# VICH Bioequivalence GL:

# An introduction to bioequivalence and biowaivers from a scientific perspective.

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Chair, VICH Bioequivalence Expert Working Group

During this one-hour session, I will address questions raised as points of interest by the VICH forum members.

https://www.freepik.com/free-photos-vectors/dog-computer

I will also highlight points to be discussed tomorrow during the bioequivalence (BE) lecture.

https://www.pexels.com/photo/white-and-black-cat-on-rock-2115746/

# Principles supporting the use of blood level studies to assess the comparability of a test product and a marketed reference product

# What is Bioequivalence (BE)?

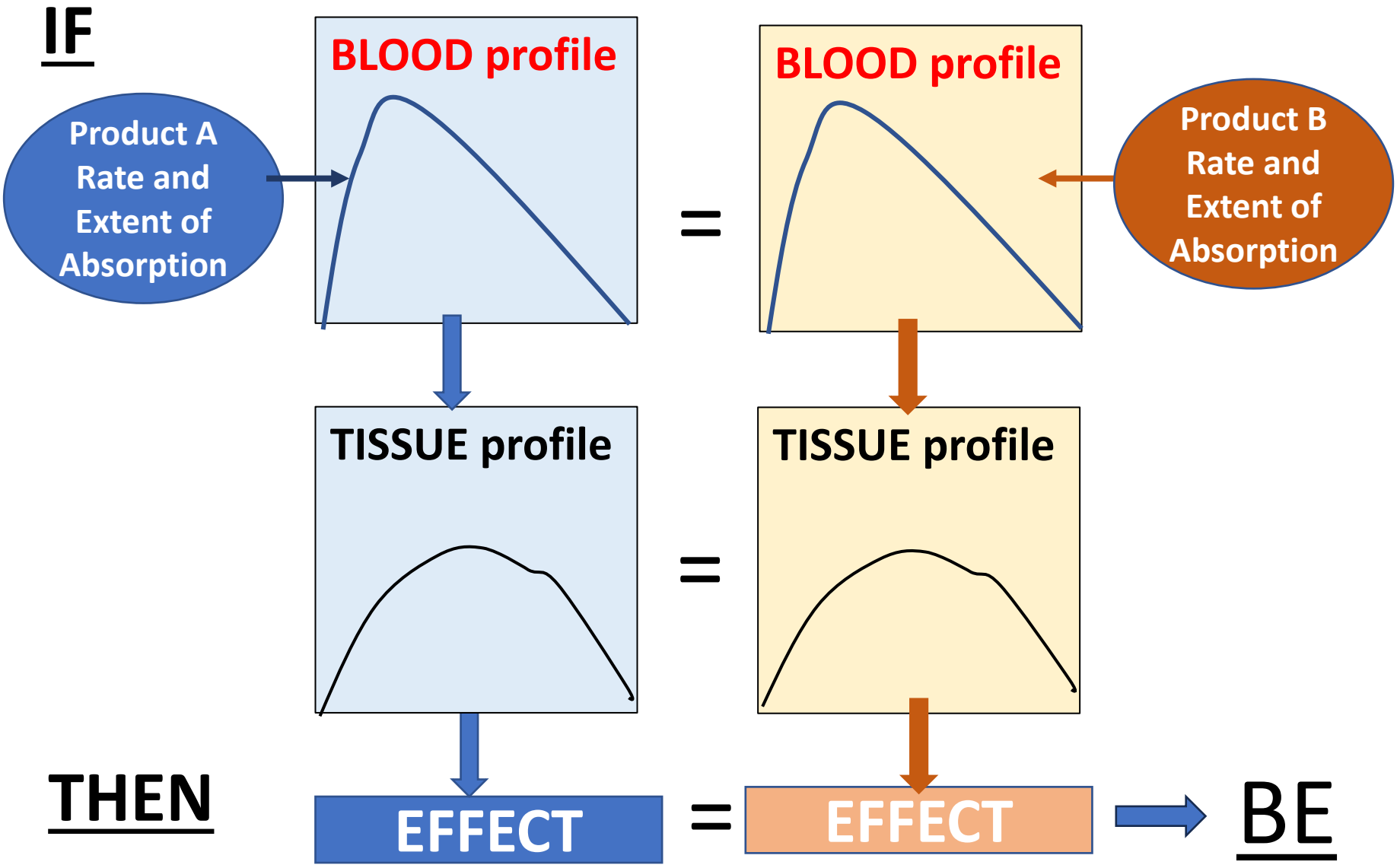
Plasma concentrations provide a surrogate for demonstrating product equivalence in terms of safety and effectiveness.

The assumption is that if two products are bioequivalent (rate and extent of exposure), then their in vivo performance (safety and effectiveness) will be indistinguishable to the patient and therefore interchangeable.

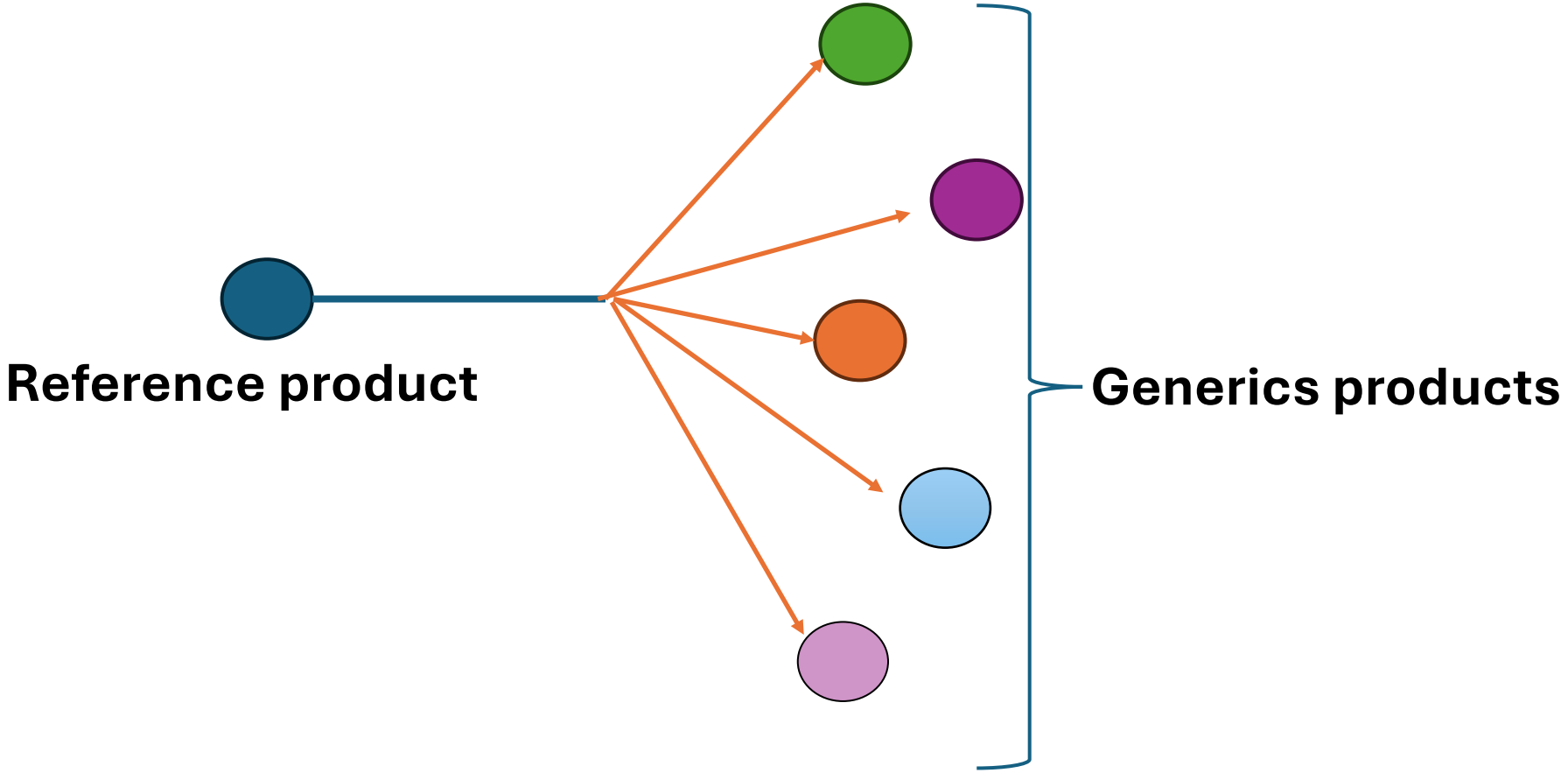
https://www.revivalanimal.com/learning-center/how-to-give-a-dog-medicine?srsltid=AfmBOoob3MrM-VKN-h8SluIvuewoZi2L1hzOnZ5uCShYIZdnCoSM7Avo

