Considerations for additional strength waivers of MR products

James E Polli

June 4, 2025

Topics

- Proportionally similar
  - BE Guidance (Aug 2021) and M13B Guidance
  - Carbatrol example
- Slower release is expected from higher strength diffusion-controlled matrix
- Questionnaire
- Future research

Terms from Aug 2021 FDA Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA Guidance for Industry

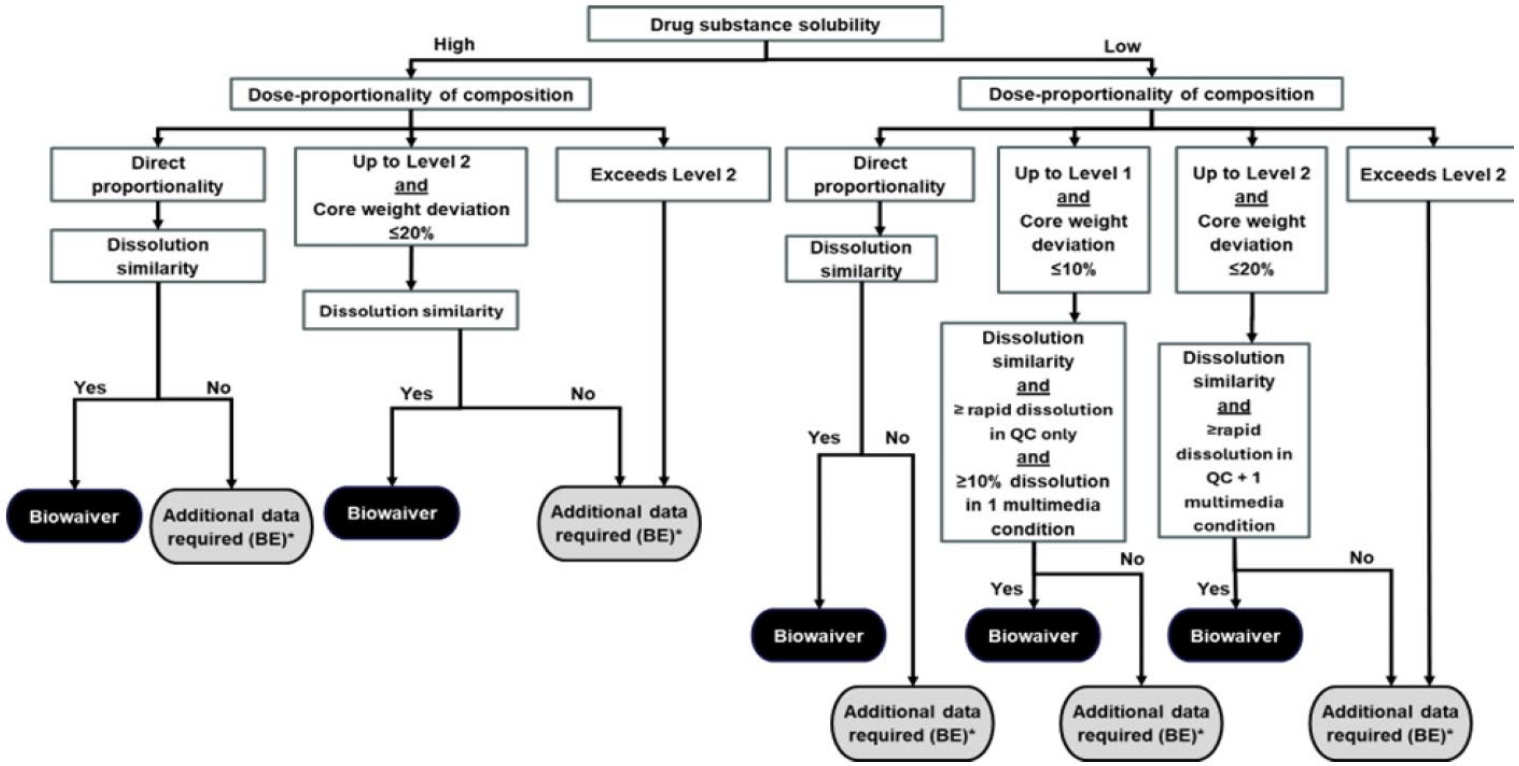
- proportionally similar - All active and inactive ingredients are in similar proportion between different strengths
- Active and inactive ingredients that are not in similar proportion between different strengths can be considered proportionally similar with adequate justification.

