Innovative Medicines Initiative (IMI) Case Study Analysis Reveals The True Added Value Of Early-phase Public-Private Partnerships (PPPs)

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Introduction

The Innovative Medicines Initiative (IMI) is a Joint Technology Initiative (JTI) between the European Union, represented by the European Commission (EC), and the European Federation of Pharmaceutical Industries and Associations (EFPIA). IMI is currently the world's largest PPP in the biomedical sciences (Box 1). The IMI was set up to boost the competitiveness of Europe in the biopharmaceutical field and was launched in 2008 upon identification of the key bottlenecks in research that should be overcome to stimulate innovation in the drug development process [1]. IMI brings the different stakeholders (pharmaceutical companies, Small- and Medium-sized Enterprises (SMEs), universities, public research laboratories, POs and healthcare regulators) together in PPPs. The IMI is situated at a pre-discovery or proof-of-concept (POC) stage and covers early research to improve needed and poorly understood science. The IMI Strategic Research Agenda (SRA), targeting key challenges such as safety and efficacy prediction, knowledge management and education and training, was implemented to enhance the competitiveness of the pharmaceutical sector in Europe for the benefit of patients and scientists [2, 3]. In 2009, the first IMI consortia conducting projects addressing the SRA key challenges were initiated. Since then, IMI has already launched 49 consortia via 11 competitive Calls, and project execution of IMI projects will run until end of 2017 [4]. The total

budget allocated to IMI is 2 billion euros (2008-2014), money equally invested by the EC (cash contribution) and EFPIA (in-kind and cash contribution) [5, 6].

The progress in view of the planned activities, the main achievements, and information about the bibliometric outcomes of IMI's consortia in terms of publications, citation impact as well as co-authorship patterns are continuously monitored by the IMI Executive Office (IMI EO) and evaluated by external reviewers [7-10]. The IMI has been positively evaluated by a panel of independent experts [11-13], not at least in view of the creation of IMI 2 under Horizon 2020 in 2014 [14]. The expert panel prepared an executive summary document to support such IMI 2 creation, stating that IMI 2 should build upon the lessons learned from IMI [15]. IMI 2 has already launched 4 Calls for Proposals.

The consortia focusing on projects targeting the development of new methods and tools for safer and more effective drugs are inherently more prone to Intellectual Property Rights (IPRs) issues than consortia focusing on knowledge management projects. The former consortia represent the majority of the IMI consortia. With the first IMI consortia heading towards the project end, it is time to take stock of the added value and the (so far unexplored) opportunities of the consortia under the umbrella of IMI. Currently there is a lack of empirical studies wherein the effectiveness of these partnerships is assessed. Not much research has been performed to identify the key components of successful PPPs [16-18]. We set up a case study analysis to investigate the outputs on the short term and the outcomes on the long term of 6 IMI consortia reaching the project end. The specific case studies define the (missed) business opportunities and reveal the added value for science and society.

Box 1: IMI in Numbers [19]

23 patient organizations (POs), 14 regulators, 714 academic & research teams, 410 EFPIA teams, 135 SMEs, More than 6000 researchers, 61% of projects reported some form of patient involvement, 12 regulators on boards of projects, 50% of projects have representatives of regulatory authorities on scientific advisory boards.

RESULTS

Launch of the projects and scientific deliverables

The scientific deliverables of the selected IMI PPP projects are listed in the Description of Work, the detailed project plan agreed by the partners before the project start and are in line with the reviewed Project Proposal. In 2 projects, some delays to start have been reported, e.g. U-BIOPRED faced scientific delay due to the withdrawal of a partner, but has managed to attract new partners and made up for the loss of time and funding. Another example was SUMMIT that faced significant scientific delays due to an unexpected higher grade of complexity for sample selection for the Genome Wide Association Study (GWAS) and accompanying work on phenotype definitions as well as on the design and negotiation of data and material transfer agreements, further also a change of scientific strategy aspects due to reappraisal of the SUMMIT strategy for genetic discovery based on current state-of-the-art. However, the delays have been argued elaborately in the Periodic Reports and have been evaluated and commented by an Independent Expert Panel. The delays have all been eliminated in the course of the project. In the 6 consortia analyzed, numerous scientific outputs have been delivered, including research tools such as rat and mouse models, biomarkers, software tools for biomarker identification or toxicity prediction and new and improved imaging techniques (Table 1).

Table 1. Main scientific results from the 6 IMI projects analyzed
Imaging techniques → Non-invasive method (patent appl) (SUMMIT) → Touchscreen cognitive testing platform (NEWMEDS) → Probe (erf meld) (SUMMIT)
Stratification tools and methods (SUMMIT, IMIDIA, NEWMEDS) → Individual biomarkers → 'Omics' platform – Phenotype handprint (U-BIOPRED) → Clinical trial design criteria (NEWMEDS)
Animal models (SUMMIT (rat – patent appl), NEWMEDS, U-BIOPRED)
Software tools → Predictive models (SUMMIT, eTOX) → Open, interoperable information platform (Open PHACTS)
Research tools → Human prancreatic β-cell line (IMIDIA)
Antibodies (SUMMIT)

Clinical trial design criteria have been designed, clinical trials have been set up and biosamples have been collected in (centralized) biobanks. Large unique datasets have been combined in massive database constructs. The scientific excellence is reflected in the number of highly-cited papers (Fig.1)

