Major role of excipients in the draft guideline ICH M09

Susana Almeida

salmeida@medicinesforeurope.com

Quality and Clinical Development Director

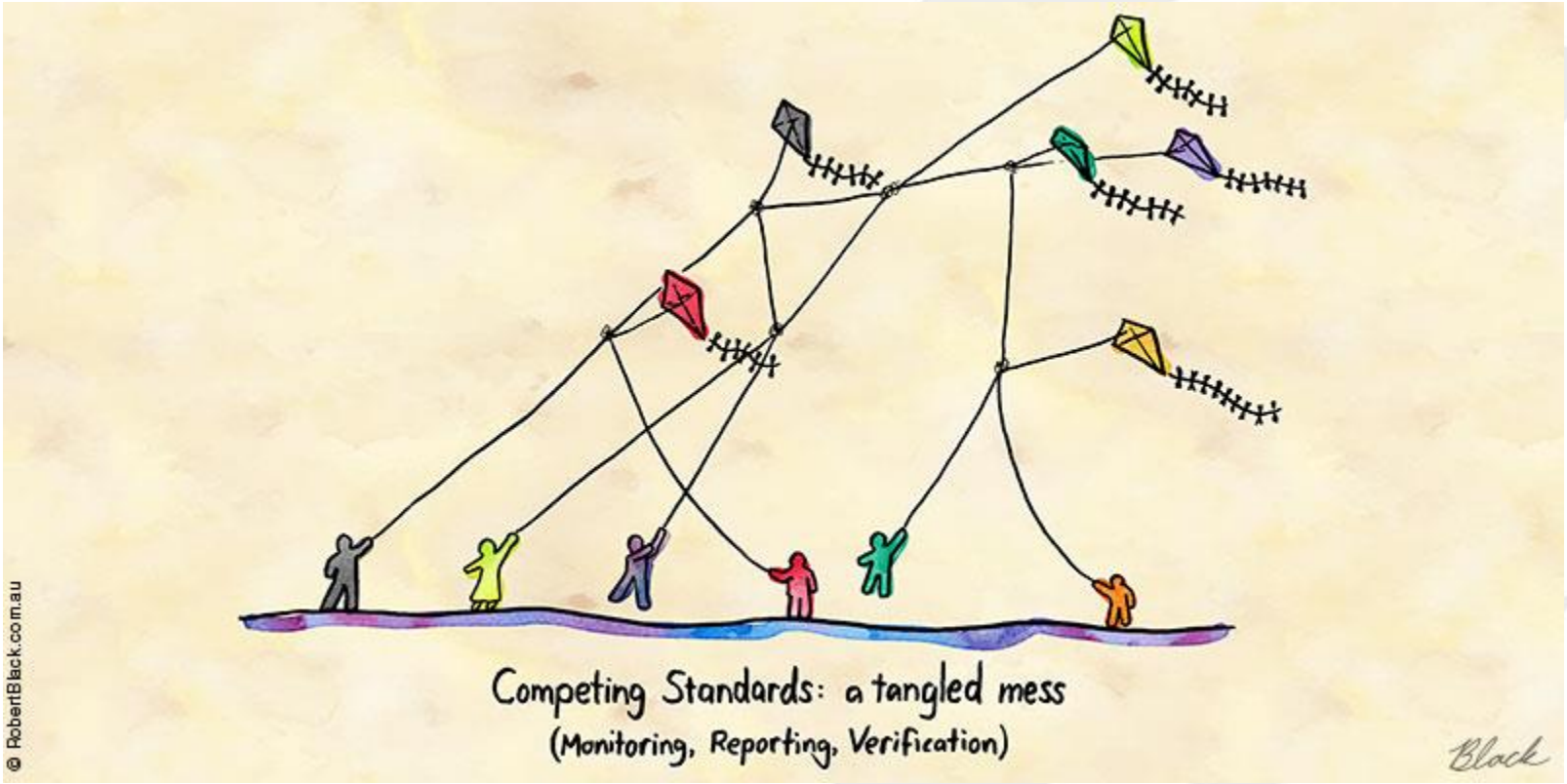
Disclaimer

- This presentation represents the author's personal opinion and does not necessarily represent the policy or recommendations of IGBA or Medicines for Europe

Current scenario

Region	Biowaiver Guideline
EU	Guideline on the investigation of bioequivalence (CPMP/QWP/EWP/1401/98 Rev. 1, 2010)
US	Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System Guidance for Industry (2017)
Japan	BCS based biowaivers currently not foreseen
Canada	Guidance Document: Biopharmaceutics Classification System Based Biowaiver (2014)

Result


Competing Standards: a tangled mess
(Monitoring, Reporting, Verification)
Black
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Excipient

2001/83 (as amended)

3b. Excipient: Any constituent of a medicinal product other than the active substance and the packaging material.

Active or inactive?...

Phenytoin (1968-69)

- Outbreak of anticonvulsant intoxication in epileptic patients
- All affected patients were taking one brand of phenytoin.
- 87% ↑↑ blood phenytoin levels (above the therapeutic range)
- Reduction of phenytoin dose relieved the intoxication in all patients.

- Culprit: when CaSO4 was replaced with lactose, absorption increased

- The dissolution profile of CaSO4 containing capsules showed a reduced dissolution rate

Tyrer JH, Eadie MJ, Sutherland JM, Hooper WD. Outbreak of Anticonvulsant Intoxication in an Australian City. *British Medical Journal*. 1970;4(5730):271-273.
Amaral Silva D, Löbenberg R, Davies NM. Are Excipients Inert? Phenytoin Pharmaceutical Investigations with New Incompatibility Insights. J Pharm Pharm Sci. 2018;21(1s):29745.

