BCS:
Dissolution Testing as a Surrogate for BE Studies

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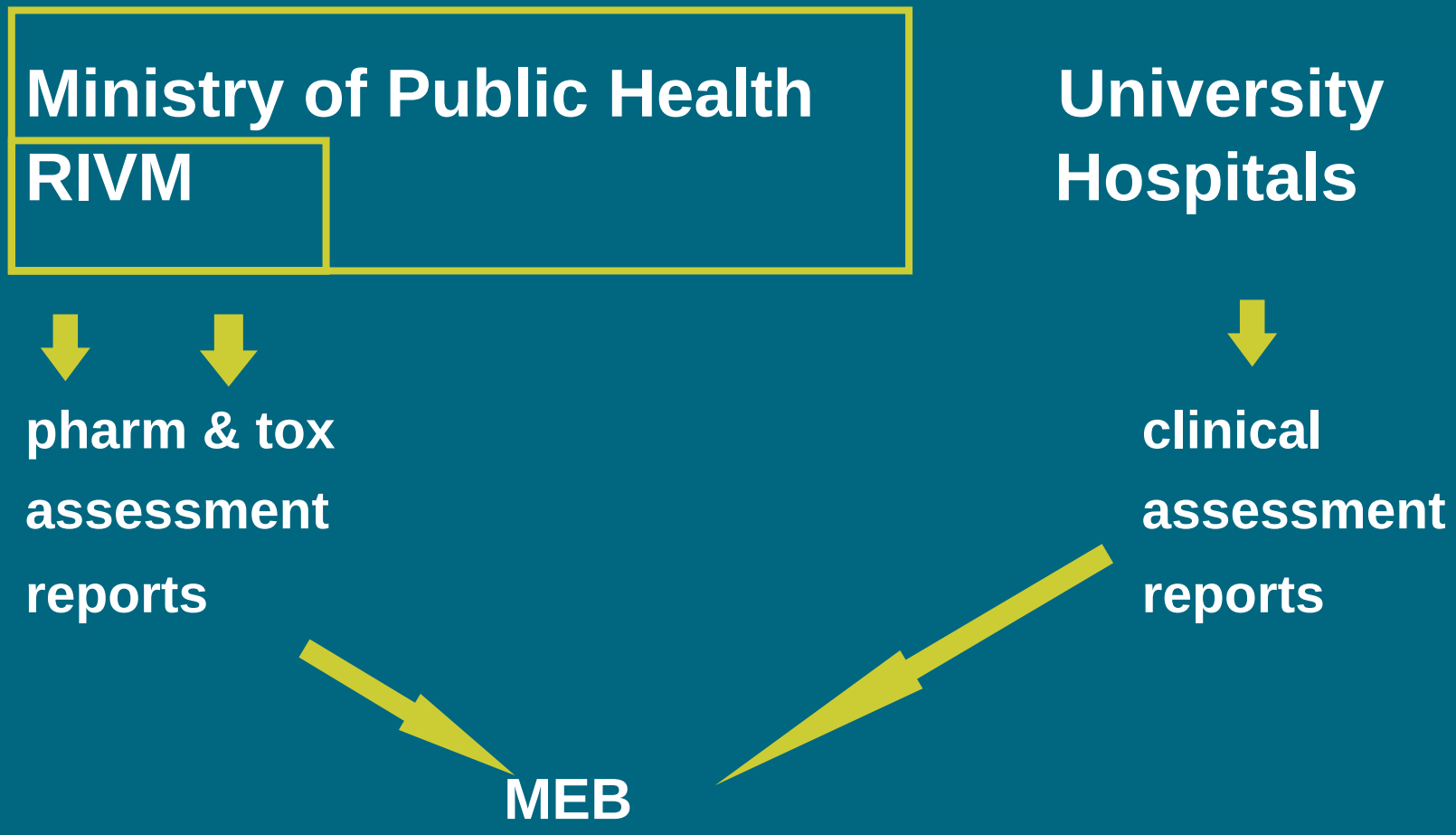
CONTENT OF PRESENTATION

- Relationship between RIVM and the MEB
- [BE as a proxy for efficacy & safety]
- BCS: dissolution testing as a proxy for BE
- FDA regulations on biowaivers
- EU regulations ob biowaivers
- Risk assessment of biowaiving