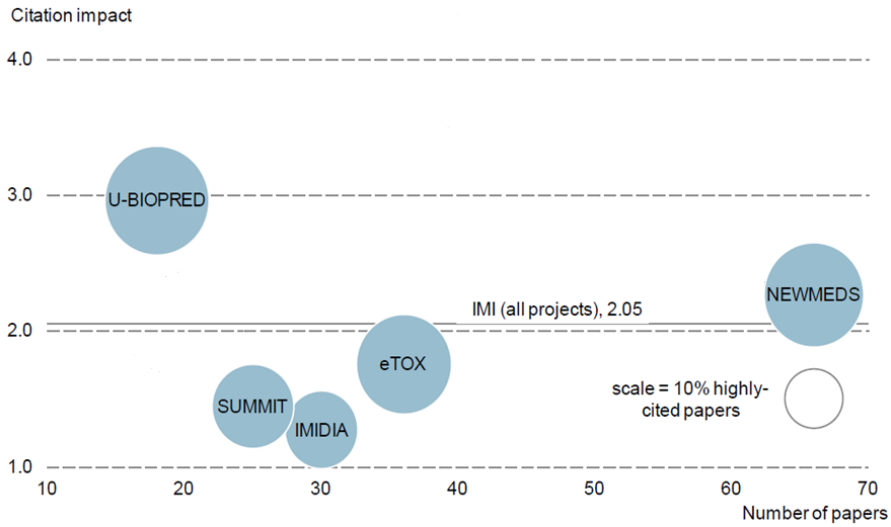

Fig. 1 – Thomson Reuters' Figure on Paper Numbers, 4-year average citation impact and share of highly-cited research for the selected IMI projects – Call 1 (the figure has been adapted to display only the projects analyzed in this case study) – The average citation impact of all research-based projects is above world average (1.0) and the percentage of highly-cited research is above world average (10%). Research associated with NEWMEDS is cited over twice world average and research associated with U-BIOPRED is cited nearly three times world average (2.96). This shows the scientific excellence of the research performance of IMI-associated research [10].

Table 2. Summary patent applications for 6 IMI projects analyzed in the case study

Project	Patent title	Patent number	Priority date	Applicant
IMIDIA	Human pancreatic beta cell lines for diagnostic of diabetes	EP2121905A1, US20110318389	Feb. 21, 2007	Sarl Endocells, Institut National de la Santé et de la Recherche Médicale (INSERM), Centre National de la Recherche Scientifique (CNRS)
SUMMIT	A new ultrasound-based method for non-invasive assessment of atherosclerotic plaque	Data not yet available	Data not yet available	Data not yet available
SUMMIT	A rat model for diabetic complications	Data not yet available	Data not yet available	Data not yet available
SUMMIT	Desmosine assay as biomarker of extracellular matrix degradation and vascular disease	Data not yet available	Data not yet available	Data not yet available

Table 2 – Summary patent applications for 6 IMI projects analyzed in this case study. The SUMMIT patent applications are the result of the project progress. The IMIDIA patent application was used as background IP included in the project by Endocells SARL[1]. Data is extracted from the 2nd Thomson

[1] A **new patent filing** to protect technologies for the creation of third generation human beta cell lines is being prepared in the IMIDIA consortium [20] – This information has been provided by IMI JU recently, and was not yet available at the time of the IMI Case Study.

Reuters bibliometric analysis report for IMI [9] and updated with patent information found on Espacenet [21]. Note that IMIDIA and SUMMIT are Call 1 projects.

Legal (IP) management

With respect to the IP management different practices have been revealed across the 6 studied consortia. Basic research projects are more prone to patenting research results and keeping trade secrets whereas knowledge management projects focusing on database creation and development of software models are more subject to *sui generis* database protection [22].

In the 6 projects, the management of IP is case-specific, negotiated at the project start in line with the IMI IP Policy [23], and contractually defined in the Project Agreement. For example, the background IP remains the ownership of the original party, while the project partners have royalty-free access rights to the background IP to achieve the project objectives [24].

Patent management

The management of patents was particularly debated with the IMIDIA project representatives. In the IMIDIA project, a patented cell line has been brought into the consortium by a SME as background IP (Table 2). The patented cell line remained the ownership of the SME Endocells SARL.

In projects prone to patentable results, Project Coordinators can advise consortium partners on potential patentable results, but generally, patenting research results is a decision made at the Work Package (WP, see further) level, by the party (i.e. large pharma company, biotechnology SME or academic partner) responsible for executing the particular research. Partners are subject to confidentiality and unless otherwise agreed, results are not made publicly available in scientific publications or via patent applications, but are kept as trade secrets among the partners involved. As agreed by all consortium partners, and consistent with the IMI IP Policy [23], foreground IP is owned by the partner(s) generating it [24]. In every project studied, the research results achieved and subject of a (potential) patent application are solely owned. Both the public and private partners carefully consider filing patent applications on the scientific achievements.

Across the 6 cases studied, few patent applications have been filed (Table 2) [7]. Moreover, since the number of applications specifically generated by IMI projects to date is small, and publication of such

data lag behind (patent applications are only published 18 months after their initial filing date), the IMI has advised not to consider patent analyzes as parameters in the 2nd, 3rd and 4th bibliometric analysis of ongoing projects [8-10].

