Brussels, 23 June 2017

COST 016/17

DECISION

Subject: **Memorandum of Understanding for the implementation of the COST Action "European Network on Understanding Gastrointestinal Absorption-related Processes" (UNGAP) CA16205**

The COST Member Countries and/or the COST Cooperating State will find attached the Memorandum of Understanding for the COST Action European Network on Understanding Gastrointestinal Absorption-related Processes approved by the Committee of Senior Officials through written procedure on 23 June 2017.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA16205
EUROPEAN NETWORK ON UNDERSTANDING GASTROINTESTINAL ABSORPTION-RELATED PROCESSES (UNGAP)

The COST Member Countries and/or the COST Cooperating State, accepting the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action (the Action), referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any new document amending or replacing them:

a. "Rules for Participation in and Implementation of COST Activities" (COST 132/14);
b. "COST Action Proposal Submission, Evaluation, Selection and Approval" (COST 133/14);
c. "COST Action Management, Monitoring and Final Assessment" (COST 134/14);
d. "COST International Cooperation and Specific Organisations Participation" (COST 135/14).

The main aim and objective of the Action is to expand our knowledge on intestinal drug absorption to make drug development and clinical treatment more knowledge-driven by focussing on four key topics: specific patient populations, regional differences in absorption along the gastrointestinal tract, advanced formulations and the food-drug interface. This will be achieved through the specific objectives detailed in the Technical Annex.

The economic dimension of the activities carried out under the Action has been estimated, on the basis of information available during the planning of the Action, at EUR 76 million in 2016.

The MoU will enter into force once at least five (5) COST Member Countries and/or COST Cooperating State have accepted it, and the corresponding Management Committee Members have been appointed, as described in the CSO Decision COST 134/14.

The COST Action will start from the date of the first Management Committee meeting and shall be implemented for a period of four (4) years, unless an extension is approved by the CSO following the procedure described in the CSO Decision COST 134/14.

TECHNICAL ANNEX

OVERVIEW

Summary
Oral administration is the most common drug delivery route. Absorption of a drug from the gut into the bloodstream involves disintegration of the dosage form, dissolution of the API, and transport across the gut wall. The efficiency of these processes is determined by highly complex and dynamic interactions between the gastrointestinal tract, the dosage form and the API.

The fraction absorbed of the drug is affected by various factors including physiological variables, pathological conditions, local differences in gut permeability, the intraluminal behaviour of the formulation, and food effects. This complex interplay determines drug delivery performance and may cause large interindividual variability, but is poorly understood. Furthermore, comparison between drug absorption studies is hampered due to knowledge fragmentation and lack of standardisation across pharmaceutical subdisciplines. As a result, the available knowledge is underutilized in drug development and clinical treatment.

The **European Network on Understanding Gastrointestinal Absorption-related Processes (UNGAP)** is a multidisciplinary Network of scientists aiming to advance the field of intestinal drug absorption by focussing on **4 major challenges: (i) differences between specific patient populations, (ii) regional differences along the gastrointestinal tract, (iii) the intraluminal behaviour of advanced formulations, and (iv) the food-drug interface.** The integration of knowledge, combined with the exchange of best practices across sectors and disciplines, will help improve our understanding of intestinal drug absorption and spur future developments in the field. The Action also aims to **advance the career of young, talented researchers from across Europe**, thereby strengthening Europe's leading position in pharmaceutical sciences.

Areas of Expertise Relevant for the Action	**Keywords**
● Basic medicine: Pharmacology, pharmacogenomics, drug discovery and design, drug therapy	● gastrointestinal tract ● oral drug absorption ● individual variability ● methodology, technology and assays ● (patho)physiology

Specific Objectives
To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination
● Stimulate interdisciplinary dialogue and sustainable public-private partnerships by organising discussions and collaborations between stakeholders from different sectors and disciplines.
● Defragment the intestinal drug absorption research landscape by organising interdisciplinary discussions and by reviewing the state-of-the-art in the field.
● Improve reproducibility and comparability of assays and results by publishing standardised protocols and best practice guidelines.
● Expand knowledge on the challenges underpinning the scientific WGs through interdisciplinary dialogue, the creation of new collaborations and the development of new research projects.
● Contribute to the viability and success of ongoing collaborative research projects by embedding existing collaborative ties in a larger, sustainable Network.

● Reflect on the impact of recent advances and emerging concepts (e.g. supersaturating drug delivery systems) on the field of drug absorption in WG meetings and Network-wide events
● Facilitate the development of new research projects by developing a future research agenda and initiating discussions with this specific aim.

Capacity Building
● Identify and interact with stakeholders throughout different stages of the innovation cycle: drug discovery, drug development, regulatory decision making, and drug treatment.
● Promote access to state-of-the-art research infrastructure by compiling a list of research institutions that posses or have access to such technology.
● Improve career perspectives of early-stage researchers, particularly in less research intensive countries, by supporting researcher mobility and expanding professional networks.
● Facilitate scientific collaboration by organising and coordinating a sustainable Network
● Offer a balanced vision and expertise to regulatory agencies and decision makers through their participation in the Network as external advisors and through targeted communication measures

1) S&T EXCELLENCE

A) CHALLENGE

I) DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Oral intake is the preferred route of drug administration due to its non-invasive character and convenience for the patient. The bioavailability of the active pharmaceutical ingredient (API) is an important property of oral drugs. Large interindividual variability in bioavailability exists across the patient population. The underlying causes of this variability are often not well understood. This is a major source of drug candidate and clinical treatment failure and leaves **ample room for improvement in drug development as well as drug treatment**.
Absorption from the gastrointestinal (GI) tract into the bloodstream is a major challenge for orally administered drugs. Absorption involves disintegration of the dosage form, dissolution of the API, and transport across the gut wall. The fraction of the API absorbed is affected by various GI factors. Bile salt secretions have a solubilising effect, but vary greatly among healthy volunteers [1]. Food intake results in delayed gastric emptying and changes the composition of intestinal fluids, affecting drug solubility [1]. Fluctuations in gastric pH may change API ionisation, possibly affecting its dissolution, solubilisation and absorption [2]. Lipases and food-derived lipids affect the behaviour of lipid-based formulations [3]. Inflammation affects the permeability of the gut wall [4]. Gut microbiota can affect absorption by metabolising drugs in the intraluminal environment [5]. Finally, the expression and activity levels of drug transporters and metabolizing enzymes can differ among populations and are important determinants of pharmacokinetics [6]. These are just a few examples of variables affecting intestinal drug absorption. **The complex interplay of variables has repercussions on overall drug absorption, but a thorough understanding is lacking.** Many studies focus on only one or a few drugs and extrapolation to other drugs is complicated. Even comparison between studies with the same drugs is often hampered by a lack of standardisation in methodologies across the pharmaceutical subdisciplines. In addition, high quality data corresponding to specific patient populations are scarce. As a result, the data is often insufficient to efficiently guide patient treatment or drug development, forcing clinicians and drug developers to fall back on empirical trial-and-error methods and rules of thumb. However, successful methods from the past hold no guarantee for the future, as the number of APIs with challenging physicochemical properties, such as low aqueous solubility (Biopharmaceutics Classification System (BCS) class II and IV compounds), low stability or permeability (e.g. BCS class III and IV), or high molecular weight (peptides, proteins), has increased dramatically. Therefore, there is **a need to strengthen the oral drug absorption knowledge base to make drug development and clinical treatment move from empirically- to knowledge-driven**.
The **European Network on Understanding Gastrointestinal Absorption-related Processes (UNGAP)** aims to provide this solid knowledge base by creating a multidisciplinary Network of scientists. The Network will focus on 4 major challenges in intestinal drug absorption, each corresponding to a scientific working group (WG) (Fig. 1). **WG 1** will focus on **specific patient populations** and their differences in oral drug absorption. **WG 2** will focus on **regional differences along the GI tract**. **WG 3** will study the specific **intraluminal behaviour of advanced formulations** such as supersaturating drug delivery systems, nanoparticles,

