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Review

Oral biopharmaceutics tools – Time for a new initiative – An introduction to the IMI project OrBiTo

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ABSTRACT

OrBiTo is a new European project within the IMI programme in the area of oral biopharmaceutics tools that includes world leading scientists from nine European universities, one regulatory agency, one non-profit research organization, four SMEs together with scientists from twelve pharmaceutical companies. The OrBiTo project will address key gaps in our knowledge of gastrointestinal (GI) drug absorption and deliver a framework for rational application of predictive biopharmaceutics tools for oral drug delivery. This will be achieved through novel prospective investigations to define new methodologies as well as refinement of existing tools. Extensive validation of novel and existing biopharmaceutics tools will be performed using active pharmaceutical ingredient (API), formulations and supporting datasets from industry partners. A combination of high quality *in vitro* or *in silico* characterizations of API and formulations will be integrated into physiologically based *in silico* biopharmaceutics models capturing the full complexity of GI drug absorption. This approach gives an unparalleled opportunity to initiate a transformational change in industrial research and development to achieve model-based pharmaceutical product development in accordance with the Quality by Design concept. Benefits include an accelerated and more efficient drug candidate selection, formulation development process, particularly for challenging projects such as low solubility molecules (BCS II and IV), enhanced and modified-release formulations, as well as allowing optimization of clinical product performance for patient benefit. In addition, the tools emerging from OrBiTo

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are expected to significantly reduce demand for animal experiments in the future as well as reducing the number of human bioequivalence studies required to bridge formulations after manufacturing or composition changes.

Contents

1. Introduction

The Innovative Medicines Initiative (IMI) (http://www.imi.europa.eu/) is Europe's largest public–private initiative in the life science sector between the European Union (EU) and the European pharmaceutical industry association (EFPIA). The aim is to speed up the development of better and safer medicines for patients and build networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe. OrBiTo is a key initiative within IMI, designed to streamline and optimize the development of orally administered drug products with a strong focus to develop novel experimental and theoretical models to increase our knowledge of biopharmaceutical factors and their interplay with the dynamic gastrointestinal (GI) physiology (http://www.orbitoproject.eu, http://www.imi.europa.eu/content/orbito). The project started October 1 2012 and will continue for five years and expected to start report novel findings during its second year.

The OrBiTo project will address key gaps in our knowledge of GI drug absorption and deliver a framework for rational application of predictive biopharmaceutics tools for oral drug delivery. This will be achieved through prospective studies to define new methodologies and to refine existing tools. Extensive validation of novel and existing tools will be performed using historical datasets from industry partners. A combination of high quality *in vitro* and *in silico* characterizations of active pharmaceutical ingredient (API) and formulations will be integrated into physiologically based *in silico* models capturing the full complexity of GI drug absorption. Thus, the OrBiTo project is expected to "change the game" in industrial product development from an essentially empirical approach ("trial-and-error") to a more rational model-based approach. Scientific advances in the biopharmaceutical field will provide a step change in our ability to predict product *in vivo* performance in patients that will strongly impact the pharmaceutical development in a positive way. It may also provide the basis for revised regulatory guidelines in the context of Quality by Design (QbD) by providing reliable biopharmaceutics links between the API and its formulation on the one hand, and the patient and therapeutic goal on the other hand enabling more clinically relevant development targets and quality specifications. In order to achieve all of these goals, four separate work packages (WP1–4) have been created to develop suitable tools for characterizing the API, designing and characterizing the formulation, understanding the conditions in the GI tract better and optimizing the absorption aspects of physiologically based pharmacokinetic (PBPK) models.

The objective of this overview is to describe the scope and objectives of the OrBiTo project. In the subsequent review articles in this special issue of European Journal of Pharmaceutical Sciences (EJPS), the status and gaps regarding *in vivo* predictive biopharmaceutics tools and the associated underlying science are addressed in more detail.

2. Intestinal absorption – definition

Oral administration of pharmaceutical products is the preferred route for the majority of medical treatments. It is feasible and useful to evaluate the performance of orally administered drugs and dosage forms in the GI tract by analyzing the plasma drug exposure-time profile. The oral bioavailability (F) is one of the most useful pharmacokinetic (PK) parameters in this context and F is strongly related to the pharmacological effect and safety for systemically acting drug products. F is affected by a number of processes, discussed below. F is the result of three general processes: fraction dose absorbed across the apical cell membrane into the cellular space of the enterocyte, described as fa, intestinal first-pass metabolism (E_G) and hepatic first-pass metabolism (E_H) (Eq. (1)) (Rowland and Tozer, 1995).

$$F = fa \cdot (1 - E_G) \cdot (1 - E_H) \quad (1)$$

A schematic overview of most relevant processes involved is also provided in Fig. 1. The fraction of the dose absorbed (fa) is affected by various factors which influence drug release, dissolution, luminal degradation/complexation and intestinal wall permeability. In general, these factors can be grouped into three categories: (i) physico-chemical factors of the drug molecule itself, (ii) pharmaceutical factors such as design of formulations, including choice of excipients and the physical/solid state form of the drug in the final product, and (iii) physiological and pathophysiological factors in the intestine.

The focus of OrBiTo is to characterize and predict the impact of both physical drug form (i) and formulation technology (ii) on bioavailability. These factors control drug release and dissolution in the GI tract. The composition, volumes of the GI fluids and hydrodynamic conditions generated by the GI motility which are controlled by endocrine and neural factors, also influence drug release and dissolution. However, the effect of dissolution on GI absorption is also modulated by a plethora of other factors involved in the drug absorption process (Fig 1). As an example, the overall impact of dissolution on GI drug absorption is strongly influenced by the effective intestinal permeability (P_{eff}) (Bønløkke, 1999, 2001). In a similar fashion, capacity limited processes such as intestinal degradation and/or complexation, carrier-mediated transport and/or efflux processes through the intestinal wall,