# Theoretical Basis Behind BE Concepts

## Assumption: drug must go through blood to site of action



# Why is it necessary to limit BE evaluations to a single reference product when evaluating generic formulations?

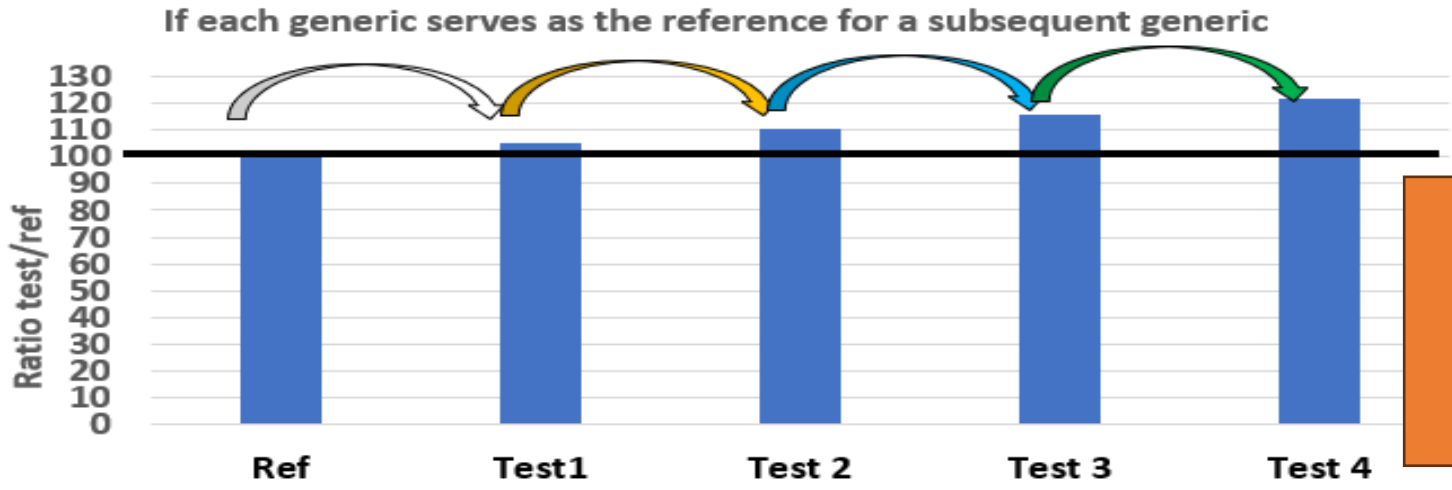


# Why limit BE evaluations to a single reference product?

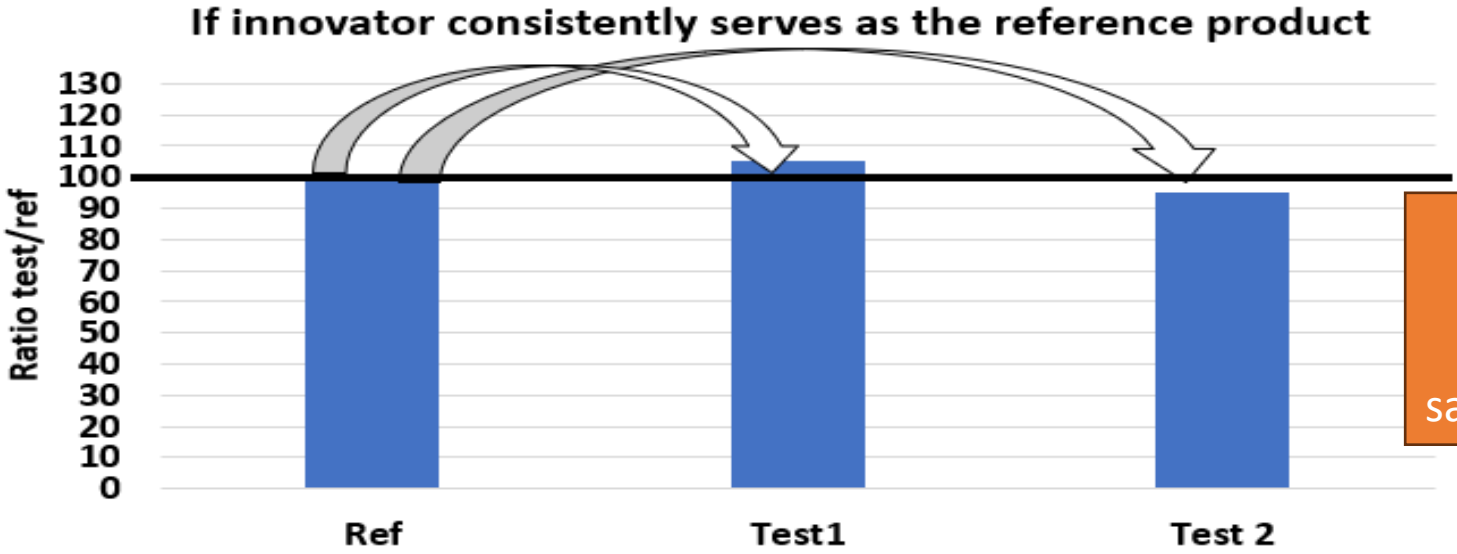
By constraining all BE studies to use of the same reference product, we avoid the between-generic drift that can occur if different products are selected as the reference formulation (e.g., using a previously approved generic formulation in lieu of the marketed innovator).

