

Public-Private Partnership Models in France and in Europe

Jacques Demotes-Mainard,¹ Emmanuel Canet,² Lionel Segard³
and the participants in Round Table N° 6, Giens XXI*

- 1 Ministère de la Recherche, Paris, France ; European Clinical Research Infrastructures Network (ECRIN) ; INSERM, Bordeaux, France
- 2 Laboratoire Servier, Neuilly sur Seine, France ; LEEM Recherche, Paris, France ; European Federation of Pharmaceutical Industries and Associations, Bruxelles
- 3 INSERM-transfert, Paris, France

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Abstract – The workshop entitled “Public-Private partnerships models in Europe – comparison between France and European countries” brought together representatives of academia and industry, of national or European health research programs, of regional or national public-private partnership (PPP) initiatives, and of biotechnology with the following objectives:

- sharing a common vision on the needs, expectations and challenges of public-private partnership,
- based on the analysis of actual and original cases, and of new initiatives on public-private partnership,
- drawing conclusions and identifying key success factors,
- identifying trails for progress and drawing recommendations.

The major event in this field is a European public-private partnership initiative between pharmaceutical industry (European Federation of Pharmaceutical Industry and Associations, EFPIA) and the European Commission (DG Research - health priority) resulting in the European Technology Platform project “Innovative Medicines Initiative” (IMI). Its architecture is based on the identification of the main bottlenecks to the development of innovative treatments (predictive pharmacology and toxicology, identification and validation of biomarkers, patients’ recruitment, risk evaluation, and cooperation with the regulatory authorities).

Simultaneously, initiatives both at the national and regional levels also foster PPP in the therapeutic field. Regional competitiveness clusters acting in the biomedical sector, and national PPP calls such as the ANR (National Research Agency) RIB (Research and Innovation in Biotechnology) call are incentives for PPP projects. These regional and national PPP levels help public and private partners to further build consortia able to compete for EU-level calls, thus acting as incubators for EU PPP projects.

In spite of incentives and of the regional and national structuring of PPP, weaknesses in the French system are linked to its fragmentation – multiple transfer agencies, multiple research organisations (operator or funding agency) – making contracts more difficult. This requires a simplified organisation, with a single referent per area (health, technology. . .). Improvement may also result from adaptation in the career, recruitment and mobility, from support to scientists in the management of projects, and from consistent support (without maintaining them artificially alive) to emerging companies from concept through clinical development.

Pathways have been proposed to improve the efficiency of clinical research in France and Europe, involving the public hospital sector, and this requires the connection of disease-oriented networks and integrated infrastructures in Europe. As stated in the IMI strategic research agenda on efficacy, the quality of public infrastructures in Europe will be a key factor for its competitiveness and attractiveness for both academic and industry projects.

1. Introduction

The recommendation to invest, by 2010, 3% of gross domestic product (GDP) in research and development (the Lis-

bon objective, expected to make Europe the most competitive knowledge-based economy) states that the public and private sectors should invest 1% and 2%, respectively. As France already invests 1% in public R&D, attracting private investment through public-private partnership (PPP) becomes a major challenge. In

* For the list of participants, please see the end of the article.

addition, the increasing complexity of the scientific issues requires co-operation between larger teams with diverse competences and stronger infrastructures, leading to join the efforts of public and industry research to optimize the use of available resources. Therefore various PPP models are considered as key strategies in the innovation policies.

This applies to the drug development area worldwide, as an OECD (Organization for Economic Cooperation and Development) working group performs an inventory and analysis of relevant initiatives outside Europe (Critical Path from FDA,^[1] NIH Roadmap in the US,^[2,3] Kobe Biomedical Cluster and translational research centres in Japan) and also in Europe. Mature initiatives in European regions include the Medicon Valley covering Denmark and the south of Sweden, the Top Institute Pharma (TIPharma) in the Netherlands, or biotechnology centres in Munich or Oxford-Cambridge-London.

These initiatives aim at optimizing the drug development process, from the drug discovery step through the use of innovative health products by the patients, and not only for orphan drugs^[4] or neglected diseases.^[5] Besides proposals expected to facilitate the clinical development^[6] and the regulatory process,^[7] all the proposed solutions are based on efficient PPP, on the availability of relevant infrastructures, on the co-operation between research organizations at the regional, national and EU levels, on training and mobility programs promoting a common culture between academia and industry, and on optimal management of intellectual property.

