THE REFLECTION PAPER ON DISSOLUTION SPECIFICATION FOR GENERICS

Jiri Hofmann
Clinical Development Department, Zentiva, k.s.

Bioequivalence & Development workshop

Prague, September 21-22, 2017

SANOFI GENERICS

REFLECTION PAPER: DRAFT

During the last few years the suitability of dissolution specifications has been discussed in marketing authorization procedures. Some referrals concerning this topic have been through the CMD(h).

Draft Reflection paper on the dissolution specification for generic oral immediate release products (EMA/332805/2016)

EMA / 332805 / 2016	
Draft agreed by the QWP	March 2016
Draft agreed by the CHMP	March 2016
Draft adopted by the CVMP	April 2016
Start of public consultation	13 May 2016
End of consultation (deadline for comments)	13 August 2016

REFLECTION PAPER: COMMENTS

- General (16) and specific (206) comments
- 19 stakeholders: companies, associations, individual(s)

Overview of comments: 95 pages

Overview of comments received on ‚Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action' (EMA/CHMP/CVMP/QWP/257305/2017)

REFLECTION PAPER: FINAL

EMA / 33603 / 2017	
Agreed by the QWP	24 May 2017
Adopted by the CHMP	June 2017
Adopted by the CVMP	**July 2017**
Published by EMA	**15 August 2017**

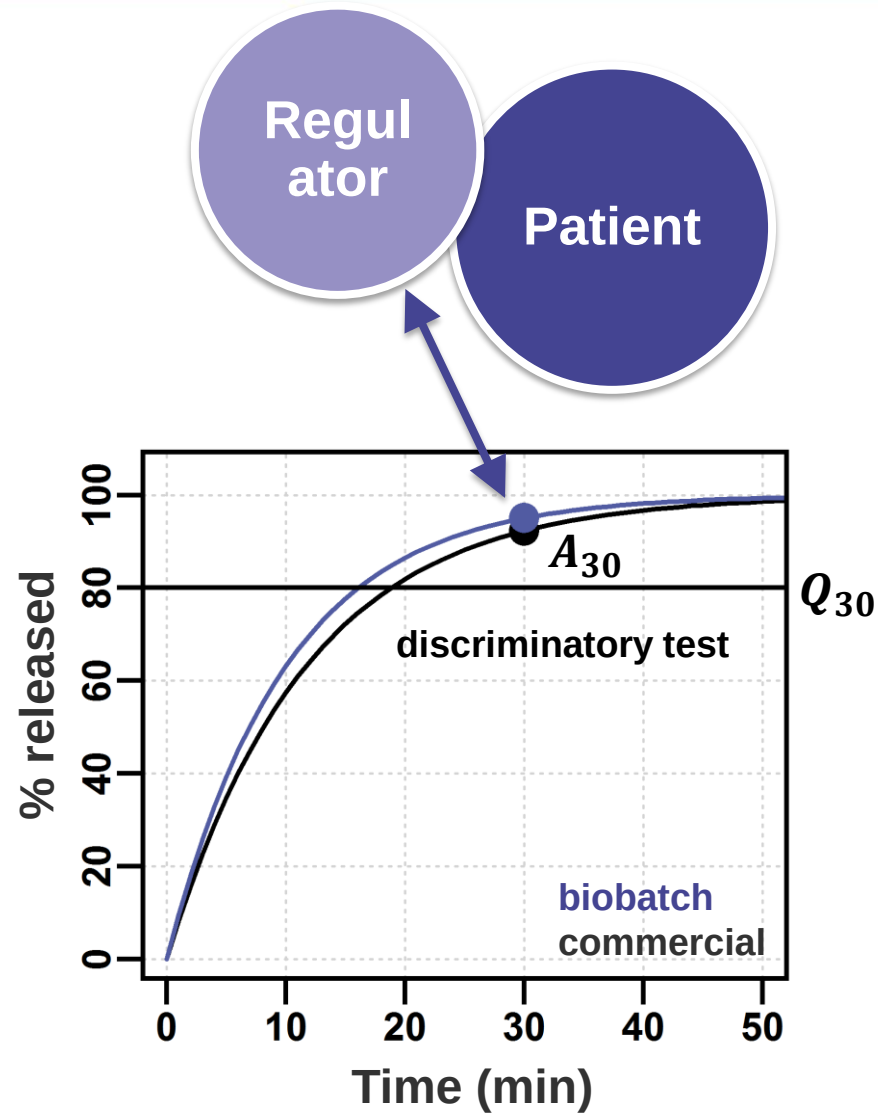
Reflection paper on the dissolution specification for generic oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017)

Deficiency letter provided at Day 145 (18 July 2017)

Quality: The limits for dissolution should be (..) established according to Annex 1 of the (..) reflection paper.

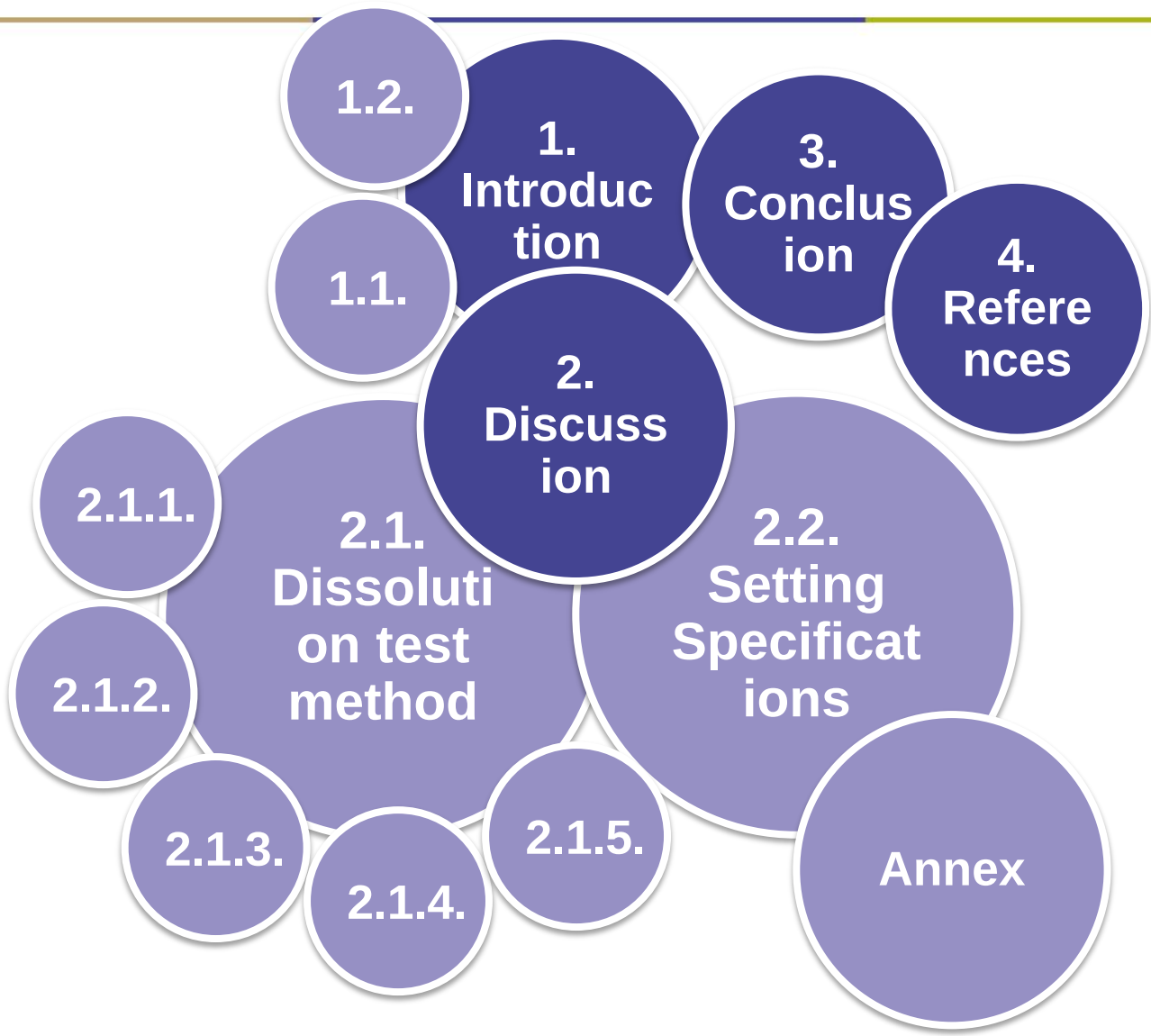
REFLECTION PAPER: AIM

- **Facilitate decisions on setting specifications for in-vitro dissolution of generic immediate release products**
- **Ensure that results from bioequivalence study/ies may be extrapolated to the product administered to the patient: *‚all commercial batches should show similar behaviour compared to biobatch.‘***

