Establishing Bioequivalence for "Additional Strengths" of Oral Modified-Release Drug Products

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Session Description and Objectives

- Points to consider for establishing bioequivalence (BE) for “additional strengths” of oral modified-release (MR) drug products
- Case example 1: Bupropion hydrochloride (HCl) Extended Release (ER) tablets
- Case example 2: Venlafaxine HCl ER tablets
- Take-Away and Further Discussions

Biography and Contact Information

- Received Ph.D. in Pharmaceutical Sciences
- Research scientist and reviewer for the Office of Research and Standards, Office of Generic Drugs at FDA
- Special research topics of interest include generic equivalency of oral, modified release pharmaceutical products

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Disclaimer

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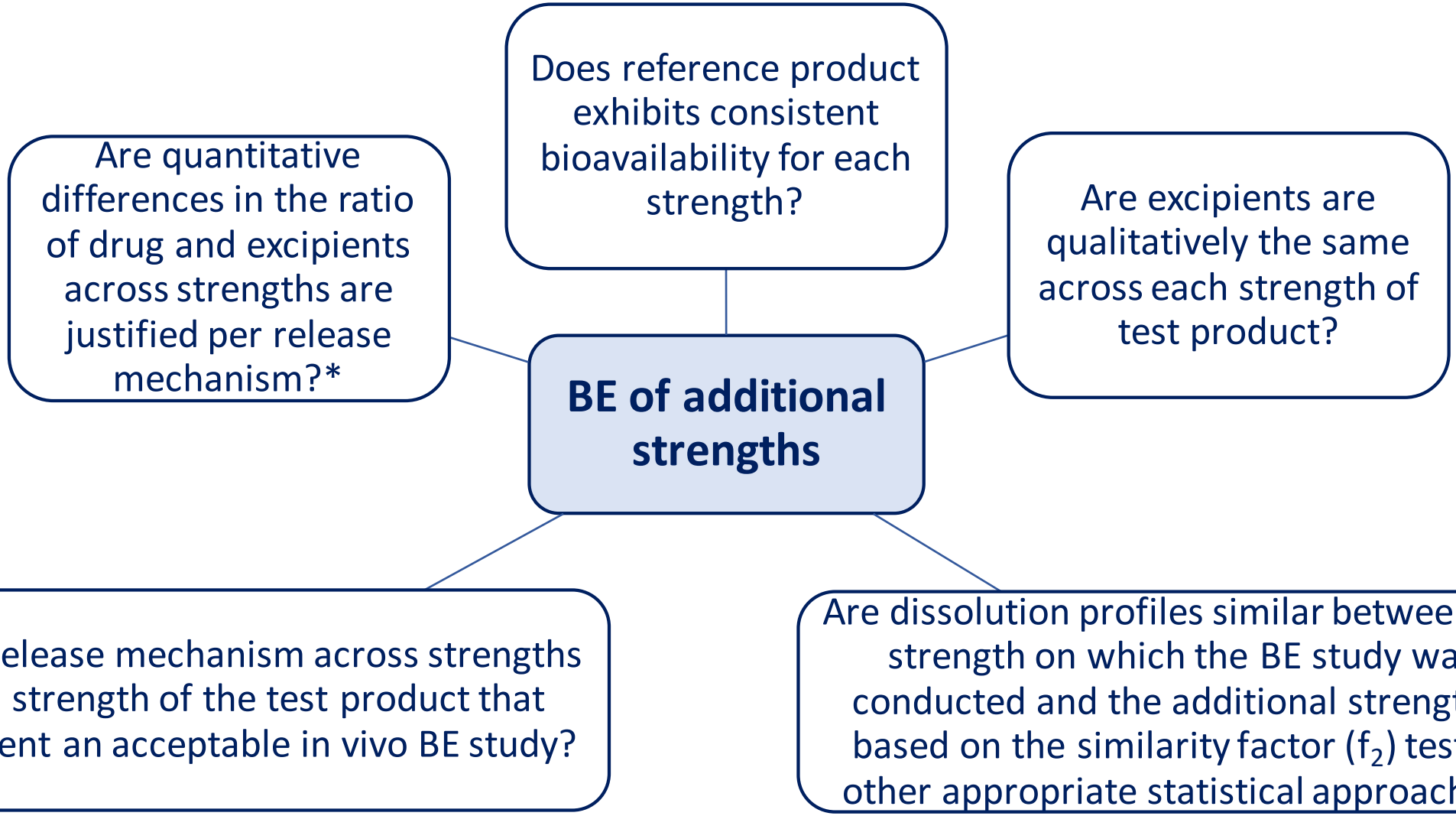
Points to consider for assessing BE of additional strengths of MR products



