OrBiTo 6th Annual F2F Meeting – AstraZeneca, Granta Park, Cambridge, Sept 17th – Sept 18th 2018

"5 Years of progress in Oral Biopharmaceutics - IMI OrBiTo project and global biopharmaceutics research"

The sixth and final annual OrBiTo F2F meeting took place during September 17th to September 18th at the AstraZeneca Medimmune facility at Granta Park, Cambridge, UK. The meeting, jointly hosted with the UK Academy of Pharmaceutical Sciences (APS) was an open science event and provided an opportunity for the OrBiTo team to share highlights of key advances made by the consortium across the four technical work packages, progress with industrial implementation of tools and the regulatory opportunities for improved guidance on the use of *in vitro* and *in silico* approaches for oral biopharmaceutics. Recognising that the Biopharmaceutics collaborative ecosystem has significantly changed during the period of the OrBiTo programme, the meeting also included updates from groups such as the Pharma IQ working group on dissolution, PEARRL, UNGAP and the FDA US oral biopharmaceutics research programme.

Around 120 attendees (of which approximately 70 were from the OrBiTo consortium partners) were present on both days of the meeting. The significant number of non-OrBiTo attendees reflected the interest in the wider scientific community in the progress made by the OrBiTo group and it was great to see a number of poster presentations from the external attendees sharing progress in biopharmaceutics research from outside the programme.

Bertil Abrahamsson (scientific coordinator for OrBiTo) opened the meeting with a welcome to all participants and Mark McAllister (deputy scientific coordinator) chaired the afternoon session and introduced the summary presentations from the four OrBiTo work packages. Starting with a summary of WP1 (small-scale in vitro tools for profiling API biopharmaceutics properties), Anette Müllertz (university of Copenhagen) and Gavin Halbert (Strathclyde University) shared the extensive work performed in both labs with design of experiments approaches for determining biorelevant solubility. This more in-depth assessment of biorelevant solubility allows the contribution of the critical factors driving solubility to be determined much earlier in development and a detailed solubility map/fingerprint to be developed for each API. Whilst the DoE format requires more experimental resource than simpler measurements, the possibility to automate the methods is likely to facilitate industrial implementation. Christel Bergström (Uppsala University) presented data on the

controlled suspension intrinsic dissolution rate (IDR) method developed during OrBiTo. This method over a number of advantages over conventional techniques including the ability accurately profile IDR with very small quantities of API for compounds which have solubility values less than 100µg/ml. It may also be combined with apparent solubility to create an IDR/Sapp ratio which may be useful in determining the predominance of a dissolution or solubility limitation for absorption. Further work is in progress with this method at Uppsala to extend the compound dataset. Karl Box (Pion, UK) completed the overview of WPI with data on supersaturation-precipitation for a number of weak bases generated using the Pion inForm and micro-Diss equipment platforms. Karl proposed the use of a precipitation propensity term (calculated using supersaturation concentration data and precipitation rate) to rank order compounds displaying this type of dissolution behaviour.

James Butler (GSK, UK) opened the presentation for the WP2 (*in vitro* dissolution) team and described the development of the dissolution decision tree to guide scientists through a "*maze of possibilities*" when selecting an appropriate dissolution methodology. A number of scientists and task leaders from WP2 then shared brief insights into their research. Mirko Koziolek (University of Greifswald) discussed the development of new dissolution models which account for gastrointestinal (GI) motility and how these could applied to characterise the performance of gastro-retentive (GR) dosage forms. The team at Greifswald have also developed a model of the gastric antrum compartment to assess hydrodynamic effects on GR dosage forms, more information can be found at their aptly named website – www.thegastronauts.org !! Maria Vertzoni (University of Athens) summarised work on an extensive inter-laboratory ring study using carvedilol formulations and USP IV equipment before Philippe Berben (Katholieke University, Leuven) described how different systems had been developed to assess the impact of combining dissolution and permeation in a single system to profile the performance of different fenofibrate formulations. The WP2 presentation was concluded by Jenny Dressman (Goethe University, Frankfurt) with an overview of the dissolution decision tree, for which the interested reader can find further details at www.orbito-dissolution.eu.