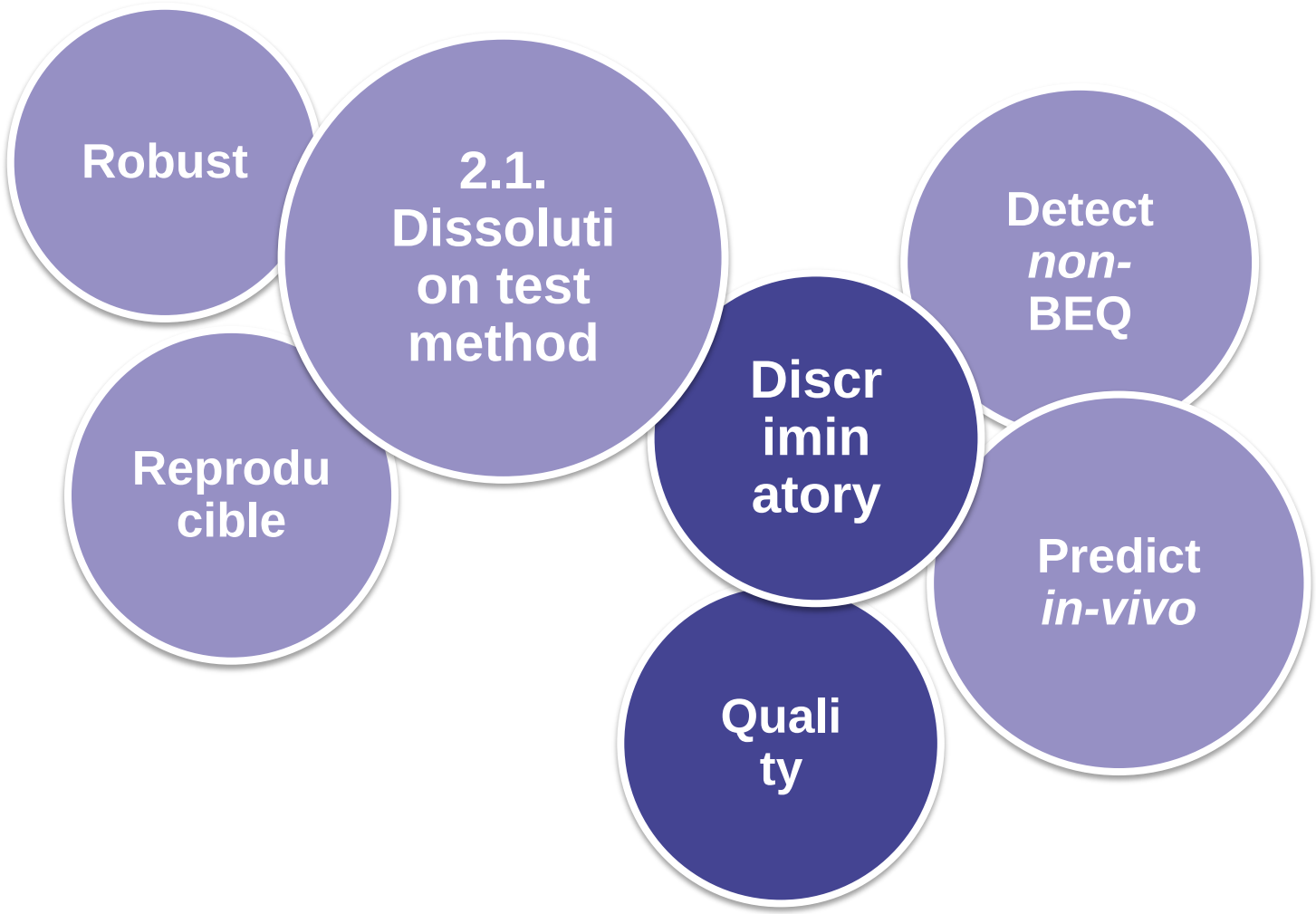


Q_{30}-specification limit
A_{30}-amount dissolved in 30 minutes

REFLECTION PAPER: STRUCTURE

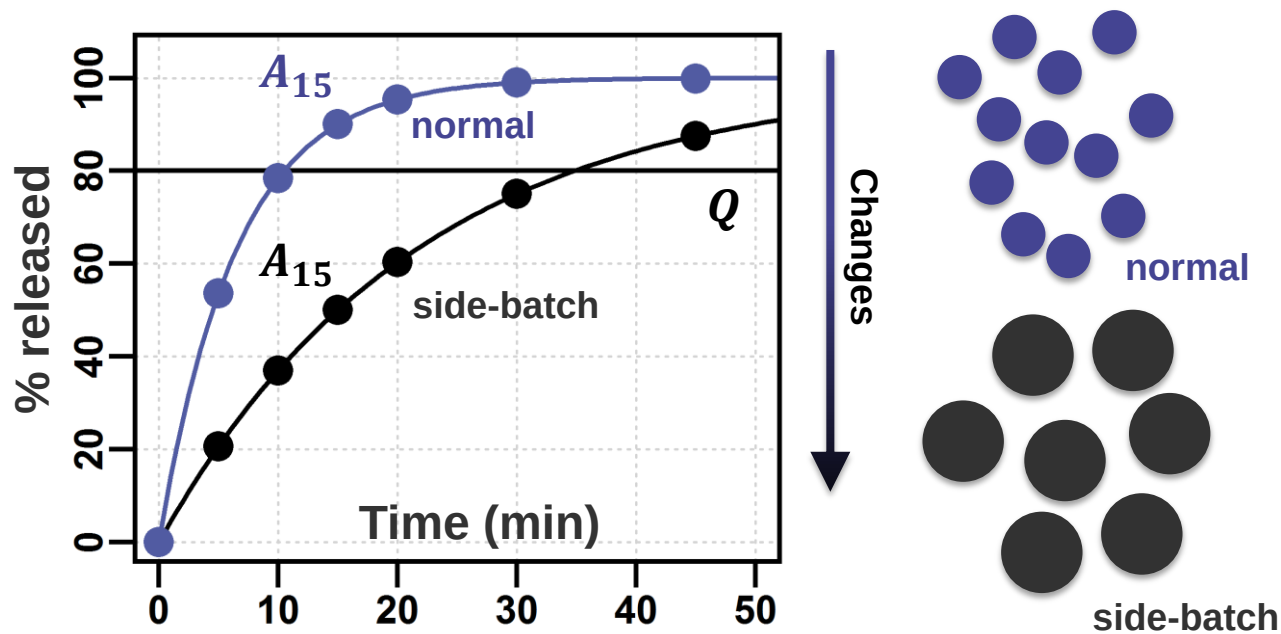


DISSOLUTION METHOD: DISCRIMINATORY



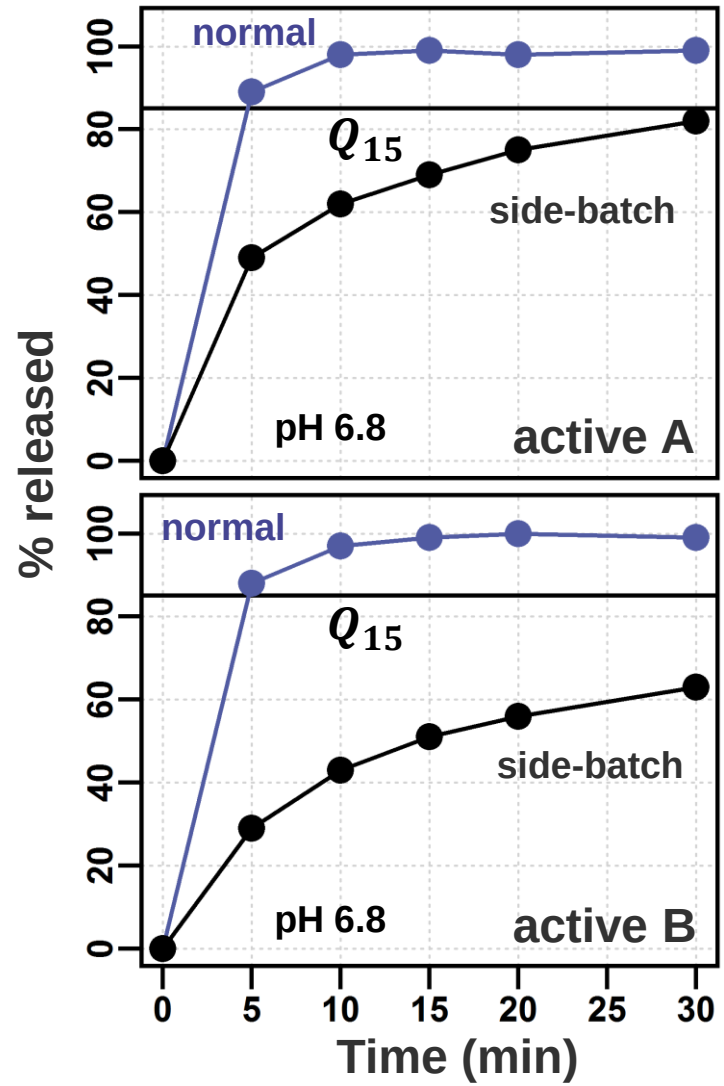
DISCRIMINATORY POWER: QUALITY

*2.1.2. **The suitability (..) should be demonstrated using batches with different quality attributes. (…), batches with meaningful changes (…) should be manufactured. Such changes (..) quantitative formulation, material specifications and/or using slightly modified process parameters.***



EXAMPLE: BCS CLASS III

FDC composition (mg)		
Batch	normal	side-batch
APIs	21.868	21.868
MCC	149.932	49.180
CaHPO4	90	190.752
Crosscarmelose	14	0
Silica+MgSt	4.2	4.2
Total (mg)	280	266



CHANGES: QUANTITATIVE ONLY

*2.1.2. **Changes (..) covered by the qualitative (..) formula (…), only the proportions of the employed excipients might be changed. The complete omission of one or more specific excipients from the formulation (e.g. binder, disintegrant) is not supported.***

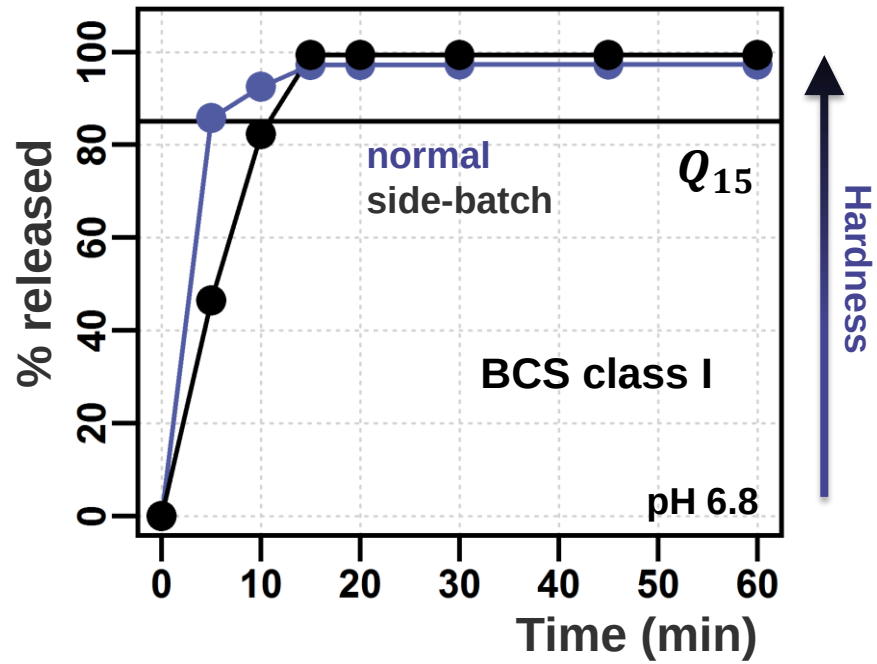
Composition (mg)		
Batch	**normal**	**A**
API	20	20
Filler 1	100	50
Filler 2	64	121
Disintegrant	14	7
Lubricant	2	2
Total (mg)	**200**	**200**

Composition (mg)	
Batch	**B**
API	20
Filler 1	100
Filler 3	64
Disintegrant	14
Lubricant	2
Total (mg)	**200**

HIGHLY SOLUBLE API: BAD BATCHES

2.1.2. [Draft] ***(..) for (..) BCS (..) I or (..) III (..) with very high solubility (..), it may not always be possible to detect any differences in dissolution behavior after meaningful changes (..) have been made.***

[Final version] ***In these cases the method (..) adequate without further justification (..) or be replaced by a disintegration test.***

