Regulatory Education for Industry (REdI) and CERSI Workshop

Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls

September 23-25, 2019

College Park, MD

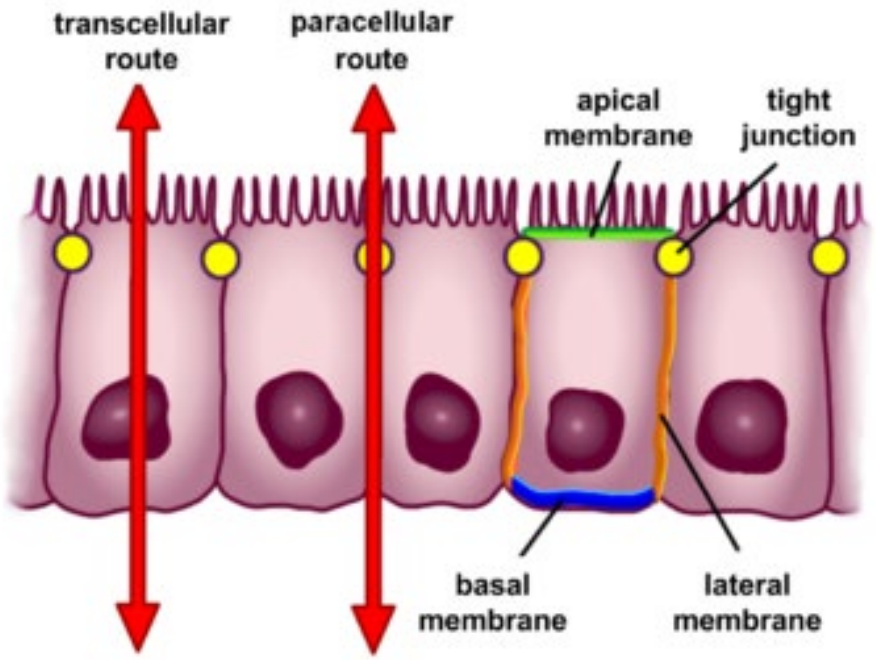
BREAKOUT SESSION D DAY 1:

Permeability Along the GI tract. Translation from Biopharmaceutical Measurement to a Model Parameter?

Moderators and scribes: Xinyuan Zhang (FDA); Neil Parrott (Roche); Andrew Babiskin (FDA); Erik Sjögren (Pharmatheus)

Session Background

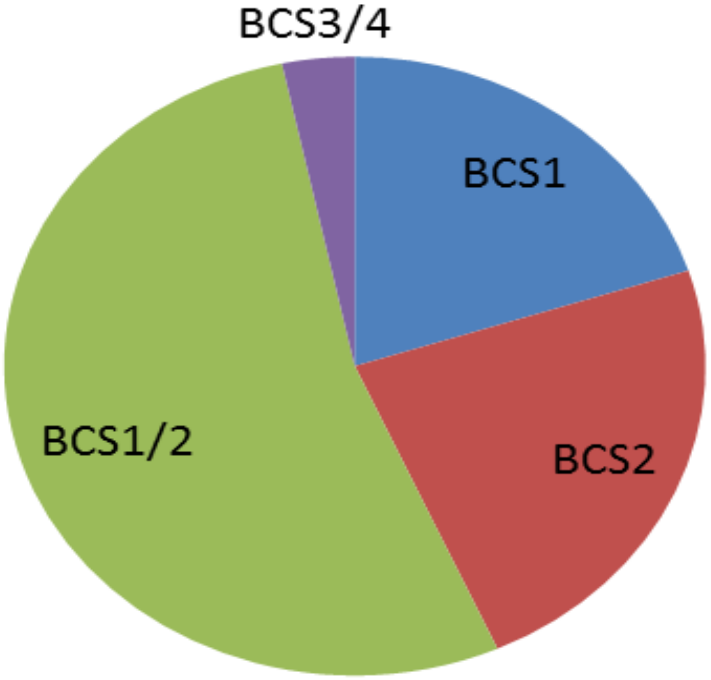
Permeability probably receives less attention from this community than solubility/dissolution



Does it matter?