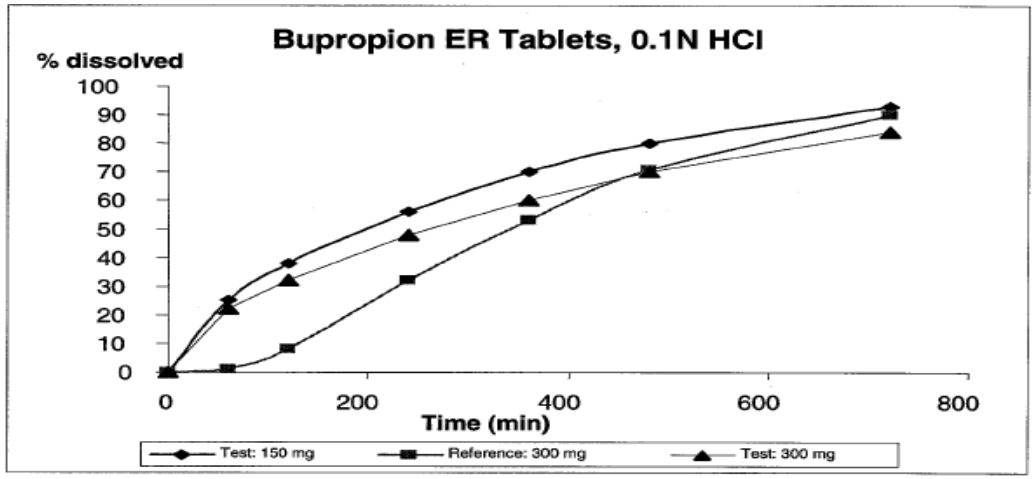
www.fda.gov *There may be instances in which an in vivo BE study for non-proportionally formulated strengths is necessary to demonstrate BE

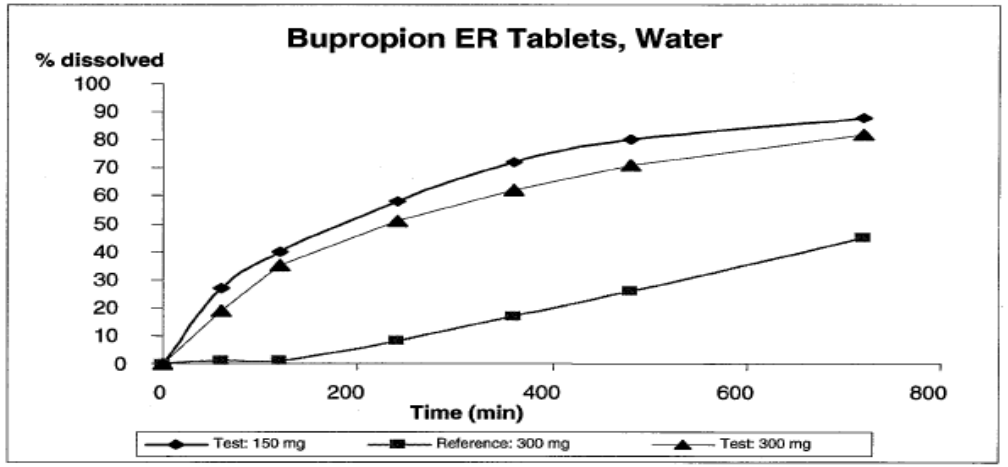
Case example 1: Generic bupropion HCl ER tablets