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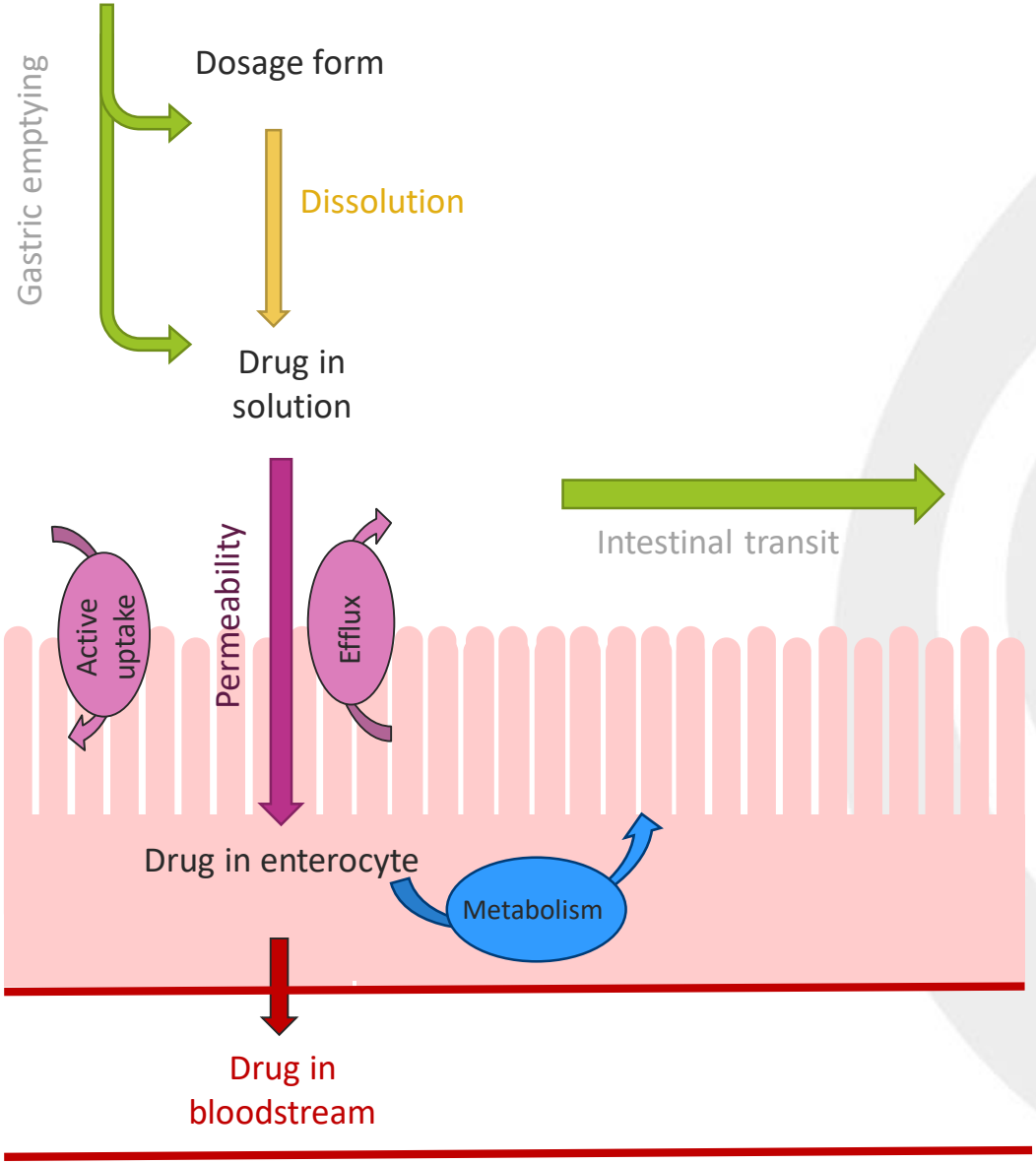
better access. better health.

Scientific Rationale

How can excipients impact absorption?



Release rate/amount of drug in solution
- Altered disintegration time
- Altered dissolution rate
- Altered local pH
- Complexation (excipient-drug complexes)

Transit and luminal volumes
- Faster gastric emptying
- Increased luminal volume (osmotic effect)
- Altered small intestinal transit time

Altered effective permeability
- Damage to intestinal surface/ tight junction modulation
- Inhibition of efflux
- Inhibition or enhancement of active uptake

Altered metabolism
- Inhibition of gut wall metabolism

Source: Talia Flanagan Excipient effects on absorption; Summary of initial assessment. M9 EWG

Some examples

1. Release rate/amount of drug in solution

- Altered disintegration time
- Altered dissolution rate
- Altered local pH
- Complexation (excipient-drug complexes)

HPMC, Magnesium stearate

- Lower absorption of model BCS Class III drugs (cimetidine, acyclovir) in formulations containing HPMC or magnesium stearate

(in vivo data; two drugs only)

Table 2
Prototype Study 2 Test Formulations

Formulation	Formula	Excipient	% Dissolved in 15 min[a]
CimTest-A-10 mg	Cimetidine (100 mg); microcrystalline cellulose (300 mg); sodium lauryl sulfate (25 mg)	HPMC: 10 mg (2.3%)	92.9 ± 3.3
CimTest-A-20 mg[b]		HPMC: 20 mg (4.5%)	89.5 ± 2.8
CimTest-A-45 mg[c]		HPMC: 45 mg (9.5%)	38.6 ± 8.1
CimTest-A-75 mg		HPMC: 75 mg (15%)	23.5 ± 3.6
CimTest-B-20 mg[b]	Cimetidine (100 mg); pregelatinized starch (100 mg); croscarmellose sodium (60 mg)	Mag st: 20 mg (7.1%)	94.5 ± 2.4
CimTest-B-40 mg		Mag st: 40 mg (13.3%)	60.2 ± 3.2
CimTest-B-40 mg-L		Mag st: 40 mg (8%) + Lactose: 200 mg	60.0 ± 5.0
CimTest-B-40 mg-T[d]		Mag st: 40 mg (13.3%): turbular mixer	29.0 ± 5.1

HPMC: hydroxypropyl methylcellulose

Vaithianathan et al. 2016**(and subsequent correspondence)**: Effect of Common Excipients on the Oral Drug Absorption of Biopharmaceutics Classification System Class 3 Drugs Cimetidine and Acyclovir. J Pharm Sci. 105(2):996-1005

Are they candidates for a biowaiver in the first place?

Table 1
Study 1A and 1B Test Formulations: Compositions and *In Vitro* Dissolution

Formulation	Excipient 1	Excipient 2	Excipient 3	% Dissolved in 15 min[a]		
				pH 1.2	pH 4.5	pH 6.8
CimTest-1	Microcrystalline cellulose (300 mg)	Hydroxypropyl methylcellulose (45 mg)	Sodium lauryl sulfate (25 mg)	106 ± 2.0	97.5 ± 1.7	82.6 ± 5.4
CimTest-2	Corn starch (450 mg)	Sodium starch glycolate (100 mg)	Colloidal silicon dioxide (20 mg)	104 ± 1.5	100.1 ± 2.0	100.6 ± 1.4
CimTest-3	Dibasic calcium phosphate (300 mg)	Sodium lauryl sulfate (25 mg)	Crospovidone (50 mg)	95.3 ± 2.8	97.9 ± 1.8	93.9 ± 2.5
AcyTest-1	Microcrystalline cellulose (300 mg)	Hydroxypropyl methylcellulose (45 mg)	Sodium lauryl sulfate (25 mg)	83.9 ± 2.7	70.4 ± 2.8	81.2 ± 3.6
AcyTest-2	Lactose (450 mg)	Povidone (35 mg)	Stearic acid (40 mg)	99.7 ± 0.6	85.1 ± 3.3	67.1 ± 5.1
AcyTest-3	Pregelatinized starch (100 mg)	Croscarmellose sodium (60 mg)	Magnesium stearate (40 mg)	75.6 ± 2.9	73.6 ± 1.7	59.6 ± 3.9

Capsules for study 1A included 100 mg of cimetidine. Capsules for study 1B included 100 mg of acyclovir. All capsules contained three excipients. Study 1A and 1B collectively evaluated 14 excipients across six test capsule formulations. Formulation CimTest-1 and AcyTest-1 employed the same excipients. Sodium lauryl sulfate was included in formulations CimTest-1, CimTest-3, and AcyTest-1. In the *in vivo* study of each formulation, two capsules were administered as a single dose of 200 mg of drug.

