efpia

innovative medicines initiative

IMI - the full story
IMI responses to the GHA / CEO report "In the name of innovation"

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INTRODUCTION

At the Innovative Medicines Initiative (IMI), we are always open to justified, balanced, and constructive criticism of the model of public-private partnerships (PPPs) that is exemplified by IMI. We are the first to acknowledge, as in any cutting-edge collaborative model for biomedical research, that ongoing improvement, corrective measures, and new ideas are imperative in ensuring that PPPs serve the interests of EU citizens.

We therefore read the recent report of Corporate Europe Observatory (CEO) and Global Health Advocates (GHA) with great interest. There are some valid points in the report, for example, the relatively low levels of participation of small and medium-sized enterprises (SMEs) and partners from the EU-13 countries, and the need to open up IMI's advisory bodies to a wider spectrum of stakeholders. These were also mentioned as part of the most recent European Commission evaluation of IMI and will require design changes in any subsequent programme[1].

However, we are disappointed that the authors missed the opportunity to contribute to a constructive debate on IMI and health PPPs. We regret the fact that the report identifies isolated challenges that IMI has faced and uses them to level a sweeping challenge to the integrity of the entire programme itself. Our intention in the following pages is to put the CEO/GHA assessment in the right context, in order to facilitate a rigorous review of the IMI programme based on facts.

The overriding thesis of the CEO/GHA report is that the entire IMI programme is being manipulated by the pharmaceutical industry. This biased interpretation comes at a price: GHA's complete disrespect for the integrity and intellectual independence of all the academics, SMEs and patients that contribute their passion, knowledge and professionalism to IMI projects.

Concerning academics specifically, the report disregards the dedicated and rigorous work of all the excellent researchers committed to IMI's projects. In fact, the best European teams have been successful in IMI competitions, as attested by the fact that 60% of the institutions involved in IMI projects are representatives of the top 200 European universities.

Many of these top European researchers have seen the quality of their research increase due to the public-private nature of the work, as shown by the annual bibliometric analysis performed on the scientific papers generated by IMI projects since 2012. The analyses have consistently demonstrated both the sheer volume and high quality of research taking place in IMI projects.[2]

- Between 2010 and 2019, IMI projects produced 5 837 publications, including 944 in 2019 alone. IMI-funded papers are cited more often than average; the field-normalised citation impact for all IMI papers is 1.99 (compared to 1.10 for the EU and the baseline of 1 for the world). IMI also compares favourably with similar organisations such as the Wellcome Trust, the Medical Research Council (MRC) and the Foundation for the National Institutes of Health (FNIH). Over a quarter (26.9%) of IMI papers were in the world's top 10% of most highly cited papers in the relevant field and year of publication, suggesting very strong performance.
- IMI project research is collaborative across sectors, institutions and countries. Nearly two-thirds (64.1%) of IMI project papers

1 Interim Evaluation of the Innovative Medicines Initiative 2 Joint Undertaking (2014-2016) operating under Horizon 2020

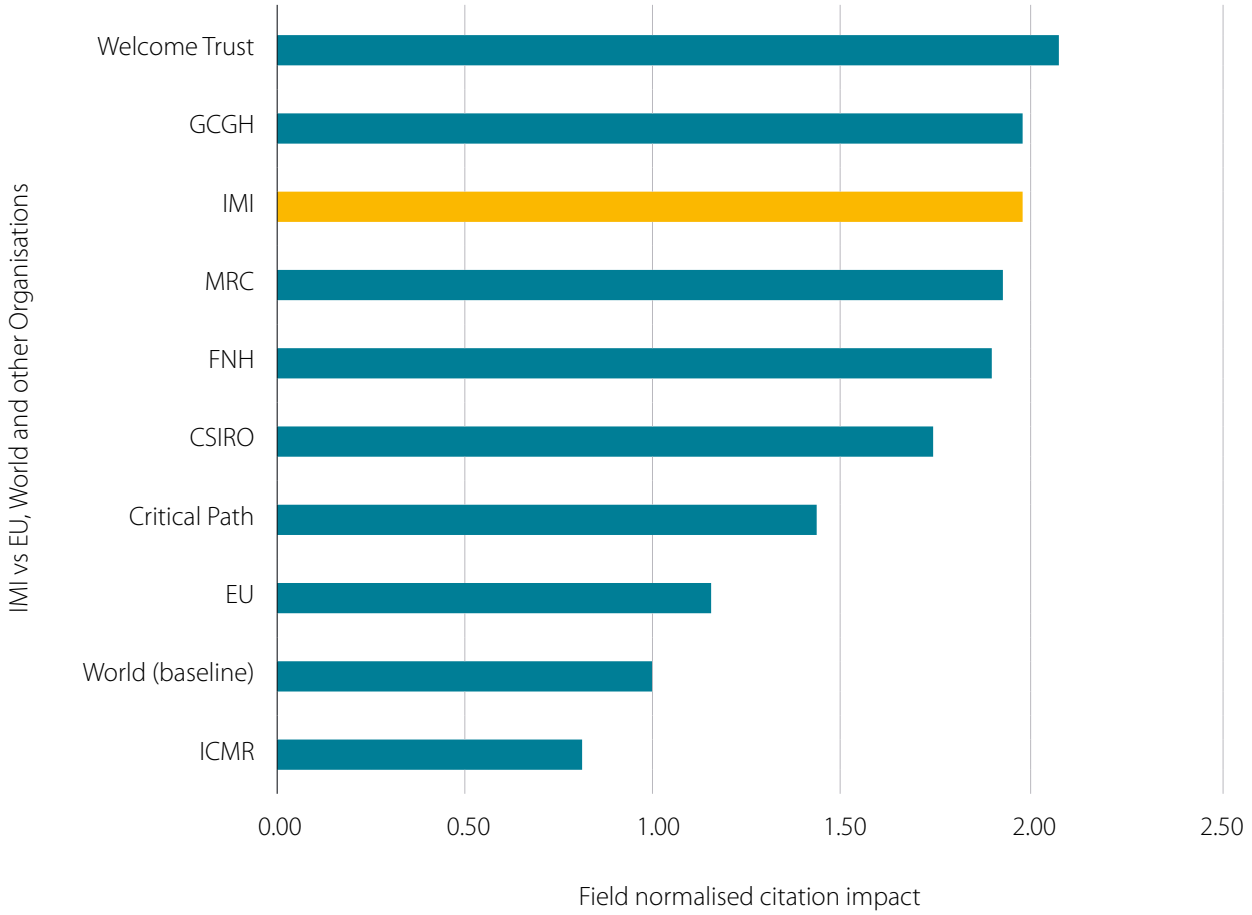
2 IMI Bibliometric analysis of ongoing projects, 11th Report - 2020

were co-authored by researchers from different sectors. More than three-quarters (83.8%) of IMI project papers involved collaboration between different institutions. And more than half (61.8%) of all IMI project papers were internationally collaborative. As an example, the University of Oxford has collaborated with 1 446 institutions in the framework of IMI project papers.

From the data mentioned above it can be clearly demonstrated that joint public-private publications have an increased citation index and impact factor. These are important metrics for the scientific community and they show that rather than being at the service of industry, the academics participating in IMI projects are using their cutting-edge technology and brainpower to further scientific knowledge so that it can be translated into use, enabled by close partnership with industry.

The relevance of the research taking place in IMI projects is further evidenced by the many awards and grants our projects have won. For example, the European Medicines Agency (EMA) selected IMI's ADVANCE, EHDEN and CONCEPTION projects to contribute to projects that will gather real world data on COVID-19 vaccines and treatments once they are approved and being used in day-to-day clinical practice. The Horizon 2020 (H2020) coronavirus project MANCO builds on results from IMI's ZAPI project. EIT (European Institute of Innovation & Technology) Health awarded a grant to our EUPATI project to build on its patient education work. And the Open PHACTS Foundation, which was set up to continue the work of IMI's Open PHACTS project, is part of two H2020 projects. Many more IMI projects have won prizes at conferences.

Citation impact of IMI funded publication and papers 2010 to 2019



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PART I.
IMI HEALTH RESEARCH PRIORITIES

IMI'S RESEARCH PRIORITIES: ADDRESSING PRIORITY HEALTH NEEDS IDENTIFIED IN THE HORIZON 2020 REGULATION AND THE WHO LIST OF PRIORITY RESEARCH AREAS

In compliance with the regulations that govern IMI, the Strategic Research Agenda (SRA) is fully aligned with the EU health research priorities, which were decided by the European Parliament and the Council during the negotiation of Horizon 2020.

Prioritisation of research areas also takes into account the *Priority Medicines Report of 2013* by the World Health Organisation (WHO), from which the SRA takes on those that (i) are most relevant for a public-private partnership; and (ii) consider IMI's remit to support pre-competitive research and innovation activities with the aim of improving European citizens' health and well-being. These are: antimicrobial resistance, osteoarthritis, cardiovascular diseases, diabetes, neurodegenerative diseases, psychiatric diseases, respiratory diseases, immune-mediated diseases, ageing-associated diseases, cancer, rare/orphan diseases and vaccines. The total IMI2 budget committed (coming from IMI, EFPIA and Associated Partners) to these priorities by the end of 2019 was EUR 1 846 613 930.

The table below illustrates current IMI2 investment in major disease/research areas – WHO and H2020 research priorities - with a cut-off date of August 2020.

Contrary to the report's criticism, focus on areas such as cancer, Alzheimer's disease and diabetes is particularly relevant since, according to the WHO's report *The World Health Statistics 2020*, "compared with the advances against communicable diseases, there has been inadequate progress in preventing and controlling premature death from non-communicable diseases (NCDs)". The report warns that an estimated 41 million people worldwide died of NCDs in 2016, equivalent to 71% of all deaths, listing cancer (9 million deaths) and diabetes (1.6 million deaths) among

the four biggest culprits. The main reason for the lack of significant scientific progress is that these are extremely complex diseases, and, as such, they are the ones with the most acute need for a collaborative, multidisciplinary approach of the kind facilitated by IMI.

The report once again demonstrates bias by implying that IMI does not address the diseases that affect middle- and low-income countries when, in fact, non-communicable diseases such as diabetes, depicted as only relevant to developed countries' health systems, are increasingly straining the health systems of low- and middle-income countries. Therefore, the significant work done by IMI projects in these areas will be of value not only to European patients but to non-European patients too. According to the International Diabetes Federation, 79% of diabetes patients live in low- and middle-income countries.