2. The framework for public-private partnership

2.1. At the European level

The impact of industry on research policies is more prominent at the European than at the national level, and this is even more true for the drug industry. Due to its high impact on national budget, health policy remains governed by the member states, and the European Medicines Agency (EMA) is under the supervision of DG Enterprise, not of DG Health. Moreover, the DG Enterprise is in charge of preparing the Directives on clinical trials (2001/20/EC, 2005/28/EC) and of promoting incentives for clinical trials in children, including the set-up of a paediatric network.^[8]

DG Research mainly acts through the 6th framework programme (FP6, 2002-2006) thematic priority 1 (*i.e.* genomics and biotechnology for health). Among the proposed calls, the integrated projects (IP) specifically target PPP research applications as they require industry participants. However, such applications

with multiple partners in the preparation step may prove difficult for SMEs, as the duration of the evaluation and the contract may exceed the usual timelines of those highly reactive enterprises. Funding of more targeted projects (STREP) probably better meets the industry expectations.

The FP6 infrastructure programme provides funding to public infrastructures opened to industry projects, however only few biomedical projects were funded through these FP6 calls. The FP6 “bottom-up” approach will be coupled in the FP7 (2007-2013) to a “top-down” approach, and the European Strategic Forum for Research Infrastructures (ESFRI, including a group of experts for biomedical sciences) is in charge of defining priorities for research infrastructures in the FP7.

The FP7 will receive more funding (more than 50 billion € over the 2007-2013 period) and includes four areas: **people** (to attract the best researchers), **ideas** (to promote creativity), **capacity** (to develop infrastructures) and **cooperation** (to create European centres of excellence through collaboration and incentives similar to the FP6 ones, including the PPP integrated projects). The thematic priority 1 (health) has three objectives: improving health of European citizens, promoting the competitiveness of European health industry, and participating in global solutions to public health and epidemic challenges. Priority 1 will mainly focus on three topics: biotechnology for human health, translational research for human health, and the use of the best therapeutic strategies by the European population, with special reference to children and elderly.

The FP7 will also launch European technology platforms to strengthen industry research and public-private partnership leading, in the health sector, to the Innovative Medicine Initiative (IMI) project.^[9] This European public-private partnership steered by the European Federation of Pharmaceutical Industry and Associations (EPFIA) and the European Commission (DG Research) will provide incentive funding for public-private partnership projects in the precompetitive development of innovative medicines. An ongoing project (InnoMed, an FP6 integrated project) serves as a proof of concept for such PPP on precompetitive research, through two different approaches: the comparison of conventional and predictive toxicology, and the identification of biomarkers in Alzheimer disease.

Briefly, the IMI strategic research agenda is based on the identification of, and solution to the main bottlenecks to innovative drug discovery and development (predictive pharmacology and toxicology, identification and validation of biomarkers, patients' recruitment, risk assessment and collaboration with the regulatory authorities). Four areas are considered in the research strategy:^[10] the two transversal areas cover the knowledge management and exploitation of data on the one hand, and on the other hand the education and training programme to offer

multidisciplinary profiles able to bridge the gap between basic biology and clinical development, between industry and academia, and between countries. The two main areas closely relate to drug development and focus on safety and predictive toxicology, and on assessment and prediction of efficacy. In this last area four topics were selected as model diseases: cancer, neurosciences, inflammation and diabetes. A fifth topic was added in the revised version of the strategic research agenda (anti-infectious drug resistance), and diabetes was turned into metabolic diseases.

A decision on the funding (440 M€/y) of this technological platform is expected very soon, with 220 M€ per year from the EU commission to support public partners, and an equivalent amount 'in kind' from the industry partners. Following the industry and SME requirements, applications will undergo rapid evaluation, and the contracts on intellectual property will be flexible. The IMI governance is based on a board of directors, on a secretariat supported by both the industry and the EU commission, on a scientific board, on a stakeholder forum, and on the member states' group.

The role of national counterparts consists of collecting and disseminating information, of preparing national infrastructures, and of participating in the knowledge management and education programs. They are encouraged to develop national PPP platforms and to prepare the industry and academic partners to apply to IMI calls. Based on the strategic research agenda, these calls will target the creation of expert centres, collaborative projects, education programs, partnership with the regulatory agencies, and the development of a few infrastructures including a medical imaging network (and there is a need to coordinate the ESFRI priorities on research infrastructures with IMI expectations).