Relationship between RIVM and the MEB

Relationship between RIVM and the MEB



Relationship between RIVM and the MEB

Ministry of Public Health

RIVM

University Hospitals

Most countries

MEB

NL

MA

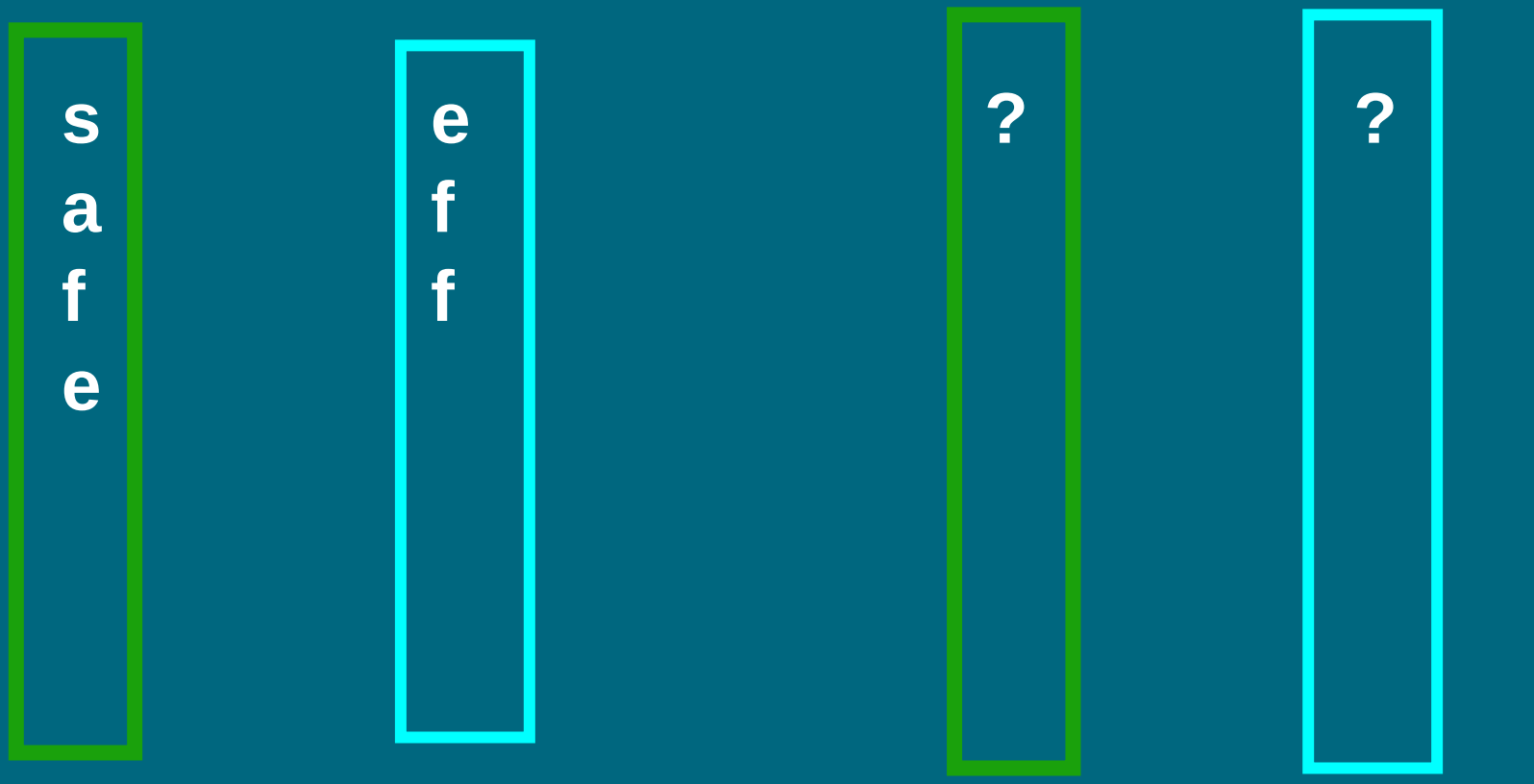
Relationship between RIVM and the MEB

The MEB is :

- **independent from the Minister of Public Health**
  - **the Minister has no influence on decisions of MEB**
- **independent form the assessors and vice-versa**
  - **my views do not necessarily reflect the views of the MEB**