According to the participants in the case study, the management of patents is strategically and thoroughly considered. Not all patentable results are patented by default. Partners state that securing access rights to basic technologies is more important than claiming patent protection. In some collaborations within the selected IMI projects, participants stated that patents on early stage inventions would have hindered smooth collaboration. In IMIDIA and NEWMEDS, for example, new research tools, such as animal models, have been developed. Instead of patenting those research results, thereby potentially hindering further research and forcing participants having to deal with high patent maintenance costs, the choice to keep the research results as trade secret is made and based upon this strategic decision; the non-patented animal models will be licensed out to academia and pharma. In the IMI project U-BIOPRED, dedicated to the classification of patients suffering from severe asthma to enable more personalized and targeted treatment, it was agreed by all partners that the research results, especially biomarkers, would be made publicly available, bearing in mind the Myriad debacle[2]. Knowledge about the patentability of results, especially biomarkers, among the researchers, however, is limited.

Data management

In all 6 projects analyzed, databases have been developed. The databases combine non-confidential and confidential datasets from public and private partners leading to datasets which, due to their size, allow for new insights and approaches. Every party remains owner of the data provided. The database producers, mostly 1 or 2 consortium members, own a *sui generis* right on the database [22]. Access rights to the database may vary. In some cases, all project participants can freely access the

[2] Myriad aggressively enforced its patents on two human genes associated with breast and ovarian cancer (BRCA1 and BRCA2). The US lawsuit alleges that those patents were invalid and unconstitutional (*Association for Molecular Pathology v. Myriad Genetics*, 569 U.S. 12-398 (2013)) [25]. It was argued by proponents that those patents were stimulating research by making the results from genetic research publicly available in a patent, and that these were essential for investments in biotechnology. Opponents argued that the claims were not valid as they claim non-inventive genetic information (a product of nature). They warned for patent thickets, they stated that these patents were stifling innovation by preventing others from conducting cancer research, and patients seeking genetic testing were limited in options. After intense legal proceedings, on June 13, 2013, the Supreme Court unanimously invalidated some of Myriad's claims to isolated genes. The Court held that merely isolating genes that are found in nature does not make them patentable.

database, whereas in other projects, only certain WP members can access and use the database. Regarding the access rights for third parties, no detailed rules are designed yet for the selected projects.

In case of the knowledge management projects eTOX and Open PHACTS, wherein the development of a knowledge platform is the key objective, the platform with the databases is owned by the consortia as a whole and managed by a partner specialized in the establishment and maintenance of databases. A first way of data management, in such type of projects, is the creation of a knowledge platform combining public and company data, whereby data can be extracted by users using a Creative Commons-based licensing framework (Open PHACTS). Another way is by creating a similar knowledge platform, whereby company-specific and highly confidential data, safeguarded by an honest broker (see below), are included into the platform and where data can be accessed according to a layered security level (eTOX).

The studied IMI projects focused on basic biomedical research (IMIDIA, SUMMIT, NEWMEDS and U-BIOPRED) are all considering sustainability plans for the data and databases generated and explore ways to guarantee continuous information upload and extraction from the database. The ownership of the database is not the participants' major concern, the accessibility of confidential information it contains, on the other hand, is.

Project management

Operational organization

Both a public and a private partner, often assisted by an administrative project officer, coordinate each consortium/project. From the project start, this 'coordination team' deals with scientific and organizational daily business. Each project is divided into WPs, wherein even so both an industrial and an academic representative take the lead. According to the interviewees, the scientific tasks are allocated according to the parties' (academia or industry) capabilities to perform the research. A myriad of project management tools are used and developed to optimize the operations of such multi-stakeholder partnerships, such as a traffic lights system to monitor the progress of WP tasks and the Quarterly Monitoring Reports (QMRs) providing an accurate and summarized overview of the projects' progress.

Honest broker model

It was a true challenge for the pharmaceutical companies to share non-confidential, and more importantly, and new to the sector, confidential data with consortium partners, which are considered future competitors. The honest broker model, whereby one neutral trusted party supplies a data warehouse (i.e. a computer system for staging, integration and access of data) (Fig. 2), is a model that convinced the companies to increase their level of openness with respect to (confidential) data sharing. For example, to build the toxicology information database in the eTOX consortium (eTOXsys), the companies share two types of data with an honest broker: non-confidential data, available to other consortium partners, and confidential data. The confidential data is only accessible by the owner thereof. The different sets of confidential data are anonymized when integrated and can only be access by the honest broker. The more companies share non-confidential but also confidential data, the more data is available to train toxicity prediction models that serve all parties.

