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THE PEARRL REVIEWS –innovative drug development strategies tailored to facilitate earlier access to new oral medicines.

Guest Editors: Brendan T. Griffin and Jennifer B. Dressman

Pharmaceutical Education and Research with Regulatory Links (PEARRL) is an EU-sponsored partnership consisting of contributors from the pharmaceutical industry, academia and regulatory agencies, with the collective goal of developing innovative drug development strategies and regulatory tools tailored to facilitate earlier access to medicines (www.pearrl.eu).

A major bottleneck to development of new oral medicines is the poor solubility of many drug candidates. The need to develop bioenabling formulations for poorly soluble drug candidates which offer new and clear therapeutic benefits is particularly urgent. The PEARRL consortium is addressing this formulation issue by developing innovative bio-enabling formulation technologies to develop the new drugs, and by providing guides ("scorecards") for formulators to use in selecting the most suitable bio-enabling formulation on the basis of the drug properties. Additionally, PEARRL is providing a series of *in vitro* and *in vivo* biopharmaceutics tools which can be used in conjunction with PBPK models tailored for specific patient populations to predict *in vivo* performance of the bio-enabling formulations.

This special issue of the Journal of Pharmacy and Pharmacology hosts a collection of eleven review articles that showcase the research topics that are the focus of the PEARRL consortium. The objective of these review articles is to provide an up-to-date review on the current status of the target areas of research and to highlight approaches which can be used to streamline oral drug product development.

The first three articles address tools to facilitate the design of bio-enabling oral formulations for poorly water-soluble drugs. The review article by Jankovic et al. provides a detailed overview of the methods employed to calculate solubility parameters, ranging from traditional to modern approaches, and highlights how solubility parameters can be used to guide the design of bioenabling formulations for a given drug. The Ditzinger et al. review focuses on descriptors of lipophilicity and hydrophobicity as tools for guiding on oral drug product development with an emphasis on bio-enabling formulation technologies. In addition to these contributions, Price et al. address formulations intended to result in supersaturated concentrations of drug in the GI tract, providing new insights on selection of an optimal precipitation inhibitor using advanced analytical techniques. Rounding out the section on formulation development, the article by O'Shea et al. focuses on formulation approaches to overcome variable food effect oral bioavailability.

The second set of reviews focuses on bio-relevant *in vitro* approaches for assessing oral drug formulations. The article by O'Dwyer et al. provides a detailed overview of current *in vitro* methods for evaluating the potential risk of drug precipitation, with an emphasis on techniques that allow rapid screening of prototype formulations under simulated fasted state intestinal conditions. Subsequently, Pentafragka et al. provide a detailed overview of the luminal environment under fed state conditions, and highlight the need for improved *in vitro* methods for evaluating drug product performance in the fed state. The review by Henze et al. discusses in depth the value of pigs as a preclinical model for predicting oral bioavailability in humans, and highlights the need for species-specific physiologically based pharmacokinetic (PBPK) models to better link results from pre-clinical models to clinical studies in humans. The fourth review in the area of biopharmaceutical tools, by Guimarães M. et al., addresses the need for specialised bio-relevant tools to evaluate oral

formulation performance in paediatric patients, and recommends coupling *in vitro* and *in silico* methods as an approach to improve *in vivo* predictions.

The final group of review articles explores in more detail approaches to 'link the lab to the patient' using PBPK modelling, with a view to expediting clinical development. The review by Litou et al. calls out the need for greater recognition of the impact gastrointestinal medicines can have on intestinal conditions, which can lead to altered pharmacokinetics of co-administered drugs, and how to predict the *in vivo* impact of these drug-drug interactions. Analogously, Effinger et al. review the physiological changes that occur in patients with gastrointestinal disease which can result in altered drug absorption. The authors provide examples of the use of *in silico* models tailored specifically for the gastrointestinal conditions in these special patient populations as a means to improve their drug therapy. Last but not least, Loisios-Konstantinidis et al. provide an overview of pharmacokinetic/pharmacodynamic (PK/PD) models, focusing on drug-specific models to improve predictability of therapeutic equivalence between formulations and to highlight their additive value in regulatory decision-making.

Together, the PEARRL reviews describe the state of the art and identifies the key issues that will need to be addressed to bring oral dosage form development to the next level, and contribute substantially towards the much-needed integration of disciplines in the field of bio-enabling formulation design, biorelevant testing and patient-tailored PBPK approaches.

We would like to thank all of the authors, especially all members of the PEARRL consortium who have enthusiastically volunteered to contribute to this collective effort. We also would like to thank the journal's Editor in Chief, Prof. David Jones and his editorial office, who recognized the value of such a special issue and have been very supportive of the effort. Finally, we would like to acknowledge the financial support to make all this happen, with funding provided under the European Union's Horizon 2020 research and innovation programme (under grant agreement No 653296).

Brendan Griffin and Jennifer Dressman