2.2. At the national level

Whereas Spain will organise and fund a national mirror of the IMI platform, the French IMI counterpart lacks specific resources, and rather relies on existing or developing regional and national PPP programs. At the national level, some funding opportunities target PPP projects in the biotechnology and health areas. Various incentives were launched by the *Loi pour l'Innovation et la Recherche* (1999), the plan for Innovation (2002-2003), the creation of competitiveness clusters (2005) and the *Loi d'Orientation et de Programmation de la Recherche* (2006).

For instance the Agence Nationale de la Recherche (ANR)^[11] RIB call (Research and Innovation in Biotechnology) is designed to support PPP programs in the biotechnology area (25 projects funded in 2005, total budget of 25 M€). This program is more attractive for the SMEs (50% of research effort funded) than for big companies (35%). Most of the applications cover preclinical

development (this reflects the low maturity of health biotechnology enterprises in France). Similar calls are coordinated at the EU level through an ERA-net (Eurotransbio), enabling multinational projects. Before the onset of RIB, the GenHomme program also targeted PPP biotechnology research.

Similarly, the Réseau National des Technologies pour la Santé (RNTS, National Network for Health Technology) provides PPP funding for the development of diagnostic tools and medical devices. This incentive is supported by specialised translational research infrastructures, the Centres d'Innovation Technologique (CIT).

Upstream to RIB, the ANR 'Emergence and Maturation' call is designed to support the proof of concept studies in academic biotechnology projects with high economic potential, preparing them for a later PPP development. Other instruments foster PPP projects, including technology research and innovation networks, incubators for innovative enterprises in an academic research environment, a status for the young innovative enterprises, PhD and post-doctoral grants in the industry (CIFRE and CIPRE), professional mobility of academic scientists towards industry, and the possibility for institutional researchers to be involved and to invest in industry activities (whereas the US regulation now moves in an opposite direction to reduce conflicts of interests).^[12]

For both biotechnology and health technology, the translational step usually requires PPP. After completing the preclinical development of a new technology, an SME may wish to collaborate with an academic centre for its clinical implementation. On the opposite academic centres having discovered an innovative health product may seek for an industry partner for the preclinical or clinical step. In the rare disease area OrphanXchange^[13] created by Inserm and the pharmaceutical industry (Les Entreprises du Médicament, LEEM) and supported by the European Commission is a tool allowing institutional and industry teams to join in order to promote the translational step and the PPP.

Finally, numerous national initiatives aim at facilitating the interface between industry and academic partners, supporting the management of PPP projects through administrative, financial and human resources. In clinical research, the CEGEPS (centres for management of clinical trials on health products) are being created under the LEEM's auspices as a public organism funded by an extra-tax on clinical trials on medicinal products. It will improve the interaction between industry sponsor and clinical investigation sites through an interface reducing administrative burden, fostering patients recruitment and supporting investigators' tasks. In a similar perspective, the Ministry of Research has developed the Carnot label^[14] based on the German Fraunhofer institutes model, in order to promote the quality management process in academic centres, ensuring industry partners of appropriate quality and timely release of deliverables in PPP projects.

2.3. At the regional level

As some European regions, in Japan or in the US, France has developed bioclusters or biovalleys. Located in a restricted area, academic research and education centres, incubators and industry research laboratories not only promote innovation but also alter the economic features of a region – as for example Triangle Park in the US that changed the mainly agricultural North Carolina into a wealthy economic area based on innovation. Regional clustering of know-how supported by PPP incentives represents a first step towards excellence and competitiveness in innovation, hence the national counterpart of IMI takes advantage of the competitiveness clusters and biovalleys involved in biomedical research.

Among the main existing bioclusters are the genopoles, created for more than 5 years around academic programs in genomics, transcriptomics and proteomics, and surrounded by companies developing therapeutic and diagnostic agents, or high throughput tools for molecular biology. The canceropoles bring together, on a regional basis, academic and industry, preclinical and clinical competences in the cancer area. Finally, among the competitiveness clusters created in 2005, some act in the biomedical field and may be based on pre-existing genopoles and canceropoles, on biotechnology SMEs and on the pharmaceutical industry. Among the main health clusters are Meditech-Santé in the Paris area (infectious diseases, cancer, neurosciences, medical imaging) and the Lyon-Biopôle in virology and vaccines. The Alsace-Biovalley project focuses on therapeutic innovation, the Toulouse cluster on cancer, the Loire region on biotherapy, the Orpheme project at Marseille-Montpellier on tropical and age-related diseases, the Prod'Innov at Bordeaux and the the Health and Longevity project at Lille on nutrition and health.^[15] These competitiveness clusters receive 1.5 billion € funding for 3 years through ministries and agencies grants, and through tax refund.