M13B (13 March 2025): IR additional strengths biowaivers

- Direct proportionality - each strength contains the same ingredients in the same proportion
- Deviations from direct proportionality for core composition between strengths can be considered as exceptions with appropriate scientific justification (see Annex I).
- High potency Drug Products - only the amount of drug substance is changed; or, amount of diluent/filler varies to account for the change in the amount of drug substance

M13B (13 March 2025): IR additional strengths biowaivers

Figure 2: Decision tree to determine the possibility of a biowaiver for non-high-risk products*



Factors:

Dose proportionality in PK

Drug solubility

Formulation proportionality

Dissolution profile similarity

Rapid dissolution

High potency drug product

2.1 PK Dose Proportionality of the Drug

Deviations from the recommendations in this guideline may be acceptable …

M13B (13 March 2025): IR additional strengths biowaivers

- Bracketing needed when:
- Dissolution dissimilarity between strengths;
- Deviations from direct proportionality in core composition exceeding those described in Annex I; or
- Non-dose proportional PK

M13A (Oct 2024): IR additional strengths biowaivers

- "In general, PK can be considered dose proportional if the difference in dose-adjusted mean Cmax and AUC is no more than 25% when comparing the range of strengths proposed. For the purpose of an additional strength waiver, AUC and Cmax are evaluated … [S]hould the available data establish dose proportional PK for AUC but the available data for Cmax are insufficient, … the PK can be treated as dose proportional."

Carbatrol

- Carbamazepine extended-release capsules
- 100mg, 200mg, and 300mg strength differ only in number of beads
  - Beads involve fixed ratio of IR, ER, and enteric-release beads
- The pharmacokinetics of extended-release carbamazepine is linear over the single dose range of 200-800 mg. (label)
- Following multiple dosing of extended-release carbamazepine (800-1600 mg daily for 14 days), the AUC and Cmax of carbamazepine-10,11-epoxide were dose related … (label)
- The bioequivalence study for MR product was performed between 2*300mg and 3*200mg capsules. Both these strengths were found to be bioequivalent. (Drugs@FDA)

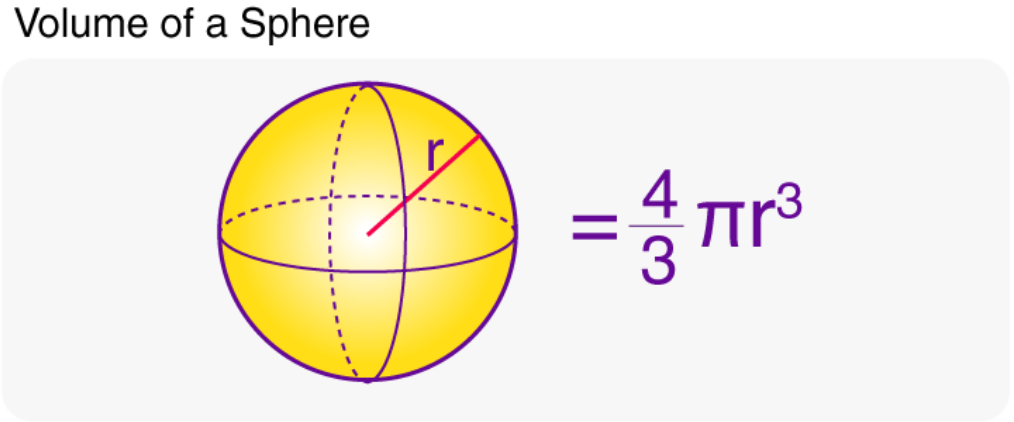
Clearance and dose

- Autoinduction is completed after 3-5 weeks … (Tegretol label)

- At steady-state, clearance is related to dose
  - Higher Cl/F was associated with higher total daily dose
  - Kong ST, et al. Estimation and comparison of carbamazepine population pharmacokinetics using dried blood spot and plasma concentrations from people with epilepsy: the clinical implication. J Clin Pharmacol. 2014 Feb;54(2):225-33. doi: 10.1002/jcph.170.
  - Yip VLM, et al. Evaluation of clinical and genetic factors in the population pharmacokinetics of carbamazepine. Br J Clin Pharmacol. 2021 Jun;87(6):2572-2588. doi: 10.1111/bcp.14667.