https://www.boat-ed.com/blog/what-is-a-boat-anchor-and-how-does-one-work/

# Why Do We Need to Always Use the Same Reference Product?

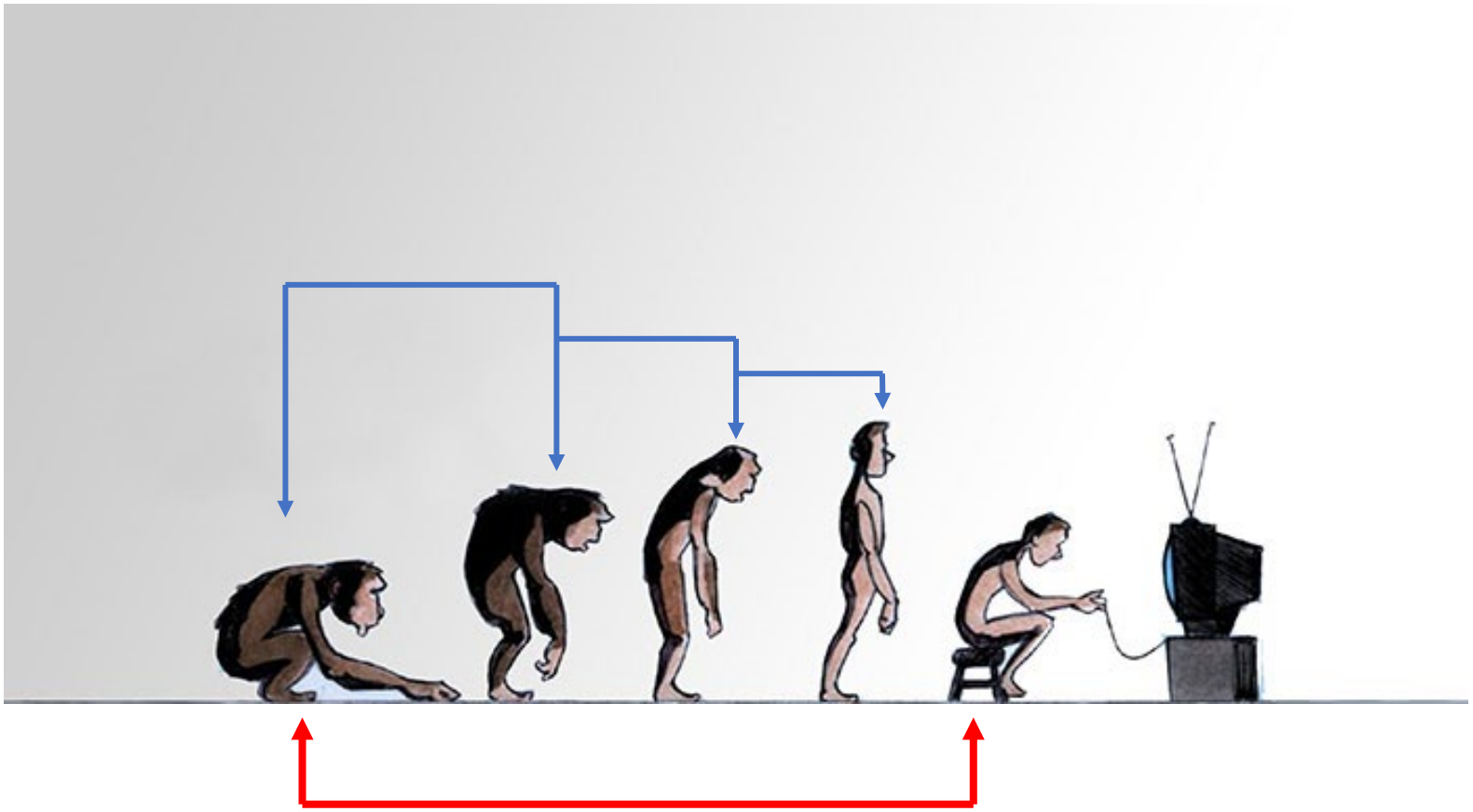



The mean for each generic differs by 5% relative to its comparator




Each generic differs by 5% relative to the same Ref product.

# A bit of humor: an example of drift.



https://www.boredpanda.com/funny-satirical-evolution-charles-darwin-day/

# How do we determine the reference product to be used in the BE study?

https://www.shutterstock.com/search/choices-confused-cartoon-woman?image_type=illustration

# Considerations when selecting the reference product.

- The reference product is typically the innovator product used in clinical trials to demonstrate product safety and effectiveness.
- For a generic product to be eligible for marketing, the reference product can no longer be protected under patent or marketing exclusivity.

# Considerations when selecting the reference product.

- If the original innovator product has undergone post-marketing formulation changes, the following points should be considered:
  - Oftentimes a revised reference formulation may itself have been approved based on an in vivo BE study. Therefore, unless the new formulation has undergone its own safety and effectiveness studies or has its own unique drug application number (i.e., is not listed under the application number of the original product), the original formulation should be used as the reference product
  - If the original formulation is no longer marketed, the currently marketed innovator product should be used.

# Point to ponder - let’s talk

https://speakzeasy.wordpress.com/2013/05/09/49998698158/

# Hypothetical situation:

- A Reference product was originally approved as a swallow tablet but later was approved as a chewable tablet. This formulation change was approved based on a blood level bridging study, where the slight increase in bioavailability (ratio chewable/swallow = **1.1500**; ratio swallow/chewable = **0.8696**) was determined to not influence innovator product safety or effectiveness and was therefore deemed approvable without the need for additional clinical data. Both the swallow and chewable formulations continue to be marketed and have identical dosage recommendations.

# Hypothetical situation:

- Sponsors of **Generic X** and **Generic Y** want to market generic versions of the **chewable tablet**. Which reference formulation should be used?

**Consider**:

**Generic X** has 10% higher bioavailability than the Innovator chewable tablet which was used as the reference product. Therefore, although it was BE to the Innovator chewable tablet, it would NOT be BE to the swallow tablet [i.e., ratio **Generic X**/Innovator swallow tablet = 1.265 ((100*1.1)/86.956 = 1.265)].

**Generic Y** has 10% lower bioavailability than the Innovator swallow tab, which was used as the reference product. Although it was BE to the swallow tablet, it would NOT be BE to the Innovator chewable [i.e., ratio **Generic Y** /Innovator chewable tablet = 0.783 ((86.957*0.9)/100).

# Hypothetical situation:

**Generic X**/**Generic Y** = 1.265/0.783 = 1.616.

**THESE PRODUCTS ARE NOT INTERCHANGEABLE!**

What would YOU want to recommend as the best product to use as the reference for **Generic X** and **Generic Y**?

a. If the Innovator's chewable and swallow tablets had different application numbers?

b. If the Innovator's chewable and swallow tablets had the same application number?

c. How does your answer influence the product that would fail to be approved based on the in vivo BE study?

***What additional points might need to be considered?***

***This is a grey area that would need further discussion.***

# How do we select the lot of the reference product to use in the BE study?

https://www.shutterstock.com/search/choices-confused-cartoon-woman?image_type=illustration

# Considerations when selecting the reference product.

- Once the product is identified, several considerations go into a determination of the reference lot to be used in the BE study. These include the following:

  - The lot of the innovator product must be within expiry throughout the duration of the in vivo portion of the BE study.
  - If possible, multiple lots of the innovator product should be tested for potency to ensure that the potency of the selected lot is representative of the marketed product. Its potency should be close to that of the label claim.
  - To be internationally acceptable, it is recommended that the assay content of the batches from which test and reference products were obtained should differ by no more than ±5%.

# Illustration:
# Selecting the BE Study Reference Lot


Reference product potencies (% Label claim)

Acceptable as reference lot

Acceptable as reference lot

102%

Generic product potency

# What should regulators consider if the BE studies are conducted in a different country?

https://www.freepik.com/free-photos-vectors/globe-flags

# Considerations when selecting the reference product.

- For most jurisdictions, generic formulations must be copies of an innovator product that is approved for marketing within that jurisdiction.
- However, at the last VICH meeting, it was stated that some jurisdictions do not have innovator products that are manufactured or approved for marketing within that jurisdiction. When this situation is encountered, I would suggest that one country within which the innovator is manufactured and marketed be selected as the reference product used for all future BE studies.

# Considerations for studies conducted abroad (note that these principles typically apply to BE studies in general).

- The contract research organization (CRO) should provide a detailed protocol for regulator review prior to conducting the study and describe any study deviations that may have occurred.
- The breed and body weights of the study animals should reflect that of the major target species in your country.
- Samples should be stored frozen and available for re-assay upon request by the regulatory body.
- For review of the data, the study report should:
  - Describe deviations from the study protocol.
  - Provide raw data to enable data re-analysis when deemed necessary by the regulatory bodies.
  - Provide software codes used to generate the data analysis to enable re-analysis by the regulatory authority if necessary.

# Considerations for studies done abroad.

- Consider the points previously made regarding the innovator product selection.
- Make certain that the CRO adheres to the principles described in the VICH BE Guidance.
- If the innovator product has not been approved for use in a species of interest (e.g., camels), you cannot perform a BE study in camels and label that generic product for use in camels since clinical data on drug safety and effectiveness was not confirmed in that animal species.

# What is a biowaiver?

https://depositphotos.com/photos/vintage-science.html

# What is a biowaiver?

A biowaiver is regulatory exemption that allows pharmaceutical companies to waive (i.e., forego) the requirement for in vivo bioavailability or bioequivalence studies, under certain conditions.

Haritha Mandula, Ph.D., FDA/CDER/OPQ. https://www.fda.gov/media/166155/download#:~:text=%E2%9E%A2%20A%20Biowaiver%20means%20that,Federal%20Regulation

Lenić I, et al., Overview of the European Medicines Agency's Experience With Biowaivers in Centralized Applications. Clin Transl Sci. 2019 Sep;12(5):490-496. doi: 10.1111/cts.12642.

