

Using Quantitative Methods and Modeling to Transform Generic Drug Development and Review

Robert Lionberger

Director, Office of Research and Standards

Office of Generic Drugs

October 3, 2017

Three Directions for the Future

- Mechanistic-based absorption models
- Model-based generic drug development and bioequivalence
- Data-based knowledge discovery for ANDA review optimization

Goals

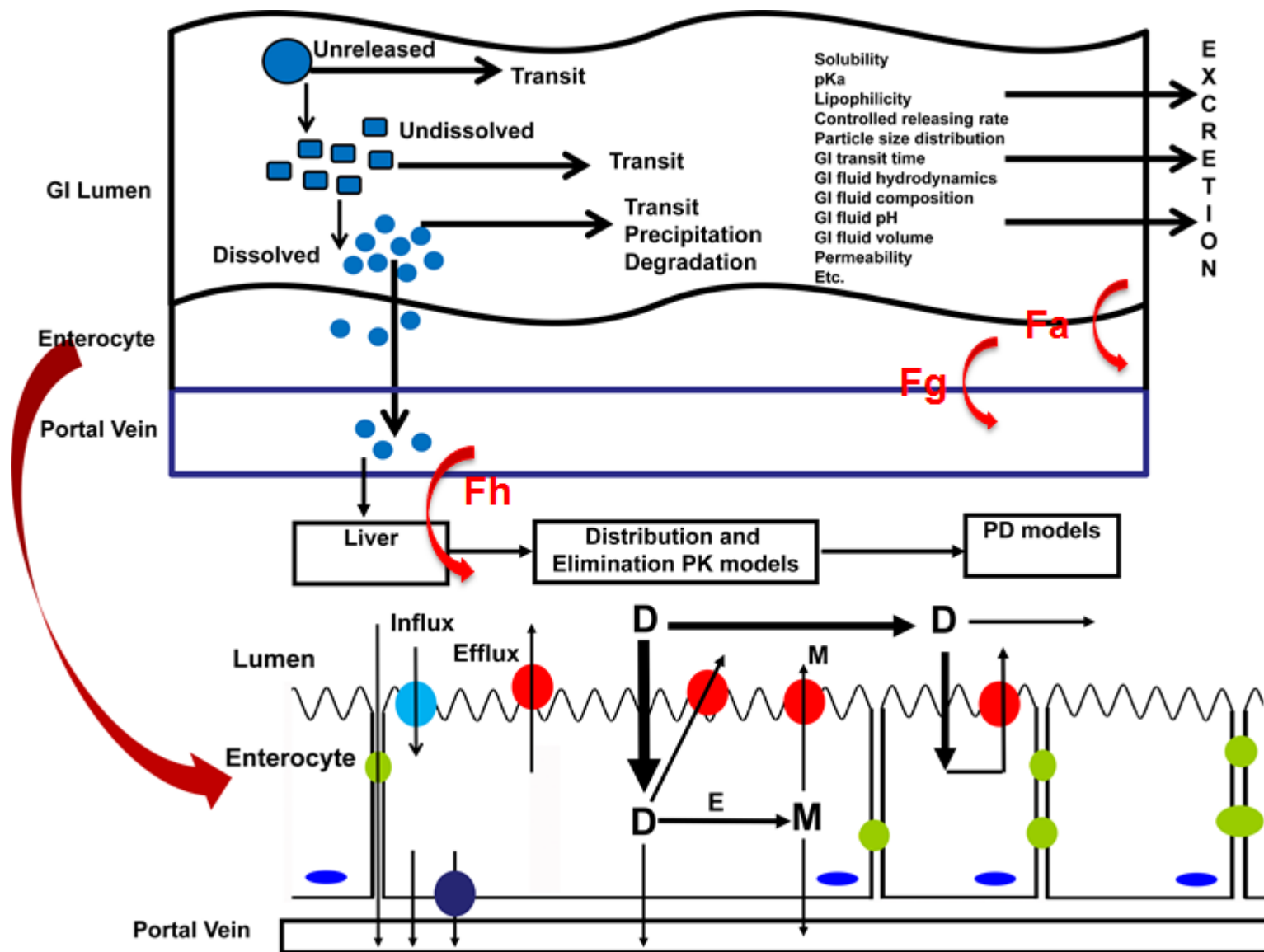
- Make generic drug development and review more efficient
 - Faster access to generics of complex products
 - Better and faster product development decisions
 - Eliminate unneeded human studies and use innovative bioequivalence methods
 - Better and faster review decisions