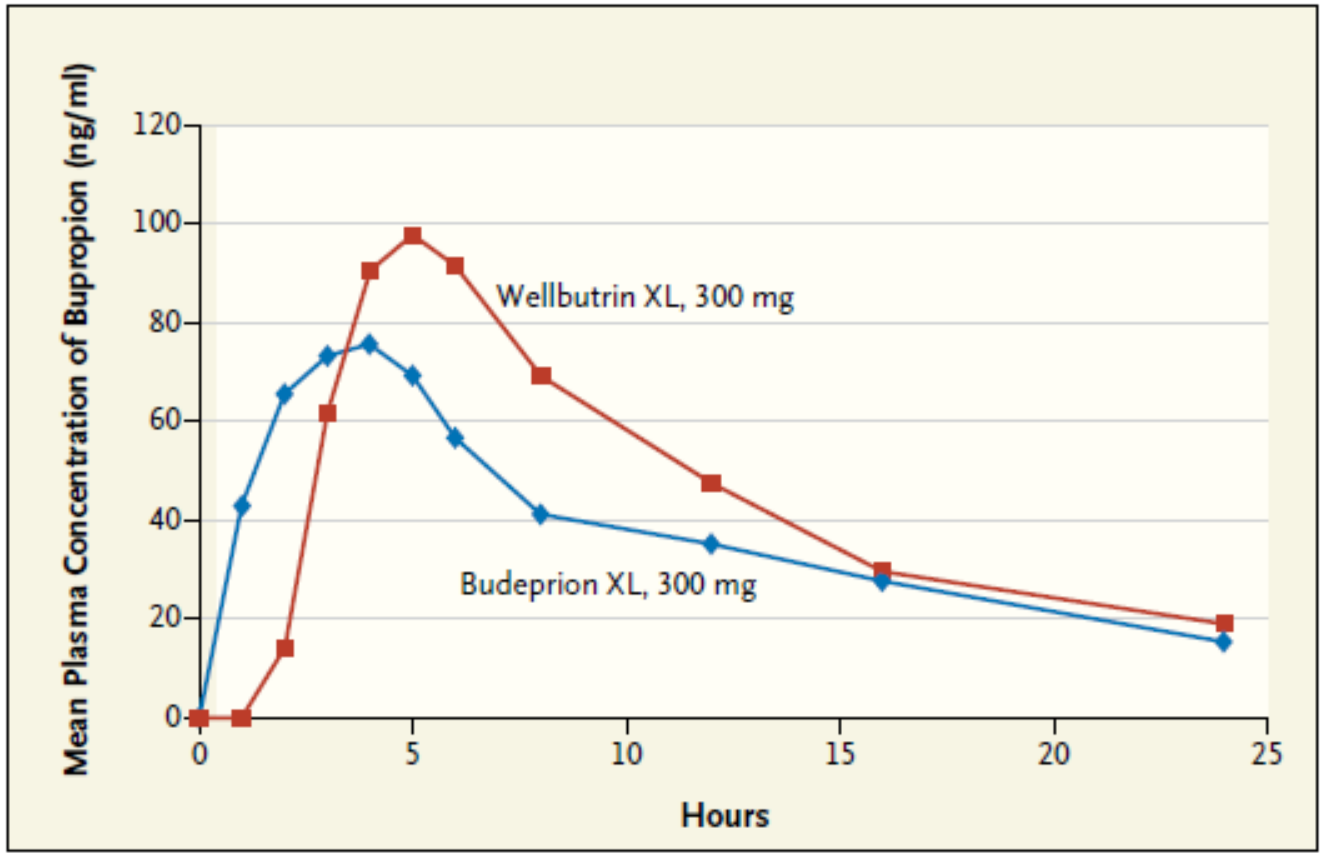
(Relatively) Slower release is expected from higher strength diffusion-controlled matrix

- “Twice the powder” approach for diffusion-controlled matrix is not a perfect target.