# Various types of biowaivers have been described.

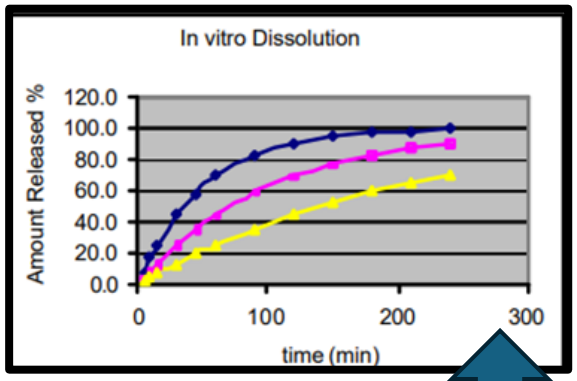
- For a true solution (oral or injectable): This pertains to aqueous solutions. Currently, lipophilic solutions are typically NOT eligible for biowaivers. This applies to human and veterinary medicine.
- Biopharmaceutics Classification System (BCS): Within human medicine, biowaivers can be granted to immediate release oral formulations that contain drugs classified as highly soluble (i.e., the highest label drug dose is fully solubilized in 240 mL of aqueous media across the range of pH values found in the human gastrointestinal tract). **However, BCS-based biowaivers are not currently an option within veterinary medicine.** *Note: many human drugs classified as highly soluble are not likewise highly soluble in dogs and cats (see publications by Marilyn Martinez and Mark Papich and ICH M9 ).*

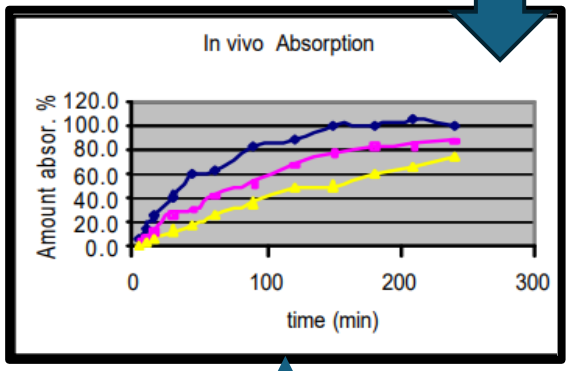
# Various types of biowaivers have been described

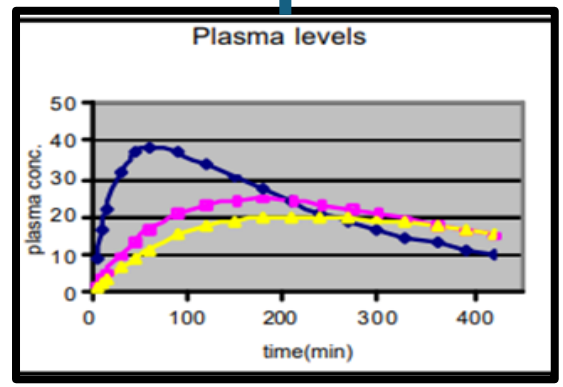
- In vivo/in vitro correlations (IVIVCs): When established, an IVIVC may be used to support a waiver of subsequent in vivo BE studies. However, this typically applies to new drug products where multiple formulations (e.g., fast, medium and slow release) can be tested both in vitro (dissolution) and in vivo (blood level study), and a mathematical relationship can be developed between the two. An IVIVC can be used to support a waiver of in vivo bioavailability study requirements associated both with pre- and post-approval changes (such as formulation composition, manufacturing process, equipment and site changes). *Although FDA-CVM has a published guidance covering the use of IVIVC's to support veterinary parenteral product applications, drug sponsor implementation of that guidance has been rare.*

https://sites.ualberta.ca/~csps/JPPS9_2/Jaber_Emami/MS_190.htm

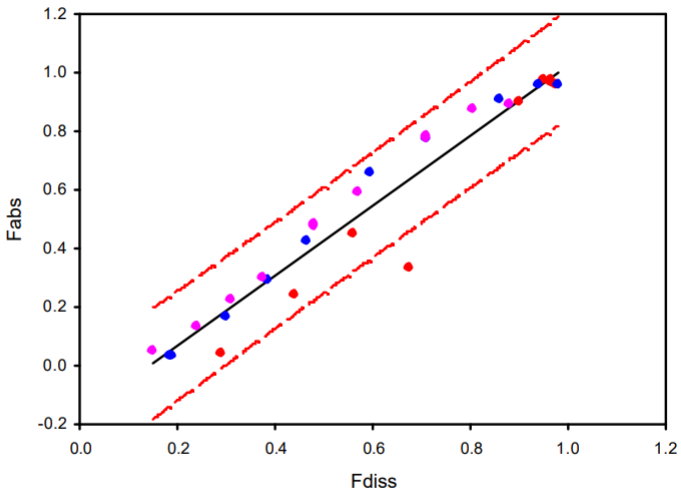
# General Design of an IVIVC




Level A correlation



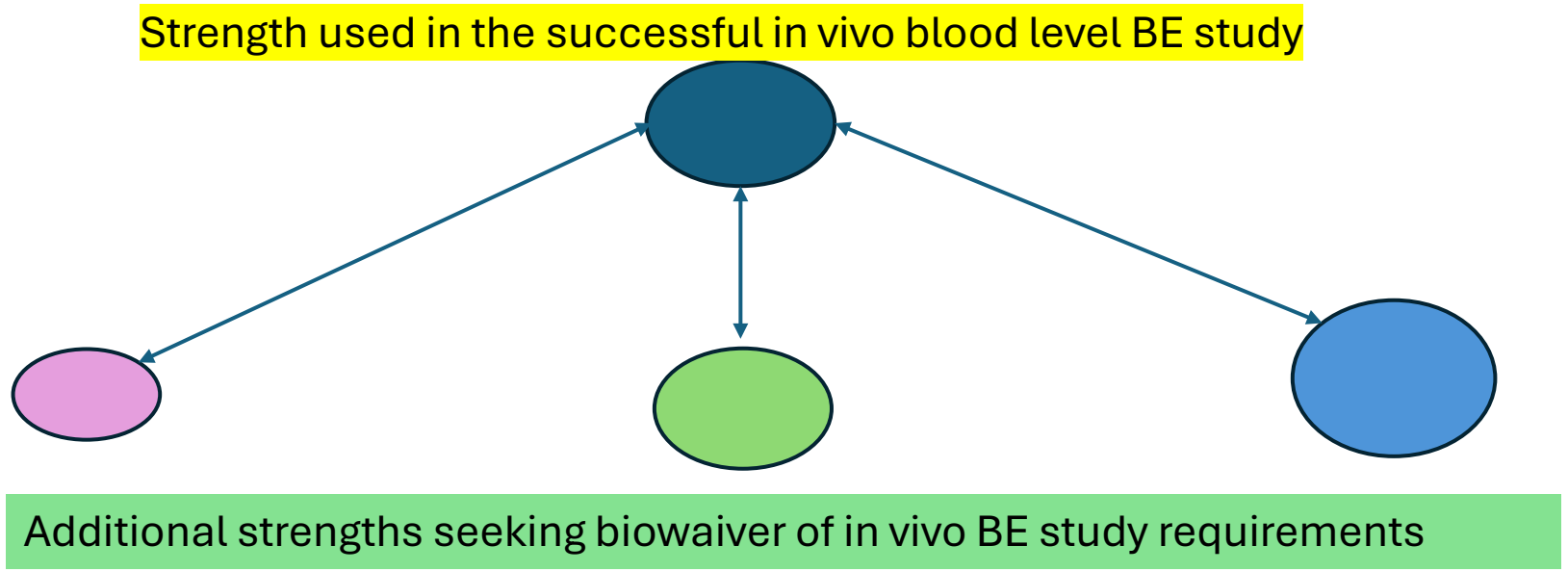

Adapted from Sirisuth N and Eddington N.
*Int. J. Generic Drugs (IVIVC series part III)*

Mathematical conversion (deconvolution) to % absorbed

(based on figures from
http://www.uv.es/~mbermejo/DissolutionC)

# Various types of biowaivers have been described

- Between Strength Biowaivers: This is the topic of the guideline currently being developed by the VICH Bioequivalence Expert Working Group.



