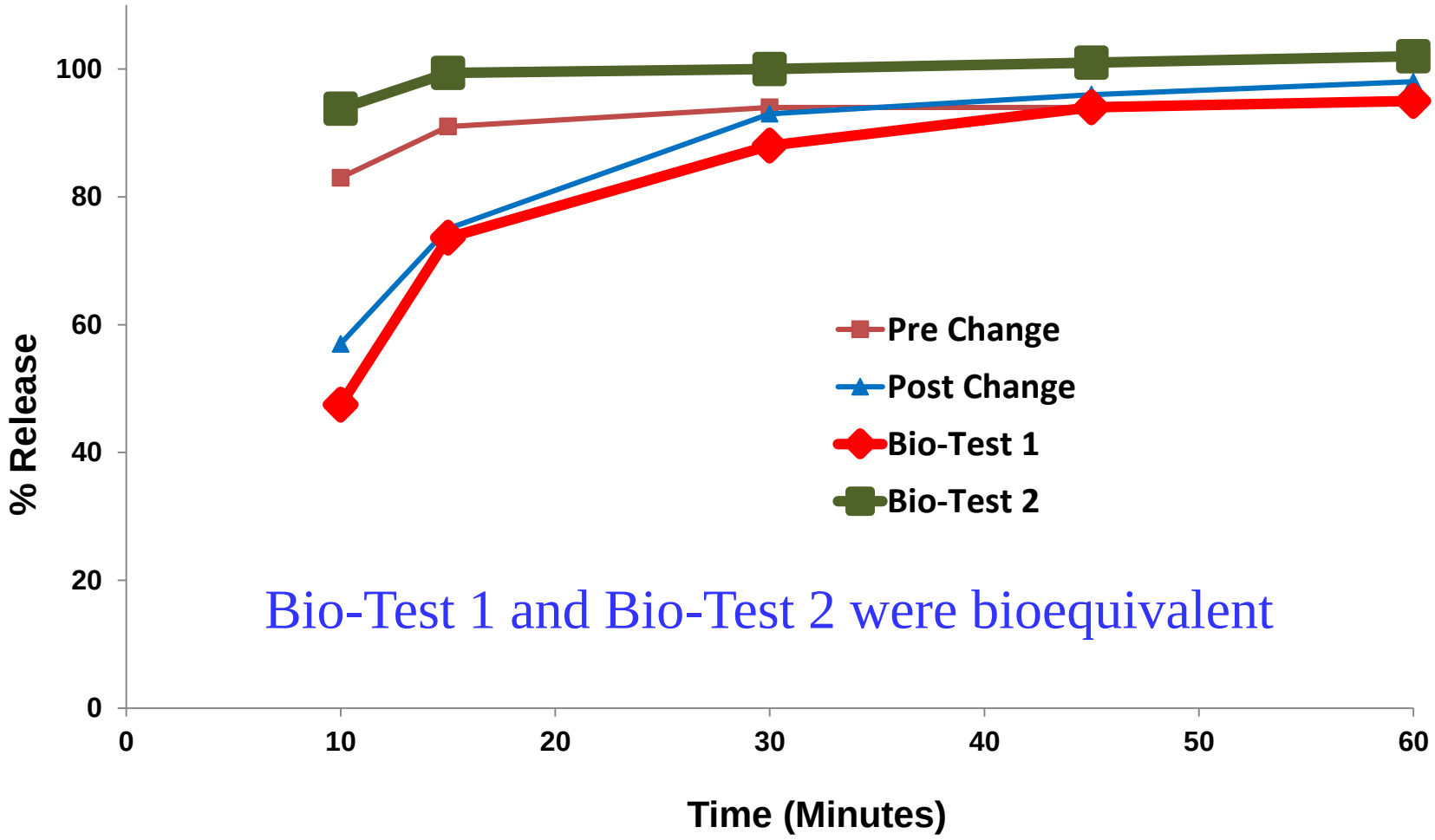
Case study 4: Site and process change..

