

Clinical Implications of Canada's Regulatory Process for Approval of Generic Drugs

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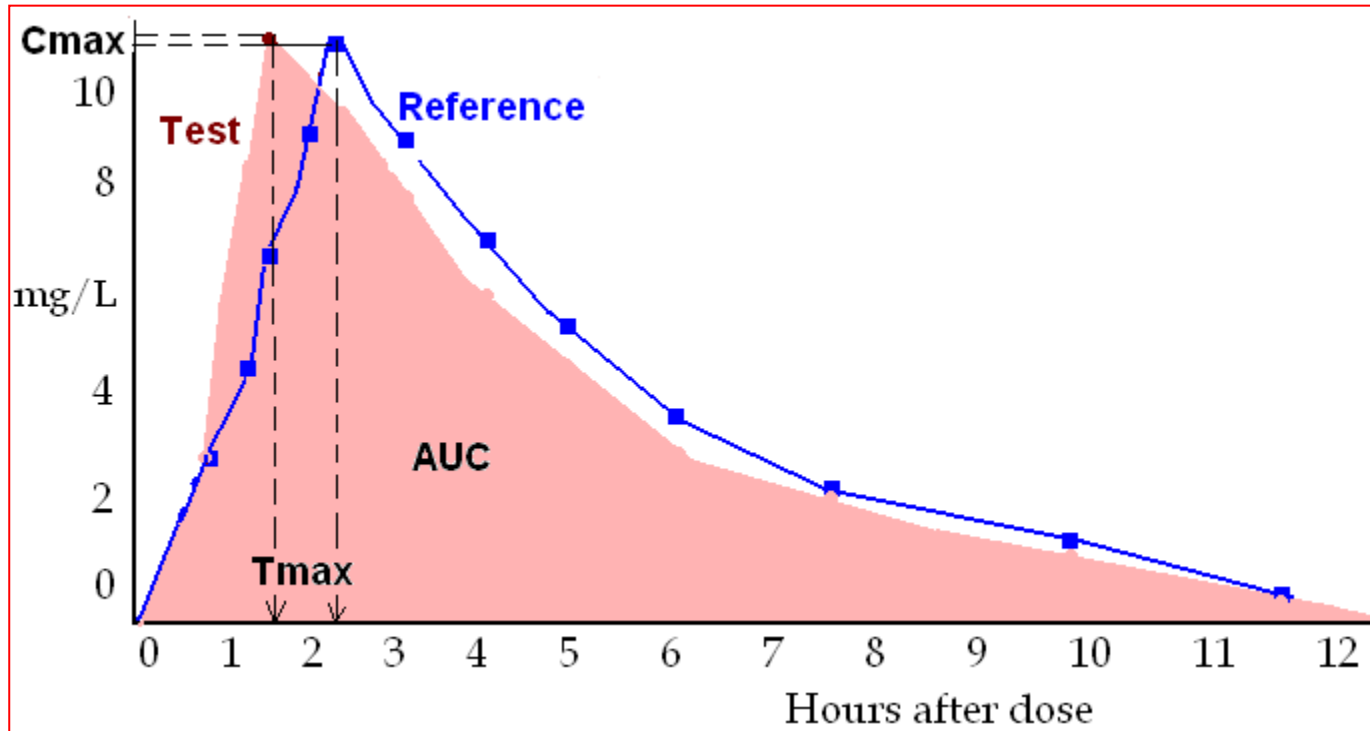
Conflicts:

Apotex, Canada	KaliChemie, Germany	Prographarm, France
AstraZeneca, Canada	Knoll, USA	Roche, USA
Astellas, Canada	MEDA Pharma, Germany	Ronbaxy, USA
Altana, Canada	Merck Company, USA	Rhone Poulenc, France
Aventis-Sanofi	Merck Frosst, Canada	Rottapharm, Canada
Basilea, Canada	Methylgene	Salmedix, USA
Bayer, Germany	Miles, USA	Sandoz, USA
Boehringer-Ingelheim	MSI Methylation, Canada	Searle, Canada, USA
Boots, UK	Mylestone Pharma, Canada	Sepracor, USA
Cayman Chemical, USA	Mylan, USA	Sterling-Winthrop, Canada, USA
Cipher, Canada	Novartis, Switzerland, Canada	Supertech, Canada
Dalton Pharma, Canada	Novapharm-Teva, Canada	Teva, Canada
Dey Labs, USA	Ontario Ministry of Health	Viron, Canada
Dupont, Canada	Ortho-Janssen, USA	Wyeth, Canada, USA
Genpharm, Canada	Pentech-Abbott, USA	Wyeth-Ayerst, Canada, USA
Great Valley Pharm, USA	Pfizer, USA	WhiteHall-Robins, USA
Iroko, USA	PharmScience, Canada	Xenon, Canada
Janssen, USA, Canada	Purdue-Fredrick, USA	

