ICH M13B: news from the draft

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BioBridges 2025

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ZENTIVA

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M13 GUIDELINE SERIES

Bioequivalence for Immediate-Release Solid Oral Dosage Forms

A

Focuses on the **bioequivalence study designs and general data analysis** considerations [effective in EU from 25/01/2025].

B

Describes **biowaiver** considerations **for additional strengths not investigated in BE studies** [draft released for public consultation on April 9, 2025].

C

Will include **1) data analysis and BE assessment** for highly variable drugs, drugs with narrow therapeutic index, and **2) complex BE study design & data analysis considerations** (e.g., adaptive BE and handling of missing samples) [M13 Concept paper supplement from January 27, 2025].

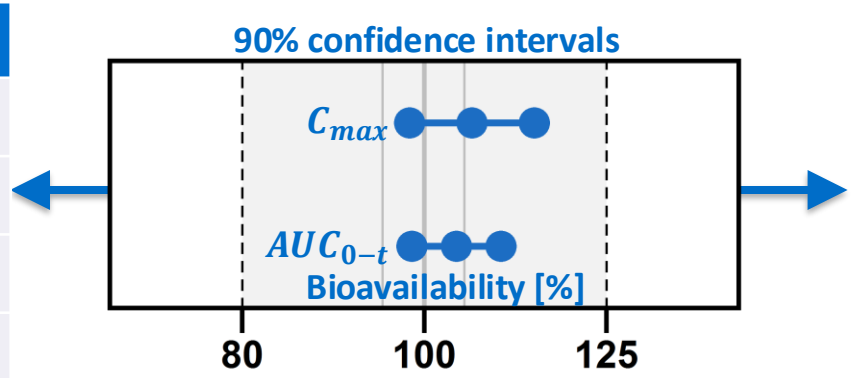
BE – bioequivalence, M – multidisciplinary, ICH – the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

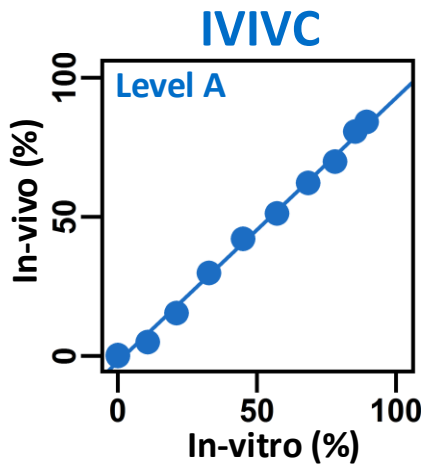
BIO·WAIVER

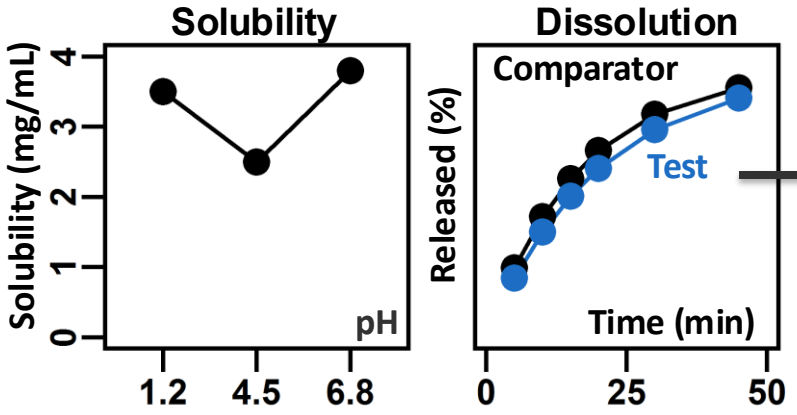
To waive additional or all *in-vivo* tests

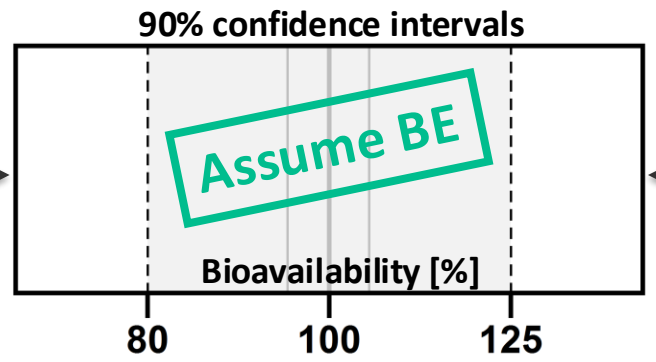
ICH M13B

Strength	Biobatch	Waiver
1		×
2		×
3		×
4	×	









ICH M9

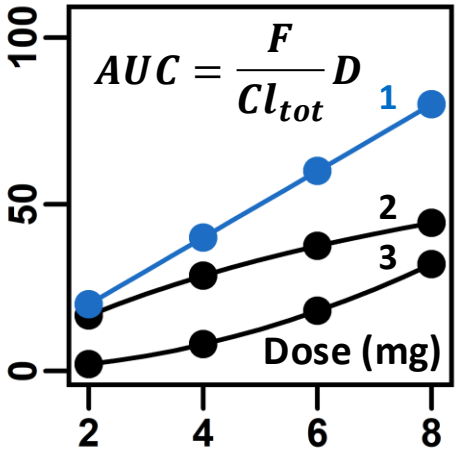
Outside ICH

Aqueous solutions

BIO·WAIVER CRITERIA

101 Overview

- **Proportionality in the PK +*API solubility***



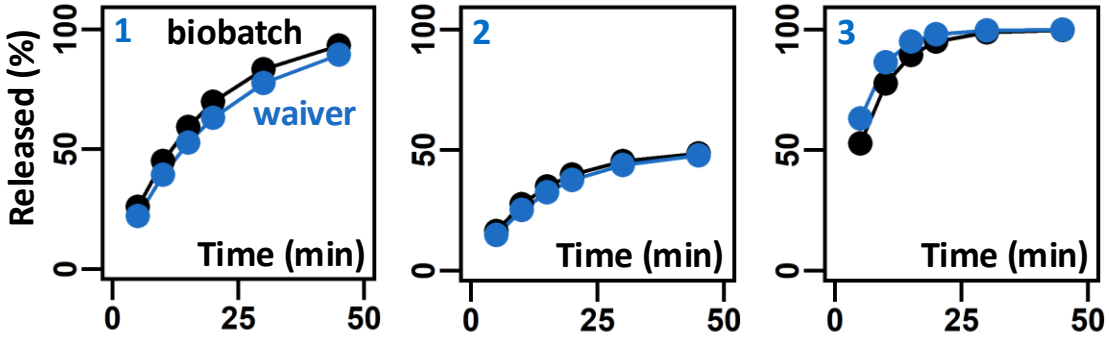
1-linear; 2-less than dose proportional; 3-more than dose proportional

Composition [mg][1)]		
Ingredients	**A**	**B**
API	5	10
Filler	50	100
Binder	10	20
Lubricant	2	4
Total	67	134

[1)]Process: roller compaction

- **Formulation factors: qualitative & quantitative composition** among different strengths & **manufacturing process**