Bioequivalence (BE) as a proxy for efficacy & safety

BE as a proxy for efficacy & safety



BE as a proxy for efficacy & safety

s
a
f
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e
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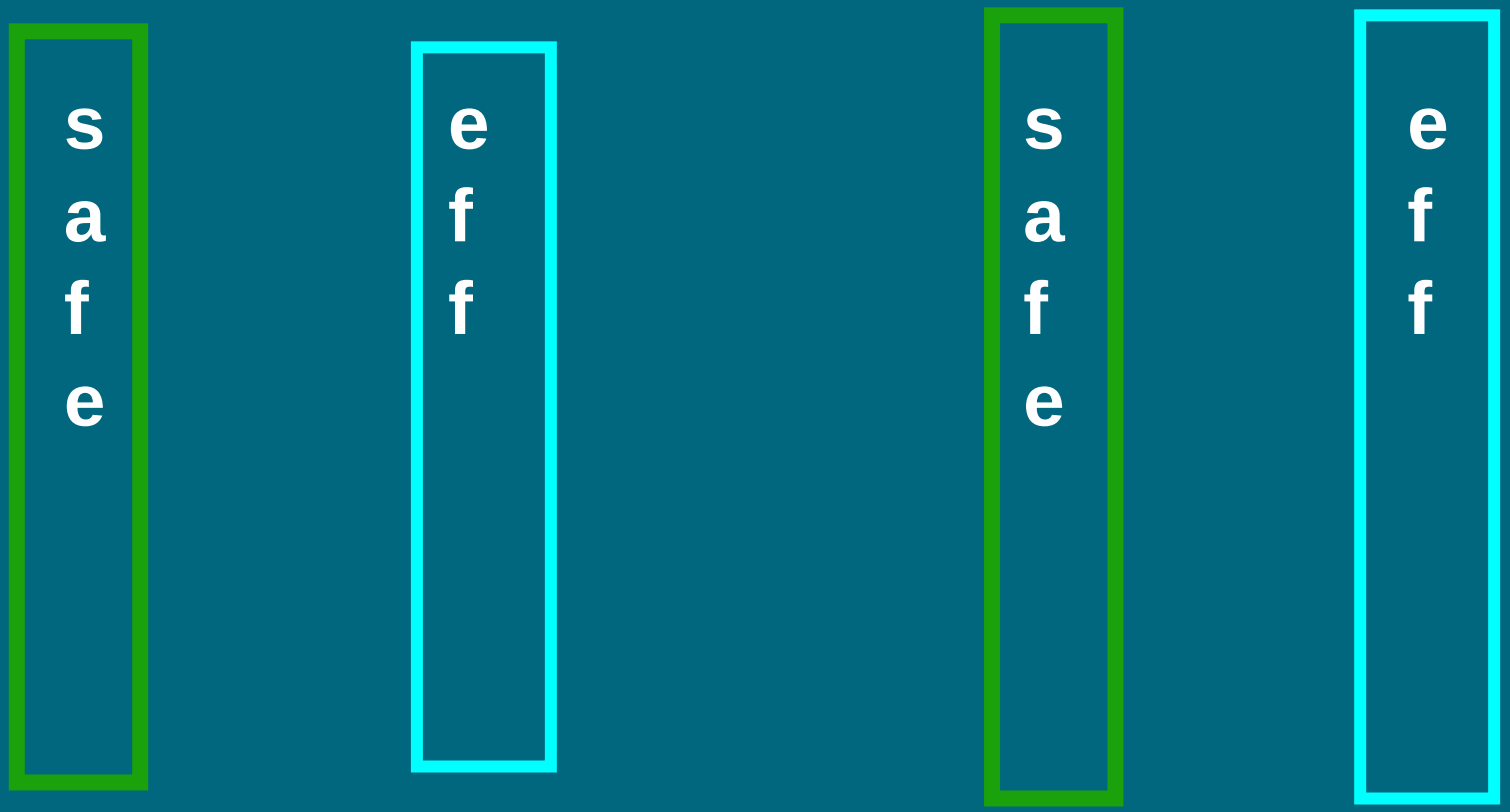
f