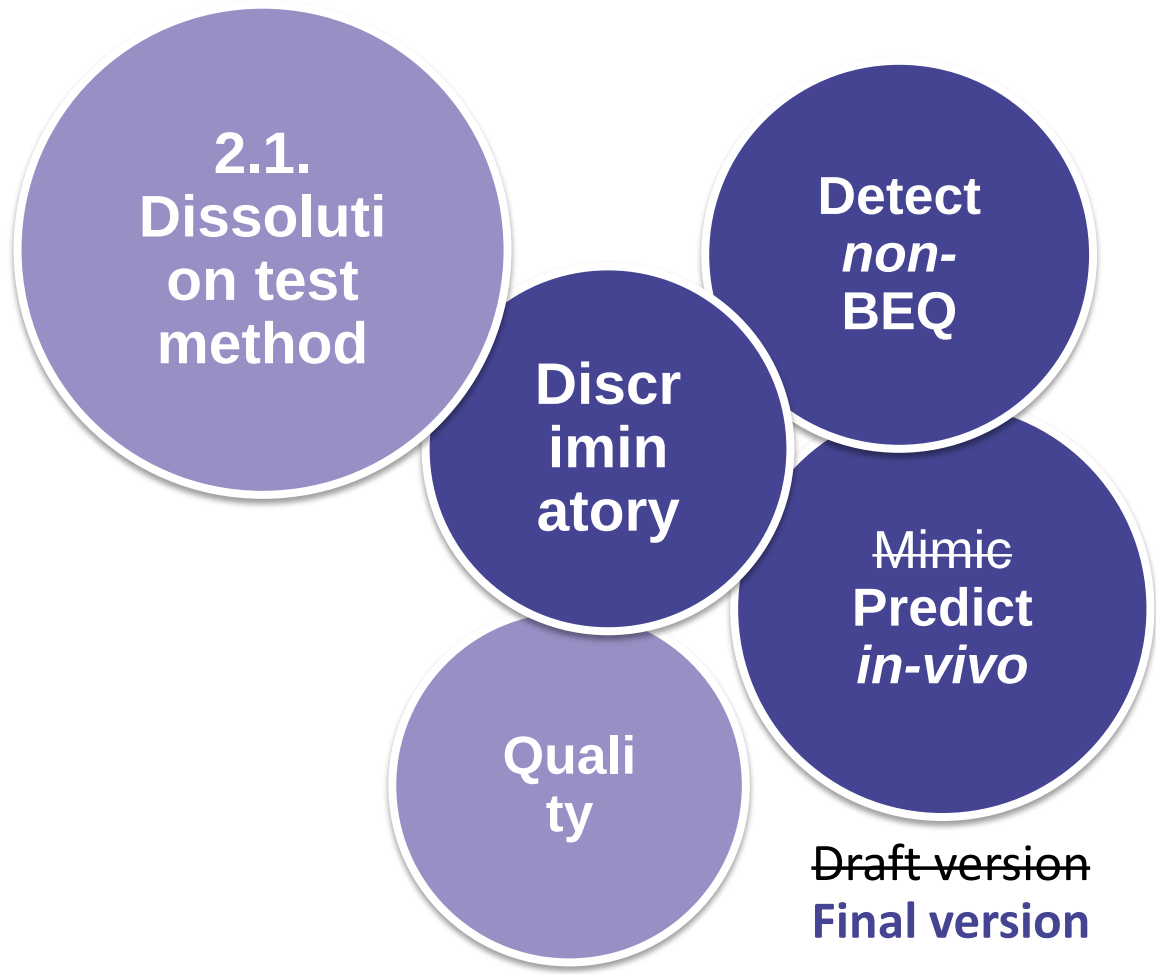


Comment 97: (..) not clear how similar situations will be dealt if present for BCS class 2 and 4 drugs.

DISCRIMINATORY POWER: IN-VIVO

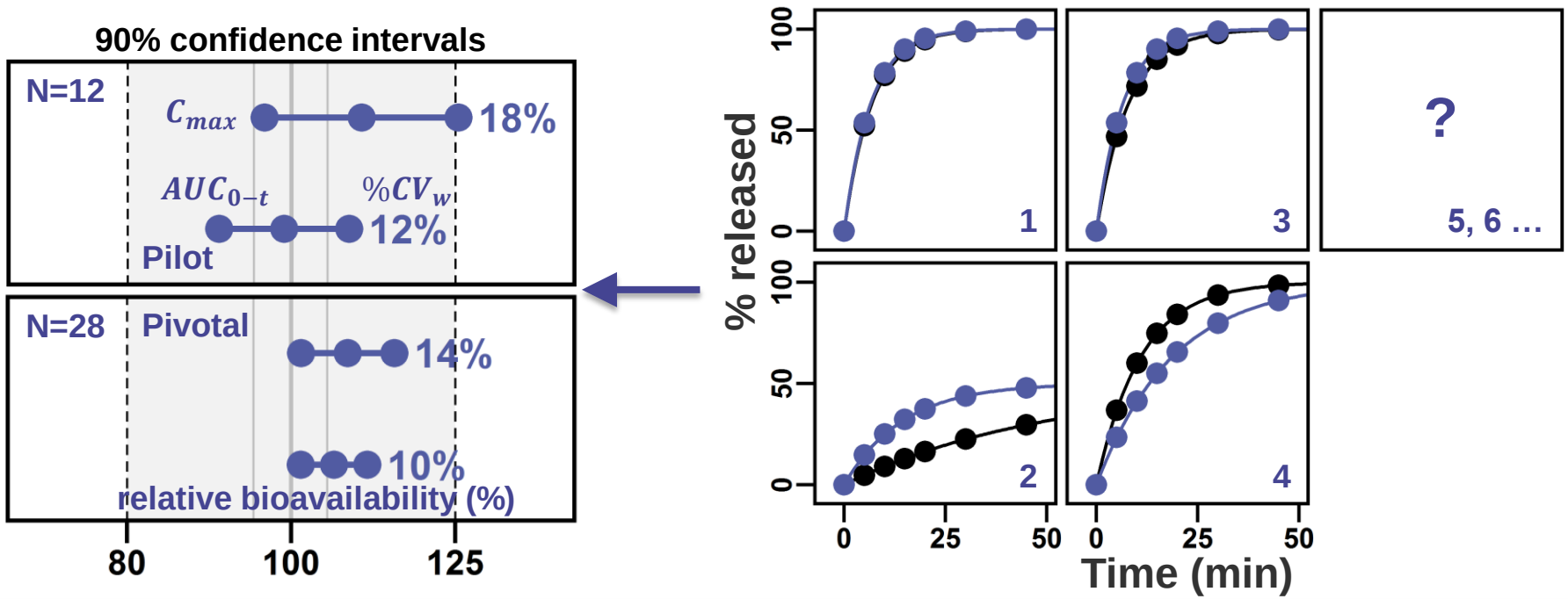
*1.1. **The dissolution specification should (..), ideally, signal potential problems with in vivo bioavailability (e.g. bioinequivalence).***

*2.1.2. **Ideally all non-bioequivalent batches should be detected.***



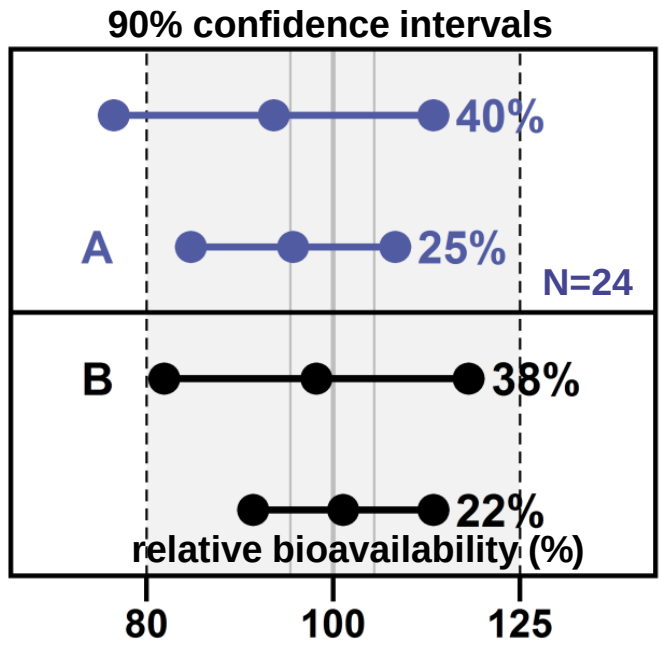
DISSOLUTION: LINK TO IN-VIVO

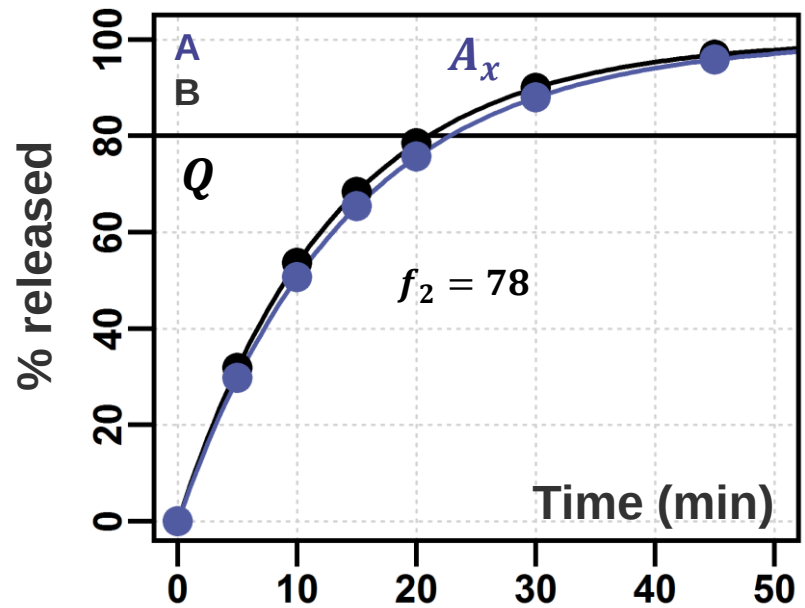
2.1.2. [Final version] ***The dissolution results, under different test conditions during development, should be compared with the pharmacokinetic data (..) to select (..) test conditions for routine testing (..). (..), all the relevant in vivo data (..) should be taken into consideration in choosing (..) dissolution test conditions.***



