Establishing New Mechanisms for Public-Private Partnerships to Address Common Challenges in Drug R&D

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Abstract

Objective To study the cases of public-private partnerships (PPPs) commonly used in Europe Union and the United States to solve common challenges such as the decline in drug R&D efficiency, and to provide reference for developing countries to deal with these challenges in drug R&D. **Methods** Multiple case study method was used to make a comparative analysis of three PPP models in European Union and the United States. **Results and Conclusion** Third-party conveners, project-based cooperation models, and PPP funding mechanisms were key elements of PPP models in European and the United States. The developing countries should establish new PPP mechanisms to solve common challenges in drug R&D in their countries based on national conditions and key elements of PPP models.

Keywords: public-private partnership (PPP); drug innovation; Eroom's Law

As early as the 1980s, researchers discovered a downward trend in pharmaceutical research and development (R&D) productivity [1]. Scannell, et al. (2012) [2] found that for every $1 billion invested in R&D, the number of new drugs approved had been reduced by about half every nine years since 1950, adjusted for inflation, drug R&D costs increased by about 80 times [2]. This phenomenon of increasing drug R&D investment and decreasing output is summarized as Eroom's Law, which is Moore's Law spelled in reverse order, also known as the Anti-Moore's Law.

According to Scannell, et al., four major factors contribute to Eroom's Law [2]. First, the difficulty of innovation iteration increases. As the number of listed drugs increases, the incremental value of drug innovation decreases, the entry threshold for drug innovation increases, and the opportunities for drug innovation in major therapeutic areas decrease, thus turning to therapeutic areas with relatively low success rates. Second, regulators become more cautious. The risk tolerance of drug authorities gradually decreases, and regulatory thresholds are raised. Third, there is a tendency for blind investment. Large companies prefer to blindly increase their budgets for R&D success. Finally, basic research is pushed forward on a massive and aggressive scale, overestimating the progress of basic research and the ability to broadly screen molecules for clinical research. The pharmaceutical industry is trying to break Eroom's Law, however, drug R&D as a whole still follows Eroom's Law till now [3, 4].

Since the causes of Eroom's Law are complex, it requires the joint efforts of all parties involved in drug R&D. The role of public-private partnership (PPP) in accelerating drug discovery has been recognized

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by many scholars [5-9]. The PPP refers to the fixed connection of public-private cooperation. The PPPs generally include the following points [10, 11]. (1) Members are different parties from both the public and private sectors. (2) Cooperative relationships should be established. (3) Public goods or services should be provided. (4) Benefit and risk should be shared. The PPP model for drug R&D can be roughly divided into two categories. The first is result oriented, with the direct goal of launching new drugs for neglected diseases [12]. The second is process oriented [13, 14], with the extensive cooperation and open innovation before competition, to solve the common challenges in drug R&D, improve the overall efficiency of drug R&D, and indirectly promote the launch of new drugs. The PPP model in this article specifically refers to the second.

In the past two decades, the U.S. Food and Drug Administration (FDA), the U.S. National Institutes of Health (NIH), and the European Union (EU) have all introduced the PPP for the drug R&D. The PPPs have had a positive impact on the drug R&D process [14, 15]. Based on market theory and innovation system theory, this paper analyzes the typical PPPs for drug R&D.

1 FDA's PPP model

1.1 Selecting partners and forming alliances

In 2004, in response to the challenge of the declining drug R&D efficiency, the FDA released the report "Innovation or Stagnation: Challenges and Opportunities on the Critical Path for New Medical Products". Subsequently, the critical path initiative (CPI) was launched to change the development, evaluation and production methods of medical products regulated by the FDA. The FDA believed that the current medical product development path became increasingly challenging, inefficient and costly because the applied science required for medical product development could not kept up with the tremendous progress in basic science [16]. There was an urgent need for an innovative new product development tool that incorporated powerful new scientific and technological methods, such as animal or computer-based predictive models, biomarkers of safety and efficacy, and new clinical evaluation technologies to improve the predictability and efficiency of the critical path. The report pointed out that it was crucial to involve all relevant stakeholders in this work. In 2005, the FDA signed a memorandum of understanding with the University of Arizona to jointly establish the Critical Path Institute (C-Path), a non-profit organization.

1.2 Funding sources mainly from direct investment by the FDA

In 2007, the U.S. Congress authorized the FDA to establish the critical path public private partnerships. In 2009, the FDA signed a "Critical Path Partnership Cooperation Agreement" with C-Path and renewed it every five years. C-Path provides stakeholders with appropriate drug development tools, including five aspects: data management and standards, biomarkers, modeling and analysis, clinical outcome evaluation, and regulatory science. Currently, it focuses on addressing unmet therapeutic needs in the fields of neuroscience, rare diseases, pediatrics, and safety science. According to the 2023 report, 54% of C-Path's funding came from the FDA, totaling approximately US$19.44 million, and 46% came from non-government funding such as membership fees, totaling approximately US $16.37 million.