lipid-based and controlled release formulations. **WG 4** will focus on the **food-drug interface** and study how food intake, specific food components and food-induced secretions affect drug absorption. Finally, **WG 5** is a generic, cross-cutting WG that will coordinate all **dissemination, exploitation and public engagement** activities. All scientific WGs are interdisciplinary and challenge-driven. Scientists from various pharmaceutical and medical subdisciplines in academia, industry and clinical practice will interact to defragment knowledge, discuss the latest developments in the field and identify solutions. Importantly, multiple connections between the WGs exist. For example, efficient treatment of patients with colitis requires knowledge on controlled release formulations, disease-mediated alterations in colon permeability and formulation behaviour in the lower parts of the gut. Furthermore, translation of findings into clinical or industrial applications requires extensive interaction between WG 1-4 and WG 5. The integration of knowledge, combined with the exchange of best practices across sectors and disciplines will improve the current understanding of oral drug absorption, spur future developments, and, in the long run, help bring better pharmaceutical products and treatments to the patient. As such, the Action will strengthen Europe's leading position in pharmaceutical sciences.

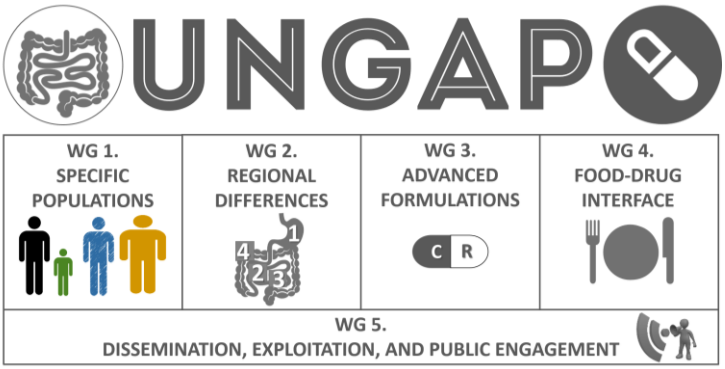

Fig. 1 UNGAP Working Group structure

II) RELEVANCE AND TIMELINESS

Issues related to pharmacokinetics and bioavailability, for which drug absorption is an important determinant, are the **third most prominent cause of oral, small-molecule drug candidate attrition** in Phase I clinical development, clearly indicating that efficient oral drug delivery poses significant challenges to drug developers [7]. Considering the increasing number of APIs suffering from unfavourable absorption-related properties in development, it is likely that efficient oral drug delivery will become **even more challenging in the future**. Therefore, more effort and knowledge will be needed to bring the next generation of complex drugs to the market.

Innovative oral drug delivery systems such as supersaturating formulations call for research into the detailed characteristics and performance of these systems. Specifically, the **US Food and Drug Administration (FDA)** calls for an evaluation of the analysis methods used to asses the performance of drug delivery systems and determine pharmacokinetics and bioavailability. In addition, the FDA highlights pharmacometrics as an area needing further investigation and recently launched a call on the integration of supersaturation-precipitation characteristsics into mechanistic oral absorption models [8, 9]. Such *in silico* models also have applications in the areas of drug safety testing and dose optimisation. The **European Medicines Agency's (EMA)** objectives include a reduction in animal studies and support for the development of medicines for specific target populations for which a thorough understanding of drug and formulation behaviour in these populations is necessary [10].

This clearly indicates a need for continued research, extensive integration of knowledge and increased interdisciplinary and intersectoral collaboration between drug formulation developers, biopharmaceutical scientists, gastroenterologists and experts in the development and use of advanced *in vitro, in/ex vivo* and *in silico* models. The proposed Action will act as a catalyst in the area of intestinal drug absorption by fostering scientific collaboration between key players in the European Research Area and establishing links with leading experts worldwide.

B) SPECIFIC OBJECTIVES

I) RESEARCH COORDINATION OBJECTIVES

Fostering scientific excellence in the field of intestinal drug absorption is the main goal of UNGAP. For this purpose, an open, interdisciplinary and intersectoral network will be created. Specifically, the network aims to achieve the following research coordination objectives:

- Stimulate interdisciplinary dialogue and build sustainable public-private partnerships by organising discussions and collaborations between actors from different sectors and disciplines in specific WGs.
- Defragment the intestinal drug absorption research landscape by organising interdisciplinary discussions and by reviewing the state-of-the-art in the field.
- Improve reproducibility and comparability of assays and results by publishing standardised protocols and best practice guidelines.
- Expand knowledge on the challenges underpinning the scientific WGs through interdisciplinary dialogue, setting up new collaborations and developing new research projects.
- Contribute to the viability and success of ongoing collaborative research projects by embedding existing collaborative ties in a larger, sustainable Network.
- Reflect on the impact of recent advances and emerging concepts (e.g. supersaturating drug delivery systems) on the field of drug absorption in WG meetings and Network-wide events.
- Facilitate the development of new research projects by creating a future research agenda and initiating discussions with this specific aim.

II) CAPACITY-BUILDING OBJECTIVES

Leveraging and embedding scientific excellence across the European intestinal drug absorption research community, improving participants' career perspectives and steering the future research agenda are the main capacity-building goals. These goals will be achieved through the following objectives:

- Identify and interact with stakeholders throughout different stages of the innovation cycle: drug discovery, drug development, regulatory decision making, and drug treatment. Stakeholders will be identified among UNGAP members and their networks. Various communication tools will be used for interacting with them (see 2.2.2 for a full list).
- Promote access to state-of-the-art research infrastructure by compiling a list of research institutions that posess or have access to such technology.
- Improve career perspectives of early-career investigators (ECIs), particularly in less research intensive countries, by supporting researcher mobility and expanding professional networks.
- Facilitate scientific collaboration by organising and coordinating a sustainable Network.
- Offer a balanced vision and expertise to regulatory agencies and decision makers through their participation in the Network as external advisors and through targeted communication measures (see 2.2.2 for a full list).

C) PROGRESS BEYOND THE STATE-OF-THE-ART AND INNOVATION POTENTIAL

I) DESCRIPTION OF THE STATE-OF-THE-ART

Drugs intended for oral administration often suffer from suboptimal performance. Despite the available knowledge and progress being made, significant knowledge gaps remain.