Evidence of Therapeutic Equivalence

- Bioequivalence
- Similar rate and extent of exposure within certain variability (Confidence interval 80-125)
- Once in the body (systemic circulation), the source (manufacturer) of the compound becomes irrelevant.

Bioequivalence Metrics:

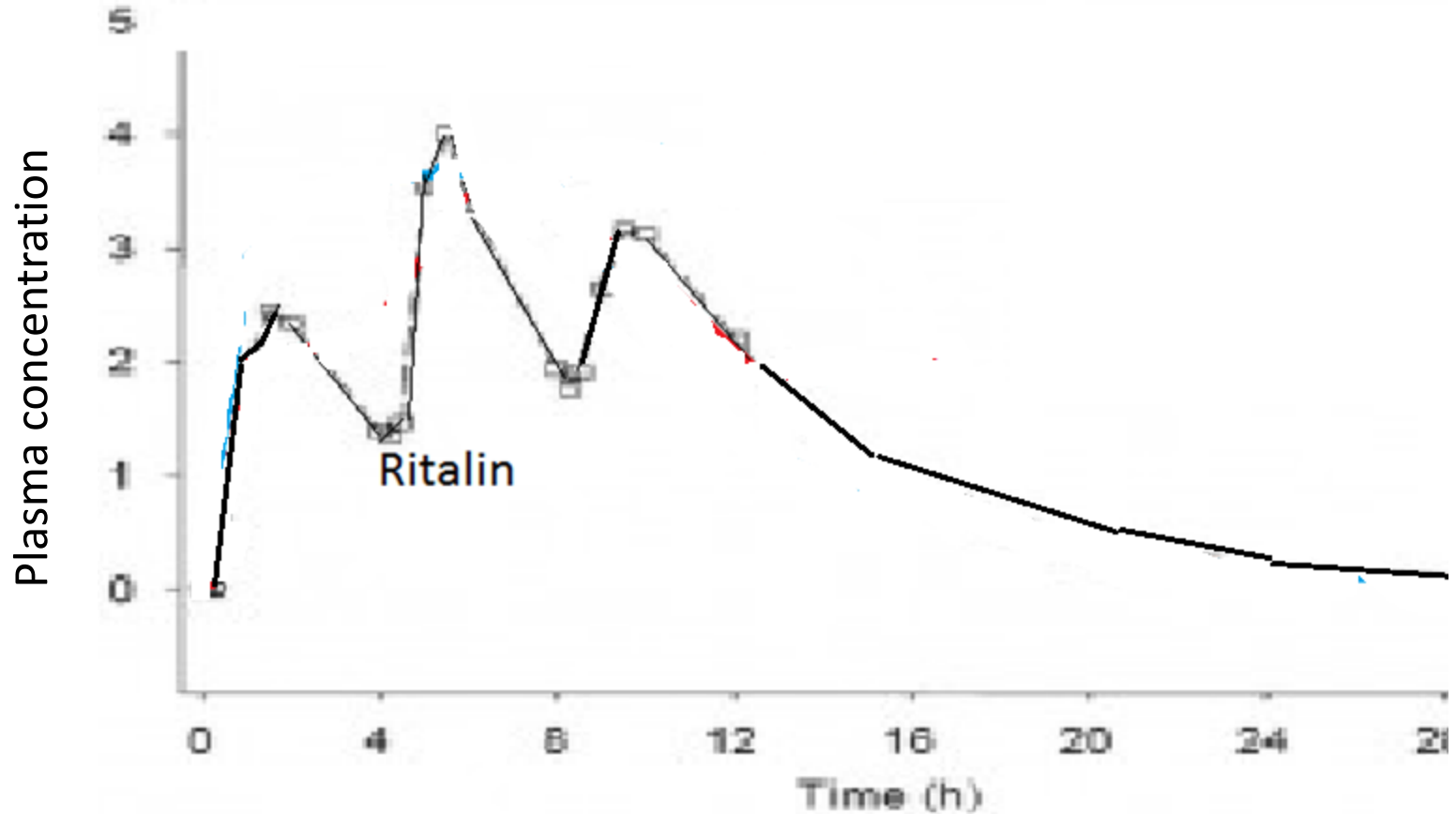


- AUC (relative **EXTENT** of absorption)
- C_{max} (reflection of **RATE** of absorption)

