How to boost and accelerate new drug development in Korea: business ecosystem perspectives

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INTRODUCTION

Vaccines against the coronavirus disease 2019 (COVID-19) pandemic were developed at an unprecedented speed. For example, tozinameran (Comirnaty®, Pfizer-BioNTech) and elasomeran (Spikevax, Moderna), mRNA vaccines against COVID-19, were granted an emergency use authorization (EUA) by the U.S. Food and Drug Administration within just 10 months since COVID-19 pandemic was declared by the World Health Organization [1]. They were the first COVID-19 vaccines approved by the regulatory authority in the world. Soon after, the regulatory agencies in other countries or regions also granted EUA or full approval to tozinameran and elasomeran as the first vaccines in their territories [1], and people in many of those areas were able to receive the COVID-19 vaccine. Interestingly, these 2 vaccines were both developed by a pharmaceutical company based in the US, i.e., Pfizer (tozinameran) and Moderna (elasomeran) [1].

The developments of COVID-19 vaccines in the US at a speed unheard of before, much faster than in other countries, are attributed to an advanced ‘business ecosystem’ in the country. A ‘business ecosystem’ refers to an intertwined economic community, in which various entities co-evolve their capabilities for innovation, exchanging dynamic influences with each other to create one value [2]. The pharmaceutical industry is research-intensive, which requires an interdisciplinary approach involving such various academic fields as medicine, chemistry, biotechnology, and pharmacology. Besides, through drug discovery, preclinical and clinical development, manufacturing, marketing authorization, and pricing, the regulation by the government is tighter in the pharmaceutical industry than in other industries. Therefore, it is difficult to achieve good results only with the sole efforts by a single company or a part of the industry. In other words, the pharmaceutical industry should be approached from the whole perspective of a ‘business ecosystem’ more than any other industries.

Although dozens of Korean pharmaceutical companies have been developing vaccines and treatments for COVID-19, only a vaccine (SKYCovione Multi) and an antibody treatment (regdanvimab) were approved by the Ministry of Food and Drug Safety (MDFS) in Korea so far [3]. Not only COVID-19 vaccines and treatments, but also most of the new drugs developed...
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by Korean companies in the past have failed to meet market expectations. To support this notion, of 31 new drugs developed by Korean pharmaceutical companies for the last two decades, only five have posted an annual production of > 10 billion Korean Won (KRW) or 8 million US dollars (USD) in Korea as of 2019 [4].

The potential for new drug development in Korea has been much improved recently. For example, more Korean pharmaceutical companies have been successful in drug discovery and early clinical trials, which enabled them for licensing out technology to other companies including major global firms. In 2021, > 13 trillion KRW were signed through 33 out-licensing contracts [5]. Furthermore, the number of new drug candidates has also increased significantly in recent years as Korean pharmaceutical companies and bio ventures invest more funds in new drug research and development (R&D). According to the Korea Drug Development Fund (KDDF), a total of 559 new pipelines were being developed by domestic companies as of 2021 [6].

However, the chances of developing new drugs in Korea are not still high because most pipelines are in the early stages of development yet [6]. If most Korean pharmaceutical companies depend on out-licensing deals to third-party developers such as global firms before they complete phase 3 clinical trials on their own, it is even more difficult to learn and accumulate internal capabilities for new drug development. We propose strategies to accelerate new drug development in Korea by highlighting key areas to improve the business ecosystem for the pharmaceutical industry in Korea.

HUMAN RESOURCE DEVELOPMENT

According to the National Science & Technology Information Service, only 1,312 respondents from colleges, research institutes, or government agencies marked their specialty as “drug/drug development” in various government-sponsored R&D projects [7]. In the pharmaceutical industry, 12,314 employees were involved in some R&D activities in 2019, accounting only for 12% of total 102,912 workers of pharmaceutical companies in Korea [8]. However, excluding those who spend most of time in the R&D of incrementally modified drugs or generics, researchers fully engaged in developing ‘new’ drugs are even fewer. A survey on the pharmaceutical industry at the Korean Statistical Information Service (in 2017, the latest) showed only 27.9% of all researchers in the industry were actually doing R&D for innovative drugs other than incrementally modified drugs or generics [9]. As the proportion of researchers has hardly increased since 2015 [8], it is estimated that about 3,300 people are currently working for R&D of new drugs in the biopharmaceutical industry in Korea. Therefore, the number of researchers fully involved in new drug development at colleges, research institutes, and industry in Korea is hardly exceeding 5,000.

The government’s major initiatives to promote the pharmaceutical business have prioritized human resource development. Their strategies for human resource development, on the other hand, have been mostly focused on providing short-term (1–2 days) education sessions for incumbents. Although the government has offered funding for graduate schools in industrial pharmaceutical sciences and regulatory science, they were not fully dedicated to drug development. Furthermore, because pharmaceutical companies were not invited when designing the curriculum, requests and on-the-job demands from the industry have not been incorporated into the curriculum. In this setting, students are unlikely to obtain the skills,
experiences, and capabilities that pharmaceutical companies expect to see from a typical graduate with an advanced degree in drug development.

