Review Article

Challenge-based approaches for policy-making in vaccine development and production

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ABSTRACT

Presently, vaccines development and production has gained more importance due to their influence on topics such as the society's health system and economy, as well as the bio-security issues and the defense affairs. Moreover, the potential innovation capabilities in vaccine production are assumed as engines of biotechnology development which is among the emerging technologies that can support the technological development of a country. This review is based on analyses of scientific articles, literature, textbooks and reports by the international organization, as well as online databases with the subject of innovation in vaccine production, in order to identify current challenges in vaccine development and production. Not long ago, the most important challenges in this field were assumed as technical or budgetary issues. However nowadays, due to a global paradigm-shift in vaccine production which has changed from innovation aimed solely at the registration of new products toward promoting public health, other challenges in competition and commercialization have stepped in. The identified new challenges and bottlenecks could be used to form practical approaches in policy-making toward vaccine development and production. Furthermore, overcoming these challenges requires identifying the bottlenecks and proper orientation with the current world circumstances to draft a functional policy that could fulfill the national health system objectives. Here, following explaining these global challenges and approaches, the situation of vaccine industry in Iran will be briefly discussed.

KEYWORDS: Policy-making, Vaccine, Enablers and blockers, Innovation, Biotechnology.

INTRODUCTION

The pharmaceutical industry is among the most lucrative industries in the world, with generated incomes topping automotive, oil, gas and media industries and its revenues are almost close to ones gained by banking and capital institutions [1]. The pharmaceutical market value has been declared as USD 1044 billion in 2015 [2] while the prescribed drugs sales in 2016 hit USD 780 billion. Interestingly, the growth rate of the vaccine market in the world is approximately twice as much as the growth rate of the pharmaceutical products market [3]. The impacts of direct and indirect costs of vaccine production on a nation's economy, security and defense issues (e.g. bioterrorism and passive defense), have made it a strategic technology in this century. In the developing countries like Iran, vaccine production is a low profit margin industry; however, it is a major driving force of the country's biotechnology sector [4, 5]. For instance, the approach of giving priority to "prevention" over "cure" in Iranian health system and the importance of producing domestic vaccines with the aim of industrial self-sufficiency have significantly pushed the country in this arena [6]. So far, the technical and knowledge-related issues of vaccine production process have been the most important challenges for the researchers in this field [7]. However, contemporary mechanisms such as long and hefty process of safe production under strict surveillance of controlling authorities or interactions in cooperative networks have created new challenges that are essential to be considered. This review article is focused on the importance of recognizing the bottlenecks as well as the new challenges in vaccine production in Iran in aftermath of a vast growth of knowledge-based companies from 2013 to 2018 and the government's current incentive policies to protect them [8,9]. It is expected that the issues raised here will be effective in directing these companies to realize the health system's objectives in terms of technology and policy.

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THE CHALLENGES

The development and production process of vaccines have certain characteristics that effective factors in this process can be divided into the enablers and the blockers which are factors such as laws, executive and regulatory affairs as well as knowledge and skills in the concerned context. It is useful to identify and analyze these factors, not only for the sake of management and policy-making in the health system but also for the development of innovation in production and introducing new vaccines.

Technical issues and the paradigm-shift

Vaccine is a product that is often injected into vulnerable populations such as babies, seniors and people with immune deficiencies; hence, its safety must be guaranteed. Therefore, the provision of information on the efficacy of the supplied product to the market in reducing the burden of the disease is essential. Moreover, policies for its rational use in other countries and the cost of vaccines are the factors that can delay the arrival of new vaccines into the consumption market in poorer countries [10]. In addition to "safety", "efficacy" and "quality", "the consumer's purchasing power" is also an important factor in the vaccine industry; specifically, for the low-income countries, considering its high production expenses and its low margin of profit. Vaccine innovation is thus shifting from the narrow realm of product development and is increasingly being developed by new, not-for-profit initiatives and institutions that creatively engage the public and private sectors to accomplish their goals. [11]. The vaccine development process is long, complicated and expensive since vaccines are the biological products of microorganisms and their development stages are different from the pharmaceuticals. These steps are summerized in Fig. 1.

