Innovative Medicines Initiative

In vivo predictive biopharmaceutics tools for oral drug delivery

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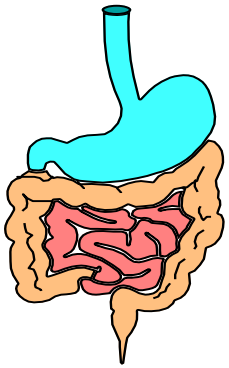
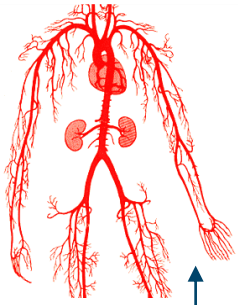
efpia

Background





non-absorbable drug complex

complex formation

drug in solid dosage form → drug release → free drug particles in GI fluids → drug dissolution → drug dissolved in GI fluids → drug permeation → drug in enterocyte → drug in liver

degradation

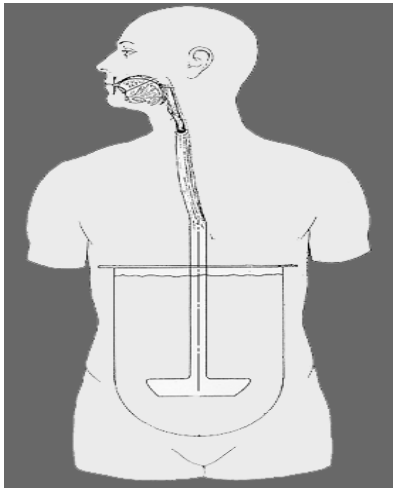
metabolism

metabolism extraction

The drug form and formulation can impact clinical effect through effects on drug release and absorption!
Great need in industrial development to understand and predict such effects!

Need for public-private collaboration

- Lack of sci understanding/tools
  - Challenging areas for novel drugs/formulations
  - Healthy young male subjects vs patients
  - Some basic areas neglected
- Poor understanding regarding optimal use/value of existing tools
- Lack of co-ordinated efforts



Objectives of the full project

- Define the critical physicochemical, formulation and physiological factors that determine product performance following oral administration of a dosage form.
- Develop both experimental and theoretical models which can be used to robustly predict the in vivo performance of formulated drug products.
- Fully leverage industrial knowledge and experience through pooling existing physicochemical, in vitro characterisation, preclinical and clinical data to assess the reliability of currently available prediction methods and to underpin the development of new modelling and simulation tools to improve the accuracy of in silico approaches.

Pre-competitive nature

- In vivo predictive biopharm tools is not a competitive business area for involved EFPIA companies.

Expected impact on the R&D process

- Improved early risk/developability assessment of candidate drugs
- Selection of optimal formulations/form in a time & resource effective manner – less “trial and error”
- Reduction/refinement of animal experimentation in accordance with 3R initiative
- Clinically relevant pharmaceutical quality criteria in context of QbD => reduce cost of goods while maintaing quality to patients
- Extend opportunities for biowaivers (in vitro based bioequivalence especially linked to Quality by Design)