WG 1. Specific patient populations.

After oral intake, drugs encounter a constantly changing GI environment. Factors known to influence drug absorption include pH, gut transit time, gut motility, bile and pancreatic

secretions, colloidal structures and food components. However, how this dynamic environment affects drug absorption exactly, is poorly understood. There are only a **few reports on the variability in drug absorption in specific patient populations (patients on proton pump inhibitors, after bariatric surgery, with obesity, pediatric) [11-14]. Similarly, little is known about alterations in gut permeability and its effects on drug absorption in patients suffering from intestinal disorders [15]. Furthermore, growing evidence on the effects of genetic variations among different ethnic groups on pharmacokinetics has emerged over the last decade, but a complete picture is still lacking [16]. Finally, drug absorption can differ considerably among different age groups [17]. Large knowledge gaps remain for specific age groups, especially for younger children due to technical and ethical limitations**. This leads to a high degree of uncertainty, both in drug development and in drug treatment. A potential solution to this problem is the development *of in vitro*, *in silico* and small animal *in vivo* models that are able to accurately describe intestinal drug absorption for specific age groups.

WG 2. Regional differences along the GI tract.

Studies on oral drug absorption typically focus on the upper small intestine, as this is the first major absorptive site a drug encounters. **However, it is becoming increasingly apparent that the upper and lower parts of the GI tract also play an important role in the overall drug absorption process. For example, the stomach can exert grinding forces strong enough to physically crush certain formulations [18, 19]. Furthermore, it has been shown that the gastric residence time plays an important role in the bioavailability of lipid-based formulations [20].** Given the steep increase in the number of patients undergoing bariatric surgery, it is important to understand the role of the stomach in determining overall drug absorption [21]. **There is also renewed interest from pharmaceutical industry in the ileum and colon. In one study, Fadda *et al.* have shown an increase in pH and buffer capacity in intestinal fluids along the length of the GI tract [22]. Other studies have focussed on the composition and ultrastructure of contents in the ileum, cecum and ascending colon of healthy volunteers, after food intake and in patients with inflammatory bowel disorders [23-26].** Important knowledge gaps remain on the number and function of drug transporters in the ileum and colon, on the composition of colonic fluids and on the drug uptake and permeation process in patients with inflammatory bowel disorders and colonic cancer. This information is particularly important for developing formulations targeting drug release in the colon [27].

WG 3. Intraluminal behaviour of advanced formulations.

The large number of candidate drugs with suboptimal biopharmaceutical characteristics (BCS II-IV) is a major hurdle for the pharmaceutical industry. Several formulation strategies have been developed to increase drug bioavailability such as reducing particle size, using self-emulsifying drug delivery systems, cyclodextrins, solid dispersions and lipid-based formulations (reviewed in [28]). However, not every aspect of such enabling formulations is understood. **Questions remain regarding the creation and maintenance of supersaturation in the gut. For instance, the effects of lipolysis on drug release from lipid-based formulations are unknown [29]. The penetration of the intestinal mucosa by nanoparticles [30], uptake of dendrimer-drug conjugates and their transepithelial transport [31] are not well understood. In general, the selection of formulations is based on *in vitro* tests with limited relevance to GI behaviour, or relies on animal models with limited predictivity for the specific patient population.** This leads to poor predictivity of the *in vivo* behaviour and inefficient selection of the best drug delivery system.

WG 4. Food-drug interface.

Significant overlap exists between food and pharmaceutical sciences. Food intake has a major effect on gastric motility [32], pH, bile secretion and intestinal fluid composition (indirect food effects) [1]. Furthermore, specific food-drug interactions can have severe effects on drug absorption, as illustrated by the interactions between grapefruit juice, the OATP2B1 and P-glycoprotein drug transporters, and CYP3A4 metabolizing enzyme [33]. Research also indicates pharmacokinetic interactions between drugs and nutraceuticals [34]. In addition, food-derived lipids can interact with lipid-based formulations [35]. **For many other food components, the specific effects on drug absorption are unknown because of the**

heterogeneous composition of a typical meal and the complex interplay between food components, the intestinal environment and the drug product. As a consequence, food effects, especially negative food effects, are very challenging to predict. Since formulations can be resistant or susceptible to food effects, this makes the decision on the type of formulation for optimal drug delivery very difficult.

General: advanced methods and models to study drug absorption.

One of the major limiting factors in tackling the abovementioned challenges, is the technical difficulty of accessing or visualising the GI tract. This hampers the development of suitable user-friendly tools to accurately mimic and study the complex GI environment in the lab. Fortunately, several advanced technologies are now available to overcome this hurdle. For example, nuclear imaging techniques have been used in diagnostics, clinical drug development, for monitoring disease progression, and have expanded the use of preclinical small animal models of disease. **Preclinical nuclear imaging** is practically non-invasive and data is acquired in real time, without the need for animal euthanasia, making it applicable to longitudinal studies in pharmacokinetics, drug disposition and metabolism [36]. Moreover, **video capsule endoscopy** has been used successfully in patients with GI disorders to visualize the gut and to study drug behaviour. Potentially, it can also be used for local drug delivery and for sampling of intestinal fluids [37]. Other advanced techniques are used for the in-depth study of formulation behaviour. For example, **Surface Plasmon Resonance (SPR)** is capable of real-time label-free monitoring of drug-living cell interactions [38]. **Coherent anti-Stokes Raman Spectroscopy (CARS)** has been used in biomedical sciences (e.g. lipid imaging in cancer cells) and can be used to probe drug distribution in dosage forms, drug and excipient release, dissolution, interactions with cells, and potentially dissolved drug distribution in cells. [39]. However, questions remain as to how the setup can be further optimized and how results from advanced dissolution testing relate to pharmacopoeial dissolution testing methods. **Synchrotron small angle X-ray scattering** can be used to understand the generation of colloidal phases and the behaviour of lipid-based formulations [40]. Computational tools addressing the impact of formulation parameters and suitable *in vitro-in vivo* and *in silico-in vivo* correlations can make formulation work significantly more knowledge-driven. **Molecular dynamics (MD) simulations** have been used to study biological membranes, transport processes and to simulate simple surfactant systems in living cells, but are still relatively unexplored in the field of drug formulation and development [41].

Similarly, **pharmacometric models** accurately describing the pharmacokinetics and pharmacodynamics of (candidate) drugs can improve drug development and drug dosing. The fast progress in the field of pharmacometrics has resulted in several models and software packages (e.g. Simcyp simulator, NONMEM, GastroPlus, PK Sim) for dose prediction, clinical trial design and simulation of individual GI variability. However, most of these products were independently developed in parallel, resulting in different capabilities, purposes, programming language and algorithms. As a result, comparison and exchange of different models without the need for extensive modification, is almost impossible in practice. Recently, the Pharmacometrics Markup Language (pharmML) exchange format was developed as a first step towards defragmentation [42]. Moreover, the widespread application of pharmacometric models is hampered by the limited quantity and quality of data underpinning the models. This results in a low confidence level for predictions concerning pediatric or geriatric patients, certain ethnic minorities and BCS II-IV compounds [43].