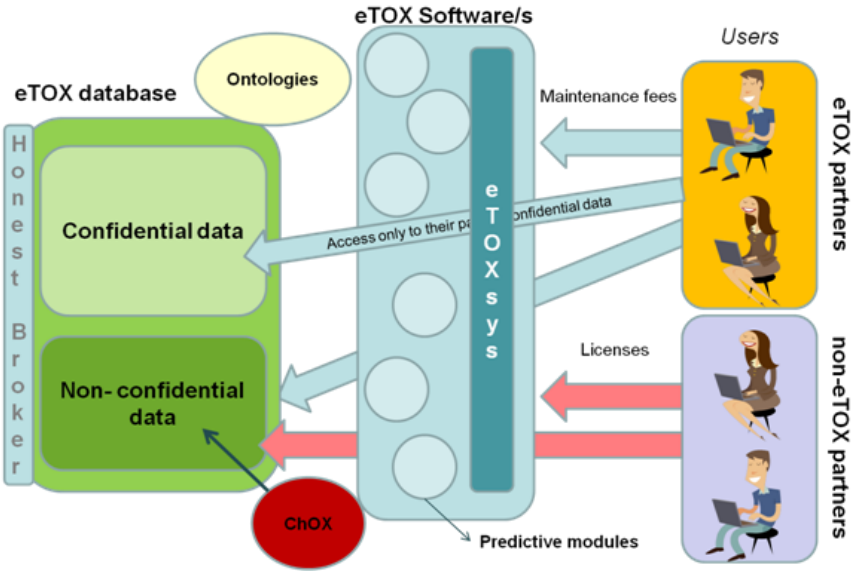

Fig. 2 – The honest broker model used in eTOX. Reproduced with permission from Synapse Research Management Partners.

Another example is the open access innovation platform in the Open PHACTS project, called Open Pharmacological Space (OPS). The platform comprises data, ontologies (i.e. vocabularies) and infrastructure needed to accelerate drug-oriented research by intelligent interrogation of the system. Due to the amount of information, and the possibility to correlate the information coming from

different sources, researchers are triggered to define new and innovative research questions and think outside the box, or even think in new boxes, for research design. The large Open Source and Open Data services allow secure querying for data, the 'plug-in' of proprietary data sources and analysis services and the demonstration of the value of semantic web technologies by establishing a user-friendly semantic data integration infrastructure. The sustainability of the system after the project (end 2014) is guaranteed by the Open PHACTS Foundation, a non-profit organization which functions as honest broker and runs the Open PHACTS Discovery Platform. The Open PHACTS Foundation participates in BigDataEurope's Horizon 2020 (H2020) project, which aims to integrate different big data infrastructures into a stack of interoperable data assets [26]. The Foundation will further act as contact point with the life science R&D community, organizes workshops and runs pilot project with other sectors [26]. Dependent on the amount of information shared by the user, different membership levels for partners, associated members and third parties are defined.

Standardization efforts

The studied IMI consortia have invested in standardizing and harmonizing protocols and agreements to facilitate communication, increase trust and improve efficiency and reproducibility, transferability and validation potential among partners. For example, Material and Data Flow Principles have been developed by IMIDIA and SUMMIT to deal with the sharing of IP within the consortium and between different consortia (Fig. 3). Those consortia agreed upon a Memorandum of Understanding (MoU) to improve knowledge transfer and reduce duplication. The MoU was later also signed by DIRECT, another diabetes-specific research project in the IMI. The MoU forms the basis for The IMI Diabetes Platform, a collaborative effort of 3 IMI consortia (IMIDIA, SUMMIT and DIRECT) to jointly overcome key bottlenecks on the way to innovative diabetes therapies. This data sharing model allows the project participants of the IMIDIA, SUMMIT and DIRECT consortia to exchange information between the projects. The consortia created an information platform wherein project results, by the consortium members identified as being potentially interesting for other diabetes-projects, are shared. The MoU defines the flow of information, e.g. when research results (foreground IP) from the IMIDIA consortium are interesting to be explored in view of the SUMMIT scientific activities, both consortia sign a subject-matter specific Confidentiality Disclosure Agreement (CDA). If the exchanged information requires exchange of materials (e.g. a specific cell line), the consortia will additionally sign

a Material Transfer Agreement (MTA), together with a General Transfer Agreement formally identifying the information and material exchanged as foreground IP owned by (a) member(s) of IMIDIA. This foreground IP can then be transferred and used as background IP in SUMMIT. In case the use of such information (and/or material) exchange generates new findings within SUMMIT (i.e. SUMMIT foreground IP), the General Transfer Agreement states that this SUMMIT foreground IP automatically needs to be transferred to IMIDIA as SUMMIT background IP (Fig. 3).