MA

investigational drug
drug product

IDENTICAL product on
market

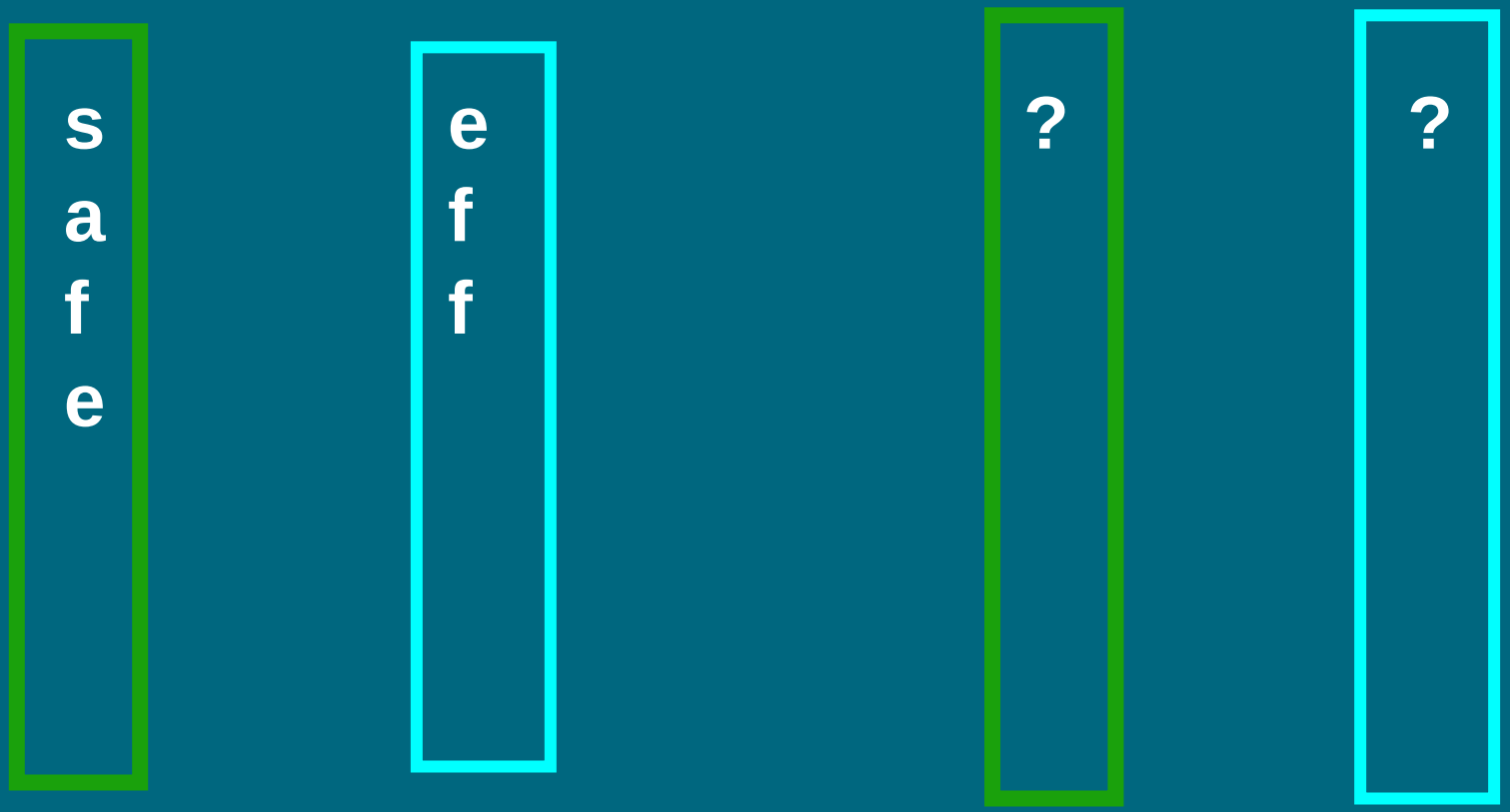
BE as a proxy for efficacy & safety



BE as a proxy for efficay & safety

but in most cases the
clinical batches and tox batches
DIFFERENT to
product for market!
(capsules versus tablet, other excipients etc.)

