# 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

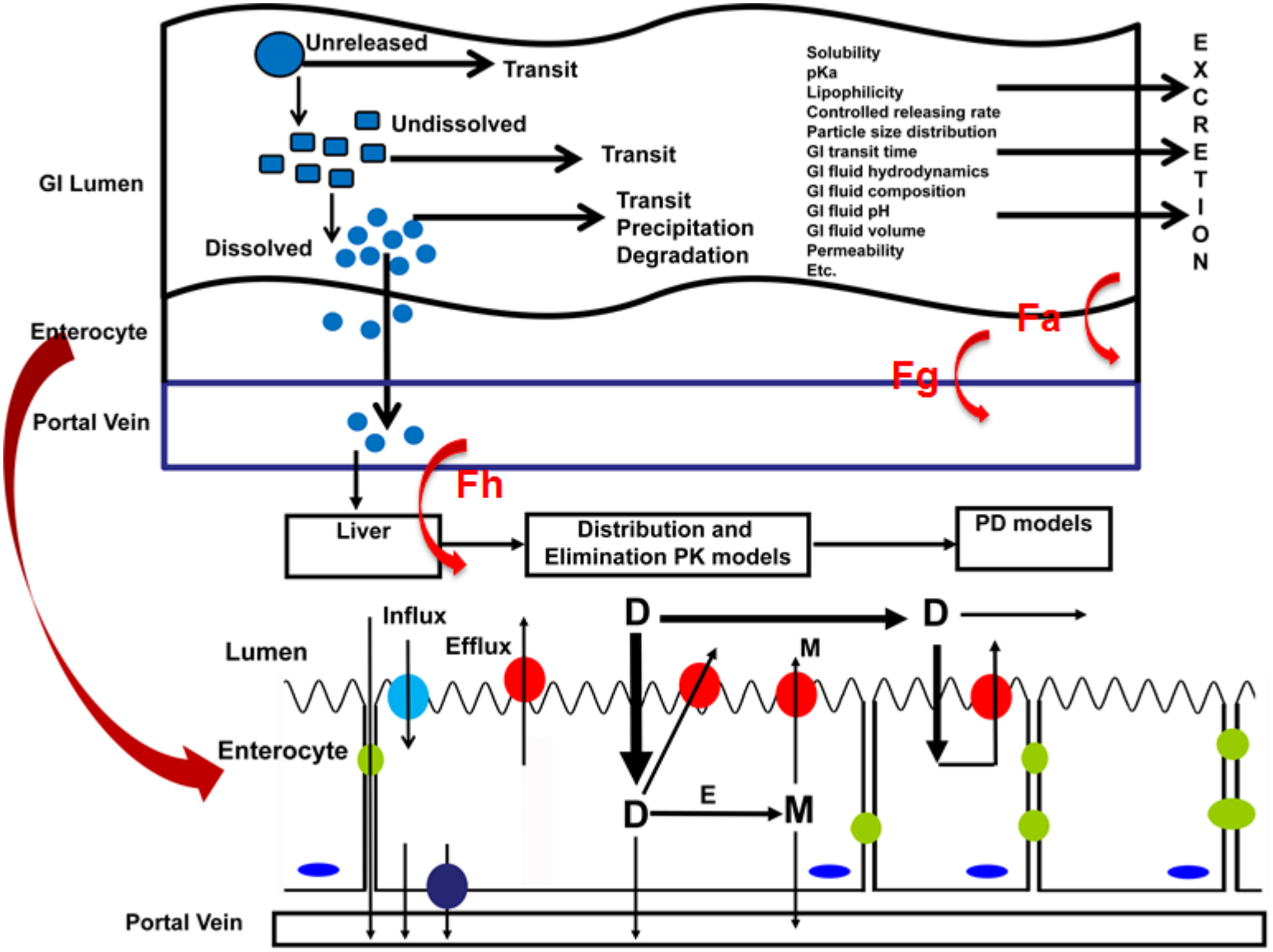
- Make generic drug development and review more efficient
  - Faster access to generics of complex products
  - Better and faster product development decisions
  - Eliminate unneeded human studies and use innovative bioequivalence methods
  - Better and faster review decisions