IN-VIVO: SEVERAL BATCHES

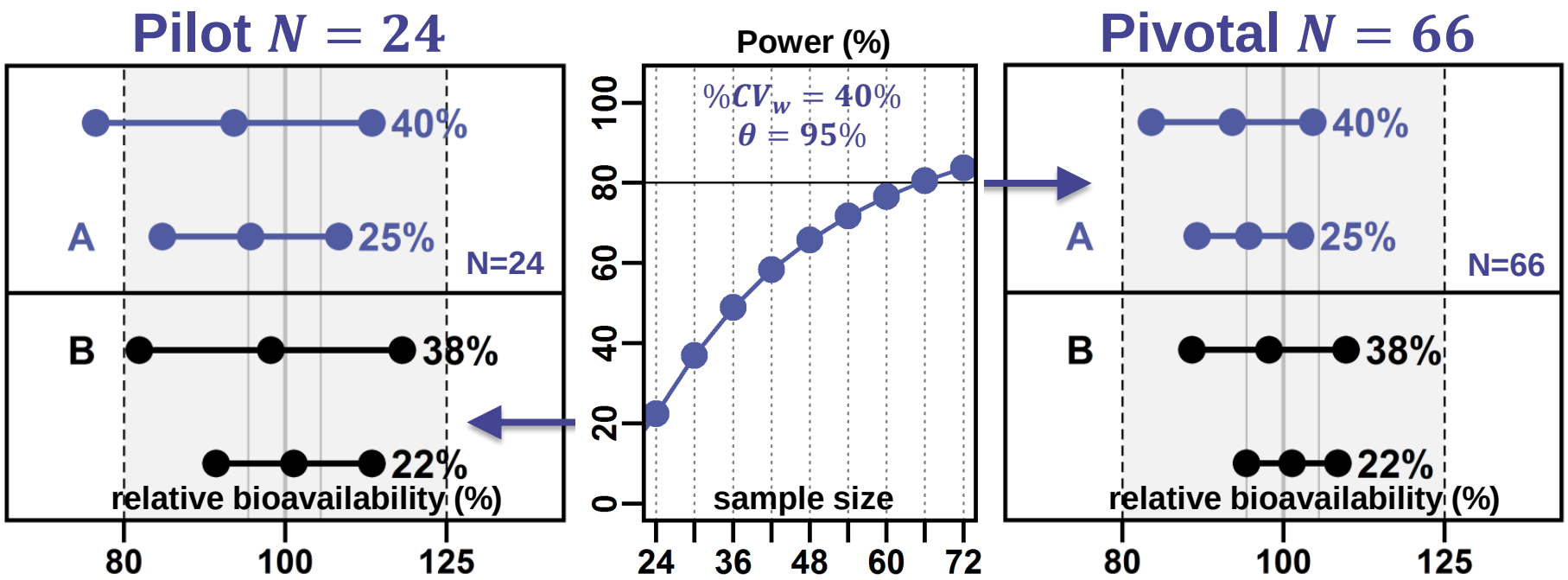
2.1.3. ***(..) where several batches (..) have been tested during development in vivo (..), dissolution test conditions should (..) allow discrimination between acceptable and non-acceptable batches by setting a suitable specification.***





Pilot study $N = 24$

IN-VIVO: PILOT VS. PIVOTAL

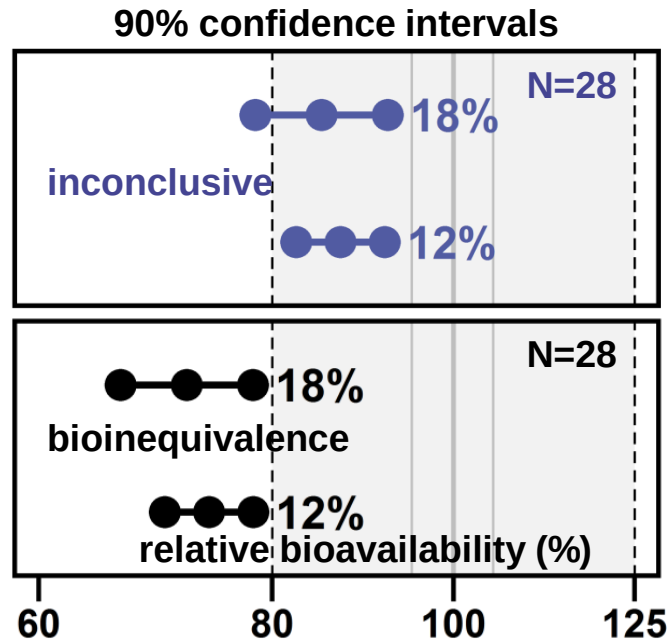


Comment 102: Issues in interpretation (..). If interpretation means that 90%CI are within (..) acceptance criteria, the interpretation will be linked with sample size/ power of the concerned studies. **EMA response:** Text revised.

IN-VIVO: ACCEPTABLE OR NOT?

2.1.3. [Draft version] ***(..) where several batches (..) have been tested during development in vivo (..), dissolution test conditions should (..) allow discrimination between acceptable and non-acceptable batches (..).***

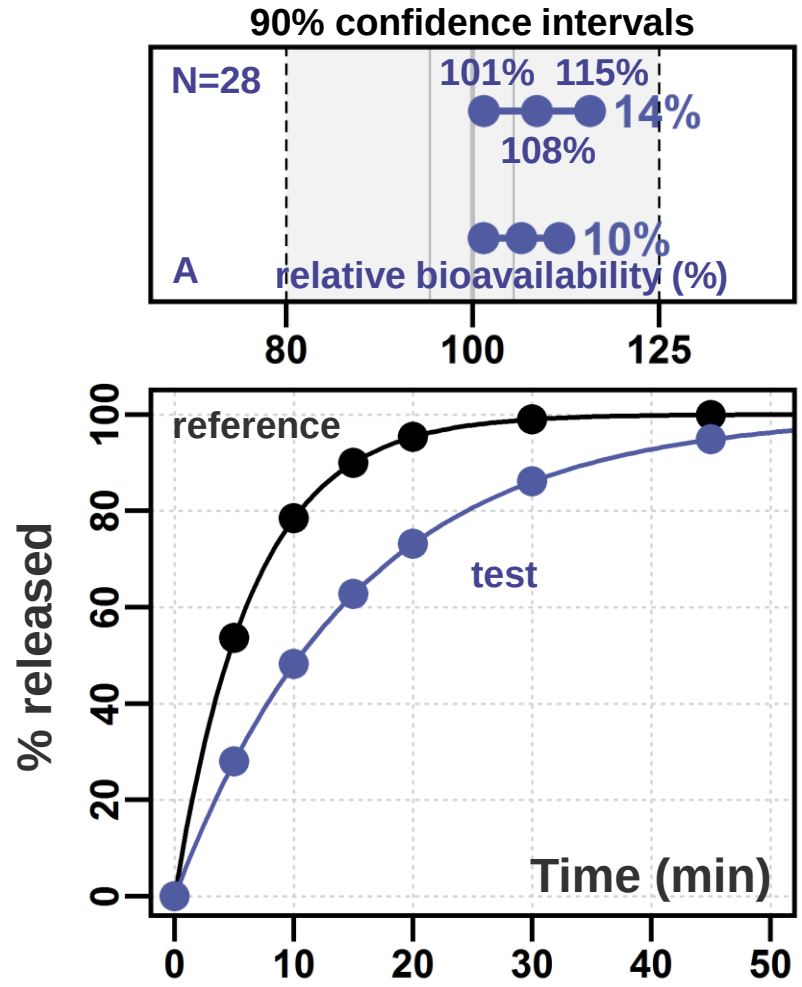
[Final version] ***Priority should be given to in-vivo discrimination over other factors influencing method selection.***



IN-VIVO: RANK ORDER

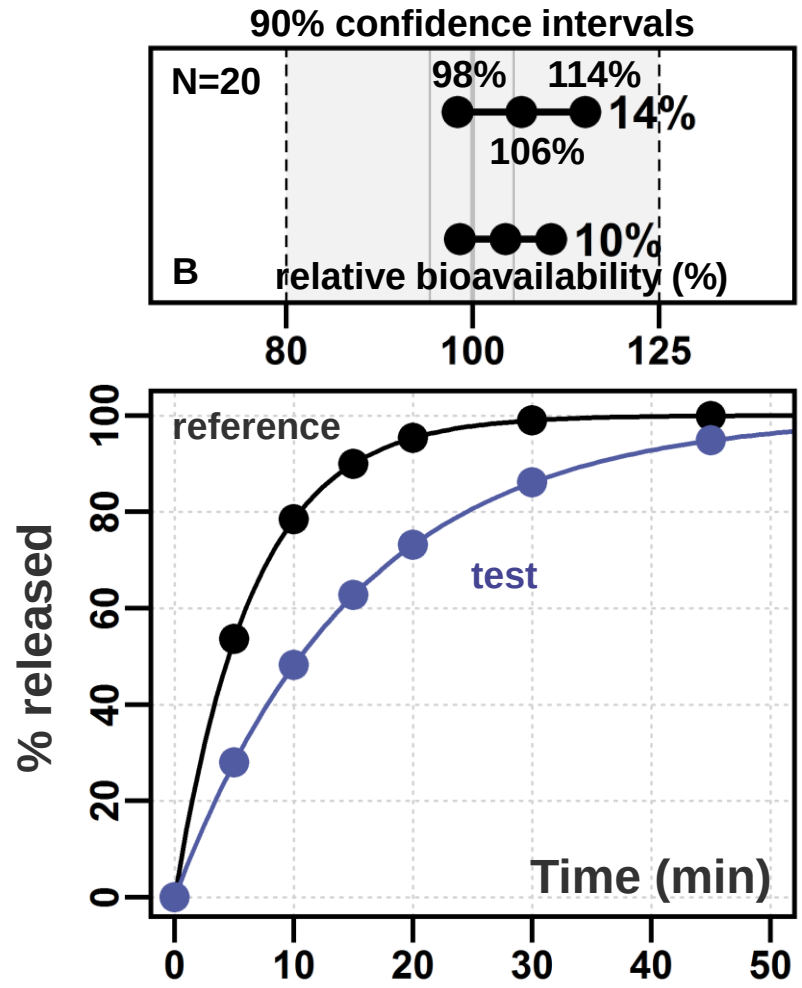
2.1.4. ***(…), rank order (..) should be compared. In case of an opposite order, i.e. a test product with significantly larger Cmax shows slower in vitro dissolution (…) or vice versa, the test conditions should be further optimized in order to reflect in vivo trend,*** [Final version] ***if possible.***