Fig. 1. The stages of vaccine development.

The cost of this long process is estimated between USD 1-2 billion by various references [12, 13]. This high cost is mainly attributed to high failure rate in finding an approved formula for a vaccine (i.e. one approved formula from 5,000-10,000 thousand formulas). Meanwhile, many of the existing products in the market have passed their product development and clinical trials phases years ago, and the introduction of a new vaccine could not suddenly occur. The vaccine development model has also changed in recent years which the most notable items could be seen in Table 1.

Table 1. The most important differences between the previous the current vaccine development models.

	Previously	Currently
Quantity of the patents	A few	Many
Patent appliers	Mostly within the industry	Mostly out of the industry
Technical uncertainties	Low	High
Required licenses	5 to 10	Numerous
Financial transaction expenses	Medium	High

Some key considerations in the process of vaccines production are:

- The importance of cooperative network of the public and the private sectors
- Existence of an expanding market
- Importance of process's scale-up
- Legal and technical challenges and restrictions on the bio-production (in terms of compliance with standards or good practices that are an urgent concern to the regulatory bodies)
- The supportive role of the World Health Organization (WHO) from National Regulatory Authorities (NRA) in providing operational guides
- Performing preliminary qualitative assessments and supporting the products registration

The challenges to develop vaccines in different dimensions such as immunology, pricing and marketing issues have led to operational recommendations and policy measures [13]. Some "push and pull" policies have been suggested in the literature to increase the access of low-income countries to the vaccines. These approaches include the commitment to purchase (push policy), granting voluntary or compulsory licenses, or even access to patents in return for a small amount of overpay for every dose of vaccine and partial compensation of R&D expenditure (pull policies). One of the most important points is: "One size does not fit all!". Therefore, there is no unique or comprehensive policy to improve the access of low-income countries to the vaccines. For example, by price reduction due to granting the patents and increasing the access to the product in low-income countries, the overpay on each dose will not be attractive for the primary producer and the innovation process will be affected.

There are debates about new approaches to reduce the production time and costs such as "vaccine on demand". The main argued issues are firstly pathogen identification and generating a protective response, followed by regulation and safety circumstances [14]. Therefore, the effort to overcome this challenge continues. The market importance in the development of the vaccine cannot be ignored because, despite the vaccine research in universities and non-profit centers, the process of market entry is conducted by companies. The phase delay in the "demand" and "purchasing power" on the vaccine market are other characteristics of the process. For example, the value of the AIDS vaccine market is in high-income countries, but the main demand is in low-income countries. On the other hand, the decision-making factor in the vaccination cover for developed countries is "cost and benefit analysis" while "purchasing power" is the dominant factor in low-income

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countries [11]. The patent expiration date and the long period of registration and licensing procedures for the market entry which reduce the profitability period are other important issues to be addressed. The most important barrier to produce vaccines in less developed countries is not the patents, but the lack of financial resources, infrastructure and technical requirements for the market entry which have been confirmed on the WHO reports [15].

The role of national institutions in vaccine research

The role of government in forming cooperation between universities and non-profit centers has always been considered for the vaccine development. Due to high vaccine demand in low-income countries and the associated long period of investment return and pertaining risks, the incentives for the independent vaccine producers are declining, naturally [16]. The importance of charities, as one of the present actors in the innovation ecosystem, as well as implementing regional or global programs have been noted to be influential for this purpose. Implementation of these programs endows well-developed regions, as well as low-income regions by reducing mortality and contagious diseases [17]. Therefore, the role of governments is important to attract the support of charities and to implement vaccination programs.

