Industry Case Study # 1

Successful Permeability Studies Supporting BCS Biowaiver in NDA

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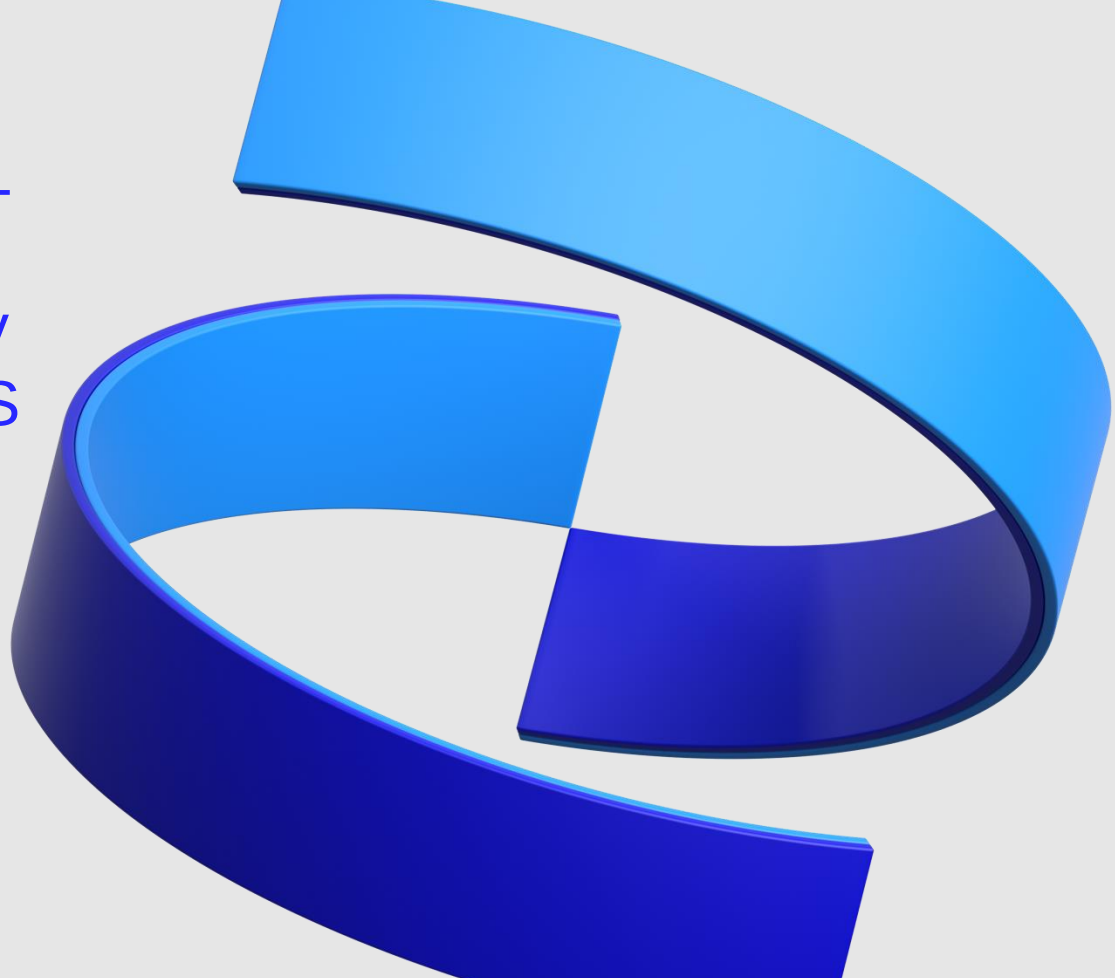

Outline

- Acknowledgement and disclaimer
- Two enigmas faced by the pharmaceutical industry
- Challenges of quantitative permeability assessment throughout the drug development process
- Uncertainties associated with BCS categorization and its implications
- BCS based biowaivers – applications, outcomes and global acceptance
- Future directions
- Conclusions