3. Models of partnership

Public-private partnership depends on a balance between academic (create and disseminate knowledge) and industry interests (discover and develop innovative drugs and create benefits partly re-invested in R&D) within the context of a high attrition rate during development,^[16] of changes in the model of drug development brought by biotechnology,^[17,18] and of a better therapeutic target identification through the pharmacogenetic approach^[19] and the personalized treatments.^[20]

Different models of PPP correspond either to a shared and simultaneous interest in an innovation, or to a sequential process in which the development is shared, at different steps, between public and private partners.

The simultaneous PPP, where the partners are involved at the same time in a common project, covers two different situations. The first one is the joint development (totally or partly) of an innovative project in order to reach the critical mass – here all the initiatives supporting PPP, not only the financial incentives and the intellectual property management, are key success factors. In other situations, the partnership rather consists of provision of services or expertise. The institutional partner acts as an infrastructure providing equipment, competences or research material for the industry – this is for instance the case for commercial clinical trials. On the other hand a SME may act as a subcontractor for an academic laboratory. In this case compliance to the contract and timelines, deliverables, and quality assurance are key success factors.

The sequential PPP models correspond on the one hand to the emergence of private enterprises created from the public area based on incentives (ex: the Emergence and Maturation ANR call), structures (ex: incubators) and specific financial support (ex: Oseo-anvar support to industry R&D projects). On the other hand, the transfer model consists of an innovation first developed in the academic field, then further developed by the industry.

In drug development this transfer is usually performed between the drug discovery and the preclinical development, or between preclinical and clinical development. We have to keep in mind that a number of marketed drugs come from the academic world, not only in the biotechnology area.^[21]

3.1. Pharmaceutical industry

For the pharmaceutical industry, the key issue is to find a partner having demonstrated its excellence and its ability to manage a competitive PPP project. In turn, these companies, thus the resulting partnership, are global, dampening regional or national constraints linked to the use of a common language or of common legal frameworks.

The main collaboration areas are the identification and validation of new targets, the design and use of relevant animal models, access to new technologies (medical imaging), pharmacogenomics, bioinformatics, understanding the mechanism of disease, identification and validation of biomarkers, and clinical trials.

Financial incentives to PPP are usually less critical than for SMEs, whereas competence and scientific excellence remain the major criteria for partner selection. However, a successful partnership also requires compliance with commitments and timelines, production of deliverables, confidentiality, understanding of intellectual property, and the capacity for the administrative interface to efficiently manage the partnership.

In other words, the human factor is critical for the success of PPP, and this requires training of academic researchers towards

an entrepreneurial culture, project-oriented rather than problem-oriented. There is also a need for specialised managers in charge of the operational management, and for the adaptation of administrative procedures in order to facilitate contracts and to optimize intellectual property rights, balancing industry (patenting) and scientific interest (publishing). Personal contacts and commitments between the partners are also a factor of success.

3.2. Small and medium-sized biotechnology enterprises

Expectations of biotechnology SMEs partly overlap those of the pharmaceutical industry, with some particularities related to their activity, size, financing, management capacity, and their involvement in transfer activities – from academia to biotechnology SMEs, and from biotechnology SMEs to the pharmaceutical industry.

Transfer originates from universities and research institutes that, unlike their north-American counterparts, rarely act as entrepreneurs managing their intellectual property portfolio and creating spin-off companies. However the Law on Innovation and Research (1999) makes it possible for a researcher to behave as an entrepreneur (as in the Bayh-Dole Act), and a hundred of them took advantage of this possibility in the biotechnology area. The lack of a consistent strategy within the institution, the fear to restrict their creativity for researchers, the lack of quality assurance, the lack of management competence and of support to project management, make transfer usually a secondary objective for institutional research, opportunistic rather than strategic. In addition, access to patent and to seeding capital is viewed as a difficult step. However, there is a substantial improvement in France, based on the support to technology transfer (within the 'pôles' in public institutions, Oseo-anvar for industry), on bio-incubators, on ANR incentives and on cultural changes.