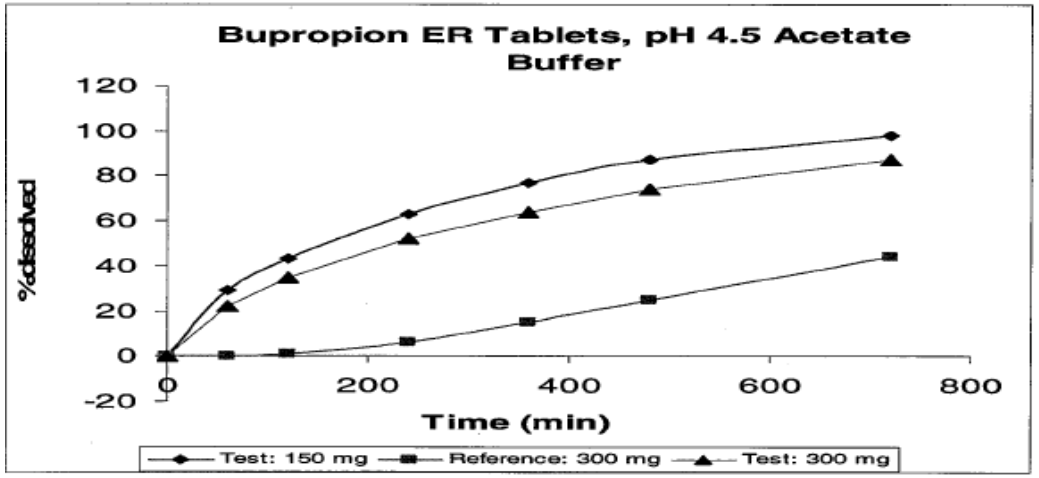
- Tablets provide for once a day dosing
- bupropion HCl ER generic product[1]:
  - was designed as a “sustained release matrix” tablet system
  - the 150 mg and 300 mg strengths were determined to be proportional in composition across strengths
- The corresponding reference product[2]:
  - A diffusion controlled tablet system. Tablet core surrounded by coatings that form a membrane that controls drug release
  - The 150 mg and 300 mg strength tablets weigh approximately 190 mg and 360 mg, respectively
  - Consistent bioavailability was shown between the 150 mg and 300 mg strength (2 tablets of 150 mg equivalent to 1 tablet of 300 mg)
- The 150 mg test product was recommended for the in vivo BE study while using alternative methods, in lieu of the in vivo BE study, to support BE of the 300 mg strength was acceptable due to safety concerns with the 300 mg strength in healthy subjects

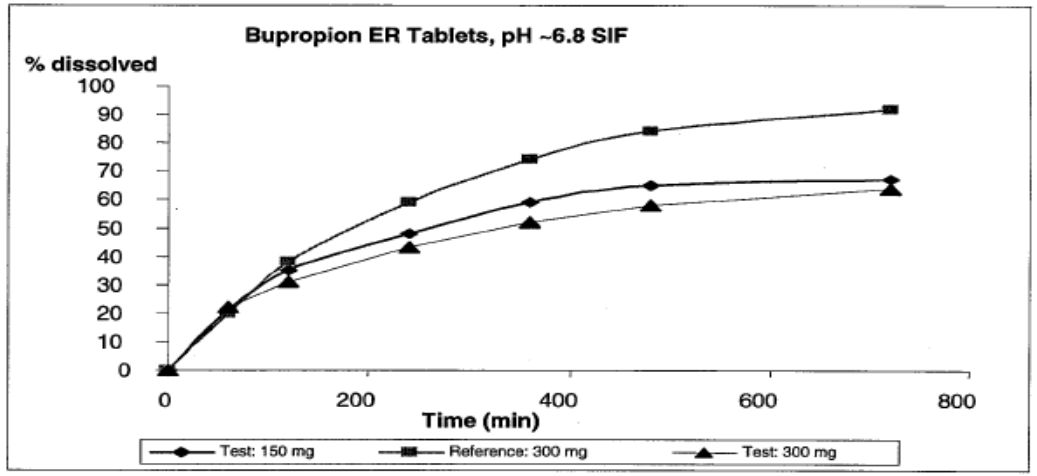
1. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/077415.pdf
2. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/021515_Wellbutrin_biopharmr.PDF

150 mg test product demonstrated similar but faster dissolution than the 300 mg test product