- **Compare** *in vitro* dissolution profiles

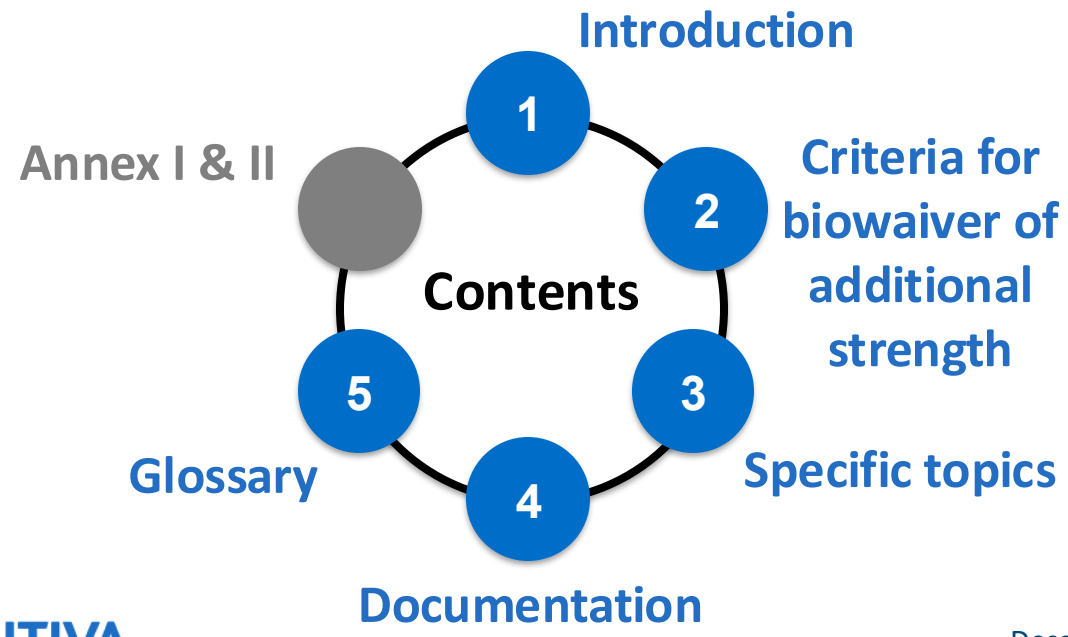


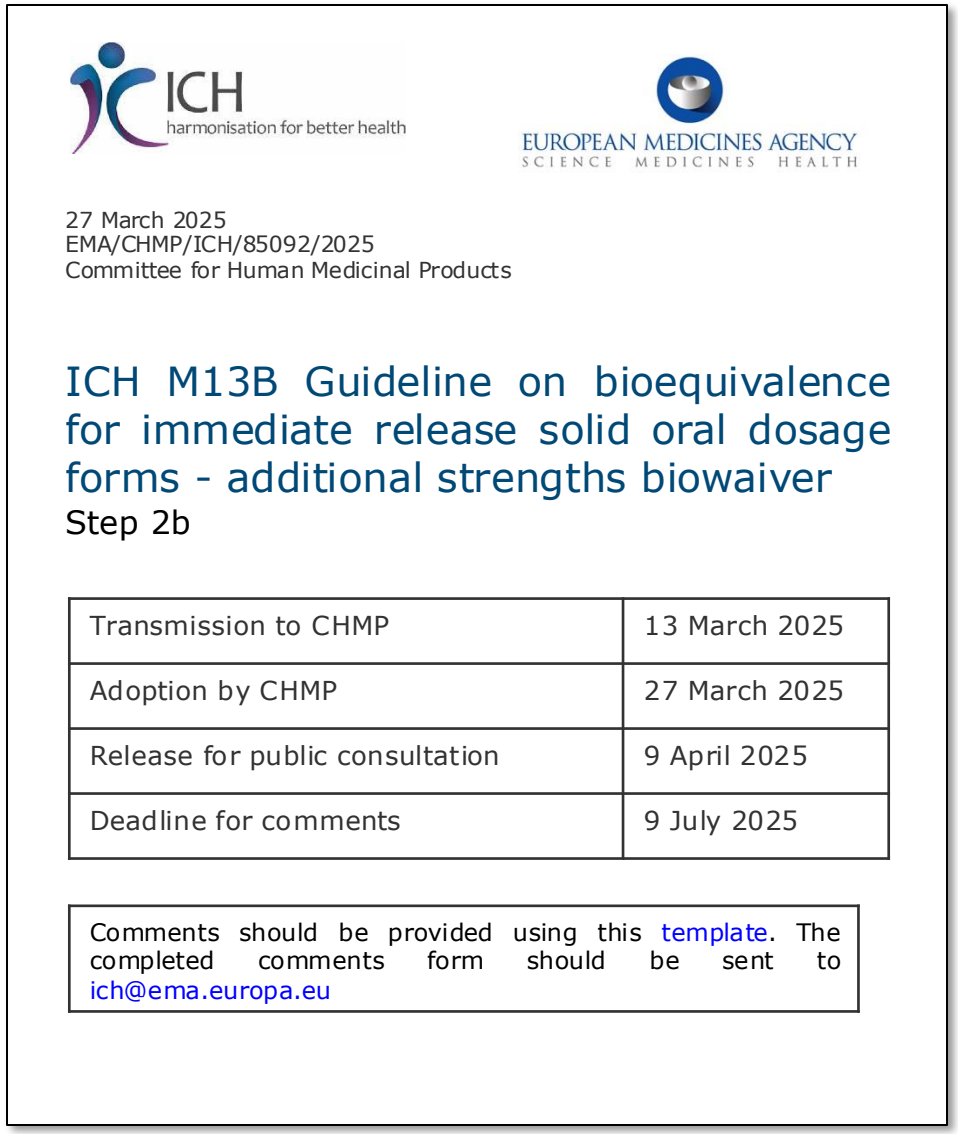
API–active pharmaceutical ingredient; PK–pharmacokinetics

ICH M13B DRAFT

Structure & Objectives

Objective … recommendations on obtaining **waivers of bioequivalence (BE)** studies for one or more additional strengths of a drug product in an application where *in vivo* BE has been demonstrated …





ICH harmonisation for better health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 March 2025
EMA/CHMP/ICH/85092/2025
Committee for Human Medicinal Products

ICH M13B Guideline on bioequivalence for immediate release solid oral dosage forms - additional strengths biowaiver
Step 2b

Transmission to CHMP	13 March 2025
Adoption by CHMP	27 March 2025
Release for public consultation	9 April 2025
Deadline for comments	9 July 2025

Comments should be provided using this template. The completed comments form should be sent to ich@ema.europa.eu

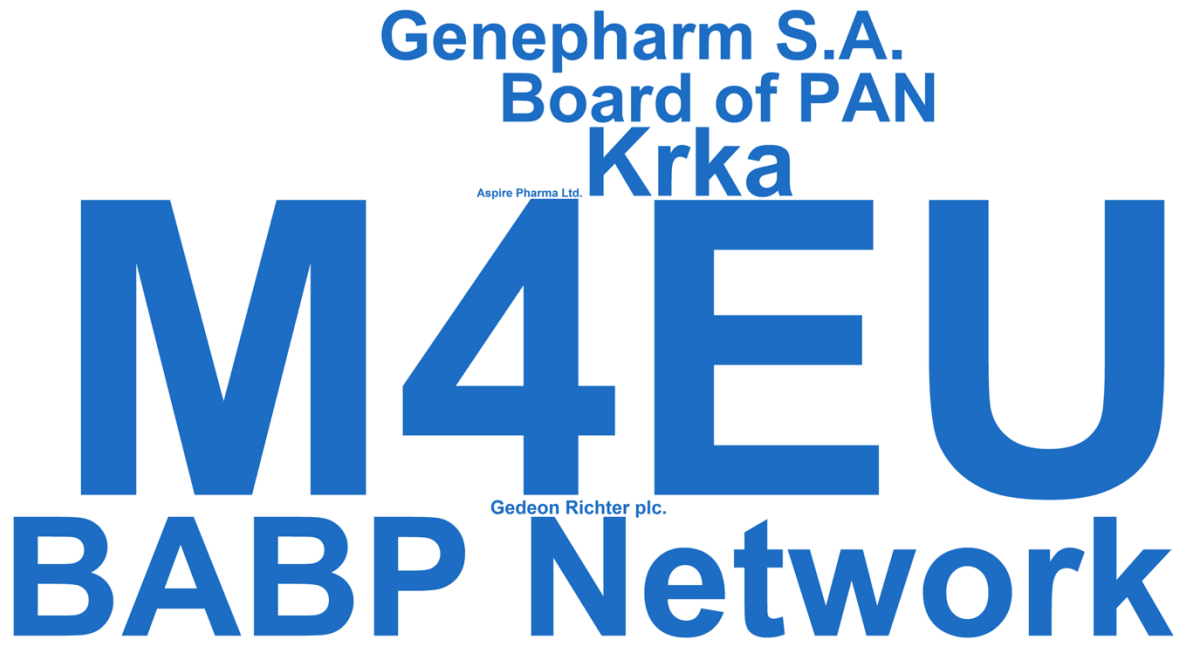
Descriptive statistics of M13B draft: ≈15 pages of text, 2 figures and 5 tables

ICH M13B DRAFT

EU Stakeholder comments (EMA/237572/2025)

Number of comments		
Section	**N**	**%[1)]**
General	3	2.6
Introduction	**5**	4.3
Criteria for biowaiver	**66**	57.4
Specific topics	**20**	17.4
Documentation	**7**	6.1
Glossary	**3**	2.6
Annexes	**11**	9.6
Total	**115**	100.0

[1)]Rounded in R (4.5.1) via IEC 60559 standard



Consortiums & Associations: BABP Network–Network Bioavailability & Biopharmaceutics of the European Federation for Pharmaceutical Sciences (EUFEPS), House of Pharma & Healthcare, German Pharmaceutical Society (DPhG), Frankfurt Foundation Quality of Medicines (FFQM) [Frankfurt am Main, Germany]; Board of PAN–Board on Cooperation with the Economic Environment, Committee on Therapeutics and Drug Sciences of the Polish Academy of Sciences

DISSOLUTION CONDITIONS

Section 2.3

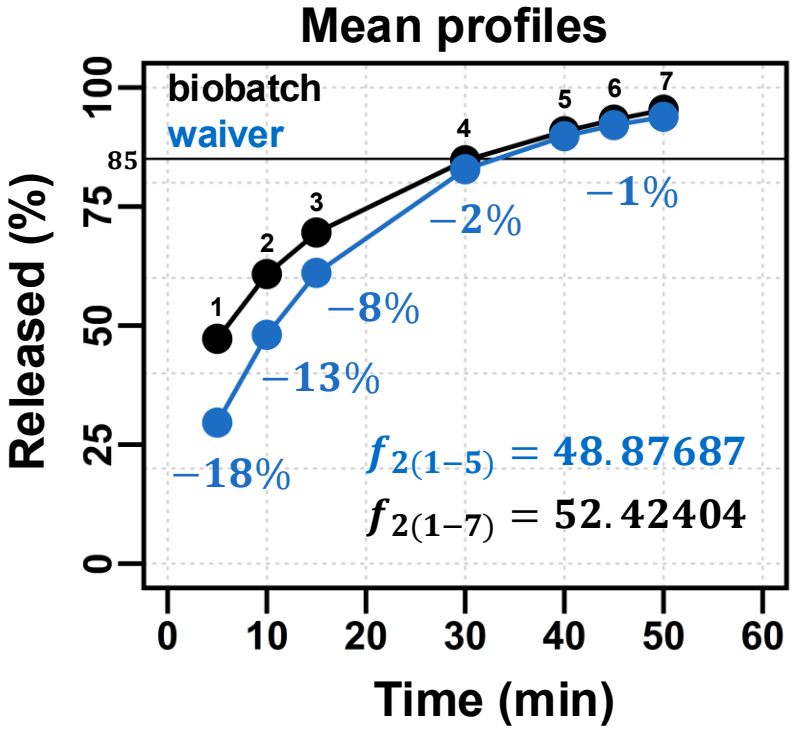
- Compendial **paddle or basket** apparatus; V=900 mL or less, **agitation:** 50 rpm (paddle), 100 rpm (basket)
- Three **compendial media** covering the range of **pH 1.2 – 6.8** (at or about pH 1.2, 4.5, and 6.8) and the **quality control (QC) medium**
- **At least 12 units of the additional strength and biobatch**
- **Surfactant** may be used in **only the QC medium** and only when appropriately established as part of dissolution method development.
- **Other** dissolution conditions, e.g., **compendial apparatuses** and **agitation speeds, may be considered** to overcome specific **issues, e.g., coning**, if scientifically justified.
- **Should use validated analytical methods that are suitable for specific use and conditions for the determination of the drug substance**