- Diffusion of drug occurs across distance.
- A 2x strength achieved via “twice the powder” of 1x strength will have longer diffusional distance (on average).

Withdrawal of Generic Budeprion for Nonbioequivalence



Mean Plasma Concentration of Bupropion (Budeprion XL and Wellbutrin XL) as a Function of Time in 24 Fasting Healthy Volunteers.

Test was proportionally formulated
(i.e. 300mg test was twice the 150mg powder)

Woodcock J, Khan M, Yu LX. Withdrawal of generic budeprion for nonbioequivalence. N Engl J Med. 2012;367(26):2463-5. doi: 10.1056/NEJMp1212969.

Survey

- Waiver of in vivo BE of lower strength products for proposed ANDA products that are oral, modified release
- May 6 2025 to May 27 2025; anonymous
- N=39-62 respondents to any one question
- Common respondent was scientist at generic company that also develops innovator products. 64% had over 10 years “MR formulations/bioequivalence” experience.

Factors

Factor	Interpretation
Dose proportionality of reference across reference product strengths.	✓ - Yes, dose proportionality of reference across reference product strengths, by either: a) “consistent bioavailability across strengths”, b) “linear PK”, or c) highest and lowest strengths of test being in vivo BE to reference. × - No, since none apply.
Same mechanism of release between test and reference	✓ - Yes × - No
Qualitatively and quantitatively the same rate-controlling excipient between test and reference (i.e. Q1/Q2)	✓ - Yes, Q1/Q2 for rate-controlling excipient × – No, Q1 but only Q2 similar (i.e. within 5-10%) and not Q2 same (i.e. not 5% or less)
Qualitatively the same rate-controlling excipient between test and reference (i.e. Q1)	✓ - Yes, Q1, but not within 10% quantitatively × – No, not Q1
High prior experience of test formulation technology by test development team	✓ - Yes, high prior experience × - No
Dissolution similarity between test and reference	✓ - Yes, dissolution similarity between test and reference × - No
Dissolution similarity of test formulations across test strengths	✓ - Yes, dissolution similarity of test formulations across test strengths × - No

Scenarios

- Assume
  - Test and reference are pharmaceutically equivalent
  - Test has demonstrated in vivo BE to reference for highest strength
- Scenario A: All good.
- Scenario B involves 6 situations, where one factor differs.
- Scenario C involves 5 situations, where test is a tablet (like reference) but involves MR beads (unlike reference). Hence, in all 5 situations, the mechanism of release differs between test and reference, along with progressively other differences.
- Scenario D is just like scenario C, but test involves any mechanism of release (i.e. not limited to beads).