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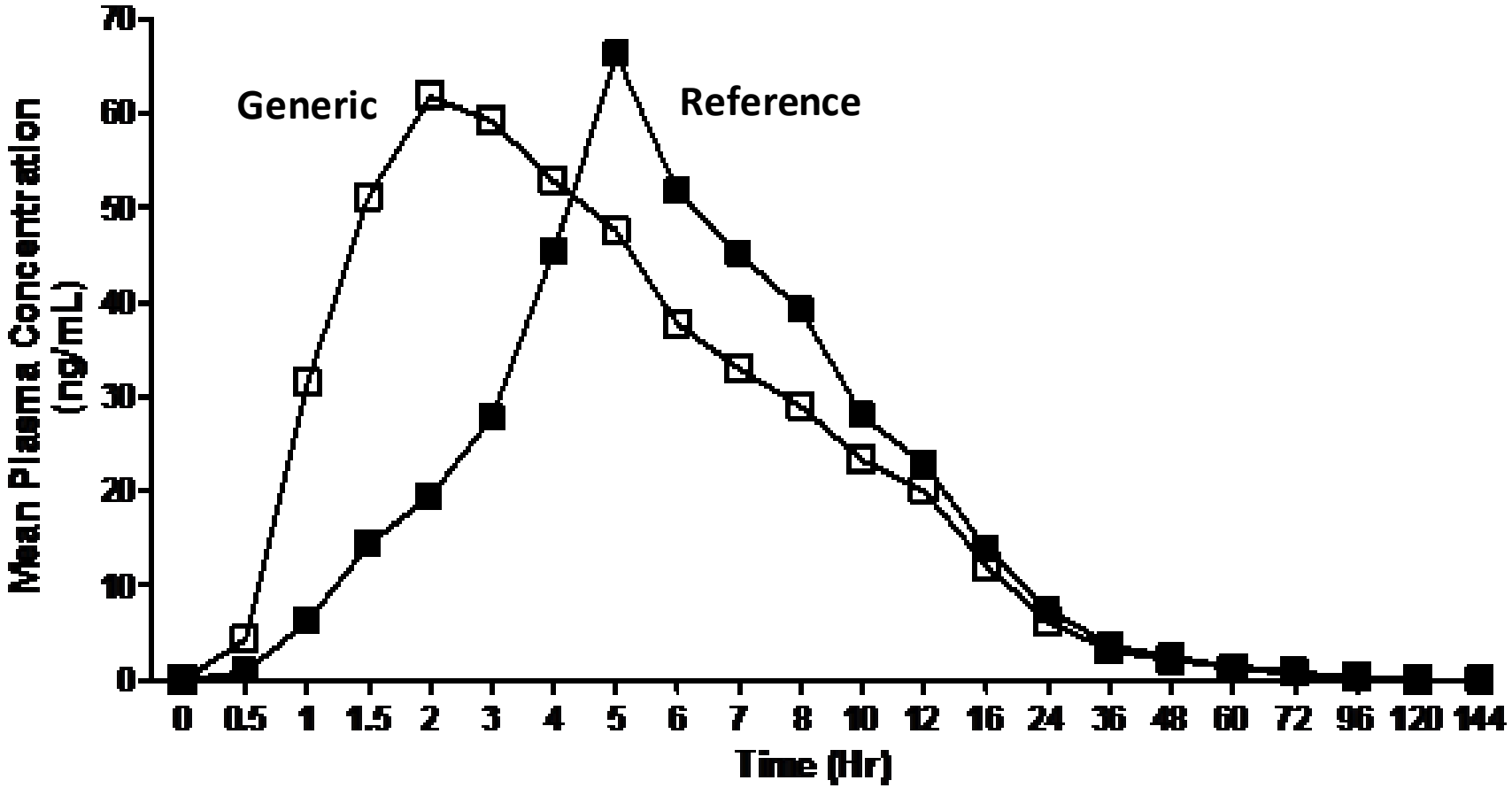
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/077415.pdf

150 mg generic strength is BE to the reference 150 mg strength



www.fda.gov https://wayback.archive-it.org/org1137/20170406044711/https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm153270.htm

A waiver for the 300 mg strength was granted based on acceptable studies with the 150 mg strength

- A single dose, fasting BE study on the generic bupropion HCl ER tablets, 150 mg strength compared to the reference product 150 mg strength was found acceptable.
- A single dose, non-fasting BE study on the generic bupropion HCl ER 150 mg tablets compared to the reference product 150 mg strength was found acceptable.
- The in vitro dissolution testing conducted on the generic bupropion HCl ER 150 mg and 300 mg tablets was found acceptable.
- The generic bupropion HCl ER formulation for the 150 mg strength was found compositional proportional to the generic 300 mg strength.
- The in vivo BE testing for the 300 mg strength was waived based on the criteria outlined above.