After the coffee break/poster session, the work package reviews resumed with a presentation from Peter Langguth summarising the progress made with in vivo tools. This particular work package had 21 research tasks and through various in vivo studies, human clinical trials and imaging experiments has yielded a wealth of data to help develop our understanding of fundamental processes in the GI tract affecting oral dosage form performance including water distribution, motility and transit. Patrick Augustijns (Katholieke University, Leuven) presented data on the various intubation studies which have been performed with weak bases to understand supersaturation-precipitation effects in the GI lumen. Werner Weitschies (University of Greifswald) described how imaging work conducted in the C-DAT research group had significantly contributed to our understanding of the stomach-road, Magenstrasse effect during which water was observed to empty as quickly under fed conditions as in the fasted state. Werner also described how a novel

capsule formed from ice had been used to deliver caffeine to measure the impact of different types of gastric emptying on PK/absorption variability. Pat Zane (Sanofi, US) overviewed the work the decision tree group had completed. Four different decision trees from Bayer, BI, BMS and Janssen had been analysed in an attempt to develop best practice for the use in vivo models for prediction of absorption. The cross-company sharing of data and formulation strategies would have been very difficult to complete outside of the OrBiTo collaborative framework and highlighted how the collaboration had enabled this work to be completed through effective data-sharing. Hans Lennernäs (Uppsala University) shared data on the effects of excipients on intestinal absorption studied using a rat-perfusion technique. The WP3 session was concluded by a final presentation from Christer Tannergren (AZ, Molndahl) who presented data describing correlation between Caco-2 Papp values with fraction absorbed in the colon and how different dose-solubility ratios effected rate and/or extent of colonic absorption.

The final presentation of day one was provided by the WP4 (in silico modelling) team. Xavier Pepin provided an overview of the different modelling assessment tasks performed and how the OrBiTo database had been used to assess prediction accuracy across a number of in silico modelling software packages. Amais Ahmad (University of Manchester) provided a detailed analysis of task T4.20 and how performance indicators had been calculated to monitor improvement of modeling strategies. Erik Sjögren (Uppsala University) presented how a modelling framework could be used to assess the impact gastric emptying, bile release and in-vivo erosion along the GI-tract on dosage form performance. Using human clinical data, a model was developed to show that gastric emptying rate was function of the caloric content in upper small intestine and it was possible to achieve reliable predictions of gastric emptying and gallbladder emptying. These models have been used to characterize the pharmacological effect on gastric emptying, to simulate the anticipated drug-drug interactions mediated by these effects and to understand effects on plasma glucose. Konstantinos Stamatopoulos (Certara Limited, Sheffield) continued with the in silico modelling theme and presented data on a dynamic bile salt model to predict bile salt disposition within the GI luminal fluids. Further work in this area will include the addition of a mechanistic hepatic model for the de novo synthesis and secretion of bile salts and fully "connecting" IMMC phase, gastric and intestinal motility, and gallbladder kinetics in a covariate model. Jenny Dressman (Goethe University, Frankfurt) presented the refined Developability Classification System (rDCS) developed by Julian Rosenberger and herself which was recently published in Journal of Pharmaceutical Sciences (107(8), 2018, p2020-2032). A further publication summarising the application of the rDCS to estimate the results of an *in vivo* rat study to predict IR formulation developabilty of 20 pipeline compounds of Bayer Pharma AG has been submitted. A lengthy session was finally concluded by Amin Rostami (Certara, Sheffield and University of Manchester) who summarised what has been learnt through the WP4 efforts and shared his perspectives on modelling Oral Absorption and performing virtual bioequivalence studies with PBPK approaches. Amin finished his

presentation with very recent data on the use of PBPK to support specifications for the Abbvie ORILISSA (elagolix) product and reflected the growing opportunity which exists for using in silico approaches in a regulatory context.