The use of advanced methods will be key to progress the field on all 4 major challenges and is therefore integrated into WG 1-4.

II) PROGRESS BEYOND THE STATE-OF-THE-ART

Novel insight into the intraluminal behaviour of drugs and (advanced) formulations in specific patient populations, in the different parts of the GI tract and in the presence or absence of food components all contribute to improving clinical treatment and the development of better performing drugs. The key to achieving significant progress beyond the state-of-the-art lies in the interdisciplinary dialogue established in each of the WGs.

Specifically, the Action aims to improve the quality of predictive simulation tools. Clinicians and biopharmaceutical scientists with experience in human studies (e.g. endoscopy capsules, sampling of intestinal fluids) and with access to patients will interact with experts in the development and use of *in vitro* and *in/ex vivo* (small animal) models. They will be complemented by technology and software developers. The close interaction between technology developers and end-users will permit rapid improvements and a widespread implementation.

The introduction of advanced techniques and models allowing more in-depth studies of drug absorption to a wider audience will benefit the research community. For example, physiological effects caused by hydrodynamics, fluid volumes and food digestion are currently not taken into account in most *in vitro* models. The multi-scale approach for MD simulations allows time and spatial scale transformation/back-transformation, simulations of compositional changes and will give insight into structural rearrangements of drug delivery systems due to changes in intestinal fluid composition. The use of SPR to study interactions between small molecules and cell monolayers in physiologically relevant systems will provide valuable insight into interactions taking place at the gut wall. Capsule technology creates the opportunity for local delivery of drugs, visual inspection of gut (patho)physiology and sampling of intestinal fluids. The Action will compile a list of research institutions that have access to such technologies to promote their use.

By bringing together gastroenterologists and pharmaceutical scientists, the Action will foster a two-way dialogue that will result in improved knowledge on intestinal disorders and their effects on drug absorption. This will guide the development of efficient new oral therapeutics for various disorders, most notably intestinal inflammatory diseases and other disorders of the GI tract. The knowhow on the disease and experimental tools provided by gastroenterologists will lead to new insight into gut permeability and provide new means to study drug absorption in the diseased gut and help design suitable formulations. Moreover, by interacting with clinicians, access to patients and patient samples becomes feasible.

Clinical data on regional differences in intestinal absorption can be used by formulation scientists to design formulations for specific targeting of e.g. the colon, which has been identified by the pharmaceutical industry as an area of major interest for the development of new treatments. The data can also be used by computational modellers to more accurately predict drug and formulation behaviour in the different parts of the gut.

Similarly, fed state data from human volunteers can be used to more accurately simulate food-drug interactions and to develop formulations avoiding or exploiting food effects. The availability of analytical methods and *in vitro* models to study food intake and composition in addition to scientific expertise on food-drug interactions and in performing clinical studies with human volunteers in fed and fasted state will be of great value to advance our knowledge in this area.

III) INNOVATION IN TACKLING THE CHALLENGE

A better understanding of drug absorption in specific populations such as obese, pediatric and geriatric patients will contribute to the development of *in vitro*, *in silico* and small animal models capable of predicting drug and formulation behaviour for these populations. For example, in-depth profiling of the GI tract in patients after bariatric surgery will result in information that can be used to improve *in vitro* models to accurately mimic specific, complex situations. **A better understanding of GI (patho)physiology will also be key to develop a strategy to efficiently deliver drugs and maintain mucosal integrity in patients with intestinal inflammatory disorders.** In particular, bringing together experts in intestinal inflammatory disorders with drug developers creates a platform where information on the disease can be used as input for drug development and where candidate drugs can be tested in preclinical disease models. **Furthermore, by bringing together drug delivery scientists with experts from a major food company, the Action aims to stimulate scientific discussions between food and pharmaceutical sciences.**

The experimental techniques at reach within the Network allow comparison between *in silico* simulations, *in vitro* models and *in vivo* data, and facilitate *in vitro-in vivo* and *in silico-in vivo*

extrapolations. **The introduction of advanced techniques to a new audience will result in multiple innovative applications** such as the use of CARS to study formulation behaviour at a microscopic level. Furthermore, MD simulations of molecular interactions taking place in intestinal fluids will benefit tremendously from the Network's interdisciplinary expertise. The direct interaction between theoretical scientists and scientists performing *in vivo* studies will improve the quality of simulations.
Significant innovation is expected for computational models predicting (candidate) drug and formulation behaviour. The biggest bottleneck in their widespread use is the lack or insufficient quality of data underpinning the models. By **fostering data exchange between members**, the Action will help to overcome this limitation. Moreover, the Action will **promote the deposition of computational models in open access repositories such as DDMoRe (see 1.4.2) and the use of the PharmML language to increase their dissemination and implementation**.

D) ADDED VALUE OF NETWORKING

I) IN RELATION TO THE CHALLENGE

Typically, researchers tend to focus mainly on their own area of expertise. However, efficient treatment of a patient with an orally administered drug is by definition the end-result of interdisciplinary collaboration, both in drug development and in drug treatment. In practice, the available knowhow and expertise is often underused, due to insufficient and/or inefficient interaction between the different actors. To design drug delivery systems that efficiently interact with and take advantage of the features of the GI tract, exploitable knowledge on gut (patho)physiology and drug disposition in specific patient populations is required. This is typically the area of expertise of gastroenterologists, biomedical scientists, and cell biologists. Drug delivery systems are designed by formulation scientists with expertise in chemical and material sciences. The behaviour of new formulations can subsequently be assessed by biopharmaceutical scientists in computational, *in vitro* and *in/ex vivo* models. For this, they rely on technology developers and (bio)informaticians to provide the experimental tools. All these actors will engage in scientific discussions in UNGAP.
To create a truly interdisciplinary network, the Network will structure itself in different WGs, each focussing on a major current challenge in oral drug absorption. This will lead to the optimal use of the available knowledge and means, a better understanding of drug disposition in specific patient populations, more profound knowledge on the specific behaviour of advanced formulations and on food-drug interactions.

II) IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

The Network is composed of scientists with expertise in several disciplines related to oral drug absorption. To maximize efficiency and impact, links with other networks or projects will be sought. Specifically, the Action will seek interaction with follow-up networks and activities from the finished COST Action **Infogest** (FA1005; 2011-2015; digestion and effect of food components on human health), in which several UNGAP members participated. Beyond COST, the Action will seek to interact with the IMI projects **DDMoRe** (www.ddmore.eu; 2011-2016; pharmacometrics), **COMPACT** (www.compact-research.org; 2012-2017; macromolecular therapeutics) and **OrBiTo** (www.orbitoproject.eu; 2012-2017; *in vitro* tools for oral drugs), the FP7 project **TRANS-INT** (www.trans-int.eu; 2012-2017; oral nanomedicines) and Horizon 2020 European Training Network **PEARRL** (www.pearrl.eu; 2016-2020; regulatory science tools).
The Action shares links with several individual research topics of these projects, but has a broader composition, with scientists from academia and pharmaceutical industry, clinicians, technology and software developers, and regulatory authorities participating. The Network aims to connect scientists from different disciplines, sectors and countries that otherwise would not or rarely interact. For example, researchers from some European countries are