Transfer between SMEs and R&D department of the pharmaceutical companies is low in France, due to the poor international visibility of the French biotechnology SMEs, the insufficient training of biotechnology managers and diverging interests between pharmaceutical industry, biotechnology SMEs and investors. However, the situation is currently evolving with the interfacing role of France-Biotech and LEEM-Biotech, and of the competitiveness clusters fostering contacts and collaborations.

For biotechnology SMEs, local collaboration facilitates the partnership and accounts for the creation of clusters (genepoles, cancerpôles, competitiveness clusters). This is based on the strong links of the SMEs with the local academic environment from which they emerged, but also on the use of a common language, and a common legal and regulatory framework. As the managers of emerging SMEs usually have a scientific background, support structures dealing with the administrative burden, the contracting

and the management of intellectual property are really helpful. On the other hand, excess of protection of new companies may keep artificially alive a non-viable project, meaning that a careful evaluation is needed after the company is granted.

Incentives to PPP have a strong impact on SMEs, and they receive more support than the big enterprises. Therefore policies promoting PPP at the regional, national or European level are critical as they drive the ability of SMEs to innovate and to grow. This is especially important for the French biotechnology SMEs who, even if their number is increasing and are as numerous as in the UK, face difficulties to grow: their mean number of employees is less than in the UK or in the US, and they often never reach the clinical development step.^[22] The lack of biomanufacturing facilities, even for clinical batches, is a weakness that will be discussed later in the paragraph on infrastructures.

However, despite the crucial role of the financial incentives to PPP, some of the calls are considered poorly adapted for the SMEs: some require an excessive workload for submission or for contract negotiation (as for example the FP6 integrated projects), some require too much time (often one year) between application and funding, which is not compatible with the reactivity and the financial and scientific agenda of SMEs. SMEs also expressed concerns with regard to IMI, as it will promote PPP between several companies at a precompetitive stage of the drug development (drug discovery models, definition and validation of biomarkers, predictive models for safety and efficacy). However this definition of precompetitive research applies to companies – pharmaceutical or biotechnology – developing therapeutic drugs, not to those developing diagnostic tools or providing services or tools, whose competitive sector corresponds to the precompetitive field of drugs developers.

3.3. Institutional partner: the CEA example

On the academic side, the CEA (the agency for nuclear energy) provides some clues on expectations and issues related to PPP. CEA has a very strong transfer background towards the industry in the nuclear field, and also some PPP experience in the health sector, particularly imaging in preclinical pharmacology, structural analysis of biomolecules, diagnostic tools and microarray development. Besides the scientific excellence and the availability of state-of-the-art technology, the key factors of the partnership are a joint researcher/engineer, project-oriented culture, a real mobility between academia and industry, a strong institutional policy regarding intellectual property (considered as a higher priority than publication) and an appropriate investment policy. Moreover, marketing and prospective actions, favourable political environment (including the competitiveness

cluster Meditech-Santé) and the industry interest help develop efficient PPP.

In PPP with biotechnology SMEs, the main problems are related to their management, particularly in negotiating and managing the joint intellectual property, its outcome in case of financial bankruptcy. Partnerships with drug companies (alone or in consortium) does not make problems with regard to management and negotiation, but rather in the exploitation of results and knowledge produced in case of negative results, and traceability of this collaboration in the subsequent industrial development.

Additional problems arise when several public research institutes are involved in PPP, due to the incompatibility in their regulation and use of intellectual property, the lack of a single outlet in charge legal issues, and excessive waste of time, especially for the SMEs.

It is thus necessary to promote training of researchers on intellectual property, the harmonisation of framework contracts, the setup of a one-stop shop allowing rapid signature of the contracts based on the competitiveness clusters' model.

4. Outside France: clinical research networks

At the preclinical step, some success models are based on a regional networking of complementary competences available in the pharmaceutical industry, biotechnology companies and academic institutions. As previously mentioned, the best models in Europe are the Medicon Valley that covers since 1995 Denmark and the south of Sweden, the Top Institute Pharma (TIPharma) in the Netherlands created in 2004 or the biotechnology clusters at Munich or Oxford-Cambridge-London. However the regional clustering model is no longer valid in clinical research, as the limiting factor is the recruitment of patients – and patients are distributed. The major challenge consists of offering an efficient access to patients, however distributed, and embedded in the health system, although some resources should be kept centralized. Several foreign initiatives provide an interesting illustration.