1.3 The consortiums carrying out specific tasks

The cooperation agreement renewed in 2024 stipulated that the FDA would provide $20 million annually in funding for C-Path to continue maintaining and managing the six existing consortiums convened and established by C-Path. The consortiums were based on collaborative research intentions in different fields. The rare disease cures accelerator data analytics platform (RDCA-DAP) aimed to provide a centralized and standardized infrastructure that supported data sharing and accelerated rare disease characterization, with the goal of accelerating the development of rare

disease treatment and cure methods. CURE Drug Repurposing Collaboratory (CDRC) aimed to promote the collection of real-world data (RWD) to generate real-world evidence (RWE) and provide drug reuse information for areas with unmet medical needs. Acute kidney injury (AKI) working group and AKI data acquisition aimed to optimize the collection of translational biomarker data for the development of better renal toxicity prediction tools. Alpha-1 Antitrypsin Deficiency (AATD) Pre-Consortium aimed to consolidate available clinical trial data and other studies to evaluate longitudinal performance of biomarkers and AATD clinical indicators for use as endpoints or alternative endpoints to assess future treatments for AATD. The Lysosomal Diseases Pre-Consortium aimed to generate feasible solutions and accelerate drug development for lysosomal diseases. The critical path for rare neurodegenerative diseases (CP-RND) aimed to accelerate and enhance understanding of disease pathology, treatment options, diagnosis, and drug development.

1.4 Collaboration between CDER and PPP

In 2017, the Center for Drug Evaluation and Research (CDER) of the FDA first published the "Manual of CDER Staff Participation in Public Private Partnerships and Consortia" (MAPP 4100.2), which had been updated to the 2023 edition. Collaboration is mainly in the precompetitive domain of drug development [17], including research and activities to fill the knowledge gaps in drug discovery, clinical research, and medical product development. In the precompetitive domain, all stakeholders benefit from the additional knowledge, tools, and data brought by the collaboration to improve the efficiency of product development and regulatory processes. Establishing a PPP or consortium is the primary form of collaboration that is managed by a convening or coordinating institution (non-U.S. government and nonprofit organization). It involves a number of stakeholders, including at least one nonprofit organization or academia, government or foundation, and at least one for-profit organization, such as a pharmaceutical, biotechnology or medical device company. PPPs can establish multiple committees or working groups. The PPP convener is responsible for submitting applications for activities and providing activity assurance for CDER staff to participate in PPP or consortium. CDER establishes a PPP liaison. PPP may jointly host conferences, seminars, symposiums, educational programs, public information campaigns, or similar activities with CDER. CDER staff's participation in PPP or consortium activities is limited to providing general perspectives on regulatory standards, scientific issues, and scientific gaps related to pre-competitive drug development.

According to the official statistics from the FDA, CDER has participated in more than 60 PPPs or consortiums with other government, academic institutions, scientific institutions, patients and industry organizations, including C-Path and the Clinical Trials Transformation Initiative (CTTI), to promote scientific collaboration, support critical path program and advance regulatory science activities, encourage the development of new tools, thus promoting medical product development and innovation.

2 NIH's PPP model

For NIH, the PPP model is mainly used for projects that cannot achieve NIH goals independently. The PPP model introduces extensive external cooperation to help NIH achieve its goals.

In 2007, the NIH Office of the Director and the Office of Science Policy issued the "NIH Manual 1167". NIH has 27 institutes and centers (ICs). PPP involves cooperation between institutes and centers and many other organizations, including patient advocacy groups, foundations, members of the pharmaceutical or biotechnology industry, and academic institutions. The agreement for signing a PPP stipulates the overall relationship between the partners, including the purpose of the PPP, the activities, responsibilities and roles of the parties, and the relevant legal institutions. However, grants, contracts, and technology transfer agreements belong to PPP.

Partnerships are diverse and wide-ranging. For example, they include from simple joint meetings to complex multi-party agreements to fund large multi-center studies. Collaboration is centered on the common goals and missions of the partners, which uses knowledge, skills, resources, and services to achieve synergies. NIH divides PPP activities into four categories: A, B, C, and D, based on whether funds enter NIH, whether it is a government activity or a partner-centered activity.

