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

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
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