BE as a proxy for efficacy & safety

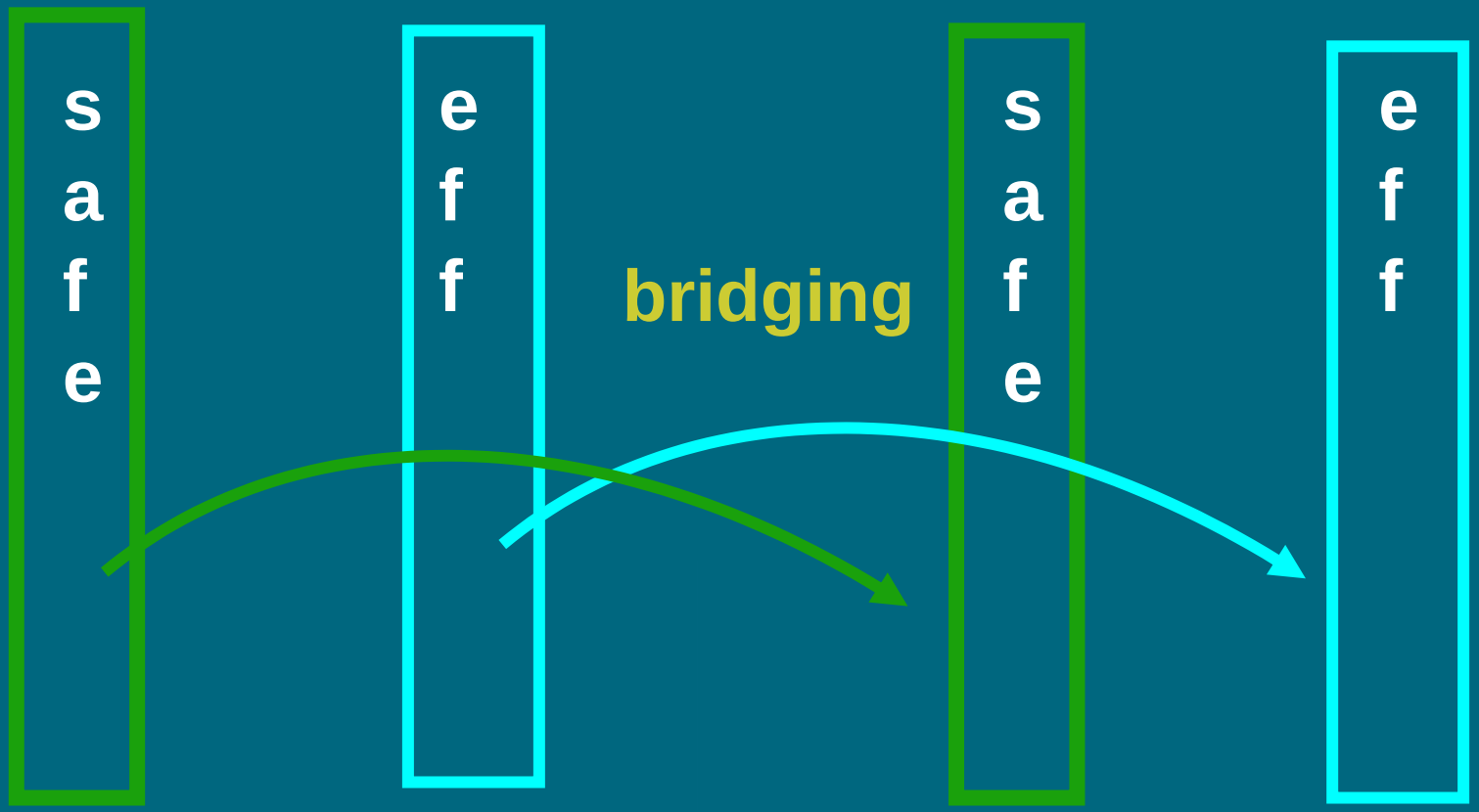


investigational drug

MA

<u>DIFFERENT</u>
drug on market

BE as a proxy for efficacy & safety

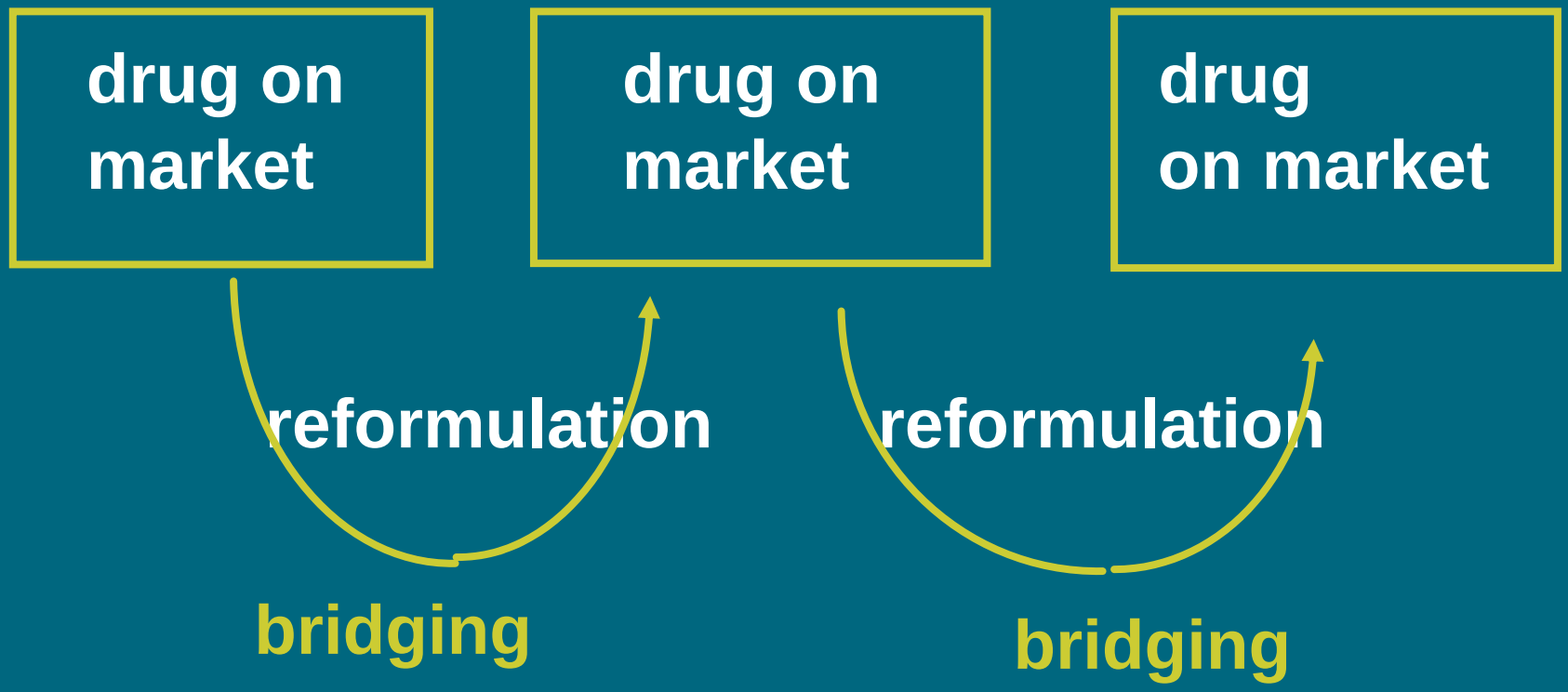


investigational drug
drug product

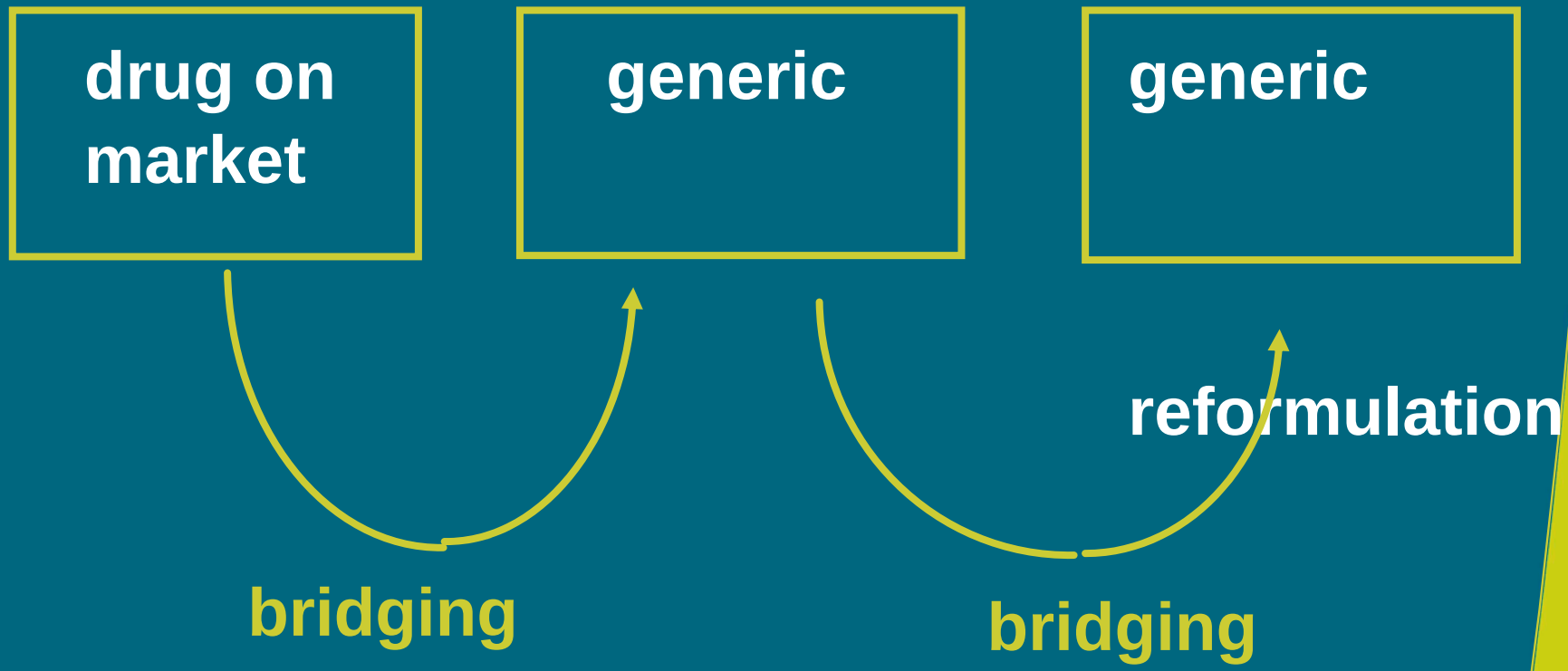
MA

<u>DIFFERENT</u> product on
market

BE as a proxy for efficacy & safety



BE as a proxy for efficacy & safety



BE as a proxy for efficacy & safety

- **Bridging normally by BE**
- **BE is a surrogate technique to demonstrate efficacy & safety**
  - **in other words:**
- **BE is a PROXY for efficacy & safety**

BE as a proxy for efficacy & safety

– **Often mixing up:**

- **BE = intrinsic property of drug**
- **BE study**

– **Compare difference between:**

- **content of active ingredient of a tablet**
- **active ingredient assay in tablet**

BE as a proxy for efficacy & safety

Sometimes:

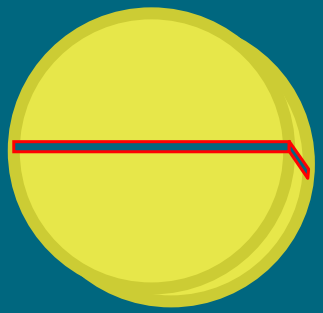
BE (intrinsic property)

can be demonstrated

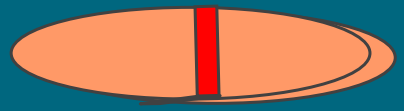
without BE study!