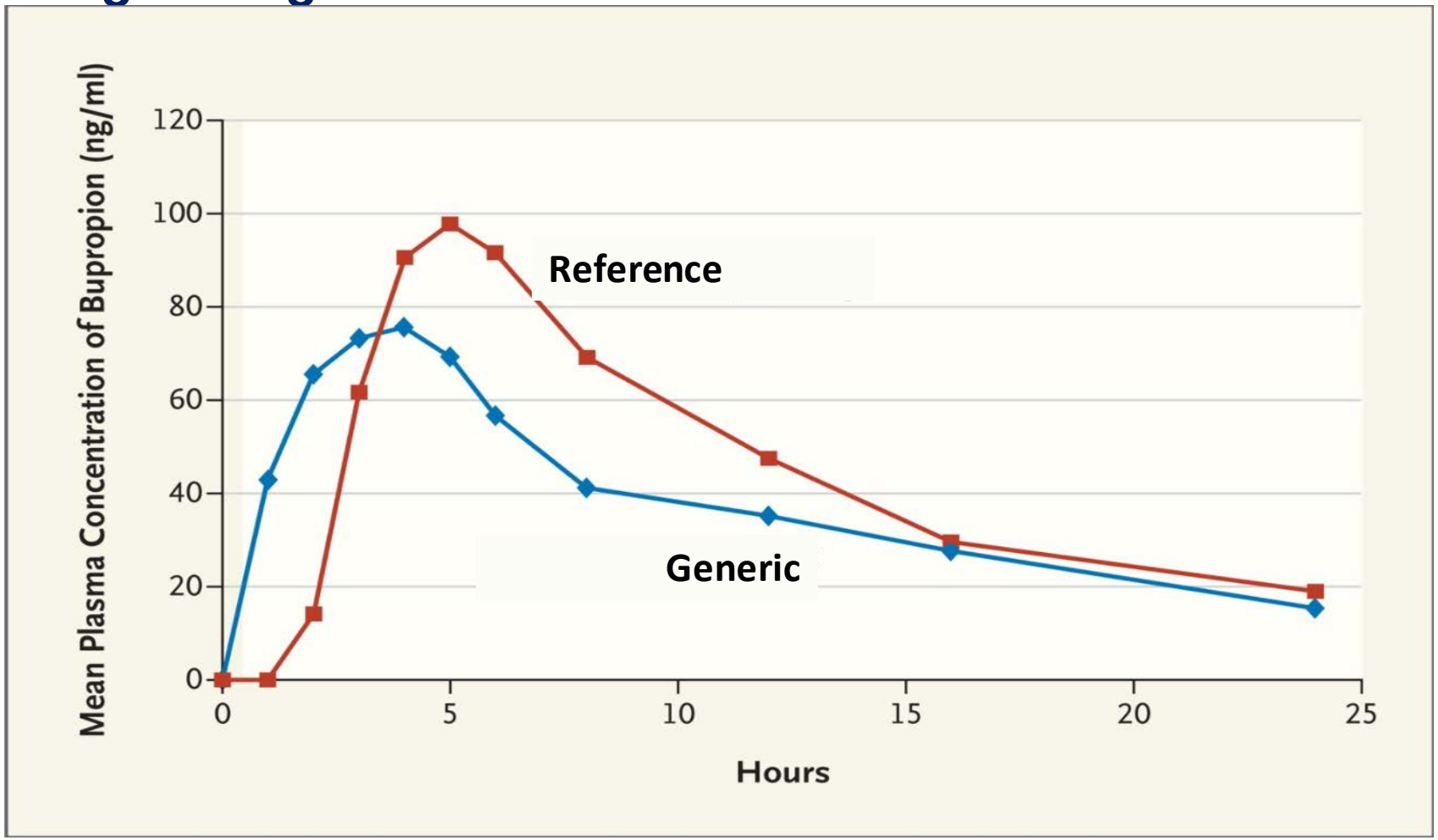
www.fda.gov https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/077415.pdf