In a different order of variables, IMI's portfolio also addresses rare diseases, which are often chronic, progressive, degenerative and often life threatening diseases. The most common cause (80%) of rare diseases are genetic variations and 98% of rare diseases currently lack effective treatments. As an example, fibrodysplasia ossificans progressiva (FOP) is a rare disease in which the muscles and connective tissues (e.g. tendons and ligaments) slowly turn into bone. There is no treatment; as the disease progresses, the build-up of bone material around the joints gradually limits patients' mobility, and can also result in difficulties eating, speaking and even breathing. By running a clinical trial of a drug call AZD0530 in 16 adults with FOP, the aim of the STOPFOP project is to see if it reduces the formation of new bone. FOP is caused by a mutation in a gene that codes for a protein called ALK2 kinase. Studies in the lab have shown that AZD0530 blocks the action of ALK2 kinase, and in mice, the drug successfully stopped the formation of bone material in the soft tissues and kept the mice's limbs moving. AZD0530, also known as saracatinib, has already been tested for safety in humans in healthy volunteers and as a treatment for certain cancers.

Beyond the 12 WHO disease areas included in SRA, IMI has been financing projects in two pivotal WHO cross-cutting priorities listed in the *Priority Medicines for Europe and the World 2013*: priority medicines for children and women.

	IMI2 contribution EUR	EFPIA contribution EUR	Associated Partners' contribution EUR	Total contribution EUR	% Total	Number of projects
Immunology	106 472 508	103 785 890	105 000	210 363 398	9%	7
Diabetes/metabolic disorders	91 093 930	84 071 454	18 911 020	194 076 404	8%	8
Neurodegeneration	135 098 435	83 086 823	56 049 619	274 234 877	12%	15
Translational safety	74 630 989	70 907 584	0	145 538 573	6%	6
Digital health and patient-centric evidence generation	222 089 523	234 429 664	2 696 394	459 215 581	19%	18
Infections control	411 750 695	309 027 416	80 935 277	801 713 388	34%	31
Oncology	58 115 625	59 096 673	0	117 212 298	5%	5
Drug discovery	18 249 993	17 669 327	810 000	36 729 320	2%	1
Other*	59 648 531	55 436 126	6 445 380	121 530 037	5%	8
Total	**1 177 150 228**	**1 017 510 957**	**165 952 690**	**2 360 613 874**	**100%**	**99**

* Under "other", IMI has funded projects in areas such as the environmental aspects of pharmaceutical products, drug delivery or manufacturing processes improvement.

The project ConcePTION is tackling the challenge of providing women who are pregnant or breastfeeding with reliable information on what medicines are safe for them and their child. Currently, just 5% of medicines come with adequate safety information on this, yet 90% of women are exposed to a prescription medicine at some time during pregnancy. The project brings together 88 organisations, including regulators, drug manufacturers, universities, hospitals and public health organisations. This is a testament to IMI's key value as a neutral platform for building a trusted, collaborative ecosystem for generating, monitoring, and providing robust information on sensitive topics[3].

Regarding priority medicines for children, IMI is investing €186 million in projects targeting two of the areas identified by the WHO in its report: paediatric clinical trials and paediatric oncology.

Fewer than half of all authorised medicines commonly used in children have been properly tested in this group, and running clinical trials involving children is hard. The conect4children project is creating a sustainable, integrated pan-European collaborative paediatric network that will speed up and facilitate the running of high-quality clinical trials in children, while ensuring that the voices of young patients and their families are heard. Meanwhile, the ITCC-P4 project is developing a large-scale platform comprising 400 novel research tools based on cells and tissues from patients covering 10 common childhood cancers, including neuroblastoma, high grade glioma, and osteosarcoma. The tools will allow researchers to explore the biology of paediatric cancers, identify sub-groups of patients that might respond better to certain treatments, and carry out tests on potential drugs.

In sum, if one looks carefully at the IMI portfolio, it becomes clear that each project/topic falls into key categories or themes that lend themselves very well to the PPP model. These are:

1. True market failures like antimicrobial resistance where traditional market dynamics do not exist.

2. Scientific failures like Alzheimer's disease, where society has collectively failed to bring new treatments to patients, and the industry has been disincentivised to invest due the increased risk of failure. Alzheimer's disease and other dementias are considered to be a global public health problem with a cost to society of over EUR 1 trillion per year.

3. Gaps in important infrastructures that need to be catalysed (big data, specific clinical trial infrastructures, high throughput screening platforms, high quality biobanks, etc.).

4. Challenging topics that require regulatory guidance and patient involvement in the context of a PPP, like ensuring better medicines for children or the safe use of medication in pregnant and lactating women.

Should IMI focus on HIV/AIDS?

The report repeatedly criticises IMI for not investing in HIV/AIDS research. As we have repeatedly explained in our interactions with CEO and GHA, the reasons for this are simple and have remained unchanged for over a decade.

- Following the Horizon 2020 Regulation, the Framework Programme should ensure that public financing is used in an optimal way, building on complementarities and avoiding unnecessary duplication. Furthermore, in its article 25.3 (f), the Regulation specifically requires that public-private partnerships should be identified based on, among other listed criteria, "complementarity with other parts of Horizon 2020 and alignment with the Union research and innovation strategic priorities, in particular those of the Europe 2020 strategy". For this reason, and in accordance with the European

3 To understand the relevance of the ConcePTION project in expanding drug safety knowledge, see Drug Safety Matters. Uppsala Reports Long Reads – Ending the pregnant pause from the Uppsala Monitoring Centre.

Commission indications, HIV/AIDs, diarrhoea and neglected tropical diseases identified in the WHO priority list are included in European & Developing Countries Clinical Trials Partnership (EDCTP) Strategic Research Agenda and are also financed through H2020 collaborative research calls, but not through IMI[4].

- In alignment with this, the private sector has chosen not to use the IMI model for investments in HIV/AIDS research, but rather, to use other dedicated international instruments such as IAVI (International AIDS Vaccine Initiative).
- In this way, both public and private sectors have contributed to the huge global research effort to tackle HIV/AIDS since 1982[5].

Should IMI focus on neglected infectious diseases?

In the period from 2007 to 2014, the EU was one of the world's largest funders of neglected infectious diseases (NIDs) research through the Seventh Framework Programme (FP7)[6]. NID research has remained a priority in Horizon 2020, principally (though not only), through EDCTP2, whose original remit has been extended to include NIDs in addition to its focus on HIV/AIDS, malaria and tuberculosis.

Although IMI was not specifically designed to focus on NIDs for the reasons outlined above, some IMI projects do. For instance, the VHFMoDRAD project, building on the EbolaMoDRAD project results, is developing a test that can diagnose, in a single blood sample, other viral haemorrhagic fevers like Lassa fever, Crimean Congo Haemorrhagic fever, Rift Valley fever, Marburg, Yellow fever, Dengue fever and Zika. The tests will also be validated in the field, and training courses will be set up in western Africa to teach locals how to use the tools. The project intends to partner with an African manufacturer so that the tests can be produced locally.

Some other IMI projects are developing tools that have relevant implications for NID diseases. For instance, ELF - and it successor, ESCulab - provide researchers with the opportunity to have their drug target screened free of charge against the project's compound collection. It has already run a screening programme on Dengue fever.

The European Commission has already indicated that support to these areas is planned to continue in the future through the EDCTP's successor, the EU-Africa Global Health Partnership, and other Horizon Europe initiatives.

4 The EU invested over EUR 175 million in HIV/AIDS research through FP7 and has committed over EUR 220 million through Horizon 2020, including the EC contribution to EDCTP2 projects. See here.

5 According to the *G-Finder report 2019*, global funding for HIV/AIDS basic research and product development in 2018 was USD 1 451 million.

6 During FP7, the EU provided EUR 169 million for 65 NID research projects; these projects involved research teams from 331 different institutions in 72 countries on 6 continents.

IMI'S EBOLA PROJECTS: TOO LITTLE, TOO LATE?

The report claims that IMI has done 'too little' on Ebola. Again, the overall context and understanding is totally absent. IMI has funded 12 projects on Ebola and related diseases with a total combined budget of over EUR 300 million.

The impact that these projects have had is enormous. In early July 2020, Janssen, a Johnson & Johnson company, received a marketing authorisation from the European Commission for its vaccine regimen to prevent Ebola virus disease in people one year and older.

In fact, Janssen has invested hundreds of millions of euros in the vaccine projects together with the EU through IMI (EBOVAC1 and EBOVAC2 and EBOVAC3), and with many other partners (NIH, WHO, Wellcome Trust, BMGF, etc.), without any profitable market visibility, so we fail to understand the underlying unjustified insinuation, i.e. that the industry will only co-invest when there is a clear profitable interest.

The real picture is that J&J is (i) working in partnership to secure vaccine pre-qualification from the WHO in order to accelerate vaccine registration in African countries and facilitate broader access to those most in need; and (ii) is in advanced discussions with Gavi, WHO and UNICEF regarding potential procurement of the vaccine, pending designation from WHO. The real picture is also that nearly 100 000 people have started the vaccine regimen to date and up to 1.5 million vaccine regimens are currently stockpiled. Yet the projects advancing the development of this vaccine regimen are ignored in the report. In the meantime, the Democratic Republic of the Congo's (DRC's) 11th Ebola virus disease outbreak was announced on 1 June 2020.

Furthermore, it is incomprehensible that the report does not mention that IMI's Ebola programme has delivered crucial and innovative assets including two rapid diagnostic tests that are being field-trialled in the DRC at this moment, together with an iris-scanning technology which is now being adapted for use in the COVID-19 context[7].

The report cites just one project, VSV-EBOVAC, and does so only to hold IMI responsible for a licensing agreement that took place between a Canadian biotech company and MSD before the IMI project even started. The goal of VSV-EBOVAC was to understand the human immune response to the MSD vaccine, to share these data with other vaccine developers and to understand more about the immune correlates of protection. On this, they have succeeded.

The report also claims that IMI's actions on Ebola came 'too late'. Firstly, Ebola was not in our Strategic Research Agenda or indeed the WHO 2013 *Priority Medicines* report because no one knew that there would be an epidemic in 2014. Nevertheless, IMI launched a fast-track Call for proposals mobilising resources within three months and the resulting projects succeeded in getting the trials up and running rapidly. As the situation fortunately improved and the number of new Ebola cases began to fall, the original plan of testing the vaccine in Ebola-infected communities became more and more difficult.

The projects responded to this development by creating alternative ways of assessing the

7 See, for instance, the IMI project FILODIAG.

vaccine regimen's efficacy by using a much larger population of healthy volunteers, which required designing a new clinical trial, seeking approval and extending the timelines for this much larger study.