4.1. EORTC

EORTC (European Organisation for Research and Treatment of Cancer^[23]) is a scientific organization able to act as a sponsor in European clinical trials on cancer. It is a centralized organization as the infrastructure (quality assurance, regulatory affairs, monitoring) is housed in the data centre in Brussels, and interacts with investigators' networks (for each type of cancer) in Europe.

The EORTC objective is to perform independent clinical trials in order to improve the therapeutic strategies (chemotherapy, radiotherapy, surgery) in cancer. A scientific board allows

EORTC to write clinical protocols and decide on their organisation. EORTC has a large experience of partnership with the industry, either through contracts casting the tasks in independent strategy trials initiated and sponsored by EORTC, or as a service provider for the pharmaceutical industry, conducting clinical trials in Europe for marketing authorisation purpose. Its activity and competence are unique in Europe as EORTC is the only institutional sponsor with substantial experience in multinational clinical trials in the EU, able to conduct high quality studies with a major scientific impact and contribution to the improvement of healthcare strategy in cancer.

4.2. GEREQ

The Canadian GEREQ model^[24] is also based on a centralised data management platform, associated with monitoring and quality assurance procedures, acting through a network of investigation centres located in the regional hospitals, and linked to disease-oriented scientific networks providing the scientific content.

Developed with public funding, this program is being developed into two different aspects of the same data management platform, GEREQ for the institutional projects, and the private ID-Globe company providing services for industrial partners.

Unlike EORTC, GEREQ is not designed to act as a sponsor but only as an infrastructure performing data management, monitoring, quality assurance and training. The protocol development, statistical analysis and results analysis are performed by the investigator or the disease-oriented network.

4.3. Orphanet

Orphanet^[25] is an initiative on rare diseases associating patients, the academic sector and the industry, allowing development a communication tool on rare diseases targeting patients and health professionals, and a tool for transfer and public-private partnership (OrphanXchange, described above) connecting pre-clinical projects with partners able to perform the clinical development.

More recently, Orphanet has created a European registry of patients with rare disease willing to participate in clinical trials. This model based on the active involvement of patients in the clinical development of treatments for their own disease led to improve trust, and to promote proactive and altruistic behaviour in well educated and informed patients. Extending this model to other chronic diseases would be highly beneficial to all the partners in clinical research.

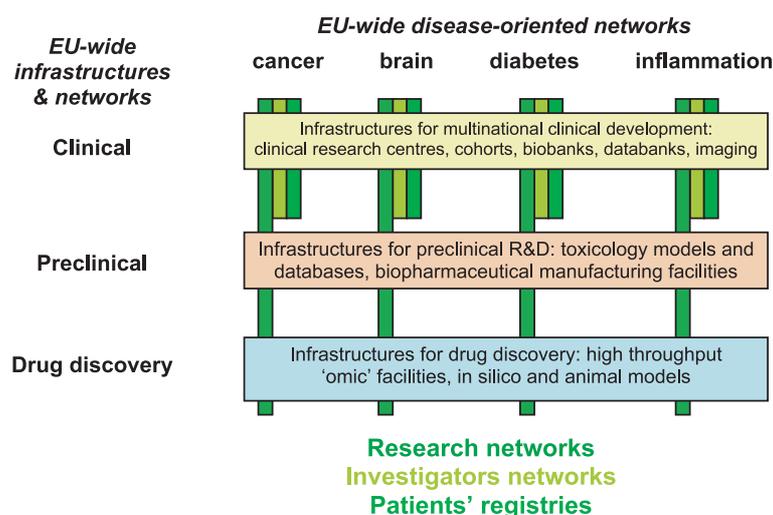


Fig. 1. (from^[27]) EU-wide infrastructures and networks in drug development.

4.4. Models for clinical research in France and Europe

The EORTC and the GEREQ models, the improved access to patients provided by Orphanet, provide clues for improving of the organisation of clinical research in Europe. Necessarily organised within the public sector, this requires to connect EU integrated infrastructures^[26] (providing tools for clinical research in any disease area) and disease-oriented networks: scientific networks providing the scientific content of preclinical and clinical projects, then in charge of publication and valorisation, investigators networks and patients registries allowing recruitment and investigation in clinical trials (figure 1). As mentioned in the efficacy section of the IMI strategic research agenda, the quality of the European public infrastructures will be a key factor for its competitiveness and attractiveness for both industry and academic projects.

5. Infrastructures

Infrastructures are key elements for PPP, as infrastructures developed in the public sector offer access to both institutional and industry projects. Similarly, several industry partners may create joint infrastructures to foster precompetitive research, or even competitive activities if their cost and use require critical mass. Each of the three drug development steps requires specific infrastructures.