Taking the "Accelerating Medicines Partnership" (AMP) program as an example, the NIH, FDA, several biopharmaceutical and life science companies, non-profit organizations and other organizations launched it in 2014 to improve the understanding of disease pathways, promote better selection of therapeutic targets, and identify platforms and processes to accelerate the provision of new and effective treatments to patients. Specific methods include identifying clinically relevant disease targets, better identifying patients most likely to respond to specific treatments, and safely shortening the development time of life-saving therapies and improving patient treatment outcomes. AMP funding mainly comes from NIH, the private sector, and in-kind donations are from the private sector, with a total of US$896 million. AMP currently involves a total of 12 projects, 37 industry partners, 44 non-profit partners, and 16 NIH institutes + cross-institute projects. Funding is mainly distributed in four disease areas: neurological diseases (55%), cardiometabolic diseases (18%), autoimmune diseases (15%), and rare diseases (12%).

A key component of each PPP in the AMP program is an agreement between partners to publicly share data and analysis generated by the collaboration.

3 The PPP model in the European Union

3.1 EU-wide joint undertaking

According to the ninth EU Framework Programmes for Research and Technological Development (FP), Horizon Europe (2021−2027), a European partnership is an initiative developed with early involvement of the Member States, in which the EU and private and/or public partners (such as industry, universities, research organizations, or civil society organizations including foundations and non-governmental organizations) commit to jointly support the development and implementation of a plan of R&D activities, including activities related to market, regulation or policy adoption. European partnerships are divided into PPPs and public-public partnerships (PuPs or P2Ps) according to the partnership relationship. European partnerships are divided into three categories according to the form of cooperation: Co-funded European partnerships, co-programmed European partnerships, and institutionalized European partnerships. According to Article 187 of the "Treaty on the Functioning of the European Union", the EU can establish a joint undertaking (JU) for technological research and development. JU is an institutionalized European partnership and can only be implemented when the objectives or expected impact cannot be achieved within the framework program and there is a long-term perspective and a high degree of integration. Council Regulation (EU) 2021/2085 establishes nine new European partnerships for JU, including the Innovative Health Initiative Joint Undertaking (IHI JU).

3.2 Four stages of the gradual expansion of the PPP model

The EU's joint undertaking on innovative medicines has gone through four stages (as shown in Table 1). The first phase is the European Technology Platform INNOMED or ETP INNOMED under FP6, with a budget of 18.53 million euros. The goal is to revitalize the European biopharmaceutical research environment. The strategic research agenda aims to address four key bottlenecks in the drug development process (safety, efficacy, knowledge management, training and education). The second phase is the first Innovative Medicines Initiative Joint Undertaking (IMI JU) under FP7), with an expanded budget of €2 billion. The goal is to significantly improve the efficiency and effectiveness of the drug development

process, with the long-term goal of enabling the pharmaceutical industry to produce more effective and safer innovative medicines for patients. The strategic research agenda consists of seven interests such as disease-drug efficacy, knowledge management, R&D strategy, development of regulatory frameworks, tools and technologies, and scientific communication (education and training). The third phase is IMI2 JU under Horizon 2020 (Horizon 2020, H2020), with a budget expansion of 32.76. billion. The goal is to support the development and implementation of pre-competitive research and innovation activities that are strategically important for the alliance's competitiveness and industrial leadership. The main part of the strategic research agenda is summarized in four main research directions such as target validation and biomarker research. (efficacy and safety), the use of innovative clinical trial models, innovative drugs (supporting the development of innovative drugs and vaccines, etc.), and patient-tailored compliance plans. The fourth phase is IHI JU under Horizon Europe (H Europe). The budget is €2.4 billion. The goal is to promote the establishment of an EU-wide health research and innovation ecosystem, promote the transformation of scientific knowledge into innovation. In addition, it can promote sectoral health innovation, create a globally competitive European health industry, and contribute to the realization of a new Europe. The strategic research agenda will cover the various activities of the health innovation chain.

Table 1 Basic information of IMI/IHI JU

Initiative	Regulation	Period	Budget (euros)	FP
ETP INNOMED	No	2005−2009	18.53 million	FP6
IMI1 JU	(EC)2008/73	2008−2013	2 billion	FP7
IMI2 JU	(EU) 2014/557	2014−2020	3.276 billion	H 2020
IHI JU	(EU) 2021/2085	2021−2027	2.4 billion	H Europe

Note: ETP INNOMED − European Technology Platform INNOMED; IMI JU − Innovative Medicines Initiative Joint Undertaking; IHI − Innovative Health Initiative Joint Undertaking; FP − The Framework Programs for Research and Technological Development; H 2020 − Horizon 2020 (FP8); H Europe − Horizon Europe (FP9); EC − European Commission; EU − European Union.
Data from: http://www.ihi.europa.eu/ and https://cordis.europa.eu/projects.