underrepresented in the aforementioned projects limiting their potential impact in these regions. By creating a true pan-European Network, UNGAP will have a leveraging effect on intestinal drug absorption research in these countries. Furthermore, because the Network has a wide scope and is not constructed with one specific research objective in mind (e.g. better *in vitro* tools), **UNGAP is better suited to develop into a long-term sustainable Network that can respond to emerging challenges and opportunities.** In this respect, the participation of representatives from several pharmaceutical companies will be a major advantage that will help identify important research areas and facilitate pre-competititve collaboration and open innovation. Finally, the aforementioned projects are all scheduled to end in the following years and it is important that existing collaborative ties are re-embedded in a sustainable Network, where they can be maintained and expanded.
Beyond Europe, the **American Association for Pharmaceutical Sciences (AAPS)** is the biggest professional society in pharmaceutical sciences. By carefully selecting network participants from the USA, the Network will be able to interact with AAPS and effectively reach a global audience. Specifically, the Action will seek to establish links with the AAPS focus group on oral absorption (www.aaps.org/FocusGroups/).

2) IMPACT

A) EXPECTED IMPACT

I) SHORT-TERM AND LONG-TERM SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS

The proposed Action will ensure a pooling of specialized means, resources and know-how that will result in an overall increase in research quality and have impact on a number of areas.
The main expected scientific impact is the improved knowledge on the specific challenges (specific patient populations, food-drug interactions, regional differences, advanced formulations) and the integration thereof to obtain a holistic view. For example, new insight into food-drug interactions and drug behaviour in specific patient populations can influence dosing regimens and formulation design. Likewise, information on changing parameters along the GI tract (e.g. pH), and the *in vivo* behaviour of advanced formulations can be used by drug developers to improve drug delivery systems. A more patient-centric and knowledge-driven drug development process will have the advantage of reducing animal and clinical studies. It will also contribute to the development of dosing regimens that are optimized for specific patient populations, thus improving clinical outcome. Moreover, the expanded knowledge can help improve the regulatory decision making process.
Technological impact will be achieved at different levels. At the level of the end-user, the Network will act as a troubleshooting platform by bringing them in direct contact with technology developers, who can help solve the problems they are faced with in research practice. **At the level of technology developers, direct feedback from end-users will spur technological improvement. At the level of the Network itself, the mix of software and technology developers and end-users is ideal to develop and/or improve *in vitro*, *in/ex vivo* and *in silico* tools and models and move rapidly across technological and intellectual barriers.** These tools and models will be made available to the wider research community by depositing them in open access repositories and through pro-active dissemination in the research community. They will also be communicated to clinicians and regulatory authorities for implementation in dose adjustment strategies and in the regulatory decision making process. In this respect, the biowaiver procedure by the FDA, EMA and the World Health Organisation based on the Biopharmaceutics Classification System presents an excellent example of how a research achievement can become part of the regulatory decision making process [44, 45]. **At the level of the wider research community, the Action will improve comparability and reproducibility of assays and results accross different disciplines** by compiling a catalogue of standardized experimental methods, protocols and best practice guidelines. This will allow the development of a consistent data set and will start an interactive, positive feedback loop for assay monitoring and improvement. This step

towards standardization of drug development research will benefit academic researchers and the pharmaceutical industry, who generate and work with the data, regulatory authorities, who review the data, and eventually also clinicians and patients, who prescribe and take the drugs respectively.
The Action will also generate **socioeconomic impact**. Firstly, **for the scientists involved, it presents an opportunity to expand their professional network**. This benefit is emphasized by the fact that the Network looks specifically for upcoming research talent and seeks to connect quality research groups from less research intensive countries with leading research groups and companies from Europe, the USA and Australia. Secondly, the abovementioned scientific and technological benefits may be used to **improve the drug development process**, making it more cost-effective and less time-consuming, thus, potentially having major socioeconomic benefits in the long run. Thirdly, the use of pharmacometric models for treatment individualisation will **improve clinical outcome and benefit the patient's health**. In this respect, it should be noted that the historical success of oral drug administration is partially based on mass production of fixed dosage units. For drugs with a large therapeutic window, it is likely that this will stay the preferred, economically advantageous route. However, for (new) drugs with a high development or manufacturing cost or a narrow therapeutic window, treatment individualisation will be preferable from both an economic and therapeutic point of view.

B) MEASURES TO MAXIMISE IMPACT

I) PLAN FOR INVOLVING THE MOST RELEVANT STAKEHOLDERS

The Action aims to set up and maintain a pan-European network of scientists focussing on oral drugs, by removing scientific, technological and geographical barriers. As a consequence, many stakeholders are connected to this Action (listed in Table 1). They will be involved through active participation in the Action or via targeted communication measures (Table 1, Section 2.2.2).**Biopharmaceutical scientists** constitute the majority of the Network. Their main interest is to better understand intraluminal drug and formulation behaviour and overall drug absorption. They will contribute to and benefit from knowledge defragmentation, the insight obtained and the scientific discussions in the WGs. **Formulation scientists** will exploit this knowledge to develop better performing drug products. They are complemented by **computational modellers**, who use the obtained knowledge as input for computational models that can guide formulation design and dose optimisation. For **technology developers** the main interest is the direct interaction with technology end-users enabling an efficient dialogue that permits faster technological advancement. The (long-term) end-users benefitting from the Network are the pharmaceutical industry on the one hand and clinicians and patients on the other hand**.** For **the pharmaceutical industry**, the goal is to develop better drugs in a more cost-effective and less time-consuming way. For this purpose, knowledge defragmentation, standardized protocols and improved simulation tools will be important. **Clinicians and patients** will benefit from models that can guide dose optimisation and improve treatment outcome. **Regulatory authorities** are looking to improve the regulatory process. Improved knowledge on interactions with food, on drug and formulation behaviour in specific patient populations, and in different parts of the GI tract will help achieve this goal. This will be further enhanced by icreased reproducibility and comparability and through computational models that can predict drug and formulation behaviour. Of note, institutional policies often do not allow the formal participation of regulatory authorities. Nevertheless, the Action plans to interact with regulatory authoritiy which will take up a role as external advisor and provide input from the regulatory point-of-view. In addition, the Action will involve experts from regulatory authorities as member(s) who will provide regulatory insight.

Table 1 Stakeholder analysis of the UNGAP network

Stakeholder	Interests	Goals	Tools
Biopharmaceutical and formulation scientists, computational modellers	New knowledge, protocols and best practices, new simulation tools	To understand absorption, to improve drug development and treatment	Network meetings, Short-Term Scientific Missions (STSMs), workshops, training school, conference, seminars, webinars, publications
Technology developers	Interaction with end-users	New or improved technology	Network meetings, STSMs, workshops, training school, conference, seminars, webinars, newsletters,
Pharmaceutical industry	New knowledge, protocols and best practices, new simulation tools	To improve the drug development process	Network meetings, STSMs, workshops, training school, conference, seminars, webinars, newsletter, factsheets, publications
Clinicians & patients	New knowledge, pharmacometric models	To improve dosing and treatment	Conference, seminars, webinars, newsletters, factsheets, posters, leaflets, publications
Regulatory authority	New knowledge, protocols and best practices, new simulation tools	To improve the regulatory process	Network meetings, STSMs, workshops, training school, conference, seminars, webinars, newsletter, factsheets, publications

II) DISSEMINATION AND/OR EXPLOITATION PLAN

A specific cross-cutting WG will be dedicated to communication, dissemination and exploitation in order to maximise the impact of the Action. To this end, WG 5 leaders will closely interact with WG 1-4 leaders (to be appointed, see 3.2) and the Action Management Committee (MC). Dissemination and exploitation plans are discussed in detail below.