QC–quality control; V–volume

CHARACTERIZATON OF PROFILES

Section 2.3

- **At least 3 time points** (zero excluded): although more points preferred but **not more than 6 points** should be included in similarity calculation. More frequent sampling during the period of greatest change.
- **Final point when dissolution ≥85%** [any profile] **or just after both strengths have reached a plateau (of <85%).**
- Sampling need **not exceed 2 hours.**



$$Q = \frac{1}{P}\sum_{j=1}^{P}\left(R_j - T_j\right)^2 = \frac{18^2 + 13^2 + \cdots + 1^2}{7}$$

$$f_2 = 50\, log\{[1 + Q]^{-0.5} \times 100\}$$

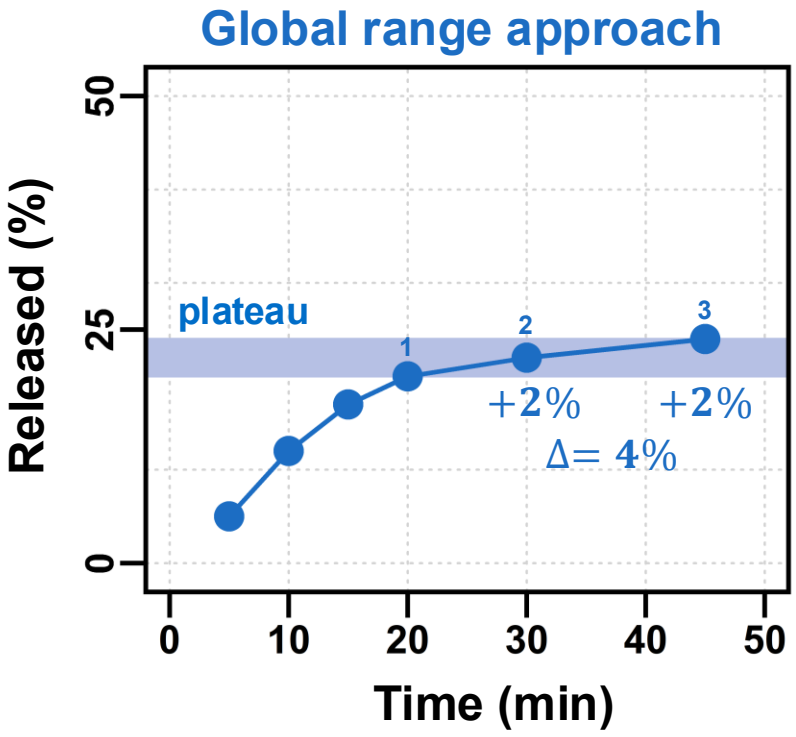
Q–average squared difference; $R(T)_j$–mean dissolved for reference(test) at time point j

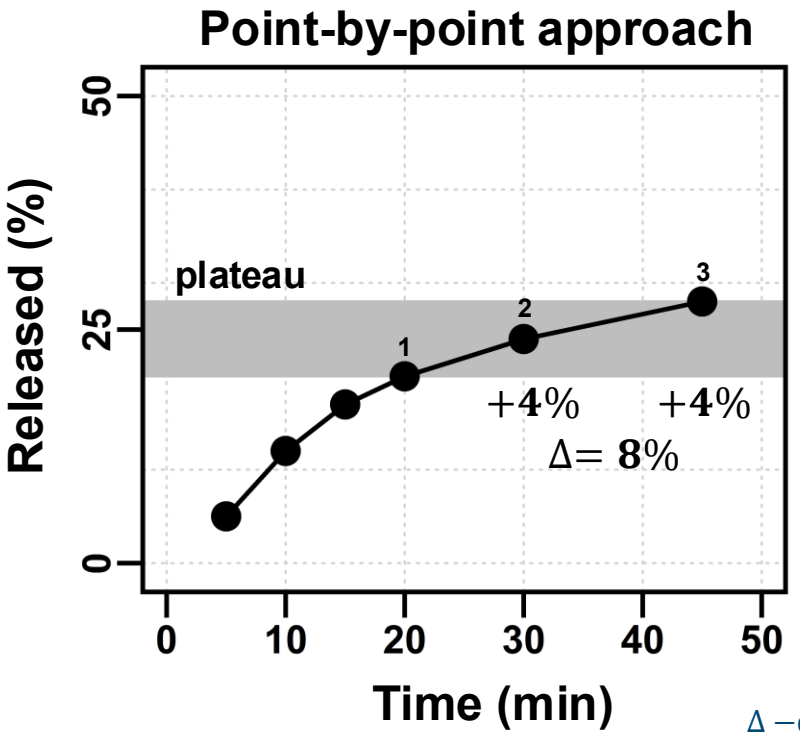
CHARACTERIZATON OF PROFILES

Plateau definition

[Line 124] **A plateau** is defined by **three successive time points** differing by **less than 5%** in mean absolute dissolution.

[Comments] … does it mean that the NMT 5% difference is between **two sequential points or between all of them?**



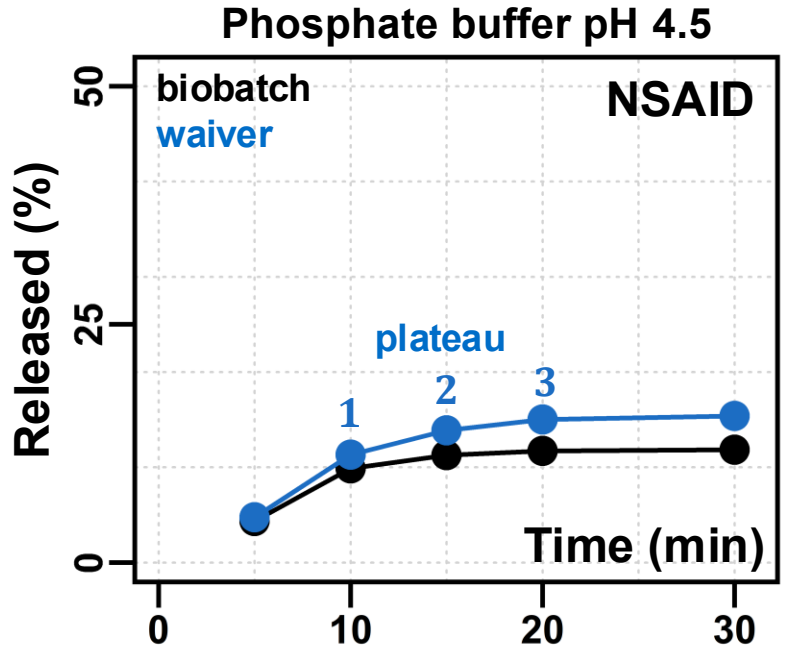


Δ –difference

CHARACTERIZATON OF PROFILES

Plateau & f_2: ♥ on a first sight?

[Comments] A plateau is defined by three successive time points … **Only the first timepoint of the plateau is then to be included in the similarity calculation.**