To properly develop human resources for drug development, the first task is to estimate how many people are required at each stage of new drug development by specific sets of skills. Then, a thorough and systematic plan for bringing up and training manpower in each area should be devised. Particularly, we propose to establish a ‘contract-based department’ at a university, for which a pharmaceutical company and a university enter into an agreement on a contract-basis to ensure preferred curriculum will be set by a company’s specific needs and requirements and the graduates are guaranteed for being recruited by the company. Because few pharmaceuticals in Korea can hire all graduates from a contract-based department, several companies may form a group together, or industry associations such as the Korean Pharmaceutical and Bio-Pharma Manufacturers Association may make agreements with colleges on behalf of participating companies.

CONTROL TOWER FOR NEW DRUG DEVELOPMENT POLICY

Because it takes 10 to 15 years to develop a new drug through various stages, the strategy for drug development should be long-term, with no overlap or omission of support at a certain stage. Therefore, it is efficient to establish and manage a nationwide new drug development strategy by a single organization. In Korea, however, too many ministries and organizations have been involved in setting up and executing policies, systems, and support grants, many of which were overlapped and redundant, while some important areas in drug development were not even touched upon. What's worse was they were sporadic and anecdotal. For example, dozens of research funding programs for drug development were run by nine different government ministries in 2019 [10].

In the US and the UK, leading countries in the pharmaceutical industry, a government agency has overseen R&D strategies for the health and medical sectors, including pharmaceutical business [11]. In Japan, three ministries used to share R&D projects in the health and medical fields, but a separate organization was established to coordinate each ministry’s programs in 2015 [11]. In Korea, the KDDF was established in 2011 as a control tower to support research and commercialization of new drug candidates [6]. The KDDF, however, is not a stand-alone control tower for drug development like the aforementioned countries because three government ministries (the Ministry of Science and Information and Communication Technologies, the Ministry of Health and Welfare, and the Ministry of Trade, Industry, and Energy) are involved in its decision-making in the form of a consortium [6]. In this way, rapid decision-making may be challenging because they must go through a process of coordinating opinions from each ministry.

Therefore, an independent control tower should be established to oversee Korea’s drug development policies on a long-term and comprehensive basis. The control tower should be an independent entity with its own budget and authority to make its own decisions including hiring, so that the policies do not change depending on the positions of government ministries involved. To design and implement long-term strategies, it should be a permanent organization rather than a temporary committee or project group. Finally, it should oversee a wide range of policies, including human resources development, infrastructural support, and R&D funding for new drug development.
FINANCIAL INVESTMENT IN NEW DRUG DEVELOPMENT

The Korean government has increased the amount of financial investment in new drug development by 3.9% annually from 2015 to 2019, which reached 391 billion KRW or 300 million USD in 2019 [10]. The government has gradually raised the share of funding dedicated to basic research and early discovery at universities and research institutes. The budget has been distributed to sporadic research projects by various ministries so far, but this could be solved if the aforementioned control tower for new drug development is established and run as planned. However, as the government invests primarily in colleges and research institutes, Korean pharmaceutical firms have been facing difficulties in raising R&D investments for new drug development.

In 2019, the government or public sector covered only 6.2% of Korean pharmaceuticals' total R&D expenses, whereas pharmaceutical companies bore the rest of R&D cost by themselves. Although venture capitalists in Korea have recently increased their investment in bio sectors, a survey found that only 7 percent of bio ventures have received funding from venture capitalists [12]. Phase 3 clinical trials, in particular, are financially unsustainable for Korean pharmaceutical companies because they cost > 200 million USD (or 250 billion KRW) per trial [13], far exceeding the annual operating profit of 48–125 billion KRW, Korea’s top 5 pharmaceutical companies in 2021 [14,15]. Hence, many of them often had to depend on out-licensing via technology transfer to foreign companies after completing only phase 1 or 2 clinical trials.

Therefore, for pharmaceutical companies to have a more stable source of funding for drug development, the government should take a leadership role in creating funds for new drug development and expanding investment. It is also critical to establish a so-called ‘mega fund’ with a fund size of 100 trillion KRW (or 80 billion USD) to invest in global phase 3 clinical trials that are outside the reach of government research grant and venture capital investment. Furthermore, to increase private investment, network opportunities should be provided, where bio ventures meet investors on an official and regular basis, e.g., seminars for commercialization or technical exchange meetings. In this process, a public-private partnership may be developed, with the government serving as a facilitator and the private sector spearheading collaborations for mutual benefits.