Since two-thirds of the total vaccine research in the world and 90% of the total vaccines are being developed in Europe, the study of EU political actions for vaccine research could contain valuable insights. Such actions include the necessity for international cooperation in the research, the importance of fundamental research and setting priorities, appropriate financial allocation procedures, the necessity of establishing and consolidating cooperation among stakeholders and the necessity of defining incentive for public and private sectors [18]. In the United States, the key role of the state and public institutions in fundamental vaccine research and the development of the scientific foundations of product development, as well as the roles of industry in production and manufacturing have been emphasized. Fundamental research in the biomedical field has a major role in the development of vaccines, thus, the importance of cooperation to translate scientific findings into technological advancements can be understood. Government institutions in the United States' vaccine innovation system are supportive of the research that is integrated with the university-industry interactions and can be transferred to the private sector. The other role of the state is to supply human resources and items that are not allowed to share for ownership reasons, such as patents or intellectual property rights [19]. The government also gets involved in the vaccine registration and certification by accelerating the long administration procedures. Moreover, monitoring of a vaccine's efficacy and immunization program, as well as coordination of activities in research institutes should be done by the state [20].

Conducting R&D funds to public health research is one of the major challenges around the world. Global investments in health R&D in both the public and the private sectors in 2009 hit USD 240 billion, of which USD 214 billion were spent in high-income countries, 60% of which were by the private sector, 30% were owned by the public sector and 10% were from other sources, such as charities and non-profit institutions. By 2016, these allocations were almost unchanged [21]. A systematic approach toward budget allocation for R&D should be taken while the support of the WHO members is essential to improve the global health [22]. The characteristics of the innovation system in the biotechnology, the role of market factors and the openness of the system in some countries, has been investigated in the report of the Organization for Economic Cooperation and Development (OECD) in 2006 [23]. The result, however, does not necessarily lead to innovation as price constraints limit innovation incentives which stimulate the use of generic products. The systematic failures in this system include the lack of performance of actors involved in production, dissemination, and application of new knowledge as well as the lack of binding and interaction between the system components. Most of the deficiencies are not just one factor (e.g., actors, functions, institutions, or processes) but are rooted in the composition of the factors. The policy recommendations based on emerging studies in OECD countries are:

- Implementing coordinated and consistent policies for innovation. For example, determination of combined goals such as improving international competitiveness through innovation policies toward pharmaceutical biotechnology and public health system.
- Paying attention to the regulations governing the public sector as the most important source of innovation, such as Open Innovation (a paradigm that assumes the firms can and should use external ideas as well as internal ideas, and internal and external paths to a market, as the firms advance their technology [24]).
- Encouraging cooperation and networking by linking the scientific and the commercial actors (due to this, 581 scientists are now operating from 52 countries around the world on vaccines, in form of the sixth EU program [18]).
- Supporting the innovator industry and creating incentives for private investors to invest in biotechnology.
- Designing the legal framework that involves clear and transparent laws which are explicit and practical in order to protect the innovations.
- Allocating more attention to the technology transfer and encouraging the application of public sector research and indexes of intellectual property rights, using an efficient and supporting infrastructure for the budding companies.
- Improving and stimulating of the scientific system and emphasizing the importance of the role of government research policies and how to provide the budgets.

The role of government in encouraging innovation and preserving innovative rights

According to Bayh-Dole act in the United States, a registered patented license which is developed with the help of the state budgets to a university or company should be transferred to the same university or company that the federal government has funded. In other words, the state provides the cost of research and then transfers the possibility of production, sales and profitability from that invention to the same university or company that it has funded. Therefore, the state-ownership is avoided while the incentive and possibility of competition for small and low-budget institutions will be provided. Moreover, the inventions and patents will turn into products which lead to further development and employment opportunities. Among the

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attributes of this act is the possibility of transferring the privileges to third parties. It is obvious that the university will benefit from the technology transfer agreements, and with greater incentives, it will continue to conduct research while third parties (usually the private sector) will commercialize the product with greater efficiency and capability. According to this act, the federal government reserves the right for the state budget allocator to transfer patents without consent and permission from the first university or company (which currently owns the patent) to the actual or its intended third person under special circumstances. This mechanism allows the government to play its regulatory role in order to prevent corruption, monopoly or overruling of the consumer rights (i.e., preventing from the price increasing by a patent holder). However so far, the government of the United States has been extremely resistant to use this right and has given priority to the original patent holder and has never used this right, despite thousands of cases and requests since past 38 years [25].