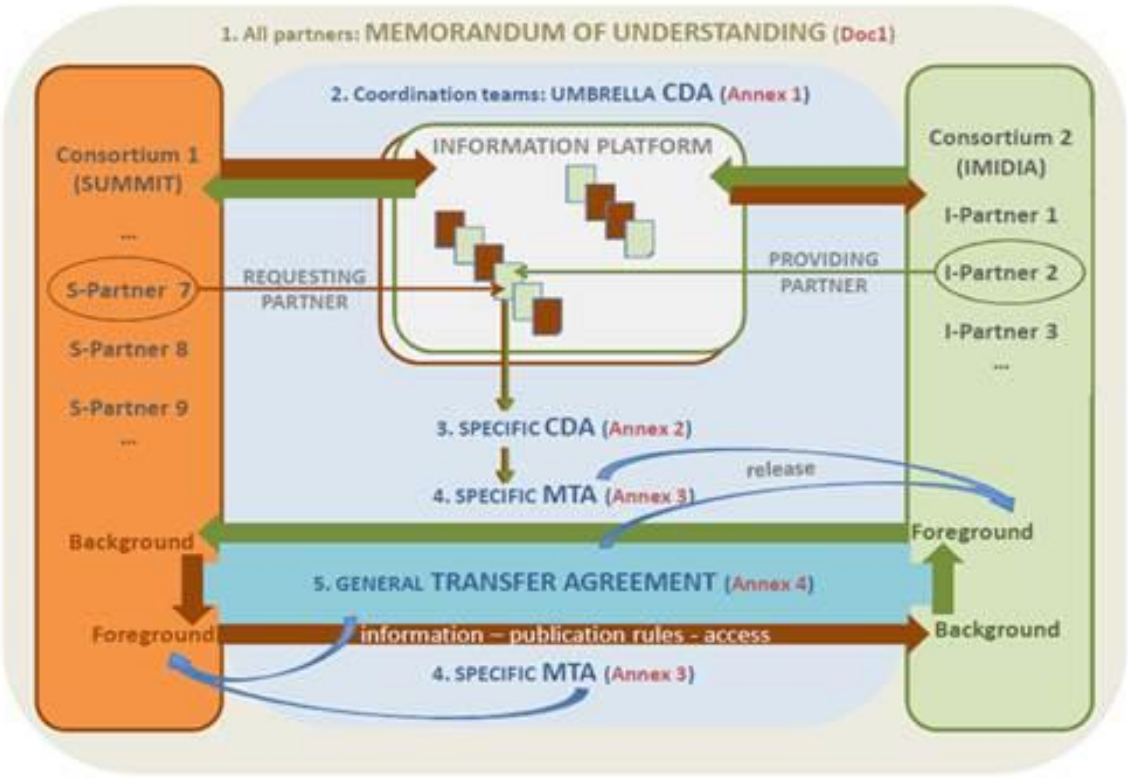

Fig. 3 – Memorandum of Understanding (MoU) between the IMI Diabetes projects. Reproduced with permission from IMI JU.

Other standardization efforts are for example present in SUMMIT and U-BIOPRED, which have put particular efforts in unraveling the complex regulatory patchwork of national legislations. The consortia dealt with the challenges in the handling of human samples and related data in multi-national setting and in accordance with all relevant legal provisions and project agreements. The existence of a web of complex and diverse country specific regulations and specifications across Europe was a major hurdle for research. Another example is the standardization efforts of the

NEWMEDS and the U-BIOPRED consortia wherein new clinical trial criteria have been developed, shortening time, reducing costs and thus improving the time to bring medicines to the patients. For example, in NEWMEDS the real opportunity resulting from this key achievement is the proposed reduction in duration of clinical trials in patients suffering from schizophrenia from 6 to 4 weeks and a number of patients needed, from 79 to 46. The estimated cost reduction is €2.8 million. According to the IMI representatives interviewed, the early involvement of the European Medicines Agency (EMA) is pivotal at this level.

Involvement of Small and Medium-sized Enterprises (SMEs)

The IMI Case Study revealed that in all the consortia analyzed, one or more SMEs participate. IMI consortia provide a platform for SMEs to have their technology validated or tested by pharmaceutical companies. For example, in IMIDIA, the SME Endocells SARL has its human pancreatic beta-cell line validated within the project by the pharmaceutical companies (Table 2). In the project eTOX, 4 biocheminformatic SMEs participate to develop prediction models. As pharmaceutical companies are the target customer of biocheminformatic SMEs, participating SMEs have the advantage of having their software models, brought in as background IP or generated within the project, validated by their target customer. The validation results are shared with the SMEs, offering them insight in flaws or potential improvements to their product. In every consortium, (part of) the administration and organizational management is outsourced to an SME acting as project management office(r). In 1 consortium (SUMMIT), the only SME involved conducts this administrative/management type of activity.

DISCUSSION

PPPs as accelerator of science

The key objective of IMI [27, 28] is to speed up the development of better and safer medicines for patients [17]. The multi-stakeholder collaboration model aims at faster, cheaper and better drug development [29]. Europe had never seen biomedical consortia of this size, with the accompanying project management skills required. Although the organizational aspects of participation in consortia

of such size are not to be underestimated, the PPP approach to addressing the world's emerging health challenges might be one of the key innovations to move science forward.

There has been some criticism [30, 31] with respect to IMI and there were a myriad of challenges at the start of IMI. IMI acted as an umbrella PPP embodying 15 consortia to be launched in the 1st Call. A major challenge was that initially IMI could not provide the resources to help the different consortia start up the project and support them during the project negotiations. However, IMI has overcome this challenge by setting up the IMI EO which currently functions at full speed.

The participants agree that the scientific results would have never been achieved so rapidly if these projects would have been executed in silos or via bi- or trilateral agreements. The scientific deliverables are numerous and projects progress considerably, as highlighted during the Interim Reviews. What makes the case study analysis unique is the revelation of many more valuable, often non-purely-scientific deliverables, of which only little external audit information is publicly available. In its review report, the expert panel stated that not only the scientific excellence needs to be demonstrated, but that it is essential to prove the impact and added value for the society beyond scientific excellence [15]. Building databases and information exchange platforms of the size and scale experienced in IMI's consortia is innovative. By sharing (non-)confidential information, competitors become colleagues striving towards a common goal.

Business plan and datasets' sustainability

Time has come to invest in setting up business plans for exploitation of the outputs. The 6 consortia are reviewing their sustainability plan. Strategies such as licensing out patented and trade secret protected inventions or involving multinational industries to produce prototypes of research tools developed, obliges the participants to consider carefully the market value of the research tools developed. The IMI EO could offer support to the consortia to set up such business plan and/or transition plan.