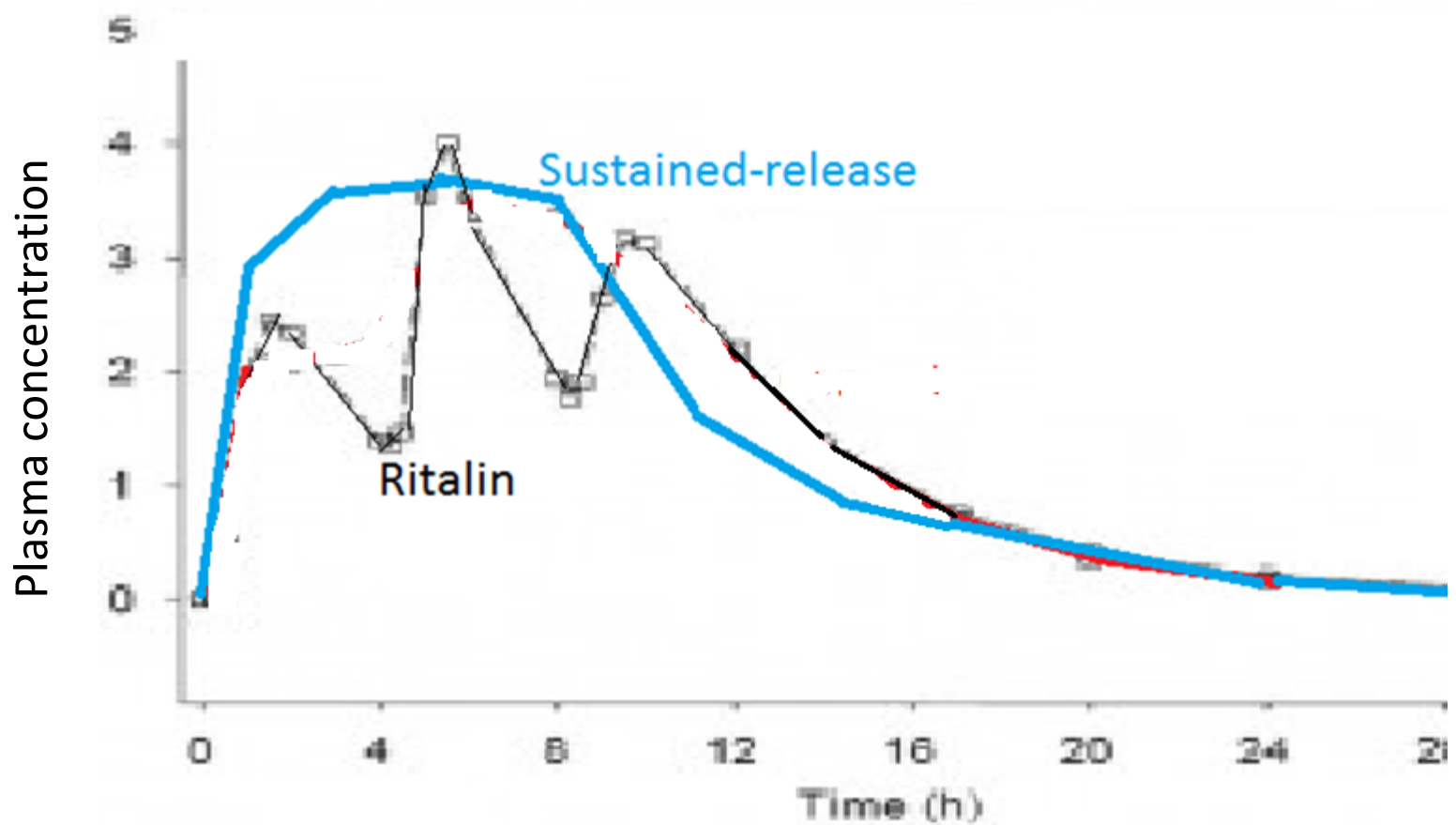
Safety and efficacy:

- A subsequent entry products (SEP; generic) is approved when bioequivalence is proven.
- SEP is marketed for identical indications assuming identical properties.
- Has proven safe and cost-saving for decades.
- Thus, **SEP uses identical product information insert (monograph)**.
- However, such a generalization may not applicable to complex formulations.
- Complex formulations: Altered release patterns; GI condition-dependent altered absorption,
 - e.g., gastric dysfunction, altered pH.