Comment 126

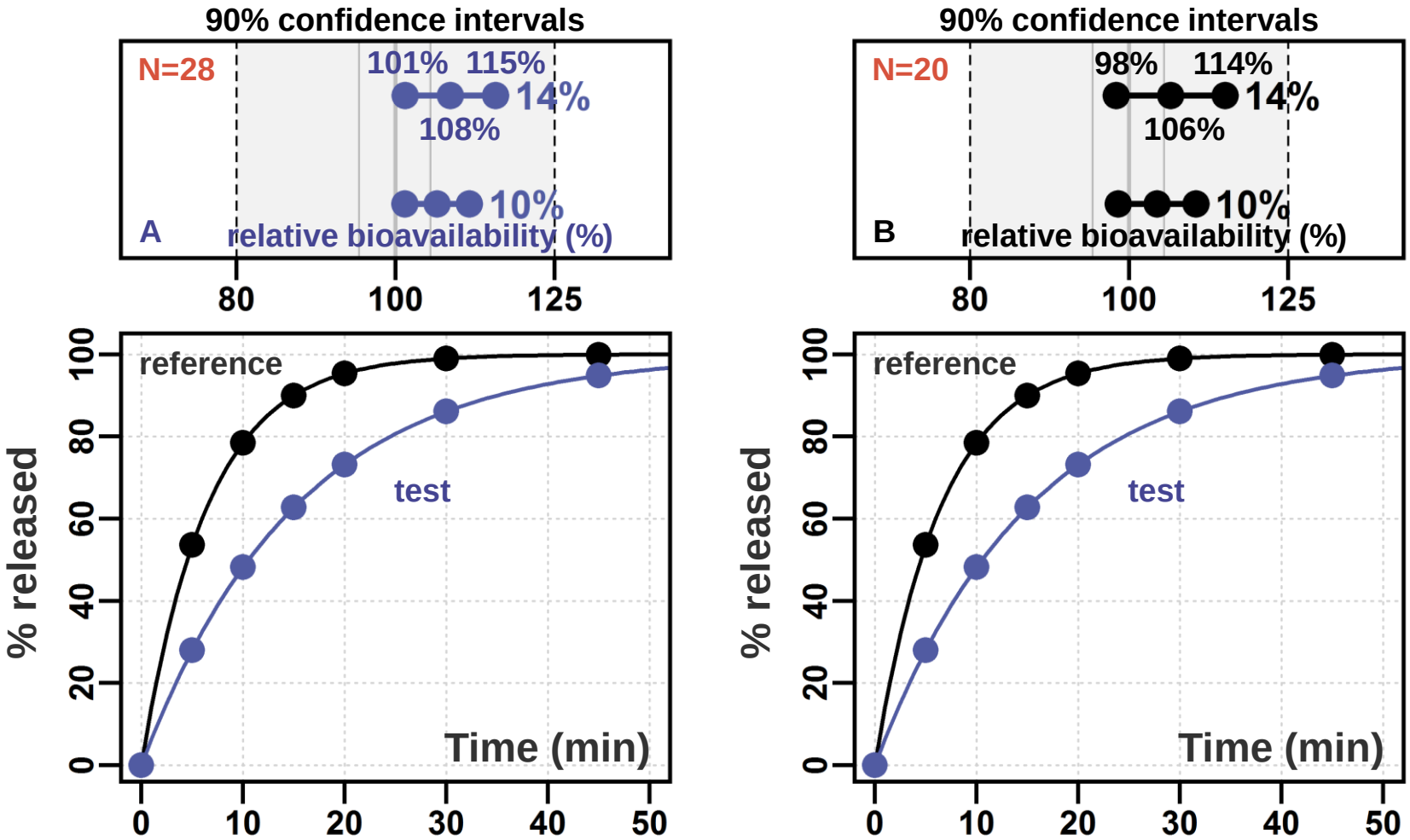


IN-VIVO: OVER-DISCRIMINATIVE

2.1.4. [Final version] ***(…), but sometimes in vitro dissolution tests are not predictive because they are over-discriminative. This is also acceptable because if dissolution (..) not altered, in-vivo equivalence can be assumed.***

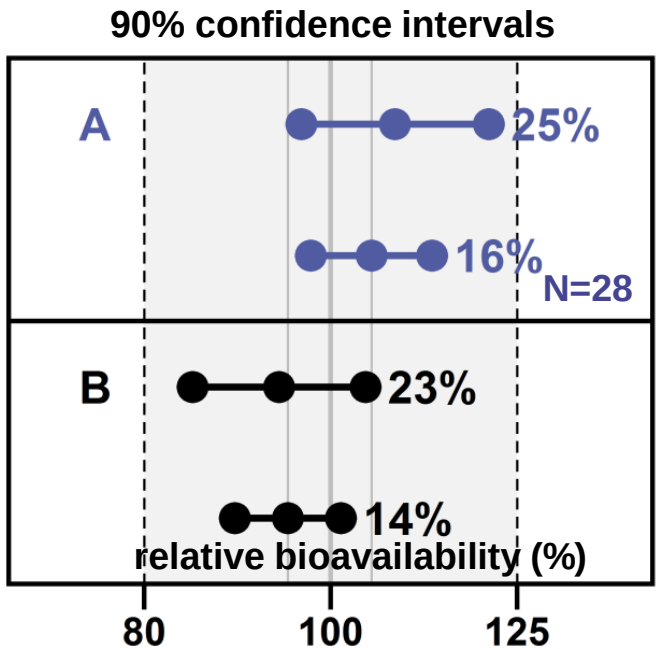


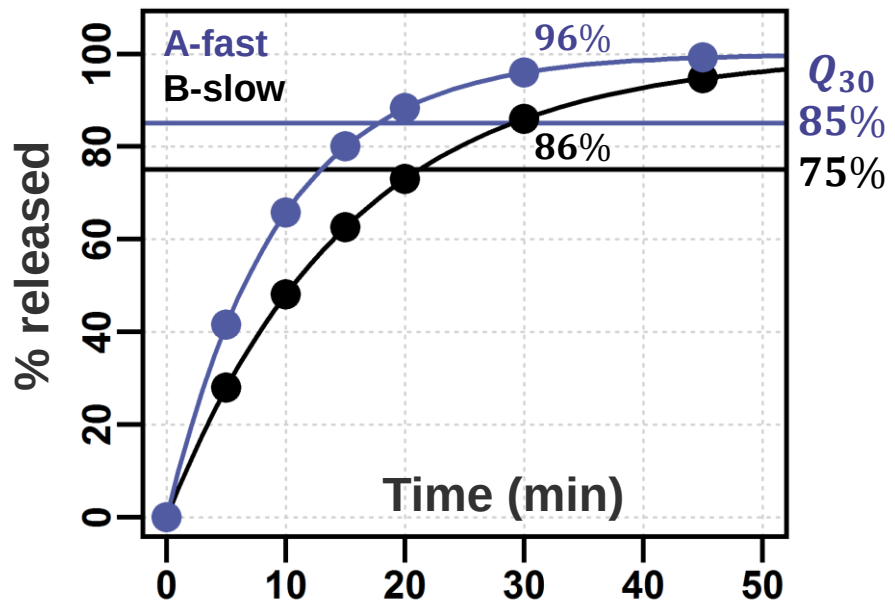
IN-VIVO: DIFFERENCES?



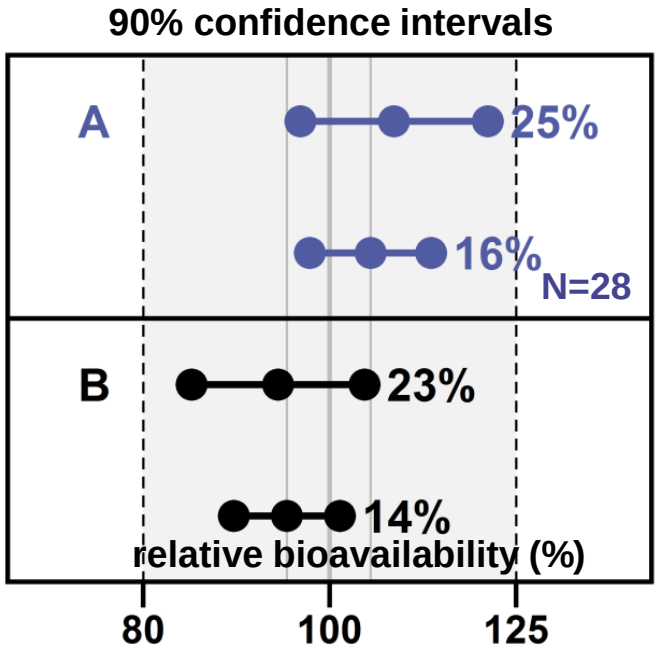
IN-VIVO: SIDE BATCHES

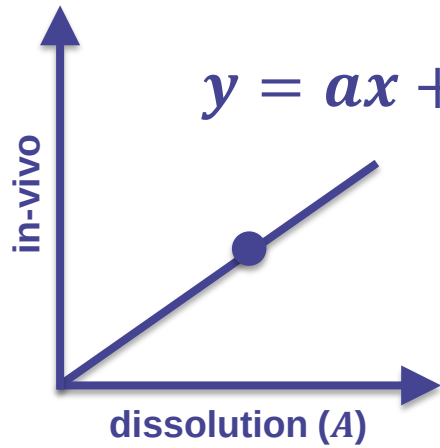
2.1.4 ***If the batches with the extreme range of in-vitro dissolution profiles (i.e. fastest and slowest) are found to be bioequivalent to the reference product (…). (…), suitable specification may be set based on the in vitro dissolution profile of (…) batch with slowest dissolution (…).***

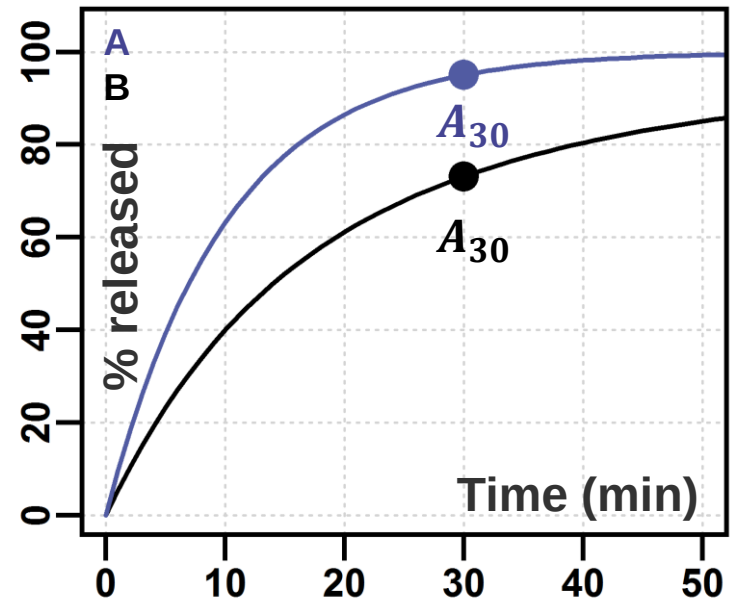




IN-VIVO IN-VITRO: SIMPLE RELATIONSHIP?