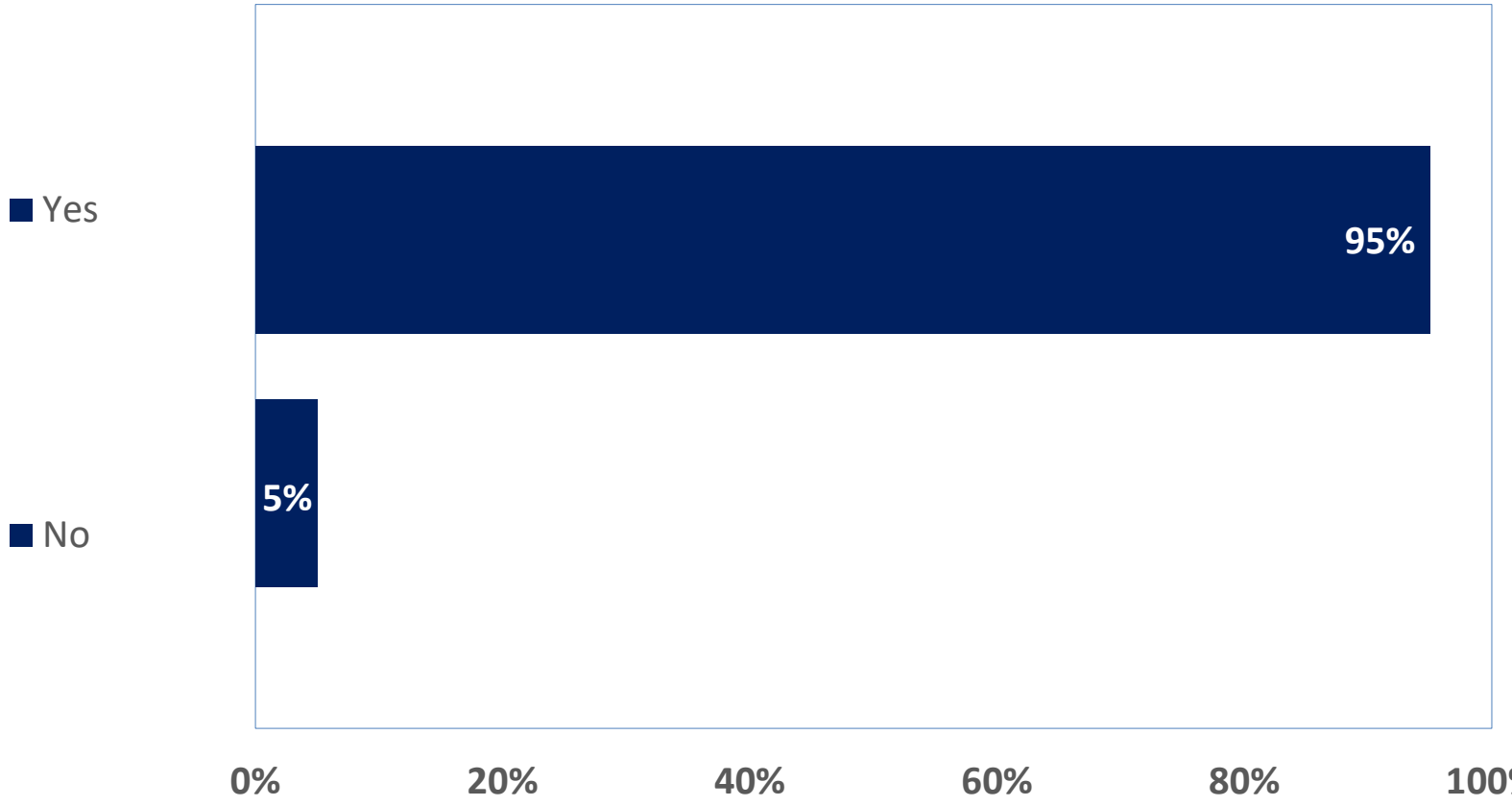
Percent responded “No” or “Uncertain” to biowaiver

Scenario A (no problems) – 13% No or Uncertain to biowaiver

Problem factor	Scenario B (same mechanism)	Scenario C (test is MR bead, a diff mechanism)	Scenario D (a diff mechanism)
Different mechanism	-	47%	45%
Dose proportionality of reference across reference product strengths	54%	-	-
Q1 but only Q2 similar	46%	55%	60%
Not Q1	67%	62%	67
Dissolution similarity between test and reference	71%	80% (and not Q1)	85% (and not Q1)
High prior experience of test formulation technology by test development team	32%	85% (and not Q1 and not Dissolution similarity between test and reference)	87% (and not Q1 and not Dissolution similarity between test and reference)
Dissolution similarity of test formulations across test strengths	80%	-	-