[a] Mean ± SEM.

To qualify for a BCS-based biowaiver for BCS Class III drug substances both the test product and reference product should display very rapid (≥85 for the mean percent dissolved in ≤15 minutes) *in vitro* dissolution characteristics under the defined conditions.

pH Regulators/Bicarbonate

- **Sodium bicarbonate**: shortened the disintegration time of capsules containing water-insoluble ingredients (dogs, radiological study)
- Ibuprofen, pH regulators (aluminum hydroxide, calcium carbonate, tartaric acid)
  - Ibuprofen **absorption much faster with sodium bicarbonate** than with aluminum hydroxide capsules
  - Rank order correlation between dissolution parameters and the in vivo bioavailability
  - due to **enhanced** in vivo disintegration of the capsule, enhanced in vivo dissolution of the drug and enhanced gastric emptying rate

Hannula AM, Marvola M, Rajamaeki M, Ojantakanen S. Effects of pH regulators used as additives on the bioavailability of ibuprofen from hard gelatin capsules. Eur J Drug Metab Pharmacokinet. 1991;Spec No 3:221-7

Marvola M, Hannula AM, Ojantakanen S, Westermarck E, Rajamäki M. Effect of sodium bicarbonate and sodium starch glycolate on the in vivo disintegration of hard gelatin capsules--a radiological study in the dog. Acta Pharm Nord. 1989;1(6):355-62

Bicarbonate

- Sodium bicarbonate: shortened the disintegration time of capsules containing water-insoluble ingredients (dogs, radiological study)
- Ibuprofen, pH regulators (aluminum hydroxide, calcium carbonate, tartaric acid)
  - Ibuprofen absorption was much slower with aluminum hydroxide capsules than with sodium bicarbonate capsules of the previous study
  - A rank order correlation between dissolution parameters and the in vivo bioavailability
  - due to enhanced in vivo disintegration of the capsule, enhanced in vivo dissolution of the drug and enhanced gastric emptying rate

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2. Altered effective permeability

- Damage to intestinal surface/ tight junction modulation
- Inhibition of efflux
- Inhibition or enhancement of active uptake

SLS - permeability

- SLS can increase 5- to 6-fold the bioavailability of alendronate (based on urine data)
- SLS is able to break the intestinal membrane to enhance drug absorption
- Data from Caco-2:
  - sodium SLS impacts monolayer integrity.
  - SLS moderately increased the permeability of almost all the drugs
  - disruption of Caco-2 cell monolayer integrity by SLS at 0.1 mg/ml and higher.

García-Arieta A. Interactions between active pharmaceutical ingredients and excipients affecting bioavailability: impact on bioequivalence. Eur J Pharm Sci. 2014 Dec 18;65:89-97.
Narkar, Y., Burnette, R., Bleher, R., Albrecht, R., Kandela, A., Robinson, J.R., 2008. Evaluation of mucosal damage and recovery in the gastrointestinal tract of rats by a penetration enhancer. Pharm. Res. 25, 25–38
Rege et al. 2001: Effect of common excipients on Caco-2 transport of low-permeability drugs. J Pharm Sci. 90(11):1776-86.
Parr et al. 2016:The Effects of Excipients on the Permeability of BCS Class 3 Compounds and Implications for Biowaivers. Pharm Res. 33:167-176.

3. Transit and luminal volumes

- Faster gastric emptying
- Increased luminal volume (osmotic effect)
- Altered small intestinal transit time

Sorbitol – transit and luminal volume

- Human data
- Ranitidine and metoprolol
- 5, 2.5, or 1.25 g of sorbitol
- Ranitidine: ↓ **PK parameters** (Cmax and AUC0-infinity) by approximately 50% and 45%, respectively, in the presence of sorbitol versus sucrose
- Sorbitol decreased the systemic exposure of ranitidine in a **dose-dependent** manner and affected bioequivalence at a level of ≥ 1.25 g
- Metoprolol: ↓ Cmax by 23% but had no significant effect on AUC0-infinity.

- Possible mechanisms: increased GI fluid volume from the osmotic pressure of sorbitol, GI motility enhancement

Chen *et al*. 2007: A modern view of excipient effects on bioequivalence: case study of sorbitol. Pharm Res. 24(1):73-80.

Mannitol - transit

In vivo, Dual isotope gamma scintigraphy (radiolabeled tablets)

- ↓ Small intestinal transit (SIT) times for mannitol (2.264 g/200 ml) by 34% vs. control solution (purified water = 240 min vs. mannitol = 158 min)

In vivo study with cimetidine

- Statistically significant ↓ in the AUC0-24 and Cmax values vs. sucrose controls.
- Mean SIT times were shortened after administration of the mannitol solution and tablet;

Adkin DA, Davis SS, Sparrow RA, Huckle PD, Phillips AJ, Wilding IR. The effects of pharmaceutical excipients on small intestinal transit. Br J Clin Pharmacol. 1995;39(4):381–7.
Adkin DA, Davis SS, Sparrow RA, Huckle PD, Wilding IR. The effect of mannitol on the oral bioavailability of cimetidine. J Pharm Sci. 1995;84(12):1405–9.

4. Altered metabolism

- Inhibition of gut wall metabolism

Excipients able to interact with metabolic mechanisms

3 different mechanisms:

- direct inhibition (chemical)
- regulation of mRNA expression (reduced or increased)
- regulation of protein expression (reduced or increased)

(mostly surfactants)

Vasconcelos T, Marques S, Sarmento B. The biopharmaceutical classification system of excipients. Ther Deliv. 2017 Feb;8(2):65-78. doi: 10.4155/tde-2016-0067.