FDA received post marketing reports shortly after the generic product approval

- Between January 1 and June 30, 2007, FDA received 85 post-marketing reports describing either adverse events or lack of an effect after switching from the 300 mg reference product to the 300 mg generic product.
- November 2007, the FDA requested that the applicant for the product conducted a BE study directly comparing their 300 mg generic product to the 300 mg reference product in patients who reported issues with switching.
- The applicant terminated the study in late 2011, reporting that despite efforts to enroll patients, they were unable to recruit a significant number of affected patients.
- In 2010, because of the public health interest in obtaining BE data, FDA decided to sponsor a BE study comparing the generic product 300 mg to the reference product 300 mg in healthy subjects.

www.fda.gov https://wayback.archive-it.org/org1137/20170406044709/https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm322160.htm#q5

FDA BE study shows the 300 mg generic strength is not BE to the reference product 300 mg strength



Janet Woodcock, M.D., Mansoor Khan, R.Ph., Ph.D., and Lawrence X. Yu, Ph.D. "Withdrawal of Generic Budeprion for Nonbioequivalence." N.Engl J. Med. Dec 27, 2012. DOI: 10.1056/NEJMp1212969

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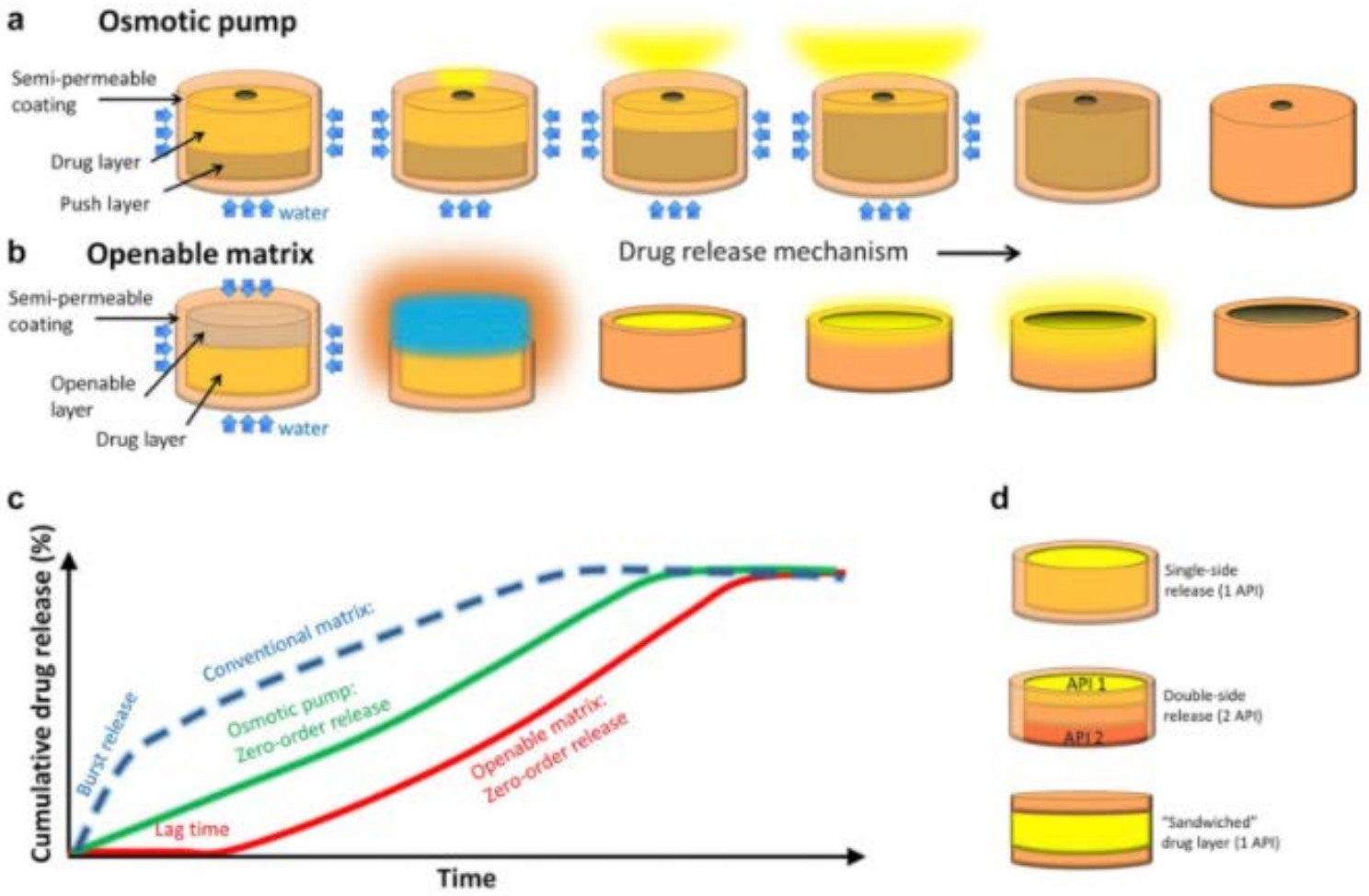
Case example 2: Venlafaxine HCl ER tablets