Dissemination

The Action aims to disseminate its key findings to all stakeholders mentioned in Table 1, by using a balanced and varied dissemination strategy. The following dissemination tools will be used:

- **Publications in peer-reviewed scientific journals** present the most obvious dissemination route. To widen exposure, the Action will adopt the Horizon 2020 open access policy.
- **Thematic hands-on workshops and a training school** will be organised. Participants will be able to gain technical expertise and exchange best practices. It will also be an opportunity for technology developers to showcase their latest innovations.
- The Action will **interact with other networks** (see 1.4.2) to wider promote and disseminate the Action.
- **Regular seminars and webinars** will be organised. Targeted communication through the institutions and professional network of Action members will be used to advertise these events to external stakeholders such as clinicians and regulatory agencies.
- **A website www.UNGAP.eu** with an open and closed part for external and internal communication respectively will be made.
- The Network will be active on **social media.** A Twitter account will be used to send short messages and keep in touch with the latest developments. LinkedIn will be used to communicate to professionals outside the Network.

- **A newsletter** highlighting Network activities and findings will be published twice a year. Interested persons will be able to subscribe to the newsletter via the website.
- **Posters and leaflets** will be used to promote the Action, attract additional members and highlight achievements. They will also be used for communication to clinicians and patients.
- **Factsheets** will be made to communicate findings, best practices and recommendations in a condensed format.
- The Action will target **mainstream media** through institutional press and media services.
- The Action will **organise a final conference to highlight and disseminate the results of the Action.**

Exploitation

Since the Action focusses on networking and establishing new connections and not on development of a specific product, a policy will be adopted to facilitate the exchange of researchers and know-how between the partners in the spirit of open science and open innovation. Within the Network, expert advise on the protection and exploitation of IPwill be available. The main exploitable results from the Action are the new insights obtained through WG discussions, knowledge defragmentation and the elaboration of new collaborative research projects between Network members. The development of new tools and models presents another exploitable Action outcome. This will be particularly important for *in silico* models where there is a high pace and relatively low development cost, making the creation of new models feasible within the timeframe of the proposed Action. Exploitation will be done in collaboration with the developers. The Action will strive to exploit and disseminate the models as wide and as efficient as possible.

Indirectly, the Action will also contribute to advances in specific research projects (funded through other sources) that may lead to exploitable results. When applicable, protection of intellectual property (IP) for a given project will be done in accordance with the project funding agencies' specific rules and guidelines. In case sensitive material with respect to intellectual property rights (IPR) or confidentiality is presented during meetings, non-disclosure agreements will be used.

C) POTENTIAL FOR INNOVATION VERSUS RISK LEVEL

I) POTENTIAL FOR SCIENTIFIC, TECHNOLOGICAL AND/OR SOCIOECONOMIC INNOVATION BREAKTHROUGHS

In order to establish a coherent Network with maximal chances of achieving significant progress and potentially a real breakthrough in a field as diverse and complex as drug disposition, we chose to limit our scope to oral drug absorption. The main objective is to make substantial progress in selected key areas and as such advance the field as a whole.

New insight into **the effects of (patho)physiological variables on oral drug absorption** can be used to tailor dosing schemes to specific populations, such as pediatric or geriatric patients. A better understanding of the **regional differences along the GI tract** will contribute to the design of formulations that efficiently exploit the GI environment to obtain optimal absorption at the desired site. For example, development of colon targeting drugs will benefit from a better understanding of formulation behaviour in the colon, but also the upper parts of the GI tract. Information on the **specific behaviour of advanced formulations** can help explain why certain formulations succeed or fail. This will make formulation design more knowledge-driven and efficient. **Exploitable knowledge on food effects and the interaction of food components with the gut, drugs and formulations** can improve drug safety and efficacy. It is also of particular interest to drug developers working with lipophilic drugs, like many drug candidates currently in development, since food intake can affect the solubility as well as the permeability. Although the challenges are major, the potential impact on improving drug development and treatment is large. The risk of not achieving significant progress in this area is reduced by the presence of experts in gastroenterology, biopharmacy, drug development, technology development as well as a major company from the food industry in the Network.

Dissemination of protocols and best practices will improve comparability and reproducibility of results and boost the overall confidence level of knowledge on oral drug

absorption. This will not lead to direct innovation, but will have a beneficial effect on the quality of future research projects and innovations resulting from them.
Technological advancements can be divided into new applications and improvements of existing applications. The latter is expected to have a medium to high potential for innovation, depending on the extent of the improvements made, but also a lower risk, since there is already a foundation to build on. In contrast, new applications have a higher innovation potential, including possible commercialisation in the future, but are more difficult to achieve within the time-frame of the Action.
Development or improvement of computational models is realistic within the Action time-frame, because of the high speed of developments in this field and the Action plans to involve experienced software developer(s). A lack of data on specific patient populations and the effects of food components, which are focus areas of WG 1 and 4 respectively, presents the biggest limitation in the application of computational models. The data obtained from current research projects on food effects and specific patient populations will contribute to the development or improvement of computational models, which in turn can be used by pharmaceutical industry or clinicians, for improved drug development or optimised dosing respectively, thus having a mainly economical or mainly societal impact.
Finally, on an individual level, the Action will have impact on two specific things. Firstly, **elaborating new research project proposals** is highly feasible. The focus on specific challenges and the multidisciplinary mix of Network participants make the Network ideally suited to respond to specific calls and develop collaborative research projects. All Network proposers have a successful track record in securing (international) funding for research projects. Secondly, the Action will allow **ECIs to expand their professional network, which is expected to have a beneficial effect on their careers**.

3) IMPLEMENTATION

A) DESCRIPTION OF THE WORK PLAN

I) DESCRIPTION OF WORKING GROUPS

The Action will consist of 5 WGs that are all interconnected (Fig. 1). A description of the WGs follows hereafter. Milestones and deliverables are listed in Table 2.

WG 1. Specific patient populations.

Objective: The objective of this WG is to acquire a profound insight into (patho)physiological variables influencing oral drug absorption in specific patient populations.

Tasks & activities:

- Publish a review on the state-of-the-art and the remaining knowledge gaps on intestinal drug absorption in specific patient populations.
- Collect and exchange emerging knowledge on drug absorption in specific patient populations.
- Organise STSMs with specific attention for interdisciplinary and inter-WG mobility.
- Publish guidelines and protocols to study drug absorption in specific patient populations.
- Organise 2 hands-on workshops on methods to study (patho)physiology and intestinal drug absorption in specific patient populations (in collaboration with WG 2-5).
- Organise a training school on intestinal drug absorption (together with WG 2-5).
- Publish a position paper with an outlook on the future of intestinal drug absorption research (together with WG 2-5).
- Develop new collaborative research project proposals (Target: 2 submitted proposals per WG)

WG 2. Regional differences along the GI tract.