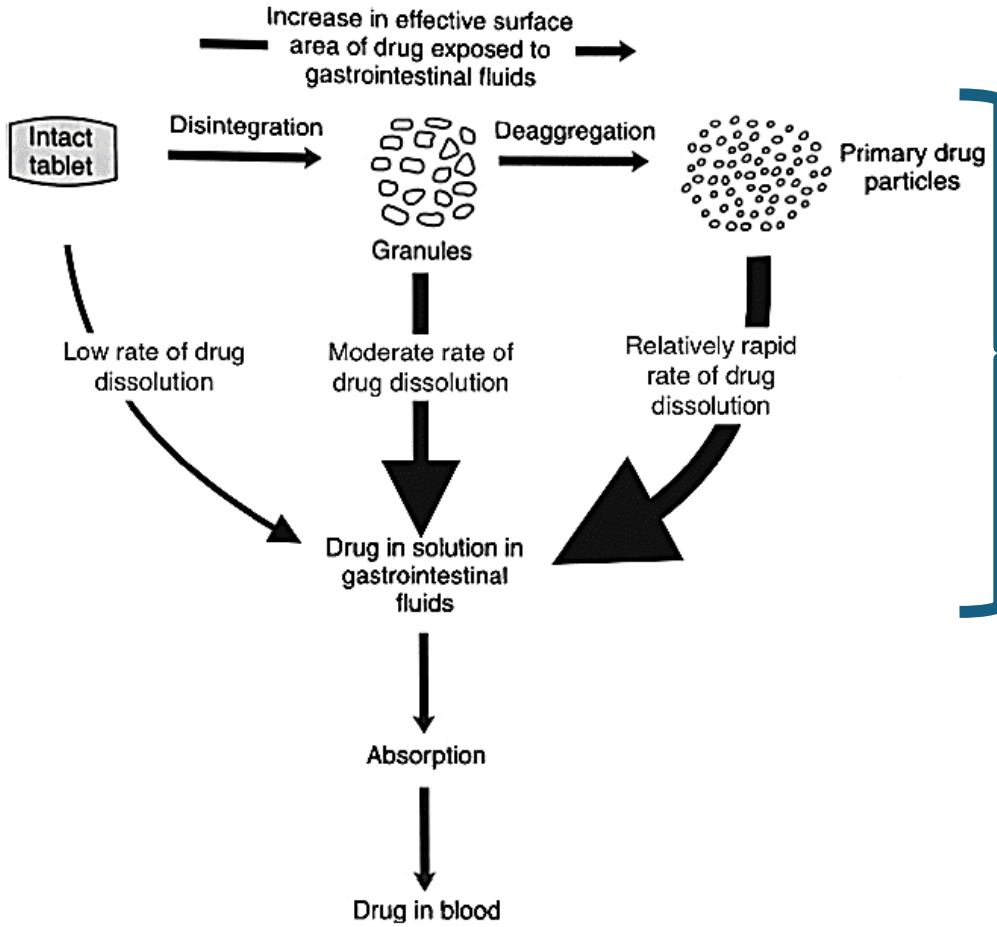
# What are the current restrictions for when the biowaiver process can be used to support tablet/capsule strengths that have not been used to in the in vivo BE study?


https://share.google/images/WidXA7i1LFQ8OMZSL

To answer this, let’s first cover some principles influencing in vitro dissolution characteristics since dissolution is a critical component of between-strength biowaivers

https://www.freepik.com/premium-vector/young-woman-raising-her-index-finger-making-point_287833122.htm

# The science of in vitro dissolution




In vitro dissolution is intended to reflect this portion of the drug oral bioavailability process. However, unless an IVIVC has been established, it may not provide an accurate measure of the rate and extent of in vivo dissolution. Nevertheless, when developed for sensitivity to product *critical quality attributes* and the composition of the tablet formulations are *proportionally similar*, in vitro dissolution can provide a reliable surrogate for in vivo BE studies for the detection of inequivalent tablet strengths .

Markl and Zeitler (2017). Pharm Res, 34: 890-917. DOI 10.1007/s11095-017-2129-z

# Fundamental considerations when evaluating a dissolution method

## Presence of Sink Conditions

https://www.bryartonfarm.com/2017/04/antique-farm-sink-makeover-tips-for-restoring-an-old-sink-on-a-budget/

- Sink conditions reflect the fluid volume necessary to maintain a fully dissolved state of the API.
- To achieve sink conditions, the volume of medium should be ≥3 × that needed to form a saturated solution of the drug substance (mg of tablets being tested).
- In vitro dissolution studies need to be conducted under sink conditions so that the rate limiting factor is the formulation and not the API itself.

# Fundamental considerations when developing and evaluating a dissolution method

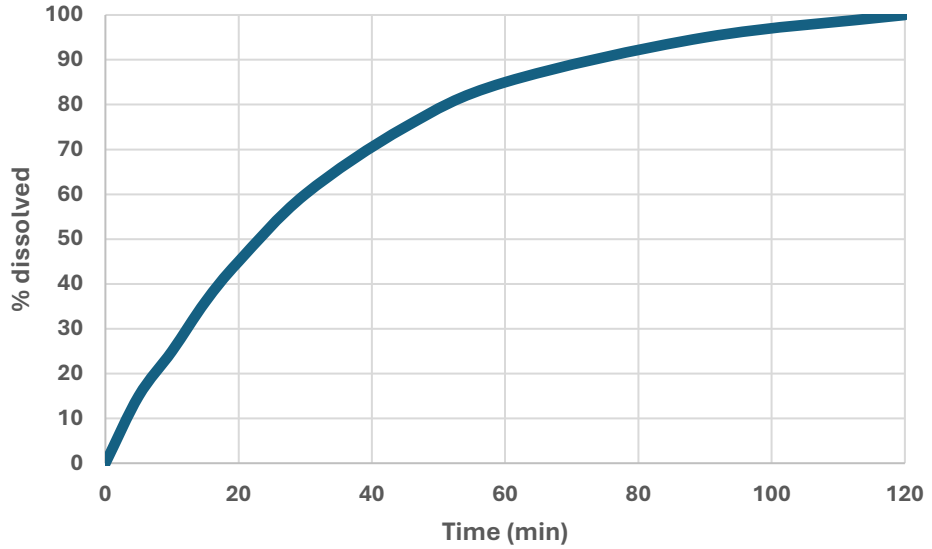
Ideally, the dissolution method should be established with the goal of being:

1) Discriminative (able to identify differences in product critical quality attributes)
2) Bio-predictive (predictive of formulation changes that will influence in vivo product performance)
3) Sensitive to changes in product integrity during its shelf life (temperature, humidity, photosensitivity, and other stresses).
4) Demonstrates acceptable precision and robustness*. With regards to precision, typical limits for early and later time-points would be $\leq$20% and $\leq$10% RSD respectively
5) Demonstrates a quantifiable increase in the amount of drug dissolved over time (this may not be possible for a highly soluble drug that goes rapidly into solution)

***robustness: consistent and accurate results even when minor operational deviations occur.**

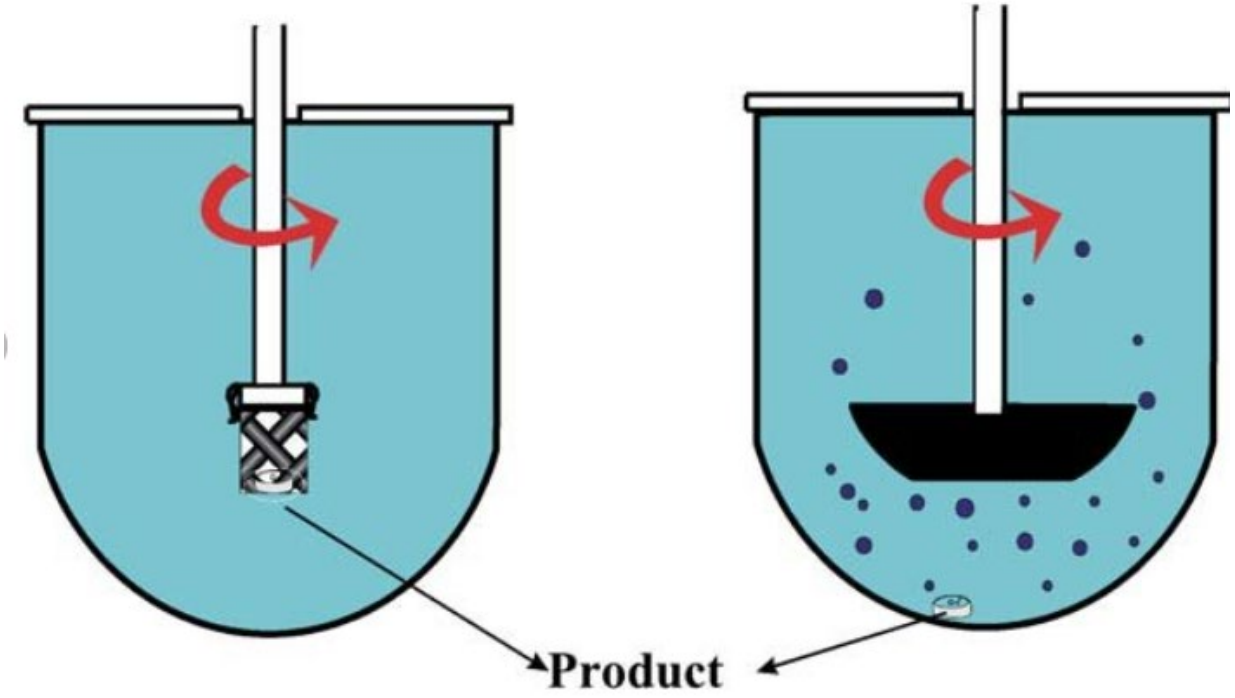
# Fundamental considerations when developing and evaluating a dissolution method

