Complex Molecules and Formulations

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Axiom of Bioequivalence:

- Once in the systemic circulation, Identical molecules have the same action and disposition regardless of the manufacturing source.
- The body recognizes the molecule not the manufacturer of the molecule.
- Originator, **Health Canada**
- **AUC and Cmax**

Subsequent Additions:

- Controlled-release
- Narrow therapeutic index drugs
- High variability in PK
- Chemically unidentical molecules
- Some Complex formulations (e.g., partial AUC).
- BCS biowavers
- etc.

… and will constantly evolve.

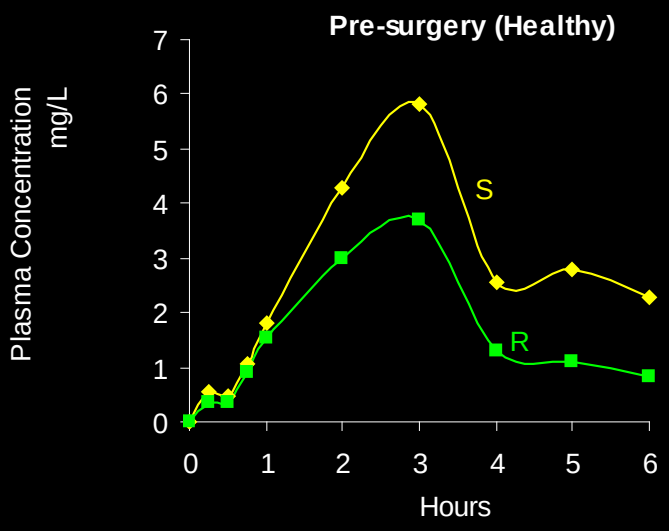
Examples not covered in this workshop:

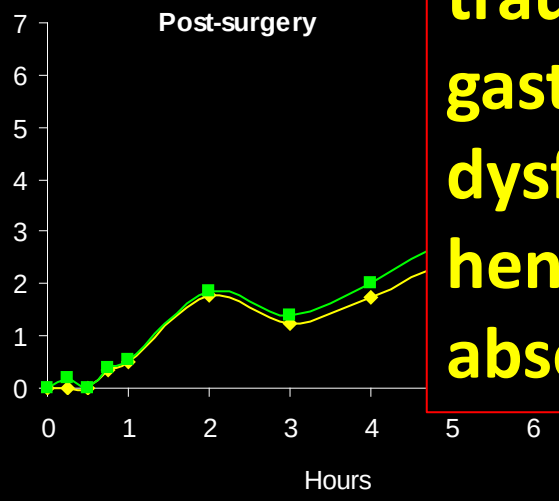
- Extremely variable products
- Formulation that are influenced by gastric function;
  - Protection from GI pH
  - Quick acting drugs (e.g., analgesics)

Drug Absorption and Pain: Ibuprofen

Jamali & Kunz-Dober Br J Clin Pharmacol 47:391-6, 1999

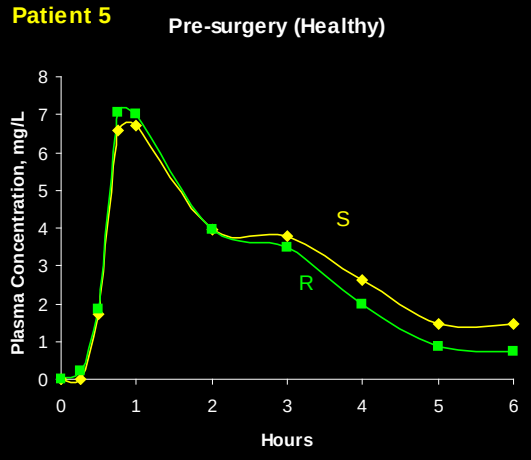
Patient 1

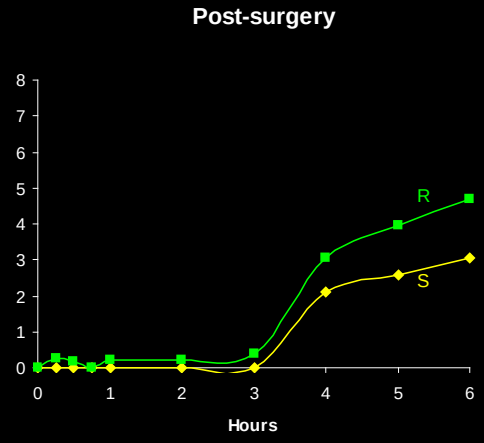




Pain and/or trauma cause gastric dysfunction, hence, reduced absorption!