More recently, the Ebola outbreak in the Democratic Republic of the Congo prompted the IMI projects to restart trials of the vaccine regimen in an outbreak situation. In 2019, following WHO/SAGE recommendations for an additional vaccine, the Janssen vaccine regimen became part of efforts to help contain the North Kivu outbreak in the DRC (with deployments in both the DRC and Rwanda). One year later, the vaccine regimen a received positive opinion for approval by the Committee for Medicinal Products for Human Use of the European Medicine Agency (28 May 2020) and was granted marketing authorisation by the European Commission (1 July 2020). Throughout all of this, the goal of the EBOVAC projects has remained constant: to evaluate the safety and efficacy of the vaccine regimen.

HOW MUCH IS IMI CONTRIBUTING TO EMERGENCY PREPAREDNESS AND THE GLOBAL FIGHT AGAINST CORONAVIRUSES?

In relation to COVID-19 research, IMI launched a fast-track Call on 'Development of therapeutics and diagnostics combatting coronavirus infections' already on 3 March. The eight large-scale research projects selected are already contributing to both the European and international response to the pandemic by addressing one of the eight immediate research actions agreed at the WHO global research and innovation forum held on 11-12 February 2020 and by collaborating worldwide with all relevant research initiatives, as mandated in the Call topic text.

Infectious diseases and vaccines have been a priority for IMI since the beginning, and we launched a project specifically on bio-preparedness, ZAPI, in 2015. The project has demonstrated that certain antibodies can stop the MERS (Middle East respiratory syndrome) coronavirus from infecting new cells and is now assessing whether the antibodies could also be effective against SARS-CoV-2. Its findings are further feeding into research on COVID-19 through two new projects, the EU-funded MANCO project and the IMI-funded CARE project. A second project with a huge impact in preparing for a speedier regulatory approval of a potential vaccine against the SARS-CoV-v2 is EBOVAC, based on their recent experience in developing the Ebola vaccine.

Another IMI project, EHDEN, is currently developing a federated network of data partners with the goal of allowing access to the anonymised health data of 150 million citizens in Europe. The data will remain at all times under the complete control of the original data owner, thereby ensuring ethical and local data privacy rules are respected. At the heart of the project is a community of SMEs selected through open calls and trained and certified by EHDEN, who are responsible for harmonising the data owned by the partners according to a common data model. The COVID-19 pandemic has confronted the project with its first real-life test.

- The project has been working since May 2020 with 25 data partners across Europe to help them map their COVID-19 clinical data to the standardised common data model. Its goal is to help clinicians, scientists, governments and the public to know more about characterising patients with COVID-19, how best to manage their care, and whether certain treatments are safe and effective.
- EHDEN partners have played a leading role in organising the OHDSI (Observational Health Data Sciences and Informatics) COVID-19 virtual study-a-thon held on 26-29 March. Five preprints have already been published as a result of this study-a-thon, directly impacting patient care. One of them is a very large study on the safety profile of hydroxychloroquine using data comprised of 14 sources of claims data or electronic medical records from Germany, Japan, Netherlands, Spain, UK, and USA. This study demonstrated that there was a striking >2-fold increase in sudden cardiovascular mortality when hydroxychloroquine is

taken concomitantly with azithromycin. The FDA, EMA, and MHRA are currently evaluating this data, and the EMA has already issued a warning that explicitly mentions the project's preprint[8].

- The project is now set to collaborate with the European Medicines Agency (EMA) on the creation of a framework for multicentre cohort studies on the use of medicines in COVID-19 patients.

More broadly, other IMI projects that are relevant to bio-preparedness and vaccines include BioVacSafe, which aims to develop tools to speed up and improve the testing and monitoring of vaccine safety; ADVANCE, which focuses on facilitating the rapid delivery of clinical data on vaccines to help public health authorities make decisions on vaccination strategies; and VAC2VAC, which is working on developing alternative in vitro, non-animal tests for vaccines[9].

The report highlights the case of a topic on bio-preparedness that was discussed in 2017-2018. Here, the report shows a lack of understanding of how IMI Call topics are developed. Many topic ideas are put forward by EFPIA companies, the European Commission, and other stakeholders. These are discussed extensively within the industry, with the European Commission, with stakeholders and with IMI's advisory bodies. Topic ideas that are taken on board take time to mature and often evolve significantly during this process. At the same time, many topic ideas are not adopted because the IMI governance bodies decide that they would be better addressed through other mechanisms or at a different time.

The topic on bio-preparedness was relatively small in scope and focused on reconsidering the suitability of current animal models and developing *in silico* models to better define/anticipate the type and level of immune response elicited in animals and humans. This would have the effect of increasing regulators' confidence in the evidence base for alternative licensing procedures. On reflection, it was felt that some elements of the topic would be better addressed through other channels. Meanwhile, those aspects of the topic that were suited to an IMI project were included in the IMI2 - Call 20 topic 2 (Innovations to accelerate vaccine development and manufacture) including mathematical/*in silico* modelling of infectious diseases and designs of clinical studies based on human challenge models.

8 See here the links to the EDHEN preprints. Publications are following on the real world adverse event profile with hydroxychloroquine, evaluating the profile of COVID-19 patients versus last influenza season, and predicting the patients at most risk and need for critical care.

9 Many other IMI projects' results are also contributing to tackle the current and future outbreaks. See here for some examples.

EARLY ENGAGEMENT OF REGULATORS: ONE OF THE GREAT VIRTUES OF THE IMI PROGRAMME, AND KEY TO ENSURING IMPACT FROM OUR PROJECTS' RESEARCH

In the context of a highly regulated sector, many IMI projects are developing scientific knowledge with a potential regulatory impact (such as, but not limited to, tools and methodologies that improve the evaluation of a medicine's safety/efficacy or alternative clinical trial designs), and provide the scientific basis for regulatory decision-making. For instance, PROACTIVE has developed an innovative tool capable of capturing both the amount and intensity of physical activity a patient with chronic obstructive pulmonary disease (COPD) actually carries out (which can be indicative of the success of medical interventions), which has obtained a Qualification Opinion by the EMA and can now be used in clinical trials.

In a similar vein, work by EU-AIMS is cited in EMA guidelines on the clinical development of medicinal products for the treatment of autism spectrum disorders (ASD), which were issued in November 2017. Most notably, the guidelines highlight the project research efforts to identify markers that could potentially be used to diagnose ASD or assess how well new treatments work. In the document, the EMA encourages clinical trial sponsors to engage in the development and validation of biomarkers and use them as 'exploratory efficacy measures' in clinical trials.

The involvement of regulators is essential to ensure project outputs meet the required standards and are good enough to be taken up and used in drug development. For this reason, IMI encourages all projects to seek regulatory / health technology assessment (HTA) / payer engagement as early as possible and provides them with detailed guidance on opportunities for interaction with regulators. The guidance document is public and can be found in the 'Documents for projects' section of IMI's website.

Still, according to the IMI2 Interim Evaluation by independent experts, we should be working even more closely with regulators. An opinion shared by the IMI Scientific Committee, which states that "in spite of the obvious importance, involvement of regulators has not yet been widely accepted and implemented in IMI2 projects". This analysis has led the Scientific Committee to provide a list of recommendations on how to improve regulatory participation in IMI2 projects. The Scientific Committee acknowledges the potential for conflicts of interest and suggests ways of addressing these.

Furthermore, regulators themselves emphasise the relevance of early engagement as shown by the conclusions of the regulatory science summits organised in collaboration with the EMA and the US Food and Drug Administration (FDA), where they explicitly state that "continued and early dialogue help increase mutual understanding and expectation setting between regulators and IMI project partners, which should result in better availability and ac-

ceptability of study outcomes for the benefit of public health. The emphasis in this context is on confluence of interest rather than conflicts of interests."

Despite this, the GHA report suggests that this approach is not advisable and should be halted because it could lower evidence standards for new medicines. The author of the report bases these allegations on three IMI projects, ADAPT-SMART, GetReal and iPiE, led by relevant institutions such as the EMA, the Universitair Medisch Centrum Utrecht and the Fundació Institut Mar d'Investigacions Mèdiques[10].

In all three research projects, potential conflicts of interest were addressed by design. The research was conducted in a transparent manner, with proper checks and balances in place, and with IMI scientific oversight. As recognised by the Scientific Committee in the recommendations cited above: "The establishment of project governance models that turn IMI2 into the often cited 'neutral broker' that enables collaboration of stakeholders with competing interests within a PPP is a special achievement of IMI and is partially based on the dedicated establishment of these governance structures."

It is widely acknowledged that the lack of specific relevant know-how in regulatory science impedes the development of new treatment strategies or limits the chances that promising innovations will reach patients. In this context, all three projects produced valuable scientific evidence to answer research questions that were novel at the time of project launch by bringing around the table all relevant stakeholders. Moreover, the resources created by these projects are open and freely available to the research community and any other interested party. They can be accessed through the IMI Catalogue of Project Tools. The projects' final reports are all published in the IMI website[11].

It is important to remember that, while projects can generate the scientific evidence, the regulatory implementation of such results that may potentially lead to change in the regulatory pathways and framework remains the sole responsibility of the regulators, thereby ensuring the independence of the authorities' decision-making. For instance, the project GetReal has delivered the tool ADDIS, a data management and analytical tool that conducts network meta-analyses and benefit-risk analyses for evidence-based decision-making in healthcare. In its Work Plan 2019, the EMA Committee for Medicinal Products for Human Use (CHMP) indicated that it would explore how the ADDIS decision-making tool could help assessors in regulatory decision-making and structured benefit/risk assessment of medicines.

Regarding the "one billion in public money" allegedly spent "to provide industry with preferential access to regulators", we fail to understand how GHA came to that figure. In the corresponding footnote, the author of the report refers to the *IMI Highlights 2017* and the funding allocated to projects listed under the headings "medicines safety", "regulatory issues" and "environmental impacts". However, the real figure on IMI funding allocated to these projects is EUR 109 600 000. Regardless, the relevant fact here is that the funding was actually allocated to research activities carried out by universities, research organisa-

10 One of the heights in the report's manipulation efforts is reached when, referring to the ADAPT-SMART project, the report twists the declaration of one project partner and links it to unsubstantiated accusations (p 24). IMI invites readers to go to the original interview to check what the project partners really said.