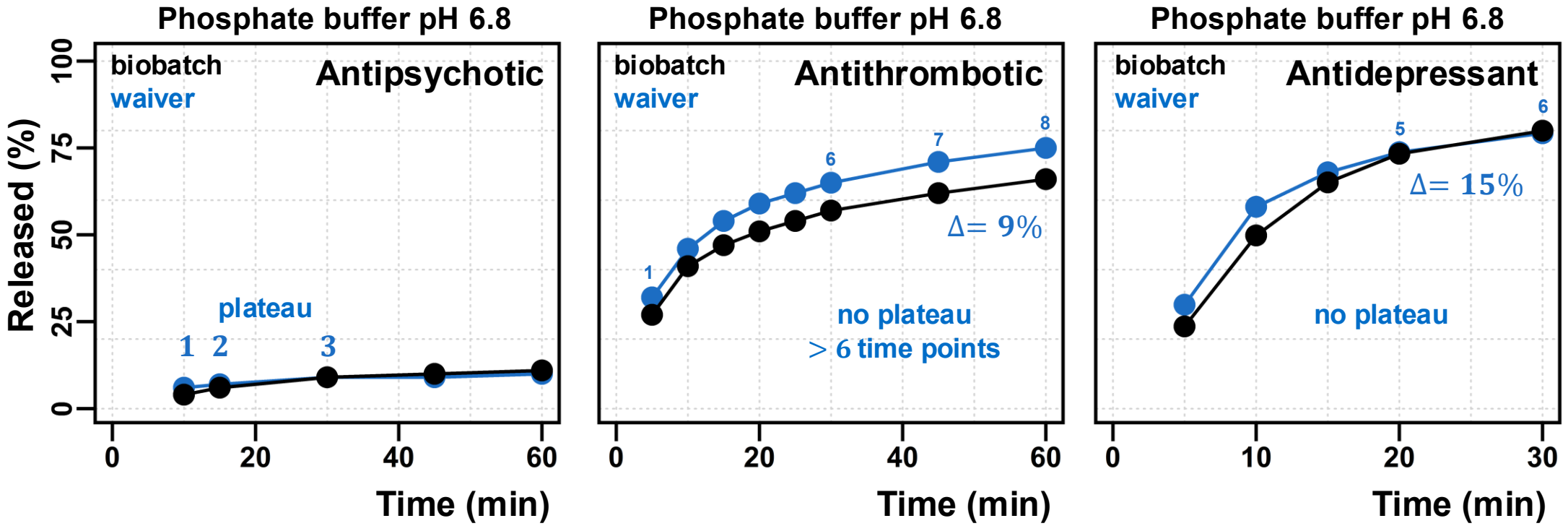


f(2) and Plateau meet in a bar

Dissolution data: USP II, V=900 mL, 50 rpm; cartoon by https://chatgpt.com/

CHARACTERIZATON OF PROFILES

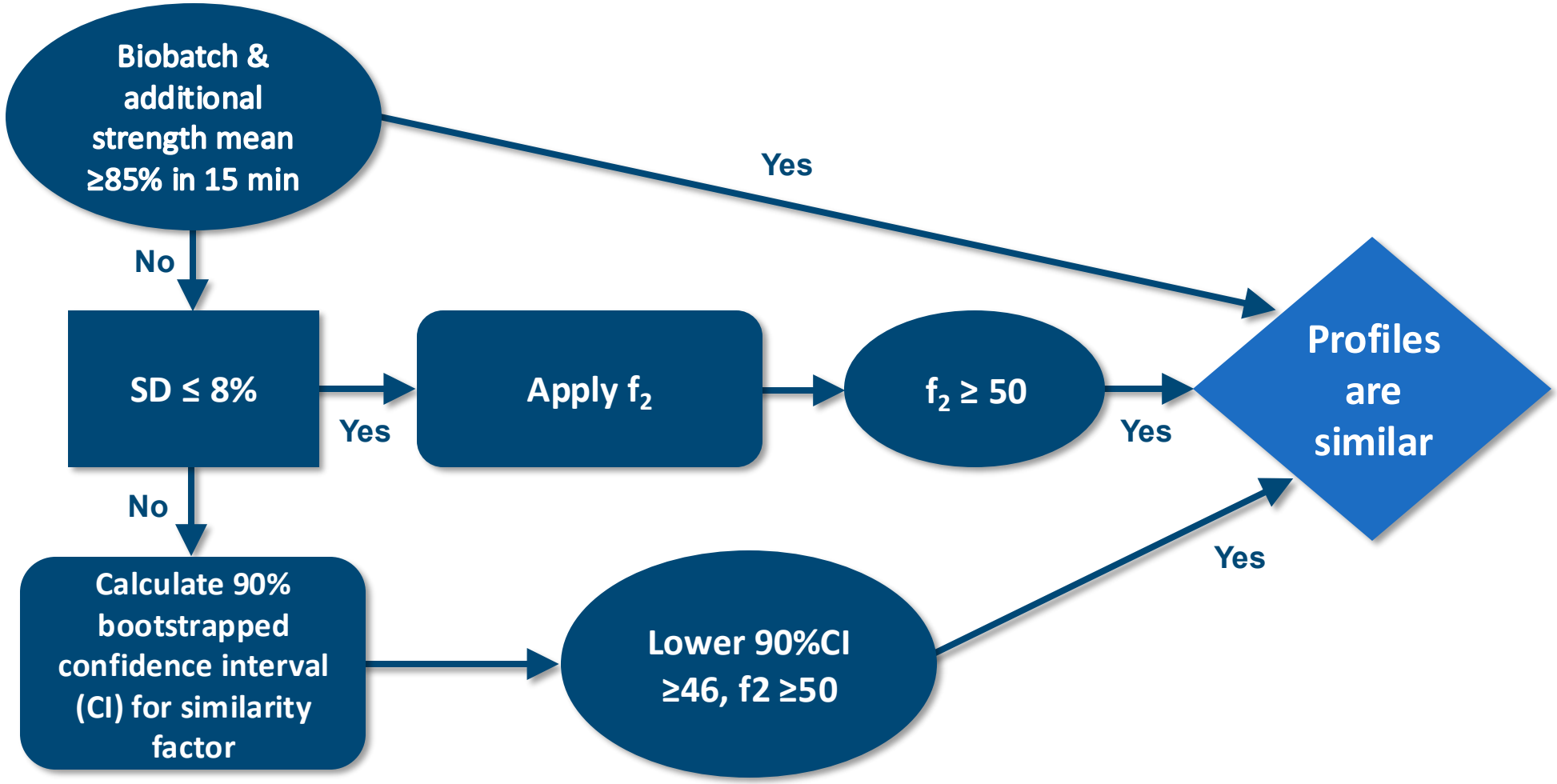
More of real-life: reaching plateau



Dissolution conditions: USP II, V=900 mL, 50(75) rpm

ASSESMENT OF SIMILARITY

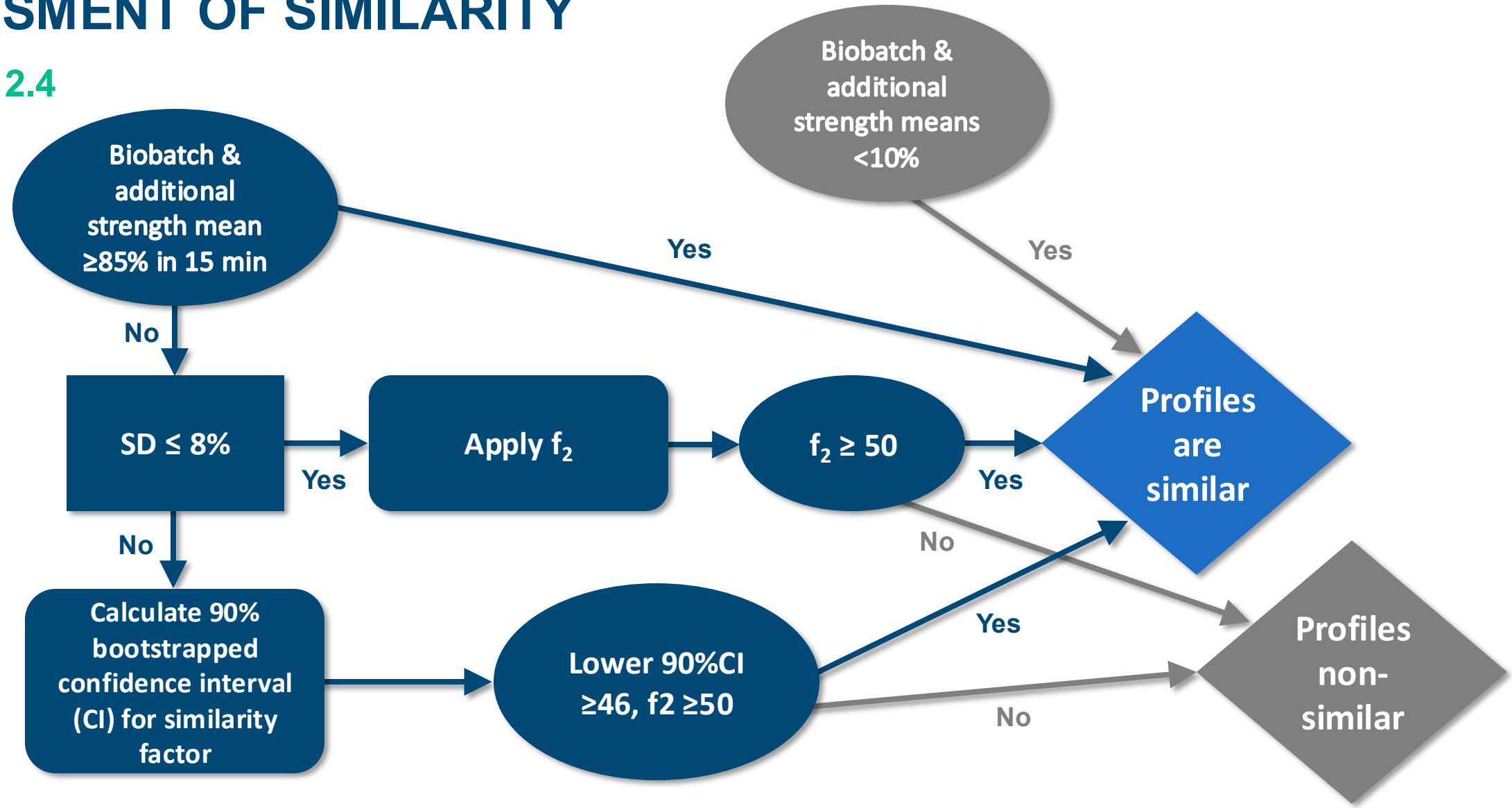
Section 2.4



CI–confidence interval, SD–standard deviation; min–minutes

ASSESMENT OF SIMILARITY

Section 2.4



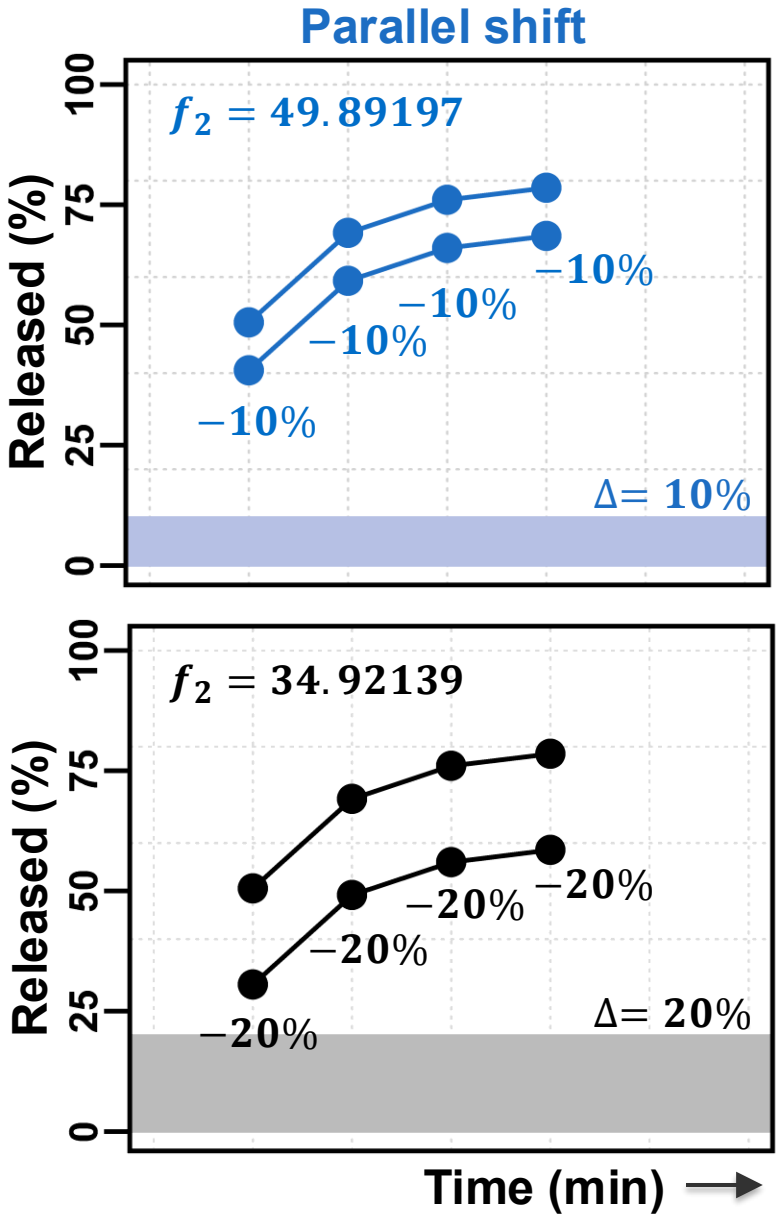
CI–confidence interval, SD–standard deviation; min–minutes

ASSESSMENT OF SIMILARITY

Profiles with $A_P < 10\%$: similar

[Line 149] …, when the maximum portion dissolved … **plateau below 10%, no similarity test needs to be applied,** and similarity can be assumed.

