European Journal of Pharmaceutical Sciences 91 (2016) 84–90

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Use of physiologically relevant biopharmaceutics tools within the pharmaceutical industry and in regulatory sciences: Where are we now and what are the gaps?

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ARTICLE INFO

Article history:
Received 14 March 2016
Received in revised form 1 June 2016
Accepted 5 June 2016
Available online 7 June 2016

Keywords:
Biopharmaceutics
Biorelevant dissolution
PBPK modelling
Biowaivers

ABSTRACT

Regulatory interactions are an important part of the drug development and licensing process. A survey on the use of biopharmaceutical tools for regulatory purposes has been carried out within the industry community of the EU project OrBiTo within Innovative Medicines Initiative (IMI). The aim was to capture current practice and experience in using *in vitro* and *in silico* biopharmaceutics tools at various stages of development, what barriers exist or are perceived, and to understand the current gaps in regulatory biopharmaceutics. The survey indicated that biorelevant dissolution testing and physiologically based modelling and simulation are widely applied throughout development to address a number of biopharmaceutics issues. However, data from these *in vitro* and *in silico* predictive biopharmaceutics tools are submitted to regulatory authorities far less often than they are used for internal risk assessment and decision making. This may prevent regulators from becoming familiar with these tools and how they are applied in industry, and limits the opportunities for biopharmaceutics scientists working in industry to understand the acceptability of these tools in the regulatory environment. It is anticipated that the advanced biopharmaceutics tools and understanding delivered in the next years by OrBiTo and other initiatives in the area of predictive tools will also be of value in the regulatory setting, and provide a basis for more informed and confident biopharmaceutics risk assessment and regulatory decision making. To enable the regulatory potential of predictive biopharmaceutics tools to be realized, further scientific dialogue is needed between industry, regulators and scientists in academia, and more examples need to be published to demonstrate the applicability of these tools.

Contents

Abbreviations: API, active pharmaceutical ingredient; APGI, Association de Pharmacie Galénique Industrielle; BCS, biopharmaceutical classification system; EFPIA, European Federation of Pharmaceutical Industry Association; EMA, European Medicines Agency; FaSSIF, fasted state simulated intestinal fluid; FeSSIF, fed state simulated intestinal fluid; F2, dissolution similarity factor; IND, investigational new drug application; IVIVC, *In vitro–in vivo* correlation; IVIVR, *In vitro–in vivo* relationship; MAA, marketing authorization application; M&S, modelling and simulation; NDA, new drug application; OrBiTo, Innovative Medicines Initiative on predictive oral biopharmaceutical tools; PBPK, physiologically based pharmacokinetics; QC, quality control; Q-time, quality specification release time; Q-value, quality specification release value; SLS, sodium lauryl sulphate; SGF, simulated gastric fluid.

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http://dx.doi.org/10.1016/j.ejps.2016.06.006
0928-0987/

1. Introduction

Regulatory interactions are an important part of the drug development and regulatory approval process, and an essential step in making a drug product available to patients. A major aspect of these interactions is to demonstrate that the drug formulation under development will reliably provide the required quality, safety and efficacy in the patient. Formulation selection and manufacturing decisions, formulation performance controls and product release specifications are all viewed through this lens. Biopharmaceutics tools, such as dissolution testing using physiologically-relevant *in vitro* systems, and *in silico* modelling & simulations can thus enable a more efficient drug product development process by helping to relate the drug product to the patient. A diverse array of *in vitro* and *in silico* predictive biopharmaceutics tools exist which can be used to understand the absorption process and assess the biopharmaceutics risk for different compound and formulation types; the current state of the art in early biopharmaceutics tools, *in vitro* models, *in vivo* models and *in silico* PBPK-based modelling and simulation have recently been reviewed, and current gaps in the biopharmaceutics toolkit highlighted (Bergström et al., 2014; Kostewicz et al., 2014a; Sjögren et al., 2014; Kostewicz et al., 2014b).

OrBiTo is a European Innovative Medicines Initiative (IMI) project (2012–2017) in the area of oral biopharmaceutics tools (Lennernäs et al., 2014). In OrBiTo, several advanced *in vitro*, *in silico* and *in vivo* tools are being investigated and validated using a diversity of drug substances and formulations as well as using data from *in vivo* studies in the project to enhance understanding of the oral drug absorption process. It is anticipated that the advanced biopharmaceutics tools and understanding delivered by OrBiTo will also be of value to provide a basis for more informed and confident biopharmaceutics risk assessment and in regulatory decision making.