11 In what seems to be a constant in the report, GHA builds its case against the iPIE project on supposed HCWH criticism, but without providing any reference of such criticism. Although, HCWH is not a partner of IPIE, IPIE project partners have actively engaged with HCWH. In none of these interactions did HCWH raise concerns about iPiE's research. Furthermore, the ECOdrug database, an IPIE project output, is listed in the HCWH-led Safer Pharma campaign resource page on "pharmaceuticals in the environment initiatives". Regarding the transparency of IPIE's research and the accessibility of the project results, it is worth noting that the project has also produced the iPiEsum database which is freely available to anyone and contains previously unpublished information on the environmental fate and behaviour of over 250 pharmaceuticals that has been generated by EFPIA members. The German stakeholder group on micropollutants has acknowledged this database as an excellent tool for data transparency.

tions, patient organisations and SMEs (it should be repeated that under IMI, the pharmaceutical industry *does not* receive any EU funding) and was awarded to projects such as:

- eTOX - this project enabled pharmaceutical companies to share their data on the toxicity of drug-like compounds for the first time on a large scale, leading to the creation of eTOXsys, the biggest toxicity database in the world. The database comprises 8 196 toxicity studies on 1 947 compounds, including 9 million preclinical data points and over 200 predictive ***in silico*** models, which will help reduce the use of animals in drug research. This database can be accessed through a powerful system currently exploited by the project's SME partners. In addition, as a result of their participation in the project, AstraZeneca is making data provided to eTOX available to the wider scientific community through its Open Innovation portal.
- SAFE-T - among the side effects most challenging to drug developers and prescribers alike are drug-induced injuries to the kidney, liver and vascular system. Current tests designed to detect problems before drugs make it to the patient do not always predict these side effects. The SAFE-T project developed and improved tools for the prediction, detection, and monitoring of drug-induced injuries to both organs and the vascular system using markers in patients' blood and/or urine. The quality of the research has been recognised by the EMA and FDA, who have issued a 'Letter of support' (first step of the validation process) for these biomarkers, and have advised for them to be used in exploratory trials.
- WEB-RADR - one of the objectives of this project was to assess whether social media offers a valuable source from which to extract and analyse information about drug use and misuse. As Phil Tregunno, of the UK's Medicines and Healthcare Products Regulatory Agency, explains: "Without the scientific research that was conducted within the project, there was a real risk of social media data being transposed into traditional pharmacovigilance systems and swamping traditional data, making it too noisy to detect safety issues."[12]

IMI remains convinced that funding strong science in the field of medicines safety to support better tools to predict, prevent and detect drug-related adverse reactions is a topic of clear relevance for a PPP, not only because it is a complex field and requires a multidisciplinary approach, but also because it has a clear benefit for society. We invite readers to explore other IMI projects working on the safety of medicines by accessing the IMI project factsheets on our website.

12 See full interview.

IMI AND ITS PROJECTS LEADING THE WAY IN PATIENT EMPOWERMENT

At IMI, we consider patients equal partners that can and should play an active role in the medicines R&D process. Including patients' perspectives in IMI activities and facilitating patient participation in projects is a top priority for IMI. This is why patients are a core third pillar in many of IMI's projects. As of the end 2019, close to 56% of all IMI projects have patient organisations, either as partners in the consortium, represented on advisory boards, or as consultants for topics of relevance. Participation increases to almost 64% in IMI2 projects alone.

IMI's engagement with patients and promotion of patients' meaningful involvement in our projects and activities takes a number of paths.

As Associated Partners

Patient organisations with their own research funding programmes can become Associated Partners of IMI and are typically involved in the development of new Call topics from the outset. In this way, they are able to participate in the definition and the scope of the project. Leading patient organisations, trusts and charities like Autism Speaks, Autistica, JDRF, the International Diabetes Federation, Children's Tumor Foundation, Parkinson's UK, TB Alliance, and Obesity Action Coalition are active IMI Associated Partners and contribute to IMI projects on various disease areas like diabetes, autism, neurodegenerative diseases and cancer. For example:

- Research foundation and charity for juvenile diabetes JDRF has contributed to IMI's IMIDIA and SUMMIT projects and is now contributing resources and expertise to the INNODIA, BEAT-DKD and Hypo-RESOLVE projects.
- Patient advocacy groups Autism Speaks and Autistica contribute to the AIMS-2-TRIALS project on autism.
- Parkinson's UK contributes to the PD-MitoQUANT project on mitochondrial dysfunction in neurodegeneration and the NEURONET coordination and support action for IMI projects in the neurodegeneration area.

Since 2014, not only have the Associated Partners brought approximately EUR 200 million (both in cash and in-kind) as a contribution to the IMI budget, but more importantly, they have brought specific expertise and networks that have been invaluable in the development of the new ecosystem for health research that IMI has catalysed, including the link with international initiatives

As full project partners

Over 30 patient organisations, including the European Patients' Forum, Alzheimer Europe and Eurordis have chosen to become full project partners. The expertise they bring to IMI projects places them on an equal footing to other partners. Their contribution to the consortium includes valuable input on many aspects of the project, namely:

- helping define the outcomes that will genuinely benefit patients;
- determining the appropriate benefit-risk balance in new treatments;
- providing input into the best ways to involve patients in project governance.

Their participation is being fostered by the inclusion of sections dedicated to patient involve-

ment in Call topic texts. In addition, IMI has produced a brief guide for potential applicants with advice for on how to ensure meaningful patient involvement.

As members of advisory boards and ethics advisory boards

Patients can sit as members on advisory boards and ethics advisory boards. This way they can bring the patient perspective to the project and provide valuable input in terms of ethical and meaningful patient involvement.

As experts in the IMI pool of patient experts

The IMI Patient Expert Pool has 118 patients and 39 informal carers from 26 European countries. Drawing from this platform, IMI invites patients and patient carers with the most suitable profile to perform a variety of roles, such as participating in project review panels and working on equal terms alongside experts from other sectors.

As participants in IMI advisory bodies

A patient representative sits as a full member on the IMI Scientific Committee.

As speakers at IMI events

Patients and patient representatives participate regularly as speakers and panellists at IMI events, and have also co-directed the organisation of entire sessions at the IMI Stakeholder Forum.

Choosing, once more, to overlook IMI's real contribution to meaningful patient involvement in the medicines research lifecycle, the report depicts IMI as a vehicle for providing industry with a direct opportunity to lobby patients, and uses the EUPATI project as an example. However, patient associations who have been prominent partners in the project have highlighted their involvement in the conceptual design and theoretical framing of EUPATI, and have stressed the collaborative methodology applied to content creation. See, for instance the 2015, 2016 and 2017 Annual reports from the European AIDS Treatment Group (EATG), a signatory of and active contributor to the *Renewing Our Voice - Code of Good Practice for NGOs Responding to HIV/AIDS* between patient organisations and the healthcare industry.

Patients and the biopharmaceutical industry need to work in synergies that secure structured and integrated patient involvement at all phases of medicines development and not only during post-launch or late-stage clinical development. However, as the WHO *Priority Medicines report* from 2013 recognises, this requires the empowerment of patients and citizens as well as the education and training of all parties involved (i.e. researches and patients)[13].

This is the reason why the IMI patient–led project EUPATI built a programme that provided education and training to help patients engage more effectively in medical research and development, and to improve the availability of medical information for the health-interested public. It did so by conducting its established Patient Expert Training Course that has trained more than 150 patient experts to date, and by providing an open-access multilingual toolbox that has served more than 4 million users around the world. The fact that the course is freely available to the public maximises its outreach and value. It also provides an opportunity for public scrutiny of the content provided[14].

A catalyst in patient empowerment, EUPATI has increased the capacity of patients to act as effective advocates and advisors to key stakeholders involved in R&D[15]. EUPATI Fellows are engaged in advisory roles, act as trainers, are involved in health policy advocacy, are invited as speakers at conferences, have started com-

13 The EU-funded EMPATHiE project final report provides further evidence on the direct link between patient empowerment and training.

14 All the information on the EUPATI website is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike.

15 Read here a journey of a EUPATI fellow.

munity advisory boards, assist and advise other patient organisations, are improving informed consent documents, reviewing clinical trial protocols and contributing to clinical trial designs.

The relevance of both the educational resources and the national platform network created by the project is demonstrated by the interest it has generated among other EU-funded instruments/organisations. Examples include the partnership agreement signed between EATRIS and EUPATI, or the EIT Health funding of the project RELOAD, that aims to adapt the current EUPATI training to individual learner's needs by tailoring it to a format similar to the popular massive open online courses.

Finally, an aspect that is often forgotten but that should not be dismissed is the contribution of EUPATI Fellows to significantly increasing public support for medical research.

A MORE ACCURATE PICTURE OF IMI'S INVESTMENT IN AMR RESEARCH: A EUR 955 MILLION PUBLIC-PRIVATE JOINT EFFORT TO ADDRESS THE MOST DANGEROUS MARKET FAILURE FACING SOCIETY

Antimicrobial resistance (AMR) is a global public health threat. Over 33 000 people in Europe die of resistant infections each year (at least 700 000 globally), making the burden of these infections comparable to that of influenza, tuberculosis and HIV/AIDS combined. According to the WHO, by 2030 AMR could push up to 24 million people into extreme poverty. What is more, without effective antibiotics, medical procedures such as organ transplants, cancer chemotherapy and caesarean sections, to name but a few, become very high risk. Yet, despite the rise of highly-resistant pathogens, the development of new antimicrobials has stagnated over the last 30 years, leading to the most dangerous market failure we currently face as a society.

While extrinsic and intrinsic barriers certainly exist, there is currently a rich activity in the early stages of research, where SMEs and, to a certain extent, universities have become the primary drivers of this sector. However, to a large degree, universities and biotech companies still need pharma intervention at late stage clinical development to assure market authorisation, which may cost too much for them. Pharmaceutical companies, on the other hand, do not have a compelling business case for investing in AMR research due to the market failures inherent in this area. A public private partnership like IMI is the right vehicle for fostering the collaboration of these different actors in order to ensure progress on these R&D challenges.

To contribute to the EU response to AMR, IMI has invested over EUR 955 million in 16 IMI projects that tackle the antimicrobial resistance threat:

- by shedding new light on the mechanisms of antimicrobial resistance (EUR 24 million), e.g. the TRANSLOCATION project;
- by providing universities and SMEs with a platform to smooth the path of promising, novel antibiotics through the challenging early stages of antibiotic development (EUR 82 million), e.g. the ENABLE project;
- by facilitating large-scale, pan-European studies on antimicrobial resistance and clinical trials of novel antibiotics, many of which are designed to treat the most dangerous resistant infections (EUR 474 million), e.g. the COMBACTE family;
- by analysing economic models to re-incentivise antibiotic discovery and advocating for the responsible use of antibiotics (EUR 10.8 million) e.g. the DRIVE-AB project;
- by accelerating the discovery of new combinations of drugs to treat tuberculosis (EUR 208 million) e.g. the ERA4TB project.

Once again, the report attempts to disparage IMI by circumscribing our significant involvement in AMR research to ReAct's decision to withdraw from the DRIVE-AB project in 2017 and the Mario Negri Institute decision not to participate in COMBACTE-NET back in 2013[16].