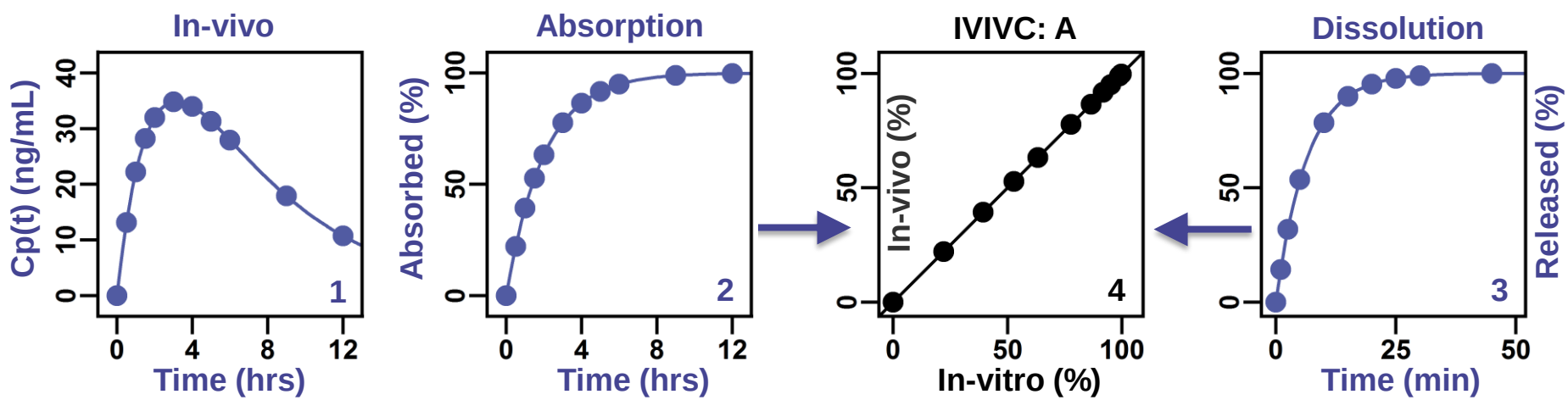


General comment 16 / EMA response: This paper is not about IVIV correlation but about selection of meaningful dissolution test conditions and specifications.

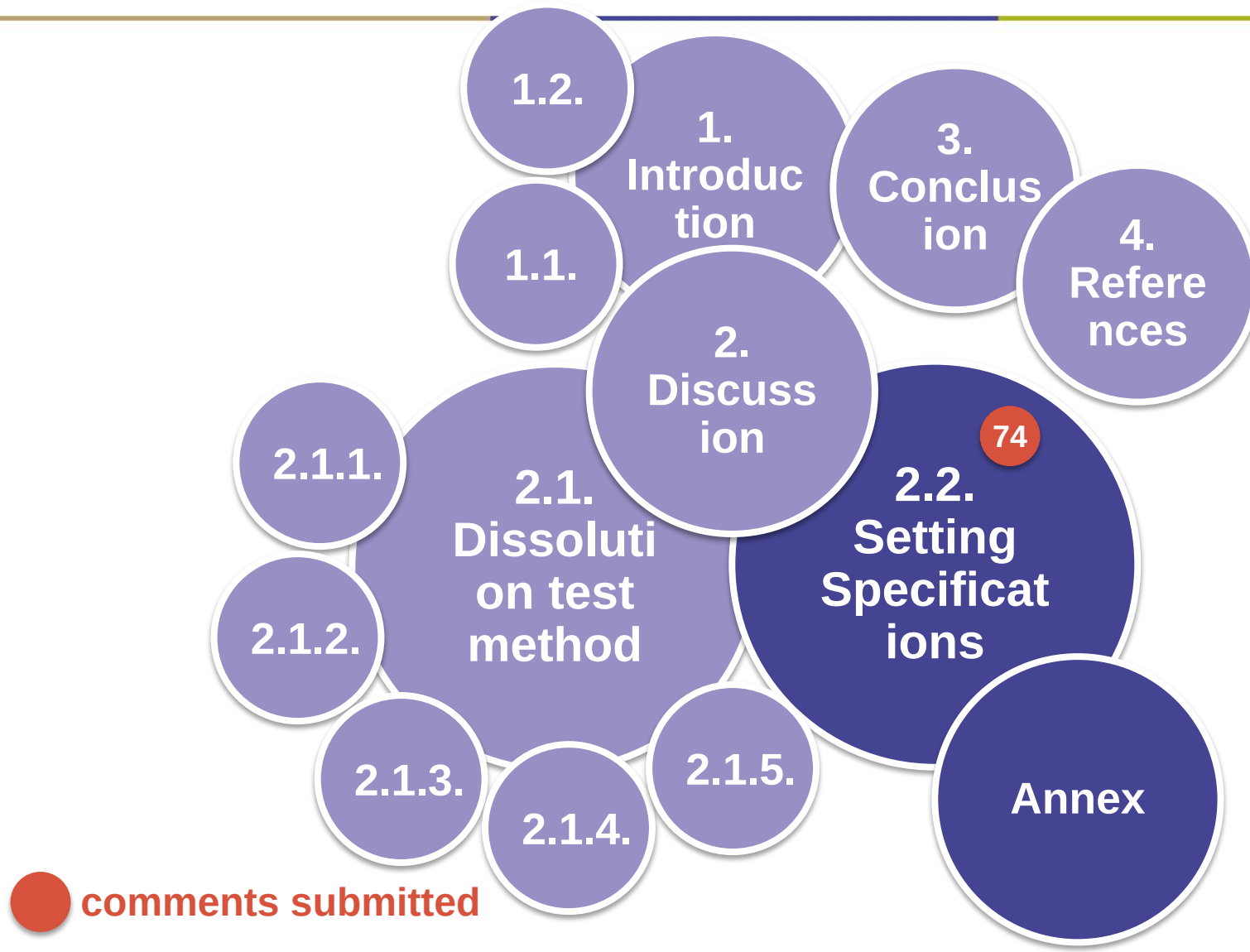
IN-VIVO IN-VITRO: NOT SIMPLE

- **Multiple-points relationship**
- **Adequate IVIV sampling**
- **Need absorption profile(s)**
- **Predictability of model**
- **In-vivo fasting conditions**

[Final version] *2.1.2* ***(..) limited amount of in vivo data in (..) generic applications, mathematical correlations may not be possible; however, all the relevant (..) in vivo data (..) into consideration (..).***

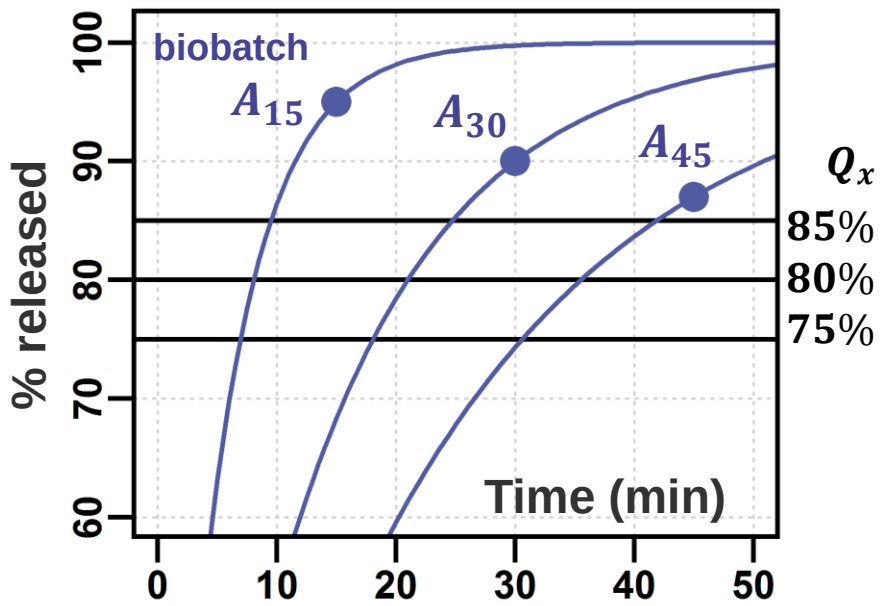


REFLECTION PAPER: STRUCTURE

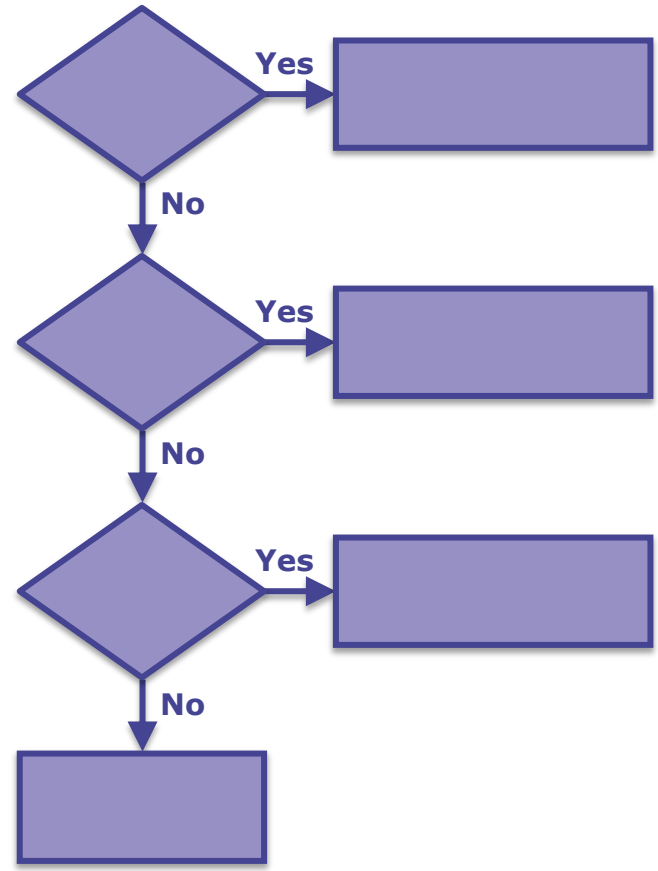


SPECIFICATION: BIOBATCH-10%

2.2. (…), the Q value is recommended to be set on the basis of the ***biobatch dissolution result (mean value of 12 units) minus 10%.***

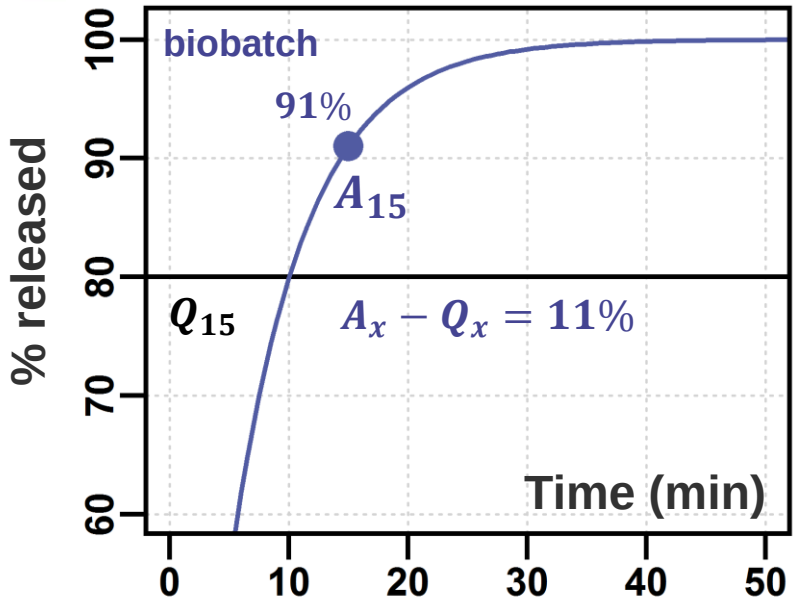


Annex: Decision tree



A_x **amount (mean value of 12 units) dissolved in** x **min**

SPECIFICATION: BIOBATCH-10%



$A_{15} = 91\%$	
Q_{15}	Δ
$75 - 81 =$	-6%
$80 - 81 =$	$+1\%$
$85 - 81 =$	$+4\%$
A_x amount dissolved	

Is dissolution of biobatch A_{15min} ≥85% in 15 minutes?