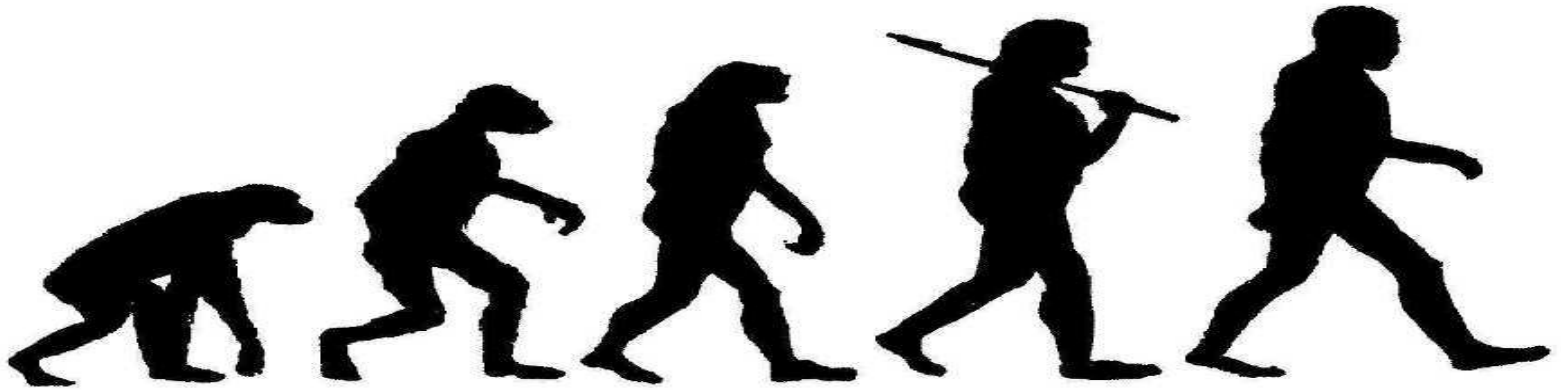
Topic need to be adressed on different levels!!

”Basic” research

Integrate& apply existing knowledge

Build and analyse industrial experience databases

Gap in fundamental science understanding → Fundamental understanding available but lack of rational methods → Method implemented in development → Optimal use of method understood



Suggested architecture of the project

Work packages

1. Physico-chemical tools (links to exposure predictions and enabling formulation space)
2. In vitro tools (dissolution, permeability, intestinal stability)
3. In vivo tools & understanding (regional aspects GI tract, patient factors, physiological characterisations of relevance for in vitro and in silico models, population PK, rationale use of animal models)
4. Integrating different tools and complex in silico models (extend BCS, in depth validations of software tools, decision trees)

Expected contributions of the applicants

- *An understanding of the variability in physiology of the GI tract, and its influence on oral drug absorption.*
- *A proven track record in delivery of innovative approaches for the measurement and understanding of complex processes influencing drug dissolution, solubility and precipitation in the GI tract and its in-vitro prediction.*
- *A proven track record and publication history in the measurement and understanding of membrane transport and metabolism during the absorption and first-pass processes, and the application of in-vitro drug permeability, metabolism and transporter methods to understand and predict in-vivo behaviour.*
- *The application of physiologically based integrated in silico absorption modelling and to understand oral absorption.*
- *Mathematics and statistics expertise to build and evaluate quantitative models.*
- *In vivo imaging of events in GI tract and access to other specialised in vivo tools such as in vivo absorption study tools.*
- *Skills in the interpretation of in-vivo pharmacokinetic data including expertise in population pharmacokinetics tools.*

- *EMA participation on a co-ordinating level is desirable to facilitate implementation of regulatory opportunities delivered by the programme*

Expected (in kind) contributions of EFPIA members

- Data from clinical and preclinical bioavailability studies. Physico-chemical and in vitro biopharmaceutical characteristics of drug compounds included in data bases.
- Specialised experimental tools for drug form/formulation physical, physico-chemical (incl. high-throughput/automated capabilities) and biopharm characterisations. In silico tools and data management/analysis tools.
- Pre-clinical experimental in vivo models also including intestinal fistulation model for local sampling and drug administration.
- Supplies of model drug compounds and formulations for experimental investigations
- Co-supervision of students and scientific input into planning and performance of project

What's in it for you?

- A unique opportunity to make a difference in oral biopharm area!
  - Significant funding
  - Opportunity to extend collaborations with uni's and SME's within Europe
  - Working with leading European industry AstraZeneca (co-ordinator), Bayer, Boehringer Ingelheim, GSK, MSD, Lundbeck, Novartis, Novo Nordisk, Orion, Pfizer, Sanofi-Aventis
  - Possibility to build and take benefit of powerful databases

Key deliverables of full project

Development of in vivo understanding & predictive tools as well as validations of emerging or existing tools

- physico-chemical tools
- In vitro tools a) dissolution b) permeability c) GI stability
- Integrating different methods - testing strategies, decision tools, framework for application of various methods, basis for refined models and use of mechanism based ”system biopharmaceutics” in silico tools

Questions?

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