Objective: The objective of this WG is to acquire a deeper insight into the regional differences along the GI tract, which is particularly important for extended release formulations, which

release the drug over a wider area, and for formulations targeting specific regions of the gut, for example the colon.

Tasks & activities:

- Publish a review on the state-of-the-art and the remaining knowledge gaps concerning differences in intestinal drug absorption along the length of the GI tract.
- Collect and exchange emerging information on regional differences in the gut in terms of fluid composition, membrane permeability, transporter and enzyme expression, and absorptive capacity.
- Organise STSMs with specific attention for researcher mobility between labs focussing on different parts of the GI tract.
- Publish guidelines and protocols with a focus on how methods can be used to study different parts of the gut and how data can be compared and integrated.
- Organise 2 hands-on workshops focussing on methodology and data interpretation (in collaboration with WG 1, 3, 4 and 5).
- Organise a training school on intestinal drug absorption (together with WG 1, 3, 4 and 5).
- Publish a position paper with an outlook on the future of intestinal drug absorption research (together with WG 1, 3, 4 and 5).
- Develop new collaborative research project proposals (Target: 2 submitted proposals per WG).

WG 3. Intraluminal behaviour of advanced formulations.

Objective: The objective of this WG is to deepen our understanding of the specific behaviour of advanced formulations, such as supersaturating formulations, extended release formulations, lipid-based drug delivery systems and nanoparticles.

Tasks & activities:

- Publish a review on the state-of-the-art and the remaining knowledge gaps concerning the intraluminal behaviour of advanced formulations.
- Collect and exchange emerging knowledge on the intaluminal behaviour of existing advanced formulations and on new types of enabling formulations.
- Organise STSMs with specific attention for mobility between different WGs.
- Publish guidelines and protocols for formulation design.
- Organise a training school on intestinal drug absorption (together with WG 1, 2, 4 and 5).
- Publish a position paper with an outlook on the future of intestinal drug absorption research (together with WG 1, 2, 4 and 5).
- Develop new collaborative research project proposals (Target: 2 submitted proposals per WG).

WG 4. Food-drug interface.

Objective: The objective of this WG is to study the effects of food intake and food components on the intraluminal behaviour of drugs and formulations.

Tasks & activities:

- Publish a review on the state-of-the-art and the remaining knowledge gaps concerning food effects and the interactions between food components and oral formulations.
- Collect and exchange emerging knowledge on food effects and food-drug interactions.
- Organise STSMs with specific attention for mobility between different WGs.
- Publish guidelines and protocols to study food effects and food-drug interactions.
- Organise 2 hands-on workshops on the interface between food and pharmaceutical science (in collaboration with WG 1-3 and 5).
- Organise a training school on intestinal drug absorption (together with WG 1-3 and 5).
- Publish a position paper with an outlook on the future of intestinal drug absorption research (together with WG 1-3 and 5).
- Develop new collaborative research project proposals (Target: 2 submitted proposals per WG).

WG 5. Dissemination, exploitation and public engagement.

Objective: The objective of this WG is to coordinate all communication, dissemination and exploitation activities to assure an efficient flow of information to all stakeholders while at the same time respecting and protecting the IP of all parties involved.

Tasks & activities:

- Establish a procedure for handling confidential or IP-sensitive information.
- Coordinate the publication of reviews, protocols and the position paper.
- Use newsletters, posters, factsheets and leaflets to present findings in a condensed format.
- Set-up and maintain a website as a dissemination and internal communication platform.
- Organise webinars, seminars and a conference on oral drug absorption.
- Coordinate the organisation of a training school on intestinal drug absorption (together with WG 1-4).
- Contribute to the elaboration of new collaborative research projects (together with WG 1-4).
- Develop new collaborative research project proposals (Target: 2 submitted proposals per WG).

Table 2 list of milestones and deliverables

Description	***Month***	***Milestone***	***Deliverable***
1st MC meeting, assignment of WG leaders and other functions	*1*	*1*	*1*
Website online and social media profiles active	*6*	*2*	*2*
Publication of WG reviews	*18*	*/*	*3*
1st STSMs	*18*	*3*	*/*
Catalogue of protocols and best practice guidelines	*18*	*/*	*4*
1st workshop	*18*	*4*	*5*
Training school (1 for the entire Action)	*30*	*5*	*6*
Publication of joint position paper	*40*	*/*	*7*
2nd workshop	*40*	*6*	*8*
UNGAP conference	*44*	*7*	*9*

II) GANTT DIAGRAM

Description	***Project month***																
	1	***3***	***6***	***9***	***12***	***15***	***18***	***21***	***24***	***27***	***30***	***33***	***36***	***40***	***42***	***44***	***48***
MC meeting	*X*		*X*		*X*		*X*		*X*		*X*		*X*		*X*		*X*
WG meeting		*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*	*X*
Website online			*X*														
Reviews (4)							*X*										
1st STSMs							*X*										
Protocol and guidelines catalogue							*X*										
1st workshop							*X*										
Training school											*X*						
Position paper														*X*			
2nd workshop														*X*			
UNGAP conference																*X*	

III) RISK AND CONTINGENCY PLANS

Description of Risk	***Proposed mitigation measures***
No input for protocol and best practice catalogue	*Rewarding active participation in Network activities through reimbursement schemes. The goal for each Network member is to submit at least 2 documents.*
Incoherent WG work plan	*Work plan adaptation by WG leaders and MC*
Insufficient WG progress	*(i) Recruitment of additional members to WG. (ii) Intensify collaboration with Action members from other WGs.*
Dormant Action members	*(i) Financial incentives (through reimbursement schemes) for active Network-members. (ii) Replacement of dormant members*
Exploitation and/or dissemination conflict	*(i) Establish a procedure to avoid conflicts. (ii) Conflicts handled by WG 5 leaders and MC to negotiate a solution*
Insufficient impact	*Impact maximization through pro-active interaction with stakeholders, coordinated by WG 5 leaders.*
Insufficient gender balance	*Pro-active recruitment aiming for 40% of the under-represented category.*
Conflict between scientific quality and COST policy	*(i) Search for a compromise by MC. (ii) If no compromise can be reached, quality will be preferred.*
Withdrawal by a network member	*All hereto identified network members have expressed their commitment. In case of withdrawal of a MC member, WG leader or task responsible, a suitable replacement will be identified (i) within UNGAP or (ii) via the professional network of other Action members.*

Note: Roman numbers refer to the order in which mitigation measures will be taken.