- A venlafaxine HCl ER generic product is designed as an "openable matrix" or "wrap matrix"[1]
  - Core bilayer tablet coated with a mixture of soluble and insoluble pore forming excipients
  - Zero order release controlled by constant surface area of drug layer
  - Onset of matrix breakage (lag time) is dependent on composition and thickness of functional coating and openable layer
- The corresponding reference product is an osmotic pump[2]
  - Only the 75, 150 mg and 225 mg strengths are proportional in composition. The 37.5 mg strength is not proportional in composition to the other strengths.[3]
  - Solubility and osmotic pressure of the core components
  - Size of delivery orifice
  - Rate-controlling membrane

1. Ho-Pi Lin, Dajun Sun, Xinyuan Zhang, Hong Wen. "Physiological Based Pharmacokinetic Modeling for Substitutability Analysis of Venlafaxine Hydrochloride Extended-Release Formulations Using Different Release Mechanisms: Osmotic Pump Versus Openable Matrix." J. Pharm. Sci. Vol. 105 (10). Oct 2016. 3088-3096.
2. Rajan Verma, Divi Murali Krishna, Sanjay Garg. "Formulation aspects in the development of osmotically controlled oral drug delivery systems. J. Controlled Release. Vol. 79 (1-3). Feb 2002. 7-27.
3. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/022104s000_ClinPharmR.pdf

Drug release from osmotic pumps and openable matrix system not dependent on composition proportionality



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In silico simulations show that formulation differences with different T_{lag} are predicted to be BE to a 0 h T_{lag}