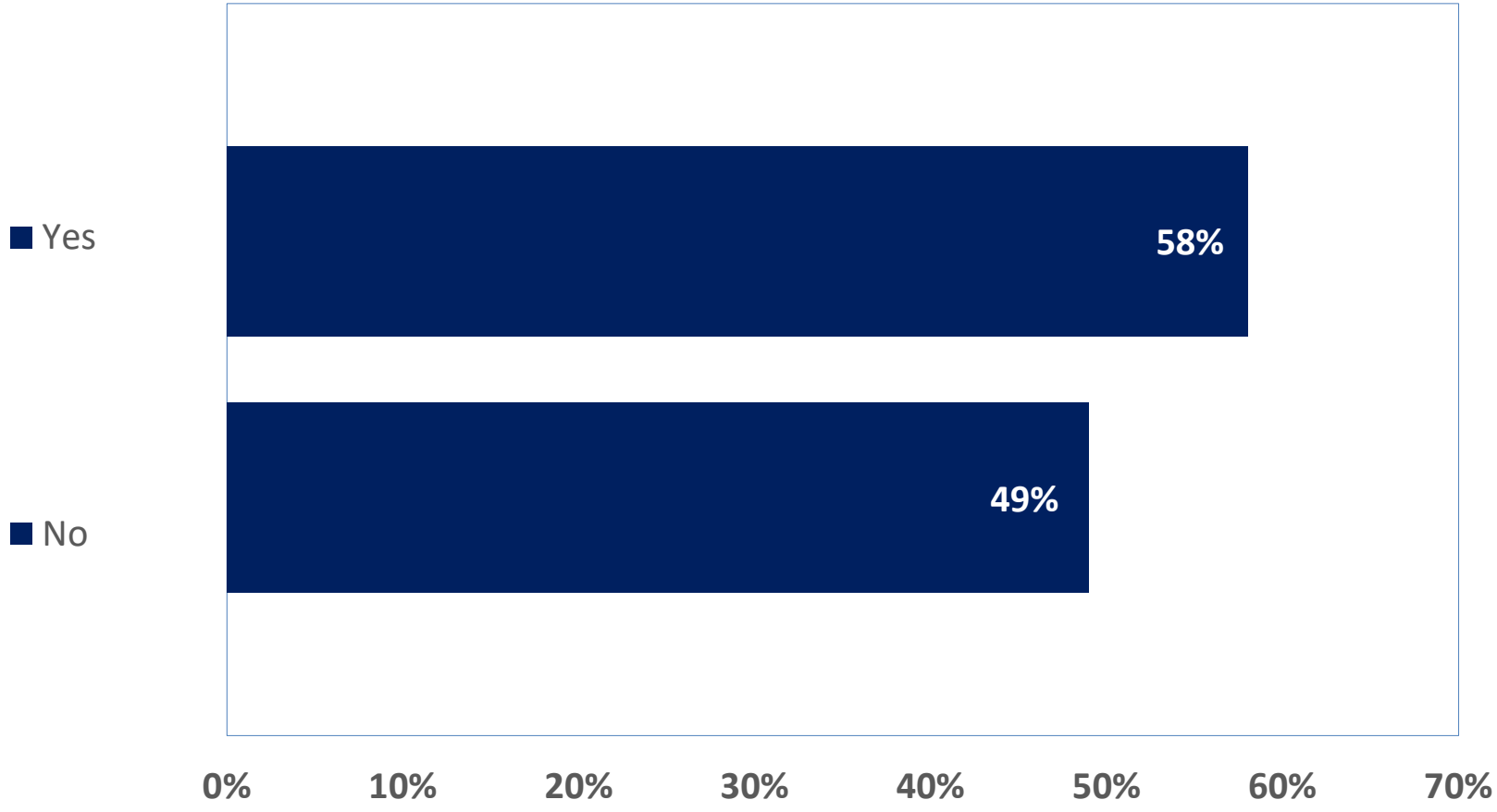
A test capsule formulation is composed of MR beads. Lower strengths use the same beads at the highest strength, but just fewer MR beads, and otherwise identical to the highest strength. There is dose proportionality of reference across reference product strengths.

Do you agree that a waiver of in vivo BE of lower strength test products is appropriate?



39 respondents

A test tablet formulation is an HPMC-based matrix system. Using the identical final blend, strengths are obtained via only using different amounts of the final blend. Do you agree that a waiver of in vivo BE of lower strength products is likely inappropriate?



39 respondents

Summary

- 13% always reply “No” or “Uncertain” to biowaiver
- 13% always reply “Yes” to biowaiver

- Several individual factors (if not present) caused biowaiver concerns (in order of concern):
  - Not dissolution similarity of test formulations across test strengths
  - Not dissolution similarity between test and reference
  - Not Q1
  - Not dose proportionality of reference across reference product strengths
  - Different mechanism = Q1 but only Q2 similar

Future research

- Reference product: Linear drug PK and/or consistent bioavailability across strengths