Antimicrobial resistance is already an extremely challenging area, both from the scientific and the economic point of view, and the question of how to balance rewards for innovation with sustainable use is particularly difficult. As the subject has gained more prominence in the political agenda in recent years, the debate has become even more tense, making very frank discussions amongst the relevant decision-makers unavoidable. There is no shame in acknowledging areas where there is still no consensus. In this case, IMI worked with the project partners to make sure that minority views were visible in the final DRIVE-AB report[17].

IMI regrets that ReAct chose to leave, as they made a number of valuable contributions to the project. We should not forget that DRIVE-AB has carried out important research in terms of developing a conceptual framework for an international standard of responsible antibiotic use, creating a multidrug resistant pathogen propagation model, preparing and analysing different reward models and raising awareness of the issues globally. This fact has been recognised by ReAct.

IMI remains convinced that, for a highly sensitive subject like this, with so many complexities and so many viewpoints, a public-private partnership is a very good place to hold these discussions, and in launching DRIVE-AB, IMI has placed itself at the cutting edge of this dialogue.

The primary goal of the COMBACTE projects is to set up high-quality pan-European hospital and laboratory networks to run efficient clinical testing of novel antibacterial drugs. This is important because a network based in just one country will struggle to find enough patients with the infection under study to run a meaningful trial. Also, the efficiency and quality of these trials needs to be improved. Here the COMBACTE projects have succeeded, and the networks now count nearly 1 000 hospitals and over 800 laboratories in all EU countries plus several neighbouring countries. In addition to the regular COMBACTE clinical trials focusing on antimicrobial resistance, the COMBACTE network is being intensively used in site selection for COVID-19 studies. One of them, REMAP-CAP, has published promising first results in *JAMA* showing that the use of corticosteroids increases the likelihood of survival of critically ill COVID-19 patients[18].

The compound cited in the report was put forward as one of the first to test the network at the beginning of the project, and in this respect, it was subject to consultation with the European Commission, EU countries, and the European scientific community. Although the resistance issue it was designed to address is more common in the US, we should not forget that antimicrobial resistance is a global phenomenon, and while some drug-resistant infections are more prevalent in some world regions than others, they are perfectly capable of moving into new regions. Ultimately, and this serves as a demonstration of the reality that investment in AMR drug development comes with significant risks, the trial did not go ahead because preclinical studies picked up safety issues with the potential drug.

16 As the report rightly mentions, ReAct is affiliated with the Uppsala University, who was the formal project partner and did not withdraw from DRIVE-AB. Regarding the Mario Negri Institute, this institution has been an active partner in 5 IMI projects since 2009, including the project PREMIER on prioritisation and risk evaluation of medicines in the environment, which is a follow up from the IMI iPIE project

17 Contrary to what the GHA report writes, the DRVE-AB final report actually states: "The recommendations it presents were not unanimously agreed among DRIVE-AB members, but do broadly reflect the results of the research carried out. The areas of contention are few in number but relate to central concepts of our recommendations. Alternative views are noted in the report." And they are.

18 See https://jamanetwork.com/journals/jama/fullarticle/2770278.

Meanwhile, the COMBACTE network has gone from strength to strength, and is conducting (and in some cases, has concluded) several clinical trials to test six novel antibacterials, as well as several clinical studies designed to add to our understanding of resistant infections. The Antibacterial Resistance Leadership Group (ARLG) has joined some COMBACTE studies, demonstrating both the strength of COMBACTE's approach and the shared, global nature of the challenge.

More recently, COMBACTE and the Horizon 2020 project PREPARE are providing the basis for the establishment of a Europe-wide sustainable network for harmonised large-scale clinical research studies for infectious diseases, with a budget of EUR 30 million. A business plan for such a network is currently being developed under the Horizon 2020 ECRAID-plan project.

With 720 public organisations involved in a current portfolio of 159 IMI projects, the fact that two organisations prematurely quit a project makes the claim that the pharmaceutical industry sidelines public partners difficult to justify. Overall, the real trend we see evolving in IMI is the increasing recognition that some challenges are just too big for anyone to solve alone, and collaboration is essential for progress. Our role at IMI is to help to forge those collaborations in an open and transparent way.

Another bias is evident in the argument relating to industry commitment. The report alleges that there is no system in place to guarantee that the industry commitments in a project will be maintained. The fact is that:

(i) at programme level, there is a legally binding commitment through the founding partners, that the European Commission's public funding will be matched by the industry partners (and Associated Partners);

(ii) the pharma industry is fast-moving and there can be changes in priorities over the course of a five or seven -year project - when this occurs, there is a mitigation strategy, developed by EFPIA, which is put in place immediately;

(iii) minor changes in the work packages are managed at project level, and the nature and quality of the in-kind contribution is thoroughly vetted and validated according to the H2020 rules.

THE ROLE OF IMI IN ACCELERATING INNOVATIVE MEDICINES

With very few exceptions in Ebola and AMR, IMI projects are not designed to directly bring new medicines to market. Rather, they will have an impact on new product development and product safety by:

(i) advancing the scientific knowledge that will underpin the development of a range of protocols, standards, technologies and medicines. For instance, the EU-AIMS project carried out the largest deep phenotyping study of autism spectrum disorder (ASD) in the world; elsewhere, scientists funded by IMI's BEAT-DKD and RHAPSODY projects have identified five subtypes of diabetes. e.g. patients in group 2 ('severe insulin-deficient diabetes') are at greatest risk of eye disease, while patients in group 3 ('severe insulin-resistant diabetes') had the highest incidence of kidney damage;

(i) improving the efficiency and productivity of the medicines development process (usually in particular disease areas), delivering future cost savings, time savings, reductions in risk or reductions in attrition rate. For instance, in the MARCAR project, researchers discovered early biological indicators that could help detect some of the more indirect ways in which drugs cause tumour formation, while the MIP-DILI project improved laboratory tests used to predict drug-induced liver injury in the early stages of drug development.

As such, the impact of these results on the development of a specific medicine is likely to be incremental, and just one element alongside many others. It will also take time before an impact can be seen. The flucytosine example mentioned in the report should be re-examined in this light.

The goal of CHEM21 was to improve the environmental footprint of drug manufacture and it achieved this by developing a unified metrics toolkit to evaluate the sustainability of all reactions, from lab-bench to industrial scales. The toolkit is freely available, and its use will allow for an increase in the quality and pace of green chemistry research. It also published a comprehensive guide to green solvent selection, ranking both classical and bio-derived solvents based on (i) safety, health and environment criteria, and (ii) physical properties. The guide is a valuable resource due to its comprehensive nature and the inclusion and promotion of bio-derived solvents, which are not typically assessed for environmental impact.

The project's research on flucytosine was another contribution to cleaner, safer and more sustainable manufacturing processes, since the new synthetic pathway proposed to produce it involves just one selective reaction instead of the four it usually takes. This means using significantly less energy and raw materials and producing less waste than conventional techniques.

Sanofi contracted MEPI, a French non-profit association, to investigate ways to scale up the process of making flucytosine via the one-step 'continuous flow' method developed by the University of Durham that uses the readily-available natural product cytosine as its starting point. With input from scientists from Durham and Sanofi, MEPI succeeded in setting up a

small reactor capable of producing 1 kg per day of raw material. The work describing this new production process in the lab was published in the scientific literature in early 2017.

IMI always encourages projects to consider the sustainability and exploitation of their results after the project has finished, and, as we wrote at the time, the new process had the potential to change the way flucytosine is produced. To that end, preliminary discussions involving Sanofi (CSR & Global Health Programs), Durham University and the Medicines Patent Pool have been initiated for a potential licensing and technology transfer agreement to make flucytosine available in low- and middle-income countries at affordable prices.

We support the claims for transparency on the real cost of research, and all figures on IMI public funding to individual projects and individual beneficiaries are published in our website. However, it must once more be highlighted that the pricing of new medicines is determined following extensive interactions between the pharmaceutical companies, relevant regulatory bodies and national governments and, as such, these discussions are not within the remit of the IMI programme or other H2020 research instruments.

SHARING THE UNSHARABLE

When it comes to big data, no other research sector has as much at stake as the health sector. There is a clear consensus that data from sources like clinical trials, health records, imaging, genome sequencing and wearables are a vital resource for much needed research to save and improve the lives of patients. For this reason, during the four-year legislative process on the General Data Protection Regulation (GDPR), research associations such as Science Europe and the League of European Research Universities (LERU) and funding organisations such as the Wellcome Trust heavily advocated an exemption for scientific research from several of the general requirements in order to facilitate health data collection and processing.

The GDPR text that was ultimately adopted was welcomed by all stakeholders as a pivotal instrument to guarantee the fundamental right to personal data protection. Yet, since its entry into application, the health research community and institutions like the European Parliament have identified some uncertainties in the implementation of the Regulation that could hinder collaborative research and create barriers that could make it more difficult to have a real impact on patients' health[19]. Failing to acknowledge that these discussions are needed and are openly taking place does not serve public health interests.

As for EFPIA, the pharmaceutical association does not need to resort to supposed discussions "behind IMI closed doors" because it can provide (and has provided) direct feedback to the Commission regarding the application of the GDPR through its participation in the GDPR Multistakeholder Expert Group[20].

The report goes one step further in suggesting that the proposal to incorporate other industries (such as diagnostics, medical devices, imaging, biotech and digital industries) as founding members in the future Health PPP responds to a cunning move from the pharmaceutical industry to better shape the regulatory environment for health data. Knowing from references elsewhere in the report that the authors are aware of the recommendations of the interim evaluation of IMI2, it would seem only fair to quote here too the experts' advice to integrate industries other than the pharmaceutical industry both in current IMI projects and in the new PPP "to capitalise on their expertise in the development of new healthcare interventions"[21].

Research organisations expressed strong support for this recommendation when consulted by the Commission during the open consultations leading to the *Draft proposal for a European Partnership under Horizon Europe*[22]. These stakeholders not only welcomed the expansion of the initiative to industries beyond the pharmaceutical industry, but also highlighted the major impact on their own work that could be derived from the increase in data sharing and digitalisation capabilities that this option would provide.

19 See for instance the European Parliament study on How the General Data Protection Regulation changes the rules for scientific research or ELIXIR's response to the 2020 public consultation of the European Commission on the GDPR.

20 Their assertion that these discussions take place in 'exclusive and non-transparent forums' is also false. The IMI Stakeholder Forum is a public event which has open, free registration and is broadcast online, so that anyone with an internet connection can watch it. The recordings and presentations are published online afterwards.

21 *The Interim Evaluation of the Innovative Medicines Initiative 2 Joint Undertaking (2014-2016) operating under Horizon 2020* (p 96-97).

22 Open public consultation on the Inception Impact Assessment (30 July – 27 August 2019) and Open public consultation on partnerships under Horizon Europe (11 September – 12 November 2019).

How do IMI projects use health data in their research?