Demonstrates a quantifiable increase in the amount of drug dissolved over time (illustration)



# Fundamental considerations when developing and evaluating a dissolution method

- Selection of an appropriate in vitro dissolution apparatus

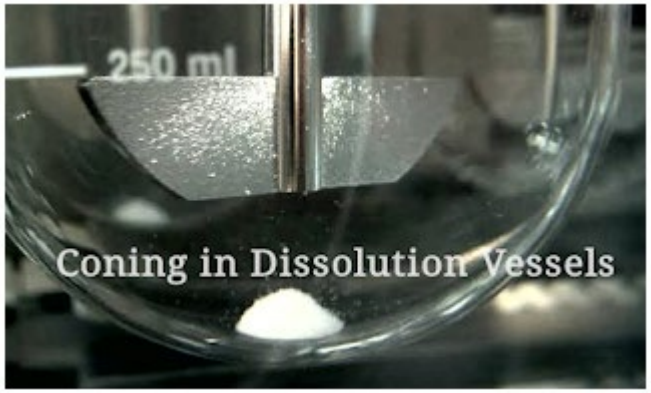



Schematic representations of Basket (USP 1) and Paddle (USP 2) Apparatus

https://www.researchgate.net/figure/Schematic-representations-of-Basket-USP-1-and-Paddle-USP-2-Apparatus_fig1_237679345

# Fundamental considerations when developing and evaluating a dissolution method

- Absence of vibrations that can influence dissolution study results
- Absence of coning




https://www.pharmaspecialists.com/2023/10/coning-in-dissolution-vessels.html

- Avoidance of excessive agitation within the vessels
- Prevention of poor mixing of contents within the vessels
- Knowledge of the pKa of the API (if ionizable)
- Determination of the appropriate media contents and volume
- Selection of an appropriate type and amount of surfactant (if needed)
- Selection of appropriate sampling timepoints
- Analytical method development and validation
- Determination of method for sample filtering (if needed)

# What is pKa?

- pKa measures the ionization of a drug as a function of pH.
- Although it is typically thought of as measuring the strength of an acid, the strength of a base can also be directly calculated from the pKa value.
- Relationship between pH and pKa is described by the Henderson-Hasselbalch (HH) equation:
- For a weak acid: $pH = pKa + \log \frac{[Ionized\ Drug]}{[Unionized\ Drug]}$

- For a weak base: $pH = pKa + \log \frac{[Unionized\ Drug]}{[Ionized\ Drug]}$

https://pressbooks.openeducationalberta.ca/abcofpkpd/chapter/hh/#:~:text=An%20equation%20that%20allows%20you,more%20ionised%20in%20the%20plasma

# Rearranging HH equation to estimate pKa

For a weak acid: $pH = pKa + \log \frac{[Ionized\ Drug]}{[Unionized\ Drug]}$

**Therefore, $pKa = pH - \log \frac{[\boldsymbol{Ionized\ Drug}]}{[\boldsymbol{Unionized\ Drug}]}$**

For a weak base: $pH = pKa + \log \frac{[Unionized\ Drug]}{[Ionized\ Drug]}$

**Therefore, $pKa = pH - \log \frac{[\boldsymbol{Unionized\ Drug}]}{[\boldsymbol{Ionized\ Drug}]}$**

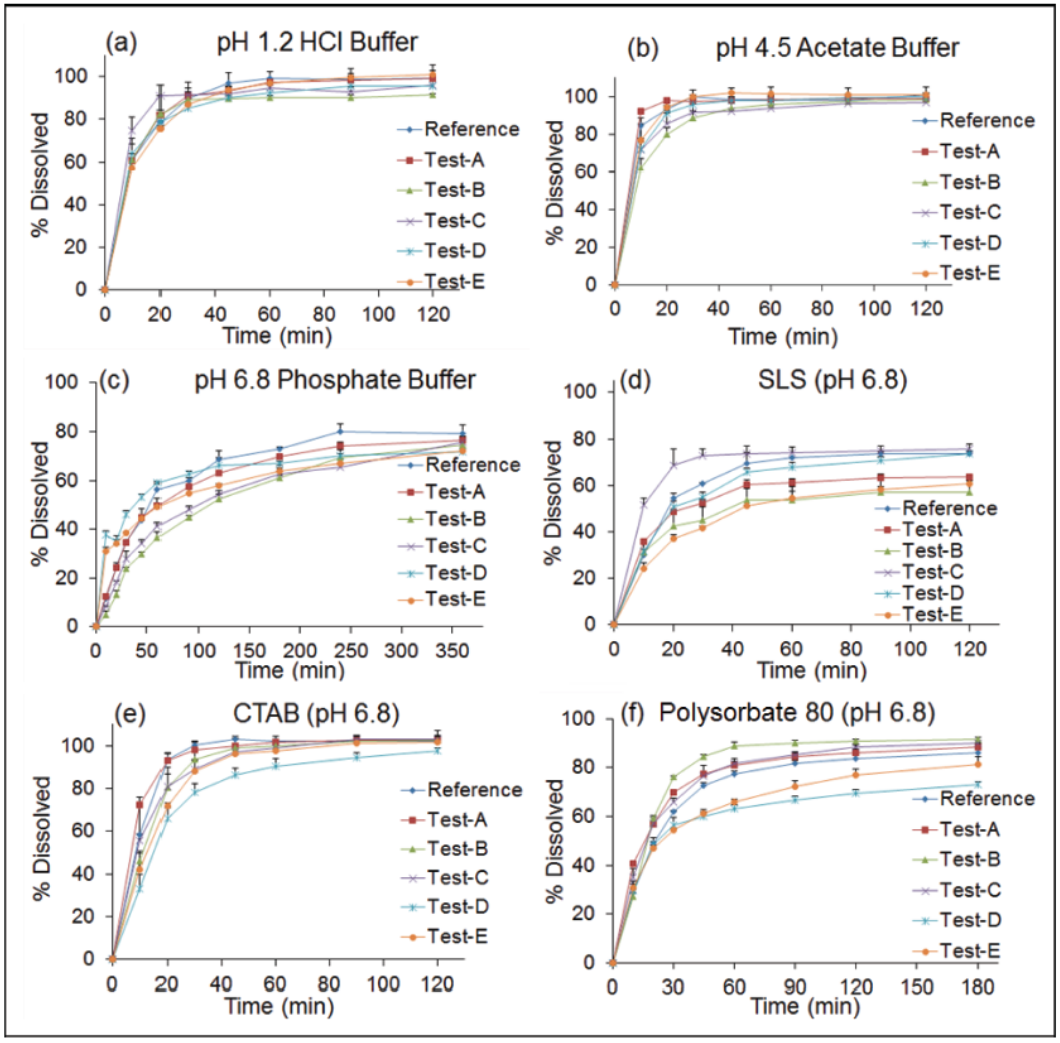
# What is pKa?

**Solubility vs. permeability:** A drug must be dissolved in gastrointestinal (GI) fluids to be absorbed. However, only the un-ionized (uncharged) form can effectively cross the lipid-rich GI membranes. Thus, there needs to be a compromise between solubility (high ionization may reduce permeability) and permeability (low ionization may limit drug solubility).