BCS: dissolution testing as a proxy for BE

BCS = Biopharmaceutical Classification System



bioequivalent??

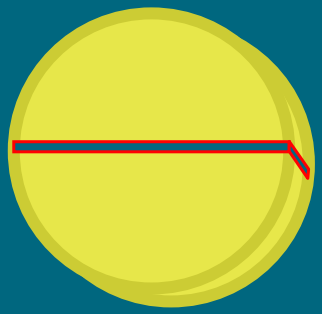


Test

Reference

BE study

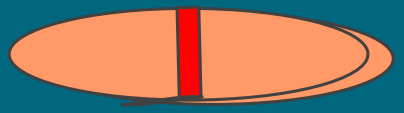
BCS:
mechanistic analysis of causes of bioINequivalence



Test

bioequivalent??

what happens in the body?

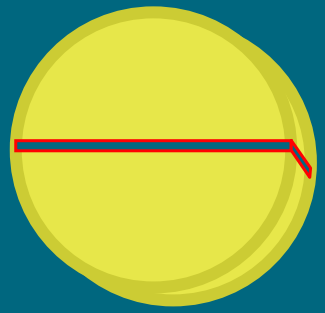


Reference

- **BE = comparison of Bioavailability (BA)**
- **of Active Pharmaceutical Ingredient (API)**
  of Test and Reference

- **BA depends on a cascade of process**

BA:



• dissolution *in-vivo*

API dissolved

•permeability
•metabolism in GI wall

GI WALL

•metabolisme
•excretion

API absorbed

API eliminated

- **BA influenced by:**
  - **dissolution *in-vivo***
  - **permeability**
  - **metabolism in GI wall**
  - **metabolism**
  - **excretion**

but in BE:

Test and Reference contain the same API!!

- **metabolism in GI wall**
- **metabolism**
- **excretion**

can be expected to be the same in Test & Reference !!

in BE:

Test	Reference
• dissolution *in-vivo*	• dissolution in-vivo
• permeability	• permeability
• metabolism in GI- wall	• metabolism in GI-wall
• metabolism	• metabolism
• excretion	• excretion

The same for same API

bioINequivalence can only be caused by:

- **difference in formulation** between Test & Reference

  in:

- **dissolution *in-vivo*** between formulations
- **permeability of API** between formulations

difference in permeability between formulations:

- unlikely for high permeable API
- could only caused by excipient interaction
- can be excluded for well known excipients
- unlikely for IR tablets

When differences in permeability can be excluded:

bioINequivalence can only be caused by a difference in dissolution *in-vivo:*

When differences in permeability can be excluded:

bioINequivalence can only be caused by a difference in dissolution *in-vivo:*

- **predictable by comparative dissolution testing *in-vitro***
- **in physiological media**

BCS:

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

BCS:

- when:
- **solubility of API is high**
  - i.e. not critical
- **permeability of API is high**
  - i.e. not critical
  - (= BCS Class I)
- **comparative dissolution testing**
  - is a reliable proxy for BE

The FDA regulations on biowaivers

FDA

- **FDA Guidance for Industry, Aug 2002: Waiver of In Vivo BA and BE Studies for OR Solid Oral Dosage Forms based on a BCS System**
  - **“biowaiving” = comparative dissolution testing as a acceptable proxy for a BE**

- **valid for generic registration and variation within product**

FDA

- waiver of BE study only for BCS Class I
  - high permeability: absorption > 90%
  - highest dose soluble in < 250 ml pH 1 - 7.5
  - dissolution in-vitro > 85% in 30 min in:
    - 900 ml 0.1 N HCl
    - 900 ml pH 4.5
    - 900 ml pH 6.8
  - f2 dissolution profile similarity Test versus Reference, unless both dissolve > 85% in 15 min

FDA

- dissolution profile similarity: f2 Test
  (unless both dissolve > 85% in 15 min)
- test contains only well established excipients
- API not drug with narrow therapeutic window

FDA

- **Extensions under discussion by FDA**
  - **biowaiver also possible for fast-dissolving Class III**
  - **highest dose soluble in < 500 ml pH 1 - 7.5**
  - **not need for in-vitro dissolution testing in all three media**

Regulations: EU

EU

- **Note for Guidance on Investigation of BA and BE, EMEA 2001**
- **valid for generic registration and variation within product**

EU

- BCS is not mentioned
- but concept is adopted:
  - A BE study …….
  - may be waived ..
  - provided that the API is ……. highly soluble……..
  - expect that it will not cause any BA problems…
- Provisions:

EU

- no know risk of therapeutic failure by BA/BE
- no history of BA-problems or bioINequivalence
- highest dose soluble in 250 ml pH 1.0/ 4.6/ 6.8
- linear and complete absorption indicating high permeability
- contains only well established excipients
- no critical manufacture