Manufacturing site change and minor changes to the manufacturing procedure. No change in the IR formulation. Drug substance has very low aqueous solubility

$f_2 = 38$



Case study 4: “Safe Space”



Bio-Test 1 and Bio-Test 2 were bioequivalent

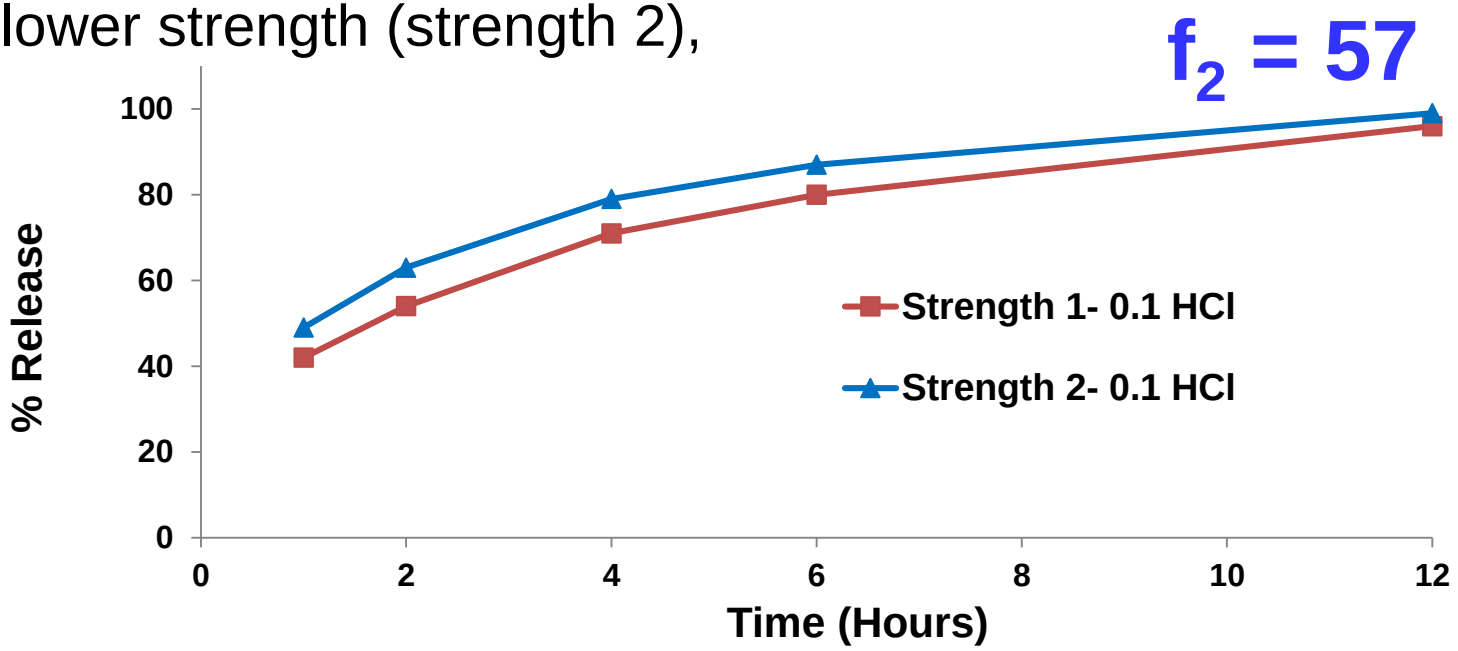
Case study 4: change with in the "safe space"…

f_2 limitations: "Safe space" supersedes f_2 similarity testing.

Lesson learnt: An f_2 value less than 50 does not necessarily indicate lack of similarity. If product changes are occurring with in the "safe space', an f_2 value less <50 is superseded by "safe space" boundaries.