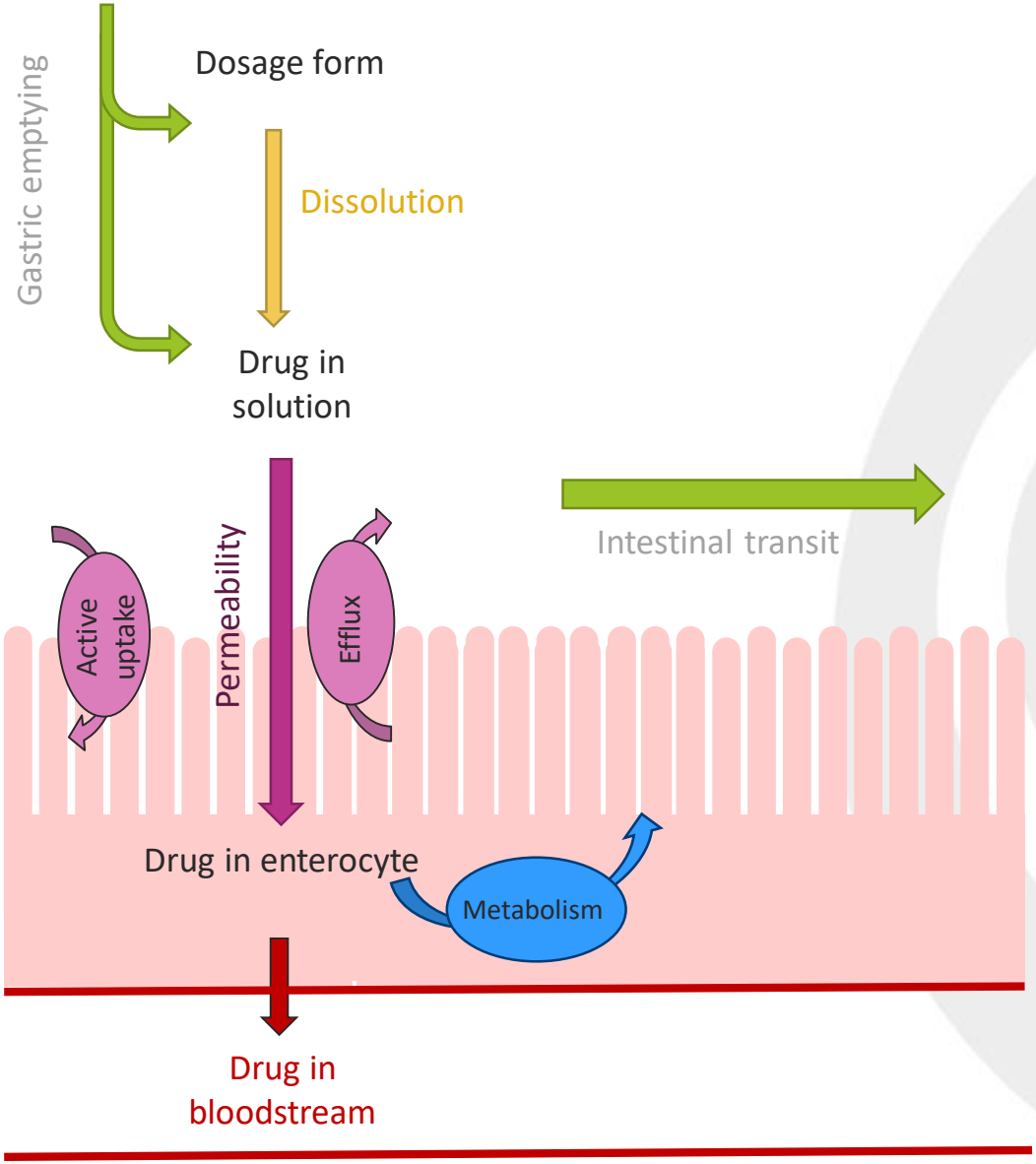
Excipients able to interact with metabolic mechanisms

- Examples

Target	Example
CYP 3A inhibition	Kolliphor® HS15, Kolliphor® EL Tween-20®, Tween-80®, PEG400, Myrj® 52 Poloxamer 188 and Poloxamer 235
CYP3A4 inhibition	Kolliphor EL, Kolliphor RH40, vitamin E TPGS, Tween-80, Poloxamer 188, Myrj 52, Brij® 35, thiomers, modified cyclodextrins and sucrose laurate
CYP3A5 inhibition	EG1000, Tween-20, cetyltrimethylammonium bromide, Tween-80 and Poloxamer 188
CYP2C9 inhibition	Kolliphor EL, Kolliphor RH40, Myrj 52, Tween-80, sucrose laurate. Vitamin E TPGS, PEG1000 and Poloxamer 188
Glucuronidation	Parabens (methyl and propyl) Surfactants (Tween-20 > Kolliphor EL > Kolliphor RH >PEG400 > Tween-80 > Kolliphor H15)

Vasconcelos T, Marques S, Sarmento B. The biopharmaceutical classification system of excipients. Ther Deliv. 2017 Feb;8(2):65-78. doi: 10.4155/tde-2016-0067.

How can excipients impact absorption?



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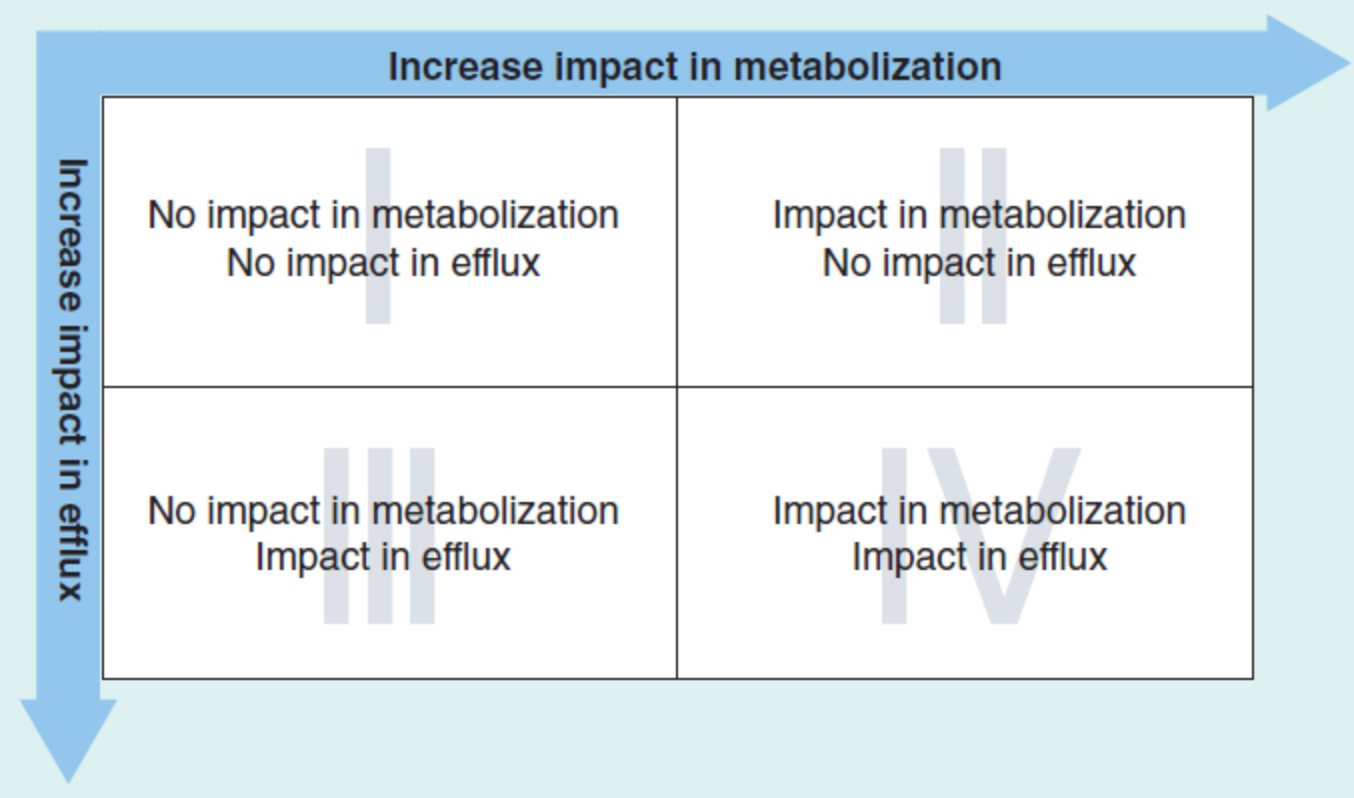
BCS for excipients?