[Comments] Change to: …, when the maximum portion dissolved … **plateau below 20%, no similarity test needs to be applied**, and similarity can be assumed.



A_P–amount dissolved across all points in dissolution

VARIABILITY CRITERIA

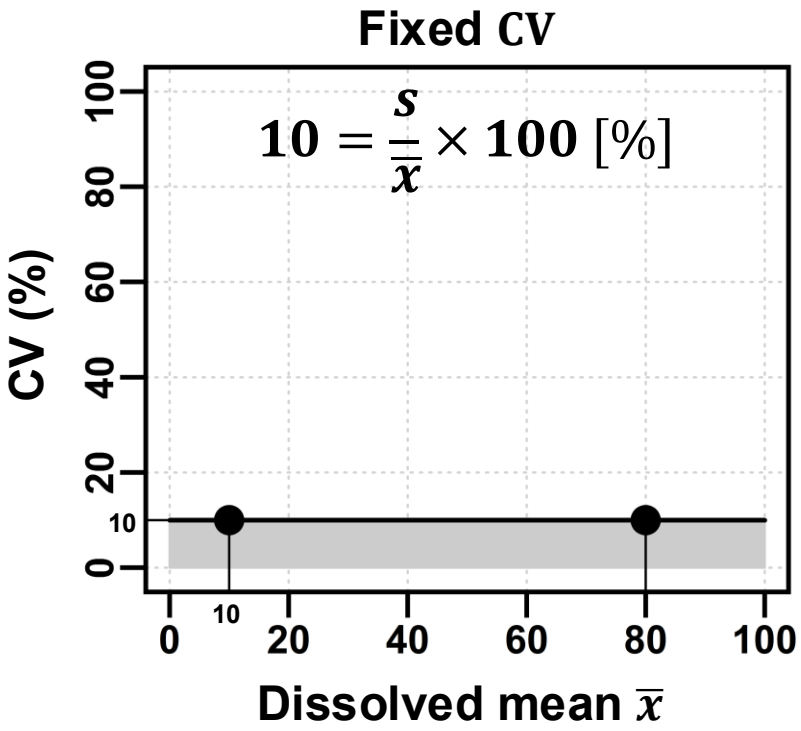
CV vs. SD s

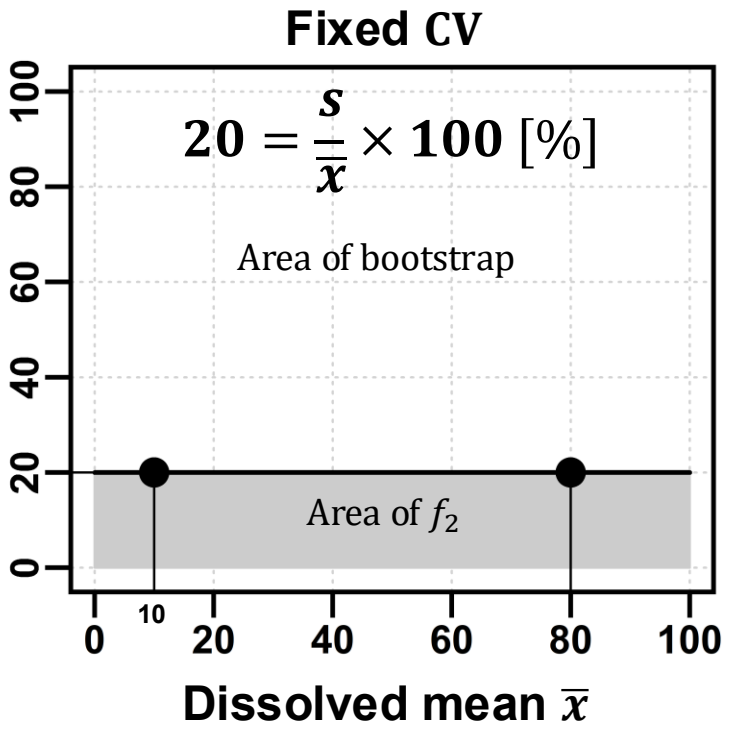
$$CV = \frac{s}{\bar{x}} \times 100\ [\%]$$

Standard deviation

Mean

Q&A





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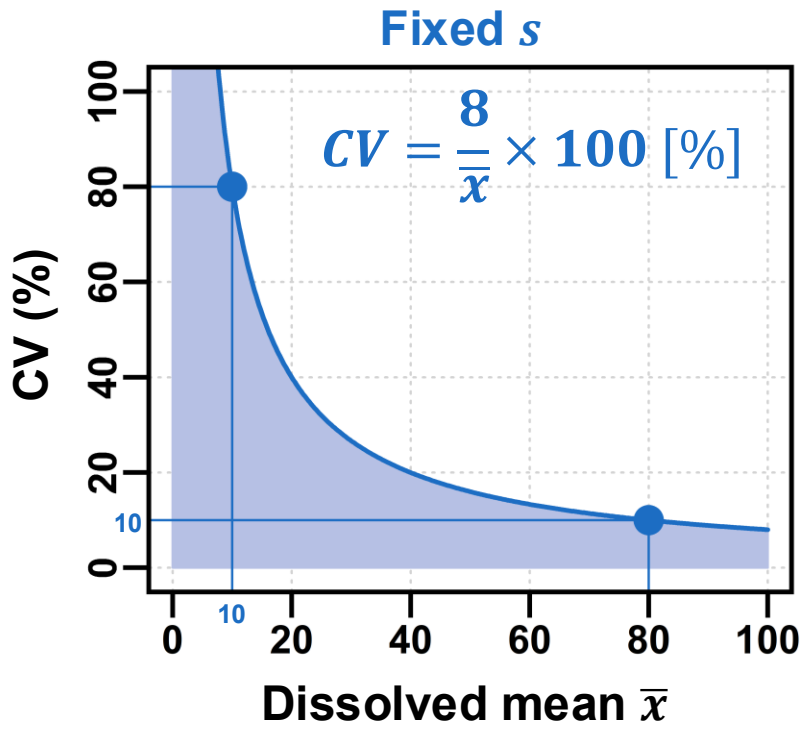
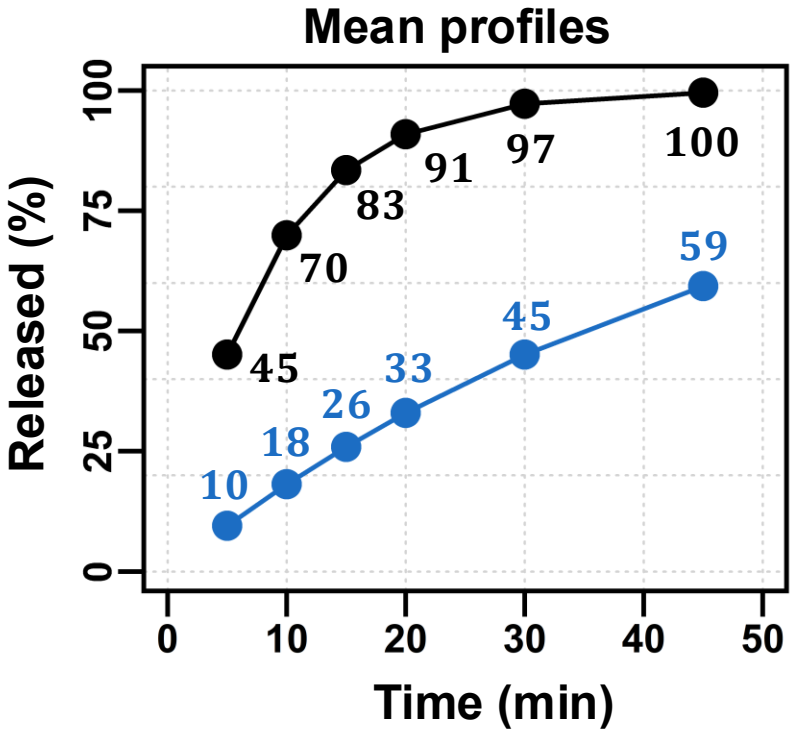


VARIABILITY CRITERIA

The role of time t

CV [%] limit to use f_2		
Time[1)]	Q&A	M13B
5	20	18
10	20	11
15	10	10
20	10	9
30	10	8
45	10	8