The sustainability of the datasets produced requires serious reflection. The amount of collected, combined and shared data has never been experienced in pharma. In all IMI consortia analyzed, databases are created allowing researchers to explore combined datasets with different access and

security levels. Databases combining publicly available information with (non-)confidential data of different partners offer researchers insight in an integrated set of data which exceeds the size of any existing dataset. The size of the IMI projects implies a new way of doing research. Researchers are challenged to interrogate databases in a more complex way. It would be a tremendous loss if the databases created would not be maintained or if the information flow would be stopped after the end of the projects. To explore the different options for datasets' sustainability, guaranteed information upload and extraction from the database, the data sustainability model developed by Open PHACTS, could serve as a role model for other IMI consortia. The EC has stressed the need to explore options to support the datasets' sustainability [32].

IMI's Best Practices Forum

The knowledge gathered in the different IMI projects exceeds pure scientific results. Many other achievements need to be treasured. An enormous amount of templates, harmonized protocols and standardization endeavors for information exchange have been developed within and between consortia. It took the consortium members considerable effort and time to harmonize and valorize these assets.

A forum could be created to exchange best practices and disseminate existing knowledge on the legal and regulatory landscape. 'IMI Consortium Guidelines and Best Practices' could be set up; a list of tips and tricks including topics such as governance, IP, dissemination of results, could be distributed among the (especially new) consortia to facilitate the start-up of new projects.

Intra- and inter-consortia collaborations

Collaborations between different IMI consortia have been established (e.g. between IMIDIA, SUMMIT and DIRECT, but also between the IMI projects eTOX and Open PHACTS, DDMORE, EMIF, EU2P, MIP-DILI, PREDECT and EHR4CR). These collaborations are strongly encouraged by IMI EO. Further, there is also a MoU signed between the umbrella PPP IMI and its US counterpart Critical Path Institute (C-Path) [33] alongside with the Juvenile Diabetes Research Foundation (JDRF) and the Clinical Data Interchange Standards Consortium (CDISC). Such international collaborations are necessary to avoid a potential overlap between the different collaborative initiatives worldwide.

IMI's IP Policy

The collaborative PPP model of IMI, engaging the pharma industry as well as (academic) research institutes, challenges the business model of industry as well as the 'protective behavior' within academia [34, 35]. For many years, IP figured as a key asset for industry as well as for (academic) research institutions [35]. Taking industry more than 10 years back, nearly every patentable invention was protected with a patent at very early stages. Academia, being aware of that approach, adopted a similar 'pro patent' attitude [36]. However, history learned that, down the road towards exploitation, many such patented inventions turn out not being useful for further development, as in reality for instance, only a few lead compounds or therapies survive the challenging Phase 3 trials and make it to the market [37]. The business model of industry (and academia) consisting of patenting inventions very early onwards becomes too costly, too risky and unsustainable [37].

Hence, industry diversified its business model. The idea is that, in order to speed up drug development, early inventions need to be shared smoothly, and preferably in an atmosphere of open collaboration [38, 39]. Patents remain important as protective instruments from the moment that market opportunities crystallize out or are envisioned in the future. Some academic institutes have a similar understanding. However, since spin-out initiatives are important business activities of academia, early inventions are still screened thoroughly at academic institutes for patentability [40].

The criticism that the influence of business entities in IMI projects is too big should be reconsidered [30, 41]. EFPIA's influence is not to be underestimated: the pharmaceutical industry decides on the Call topics, which are in line with the needs defined in the SRA [2, 3]. This should not come as a surprise, since the association of main pharmaceutical companies counts for half of IMI's budget. Moreover, EFPIA companies will do exploitation of a large part of the results; hence, it is understandable that the research topics and the expected deliverables are in their interest and in line with their business strategy. Although EFPIA's ownership and responsibility of the SRA should not be diluted, the scope and priorities should be defined by a broad group of stakeholders in a clear and transparent way [15]. According to the results of this study, the idea that EFPIA partners claim all the research results (foreground IP) is not correct. All interviewees experienced the IMI IP Policy [23] as a good and flexible framework to start negotiating the ownership and access rights on background IP and foreground IP.

Some IMI projects under study (SUMMIT, IMIDIA) delivered patentable inventions (Table 2). Clear and well-reasoned approaches are taken towards patenting and not all inventions are patented right-away. This trend could be explained by the tendency to validate research results thoroughly and to screen the interest of industry. Further, access rights to basic technologies are preferred above ownership as such. With respect to jointly developed inventions, co-ownership is possible within IMI projects, but avoided; commercially this may lead to more complex situations around more validated outcomes. The flexibility of the IMI IP Policy [23] is the basis for negotiations between the partners on ownership in the interest of the potential commercialization of the developed foreground IP [24].