MECHANISTIC-BASED ABSORPTION MODELS

Advantages of Mechanistic Based Models

- Empirical models that describe and predict what has been observed are useful for interpolation
- Building models on fundamental physics and physiology provides a stronger base for extrapolation to new situations

Understanding of Oral Absorption



Benefits of Mechanistic Based Models for Oral Absorption

- BCS based biowaivers for class I and III
- In vivo predictive dissolution (IVPD) research for class II
- Foundation built in GDUFA I
- Results in GDUFA II

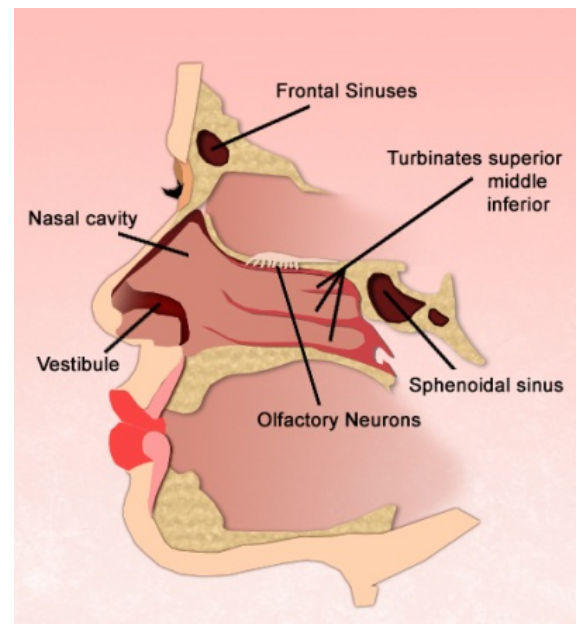
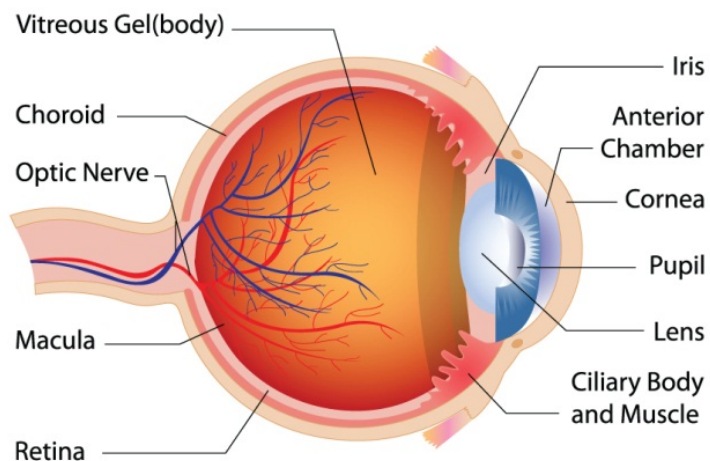
Market Size Implications

- Most generic products are in small markets
- Small markets are more susceptible to price fluctuations and less than 3 generic competitors
- Need more efficient generic drug development to provide full competition in small markets
- **Huge opportunity for IVPD to make a positive public health impact**