[1)]Minutes

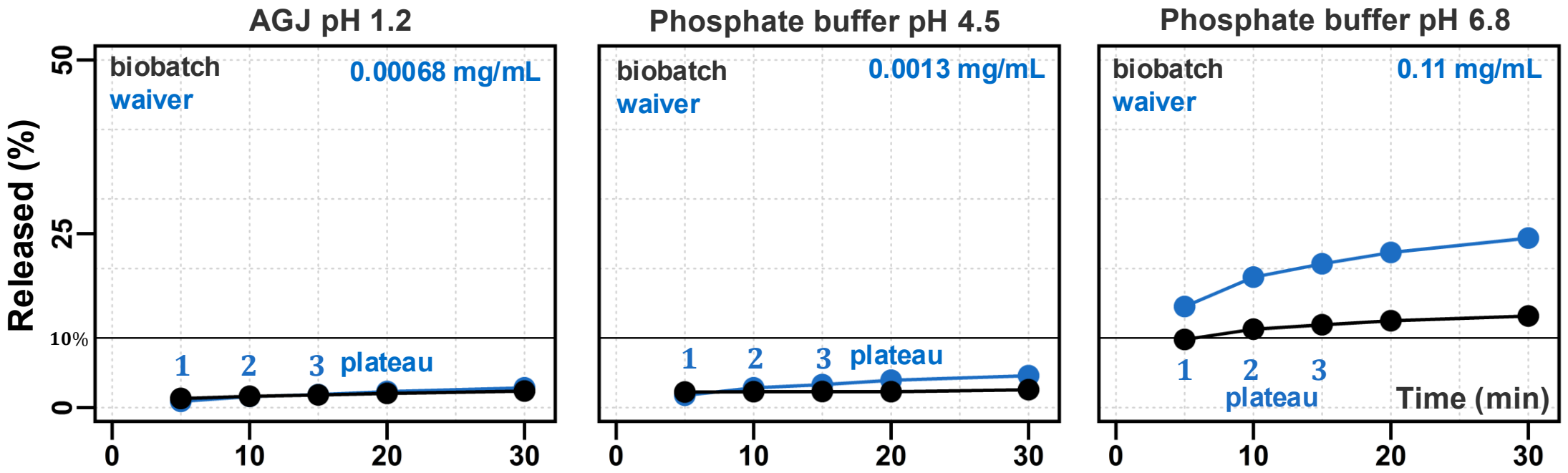


CV [%] limit to use f_2		
Time[1)]	Q&A	M13B
5	20	80
10	20	44
15	10	31
20	10	24
30	10	18
45	10	14

[1)]Minutes

VARIABILITY CRITERIA

Real-life example: oral iron chelator



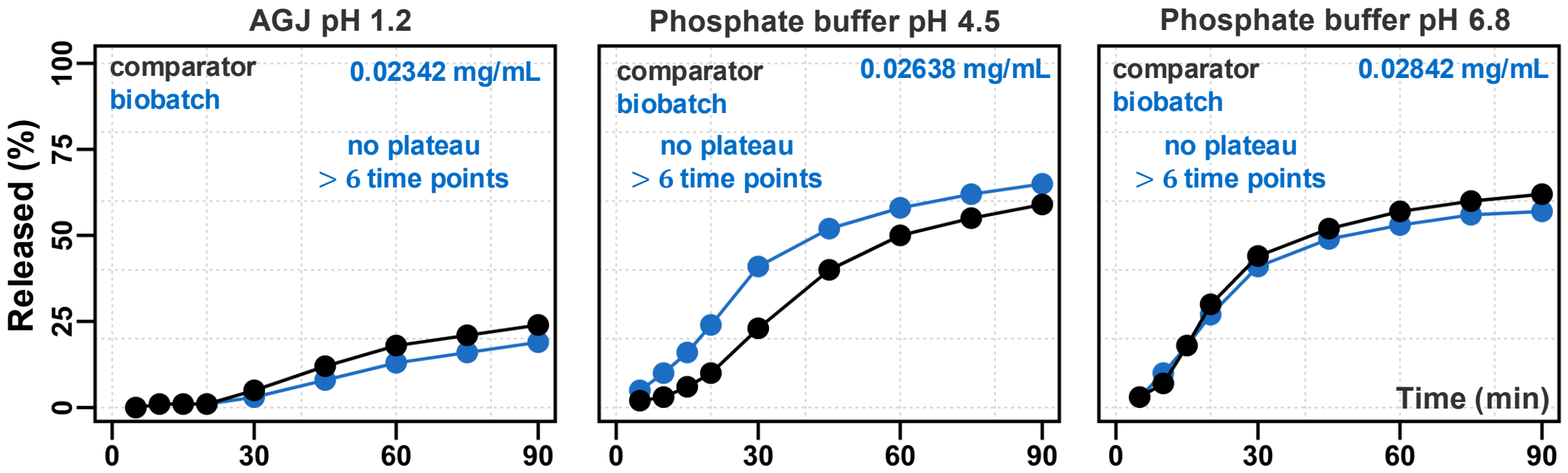
Criterion		
Q&A	$CV > 25\%$	$f_{2,exp}^{B}$
M13B	$A_P < 10\%$	NA

Criterion		
Q&A	$CV > 22\%$	$f_{2,exp}^{B}$
M13B	$A_P < 10\%$	NA

Criterion		
Q&A	$CV > 16\%$	$f_{2,exp}^{B}$
M13B	$s < 3\%$	f_2

VARIABILITY CRITERIA

Real-life example: antiretroviral drug

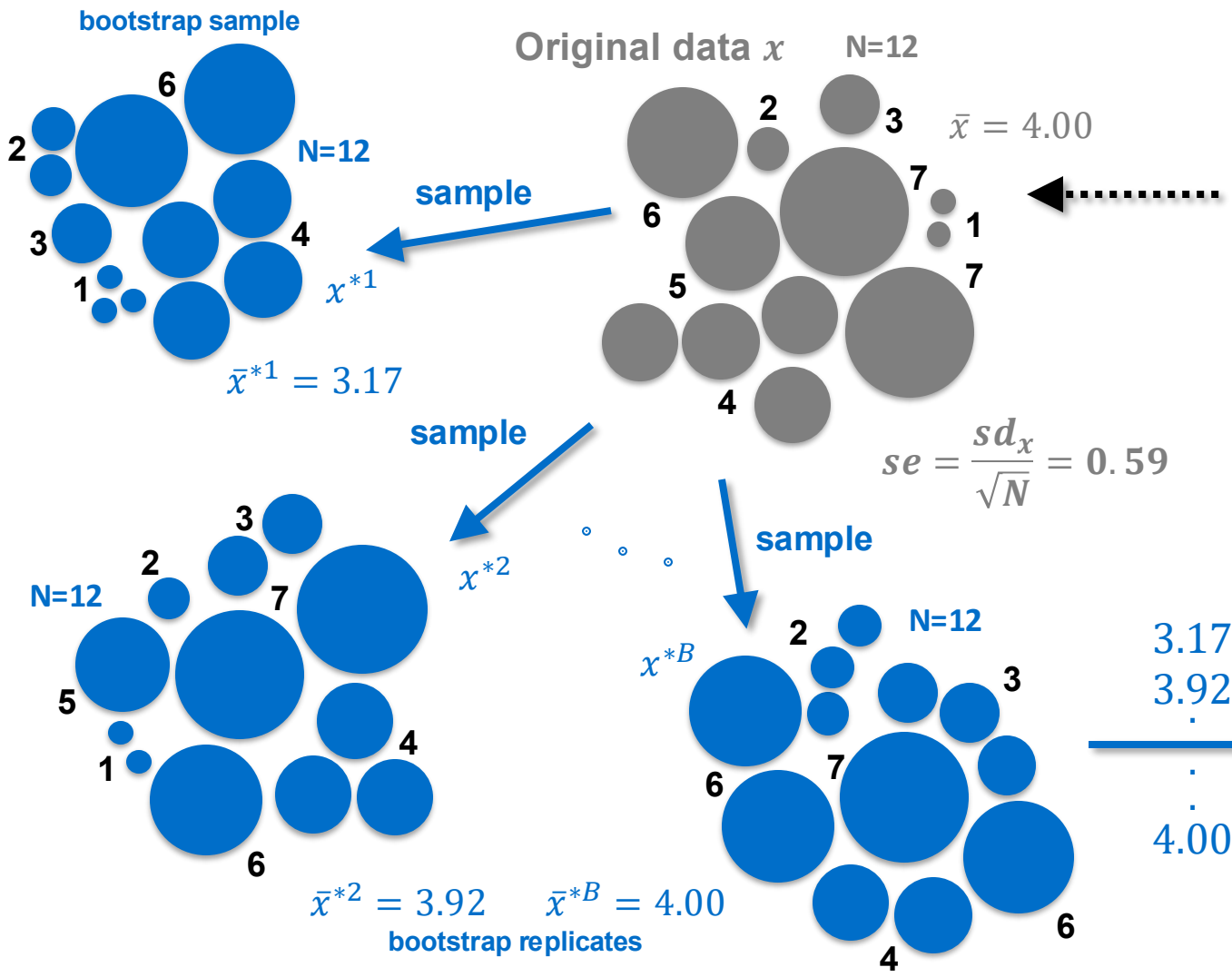


Criterion		
Q&A	$CV > 34\%$	$f_{2,exp}^{B}$
M13B	$s < 5\%$	f_2

Criterion		
Q&A	$CV > 73\%$	$f_{2,exp}^{B}$
M13B	$s > 12\%$	f_2^B

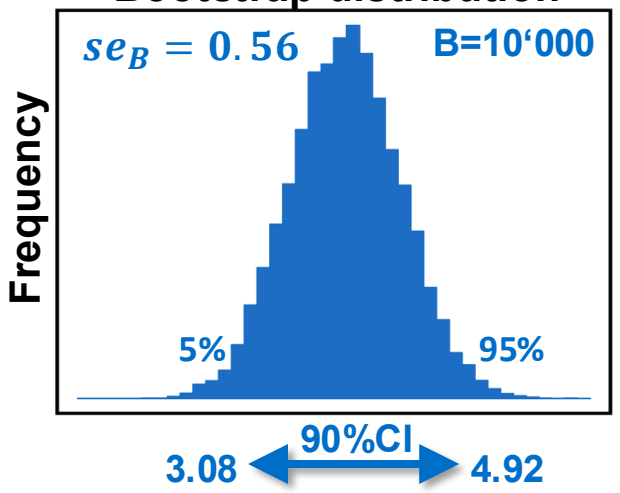
Criterion		
Q&A	$CV > 35\%$	$f_{2,exp}^{B}$
M13B	$s < 7\%$	f_2

BOOTSTRAPPING PRINCIPLE



Unknown population of cannon balls

Bootstrap distribution



se_B bootstrap standard error
se standard error of the mean

BOOTSTRAP METHODOLOGY

Nitpicker‘s corner: 5% percentile of bootstrapped f2‘s equals to lower bound of (percentile) 90% CI.