EU

- **Variations**: Type I = “small variations”
- The concept of “biowaiving” is accepted in Type I

For instance:

- **Type I, no. 18 Replacement of an excipient with a comparable excipient**
  - **Conditions:**
    - **Same functional characteristics of the excipient.**
    - **The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one**

- **Documentation needed for Type I, no. 18::**
- **Comparative dissolution profile data of at least two pilot scale batches of the finished product in the new and old composition**
- **Justification for not submitting a new bioequivalence study according to the current *NfG on BA/BE*.**

Risk assessment of biowaiving

Risk analysis

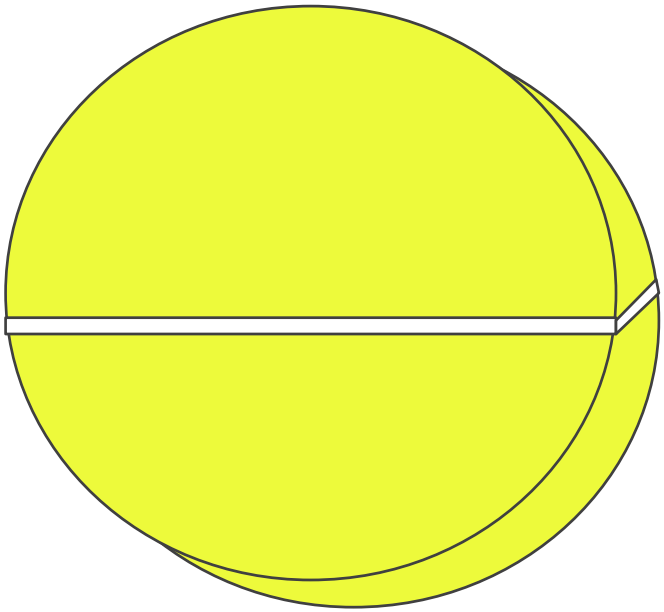
- Biowaiving remains a proxy
- High assurance of BE, but never 100.00%

no biowaiving of digoxine

- A BE study involves administration of the test product to humans
- Biowaiver will release medicines that were never administered to humans!

Example

Propranolol HCl generic IR tablet



- Propranolol HCl is BCS Class I
- Generic tablet meets comparision dissolution criteria versus reference product

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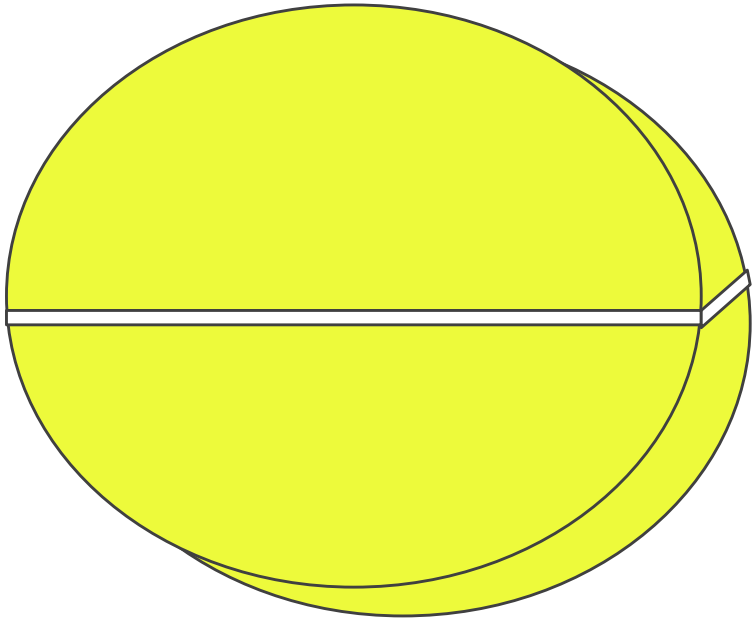
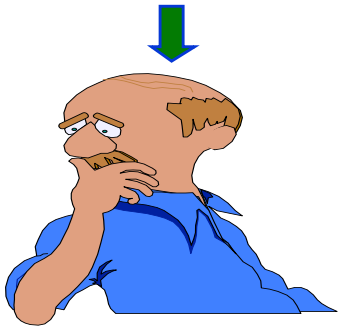
Tablet has 1 meter diameter!

Propranolol HCl generic IR tablet



Patient



But its administration is problematic!

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Conclusion

- Comparative dissolution testing
  - as per BCS
- is a very good proxy for BE
  - for BCS Class I API`s (and III)?

- But remains a proxy!

- Do not think to “regulatory = burocratic!”

Conclusion

- **Answer two question to yourself:**
  - **Would I swallow the biowaived drug myself?**
  - **Would I give it to my children?**

Thank you for your attention!