The IP framework provided by IMI is considered by the interviewees adequate for the selected IMI projects. The template Project Agreement was experienced as transparent and tailor-made adaptations to the needs of the consortium are possible. IMI has already done some reasonable efforts to explain the IP Policy [23] which was made publicly available in 2007. In 2008, the IPR Helpdesk issued an Explanatory note [42], in 2009 the IMI EO published a Clarification note [43] and in 2010, there was an additional IP Guidance note [44]. A recommendation resulting from this Case Study was to harmonize this set of documents into a revised IP Policy, explaining the concepts, the rules and the differences with the FP7 rules and the Horizon 2020 rules, illustrated with relevant and case-based examples[3]. This has been done at the launch of IMI 2. Also, available policy documents contain limited information with respect to data management and sample sharing, which needs to be further elaborated.

SME participation in IMI projects

At the start of IMI, it faced criticism regarding its IP framework. Some organizations representing SMEs, e.g. Flandersbio, or academia, e.g. the League of European Research Universities (LERU), argued strongly against participating in precompetitive PPPs, especially in the context of the controversial IP framework presented by the IMI [30, 31]. In a subsequent LERU letter (2013) it was stated that 'the IP terms seem to concentrate on the marketing of pharmaceutical and diagnostic

[3] This recommendation was included in the IMI Case Study Report presented to the European Commission, EFPIA, and the IMI JU. The recently issued IMI 2 JU Model Grant Agreement has implemented the IMI IP Policy into its Model Grant Agreement (Section 3 - Rights and obligations related to background and results, Art. 23a to Art. 31) and has implemented the information presented in the Explanatory Note, the Clarification Note and the IP Guidance Note therein [45].

developments by EFPIA partners, rather than giving equal weight to the interests of academic or SME partners, which might be to undertake further research or to put the results in the public domain' [46].

In a joint publication, four SMEs participating in eTOX have expressed their disagreement with the criticism on the proclaimed low number of biotechnology SMEs participating in IMI projects [30, 31, 47, 48]. They underline the importance of their participation in and contribution to the project [48]. The initial fear to jeopardize the SMEs' business model through participation in IMI projects (by making their background IP freely available to a large part of the customers) has disappeared and should no longer impede SMEs applying to participate in IMI projects.

At first sight, the incentives for biotechnology SMEs to participate in IMI projects are not obvious. Suppliers and customers sit at the same table, access rights on background IP and foreground IP are freely available during the project, while after the project, the access rights for project participants to IP are to be negotiated (conditions vary from 'for free' to 'on fair and reasonable conditions'). Although the larger part of SMEs' target customers (i.e. the large pharmaceutical companies) are present in IMI consortia, and hence, no or no major profits can be made by exploiting foreground IP developments during the project itself, these projects offer SMEs the opportunity to create technical standards and to occupy a preferred position in the market. The advantages of participation outweigh the disadvantages; being partner in the consortium acts as a business multiplier, participating SMEs have closer contacts with participating pharmaceutical companies, new (business and scientific) models and (research) tools are validated by the target customer, etc. For example, SMEs participating in eTOX will receive a maintenance fee from the other eTOX participants when they use the predictive models developed by SMEs within the project. This maintenance fee is expected to be lower than a normal license fee that the SME would receive to provide access to the predictive model to non-participants. However, these maintenance fees are assured, and through the SME's participation in such consortia, they develop new business opportunities. Further, by participating in consortia, SMEs gain access to large amounts of (before not accessible) anonymized data which enables them to improve models outside the field of toxicology. Another example is IMIDIA, where the SME 'Endocells SARL' has the opportunity to validate its human beta cell line as an innovative

research tool by its target customers, and potentially creating a new standard for safety and efficacy testing of diabetes drug compounds.

There is a major role cut out for biotechnology SMEs participating in IMI consortia. Pharmaceutical companies lack bio-informaticians familiar with 'wet' experiments [49] and lack the resources to develop important research tools. Development of those tools, diagnostic equipment, database models and applications are core technologies of many biotechnology SMEs. These tools and (software) applications can be built, tested and validated within such multi-stakeholder constructs, which is of extreme value for SMEs. For instance, under the organizational framework designed in the selected IMI projects, the pharmaceutical companies share the validation results with the SMEs, which is not always the case in bilateral agreements.

There are also biotechnology SMEs which aim at bringing medicinal products to the market. Such SMEs face a difficult position within IMI projects, as they may be competitors of the EFPIA member companies participating in the respective projects. One might argue that competition drives innovation and stimulates the project progress. Such biotechnology SMEs might see participation in large IMI consortia as an opportunity to compete, to acquire or gain brand awareness or to be acquired by a large pharmaceutical company, e.g. deCODE Genetics, Inc. (Icelandic: Islensk erfdagreining, based in Reykjavik) that joined the NEWMEDS consortium as a biotechnology SME. In December 2012, deCODE Genetics was acquired by Amgen. Nevertheless, biotechnology SMEs should be fully aware of their position within the consortium, their strengths and weaknesses, the disadvantages and the benefits of participation before joining the consortium, so they can adjust their strategy accordingly.

However, due to the IP position/dependence and often limited resources within SMEs, there is still room for IMI 2 to improve the framework for biotechnology SMEs to participate in research activities. It remains to be seen whether a PPP in general is the ideal construct for SMEs to share and develop their core technology.