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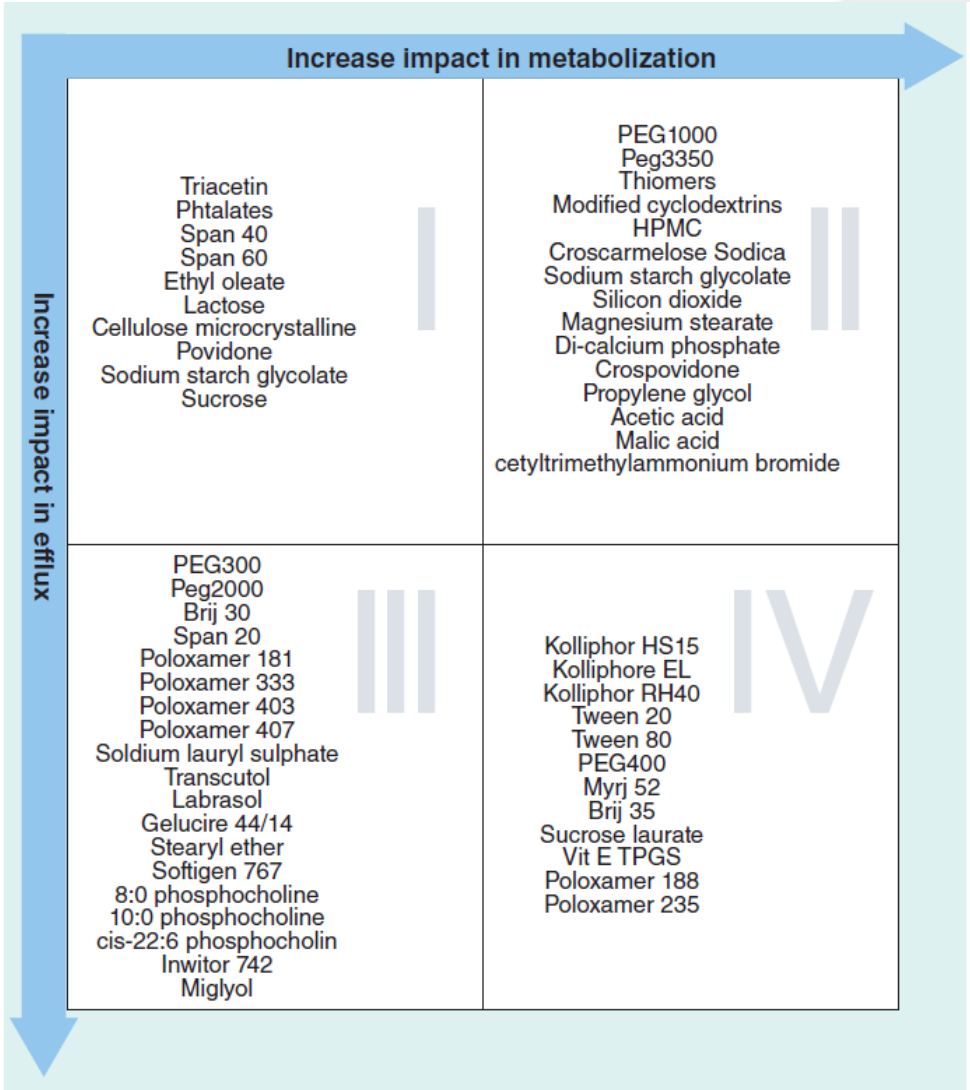

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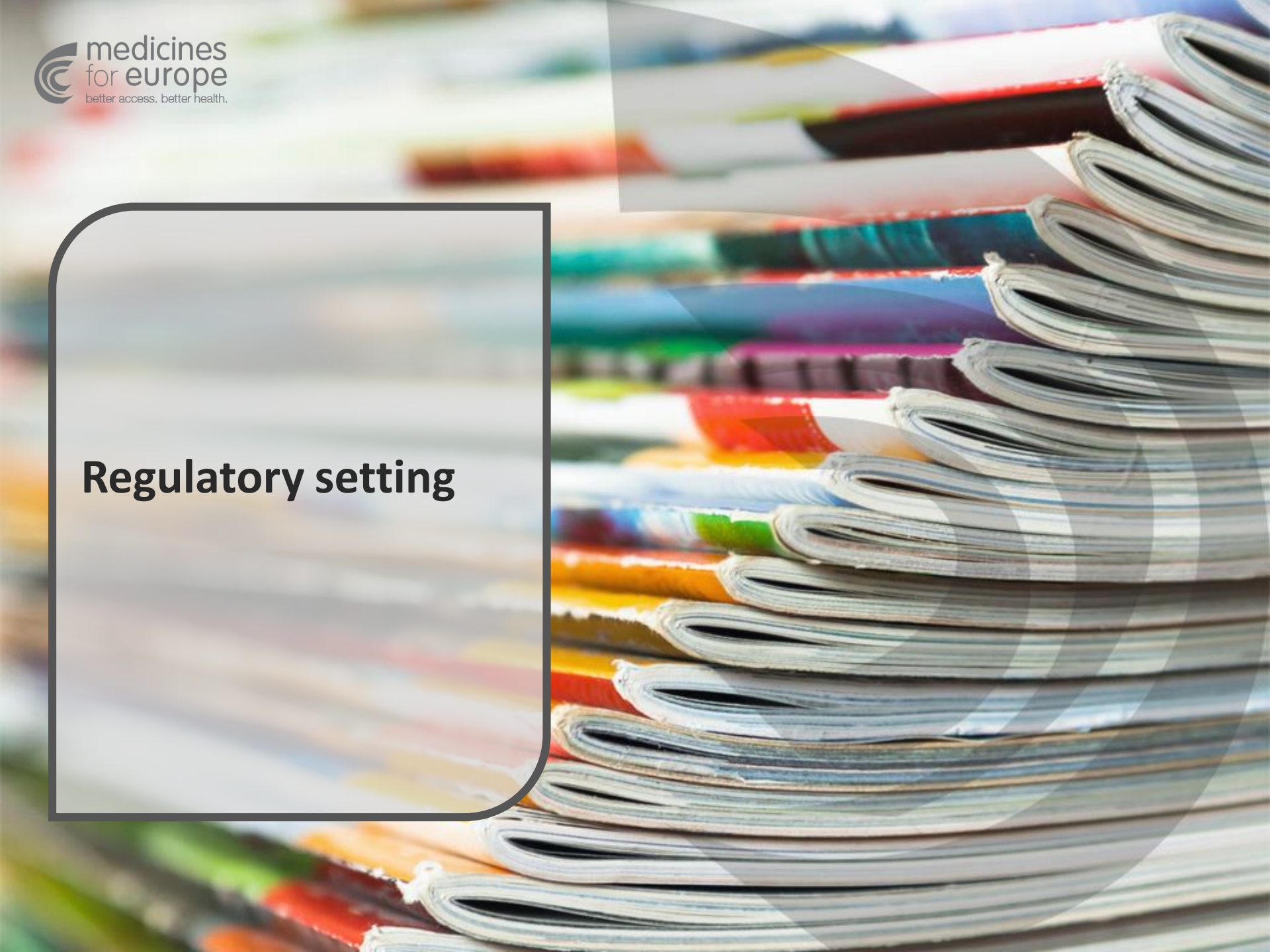
Key scientific messages