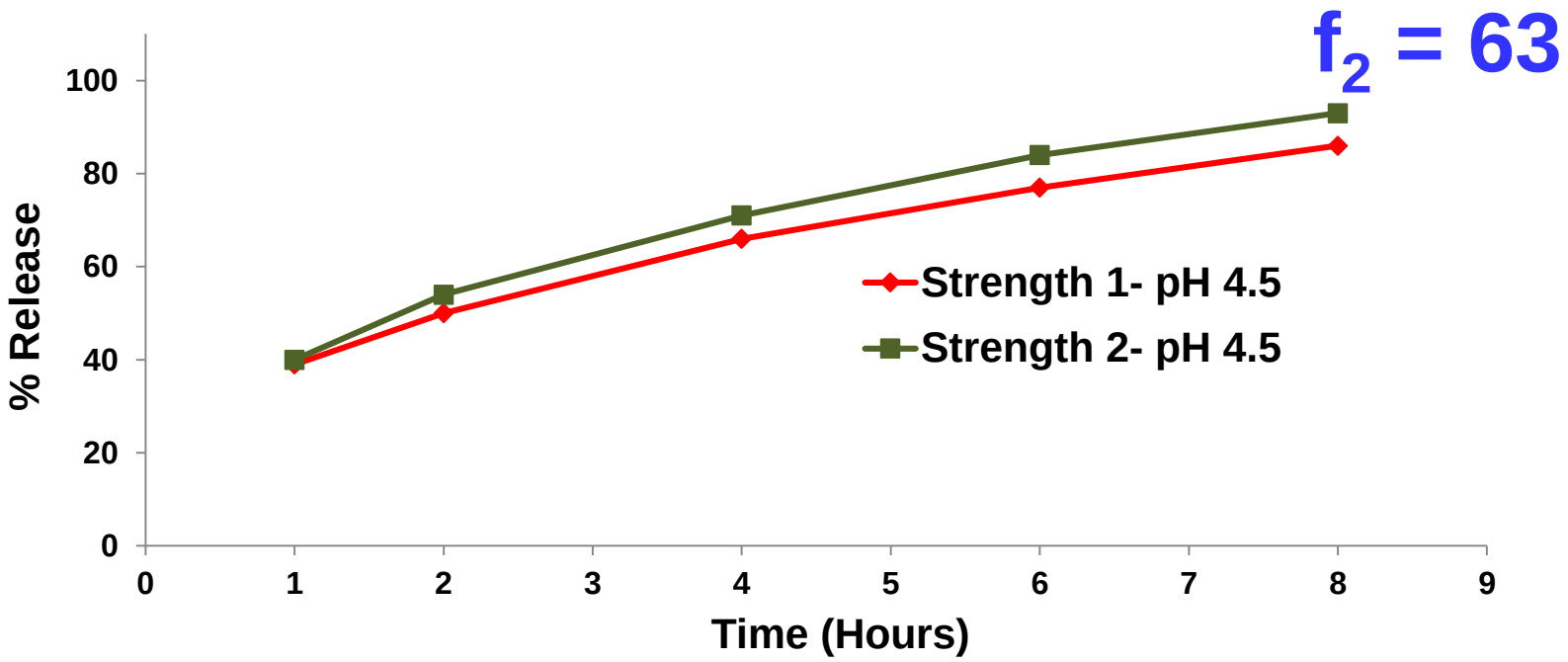
Case study 5: variable dissolution

A Modified Release (MR) product.
BE Study on higher strength (strength 1), biowaiver request for the lower strength (strength 2),