CONCLUSION

In conclusion, the case study on the business and IP opportunities and on the potential value gap within IMI projects supports the insight that there has been achieved a myriad of opportunities within the IMI consortia. IMI delivers beyond scientific project results by putting in place tools and mechanisms aimed at translating the scientific results in exploitation opportunities [19]. The study thereby largely supports the recommendations of the expert panel's review report to prepare the IMI2 creation [15]. Six IMI projects from the 1st and 2nd Call were studied and experiences of participants were examined, dating back from a time where the activities at IMI EO were at its infancy (2008-2009). Meanwhile, the IMI EO has set up many new consortia, gained expertise in the complex domains of organizing and governing large-scale multi-partner public-private consortia and provided clear and professional guidance to IMI projects. Further actions, both on the consortium level, as well as at IMI level, are needed to guarantee the sustainability of IMI project results. Several initiatives may improve future activities. A forum to exchange best practices and disseminate existing knowledge on the legal and regulatory landscape within Europe would help future PPPs to save time and energy. A data support system could be set-up to sustain the different databases constructed during the project. Several IMI project databases could be linked to each other and potentially to other PPP databases on a European or worldwide scale (e.g. the European Strategy Forum on Research Infrastructures (ESFRI) or Biobanking and Biomolecular resources Research Infrastructure (BBMRI-ERIC) platforms). The honest broker model is considered to offer trust to pharmaceutical companies to share their non-confidential and moreover, their confidential data on specific conditions. The honest broker could serve as a data warehouse and facilitate the valorization of these assets. More case-based evidence is needed to explore how the sustainability of the projects will progress beyond the project life span, and especially, what will be done to capture the value of the knowledge created.

The continuation of IMI is secured as IMI 2 has been launched in 2014. IMI 2 will further promote investment in Europe and encourage collaboration with other healthcare groups, such as imaging and diagnostics [19]. The budget has been raised to 3.3 billion euros, and the life cycle of IMI 2 will be 10 years. Being the world's largest PPP operating in the precompetitive and even POC phase in the health-care sector, IMI serves as a role model for many other collaborative models worldwide [17]. Collaboration of large pharmaceutical companies, SMEs, academic institutions and public bodies speed

up drug development [50]. Optimization of IMI as a successful PPP could serve healthcare and patients in general [6].

METHODS

Case selection

The qualitative empirical case studies were performed on behalf of the IMI EO under a service contract procedure. Six IMI consortia were selected in a joint meeting of KU Leuven and the IMI EO and based on the focus areas defined in IMI's SRA (predicting safety, predicting efficacy, knowledge management and education and training) [2, 3, 51], the variety of expected deliverables, different approaches towards protection of Intellectual Property (IP) and the expected project end. The selected consortia target problems in different fields, ranging from neuroscience (NEWMEDS), metabolic disorders (SUMMIT, IMIDIA) and respiratory diseases (U-BIOPRED) up to knowledge management projects such as development of platforms for toxicity prediction (eTOX) and integrated pharmacologic data (Open PHACTS). Five consortia were Call 1 projects (SUMMIT, IMIDIA, NEWMEDS, eTOX and U-BIOPRED) with project duration of 5 years. The sixth consortium was a Call 2 consortium with expected project duration of 3 years (Open PHACTS)[4]; this project was selected to review how sustainability of the achievements is organized.

Document analysis

Per IMI consortium, the case study involved an in-depth analysis of public as well as confidential documents signed under a NDA (Descriptions of Work, Project Agreements and Amendments thereof, Periodic Reports, Interim Review Reports). The documents were used to reveal the project progress in terms of the pre-set milestones to reach the different project objectives. Specific attention was given to the way IP was handled within the consortium, as well as the long-term view on the sustainability of the project outputs, i.e. the short-term project deliverables, and the outcomes, i.e. the difference these deliverables could mean for science and patients in the long term. The project documents have

[4] Due to the success of Open PHACTS, this project has been prolonged until February 2016 via a 1st Call for Proposals to 'Explore New Scientific Opportunities' (ENSO) granting awarded on-going IMI projects the opportunity to explore new scientific opportunities through awarding them an additional research budget. Also eTOX, SUMMIT and IMIDIA and U-BIOPRED have been awarded such ENSO grants.

further been analyzed in view of the econometric analyzes performed by Thomson Reuters and the EC's Independent Expert Panels' evaluation reports [7-12, 15-18].

Semi-structured interviews

From March 22 to Sept 25, 2013, interviews with consortium representatives (project coordinator, managing entity, legal experts and/or the project officer) were performed via telephone conferences and face-to-face meetings. Interview questions related to the project specific scientific output and valuation, IP, collaboration, SME involvement and sustainability of results generated. The interview results have been analyzed based on the thematic framework approach [52, 53]. From these results, several opinions are formulated and expressed through recommendations for the Consortia as well as IMI to optimize the functioning of the IMI. The recommendations have been presented at the IMI Governing Board in October 2013, chaired by dr. Rudolf Strohmeier, Deputy-Director General of DG RTD at the EC.

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DISCLOSURE STATEMENT

The authors declare that the qualitative empirical case studies were performed on behalf of the IMI EO under a service contract procedure, but that the research has been performed independently and cannot be perceived to influence the results and/or discussion reported in this paper.

AUTHOR CONTRIBUTIONS

Hilde Stevens: Wrote manuscript, designed research, performed research, analyzed data.

Geertrui Van Overwalle: Contributions to original manuscript, interpretation of data.

Bart Van Looy: Contributions to original manuscript, interpretation of data.

Isabelle Huys: Designed research, designed research, performed research, interpretation of data, contributions to original manuscript.

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