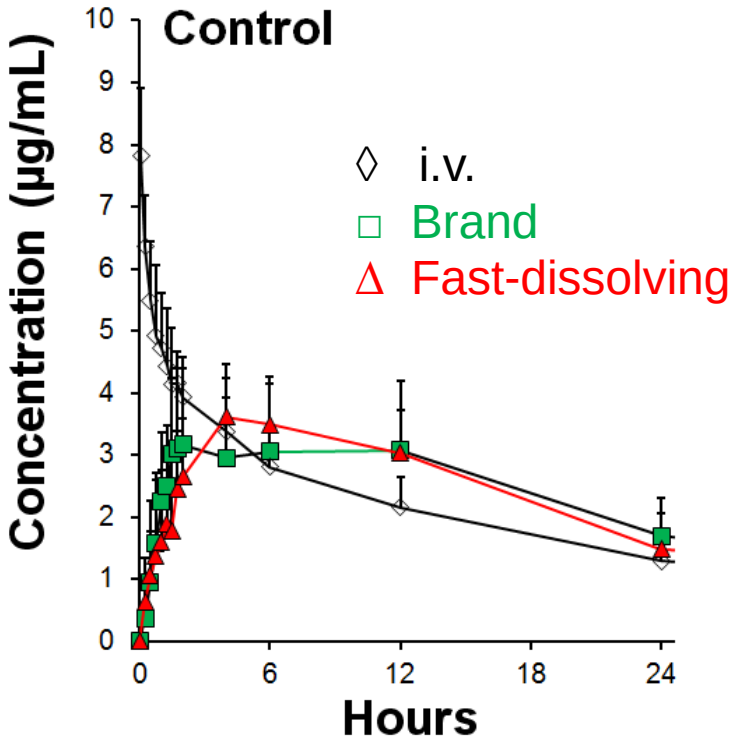
Patient 5

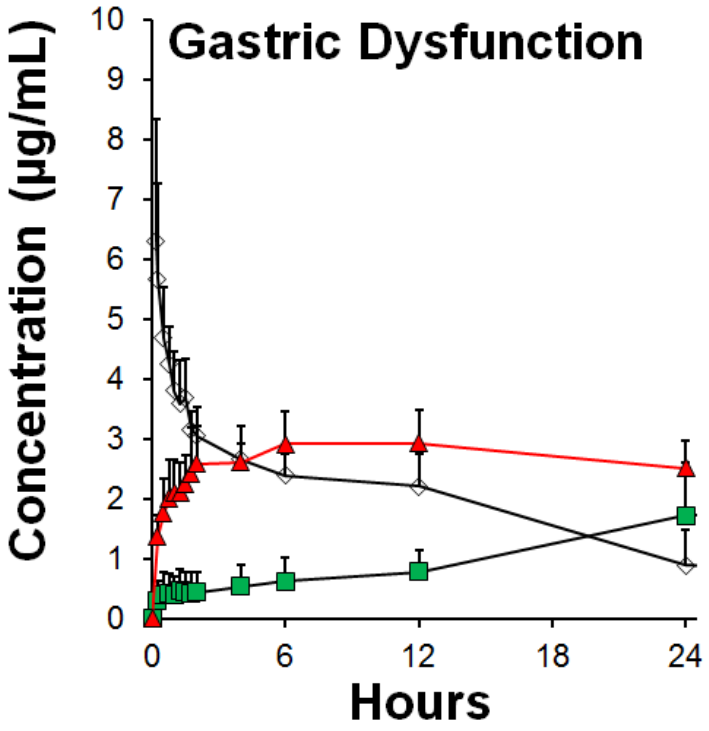




Meloxicam (rat data)

Jamali F, Aghazadeh-Habashi A. Int J Clin Pharmacol Ther. 2008, 46:55-63



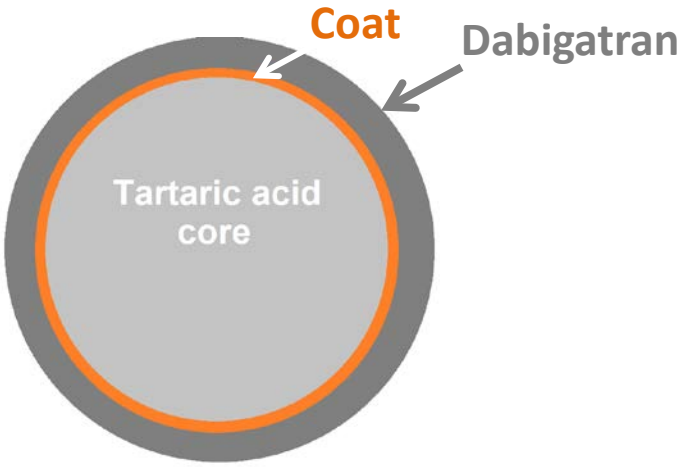


	Healthy		Gastric Dysfunction	
	Brand	Fast Dissolving	Brand	Fast Dissolving
C_{max}	**3.7** ±1.1	**3.8** ±0.6	**1.78** ±0.9	**3.16** ±0.4
90% CI	81.4 – 124		144 – 254	
AUC_{0-24}	**63.1** ±19.8	**63.1** ±16.4	**22.1** ±9.7	**64.6**± 8.9
90% CI	89.6 – 115		250 – 399	

Does bioequivalence under healthy condition provide a reliable measure of therapeutic equivalence under pain condition?

Formulations to minimize interactions

- *e.g.,* Anticuagulant dabigatran
- Reduced bioavailability at alkaline environment.
- Patients on dabigatran often take antacid PPI (hence, elevated pH, and lower bioavailability).
- Thus the following formulation is designed and used:



The acid travels with the formulation to keep the microenvironment acidic.