Q&A vs. M13B: find at least 7 differences

Q&A

Two-sided **90% confidence interval** using **percentiles** (Hyndman & Fan, 1996) using the **Expected-f_2** $(f_{2,EXP})$, with at least **5‘000 samples**. All time points until where one of the products reaches >85%. The results should be reported **rounded to the nearest integer** without decimal units. Validated **software** (report settings: seed, vectors…).

Acceptance criteria: **lower limit of the 90% confidence interval for the $f_{2,EXP}$ is ≥ 50.**

ICH M13B

The **90% confidence** interval for the **similarity factor**.

Acceptance criteria: **lower bound of the 90% bootstrapped CI should be ≥46 and the point estimate (f_2) should be ≥50.**

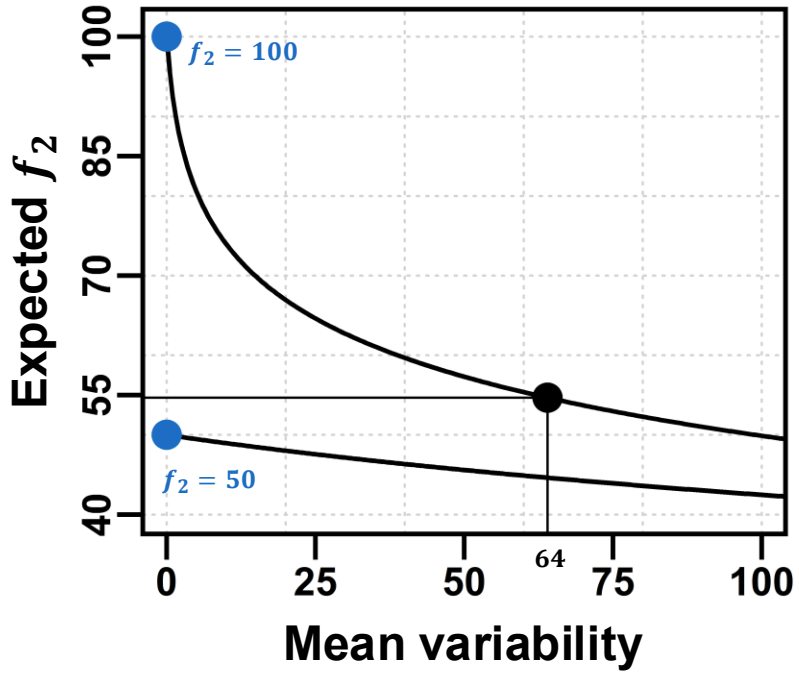
BOOTSTRAPPING DISSOLUTION

Classical and expected similarity factor

$$f_2\ (M13B)$$

Mean squared difference

$$f_2 = 50\ log\left\{\left[1+\frac{1}{P}\sum_{j=1}^{P}\left(R_j - T_j\right)^2\right]^{-0.5} \times 100\right\}$$



$$E(f_2) = 50\ log\left\{\left[1+\frac{1}{P}\sum_{j=1}^{P}\left(R_j - T_j\right)^2 + \sum_{j=1}^{P}\left(s_{Rj}^2 + s_{Tj}^2\right)/n\right]^{-0.5} \times 100\right\}$$

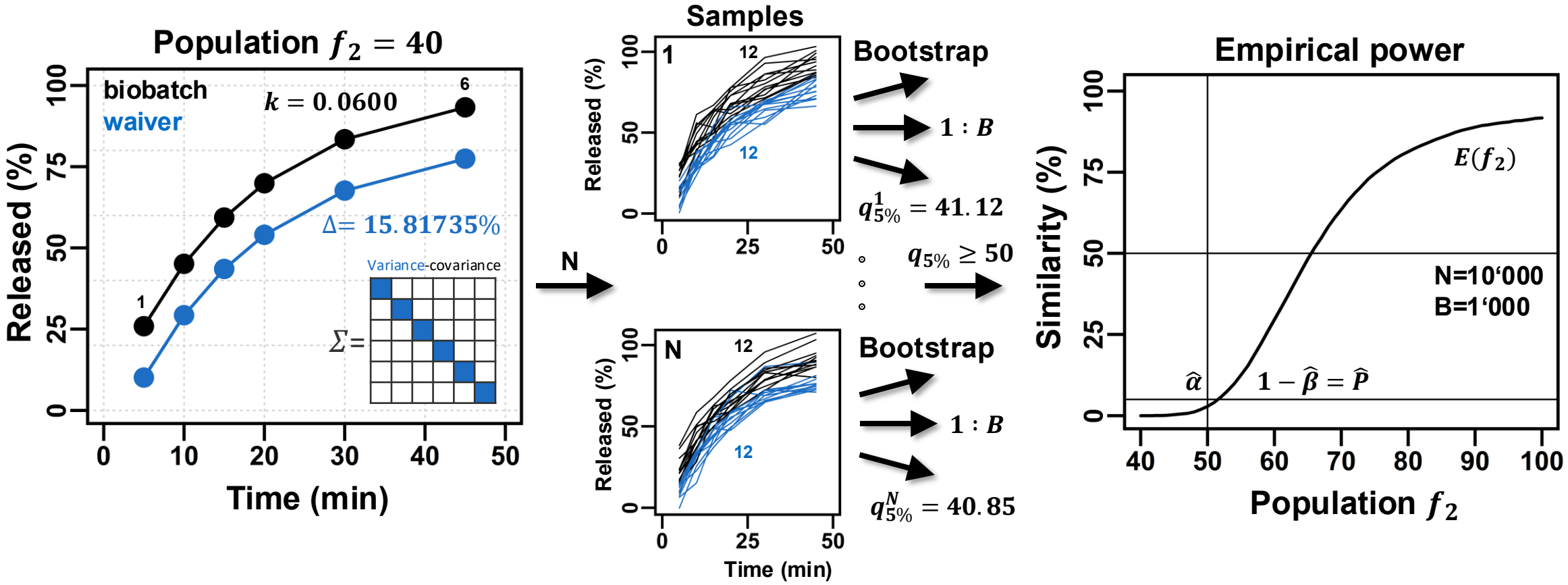
Mean variability

Expected $\mathrm{E}(f_2)$ $(Q\&A)$

$R(T)_j$–mean dissolved for reference(test) at time point j; $s^2_{R(T)j}$–variance for reference(test) at time point j; n–number of dissolution vessels

BOOTSTRAPPING DISSOLUTION $y = 100 \times \left(1 - e^{-kt}\right)$

Simulation study: 1-order model with parallel shift Δ



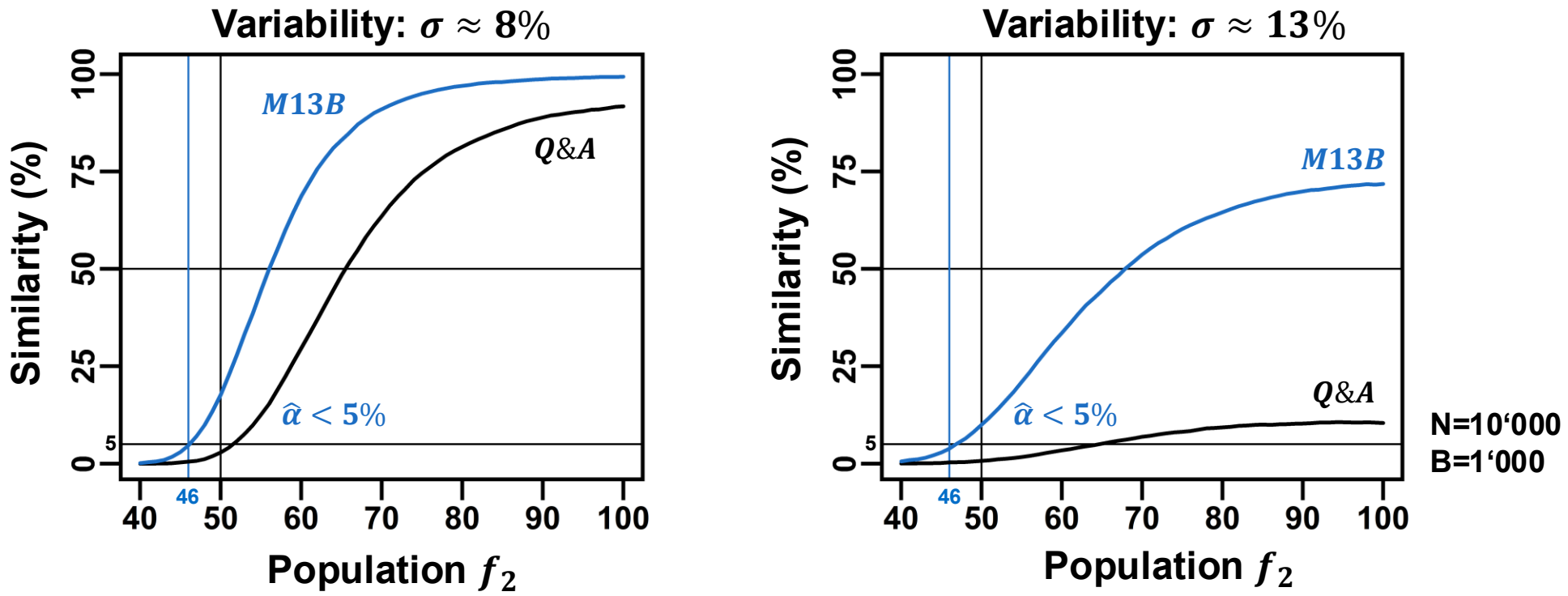
N–number of simulations; B–number of bootstraps; $q_{5\%}$–5% percentile; $\hat{\alpha}$–empirical type I error; $\hat{\beta}$–empirical type II error; $\hat{P}$–empirical power

BOOTSTRAPPING DISSOLUTION

Type I error (α) and power $(1-\beta)$

Bootstrap			
Rules	**Type**	**PE[1)]**	**5%[2)]**
$Q\&A$	$E(f_2)$	NA	50
$M13B$	f_2	50	46

[1)]PE-point estimate; [2)]Percentile



N–number of simulations; B–number of bootstraps per simulation; $\hat{\alpha}$–empirical type I error

BOOTSTRAPPING DISSOLUTION

To release Q&A to M13B?