Political and geopolitical concerns

Many political and regional issues can affect the processes of science and technology development as well as its management and innovation, as exemplified by the UK withdrawal from the European Union (EU) in June 2016, also known as Brexit. The UK pharmaceutical industry, valued at more than USD 88 billion, has created employment for more than 70,000 people. The UK has been one of the most important budget receivers for research in Europe which has received 18% of the total EU research grants [26]. It is estimated that 4 years after leaving the EU, a whopping USD 8.5 billion grant from the European budget for the UK science will be at risk, thus strengthening competitors such as Germany which had weak points in implementing BioRegio and BioProfile programs. These two programs are conducted by Germany to strengthen the biotechnology, cluster-based and regional-based respectively. Moreover, the EU is moving toward a new central system for rapid approval of new drugs consisting of a single entry point and a certification method for all clinical trials in Europe. In case of Brexit, the pharmaceutical companies will have to request a separate registration request system for the UK which will complicate the process due to the requirement for additional costs, time and regulatory procedures. Before Brexit, the world's pharmaceutical companies could have had access to all the European investments in the UK; however after Brexit, such investments will be lost to the UK which will diminish the incentives for the European companies to further invest in them. Brexit can also cause the move of the European Medicines Agency (EMA) from the UK to another European country which will reduce the influence of the UK's regulatory authority in medicine development. This may even disrupt the ongoing drug studies and the access to the related information on the network. Other hidden but fundamental consequences are problems with attracting foreign talents from abroad, keeping the current staff for the pharmaceutical companies in the UK and disruptions in the current integrated product distribution chains. It should be considered that the UK drug exports to Europe is 56 % of the UK's pharmaceutical exports which are equivalent of 53 billion pounds while it imports a large portion of its medicine from the EU which further complicates the matter upon Brexit. Therefore, the impact of decisions and political choices on the processes of product development and innovation cannot be neglected [27, 28].

The business model and some operational characteristics

A business model describes the rationale of how an organization creates, delivers, and captures value [29] in economic, social, cultural or other contexts. In other words, the business model is the logic of creating value for customers that is different from the strategy of how to create value [30]. The business model structure is considered as a key issue in successful functioning of innovative organizations. Hence, attention to the dynamism of the characteristics becomes highlighted. For instance, while the scientific and experimental skills in a product lifecycle are generally loosing importance, skills such as marketing, manufacturing and public relations are gaining prominence. So, the business model is designed based on the interactions and internal capabilities of a firm with an industrial structure which links these capabilities to the characteristics of the business model [31]. This is much regarded in some new areas of application such as e-commerce or e-health services. The business model must be simple, useful and novel. Innovative organizations need to have a set of resources suitable for solving problems to be valuable or value-creator for the customers [32]. Since the business model consists of strategic goals for the achievement of all participants, the issue of how to compose resources and capabilities based on different organizational structures has been the subject of a few studies [33]. According to today's biotechnology outlook, 4 types of companies can be identified in vaccine business:

- Drug Discovery Companies (DDC): So-called small molecule companies which are entrepreneurial firms with high scientific content which are surrounded by other firms that offer support, assistance and exit opportunities. The most outstanding of these are large pharmaceutical enterprises with access to large-scale distributed systems and resources.
- Contract research companies: They are often relatively small and entrepreneurial which provide a variety of services to the DDCs such as research or field trials.
- Tool-box companies: These companies provide tools that can be utilized in drug discovery by DDCs.
- Diagnostic companies: The providers of products that are used to diagnose various diseases.