- **Some** excipients may have an impact in absorption
- There are **multiple mechanisms** involved
- Only a **limited number** of these **would be relevant** for highly soluble drugs (BCS class I and III) – and as such potentially relevant for BCS based biowaivers
- **Most** excipients used in solid oral immediate release dosage forms **do not influence absorption**
- For BCS class I drugs, absorption is unlikely to be affected by excipients
- For BCS Class III a limited number of mechanisms could be relevant
  - Example: impact on transit time, impact on permeability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Regulatory setting

Excipients: FDA

BCS 1:

- the product does not contain any excipients that will affect the rate or extent of absorption of the drug
- the quantity of excipients in the IR drug product should be consistent with the intended function

BCS 3:

- Test drug product must contain the same excipients as the reference product. Composition: must be qualitatively the same (except for a different color, flavor, or preservative that could not affect the BA) and should be quantitatively very similar to the reference product.

  Filler (± 10%)
  Disintegrant, Starch (± 6%)
  Disintegrant, Other (± 2%)
  Binder (± 1%)
  Lubricant, Calcium or Magnesium Stearate (± 0.5%)
  Lubricant, Other (± 2%)
  Glidant, Talc (± 2%)
  Glidant, Other (± 0.2%)
  Film Coat (± 2%)
  The total additive effect of all excipient changes should not be more than 10 percent.

Excipients: EMA (1)

well-established excipients in usual amounts

possible interactions affecting drug bioavailability and/or solubility characteristics should be considered and discussed

BCS Class I

- Impact rather unlikely but cannot be completely excluded
- Advisable to use similar amounts of the same excipients

BCS Class III

- excipients have to be qualitatively the same and quantitatively very similar

What difference is needed so that similarity can no longer be accepted?

Excipients: EMA (2)

Excipients that might affect bioavailability (e.g. sorbitol, mannitol, sodium lauryl sulfate or other surfactants) should be identified as well as their possible impact on

- gastrointestinal motility
- susceptibility of interactions with the drug substance (e.g. complexation)
- drug permeability
- interaction with membrane transporters

Excipients that might affect bioavailability should be qualitatively and quantitatively the same in the test product and the reference product.

ICH M9

- Excipient differences: assessed for **potential to affect *in vivo*** absorption
- **Justify** that proposed differences will not affect absorption
- **Consider possible effects** of excipients on aspects of *in vivo* absorption such as solubility, gastrointestinal motility, transit time and intestinal permeability including transporter mechanisms
- Excipients that may affect absorption include sugar-alcohols, e.g., mannitol, sorbitol, and surfactants, e.g., sodium lauryl sulfate

ICH M9: Risk assessment

Mechanistical considerations for impact:

- the amount of excipient used,
- the mechanism by which the excipient may affect absorption,
- absorption properties (rate, extent and mechanism of absorption) of the drug substance.

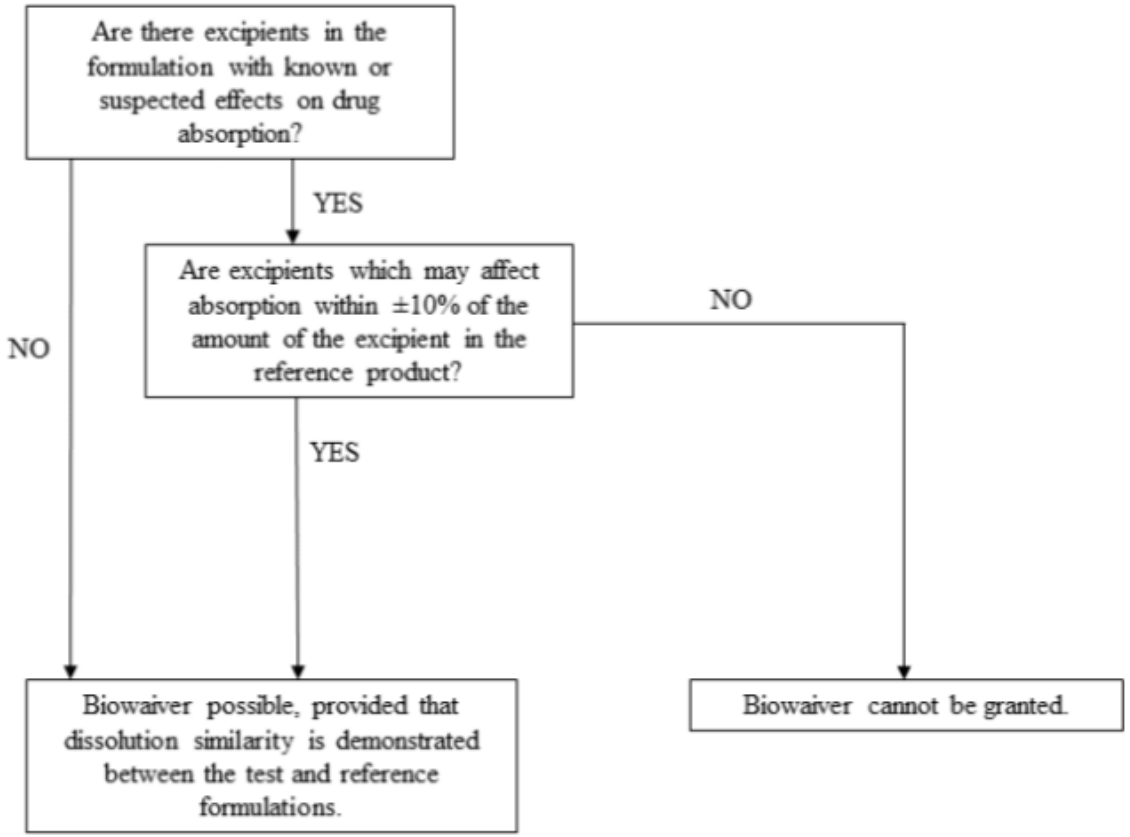
ICH M9 BCS Class I

- Qualitative and quantitative **differences** in excipients **are permitted**,
- Except for **excipients that may affect absorption**, which should be qualitatively the same and quantitatively similar.