- **Type of 90% confidence interval?**
- **Number of bootstraps** (B)?
- Time point **inclusion rules** $(A_{15} \geq 85\%$, plateau)?
- **Rounding**? (CAVE: type I error α)
- **Software** aspects (e.g., seed number, validation, code inspection required)?

90% bootstrap CI[1] (data I)		
Type	**Lower**	**Upper**
Normal	75.3720	105.6605
Percentile	62.7877	92.9877
Basic	88.0448	118.2448
BC	87.4104	99.7090
BCa	87.4081	99.7060
Bootstrap-*t*[2]	87.9071	123.3391

[1]R (v4.5.1); B0=10‘000; [2]B1=1‘000

COMPOSITION

New rules introduced

[Line 277] Deviations from direct proportionality for core composition between strengths can be considered **as exceptions** with appropriate **scientific justification in relation to API solubility:**

- **Highly-soluble:** up Level 2 (L_2)
- **Low-soluble:** Level 1 (L_1) or 2 (L_2) based on additional restrictions: dissolution [without surfactant] and total core weight changes

Deviation [%w/w][1)]			
Function	**Excipient**	L_1	L_2
Filler/Diluent	**Any**	5	10
Disitegrant	**Starch**	3	6
	Other	1	2
Binder	**Any**	0.5	1
Lubricant	**Stearates**	0.25	0.5
	Other	1	2
Glidant	**Talc**	1	2
	Other	0.1	0.2
Total absolute Δ%		**5**	**10**

[1)]Excipients with functions not described in table: keep proportionality (e.g., surfactants)

COMPOSITION

Example: decrease of lactose by 6.9 mg

Composition [mg][1)]					Relative [%w/w][1)]			Δ%	
Function	**Excipient**	***A***	***B***	***N***	***A***	***B***	***N***	$B-N$	L_1
API	API	10.0	5.0	5.0	6.67	6.67	7.34	NA	NA
Filler	**Lactose**	**128.8**	**64.4**	**57.5**	**85.87**	**85.87**	**84.43**	**1.43**	5
Binder	Starch	7.4	3.7	3.7	4.93	4.93	5.43	**0.5**	**0.5**
Glidant	Talc	3.0	1.5	1.5	2.00	2.00	2.20	0.20	1
Lubricant	MgSt	0.8	0.4	0.4	0.53	0.53	0.59	0.05	0.25
	Total	**150.0**	**75.0**	**68.1**	**100.0**	**100.0**	**100.0**	**2.19***	**5**

[1)]Process: dry mixing

[1)]Relative vs. total tablet weight

*Total absolute excipient change

Core weight $\Delta\% = 9.2\%$ $(L_1 = 10\%)$

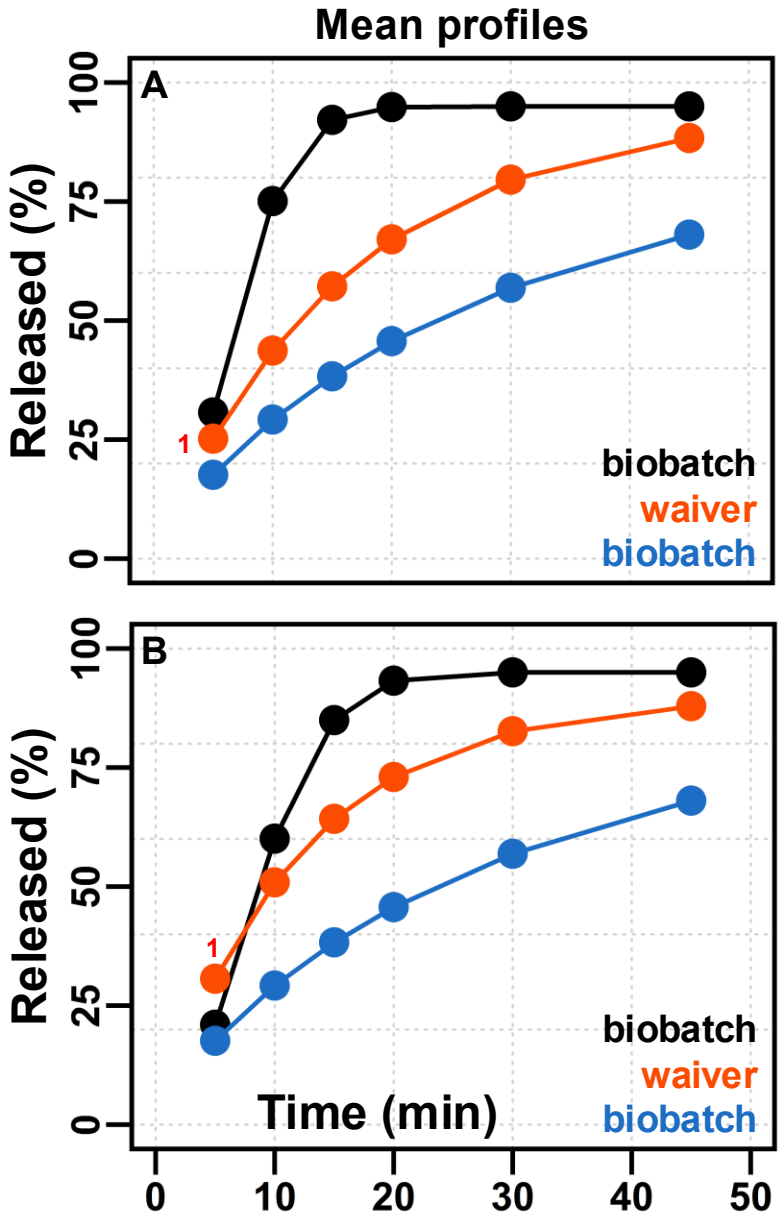
CONCEPT OF SAFE SPACE

Bracketing approach

[Line 203] … **the middle strength mean dissolution profile should fall between the dissolution profiles of the high and low biobatch strengths.**

[Comments] Would it be acceptable if **certain dissolution points exceed the area between the mean profiles of higher and the lower strength?**

Clarify the requirements on **the variability and dissolution similarity** accordingly.



OTHER COMMENTS

M13B

- Use of **the same batch(es) used in the BE** study(ies) for biowaiver
- **Variability** rules for $A < 10\%$ ($\geq 85\%$)
- **Comparative dissolution of biobatches:** complementary to BE
- Prospective analysis plan & **stand-alone report for biowaiver**
- More extensive **examples for FDC** (Q&A)
- …

Federal Register / Vol. 90, No. 172 / Tuesday, September 9, 2025 / Notices 43453

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
[Docket No. FDA–2023–D–0093]

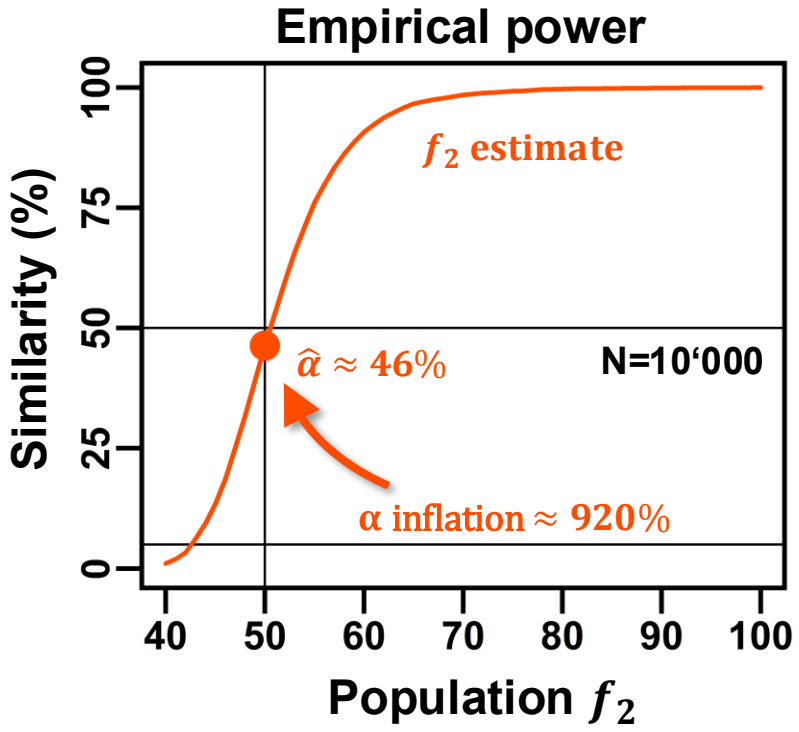
M13B Bioequivalence for Immediate Release Solid Oral Dosage Forms: Additional Strengths Biowaiver; International Council for Harmonisation; Draft Guidance for Industry; Reopening of the Comment Period

DATES: Submit either electronic or written comments on the draft guidance **by October 9, 2025** to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance.

ESSENTIAL NOTES

M13B

- **New criteria for variability** (s)**:** appears less stringent vs. current rules (different rules in ICH M9?)
- **Classical** f_2 estimate **remains standard for low-variability profiles** $(s \leq 8\%)$: plateau & number of points in similarity?
- **Additional similarity criteria for poorly soluble drug** $(A_P < 10\%)$: less stringent vs. current rules
- **New criteria for bootstrapping** f_2: higher probability to pass vs. $E(f_2)$
- Possibility to **deviate from proportional composition is** +: scientifically justified?



R QUOTES

```
library(fortunes)
```

```
> require(fortunes)
> fortune(44)
```

The Huli of Papua New Guinea use '15' to mean a very large number and '15 times 15 samting (something)' to mean something close to infinity.

-- David Whiting (in a discussion about trying to estimate the number of R users) R-help (April 2004)

```
> require(fortunes)
> fortune(172)
```

It is unusual for the actual data not to be available in real problems.

-- Brian D. Ripley (in reply to a question how to fit a distribution if not the data but only their histogram is available) R-help (June 2006)