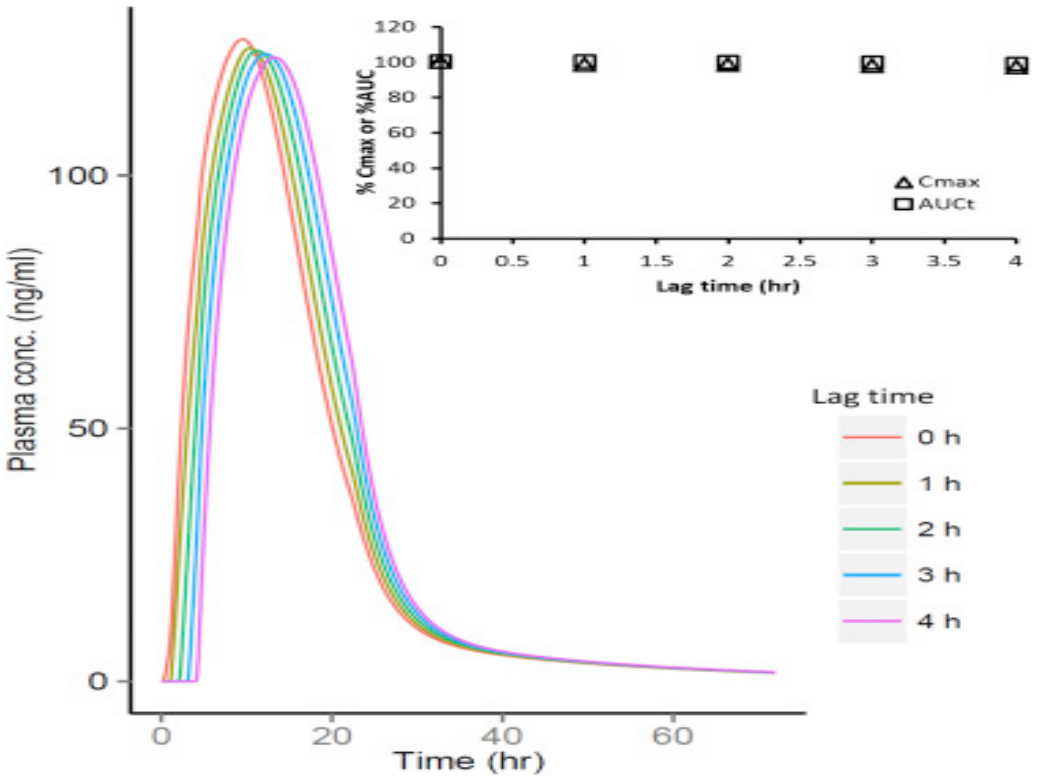

Table 3. Three-Dimensional PSA Using a Lag Time of 0, 1, 2, 3, and 4 h (First Dimension) Against Various Input Parameters (10 Test Conditions With a Uniform Spacing; Second Dimension) With Total of 50 Combinations Per Pair of Parameters

Second Dimension	First Dimension	
	Lag Time of 1, 2, 3, and 4 h/Lag Time 0 h	
	Cmax (%)	AUC_t (%)
0.1-10X Vc	93-100	96-100
0.1-10X k_{12}	93-102	97-100
0.1-10X k_{21}	93-100	97-100
0.1-10X k_{13}	96-99	97-100
0.1-10X k_{31}	97-99	99-100
0.1-10X Vmax (gut)	94-101	95-103
1-10X Km (gut)	95-105	96-110
0.2-17X Vmax (liver)	87-99	95-99
0.1-10X Km (liver)	97-100	97-100
Plasma unbound (1%-100%)	97-101	96-100
0.5-10X blood plasma ratio	96-100	98-100
Hepatic flow (0.25-2.5X)	96-99	98-100
Stomach empty time (0.5-10 h)	86-112	96-100
0.1-10X P_{eff}	93-99	95-100

For any particular test condition in second dimension, simulated Cmax or AUC_t were compared to those generated from the conditions paired with a 0-h lag time. The range of %Cmax and %AUC_t (minimum and maximum out of 40 results per pair of parameters) were reported in the table.

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Ho-Pi Lin, Dajun Sun, Xinyuan Zhang, Hong Wen. "Physiological Based Pharmacokinetic Modeling for Substitutability Analysis of Venlafaxine Hydrochloride Extended-Release Formulations Using Different Release Mechanisms: Osmotic Pump Versus Openable Matrix." J. Pharm. Sci. Vol. 105 (10). Oct 2016. 3088-3096.

Conclusions

- The case of bupropion HCl ER tablets illustrates compositional proportionality across strengths does not guarantee equivalent performance to reference product.
- The case example of venlafaxine HCl ER tablets shows that complicated dosage forms like openable matrix systems are dependent on drug layer surface area and thickness of openable layer.
- Whether a product is considered compositional proportional or not, additional justification related to the proposed product release mechanism and excipient levels should be provided to use alternative methods to support BE for additional strengths under 21 CFR 320.24(b)(6).
- De-emphasizing compositional proportionality across strengths provides flexibility to develop challenging generic MR products.

Take-Away

Scientific data suggest that less emphasis should be placed on compositional proportionality as justification to use alternative methods to support BE for additional strengths of modified release products under 21 CFR 320.24(b)(6).

Join us for the full AAPS webinar!

- ❑December 10, 2020
- ❑More case examples
- ❑More detailed discussions

Acknowledgments

Office of Generic Drugs

- Office of Research and Standards
  - Modified Release Team
    - Heather Boyce
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Questions

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