Yes

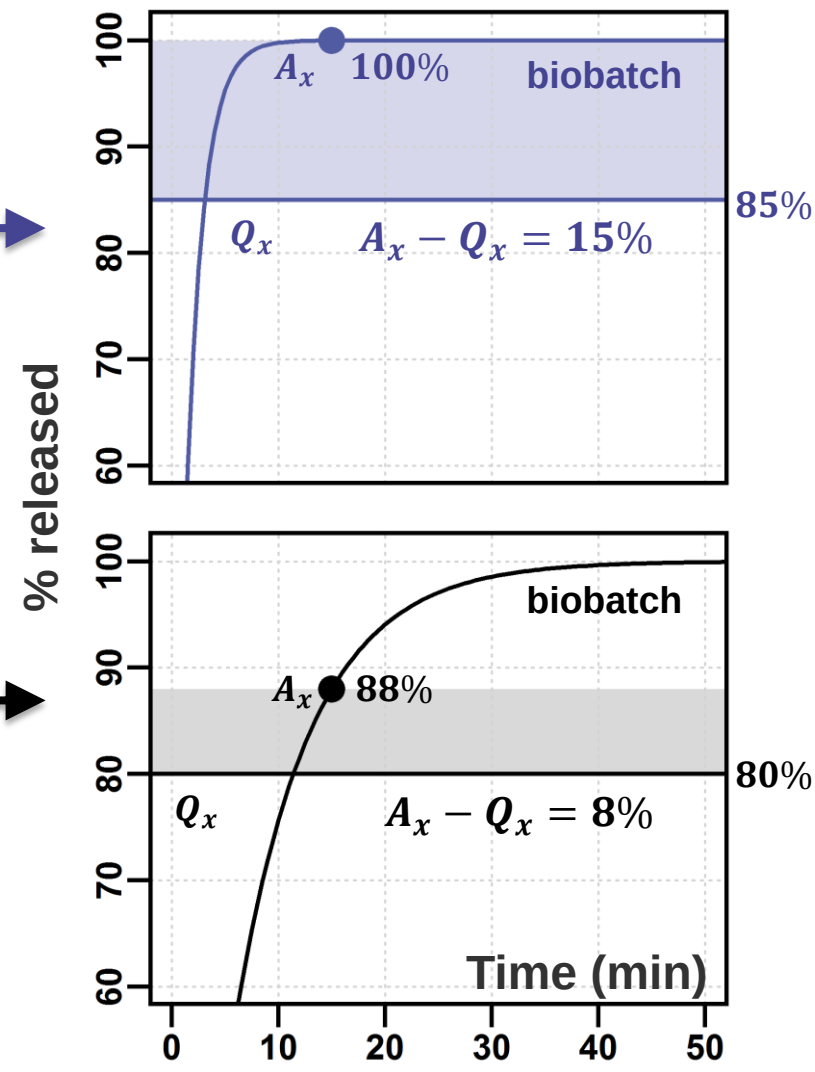
Annex: Decision tree

Specification should read Q = 75%, 80% or 85% in 15 minutes, whichever is closer to (biobatch -10%)

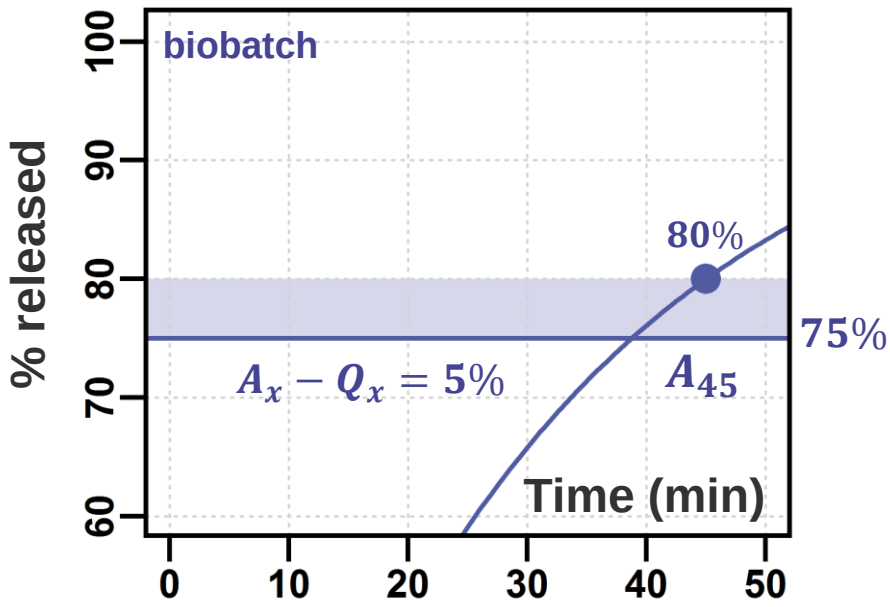
SPECIFICATION: 10% FROM Q?

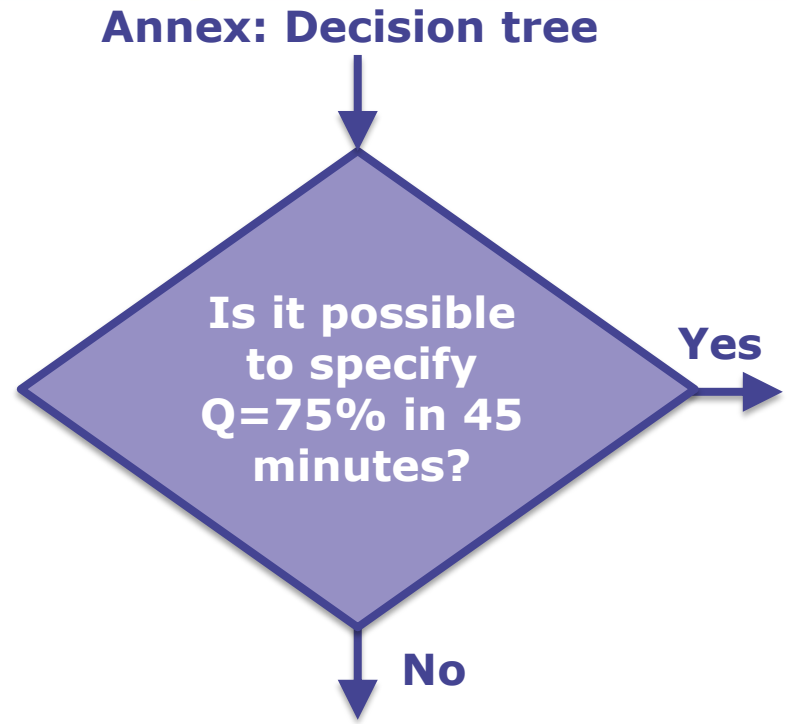
Setting specification Q (%)		
A_x	Q_x	$A_x - Q_x$
100%	85%	15%
95%	85%	10%
94%	85%	9%
93%	85%	8%
90%	80%	10%
89%	80%	9%
88%	80%	8%
85%	75%	10%
..%	75%	..%

Notes: If $Q_{45} < 75\%$, > 1 point has to be specified.



SPECIFICATION: 10% FROM Q?

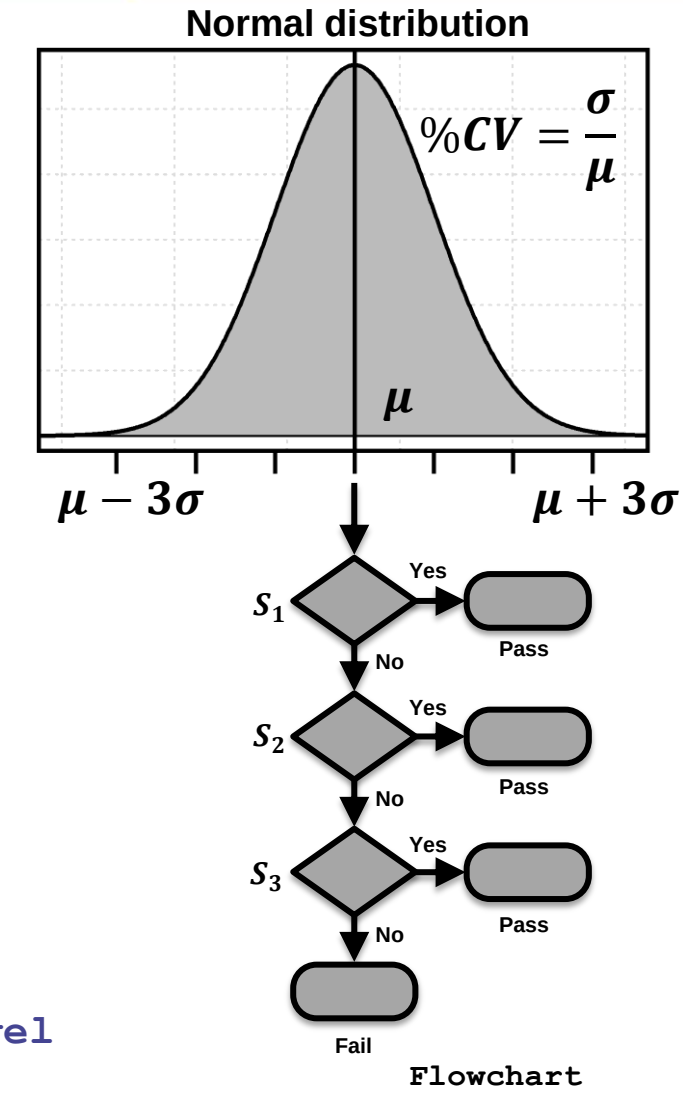




2.2. In case dissolution of biobatch is ***less than*** *or equal to* ***85%*** *after 45 minutes, a* ***minimum of 75%*** *(..) should be specified if possible. Otherwise, (..), the dissolution specification should be based on more than one point.*