Acknowledgement & Disclaimer

- Organizers of this Workshop
- Contributions and knowledge sharing by numerous Pfizer colleagues over a period of 3 decades have enabled and influenced this short presentation by the author
- Each drug molecule with its unique properties and associated scientific nuances have enriched the experiences of this author & increased level of humility towards data
- Gaps in fundamental science continues to present challenges as well as creating opportunities for making broad generalizations for biowaivers i.e., each molecule requires its own unique justification
- DISCLAIMER – the views expressed during this presentation are those of the author

Two predictability enigmas faced by the pharmaceutical industry

- Inability to predict with confidence and acceptable accuracy SOLUBILITY from molecular structure
- Inability to predict with confidence and acceptable accuracy PERMEABILITY from molecular structure
- Lack of confidence in predictability are due to gaps in basic science that can provide direct linkages between theory and experimental observations
- These two predictability enigmas form the basis for **Biopharmaceutics Classification System** (BCS)!
- Despite these enigmas it is of profound interest of industrial pharmaceutical researchers to convince regulatory agencies worldwide to grant BIOWAIVERS for some drugs based on sound, convincing scientific evidence

SOLUBILITY vs PERMEABILITY MEASUREMENTS

- Although the prediction of solubility and permeability from molecular structure continues to be the Holy Grail
- Measurements in vitro or ex-vivo or other surrogate systems form the basis for assignment of BCS categorization for molecules
- How relevant are these measurements to the actual human physiology and what is the confidence in those estimations?
- Regulatory guidance do provide clear expectations about quantitative measurement of **SOLUBILITY** – literature on sub-categorization of solubility have also evolved and begin to be accepted; solubilization by physiological components such as bile salt mixed micelles have also been investigated extensively including the creation of more complex media
- Quantitation of **PERMEABILITY** is a significant challenge throughout the development process for any drug and its **interpretation** gets **confounded** by changes in **“flux”** due to solubilization either due to physiological or formulation factors

SOLUBILITY vs PERMEABILITY ADDITIONAL POINTS

- Temporal changes in SOLUBILITY and PERMEABILITY in the human gastrointestinal tract presents added challenges
- Although pH-Solubility considerations are relatively “easily” taken into consideration for the BCS categorization
- Regional differences in permeability due to inherent physiological and anatomical differences cannot readily be taken into consideration for BCS categorization
- UNCERTAINTIES associated with PERMEABILITY measurements pose a significant challenge
- However, most Biowaivers considerations and associated regulatory guidance inherently restrict the use of BCS based Biowaivers to Class I and III drugs. Since both BCS I and III drugs have high solubility, does it imply permeability has inherently lower importance for justification of biowaivers and thus the uncertainties in permeability assessment are not as much an issue? The focus of this workshop is on permeability!

Approaches & Challenges of Permeability Assessment During Drug Development

- **During compound design and selection** – typically high throughput cell-based permeability assays. Choice of cell lines based on company's experience and preference; RRCK, MDCK, CaCo-2 etc. Standardized concentrations, pH, passage of cells, reference standards, incubation time etc.

- Progression of compound to **Phase I clinical studies** – may include assays such as PAMPA for assessment of pH-dependent to gain influence of ionization state on permeation; quantification of transporters (uptake and efflux) on permeation. Historically, rat single pass intestinal perfusion studies were used for assessment of permeability but this has not been part of routine best practice for the past 10 years!

- **ADME studies** – historically, mass balance studies with radiolabeled drug; now most often IV micro-dose combined with oral dose and advanced mass spectrometric techniques are used

- **Inherent challenge**: during drug development most molecules are internally designated to have "intermediate permeability", however, from BCS categorization and regulatory consideration the molecule has either low or high permeability relative to reference standard!