- Open PHACTS, an example of a project building on preclinical data: The early drug discovery process requires the assembly, overlay and comparison of data from many sources, as well as the development of common standards and semantics. Until now, these data sources were very fragmented and it took researchers significant amounts of time and money to answer basic research questions. By bringing together leading experts in the fields of data mining, small molecule data storage and manipulation, target bioinformatics, information handling, chemical biology and more, the Open PHACTS project connected about a dozen different drug discovery databases and developed the Open PHACTS Discovery Platform.

  The result? It used to take a researcher three months to compile a dataset of around 1 000 compounds to make a decent computational model. Now, thanks to Open PHACTS, the same researcher can create a dataset of around 2.3 million compounds in seconds with a few clicks. The Open PHACTS Foundation has made the platform free, open access and sustainable, and it continues to run beyond the lifetime of the project.

  Incidentally, Open PHACTS was one of the 'thought incubators' cited in the drafting of the original FAIR data manifesto, with its Open PHACTS Discovery Platform cited as an early example of a system in which FAIR ('findable, accessible, interoperable, reusable') principles were already being implemented.

- HARMONY, an example of a project building on real world data: The HARMONY project uses big data technologies to improve the treatment of seven haematological malignancies, including paediatric haematological malignancies. Although all seven of them affect the blood and lymphatic system, these are very different types of cancers, each one with its own research challenges that can only be answered by studying large numbers of patients. Therefore, HARMONY is looking for responses by:

  (i) Pooling datasets from patients with blood cancer such as leukaemia, lymphoma, and myeloma into one harmonised European clinical data platform. In three years, 45 000 data sets have been identified.

  (ii) Analysing the data provided through pilot studies designed to address the seven haematological malignancies. For instance, acute lymphoblastic leukaemia (ALL) is a rare disease most often seen in children. Fortunately, for children and young adults with ALL, the prognosis is excellent, but the situation in older adults (>25 years) is more serious as increasing age is associated with poorer prognosis. By having access to a large patient cohort through the HARMONY Big Data Platform, researchers have a detailed knowledge of the incidence of genetic abnormalities within adult patients with ALL, and they can examine how these abnormalities interact. The results of this study will have an impact in the short term since it will help clinicians in their therapeutic decisions by identifying those patients most in need of treatment with intensive chemotherapy.

- RADAR-CNS, an example of a project building on patient generated real-world data: Wide bandwidth networks, smartphone penetrance and wearable sensors offer new opportunities for collecting (near) real-time high resolution datasets from large numbers of participants. The goal of the RADAR-CNS project is to improve the patient-monitoring process through remote assessment by:

  (i) Developing the RADAR-Base platform, an open source platform to use data from wearables and mobile technologies. Launched in 2018, it provides both

passive and active data collection via two applications. RADAR-base is now being used by other projects including for the study of patients with atrial fibrillation, a heart condition that causes an irregular and often abnormally fast heart rate; as part of the IMI BigData@Heart project, in Alzheimer's disease in the RADAR-AD project; and in people recovering from psychosis in the UNFOLD study.

(ii) Testing and implementing wearable technologies for the remote measurement of depression, multiple sclerosis and epilepsy. For all three disorders, patients often experience periods where their symptoms are manageable, followed by periods of deterioration and acute illness (relapse). Patient surveys have repeatedly highlighted the need to predict when relapses will happen and to improve the treatments which are available to stop them from occurring. But in chronic conditions, most of the symptoms and episodes happen outside of the health care environment. Measuring individuals' symptoms, mood and daily function continuously could help doctors and patients gain better insight into their condition. The data generated by the RADAR-base platform is built on principles of clearly documented, structured and reusable data, which enables projects using the platform to comply with the FAIR principles, a feature of high interest to the open source mHealth community.

Trust is at the core of every IMI project. To ensure that all stakeholders feel confident to share and collaborate openly, project consortia often go beyond the ethical and legal frameworks in place, including the GDPR, and decide to build stricter internal guidelines and strong governance mechanisms[23].

The report claims that IMI funds a "disproportionately high" number of projects where the private sector is already investing. Since the social and economic importance of funding research in these areas is beyond any doubt, the real question here is not whether these areas are receiving enough private investment, but if the PPP construct of IMI can contribute to find a new way forward where other types of investment cannot. It is evident that Alzheimer's disease, cancer and diabetes are highly complex diseases where the input of diverse stakeholders with highly specialised backgrounds is essential if we are to make progress and deliver badly needed treatments. In the IMI model, pharmaceutical companies have to work together and share extremely valuable knowledge and resources with each other and with the public sector. This is not business as usual.

23 An example: https://www.harmony-alliance.eu/bigdata-platform/safety-and-security

PART II.
IMI'S GOVERNANCE

The IMI governance model was designed to achieve a balance between public and private interests, and keeping this balance has been one of the main driving forces guiding the work of the IMI Governing Board, the Scientific Committee, the States Representatives Group (SRG) and the IMI Programme Office since IMI's early days.

The equal representation and voting rights of the two founding members: the European Union, represented by the European Commission, and the European Federation of Pharmaceutical Industries and Associations (EFPIA) ensures that decision making is well balanced at the programme level. Decisions by the Governing Board are taken by consensus. Falling consensus, decisions cannot be taken by the industry members only as a majority of 75% of the votes needs to be reached.

At project level, the balance between public and private interests is secured because public and private consortia need to develop and negotiate their joint work programme.

Regarding the description of the Call texts, the Scientific Committee has spelt out the key questions that any IMI topic text and any consortium proposal needs to answer as a pre-condition for selection:

- Why is public funding required?
- Why is a private-only funding option less desirable?
- Why would the research carried out by one company alone or many companies not happen without the involvement of other stakeholders (e.g. academia, patients' organisations, small and medium-sized enterprises, regulatory agencies etc.)?
- Why and what kind of synergy is expected from industry and other stakeholders joining forces in this particular area of medicines innovation[24]?

In broader terms, making sure that the rationale for a PPP is clearly articulated and justified in all IMI activities is a collective effort taken very seriously by all IMI governing bodies and stakeholders taking part in IMI projects.

24 See the *IMI2 JU Scientific Committee recommendations regarding public private partnership funding – what makes a topic ultimately suitable for this kind of funding model?*

HOW IS IMI'S FUNDING DECIDED? FROM THE DEFINITION OF RESEARCH AREAS TO GRANT DECISION

As founding member and source of half of IMIs funding, EFPIA is entrusted with the drafting of the Strategic Research Agenda (SRA), but it does not do so single-handedly or in a vacuum.

1. On the research topics: In compliance with the Regulations that govern IMI, the SRA has to be fully aligned with the EU health research priorities decided by the European Parliament and the Council in Horizon 2020 and with the WHO Priority Medicines Report.

2. On the procedure: EFPIA developed the IMI2 SRA following lengthy discussions with the EC and with input from more than 80 organisations, including regulators, patients and academia. The final text of the SRA and IMI's Annual Work Plans (AWPs), which further develop the SRA, are endorsed by the IMI Governing Board and published online.

IMI's Scientific Committee (SC), which is made up of globally recognised experts, advises on the priorities to be included in the SRA and in the AWPs. The SRG is composed of representatives of the national research authorities and provides opinions on the strategic orientation of IMI and on the links to Horizon 2020.

Call topics must be aligned with IMI's objectives (as set out in the legislation) and the SRA. Although many topic ideas come from EFPIA companies through the Strategic Governing Groups (SGGs), the EC has proposed topics on AMR, Ebola and COVID-19 as well as cross-sectoral areas aiming to bring together the diagnostics and the pharmaceutical industry sectors. Associated Partners also influence topic design; for instance, JDRF has generated three topic ideas on diabetes research and regards its input as a true co-creation process involving the type 1 diabetes (T1D) community[25].

Following extensive consultation with the Scientific Committee and the EU Member States via the SRG, Call topics are approved by the Governing Board with equal voting rights for the EC and for industry.

3. On the execution: The decision on grants follows Horizon 2020 rules. Projects are funded following open, competitive Calls, where independent experts (mainly, but not exclusively from academia) evaluate the proposals. Independent observers oversee the whole process and their reports are published online.

This whole process has created the conditions for the participation of over 11 500 researchers in IMI projects and a leverage effect that, according to the IMI1 Interim Evaluation, could not be achieved under the regular H2020 framework instruments. Every euro invested in IMI by European taxpayers leveraged an additional euro from EFPIA companies and Associated Partners.

25 The Strategic Governing Groups are set up in order for industry to identify the areas where they want to work on together and where they are willing to jointly commit resources. To ensure these conversations are transparent, representatives of the Scientific Committee, the European Commission and the IMI Office participate in these meetings.

What is the role of IMI's Scientific Committee?

The Scientific Committee gives strategic science-based recommendations to IMI and advises on the continued relevance of the Strategic Research Agenda and the scientific priorities. More specifically, the SC provides advice on:

- scientific priorities to be included in the Strategic Research Agenda taking into account related activities in Horizon 2020;
- scientific priorities to be addressed in the IMI Annual Work Plans.

More notably, the SC is formally consulted on documents that are subject to GB approval, including Call texts, work plans, etc. The feedback provided on the topic texts – which are based on the scientific priorities- is incorporated in the Call documents before GB endorsement.

Scientific Committee members also participate, upstream, in the topic development process, by taking part in IMI's Strategic Governing Groups, and downstream, in the project implementation phase, by attending project reviews as evaluators.

In addition, the Chairs of both the SRG and SC attend the meetings of the IMI Governing Board as observers and take part in the deliberations. They always provide feedback on the Board meetings to their respective committees.

What is the role of civil society organisations?

IMI's governance bodies include a range of stakeholders, including academics, SMEs, regulators, patient groups, and Member States. However, we do agree with GHA that civil society organisations, other than patient organisations, could be better represented. We hope this will be addressed in the future health PPP through the Innovation Panel, as proposed by the European Commission in its "Draft proposal for a European Partnership under Horizon Europe European Partnership for Health Innovation".

According to the proposal, a new multi-stakeholder body would be created to include not only EU and industrial partners but also other stakeholders representing constituencies such as health care authorities (e.g. regulators, health technology assessment [HTA] bodies, payers), health care professionals and providers, patients, regulators, research and technology organisations, regions, scientists, Member States and ad-hoc members, totalling over 20 members. The Innovation Panel would be in charge of identifying and prioritising areas for support so as to reflect end users' and public health needs, in this way addressing the calls for the partnership to better reflect the public interest.

IMI'S IMPACT AND ADDED VALUE

What is the added value of IMI-funded research?