Similar = within ± 10.0% of the amount of excipient in the reference product.

Flow chart for BCS Class I

Figure 1. BCS Class I Drug Substances



ICH M9 BCS Class III

- Greater number of mechanisms through which excipients can affect absorption
- All of the excipients should be qualitatively the same and quantitatively similar
- (except for film coating or capsule shell excipients).

Allowable differences in excipients for drug products containing BCS Class III drugs

Excipient class	Percent of the amount of excipient in the reference	Percent difference relative to core weight (w/w)
Excipients which may affect absorption:	**± 10.0%**	
All excipients:		
Filler		± 10.0%
Disintegrant		
Starch		± 6.0%
Other		± 2.0%
Binder		± 1.0%
Lubricant		
Ca or Mg stearate		± 0.5%
Other		± 2.0%
Glidant		
Talc		± 2.0%
Other		± 0.2%
Total % change permitted:		**10.0%**

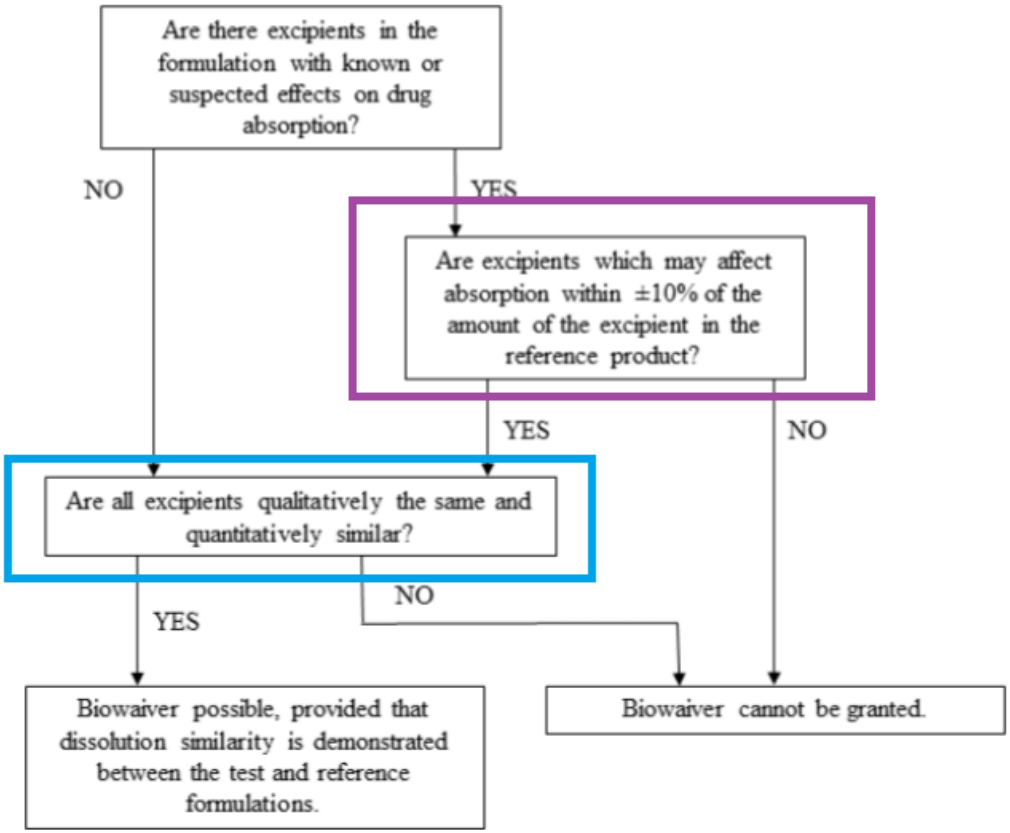
Note: Core does not include tablet film coat or capsule shell

Active substance assay
±5%

SUPAC
Post-approval
(different objective)

Flow chart for BCS Class III

Figure 2. BCS Class III Drug Substances



Why is this an issue for generics?

1. Qualitative composition known
2. Quantitative composition?
3. Ranges of use of excipients
4. Patents
5. Reverse engineering (experimental methods with variability and limitations)

Source: https://www.kitchenstewardship.com/wp-content/uploads/2010/01/How-to-Reverse-Engineer-a-Recipe.jpg

Quantitative composition

- Public databases (not available from most highly regulated countries)
- Considered to be confidential information in most regions

- Alternative?

"This doesn't exactly fill me with confidence, I must admit."

Source: https://www.cartoonstock.com/directory/g/guesstimate.asp

Magnesium stearate

- Vaithianathan et al. 2016 **(and subsequent correspondence)**: Effect of Common Excipients on the Oral Drug Absorption of Biopharmaceutics Classification System Class 3 Drugs Cimetidine and Acyclovir. J Pharm Sci. 105(2):996-1005
- The other selected cimetidine capsule formulation for clinical study 2 was denoted CimTest-B and contained 20 mg of magnesium stearate, a reduced amount compared with the 40 mg of magnesium stearate in AcyTest-3 from study 1B.
- Magnesium stearate is known to slow dissolution and possibly reduce drug absorption via overlubrication.
- One main observation is that magnesium stearate in CimTest-B did not modulate drug absorption. Hence, Table 8 denotes acceptable quantities of magnesium stearate for BCS class 3 biowaivers to be 40 mg (from dosing two capsules here) or less.

Maximum Amount of Excipients That BCS Class 3 Biowaivers Can Accommodate

Excipient	Recommended Maximum Allowable Amount for a Class 3 Biowaiver (mg)	Maximum Excipient Amount Studied Here (mg)[a]	Typical Excipient Amount (when present) in an IR Tablet or Capsule With a Total Weight of 300 mg[26]	Maximum Amount (mg) in Inactive Ingredient Database[27]
Microcrystalline cellulose	Qualitatively the same and quantitatively very similar to reference product	600[b]	100 mg (20%-90%)	1385.3[g]
Hydroxypropyl methylcellulose	Qualitatively the same and quantitatively very similar to reference product	40[b]	10 mg (2%-5%)	444.4[g]
Sodium lauryl sulfate	50	50[b,d]	4.5 mg (0.5%-2.5%)	51.69[g]
Corn starch	900	900[c]	150 mg (25%-75%)	1135[h]
Sodium starch glycolate	200	200[c]	12 mg (4%)	876[g]
Colloidal silicon dioxide	40	40[c]	1.5 mg (0.1%-1%)	100[i]
Dibasic calcium phosphate	600	600[d]	150 mg (25%-75%)	635.5[k]
Crospovidone	100	100[d]	10 mg (2%-5%)	340[j]
Lactose	900	900[e]	240 mg (80%)	1020[g]
Povidone	70	70[e]	7.5 mg (0.5%-5%)	240[k]
Stearic acid	80	80[e]	6 mg (1%-3%)	72[l]
Pregelatinized starch	200	200[f]	150 mg (5%-75%)	435.8[g]
Croscarmellose sodium	120	120[f]	37.5 mg (0.5%-25%)	180[g]
Magnesium stearate	40	40[f]	7.5 mg (0.25%-5%)	400.74[g]