5.1. Target identification and drug discovery

France has developed through the genopoles a number of functional genomic, transcriptomic and proteomic platforms. However there is a need to further develop proteomic facilities

as the therapeutic targets, and often the innovative drugs, are proteins: high-throughput facilities, accessible to academic and industry projects, allowing analysis of structure, conformation, post-translational alterations, protein-protein or protein-ligand interactions in order to predict efficacy or toxicity. Animals models (transgenic or not) and tools for the development of biomarkers in these models (including functional imaging in animals) are also necessary. Finally system biology and tools providing a comprehensive understanding of the pathophysiology of complex biological systems are powerful predictors of efficacy.

5.2. Preclinical development

On top of animal models, infrastructures for preclinical development cover toxicology with predictive models, optimal use of shared databases, identification of biomarkers predicting toxicity, including animal imaging. A limiting factor is the low number of biopharmaceutical manufacturing facilities for clinical batches.^[28] These manufacturing facilities are expensive and require a very high level of professional skills. Improving the national capacity for biomanufacturing would appear as a strategic decision to promote the growth of biotechnology SMEs in France (whereas France remains the leader for classical drug manufacturing in Europe). France is currently being equipped with facilities for preclinical and clinical gene, cell and tissue therapy, based on the know-how of the French blood transfusion agency, and on the development of clinical investigation centres specializing in biotherapy.

5.3. Clinical development

Access to patients, the capacity to investigate and the quality of data represent key factors for the attractiveness and

competitiveness of western European countries (particularly when compared to emerging countries). This requires distributed infrastructures – as patients are distributed – allowing high quality investigation and data collection, biological resource facilities, and medical imaging centres.

Clinical research play a specific role in PPP as drug development requires partnership between industry sponsor and public hospitals. Simultaneously, institutional clinical research undergo a rapid evolution to become more effective, with regard to the rapid evolution of investigators' and sponsors' tasks within the new legal and regulatory framework, both in Europe and in France.^[29] Various initiatives are currently being launched that, if consistently organized, may improve the efficiency of clinical research in France.

Changes have been brought to the academic environment, with the development of hospital infrastructures. At the local level, clinical investigation centres (CIC) in the University Hospitals in partnership with Inserm, then biotherapy-CIC for cell and gene therapy, epidemiology-CIC for clinical research in outpatients, technology innovation centres (CIT) as translational research centres for health technology, clinical trials units for the methodology, data management, monitoring and biostatistics have been created. At the national level, a CIC network was created to harmonise practice, to share tools and procedures, and to interact with European partners. Simultaneously, disease-oriented networks were developed within the CIC network to share scientific content and promote multicentre studies: scientific networks, investigators networks, patients' registries and cohorts.

The new requirements for institutional sponsorship led to strengthen public sponsor capabilities and to share some of their activities, merging the 22 regional clinical research offices into 7 interregional offices. However additional competences should be fully implemented in each of these offices (data management, monitoring, regulatory affairs, vigilance, quality assurance) in order to allow national public sponsors, but also European institutional sponsors, biotechnology or medical devices SMEs to benefit from such support to sponsor activities. Strengthening the coordination of national networks may also help them play a supportive role for public or SME sponsors.

Simultaneously, the pharmaceutical industry is willing to improve its PPP interfacing with the investigators, the clinical research centres and the hospital administration, and to foster patients enrolment. This led to create the centre for management of clinical trials on health products (CeGEPS) as a one-stop shop facility for multicentre trials, facilitating the administrative procedures, the cost evaluation and financial contracts, fostering patients recruitment, providing support to investigators and investigators networks, thus improving the efficacy and quality of clinical trials. The CeGEPS is based on a national coordination with 7

interregional relays, and is funded (10 M€/year) by the industry through an extra-tax paid to the competent authority. Its activity will take advantage of the existing infrastructures and networks, and will also require the setup of specific tools and personnel.

The infrastructure for clinical development also includes patients' registries like those developed by Orphanet for rare diseases, and biological resource facilities making high quality biological data, coupled to clinical data, available for both academic and industry research. Networking biological resource facilities^[30] at the EU, then at the global level under the auspices of OECD, will avoid duplication and result in a considerable added value.

6. Recommendations

Following this round table, several recommendations were issued in order to facilitate PPP in drug research and development, and to promote the French participation in the European Innovative Medicine Initiative PPP program.