RELEASE OF BATCHES: SIMULATION

European Pharmacopoeia Table 2.9.3.-1		
L	**n**	**Acceptance**
S_1	6	Each unit not less than Q+5%
S_2	6	Average of 12 units $(S_1 + S_2)$ is equal to or greater than Q, and no unit is less than Q-15%
S_3	12	Average of 24 units $(S_1 + S_2 + S_3)$ is equal to or greater than Q, not more than 2 units are less than Q-15%, and no is less than Q-25%



Flowchart

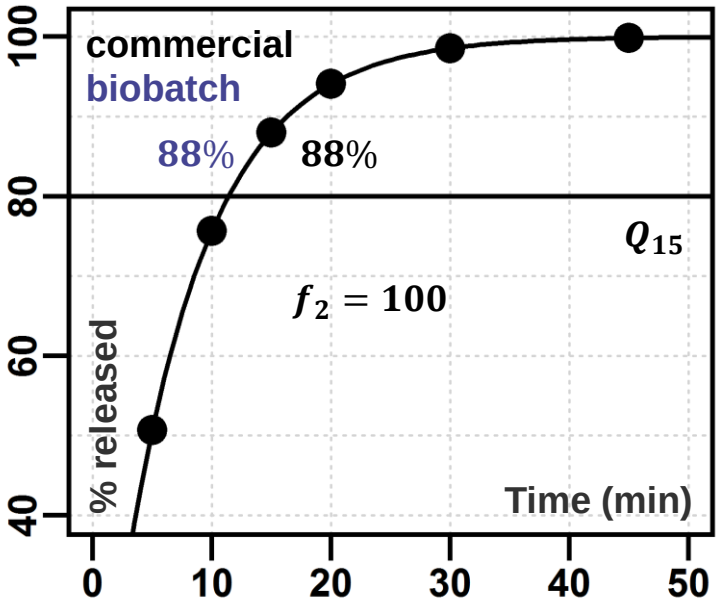
Simulation:

Set dissolution mean μ and $\%CV$ of a batch

Simulate individual unit(s) $n_1..n_6..n_{12}..n_{24}$

Calculate probability of pass at each S-level

BATCH RELEASE: %CV

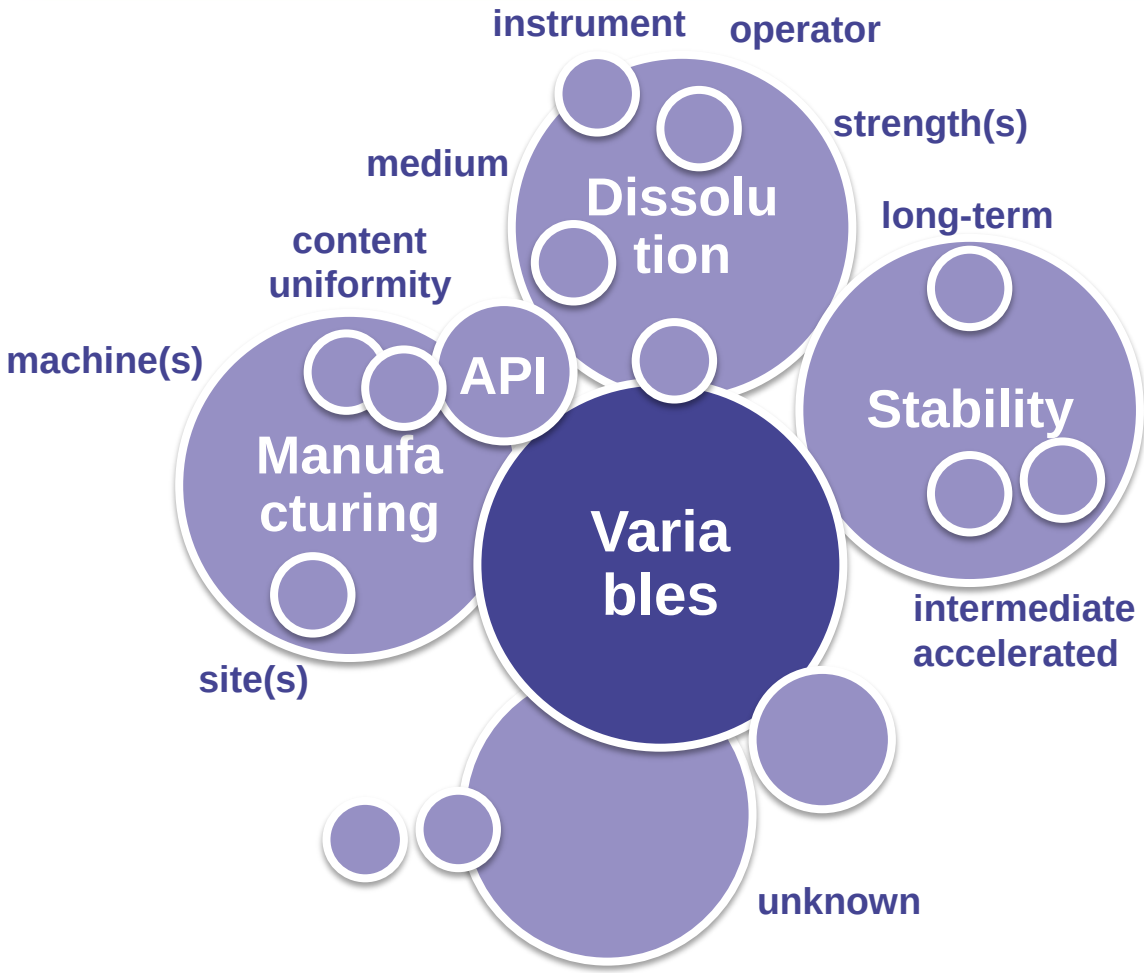


% passes at release stages $Q_{15} = 80\%$				
A_{15min}	88±1%	88±2%	88±5%	88±10%
S_1	99.82	76.36	18.42	6.29
S_2	0.18	23.64	81.58	89.04
S_3	0.00	0.00	0.00	4.56
$fail$	0.00	0.00	0.00	0.11

Notes: based on 10,000 simulations (assuming normal distribution); no rounding in algorithm; identical dissolution of commercial batch(es) and biobatch

Conclusion: commercial batch(es) with identical dissolution to biobatch will likely be released at S_2-level (higher probability with higher variability in dissolution and lower $A_x - Q_x$)

BATCH RELEASE: VARIABLES



Dissolution	$\%CV^{(1)}$
Project 10	$\pm 1.0\%$
Project 37	$\pm 9.6\%$

(1) at A_{15min}; tablet

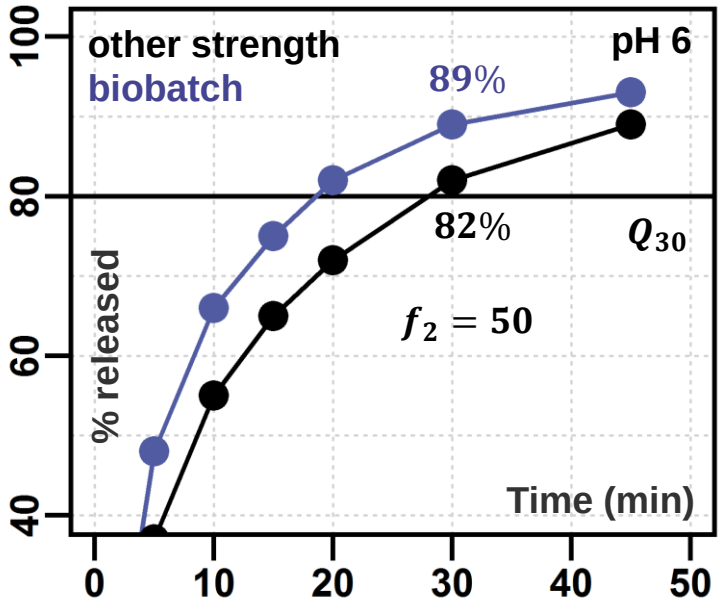
Site(s)	A_{15min}
Site A	93%
Site B	89%

Project 32; tablet

Stability	A_{45min}
Release	100%
Shelf-life	96%

Project 17; shelf-life 36 M

BATCH RELEASE: STABILITY



% passes at release stages $Q_{30} = 80\%$				
A_{15min}	82±2%	81±2%	80±2%	79±2%
S_1	0.00	0.00	0.00	0.00
S_2	100.00	98.46	49.49	1.24
S_3	0.00	1.52	12.38	0.03
$fail$	0.00	0.02	38.13	98.73

Notes: based on 10,000 simulations (assuming normal distribution); no rounding in algorithm

Conclusion: **a decrease of 2-3% in stability will cause commercial batch(es) of the other strength to fail the specification and will have to be withdrawn from the market.** Note: %CV very low (2%).

RELEASE OF BATCHES

*2.2. **The specification should be set in such a way so that during routine manufacture and testing it would be expected that compliance with S_2 is attained.***

Comment 156

EMA response: (..) it is not intended to allow necessarily a pass result at the abbreviated (6 vs 12 units) S1 level.

% Passing S_1 stage $A_x - Q_x = 10\%$	
σ (%)	P (%)
1	100.00
2	96.33
3	74.54
5	35.47
10	10.93
Notes: calculated from normal distribution	

ESSENTIAL NOTES

- **General (16) and specific (206) comment(s) submitted to EMA by 19 stakeholder(s): adequately responded by QWP?** (topic of CMD*(h)* meeting 11-13 September 2017)
- **Discriminatory dissolution method: quality and in-vivo**
- **Simple relationship between in-vitro & in-vivo expected: correlations at single time point (Q)**
- **(Non-)acceptable & non-bioequivalent: interpretation linked to acceptance criteria?** (if yes: power / sample size dependent)
- **Significant effort to comply with new rules: re-assessment of Q-value / QC-method only after finished biostudy(ies)**
- **Majority S_2-release(s); expect S_3-release(s) failure(s)**

BCS-BASED BIOWAIVER

2.1.5 ***(…), there is no batch used in bioavailability / bioequivalence study or in clinical testing (biobatch) (..), the batch that has been shown equivalent with a reference (…) based on satisfactory in vitro*** [Final version] ***~~discriminatory~~ dissolution data in at least three different pH media is considered to be the test batch.***

Comment 130: (..) too restrictive conditions. The BCS based biowaiver is an approach built on standard similar dissolution setting for all formulations. Delete the term discriminatory in line 178.

EMA response: Proposal accepted.