The first day of the OrBiTo meeting concluded with a quick-fire '*present your poster in one minute session*' for all poster presenters. This helped energise the audience for the networking and poster session which closed the meeting.

Day Two began with overviews from each of the three cross-work package groups established to ensure that learnings were effectively integrated across relevant research tasks. The first of these, presented by Kerstin Schaefer (Bayer, Germany) assessed how different approaches could be used to effectively integrate permeation within a dissolution test. Kerstin focused on work performed with JNJ-39393406, a lipophilic weak base which has high gastric solubility but low solubility in intestinal fluids and is observed to precipitate on gastric transfer. Different biphasic systems utilising a range of organic solvents to create a partitioning layer were used across a number of different labs to assess the impact of permeation on the precipitation of JNJ-39393406. Further work is currently in progress with the biphasic systems to assess formulation differences for fenofibrate. Sara Carlert (AZ, Molndahl) presented an update on behalf of the cross-work package team set-up to assess the different approaches to study supersaturation and precipitation. In addition to the small-scale in vitro systems developed in WP1 and the dissolution technologies (Bio-GIT, Artificial stomach-duodenal model and transfer models) evaluated in WP2, Sara also presented data on how in silico modelling could be used to understand supersaturation and precipitation. Future work in this area will focus on a more comprehensive evaluation of the different in vitro models combined with PBPK modelling. The final cross-work package theme of integrating dissolution data with PBPK modelling was jointly presented by Filippos Kesisoglou (Merck, NJ, USA) and Masoud Jamei (Certara, Sheffield). Work with etoricoxib was presented and described how the Z-factor could be used an input to Gastroplus to model dissolution differences. Filippos concluded that using dissolution data to describe formulation performance as an input to PBPK models was a viable approach to help define the clinical relevance of dissolution specifications.

The first presentation in the regulatory biopharmaceutics session was provided by Sandra Suarez Sharp (FDA). Sandra's presentation summarised the current regulatory perspectives on the future of biopredictive dissolution testing for drug product development and started with a recognition that the SUPAC/BCS based guidance in this area is now 20 years old and doesn't always reflect current industrial development scenarios. The drivers for biopredictive testing come from a number of sources, with the emergence of a patient-centric assessment of quality being critical when considering dissolution method and specification development. Sandra described how clinical PK data, IVIVC or physiologically based biopharmaceutics PK (for which Sandra coined the new acronym - PBBP-PK) modelling could be used to link dissolution with clinical impact. FDA are encouraging

companies to apply the modelling approach and submit their data. Guidance to support companies on the use of modelling is being drafted and it is likely to be issued for comment towards the end of 2019. Sue Cole (MHRA) completed the regulatory biopharmaceutics session with a presentation on the EU regulatory perspectives on PBPK modelling. MHRA are promoting the use of PBPK modelling to help develop an understanding of the absorption process and (through the EMA) are currently working on a guidance document to help companies with this application of PBPK modelling (draft guidelines are due by the end of 2018, driven by the need to complete authoring by October ahead of the relocation of EMA to their new Amsterdam headquarters). Sue reflected that biopharmaceutics sections in marketing authorisation applications are often lacking detail and in some cases the MHRA are requesting applicants to provide a mechanistic PBPK model to help with understanding problems such as high variability and delays in absorption. Sue also provided an overview of modelling work performed by Angela Effinger (a PhD student from the PEARRL programme) which showed the potential of PBPK modelling to assess the validity of BCS based biowaivers for hydrocortisone and dexamethasone immediate-release tablets. Sue concluded that companies could help validate the application of the PBPK modelling by publishing more examples of the use of PBPK to support particle size specifications, food effects and PPI interactions.