- **Weak acids:** Are mostly un-ionized and less soluble in the acidic conditions of the stomach. They become more ionized and more soluble in the more alkaline environment of the small intestine.
- **Weak bases:** Are mostly ionized and more soluble in the stomach's acidic environment. They become less ionized and less soluble in the small intestine (can lead to supersaturation and subsequent precipitation in the small intestine).

https://www.youtube.com/watch?v=8VXyvMXbUa8&t=195s

# Media selection can influence product profile comparisons




Incecayir T, (2015). Pharmazie 70: 784-790. *doi: 10.1691/ph.2015.5081*

Comparison of dissolution profiles of carvedilol reference and test tablets across media (n = 3).

# But the addition of surfactants to dissolution media can hide product in vivo inequivalence.

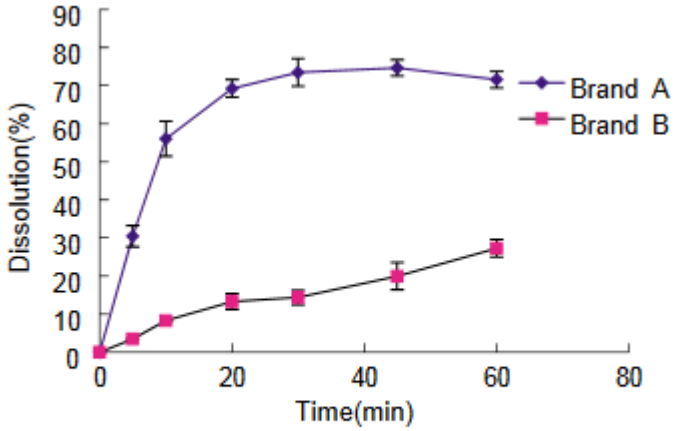



Fig. 1. Dissolutin of two brands of nimodipine tablets in water (mean ± S.D., $n = 6$).

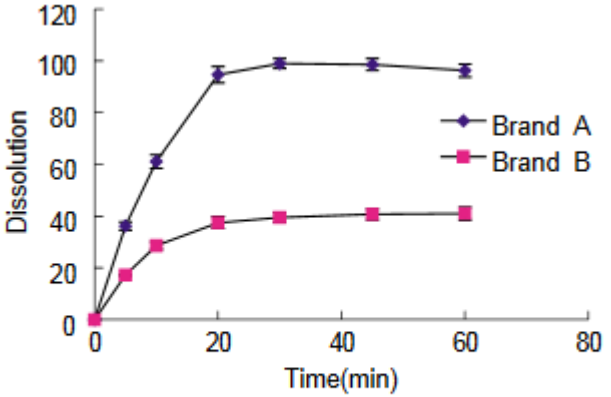



Fig. 2. Dissolution of two brands of nimodipine tablets in pH 4.5 acetate buffer containing 0.05% (w/v) of SDS (mean ± S.D., $n = 6$).

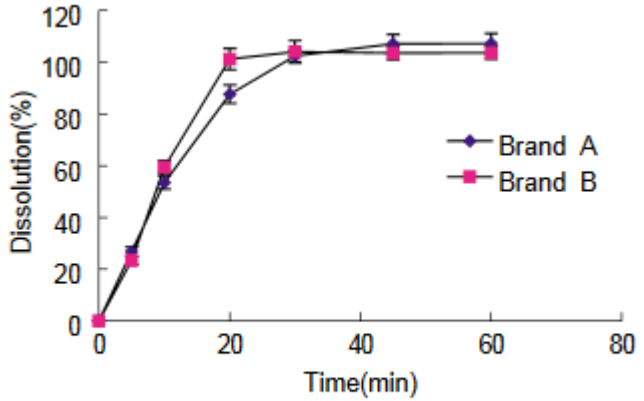



Fig. 3. Dissolution of two brands of nimodipine tablets in pH 4.5 acetate buffer containg 0.3% (w/v) of SDS (mean ± S.D., $n = 6$).

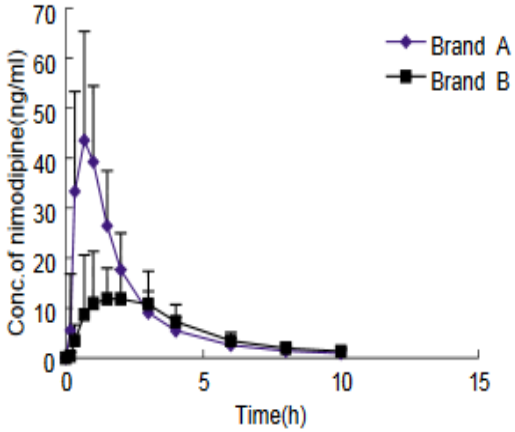



Fig. 5. Plasma concentration of nimodipine after oral administration of two brands of nimodipine tablets.

He Z, et al. Eur J Pharm Sci. 2004 Mar;21(4):487-91.

In view of these considerations, the in vitro dissolution test method used to evaluate the between strength biowaivers needs to be selected with care and validated on the dissolution equipment to be used in the pivotal study.

# Biowaiver limitations and restrictions

VICH discussions have been limited to immediate release tablets and capsules.

- Each tablet or capsule strength needs to be compared to the test product lot used in a successful in vivo blood level study.
- The potencies of all lots used in the in vivo and in vitro studies need to fall within ± 5% of the labeled potency.

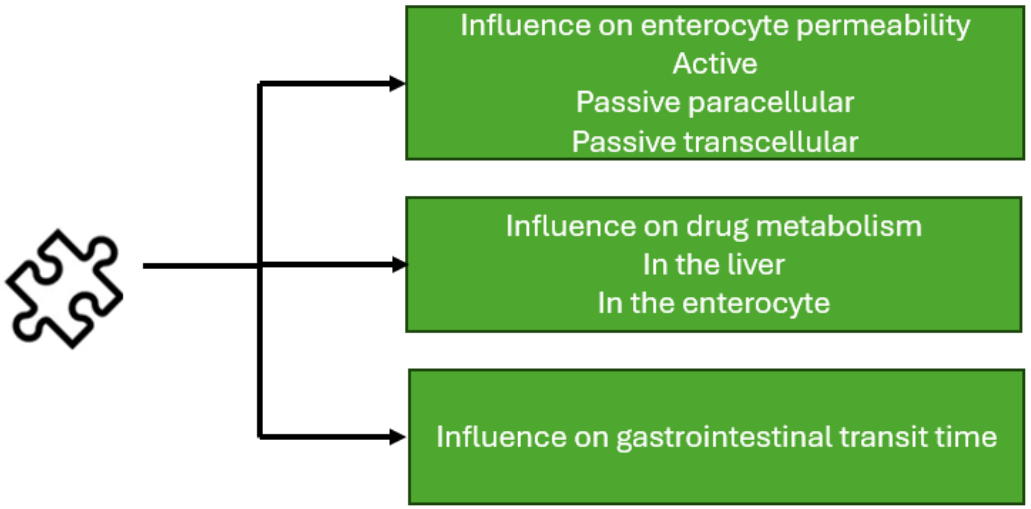
# Biowaiver limitations and restrictions

- All additional strengths need to be manufactured using the same manufacturing process as that used for the test lot used in the in vivo BE study.
- Additional strengths are evaluated based on comparability of in vitro dissolution to the biobatch of the test product (additional considerations for the acceptability of situations that may warrant comparisons to the corresponding innovator strength are currently under discussion).

# Biowaiver limitations and restrictions

- The formulations of the strengths undergoing the biowaiver process need to contain the same formulation (active and inactive ingredients) and in the same proportion as that of the lot used to support in vivo BE.

Point to Ponder: What in vitro dissolution tests cannot reveal about potential excipient effects




Martinez, M.N., Sinko, B., Wu, F. *et al.* A Critical Overview of the Biological Effects of Excipients (Part I): Impact on Gastrointestinal Absorption. *AAPS J* **24**, 60 (2022). https://doi.org/10.1208/s12248-022-00711-3

Hopefully, a VICH Biowaiver Guideline will soon be ready for circulation and public comment.

https://unsplash.com/photos/man-standing-on-stone-looking-at-sunset-ICE__bo2Vws

Thank you for your attention.

Questions?