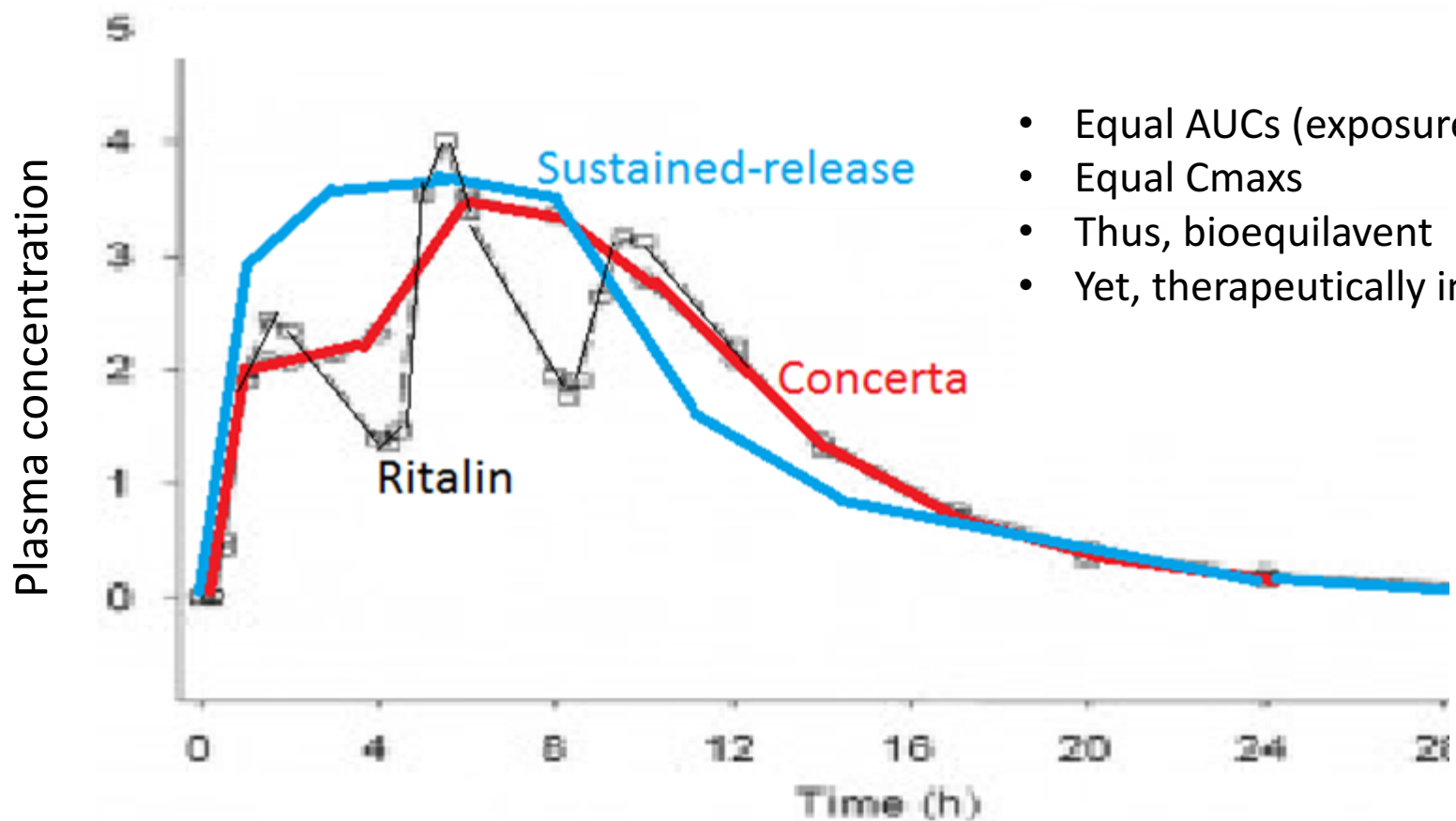
Development of Concerta (methylphenidate)



Development of Concerta (methylphenidate)



Development of Concerta (methylphenidate)



- Equal AUCs (exposure)
- Equal Cmax
- Thus, bioequivalent
- Yet, therapeutically inequivalent

e.g., Monograph may specify interactions

Systemic interactions deal with molecules already in the body

- hence, are independent of formulation factors

PRADAXA Monograph:

Ketoconazole	Single and multiple oral doses of 400 mg ketoconazole increased total dabigatran AUC _{0-∞} by 138-153% and C _{max} by 135- 149%.	Co-administration of systemic ketoconazole with PRADAXA is contraindicated
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A systemic interaction regardless of the type of product.