[a] Reflects that two capsules of either cimetidine 100 mg or acyclovir 100 mg were administered in single-dose studies here.
[b] Employed in dosing of capsule formulation CimTest-A in study 2.
[c] Employed in dosing of capsule formulation CimTest-2 in study 1A.
[d] Employed in dosing of capsule formulation CimTest-3 of study 1A.
[e] Employed in dosing of capsule formulation AcyTest-2 of study 1B.
[f] Employed in dosing of capsule formulation CimTest-B of study 2.
[g] Oral tablet.
[h] Oral capsule.
[i] Oral granule.
[j] Oral dispersible tablet.
[k] Oral tablet film coated.
[l] 72 mg from oral table and 180 mg from extended-release table.

Vaithianathan et al. 2016 **(and subsequent correspondence)**:: Effect of Common Excipients on the Oral Drug Absorption of Biopharmaceutics Classification System Class 3 Drugs Cimetidine and Acyclovir. J Pharm Sci. 105(2):996-1005

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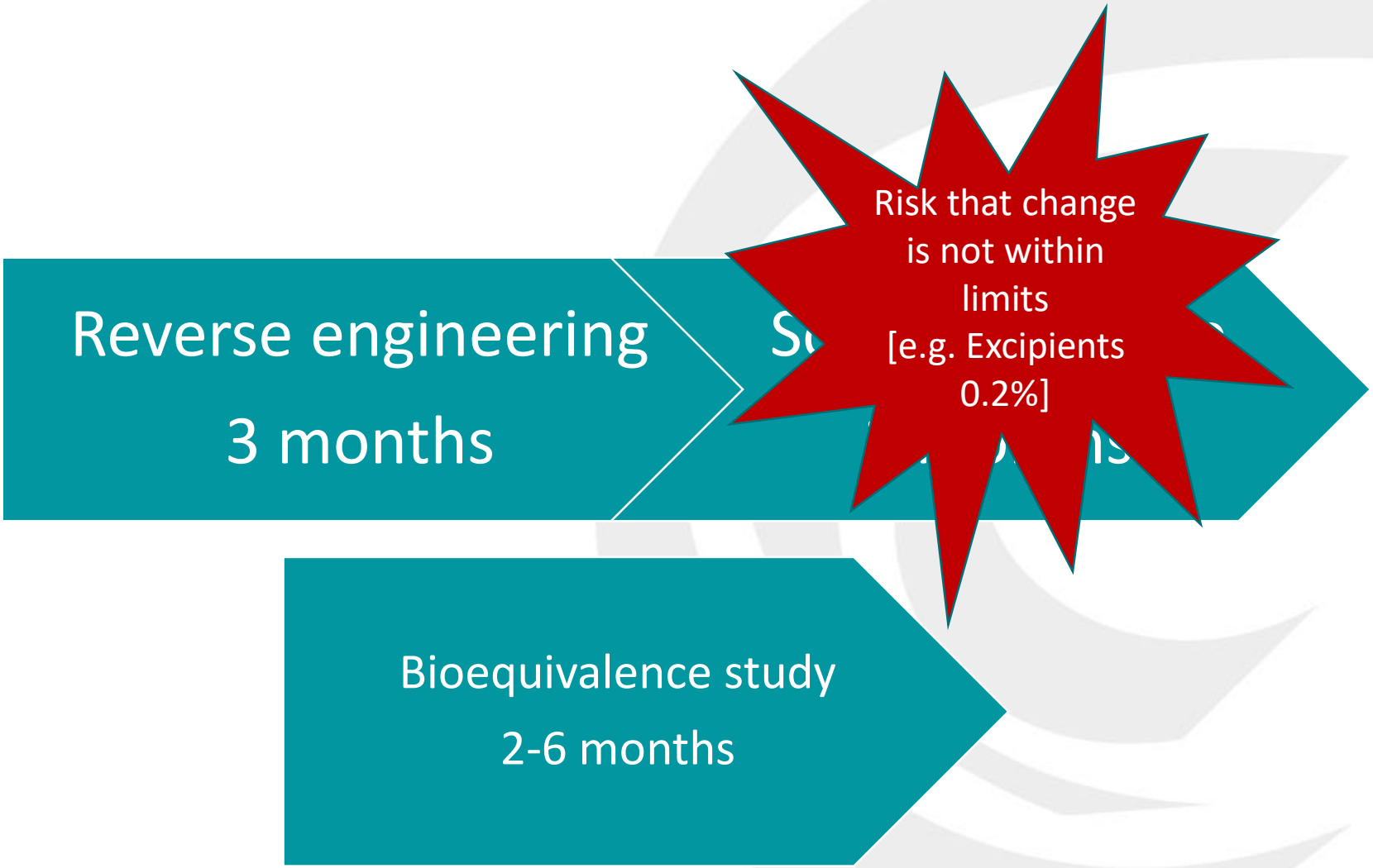
Example in practice



Question

- What is the feasibility for BCS Class III?

Are excipients important?

- They may be!

- Accepted ranges: SUPAC was developed with a different intent
- Reverse engineering is based on experimental data (variability)
- (Assay of API ±5%)
- Feasibility to guesstimate at ≤2% (0.2%, 0.5%. 1%, 2%...)

Public consultation

ICH M9 on biopharmaceutics classification system based biowaivers

Email Print Help Share

Current version	**Draft guideline** For public consultation
Reference number	EMA/CHMP/ICH/493213/2018
Published	06/08/2018
Start of consultation	06/08/2018
End of consultation	06/02/2019
Keywords	Bioequivalence study exemptions, solubility, permeability, in vitro dissolution
Description	This new multidisciplinary guideline is proposed to address biopharmaceutics classification system (BCS)-based biowaivers. BCS-based biowaivers may be applicable to BCS Class I and III drugs, however BCS-based biowaivers for these two classes are not recognized worldwide. This means that pharmaceutical companies have to follow different approaches in the different regions. This guideline will provide recommendations to support the biopharmaceutics classification of medicinal products and will provide recommendations to support the waiver of bioequivalence studies. This will result in the harmonisation of current regional guidelines/guidance and support streamlined global drug development.

Why you should participate in the public consultation?

- Now is the time to provide comments!
- Especially helpful if supported by data / case studies
- EWG to analyze comments before coming to the final version of the guideline

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