# 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




•Source: Xinyuan (Susie) Zhang

# 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

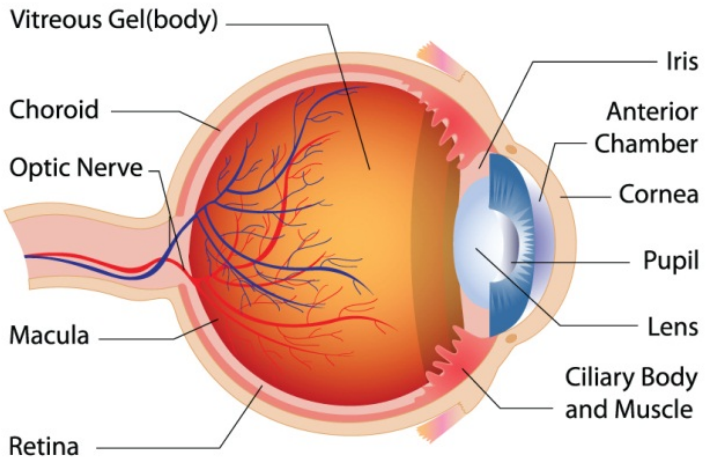
# Market Size Implications

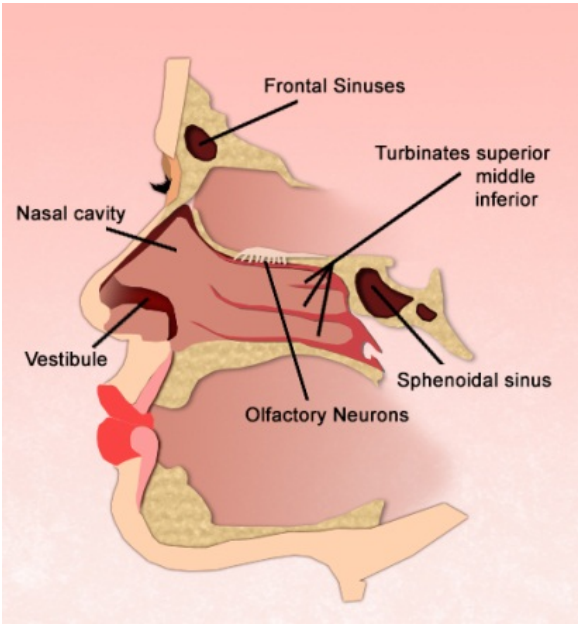
- Most generic products are in small markets
- Small markets are more susceptible to price fluctuations and less than 3 generic competitors
- Need more efficient generic drug development to provide full competition in small markets
- **Huge opportunity for IVPD to make a positive public health impact**

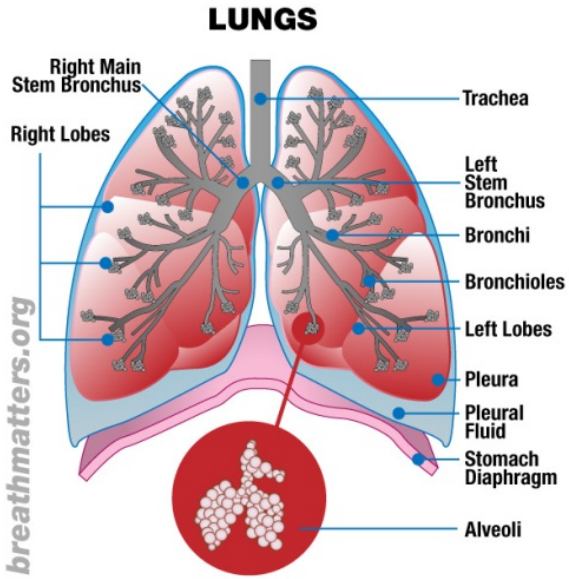
# Vision for Oral Absorption

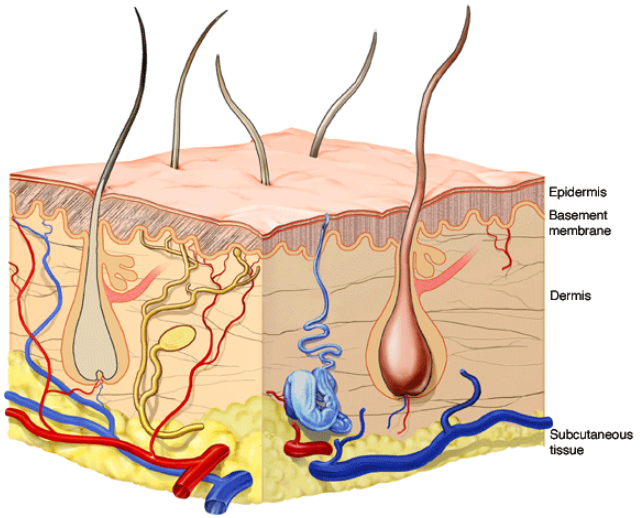
- Significantly reduce the need for in vivo bioequivalence studies for immediate release dosage forms
  - Scientific consensus
  - Need standard, affordable and reproducible IVPD methods
  - Need to de-risk the use of alternative BE demonstration

# Non Oral Absorption






•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