6.1. Through action on human resources

In order to establish the basis for a common culture on project management and intellectual property, and to promote transdisciplinary profiles:

- training of personnel (researchers, but also public administrative staff) to project management in line with contract objectives, timelines, quality assurance and production of deliverables;
- mobility between public and private sector;
- creation of a specific training in translational^[31] medicine or pharmaceutical medicine covering target and drug discovery, preclinical development, clinical trials and management.

6.2. Through financial incentives

Based on existing ANR calls or the Oseo-Anvar support for the preclinical step, but also with the development of:

- PPP incentives for clinical proof of concept studies (phase I and IIa) for the innovative products and/or biotechnology products in order to facilitate the access of French SMEs to the clinical development;
- strengthening the support to preclinical development to ensure compliance to regulatory requirements before starting the clinical phase;

- PPP incentive calls^[32] for large phase IV studies on marketed products, assessing treatment strategies, or identifying responder populations (including pharmacogenetics), and available for European studies^[33] such as those performed by the EORTC in cancer.

6.3. Through a better follow-up and evaluation of emerging enterprises

To discontinue public support to industry projects non-viable under the market condition.

6.4. Through structuring actions such as

- The development of disease-oriented investigators networks in order to facilitate the conduct of clinical trials (EMA is currently preparing a paediatric network at the EU level) coupled to patients registries;
- strengthening the coordination of the disease-oriented networks (existing or under development) by the training and the recruitment of specialized clinical scientists.

6.5. Through the development of infrastructures

Equipment, competences and quality assurance – determining the country's attractiveness for R&D academic and industry projects, and the quality of the data, particularly:

- proteomics and molecular pathology,
- structural biology and chemistry-biology interface,
- biomedical manufacturing units,
- biotherapy centres,
- preclinical and clinical functional imaging,
- the coordination of clinical research infrastructures networks, (CIC-CIT- Clinical Trials Units), with centralised resources (data management) and the capacity to participate in European collaborations (through ECRIN),
- the support to SMEs as sponsors of clinical trials,
- networking biological resources facilities at national and European level.

6.6. Through local networking adapted to SMEs and academic centres

Promoting PPP within regional bioclusters having a real autonomy in the management of small-sized PPP project, and acting as a facilitator for emerging activities, transfer, and initiation of larger-scale PPP, thus improving the capacity of management of SMEs, the culture of academic actors, and directing the strategy of the public partners towards innovation and valorisation.

6.7. Through incentives to patenting, and harmonisation of its legal framework

- Creation of a standardized European patent, at low cost, favouring innovation,
- taking into account, in the evaluation of researchers, patents on at least the same level as publications,
- preparing standard PPP contracts.

6.8. Through the development of competences in project management, and of one-stop shop interfaces

- Training in project management in the curricula of scientists and administrative personnel of hospital and public research,
- providing projects managers for the emerging enterprises, and for PPP projects,
- developing one-stop shop interfaces improving the preparation and the conduct of projects (as proposed in the CeGEPS for clinical studies),
- developing partnership with institutions or networks committee to produce deliverables, rather than with the isolated scientist or investigator,
- increasing the requirements on quality assurance in the academic field, leading to certification or to spread the Carnot label model,
- reducing complexity through an harmonisation of contracts and cost evaluation, and through a single, one-stop shop, public contractor for PPP involving several academic institutions.

Participants

Allain H. (Faculté de Médecine, Rennes), Amédée-Manesme O. (Paris Biotech), Aymé S. (Inserm), Boubekeur K. (Hoffmann Laroche Ltd), Chabrier P.-E. (Groupe Ipsen), Clément B. (Inserm Transfert), Collet J.-P. (Gereq, Montréal, Canada), Deregnaucourt J. (Ministère de la Recherche), Habert Ortoli E. (AP-HP), Halioua E. (Arthur D. Little), Hamelin B. (Astra Zeneca), Juillet Y. (Leem), Lacombe D. (EORTC Data Center, Bruxelles, Belgique), Lassale C. (Leem), Longuet M. (Ministère de la Recherche), Pletan Y. (Pfizer), Vasmant D. (Sanofi-Aventis), Vincent C. (CEA, Paris).

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Correspondence and offprints: Jacques Demotes-Mainard, Ministère de la Recherche, DGRI - A5 1 rue Descartes, 75231 PARIS cedex 05.
E-mail: demotes@bordeaux.inserm.fr