- **Do bioequivalence data in the absence of PPI provide information on in the therapeutic equivalence in patients taking PPI?**

- **Pre-systemic interaction.**

Oral Formulations for Local Action

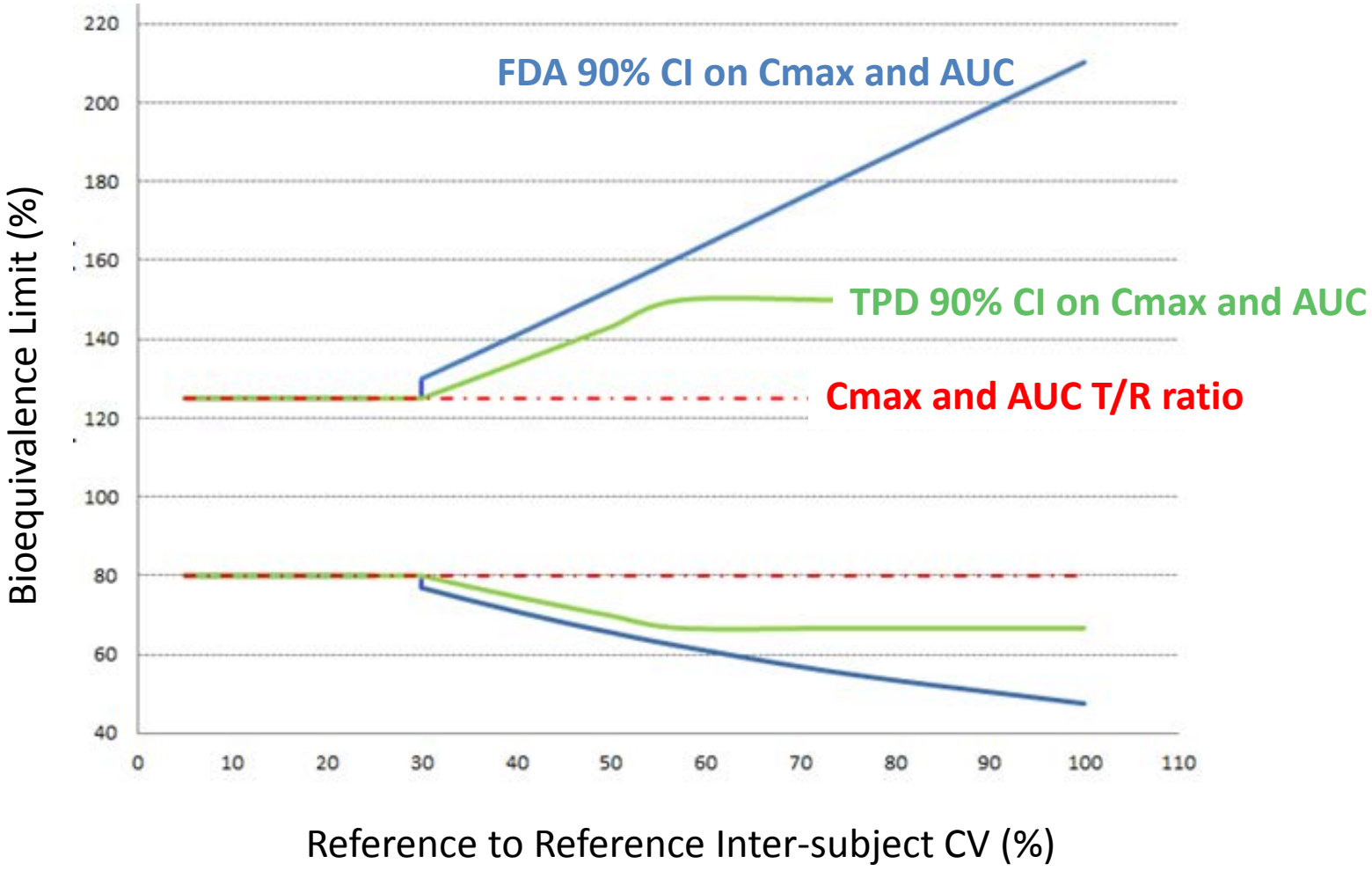
- *e.g.,* 5-ASA

https://www.intexo.it/wp-content/uploads/2017/08/Regulatory-framework-on-bioequivalence-criteria-for-locally-acting-gastrointestinal-drugs-the-case-for-oral-modified-release-mesalamine-formulations.pdf

Drug product	Bioequivalence approach adopted
5-ASA delayed release capsules	*In vitro* comparative dissolution test PK study based on the evaluation of conventional PK parameters (C_{max} and AUC) in addition to partial AUC_{8-48}

- Systemic exposure and therapeutic outcomes?
- Variability

Extremely Variable Drugs



Should the CI gate be widen as reference/reference CV widens?

Conclusion

As any other branch of science, the regulatory sciences evolve as more rationale questions are raised, and/or there is a need to address therapeutic equivalence of new products.