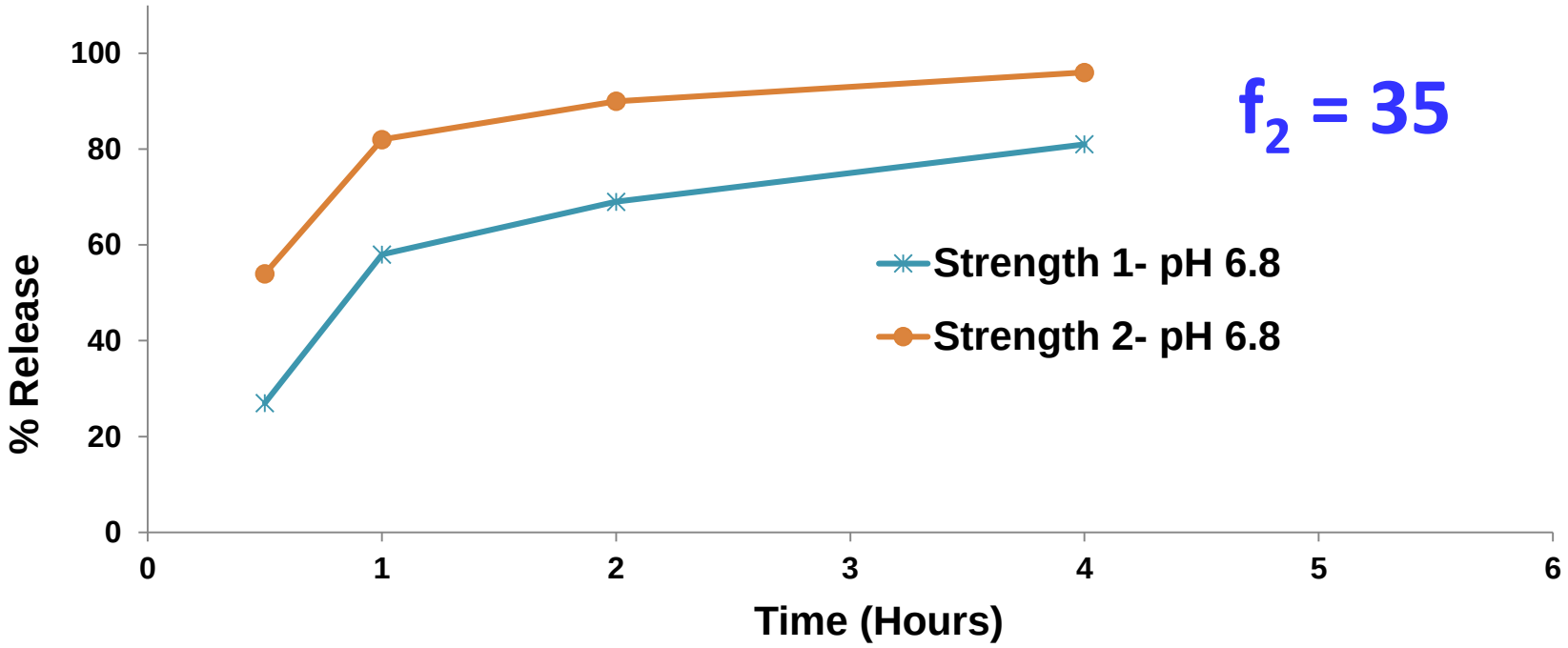
	% RSD				
Time (hours)	1	2	4	6	12
Strength 1	16.8	13.7	8.9	7.1	2.6
Strength 2	13.1	9.5	6.4	4.5	0.9

Case study 5: variable dissolution..



	% RSD				
Time (hours)	1	2	4	6	8
Strength 1	11.3	8.8	6.3	5.1	3.9
Strength 2	14.2	11.5	8.8	6	4

Case study 5: variable dissolution..



	% RSD			
Time (hours)	0.5	1	2	4
Strength 1	19.1	15.7	10.8	9.5
Strength 2	16.5	12.6	8.4	3.9

Case study 5: variable dissolution..

- Investigate the root cause of high variability; and differences in dissolution profiles in pH 6.8.
- Response: No specific reasons for the variability and the differences.
- BE study was recommended.
- BE study failed to meet the 90% CI.