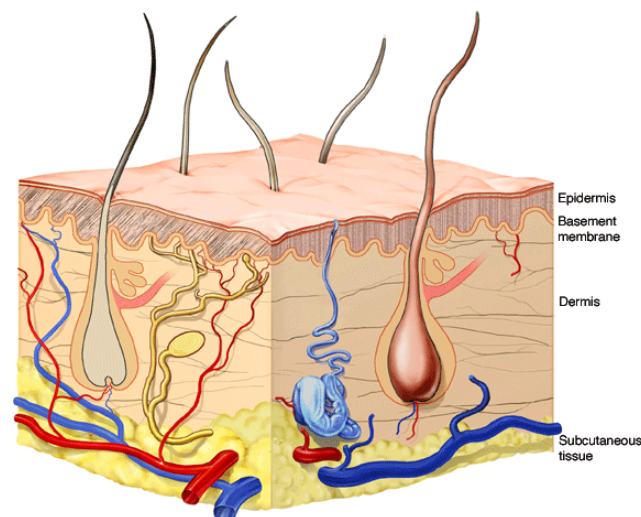
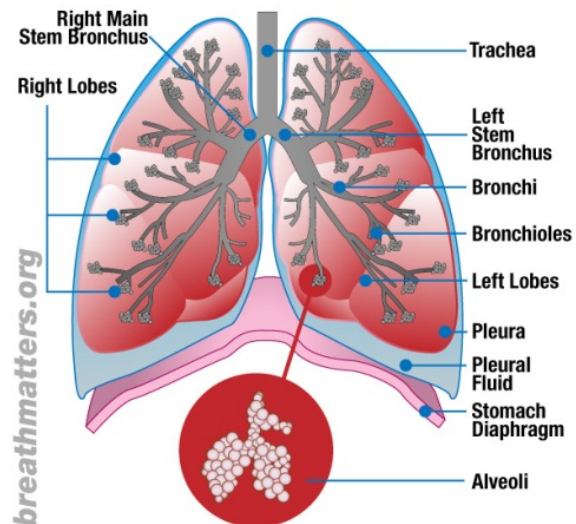
Vision for Oral Absorption

- Significantly reduce the need for in vivo bioequivalence studies for immediate release dosage forms
 - Scientific consensus
 - Need standard, affordable and reproducible IVPD methods
 - Need to de-risk the use of alternative BE demonstration

Non Oral Absorption



LUNGS



•Based on the publication by Jiang W, Kim S, Zhang X, Lionberger RA, Davit BM, Conner DP, Yu LX. Int J Pharm. 2011 Oct 14;418(2):151-60.

Benefits of Mechanistic Based Models

- Complex generics without competition are concentrated in the non-oral routes
- PBPK models for these route will aid formulation development and review
- As in oral route need models or drug release from the formulation as an input

MODEL-BASED GENERIC DRUG DEVELOPMENT AND BIOEQUIVALENCE

What is Model-Based BE?

- Assuming the structural model
- It is a way to link to Bayesian inference in a systematic way
 - The prior is the level of confidence in the structural model
 - Structural models can be mechanistic based and thus supported by fundamental laws of physics or physiological mechanisms of action

What is Model-Based BE?

- Virtual Bioequivalence Studies
 - Clinical Trial Simulation
 - Use of model to compare test and reference formulations
 - The model must have a formulation input that represents the difference between T and R (IVPD)
 - The model generates a population for BE study, compares T and R in that population
 - Simulate many studies to estimate probability of success or failure
- Key for new BE approaches
 - Is it accurate sensitive and reproducible?

Need for Model-Based BE

- You cannot accelerate access to complex generics without model-based BE
- We need to leverage what we know and have learned from experience with the RLD to have an efficient generic drug review system

Need for Virtual BE Studies

- Predict what will happen
 - In a specific study
 - In a range of different regulatory and product development scenarios
 - In a range of patient population or use scenarios
- Both FDA and industry would benefit from this capability

FDA Uses Virtual BE

- Every product specific guidance that has novel PK BE methodology
- For all of our own in vivo studies
- To evaluate sponsor submissions that propose alternative BE approaches

DATA-BASED KNOWLEDGE DISCOVERY FOR ANDA REVIEW OPTIMIZATION

Context

- Modern organizations analyze data about their own performance and their external environment to make better decisions and rapidly adapt to changing circumstances.
 - Within FDA and the generic drug program there is a significant amount of data in both the content of the applications and the meta-data about the applications themselves.



Optimization of Internal Review Process

- Prediction of future submissions
- Prioritization of regulatory science and guidance development for complex products
- Data warehouse of ANDA Bioequivalence studies
- Identification of data integrity issues in submissions

Conclusions

- New Quantitative Methods will transform generic drug development and review
 - Mechanism-based
 - Model-based
 - Data-based
- If we are prepared, we can make better and faster decisions about generic drug development and review