Session Background

Entries into Clinical Development at Roche 2003 - 2015



Industry Trends in Novel Chemical Entities entering clinical development

- Increasing number of non drug-like small molecules
- Higher MW, poorer permeability
- Driven by challenging targets, e.g. protein-protein interactions

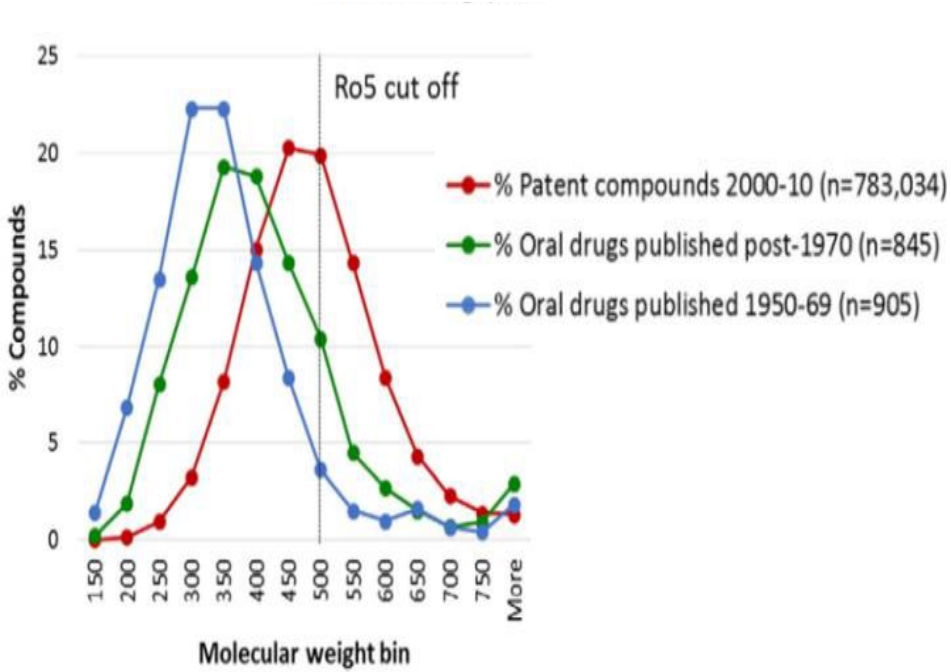


Figure taken from Leeson (2016) Adv Drug Deliv Rev.;101:22-33.

Session Outline

Question	Moderator
• What are the strengths/weaknesses of in silico and in vitro tools to estimate permeability for PBBM at different stages in drug product development?	Neil
• What is the best practice for optimization of permeability using in vivo PK?	Susie
• What is the best practice for predicting regional permeability given an estimate of jejunal Peff?	Neil
• Can formulation factors or food change permeability? If yes, what are the potential mechanisms? • How do we incorporate this into a mechanistic model?	Susie
• What is the best practice to incorporate GI active transport? What are the pitfalls?	Neil
• What are the limitations which we should overcome to obtain better models for intestinal permeability? • What are the feasible paths to overcome these limitations?	Susie

Key Points from BO Session D, Day 1, Question 1

What are the strengths/weaknesses of in silico and in vitro tools to estimate permeability for PBBM at different stages in drug product development?

- Discuss the available methods / conditions

Key Points from BO Session D, Day 1, Question 2

What is the best practice for optimization of permeability using in vivo PK?

- Discuss the assumptions and methods
- Discuss the utility of animal data

Key Points from BO Session D, Day 1, Question 3

What is the best practice for predicting regional permeability given an estimate of jejunal Peff?

- Discuss the scenarios where animals can be misleading for human
- Discuss the utility of various in silico permeability models such as (MechPeff model and logD moel)

Key Points from BO Session D, Day 1, Question 4

Can formulation factors or food change permeability? If yes, what are the potential mechanisms?

- How do we incorporate this into a mechanistic model?

Key Points from BO Session D, Day 1, Question 5

What is the best practice to incorporate GI active transport? What are the pitfalls?

Key Points from BO Session D, Day 1, Question 6

What are the limitations which we should overcome to obtain better models for intestinal permeability?

- What are the feasible paths to overcome these limitations?

Overall Conclusions