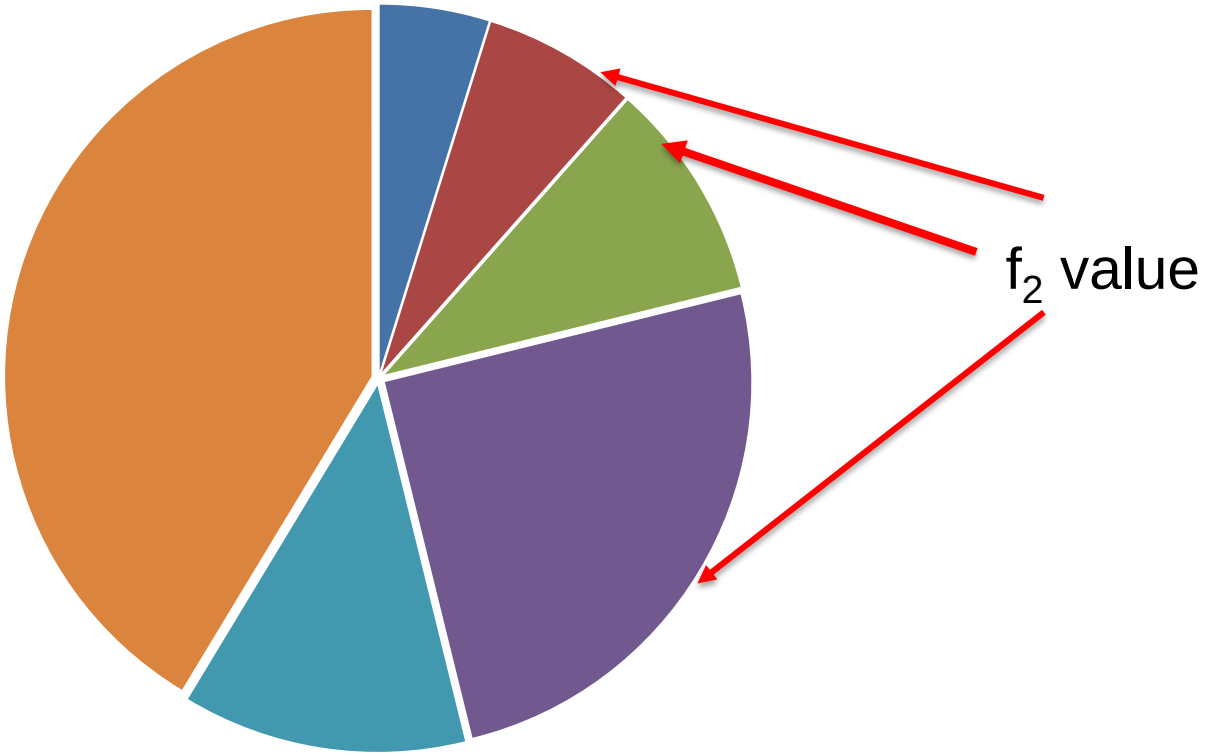
Case study 5: variable dissolution

f_2 limitations: Due to high variability in the dissolution data, comparison of mean f2 profiles is not recommended.