The afternoon session describing the evolving collaborative biopharmaceutics ecosystem began with a presentation from Bart Hens (University of Michigan, standing in for Gordon Amidon who was unable to attend the meeting). Bart described the FDA oral biopharmaceutics research programme and focused on the work conducted at the University of Michigan to understand the impact of GI motility and buffer capacity on the absorption of ibuprofen. The use of phenol red as non-absorbable marker to quantitate GI fluid changes related to dilution, secretion, and absorption was also discussed. It was possible to use the Berkley-Madonna software platform to construct an in silico model which could simulate the impact of fluid changes as material transited from different gastric pathways to the duodenum and jejunum. After sharing further data obtained through MRI studies to assess the connections between gastric emptying, motility and bowel water volumes, Bart concluded his presentation with an update on the latest revisions to the gastrointestinal simulator (GIS) model being developed at the University of Michigan. 3D printing was being used to optimise the GIS paddle design in terms of vessel hydrodynamics and the use of polydimethylsiloxane membranes to provide an absorptive compartment was being investigated. The next presentation on the work of the IQ consortium bioperformance and food-effect PBPK modelling working groups was delivered by Filippos Kesisoglou (Merck, NJ, USA). Filippos described how the bioperformance working group had compiled a database containing details of biorelevant dissolution methodology and PBPK models. Around 30-40 examples have been provided by partner companies and the database will be used to underpin the development of a decision tree for the use of biorelevant dissolution with PBPK, this is likely to take the form of a white paper. Filippos commented that two-

stage dissolution methods are becoming standard practice but are applied differently across companies. He is still looking to add compounds to the database so if anyone would like to add to the efforts of the IQ group they should get in contact with him or the working group. Filippos also shared some details on the work of the food-effect PBPK working group. Whilst there is moderate to high confidence in the industry with the use of PBPK to predict food effects, this is not reflected in the regulatory area. The group have identified around 60 compounds from literature data and are filling in gaps in the dataset by generating experimental data to allow simulations to be performed with standardised datasets. They hope to recommend a workflow which Filippos considers likely to be similar to that published by Tistaert et al in J Pharm Sci 2018. The next presenter, Jenny Dressman (Goethe University, Frankfurt), provided an overview of the EU-based Marie-Sklowdska Curie training network called PEARRL (Pharmaceutical Education and Research with Regulatory Links). This novel programme comprises 15 PhD projects across a range of biopharmaceutics topics and is configured to allow the students to have secondments at regulatory agencies and industrial partners. The final presentation in the ecosystem session was delivered by Patrick Augustijns (Katholieke University, Leuven) who summarised the UNGAP cost action which is an EU-funded network focused on understanding gastrointestinal absorption processes. This network now has 300 members, spread across 31 countries, located in different academic, industrial and hospital sites. At the first yearly meeting in Leuven, around 120 members attended and the next meeting is planned for the 11-13th Feb 2019 in Sofia, Bulgaria. Further details for the UNGAP network can be found here.

The meeting was brought to close with a combined presentation from the OrBiTo scientific coordinators (Hans, Bertil and Mark) which summarised the opportunities for industrial implementation of the OrBiTo tools (with early adoption examples from GSK and Orion provided by James Butler and Krista Ojala respectively) and the future opportunities for collaborative research across a number of different areas of biopharmaceutics science. With that, the curtain was finally brought down on the sixth and final OrBiTo open science meeting. Around 200 researchers, located within 27 different partners have collaborated for six years on the 75 research tasks specified within the OrBiTo project. The primary objectives to develop the next generation of predictive tools for oral biopharmaceutics for industrial application and to train the next generation of young researchers who will be at the centre of biopharmaceutics research for years to come have been achieved. On behalf of all involved in this fantastic programme, I would like to thank you all for your dedication, hard work and collaboration, it’s been quite the journey!!

Mark McAllister

On behalf of the OrBiTo EXCO team