INVESTIGATIONAL NEW DRUG APPLICATION (IND) REVIEW SYSTEM OF THE MFDS

Another important area of new drug development to be improved in Korea is the IND review process by the MFDS, which is too long, thereby hampering fast and efficient new drug development. The standard review duration for an IND in Korea is 30 business days, but few have been granted within that time frame. For example, it took up to 421 days in 2019 from an IND application to its grant by MFDS [16]. The main reason of the delay in IND review in Korea is the lack of human resources in MFDS. According to a press release that was recently distributed to professional journalists, the MFDS stated that there were only 19 medical doctor reviewers affiliated with the MFDS as of March 2022 [17]. Though medical doctor reviewers are primarily responsible for IND application evaluation, the MFDS has not employed enough medical doctor reviewers [17]. Since there were 842 IND approvals in 2021, this indicates that more than 44 IND applications are reviewed annually by one medical doctor reviewer. MFDS has established a few systems to shorten the period of IND review,
such as the ‘Innovative Review Team for Early-Phase Clinical Trials’ and the ‘Preliminary Review System’ [18]. However, even if multiple new systems are implemented, the Preliminary Review System’s 30-day target is unlikely to be met and there will still be delays in IND approval if the manpower shortfall remains.

Therefore, MFDS has to recruit, train, and empower more IND reviewers if they truly want to shorten the IND time. To secure and maintain reviewers at MFDS, we propose to dramatically increase the user fee imposed on the IND sponsor to a reasonable amount and use it to hire more reviewers and increase their compensations. If recruiting IND reviewers in a timely manner remains difficult, an external expert committee, preferably in the form of a standing committee, should be established. In this case, recommendations by the external expert committee should not only be forwarded to the IND review, but also construed as the final decision unless there is strong evidence against.

PATIENT ACCESS TO NEW DRUGS

After a new drug is developed huge capital investment through > 10 years of R&D period, patients can access to it only when it is authorized for marketing and reimbursed through a certain kind of health insurance. The marketing authorization and reimbursement of a new drug means more than the completion of a drug development project. Because pharmaceutical companies are incentivized to invest more in R&D to develop innovative new drugs when a new drug is listed on the formulary at an appropriate price and gets reimbursed. In comparison to other advanced countries, however, patient access to new drugs in Korea is limited. For example, Korea was ranked 19th out of 31 nations surveyed in terms of patient access to new drugs, as measured by the number of drugs launched in each country since 2005 [19]. It is critical to improve access to new drugs not only to lower medical expenses and improve public health, but also to ensure the sustainability of drug development.

As we discussed in our prior study [20], we propose the following strategies be adopted to improve patient access to new drugs in Korea. First, the incremental cost effectiveness ratio (ICER) threshold, a criterion for determining a drug’s cost-effectiveness, should be applied flexibly given the increase in national incomes, disease severity and specificity, and patient needs. The explicit and inflexible ICER threshold was not supposed to be referenced to in Korea according to the recently modified regulations in 2021 [21], but it was expected to refer to the previous review results, which employed a very low ICER threshold. Second, Korea needs to establish alternatives to economic evaluation and to employ multiple reimbursement mechanisms. For example, risk-sharing agreements, an alternative to economic evaluation, are now only used for drugs that treat cancers, rare diseases, or severe and incurable diseases, but they should be considered for chronic diseases where an economic evaluation is difficult or inappropriate. Third, if alternative medications or therapies are not available, we suggest initially listing the drug for reimbursement first and then adjusting its reimbursement status or drug price through a post-evaluation after a defined period. Lastly, Korea has to come to a point that a separate fund to cover reimbursement should be formed on top of the existing national health insurance. A separate fund should be spent to reimburse for patients with the same disease category as the diseases, in which profits were generated by institutions or organizations participating in the fundraising. A social consensus on how to create and operate a separate fund is required, and the government should play a pivotal role in achieving that consensus.
CONCLUSION

Korea has developed 34 new drugs in the last 2 decades, but has little experience in commercializing them globally. Though the government has invested in new drug development since the 2000s, it has increased only the number of studies for which it supports grants, rather than establishing a comprehensive, long-term plan. Thus, Korean new drug development endeavors have not worked at their full potential in the global market. Only recently has the number of pipelines developed by Korean pharmaceutical companies grown to over 500 and have R&D achievements such as out-licensing to global pharmaceuticals begun to be delivered. The Korean pharmaceutical industry, however, cannot evolve solely through out-licensing. It will only be able to develop new global blockbuster drugs and continue to thrive if it has the capital, experience, and capability to conduct clinical trials until the end stages on their own.

Unlike the US, which developed COVID-19 vaccines at an extraordinary speed, Korea currently lacks capital, strong basic science and technology, expertise, and collaborative experience among enterprises, universities, and research institutions to develop a vaccine. To develop innovative new drugs in Korea, the government and private sector should collaborate to increase investment in new drug development and cultivate human resources for basic research, clinical trials, and regulatory affairs. Above all, to boost and accelerate new drug development in Korea, the whole business ecosystem should prioritize innovation to the other values. To this end, a research culture should be established, in which researchers can freely try out innovative ideas, more professionals should be encouraged to develop innovative technologies, and the government should appreciate the value of innovative drugs to the whole nation.

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