Large pharmaceutical companies that are members of EFPIA do not receive any funding from the EU through IMI. Rather, they match the funds provided by Horizon 2020 with their own resources. The pharmaceutical industry funds the cost of the projects mostly through in-kind contributions, such as their valuable researchers' time or by providing access to unique infrastructures, data, samples and compounds. By doing so, for every euro invested by the EU budget, an extra euro is leveraged by the pharmaceutical industry.

What IMI funding supports (i.e. funds from H2020) is the participation of organisations like universities, research organisations, SMEs and mid-sized companies, patient organisations and regulatory agencies.

The additionality of IMI's research lies precisely in the value of collaboration among a multidisciplinary group of stakeholders that have never before been brought together, and this has been recognised in all impact analysis studies published so far. IMI projects specifically focus on areas where progress relies on the input of diverse partners, and not the pharmaceutical companies alone. Furthermore, IMI works to address bottlenecks that are shared by many in medical research and, again, not just by individual pharmaceutical companies.

As the report rightly points out, researchers from different sectors have no doubt about the instrumental role played by IMI's funded research. However, by dismissing their statements as mere PR, the report chooses to omit the reasons provided by public and private sector researchers to explain the "additionality" allowed by IMI-funded research. For instance, Dr Jonathan Moggs from Novartis, talking about the MARCAR project results, explains[26] how the strong collaborative framework made the difference. "[Without IMI] it would have been possible to run the ***in-vivo*** studies that we performed and to profile them with standard gene expression tools, as long as someone had the funding. But it wouldn't have been possible to make the interpretation and do the follow up on the hypothesis because that depended upon multiple partners. Nor would have there been the possibility of really strongly enhancing the ability to look at the epigenome in tissue. I don't think we would have the scope as individual partners to go deeper into the context of the drug-induced changes."

Too early to identify the socio-economic impact of IMI projects?

The IMI1 Final Evaluation report does, indeed, mention that "no socio-economic benefits from IMI JU activities could be identified". However, what the GHA report omits is that the evaluators qualified this assertion in the same paragraph, by noting that: "To realise a measurable socio-economic impact or a measurable impact for patients and their health, it was clear that more time was needed." Elsewhere the IMI1 evaluation report concludes: "at the same time, the timelines for pharmaceutical development are very long. IMI projects were nevertheless, already now establishing resources, training and facilities to boost drug discovery in Europe and are developing new tools for research. The

26 MARCAR discovered early biological clues which could help detect some of the more indirect ways in which drugs cause tumour formation. See the interview here.

research topics addressed important areas like dementia, or diabetes, and contributed to medicines safety and the reduction in the use of animals in research."[27]

With some notable exceptions, the goal of IMI has not been to develop new treatments, but to develop tools and resources to facilitate the development of new treatments by making it faster and more efficient. Nevertheless, there are already some examples of IMI projects that are starting to have an impact on patients.

- For 50 years, metformin has helped type 2 diabetes patients worldwide to control their blood sugar levels and avoid the heart, eye and kidney problems that often come with diabetes. However, over a third of patients do not respond to normal doses of the drug. Scientists from SUMMIT and DIRECT have found that a variant of the gene SLC2A2 is associated with a stronger response to the drug. This gene is behind the creation of a protein called GLUT2 that is involved in transporting glucose around the body, and people with the gene variant were found to have lower levels of this protein in their liver and other tissues, impairing their bodies' ability to handle glucose. Metformin reverses this deficiency, explaining why these people respond so well to the drug. What's more, the genetic variant had a stronger effect in overweight people. In fact, overweight people with two copies of the variant had a response that was equivalent to taking an extra 500 mg dose of metformin. These findings need to be confirmed in further clinical studies, but they already suggest that some patients should be treated with higher doses than others to achieve the same effect.
- Only 30% of patients with chronic pain receive effective treatment and when it comes to neuropathic pain, which results from nerve fibres being damaged, dysfunctional or injured, this figure is even lower. EUROPAIN researchers assembled a database of more than 2 300 neuropathic pain patients and 1 000 healthy volunteers – the largest of its kind in the world - to investigate how patients could be classified by their sensitivity to pain, rather than the pain-causing condition. The European Medicines Agency (EMA) has acknowledged that this is a valid way of classifying patients in early clinical trials and included this new stratification in their guidelines for the development of pain drugs. This represents a paradigm shift in the field of developing treatment for neuropathic pain. The project also discovered that people prone to catastrophising (believing that something is far worse than it actually is) have a higher risk of developing chronic pain in the aftermath of surgery, which is already helping doctors personalise post-surgery follow-up treatments in some countries.
- In a conventional clinical trial, typically half of the people participating in the trial receive the drug under investigation, and half receive a placebo. Trials may last years and cost a lot of money. In addition, if there are many trials in a disease area, it can be hard to find enough patients for all the trials taking place at a given time. For their part, patients struggle to find the right trial for their needs. The EU-PEARL project aims to revolutionise the way we do clinical trials by making them more efficient and patient friendly. The project team will do this by setting up adaptive clinical trial platforms which allow multiple companies to test their candidate drugs simultaneously against a shared placebo group. As Edwin van de Ketterij, Clinical Project Director of EATRIS, explains, one of the clear benefit for patients is that this design "increase patients' prospects of receiving novel techniques and treatments during the clinical trial, rather than a placebo or standard of care""[28].

27 *The Final Evaluation of the Innovative Medicines Initiative Joint Undertaking (2008-2016) operating under Framework Programme 7* (p 14 and 15).

28 Eatris Annual Report-2019, p. 34-35 features EU-PEARL as one of EATRIS flagship projects.

When IMI projects have been directly targeted to develop treatments or diagnostics, they have succeeded, as showed by the recent EC marketing authorisation granted to the IMI funded Janssen vaccine against Ebola or the two rapid diagnostic tests that were field trialled in the Democratic Republic of the Congo (DRC) during the recent Ebola outbreak, all of them with huge direct impact on the population at risk of contracting Ebola.

It is also too early to assess IMI's impact on boosting the competitiveness of the European pharmaceutical industry[29]. Nevertheless, we are increasingly getting reports of IMI project results being integrated into companies' internal research procedures, indicating that the results have value to the industry. Some of them are:

- predictive algorithms for safety (e.g. eTRANSAFE);
- definition of biomarkers/endpoints of regulatory relevance for autism, sarcopaenia, asthma, pain (e.g. SPRINTT);
- patient preference elicitation in benefit risk evaluations (e.g. PREFER);
- definition of evidentiary standards for pragmatic trials (e.g. GetReal);
- master protocols for platform trials (e.g. EU-PEARL, EPAD);
- use of apps and social media for detection of safety signals (e.g. WEB-RADR);
- environmental risk assessment methodologies (e.g. iPiE);
- robust paediatric trials network (e.g. c4c);
- evidence for ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) S1 guidance on carcinogenicity discussions (e.g. MARCAR);
- SmPC-ADR Database, inventory of drug consumption databases, integration of recommendations on good signal detection for pharmacovigilance and pharmacoepidemiology (e.g. PROTECT).

Further proof comes from companies' continued willingness to commit to projects via new Calls for proposals, even in those fields that are typically disinvested – in particular in central nervous system and infectious diseases.

Regarding pharmaceutical industry investment in the EU, the sector's resilience during the economic crisis can be attributed to the evolving collaboration model which was pioneered by IMI. Since the set-up of IMI in 2008, research investments, the number of research jobs and positive trade balance remained stable.

Moreover, the infrastructures created by IMI in particular in data and clinical trials have attracted drug development activities. This corresponds to the European Court of Auditors findings. In its special report on antimicrobial resistance (AMR), the Court wrote that, "despite the general withdrawal of pharmaceutical industries from antimicrobial research, IMI together with its partners was overall able to maintain the expected level of public-private collaboration in the ND4BB [New Drugs for Bad Bugs] programme"[30].

IMI's socio-economic benefits go beyond the pharmaceutical sector. By facilitating large-scale academia-industry collaboration, IMI has helped to demonstrate that there is a strong research base in Europe that the pharmaceutical sector can work with, and from which it can get value. This endorsement has helped to raise the

29 For a thorough evaluation of an IMI project from the industry perspective, including a description of the impact of the project's results in the participating industries own drug development programmes, see the scientific publication *Drug Discovery Today*, Volume 23, Issue 9, September 2018, p. 1622-1634 at: https://www.sciencedirect.com/science/article/abs/pii/S1359644617305925.

30 ECA special report n21 (2019) *Addressing antimicrobial resistance: progress in the animal sector, but this health threat remains a challenge for the EU*.

profile and reputation of the European medical research academic sector and, hence, the profile of Europe as a good location for pharmaceutical R&D in the context of a very volatile landscape for the industry. For instance, Dr Leif Groop from Lund University and SUMMIT project coordinator, explains the leap forward enabled by the IMI-funded project. "Diabetes complications have not been a really strong research area in Europe; the research was much stronger in the US. Thanks to SUMMIT, the awareness of diabetes complications in Europe has really changed and people from academia, industry and SMEs, have been brought together to work on it. Honestly, thanks to the work done in this project, I think we even took the lead over US-based projects."

Furthermore, calls for continued access to IMI funding were repeatedly made in the discussions preceding Brexit. The main argument used by UK researchers and remain-supporting political parties was the need to assure the competitiveness of the UK health research community[31].

In addition, by playing a relevant role in strengthening and integrating the EU's research ecosystem IMI contributes to training the next generation of scientists and reversing brain drain not only by providing opportunities for PhD students in each IMI project, but also through its education-focused projects. As an example, Eu2P developed the first internationally recognised European online education & training programmes in pharmacovigilance and pharmacoepidemiology.

New KPIs to give ourselves the right accountability mechanism

The IMI2 objectives are far reaching and ambitious and with that come inherent challenges in order to ensure that project deliverables can be measured in a manner that is in line with these objectives. While IMI has reported on specific key performance indicators (KPIs) in its annual activity reports since the very start, the Governing Board deemed the initial KPIs inadequate and called for a restructuring of the performance measuring framework. Following this decision, the IMI office initiated in 2016 a plan to restructure the existing KPI framework to better assess the programme's overall alignment with IMI2 objectives and to fully measure project deliverables. In full transparency, the logic model and the draft KPIs were presented to the IMI2 Interim Evaluation expert panel in February 2017.

The IMI Governing Board adopted a series of 10 KPIs in November 2017. The KPIs are based on a logic model that maps IMI's contribution to the intended outputs and outcomes as articulated in the Horizon 2020 intervention logic. The goal here is to ensure that IMI's KPIs are fully aligned with its own objectives and those of the wider Horizon 2020 programme. The KPIs effectively provide a roadmap that shows how IMI's activities will eventually lead to the outcomes and long-term impacts that IMI hopes will result from its work.