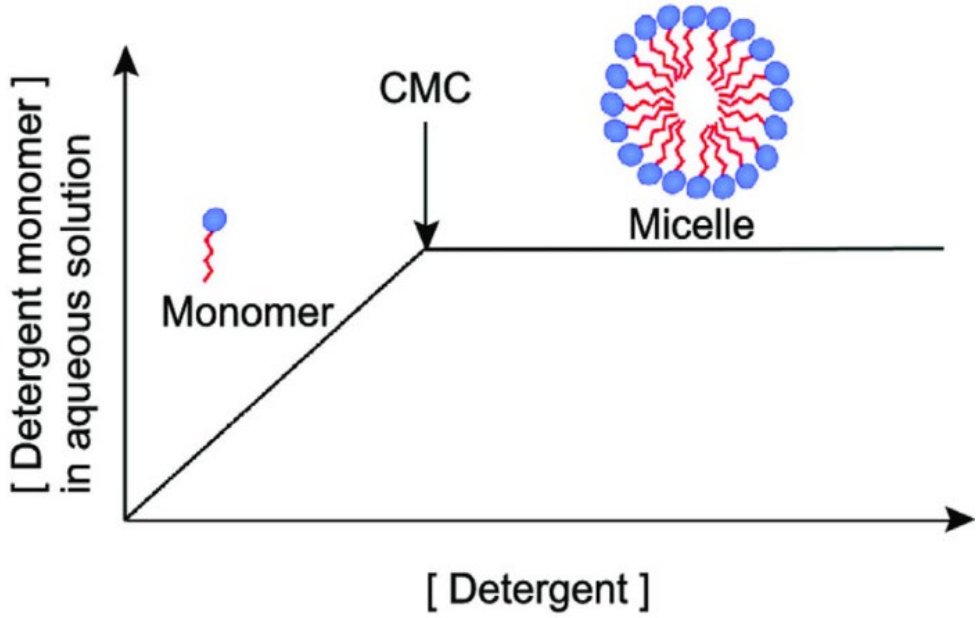
# Information about surfactants

Fotaki et al., 2013
surfactants

- The effect of pH on the micellar solubilization of a nonionic surfactant depends solely on the ionization properties of the solubilizate.
- Unionized solubilizates are expected to partition into micelles more favorably than ionized solubilizates.
- The effect of pH on the micellar solubilization by an ionic surfactant will depend on the pKa of the surfactant and the ionization properties of the solubilizate. As the pH decreases towards the pKa of an ionic surfactant, it becomes less soluble, resulting in a lowering of its Critical Micellar Concentration (CMC).
- Generally, the CMC of ionic surfactants is lowered when concentration of dissolved ions is increased.

# What is CMC

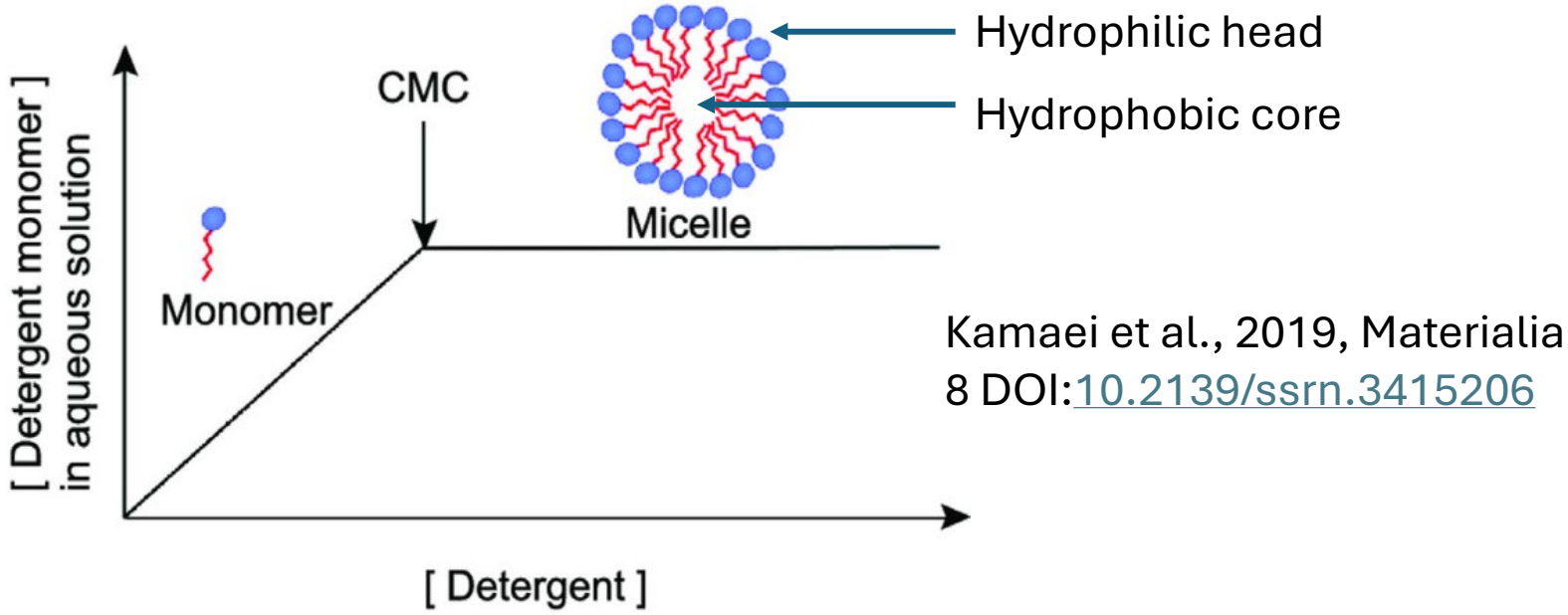
CMC is the concentration of a surfactant in a solution at which micelles begin to spontaneously form . Below the CMC, surfactant molecules exist as individual units (monomers) in the bulk solution or at the surface. Above the CMC, any additional surfactant will self-assemble into micelles to reduce free energy.




Kamaei et al., 2019,
Materialia 8
DOI:10.2139/ssrn.3415206

# What is CMC

- **Enhanced solubilization of hydrophobic molecules**: Micelles have hydrophobic cores that can encapsulate poorly water-soluble drug molecules. This greatly increases the apparent solubility of a drug in the aqueous medium.
- **Enhanced dissolution:** The formation of micelles and subsequent solubilization of the drug within them leads to a substantial increase in the drug's overall solubility and dissolution rate.




Kamaei et al., 2019, Materialia 8 DOI:10.2139/ssrn.3415206

Basic –ionized at lower pH. Expect lower CMC at lower pH

Acidic –ionized at higher pH – expect lower CMC at higher pH

USP <1092>

**Table 1. Commonly Used Surfactants with Critical Micelle Concentrations**

| Surfactant | | CMC (% wt/volume) | Reference |
|---|---|---|---|
| Anionic | Sodium dodecyl sulfate (SDS), Sodium lauryl sulfate (SLS) | 0.18%–0.23% | *(2–4)* |
| | Taurocholic acid sodium salt | 0.2% | *(3)* |
| | Cholic acid sodium salt | 0.16% | *(3)* |
| | Desoxycholic acid sodium salt | 0.12% | *(3)* |
| Cationic | Cetyltrimethyl ammonium bromide (CTAB, Hexadecyltrimethylammonium bromide) | 0.033%–0.036% (0.92–1.0 mM) | *(5,6)* |
| | Benzethonium chloride (Hyamine 1622) | 0.18% (4 mM) | *(2)* |
| Nonionic | Polysorbate 20 (Polyoxyethylene (20) sorbitan monolaurate, Tween 20) | 0.07%–0.09% | *(3,7)* |
| | Polysorbate 80 (Polyoxyethylene (20) sorbitan monooleate, Tween 80) | 0.02%–0.08% | *(3,7)* |
| | Caprylocaproyl polyoxyl-8 glycerides (Labrasol) | 0.01% | *(4)* |
| | Polyoxyl 35 castor oil (Cremophor EL) | 0.02% | *(8)* |
| | Polyoxyethylene 23 lauryl ether (Brij 35) | 0.013% | *(9)* |
| | Octoxinol (Triton X-100) | 0.01%–0.03% | *(3,10)* |
| Zwitterion | Lauryldimethylamine *N*-oxide (LDAO) | 0.023% | *(11)* |