The required factors for an effective biotechnology business model structure are cost-efficiency, appropriation with the product line of a pharmaceutical company, strong intellectual property position and lucrative product to provide cash flow to support R&D [34]. Furthermore, critical success factors in the drug development sector of the biotechnology industry could be pointed out as characteristics and composition of the administration team, budgeting and adaptability. The qualified management team, the strong position in intellectual property and access to financial resources, the predictability to access skills required in different stages, as well as long-term forecasts under uncertainty conditions are other important features of today's companies in this field.

The emphasis of new business models to attract more cooperation, networking and unification methods to achieve corporate goals has been the focus of some researchers [35]. Despite the budgeting difficulties, domination of small and medium-sized enterprises can lead to opportunities to innovate and reduce the dependence on large enterprises and can

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promote cooperation with universities. However, the injection of money and strengthening or carrying out innovation requires involving large companies. For some highly innovative products such as anticancer vaccines (with special scientific dynamism) business models based on cooperation have been offered [36, 37], and the upstream research (focused on the early stages in the operations or exploration) has been considered as the main driver of gaining competitive advantage [38].

Innovation

A study on Japanese pharmaceutical companies reveals that national policies support small innovations which are the results of focusing on a series of small ideas that have measurable impact over time. Small innovations and small to medium-sized firms are compelled to concentrate their R&D investment into niche markets in order to allow their restricted resources be used to accomplish innovative breakthroughs [39]. According to a study on technology-based industries in the United States, internationalization helps these companies to unfold their investment over a bigger sales volume before their product becomes obsolete [40]. This result was later confirmed in a broader range of high-tech firms [41]. To enter the market for new technological products, it is essential to gain international experience of product entry to the market [42]. However, market demand is not enough to fill the gap between the technical ability and its application. For successful commercialization of R&D, management control system based on explicit authority has a critical importance and the key is budgeting, based on the market [43].

Although the lack of resources is treated as a stimulus to innovation, the existence of natural and absorbed sources (i.e. easily available recourses) will be tempting to use of them which reduces the need for exploration [44]. Only in case of certain environmental threats the untapped resources (scarce, common and available) cause increased exploration and exploitation of the resources. The pharmaceutical companies of India, as one of the emerging poles in Asia, are using imitation and innovation, as well as the combination of skills and know-how strategy [45]. Some successful firms that have achieved high-end innovations have used strategies to make ambiguity to useful learning. For instance, focusing to understand and clarify the uncertainties was a process with lessons-learned to overcome the ambiguities for ground-breaking innovations [46]. GSK Company, as one of the world's biggest pharmaceutical companies, had successful results by re-arranging its R&D activities to similar innovation firms, in order to encourage and stimulate its researchers for greater productivity, [47]. The integrated pattern of the innovation process, the evolution of innovation patterns (from a simple linear and stage-wise model to the impact of innovation from the market and organization, and ultimately, its evolution into an integrated approach) can be followed in other references [48].

Strategic alliances

Biotechnology companies are typically inspired to participate in strategic alliances. For instance, small firms often participate in exploration alliances to develop new products and then enter into exploitation alliances to bring these products into the market [49]. These firms will ultimately withdraw from the alliances to find new other molecules, or to do vertical integration (when a firm extends its operations within its value chain). Pharmaceutical enterprises tend to invest in high potential areas that had been previously winning. In the beginning of a new technology, funding in a specific field by a competitor can lead others to fund similarly in that field [50]. The firms with greater inter-firm collaboration are more frequently involved in mergers and acquisitions which are not related to monetary problems [51]. Inter-firm collaborations are thought to provide more assets and legitimacy which can protect firms from unfavorable situations [52]. Evidence shows that Swedish biotech companies are more likely to rely on intangible resources of the new networks for their development [53].