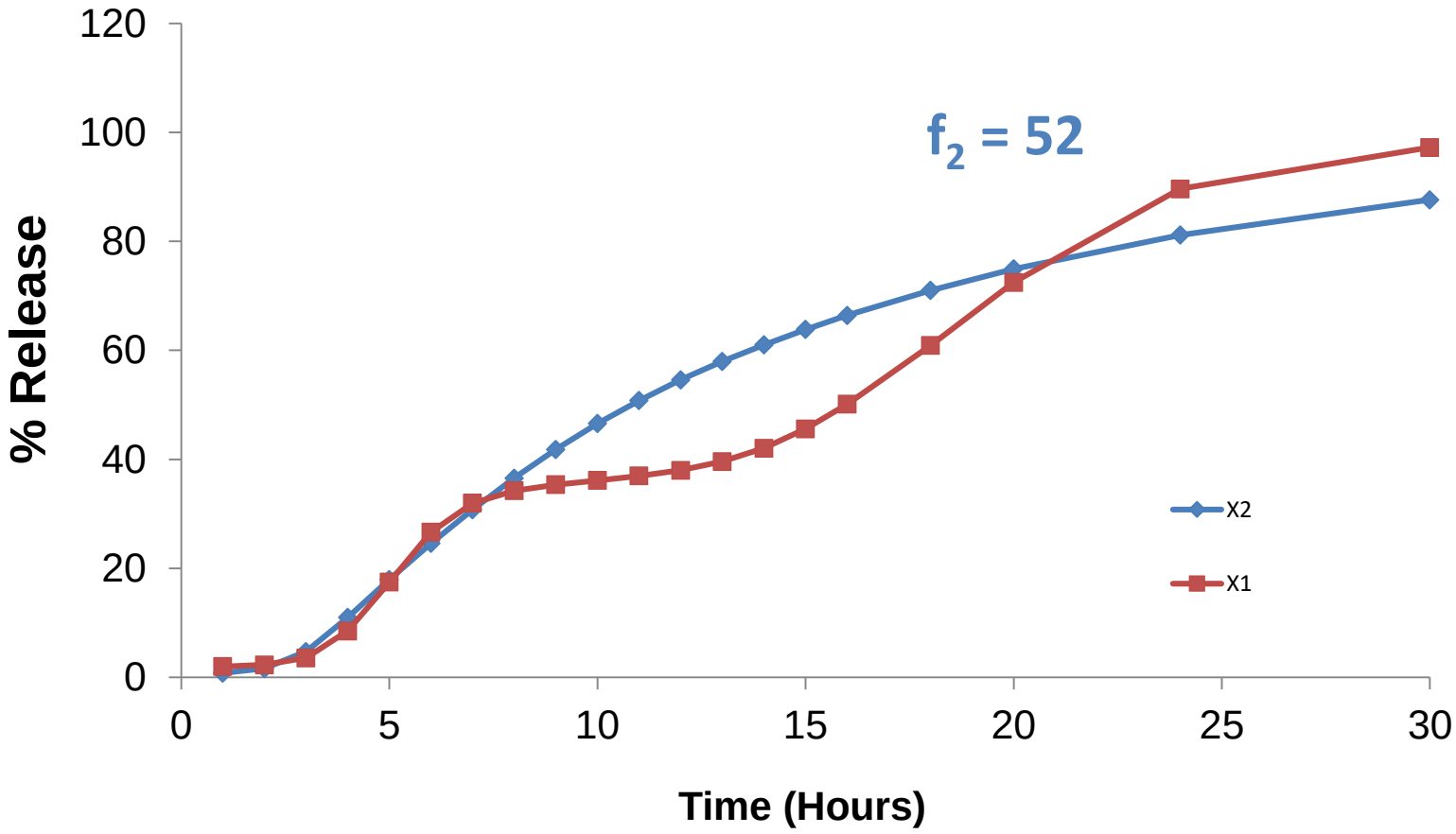
what is early timepoint for an ER product?

Lesson learnt: In case of high variability in the dissolution profiles, the root cause of high variability should be determined prior to using alternate approaches to demonstrate the similarity between the profiles.

f_2 values are only part of the total information



Question



Should we use f_2 for comparing these dissolution profiles?

Challenges in the Implementation of Similarity Testing

- f_2 similarity may have limited or no application for very rapid dissolving products.
- Selection of sampling time points (both number and sampling time distribution) are critical.
- High variability in the dissolution data. An early timepoint for ER products is not defined.
- f_2 calculations does not consider shape of the profiles.

Conclusions

- **For a reliable calculation of f_2, the dissolution method should be discriminating/meaningful.**
- **To evaluate the similarity of the drug product performance, it is important to assess the totality of the information. f_2 values are only the part of the total information.**
- **In case of high variability in the dissolution profiles, the root cause of high variability should be determined and variability in the data should be reduced, if possible, without compromising on the discriminating ability of the method.**

Conclusions

- **An f_2 value less than 50 does not necessarily indicate lack of similarity. The potential effect of the proposed change resulting in differences in dissolution profiles can be justified including additional data to support the claim of similarity, as well as supporting statistical analysis (e.g. 90% confidence interval analysis), and 'safe space' etc.**

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- *Thanks To:*

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  - *Poonam Delvadia, Ph.D.*

FDA Guidances and Similarity f2 Metric

Several Guidance documents recommend f2 metric to evaluate products sameness

- **Dissolution Testing of Immediate Release Solid Oral Dosage Forms**
- **Waiver of in vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System**
- **Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations**
- **Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation**
- **SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation Bioavailability and Bioequivalence Studies for Orally Administered Drug Products, General Considerations**

Thank you!


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