



## METABODERM: Development of a new tool to predict metabolism in human skin

### Background

Establishing the absorption, distribution and metabolism properties of xenobiotics in skin is critical in the design and risk assessment of topically applied drugs and excipients, cosmetics for direct application and indirect dermal exposure, and the hazard assessment of chemicals in the environment.

Substantial progress has been made in understanding absorption and distribution of xenobiotics in skin through combined clinical, *in vitro* and modelling efforts (Mitrasoni *et al*, 2011; Mohammed *et al*, 2014; OECD, 2004; Roberts 2013). However, the extent to which skin metabolism plays a role in determining local dermal availability of xenobiotics is not well understood (Gibbs *et al.*, 2007). Very little advance has been made clinically and determining metabolic activity in *ex vivo* human skin has proved problematic due to both lack of sensitivity in measurement techniques and the rapid loss of enzyme activity, even in freshly isolated human skin (Jacques *et al*, 2014). Consequently, it has been difficult to establish how representative existing results from *in vitro* 3D skin models might be of metabolism in human skin (Götz *et al*, 2012a; Götz *et al*, 2012b). *In silico* models predicting sites and products of metabolism are predominantly built on liver data and may be of limited relevance for skin. A more useful approach may be to apply the available knowledge on enzymes expressed in skin with docking approaches more specific to the protein-ligand interaction (Kirchmair *et al*, 2012). Quantitatively, metabolic clearance data is fundamental to understanding xenobiotic availability in major tissues through physiologically based pharmacokinetic (PBPK) modelling, but currently there are no tools available to kinetically model skin metabolism or its impact on xenobiotic availability in skin.

### 3Rs benefits

For regulatory submissions in the development of drugs for topical administration, a pharmaceutical company will use around 1,000 animals in studies relating to skin toxicity per year- approximately 30% of which involve non-rodent species, in particular, the minipig. While a successful Challenge will not completely eliminate the use of these animals, the novel modelling approaches developed through this Challenge will reduce and replace significant numbers of animals and where animals are still used, minimise the number of required time points/doses. As the market for developing new chemical entities specifically for topical applications is expanding, (Kelly Scientific, 2015), the 3Rs impact of this Challenge will continue to increase.

The development of PBPK models based on dermal exposure is currently an area of active research. Currently, these models may be used in addition to *in vivo* approaches to predict pharmacokinetic (PK) and toxicokinetic (TK) properties of candidate drugs. A GlaxoSmithKline study reviewing drug attrition between 2007 and 2012 found that around 2% of drugs failed due to skin-related toxicity. This attrition could be prevented by the outcomes of a successful Challenge. Better understanding of skin metabolism will improve dermal PBPK models, enable better selection of chemicals and reduce the use of *in vivo* toxicokinetic models. A platform which could deliver this would impact animal use across the personal care product, pharmaceutical and agrichemical industries where concerns around skin toxicity exist.

Frequently, *in vitro/in silico* methods in toxicology aim to reproduce data generated using animal models. The aim of this Challenge is not to predict animal toxicity data but rather focus on safety risk assessment based on data relevant to human use as outlined in *Toxicity testing in the 21st century: A vision and a strategy* (TT21C) (Krewski *et al*, 2010). Specifically, the tools developed in this Challenge will allow skin metabolism studies to be conducted without the use of animals and also improve approaches to address the impact of xenobiotic metabolism in skin, informing the understanding of dermal and systemic availability of materials applied to the skin in humans.

### Need for collaboration

As has been the case for absorption and distribution in skin, it is most likely that a qualitative and quantitative understanding of skin metabolism will only be achieved through combined use of clinical, *in vitro*, *in silico*

and kinetic modelling approaches. Bringing together scientists from different disciplines, for example mathematical modelling, software engineering and *in vitro* biology is critical to the success of this Challenge. The collaboration and sharing of expertise between the pharmaceutical and consumer product sector in skin modelling and metabolism brings considerable added value to this Challenge.

## Overall aim

To establish, both qualitatively (which metabolites are produced) and quantitatively (concentration of the metabolites produced), the extent to which skin metabolism determines xenobiotic availability in human skin. Successful completion of this Challenge will deliver new capability to understand and interpret human relevant skin metabolism, including rates of metabolism in the skin and approaches towards metabolite identification.

## Key deliverables

- Identify studies and test systems to investigate the skin metabolism of topically applied xenobiotics (*in vitro*/minimally invasive in human).
- Establish suitable analytical techniques for measurement of metabolites.
- Use of modelling to provide a kinetic understanding of the extent to which metabolism determines xenobiotic availability in skin.

Possible solutions to the Challenge could result through the use of a combination of metabolically stable 3D *in vitro* skin systems, *in silico* prediction models, skin PBPK modelling and computational modelling of enzyme kinetics, and measurement of metabolites (e.g. high content cell imaging, and mass spectrometry). However, potential solutions need not be limited to these areas.

### Phase 1 deliverables

- Develop an experimental and/or clinical approach to investigate topically applied xenobiotics that is representative of human skin metabolism.
- Demonstrate the advantages of this approach compared to existing methods (e.g. liver microsomes or existing 3D skin models).
- Provide data and evidence that the approach can measure both phase I and phase II metabolism.
- Present computational approaches which will be developed further in Phase 2 of the Challenge.
- Present plans for wider use of the approach in industry (routes-to-market).

### Phase 2 deliverables

Development and evaluation of the experimental/clinical approach to determine:

- Phase I metabolism induction.
- Phase I and phase II metabolism pathways, including characterisation of metabolites and their rates of elimination from the skin.
- Spatial localization of active metabolic processes in the skin and their relationship to xenobiotic gradients in the skin.
- The cellular and subcellular localisation of the metabolic processes.

Development of computational approaches with the ability to:

- Predict expected metabolites for a given chemical structure.
- Calculate the rates of metabolism that determine bioavailability in skin.
- Predict skin exposure for parent chemical and metabolites (PBPK model parent chemical and metabolites in the skin) with consideration given to possible permeation enhancement.
- Provide the science and mathematics necessary for the incorporation of skin metabolism kinetics within existing open-source or commercial PBPK software.

Deliver a platform that combines *in vitro* and *in silico* approaches to better predict the metabolism of novel products applied to the skin. The Challenge should deliver a practical and commercially viable solution that would apply across the personal care, pharmaceutical and chemical sectors, that delivers improved safety risk assessment and reduces the reliance on *in vivo* TK models.

It is important to note that the CRACK IT Challenges competition is designed to support the development of new 3Rs technologies and approaches, which will improve business processes and/or lead to new marketable products. The applications for both Phases must include a plan to commercialise the results into a product or service. This should be taken into consideration when completing your application.

## In-kind contributions

### Phase 1

- Provision of known chemicals that have relevance to skin metabolism along with relevant data.
- Scientific advice and modelling experience.

### Phase 2

- In house assessment of the approaches developed through this Challenge as appropriate - to facilitate industry uptake.
- Access to relevant findings from ongoing research programmes focussing on toxicity testing in the 21st century (TT21C) approaches to mechanistic-based risk assessment of human relevant toxicity ([www.tt21c.org](http://www.tt21c.org)).
- Provision of risk assessment expertise for chemicals used in a personal and home care context, and understanding of their chemistries.
- Provide expertise/ knowledge gained from in-house *experimental* approaches currently employed for prediction of metabolic fate and PBPK.

## Duration

Phase 1: six months. Phase 2: up to three years

## Budget

Phase 1: up to 3 awards of up to £100K. Phase 2: up to £0.8 million

## Sponsors

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