Pre-systemic interactions occur before the molecule enters the body

- hence, may be influenced by the nature of the formulation.

PRADAXA Monograph:

Pantoprazole/ Proton Pump Inhibitors (PPIs)	When dabigatran etexilate was coadministered with pantoprazole, a decrease in dabigatran AUC of about 30 % was observed. In RELY, PPI co-medication did not result in lower trough levels and on average only slightly reduced post-dose concentrations (- 11 %).	No dose adjustment is recommended. Diminished clinical effect of PRADAXA may occur, as may be expected for any drug resulting in an increase in gastric pH.
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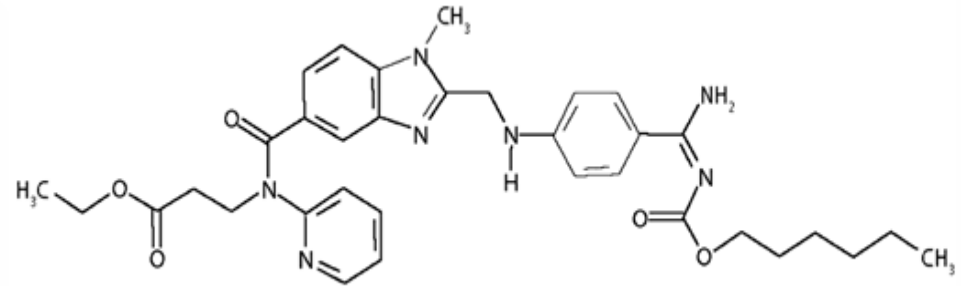
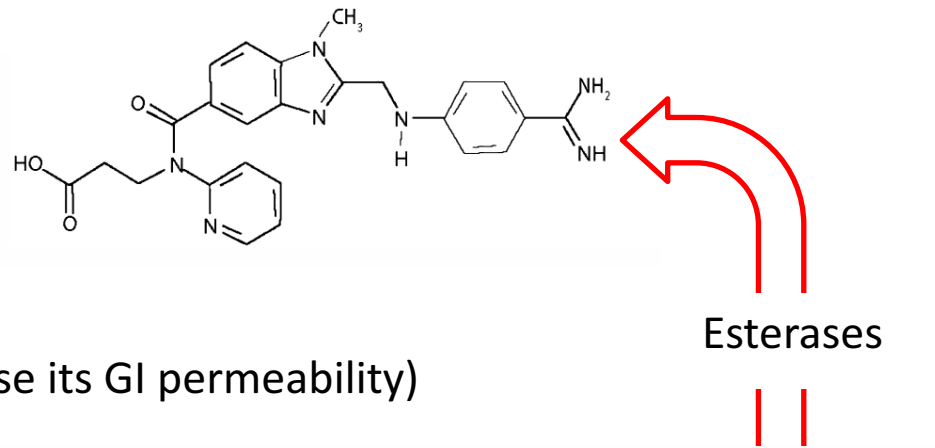
A pre-systemic interaction; product or formulation-dependent.

Dabigatran

A very polar molecule with negligible membrane permeability

To be absorbed optimal solubility and permeability are needed

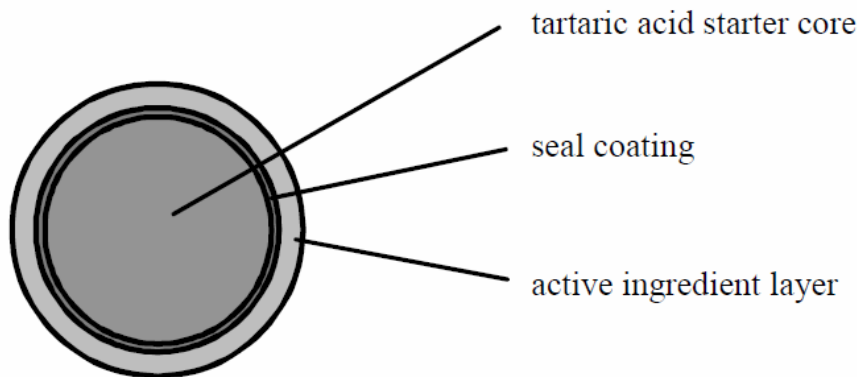
Marketed as an etexilate prodrug (to increase its GI permeability)



- The marketed molecule is a prodrug with low solubility, thus, a very low bioavailability (~5-7%).
- Solubility is better at lower pH (≤ 3), virtually insoluble at neutral pH.