3.3 Partners

The partners of the PPP model for drug R&D consist of the European Union and industry associations. The partners in the first three stages are the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA). IHI JU partners consist of the European Union and five industry associations, including EFPIA, Vaccines Europe (the member of EFPIA), the European Trade Association Representing the Medical Imaging, Radiotherapy, Health ICT and Electromedical Industries (COCIR), the Industry Association for Biotechnology in Europe (EuropaBio), and the European Trade Association for the Medical Technology Industry (MedTech Europe).

3.4 Operational model and funding allocation

First, the business consortium from EFPIA determines the research topic and publicly solicits proposals. Second, stakeholders spontaneously form consortiums and submit proposals. Third, the business consortium from EFPIA and the stakeholder consortium with the top-ranked proposal jointly form a complete project consortium. EU funds and in-kind input from EFPIA are provided in a 1:1 ratio. EU funds are mainly provided to the stakeholder consortiums, while the business consortiums from EFPIA provide in-kind inputs.

3.5 Achievements

The achievements of IMI JU include more than

400 assets and 40 regulatory procedures, the open resources from more than half of the IMI JU projects, hundreds of tools and programs, and nearly 10 000 high-quality publications. IMI JU has built a huge cooperative network for drug innovation, with nearly 200 projects in IMI1 JU and IMI2 JU, including the neurodegenerative diseases (NDD) combination, and the cooperative network of 18 projects with 236 organizations [18].

4 Discussion

4.1 Establishing a new mechanism to solve common problems in drug development

PPP model is a new mechanism widely adopted internationally to solve common problems in drug R&D. The definitions of different PPP models vary, but they are all established to address the decline in R&D efficiency. The FDA's PPP or consortium model is defined as "non-profit organization + profit organization". The NIH's PPP model is defined as "NIH or IC + one or more non-federal parties". The EU's PPP model is directly included in the definition of European partnership "EU + private and (or) public partners". Solving the common problem of declining drug R&D efficiency is reflected in the original purpose of the PPP model. C-Path aims to address the current situation of low R&D efficiency and high costs, bridging the gap between product R&D science and basic science, and improving the efficiency of drug R&D and regulatory processes. AMP aims to improve the understanding of disease pathways, promote better selection of therapeutic targets, and identify platforms and processes to accelerate the provision of new effective treatments to patients. IMIJU and IHI JU aim to revitalize the European biopharmaceutical research environment, solve drug R&D bottlenecks, and improve drug R&D efficiency.

4.2 Finding a convenor to lead the work

Different PPP models differ in the convener, but all are neutral third-party organizations. The FDA and the University of Arizona jointly established the C-path nonprofit organization. The C-Path worked as the convener to create PPPs or consortiums in different research fields led by the FDA. NIH launched AMP together with the FDA, companies, nonprofit organizations, and other organizations. With AMP as the convener, PPPs in different research fields led by NIH or partners were created. IMI and IHI are the PPPs established by the European Union and industry associations. With IMI and IHI as the conveners, the PPPs in the different research fields led by EFPIA were created.

4.3 Establishing a project-based cooperation model

The PPP is a project-based approach that brings together stakeholders in the same research field to establish an open innovation network. The launch of each project means the establishment of a PPP or consortium. In the latest agreement, C-Path's project is directly centered around 6 research aims or consortiums. AMP involves 12 projects in different disease areas including Alzheimer's disease. IMI1 JU and IMI2 JU even have nearly 200 projects.

4.4 Establishing a PPP funding mechanism

There are differences in funding sources and forms for all kind of PPP models, but they are jointly funded by the public and private sectors. Taking three PPP organizations as examples, more than half of C-Path's funding comes from the FDA, and the rest comes from non-governmental sources (including membership fees). AMP's funding comes from NIH, the private sector, and in-kind donations are from the private sector. IMI JU and IHI JU's funding mainly come from EU funds and in-kind funding from industry associations that is equivalent to EU funds.

4.5 Sharing of data and achievements

The research organized by PPP is mainly focused on pre-competitive areas. The sharing of data and achievements is often the key to industry

benefits, but it needs to be explained or negotiated in advance. C-Path promotes the development of feasible solutions through data and expertise sharing methods, changing the development process of drugs for some diseases. The "PPP Manual" of NIH clarifies that all partners need to jointly negotiate the sharing of data within the PPP and the achievements of the PPP become public resources. Data sharing within and outside the consortium is a common feature of many IMI JU and IHI JU projects. Sharing data may raise legal, technical, data protection, ethical and intellectual property issues. IMI JU and IHI JU helps the consortium understand challenges and quickly find solutions through the "Data Sharing Playbook". At the same time, it is necessary to ensure that all publications of IMIJU and IHI JU should be open access.

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