Uncertainties of BCS Categorization & Its Implications

- **Reliable and quantifiable assessment** of PERMEABILITY continues to be a significantly challenging aspect during drug development
- **Confounding factors** mentioned previously e.g., solubilization by physiological and or formulation factors present considerable challenges
- **Assessment of fraction dose absorbed** with micro-dose,radiolableed studies is helpful in some cases but it not always the case especially if molecule is subjected to intestinal first pass or absorption is influenced by transporters (uptake or efflux)
- **Uncertainties in BCS categorization** due to challenges in permeability assessment has significant impact on justification for biowaiver
- **Dissolution testing** (multi pH media) is an integral part of biowaiver justification, and it also presents significant challenges especially if solubility is very low at one or more pH and use of surfactants are necessary to demonstrate rapid dissolution

BCS Based Biowaivers – Partially Successful Applications

BCS Class I Drug (NDA)

BE study conducted between Phase III and Commercial Drug Product

Biowaiver for low dose strengths with "common blend" based on BCS

Well accepted in majority of markets

BCS Class III Drug (NDAs)

rBA studies demonstrated equivalence for API particle size, formulation & processing

Biowaiver for new dose strength "common blend" **only accepted by FDA & EU: BE Study!**

BCS Class I/III "Legacy" Drugs with No Dissolution Concerns

Many examples of SUPAC changes: site, process and in most cases identical formulation composition & some cases minor changes

Not accepted globally. BE study!

BCS Class I/III "Legacy" Drugs with Dissolution Concern at one pH

Many examples of SUPAC changes: site, process and in most cases identical formulation composition & some cases minor changes

Not accepted globally: BE Study!

BCS Based Biowaivers – Global Acceptance

- Since Pfizer **products are registered globally** often several BoH authorities do not accept BCS based biowaivers
- Even if Biowaiver can be obtained in the US and with a few other regulatory agencies, often **BE studies are conducted for global registration**
- The **impact of ICH M9** on new NDA's worldwide **remains to be seen** although very recent experience has presented challenges with some BoH authorities
- Overall, for NDA's the successful use of **BCS based biowaivers** for global submission has **not been promising**
- Justification of BCS based **biowaivers for legacy products** (anywhere from 50 plus year old products to perhaps 15-year-old products) has also **not been universally accepted** even for BCS Class I or Class III drugs by BoH authorities worldwide
- Even in jurisdictions where biowaivers have been accepted the primary basis for **grant of biowaiver** is **dissolution data rather than permeability considerations**

Future Directions?

- Great opportunity exists to utilize **PBPK/PBBM** modeling (verified and validated) for justification of biowaivers in future NDA's. Would it be accepted globally?
- **PBPK modeling** can demonstrate and quantify **sensitivity to parameters** such as permeability and dissolution (based on understanding of parameters influencing dissolution). Would it be accepted globally?
- **PBPK modeling** supported by **Clinically Relevant Dissolution Specifications** established through rational design of variant formulations could provide strong scientific justification for biowaivers. Would it be accepted globally?
- **ICH M9** – will it provide successful outcomes for the pharmaceutical industry? Will it be accepted using common data and common criteria by BoH authorities worldwide?
- **Improvements in quantitative assessment of permeability** of molecules

Conclusions

- Based on **body of evidence to-date**, successful application of **BCS based biowaivers in NDA's** is **not very common** due to need for global filing
- Application of **BCS based biowaiver for "legacy" products** is also **not universally accepted** even for BCS Class I drugs
- **Amount of dissolution data** that needs to be provided in support of biowaiver is **extensive** without the confidence for successful outcome
- For **compounds with high permeability** and high fraction dose absorbed, **if dissolution data is not acceptable even at one pH** or due to high variability at the first time point, probability of **grant of biowaiver may be reduced considerably** by some BoH authorities
- **Rarely** have there been **BE failures** for which biowaivers were considered, proposed or rejected

THANK YOU

for the opportunity
& for your attention