B) MANAGEMENT STRUCTURES AND PROCEDURES

Management Committee: The MC will be formed and will function according to the Rules and Procedures described in COST 4112/13 “COST Rules for Participation in and Implementation of COST Activities”. The Action Chair is responsible for management and coordination of the Action. The MC consisting of the Chair, Vice-Chair and max. 2 representatives per country, is the primary decision-making body and will meet twice a year to oversee all activities carried out under this Action. At least one MC meeting per year will be face to face and organised in conjunction with a meeting of the WGs. If deemed feasible, the other meeting may be done via teleconference to restrict travel demands for MC members. The MC will carry out the following tasks: (i) prepare and manage the annual detailed work and budget plan, (ii) create a set of rules for the WGs to carry out their activities, (iii) allocate funds to activities according to Grant Period goals of every WG, (iv) monitor progress in the WGs, based on the milestones and deliverables described in Table 2, interaction with WG Leaders and annual WG progress reports, and take corrective action when necessary, (v) coordinate the organisation of meetings, workshops, training school and conference, and (vi) coordinate interactions with external stakeholders.

Working Groups (WGs): WG 1-4 have a scientific focus, with each group acting as a coordination node for their respective research topic. WG 5 will entail all dissemination, exploitation and public engagement activities and will as such extensively interact with WG 1-4. Each WG will be organised by two WG Leaders who will be nominated during the first MC meeting. WG Leaders will identify additional Task Responsible persons to carry out specific tasks (organisation of workshops, coordinate STSM programme, website maintenance). The WG Leaders will oversee the organisation of these activities and will act as liaison with the MC. In addition, they will be responsible for submitting an annual report to the MC to evaluate progress on the milestones, deliverables and the different tasks and activities. The WG Leaders will meet face to face at least once a year in conjunction with an MC meeting. Task Responsible persons may be invited to this meeting, when their participation is deemed

necessary. Ordinary WG meetings (every three months) will be done via teleconference as much as possible to reduce travel and time demands. Face to face WG meetings will be organised on 1 location to promote interactions between WGs. Meetings will be planned by the WG Leaders, following the approval of the MC and the Action Science Officer.

C) NETWORK AS A WHOLE

Several of the world's leading **pharmaceutical companies** will be involved in the Network, in addition to several **gastroenterologists** and a large number of **pharmaceutical, biological and biomedical scientists**. The consortium will contain well established as well as upcoming research groups and will cover various disciplines including biopharmacy, gastroenterology, physical chemistry, drug delivery, (bio)imaging, and pharmacometrics. All research groups participating in this Action will have (inter)national funding for their own research programmes. The presence of **technology and computational software developers** will ensure promotion of the latest products, their proper use and the creation of an efficient feedback loop from end-users to developers. Finally, an external advise will be provided by representative(s) from **regulatory authority**, in line with the institutional policy. The network in composition as described above will guarantee that the planned work will be carried out successfully and that significant impact will be achieved.
The Action plans also to establish links with the oral drug absorption research communities in Australia and the USA. The researchers from Australia are leaders in the use of lipid-based systems, dendrimers and nanomaterials for drug delivery and experts in synchrotron small angle X-ray scattering, and the researchers from the USA, authorities in the fields of drug solubility, drug transport, and drug absorption, and the representatives from major pharmaceutical companies. The international members will increase the Network's scientific critical mass and allow the Network to achieve worldwide impact. In return, they will be invited to attend Network events and temporarily host ECIs and other researchers.

REFERENCES

1. Riethorst et al. J Pharm Sci. 105(2):673-81 (2016)
2. Jinno et al. J Pharm Sci. 89(2):268-74. (2000)
3. Porter et al. Nat Rev Drug Discov. 6(3):231-48. (2007)
4. Michielan, D'Incà. Mediators Inflamm.2015:628157. (2015)
5. Li et al. Expert Opin Drug Metab Toxicol. 12(1):31-40. (2016)
6. Mukonzo et al. PLoS One. 9(1):e86919. (2014)
7. Waring et al. Nat Rev Drug Discov.14(7):475-86. (2015)
8. The CDER Science Prioritization and Review Committee. Identifying CDER's Science and Research Needs Report. (2011)
9. FDA call: "Integrating Supersaturation-precipitation Mechanisms in Mechanistic Oral Absorption Models for Predicting In-vivo Performance of Associated Formulations" (U01) https://grants.nih.gov/grants/guide/rfa-files/RFA-FD-16-025.html
10. European Medicines Agency Work Programme 2016. EMA/92499/2016. (2016)
11. Budha et al. Clin Pharmacol Ther. 92(2):203-13. (2012)
12. De Smet et al. J Clin Pharmacol. 53(4):361-76. (2013)
13. Ranmal et al. Int J Pharm. 30;514(1):296-307. (2016)
14. Knibbe et al. Annu Rev Pharmacol Toxicol. 55:149-67. (2015)
15. Bischoff et al. BMC Gastroenterol. 14:189. (2014)
16. Ono et al. Pharmacogenomics. 14(14):1745-64. (2013)
17. Merchant et al. Int J Pharm. 30;512(2):382-395 (2016)
18. Katori et al. Pharm Res. 13(10):1541-6. (1996)
19. Kamba et al. Int J Pharm. 208(1-2):61-70. (2000)
20. Lee et al. J Pharm Sci. 102(11):3957-65. (2013)
21. Brocks et al. Expert Opin Drug Metab Toxicol. 8(12):1505-19. (2012)
22. Fadda et al. Mol Pharm. 7(5):1527-32. (2010)
23. Müllertz et al. J Pharm Pharmacol. 65(10):1482-7. (2013)
24. Reppas et al. Pharm Res. 32(10):3338-49. (2015)
25. Diakidou et al. Pharm Res. 26(9):2141-51. (2009)
26. Vertzoni et al. Pharm Res. 27(8):1620-6. (2010)
27. Amidon et al. AAPS PharmSciTech. 16(4):731-41 (2015)
28. Williams et al. Pharmacol Rev. 65(1):315-499. (2013)
29. Carrière. Biochimie. pii: S0300-9084(15)00363-6. (2015)
30. Li et al. J Control Release. 133(3):238-44. (2009)
31. Sadekar et al. Adv Drug Deliv Rev. 64(6):571-88. (2012)
32. Koziolek et al. J Control Release. 220(Pt A):71-8. (2015)
33. Nakanishi, Tamai. Curr Drug Metab. 16(9):753-64. (2015)
34. Sprouse, van Breemen. Drug Metab Dispos. 44(2):162-71.(2016)
35. Mueller et al. Pharm Res.11(1):151-5. (1994)
36. Lienemann et al.Sci Rep. 5:10238. (2015)
37. Koziolek et al. J Pharm Sci. 104(9):2855-63. (2015)
38. Viitala et al. PLoS One. 8(8):e72192. (2013)
39. Potcoava et al. J Biomed Opt. 19(11):111605. (2014)
40. Phan et al. Eur J Pharm Biopharm.96:117-24. (2015)
41. Bergström et al. Adv Drug Deliv Rev. pii: S0169-409X(16)30056-4. (2016)
42. Swat et al. CPT Pharmacometrics Syst Pharmacol. 4(6):316-9. (2015)
43. Jones et al. Clin Pharmacol Ther.97(3):247-62. (2015)
44. Amidon et al. Pharm Res. 12:413–20. (1995)
45. Davit et al. AAPS J. Epub ahead of print. (2016)