As part of the OrBiTo project, a survey on the use of biopharmaceutical tools during formulation development and in regulatory interactions has therefore been carried out among the industry (European Federation of Pharmaceutical Industry Association (EFPIA)) partners. The aim of the survey was to capture current practice and experience in using more physiologically relevant *in vitro* and *in silico* biopharmaceutics tools in a regulatory setting at various stages of oral drug formulation development, compared to their internal use within the company; to understand barriers that may exist or are perceived, and to understand the current gaps in regulatory interactions on biopharmaceutics. The survey was expected to provide a basis for dialogue between industry, academics and regulators on how to optimally use these tools in the regulatory setting for the benefit of the patient. The survey will also provide a benchmark to determine if there is any increased application of novel or optimized techniques at the end of the OrBiTo project.

2. Materials and methods

The survey was developed within the regulatory workstream of OrbiTo, and sent out to all 13 EFPIA partners in May 2015 (these were: Abbvie, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Lundbeck, MSD, Novartis, Orion, Pfizer, and Sanofi). It contained sections on biorelevant dissolution, *in silico* physiologically based absorption pharmacokinetic modelling and simulation (PBPK-based M&S, *e.g.* using software such as GastroPlus™ or SimCYP (Kostewicz et al., 2014b)), and general questions to draw out perceived barriers and gaps. Results were blinded towards the responding company. Respondents were free to choose not to respond to any of the questions (for example if not permitted to disclose the information). Each EFPIA company provided a single response capturing the collected knowledge and experience in their company. A copy of the Questionnaire is provided as supplementary material, which the reader is encouraged to view.

In the context of the survey, biorelevant dissolution testing was defined as testing in media that resemble or simulate the composition of human gastric and intestinal fluids, and other modifications of experimental set up aiming to better simulate from first principles *in vivo* dissolution. Testing in simple aqueous buffers or non-physiological surfactants such as Tween or SLS were excluded. Use of simulated biorelevant media in pharmacopoeial apparatus and use of non-pharmacopoeial apparatus (*e.g.* TNO-TIM 1 (Minekus et al., 1995), or the Modelgut Dynamic Gastric Model (Wickham et al., 2012)) were separated out in the survey, to capture any differences in their use. Definitions were provided to survey respondents to ensure clarity.

3. Results

3.1. Use of biorelevant dissolution testing during product development

Eleven of the thirteen EFPIA companies responded to the survey. The survey showed that biorelevant *in vitro* dissolution is widely used within the pharmaceutical industry to address a number of biopharmaceutics issues (Fig. 1a). It is most often performed for formulation selection and optimization, and to mimic solubilisation and precipitation in the GI tract. Prediction and understanding of food effect and relative bioavailability-type applications (*i.e.* linking formulations during development) were also relatively common applications. It is also of interest to note that all of the respondents used biorelevant dissolution testing for some of these purposes, *i.e.* none of the companies responded that they do not use such testing at all. The number of different purposes for applying biorelevant dissolution ranged from two to thirteen, with the median being eight. This indicates that most of the EFPIA companies are applying such testing for a wide range of purposes during development.

Eight out of eleven respondents start dissolution testing in biorelevant simulated media, such as SGF, FaSSIF, or FeSSIF, as a first step prior to any testing in simplified buffers for BCS class 2 or 4 compounds. Use of advanced *in vitro* testing mimicking the transition from the stomach to the intestine, is also relatively common, and five out of eleven respondents stated that they applied such testing often or very frequently. Use of combined dissolution/permeation models is less common at present, with six respondents stating they never use this, and three respondents only seldom using such techniques. For a review of the different advanced *in vitro* dissolution models currently in use, the reader is referred to Kostewicz et al. (2014a).

In terms of timing, the survey revealed that biorelevant dissolution testing is performed throughout development (Fig. 1b). Its use is especially common in the early stages, however a significant number of respondents continue to perform such testing during Phase 2 and Phase 3 (six and five out of eleven, respectively). This fits with the different applications described above, demonstrating that biorelevant dissolution testing is not just for early compound profiling but continues to be useful to answer the biopharmaceutics questions that arise later in development, such as formulation switching and Quality by Design.

3.2. Use of data from biorelevant dissolution testing in regulatory interactions

As described above, biorelevant dissolution testing is widely applied throughout development. However, the survey revealed an interesting