The IMI2 JU assesses its performance in light of the revised KPI framework, in accordance with Art. 3 of the Council Regulation (EU) No 557/2014. The results of these assessments are presented in the annual activity reports (AARs), and these show that IMI's projects are clearly positioned on a trajectory which can deliver the expected impact.

It should also be noted in addition to its own KPIs, IMI reports as required by the European Commission on (i) the Horizon 2020 Key Performance Indicators common to all JTIs, and (ii) on the Indicators for monitoring H2020 Cross-Cutting Issues common to all JTIs.

31 See, for instance, Financial Times (UK), 20 May 2016 EU exit would lessen the influence of UK scientists; The Lancet (UK), 30 May 2016 Better together for better dementia research and care and the Huffington Post (UK), 12 October 2016 Labour's 170 Brexit Questions For The Government And David Davis To Answer.

STRINGENT APPLICATION OF HORIZON 2020 RULES FOR PARTICIPATION IN IMI PROJECTS

Is the IMI intellectual property regime more complex than the IP regime applicable to Horizon 2020 projects?

In fact, current IPR provisions follow the Horizon 2020 Rules for Participation with only minor derogations needed to provide the flexibility that allows IMI to support projects across a wide range of topics and the involvement of a wide range of stakeholders.

The open collaboration fostered by IMI projects confronts partners with the challenge of finding the right balance between the protection of partners' interests and the need to share compounds, data and knowledge. It should be stressed, however, that: a) the generator remains the owner of the results; and b) that such sharing is purely the purposes of research use. Commercialisation remains the purview of the generating beneficiary.

In this context, it is important to underline that IPR rules apply equally to all partners and all IP issues are discussed up front and agreed on by all partners before a project starts with the aim of assuring legal certainty. During this period, IMI puts a lot of effort into supporting projects through a dedicated legal IPR team and providing training to academic and SME project candidate partners.

Since IMI's IPR policy derives directly from the H2020 Rules for Participation, it logically follows that the review of the current policy needs to be discussed in the framework of the (future) Framework Programme Rules for Participation, which are not under the prerogative of the IMI Governing Board. It should therefore not come as a surprise that the recommendation from the interim evaluation of IMI2 could not be addressed by the IMI Office or by the IMI GB under the current Regulation establishing IMI2. Furthermore, the Governing Board has taken a firm stance in keeping all discussions around the proposed new partnership out of the IMI2 Governing Board agenda.

What is IMI's policy on open access?

The report mistakes projects' obligations related to open access for publications with obligations related to open access to data. Following the H2020 Rules for Participation, open access to publications is mandatory for all IMI2 projects. Contrary to what is suggested in the report, there is no possible opt out to protect pharma IP. In addition, although this was not an obligation under IMI1 - since it was not required by FP7 -, the IMI scientific officers that oversee IMI1 projects strongly encourage them to opt for open access for their publications.

Whereas the H2020 Rules for Participation contemplated an Open Research Data Pilot for some selected research areas, the scope of the pilot was extended in 2017 to cover all H2020 thematic areas. In consequence, depending on which IMI2 Call the project is linked to, different rules related to open access to research data apply.

- From Calls 1 to 10, participation in the Open Access to Research Data Pilot was optional. IMI projects funded through any of these Calls have the option to amend their grant

agreement at any time during the project life cycle to request a partial or total opt-in to the pilot.

- From Call 11 onwards, all IMI2 projects participate by default in the Horizon 2020 Open Research Data Pilot. As with the rest of H2020 projects, they have the right to opt out, but only by providing via an amendment a written justification to the IMI Programme Office, following a consortium decision, providing valid and specific reasons for the exclusion.

In addition, IMI systematically reminds projects about their obligation to submit the protocol information and results of all clinical trials to EudraCT. This information is publicly available through the EU Clinical Trials Register.

For the projects addressing the coronavirus pandemic, IMI has required research consortia to make available in open access all research data relevant for the response to the emergency within 30 days after generating them. This will be a contractual obligation for all projects funded under IMI2 - Call 21, meaning that end users will indeed be able to freely access, mine, exploit, reproduce and disseminate the data via a research data repository. These projects are also expected to apply the principles established in the Statement on Data Sharing in Public Health Emergency, where the Commission is a signatory.

Furthermore, IMI supports the 'FAIR data principles', i.e. findable, accessible, interoperable and re-usable. To put the principles into practice, we have funded the FAIRplus project. Based on a range of criteria, such as scientific value, societal impact, or relevance to the scientific community, FAIRplus selects datasets from IMI projects which are prioritised for FAIRification.

In 2019, datasets from four IMI projects (TRANSLOCATION, OncoTrack, eTOX and RESOLUTE) were selected for early FAIRification and are now available in the ELIXIR-hosted IMI FAIR Data Catalogue. A further nine IMI datasets will be incorporated from 2020 to reach the total of 20 by the end of the project. The data sets cover a diverse range of data types and scientific domains, from environmental toxicity assessment methods through to identification of new targets relevant to neurodegenerative diseases.

There are many proteins that could potentially be targeted in autoimmune and inflammatory diseases like rheumatoid arthritis, lupus and Sjögren's syndrome. The problem is that a lot of research needs to be done to find out which proteins are good targets while also being amenable to treatment with molecules. The ULTRA-DD project was set up to make some headway in identifying which proteins are worthy candidates for further study, in the hope that the publicly-available knowledge they generate will lead to future clinical trials for new drugs.

The tools and data generated by ULTRA-DD are being made available open access. According to the project coordinator, Michael Sundström: "None of our outputs are patented and there are no restrictions on its use for the research community. The industry partners won't have exclusive rights to any of it; the databases, websites and publications are in the public domain in various open repositories, so everybody can benefit from the discoveries we've made and the research tools we've generated, long after the project ceases to exist." The project is already aware of widespread use of the research tools in the community and expects, with time, to disseminate to several thousand research groups[32].

In brief, regarding the data produced by our projects, IMI's policy on research data is completely aligned with the position of the EC and the health research sector, which Science Europe summed up in the following terms: "The research sector broadly promotes research data

32 See the interview with the ULTRA-DD coordinator here.

being FAIR and as open as possible. There are some reasons why open data policies should not be generalised by default. These reasons include personal privacy, national security, and competitiveness. In public–private collaborations, even more legal requirements will need to be taken into account, such as intellectual property rights. Data accessibility should therefore always follow the principle 'as open as possible, as closed as necessary."[33].

What is the value of the industry in-kind contributions to IMI? How are they recorded?

EFPIA companies do not receive any EU funding through IMI, but contribute to the projects 'in kind'. A common mistake is to underestimate the value of pharma in kind contributions (IKC) to individual IMI projects. Traditionally, research in this sector has been led by the pharmaceutical industry, therefore, their in-kind contributions are very valuable in terms of both knowledge and resources. IKCs include, for instance, the costs of highly trained researchers' time, expertise and knowledge, or access to unique collections of samples, compounds and a wealth of data. These resources are brought to the project to match the funds provided by the European Commission.

A rigorous control system is established for scrutinising industry EFPIA declarations of in-kind contributions throughout the project life cycle.

1. Proposals for new projects are evaluated by independent high-level experts. During the evaluation, the level of estimated in-kind contributions of the companies is subject to a stringent review in order to ensure that they are appropriate in relation to the proposed work to be carried out in the project.

2. In-kind contributions are reported by participating EFPIA companies and Associated Partners annually. The contributed work/performed activity is presented in each project's annual technical report, while costs incurred are reported directly to the JU through a specific financial report. Before validating each annual report and the related contributions, IMI verifies the eligibility of in-kind contributions, by ensuring it is covered by the project's description of work and that that the relevant costs are certified by independent auditors as being in line with the requirements established IMI2 JU Regulation.

3. In addition, under the IMI1 legal framework, IMI has performed ex-post audits to independently verify that the in-kind contributions accepted by IMI have been effectively committed to the projects. To date, IMI has completed ex-post audits of 20 EFPIA companies, covering a total of EUR 617.9 million of accepted contributions to IMI1 projects or 90% of all EFPIA contributions. 13 EFPIA companies providing IK contributions to IMI projects have been audited. The audit coverage is EUR 282 million or 92% of total contributions.

4. The IMI Governing Board regularly monitors the state of play on reported and validated industry contributions.

The European Court of Auditors, the supreme audit institution of the EU, audits IMI's accounts annually. In doing so, the Court has full access to each step of the IKC validation and accounting documentation, all the documentation linked to the reporting of the in-kind contributions, and the validation and auditing of reports. Moreover, the European Parliament's Committee on Budgetary Control (CONT) further scrutinises the in-kind contributions during the annual discharge procedure.

The in-kind contributions are also reported in a transparent manner in the annual accounts and the annual activity reports of IMI, which are published on IMI website and also transmitted

33 *Do Not Forget the Research Sector. Science Europe Response to the European Commission Consultation on the European Strategy for Data*, Brussels, 29 May 2020.

to the budgetary authorities in full compliance with the regulatory requirements. Before their formal approval, the draft annual accounts of IMI are carefully scrutinised by the European Commission. IMI's annual accounts including the in-kind contributions (in the form of net assets from Member contributions), are prepared by the European Commission Accounting Officer acting as the appointed IMI Accounting Officer, audited by the statutory financial auditors and voted upon by the Governing Board. The establishment of the annual accounts, including the in-kind contributions, is part of the decision-making process in which the European Commission has a controlling vote at the level of the IMI Governing Board.

The IMI Programme Office implements two framework programmes under two different legal frameworks. The major regulatory change from FP7 is in the reporting of EFPIA and Associated Partner contributions during project implementation. Under FP7, these contributions are declared on a per-project basis, together with the annual report of each project. By contrast, in IMI2, each EFPIA company and Associated Partner is required to report its contributions once a year for the totality of all costs generated contributing to IMI2 projects. In line with the legislator's horizontal goal of simplification and reducing the burden to beneficiaries receiving and not receiving funding, under H2020 programme rules there is no requirement to submit timesheets. The reasonable assurance is acquired via the audit certificates on financial statements that are thoroughly assessed and questioned by the IMI Programme Office.

All the reported costs must be accompanied each year by a certificate from an independent external auditor, confirming that the costs are in line with the requirements of the IMI2 Regulation. The certificate must be based on the standard terms of reference (audit procedures) provided by IMI2. IMI analyses the audit reports and adjusts the amounts where necessary. EFPIA and Associated Partner contributions are only validated for inclusion in IMI's accounts after these checks and adjustments. IMI may carry out an additional audit itself, before validating the EFPIA and Associated Partner contributions. This is done on a risk basis only, should the audit certificate provided with the cost declaration leave uncertainties as to the valuation of the contribution.

In conclusion, IMI has developed novel, successful and flexible PPP funding mechanisms to address European and global health-related challenges, while being integrated within European Commission (EC) funding rules.

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