Proton Pump Inhibitor

- Used by many patients who are on dabigatran;
- Thus, the gut pH is elevated;
- **Absorption ofn dabigatran is reduced with PPI**
- Special dabigatran formulations; pH-independent absorption.
- e.g., Pradaxa delivers dabigatran in an acidic environment



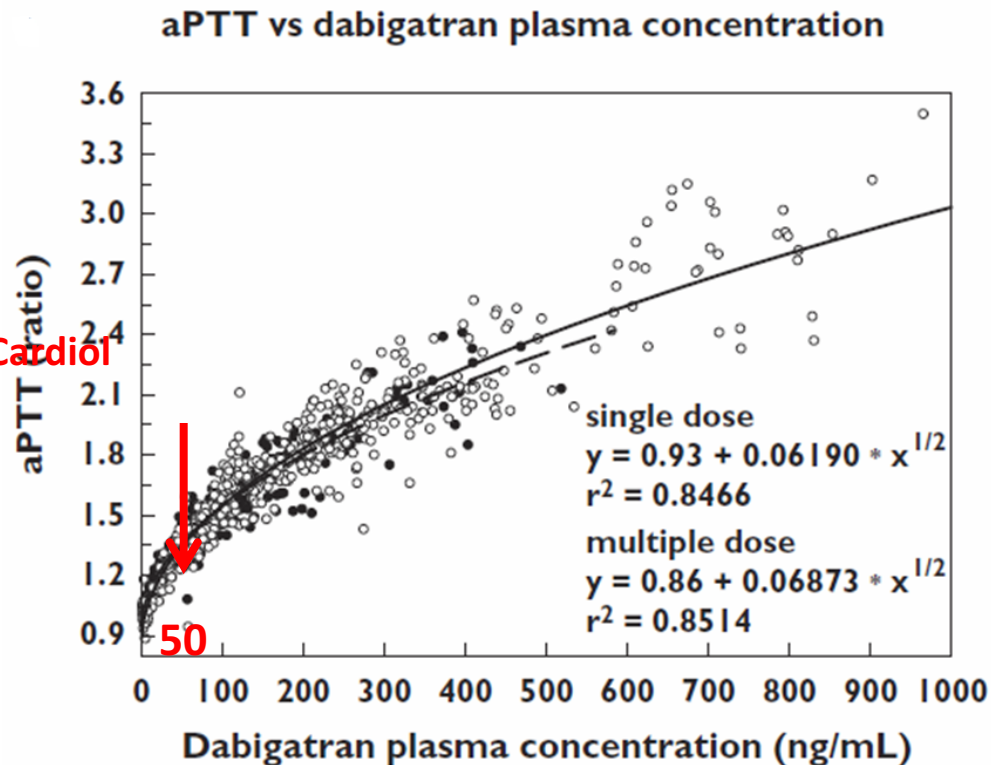
- The protective effect is due to **both** the unique formulation and the presence of tartaric acid.

Exposure (concentration) – Effect Relationship: Does a change in concentration due to interaction matter?

Read Stangier and Clemens. Clinical and Applied Thrombosis/Hemostasis 15: 9s-16s (2009).

Activated Partial Thromboplastin Time (aPTT) depends on dabigatran plasma concentration

Reilly et al., J Am Coll Cardiol
2014;63:321–8).



Consequence of the interaction:

- Addition of PPI
 - Decreased exposure; possibility of reduced effect.
- This may be extrapolated to any condition that influence gastric pH (e.g., food)

Conclusion:

Subsequent Entry Products (Generics)

- Dabigatran-PPI interaction is pre-systemic and formulation-dependent.
- Conventional bioequivalence rules do not include such tests.
- Generics need to be tested in the presence of PPI
- Two generics have just been approved
 - 75 and 150 mg
 - 75, 100, 150 mg
- Let's hope that Health Canada has paid attention to PPI interaction.