Networks and social capital

In order to design organizations involved in product innovation, managers must create a knowledge integration mechanism, adapted to the type of the market knowledge used for the product development process [54]. The distribution of knowledge for the success of product innovation is critical and allocation of financial and human resources to implement this mechanism effectively is essential. While cross-functional communication inside a company unit could occur, multi-divisional enterprises typically fail to realize innovations that integrate resources from other divisions. This can be the results of organizing the enterprise's design on product lines instead of core competencies.

Social structures may fill this coordination gap. The manager's support for these innovation networks is effective in strengthening communications and stimulating innovation [55]. The networks and the social capital play big roles in permitting the transfer of implicit knowledge in high ambiguity condition (a condition similar to a radical innovation) or an effort for new product development. Various sources of information will reduce the ambiguities.

Enabling the search for new opportunities, networks may be more open and loose while implementing product development can be more closed and dense [56]. Therefore, the importance of the networks as a resource identifier (direct knowledge, or scattered knowledge from different organizational areas) is emphasized. The importance of the networks as sources of resource identification (knowledge directly or scattered knowledge from different organizational areas) has been emphasized [57].

Changing requirements over time

The market potential and robust intellectual property protections were important drivers of R&D investment choices. Shortly at the beginning, the biotechnology companies are usually concentrated on their scientific problems. As they grow, the stress is often shifted to commerce and later to production. The decision-making process in companies is different, based on their size. The decision-making in small firms are limited to the CEO or their scientific manager; however, in large corporations, middle managers greatly affect the decision-making process. In very large companies, senior management involvement is limited to explaining long-term goals and final approvals [58].

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CONCLUSING REMARK

Despite the complexity of bio-production, particularly in case of vaccines, the above descriptions suggest that today's challenges for developing and producing vaccines are not limited to the technical issues of the production line, but many other factors in this competitive environment can act as the enablers or the blockers in this process. The laws and regulations, political issues, networking, intellectual property rights, governance, and organizational approaches can be counted among those factors. Hence, identifying the influencing factors and paying attention to them will be effective in taking appropriate strategies to stimulate innovation in vaccine development process, as the world's pioneer producers have noticed them appropriately. It should be mentioned that mainly the governments try to support the producers, and that's why the above-mentioned items could be important for policymaking globally. However, the newcomer countries must pay more attention to these issues to compete in the world market.

In case of Iran and the country's objectives such as "National Resilience Economy Plan" and "Knowledge-Based Economy Program", the above-mentioned approaches should be the concern of the Iranian policymakers, too. The history of the production of human vaccines in the Iran goes back to the 1920's, when Pasteur Institute of Iran was established [59]. Following the course of the first 50 years, many innovations in terms of the products and the production methods have been done in the field along with the world's technical advancements. These efforts combined with direct training in European countries as a mean of technology transfer had important roles in curbing many epidemic diseases in the country. Even the creation of spin-off institutions, such as Razi Vaccine and Serum Research Institute can also be considered as an organizational innovation in those early years. However, it should be noted that in practice, since 1970's, no domestically mass-produced vaccine has been added to the country's mandatory immunization program (except Hepatitis B vaccine as a result of a technology transfer project). Moreover, no new human vaccines have been developed inside the country since then, although efforts were made in that direction. The realization of the ambitious and lucrative objectives of the country's science, technology and innovation system by 2025, such as entering to the list of 10 vaccine makers in the world, achieving 3% of the world's vaccine market, or establishment of at least 2 distinguished Iranian brands in the vaccines' world, requires identification of the challenges and bottlenecks. To overcome these problems, identifying the pinches, using the findings and lessons-learned, and appropriate orientation with the current world circumstances would be necessary.

The above-mentioned approaches could be used as a roadmap for policy-making in vaccine production and development. Each country should hence design an appropriate strategy and make its own policy to realize their goals based on a gap analysis between "as-is" and "to-be" conditions. Fortunately, the availability of many knowledge-based firms, more advanced hardware and institutional infrastructure in the country are the current advantages of Iran in comparison with the past years which may lead to breakthroughs in this highly important industry.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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