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REVIEW ARTICLE

Biosimilars for Healthcare Professionals

An overview of the current status of follow-on biologicals in Iran

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Background: The advent of follow-on biologicals in Iran and biosimilars worldwide have provided various treatment options for several severe and chronic diseases. The goal of the present study was to provide an overview of their current status in Iran.
Methods: A comprehensive search of clinical trial registry sites and other databases that publish scholarly articles, such as PubMed and Google scholar, enabled the current follow-on biologicals landscape in Iran to be mapped. In addition, the annual national wholesale data of pharmaceutical products published by the Iranian pharmaceutical regulatory were analysed. The share of biotechnological therapeutics in terms of the whole medicines market, was evaluated, along with the share of follow-on biologicals and the potential and actualized cost-saving associated with using them. Data were collected and analysed over the 2013–2018 time period.
Results: At the time of writing, 21 follow-on biologicals were available in Iran and these represent 17 different originator molecules. In 2018, approximately 13.5% of medicines spending in Iran was devoted to biotechnological therapeutics. Follow-on biologicals comprised approximately 47.2% of the biotechnological therapeutics' total market value, up from 35.2% in 2013. The use of follow-on biologicals in Iran was associated with more than US$300 million cost-saving in 2018. A number of follow-on biological candidates, mostly monoclonal antibodies, are under development and will be subject to head-to-head clinical trials against originator products prior to regulatory approval and marketing.
Conclusion: Despite a significant rise in the use of follow-on biologicals in Iran, the proportional use of biotechnological therapeutics compared to the total medicines market has remained constant in recent years. Iranian healthcare authorities can improve patients' access to life-saving biological medicines through promoting the use of follow-on biologicals instead of costly originators after making sure of the quality, efficacy and safety of the follow-on biologicals. The significant cost saving associated with using follow-on biologicals can also be utilized for other biotechnological medicines that are not currently in Iran's drug list.

Keywords: Biosimilars, biotechnological therapeutics, follow-on biologicals, Iran

Introduction

Since the development of human insulin via recombinant DNA technology in 1982, several medicinal biotechnological therapeutics have been marketed. These products have broadened the treatment armament for use against life-threatening and chronic diseases [1]. Due to costly manufacturing processes and the considerable investment in research and development required prior to their approval, these products are generally high priced. The mean daily cost of treatment with biotechnological therapeutics is estimated to be 22 times higher than conventional small-molecule medicines [2]. Therefore, despite biologicals' well-known benefits, including providing more specific and life-saving treatments for a variety of diseases, their use will be restricted by ever-increasing healthcare costs. Healthcare authorities have been eager to find more affordable choices to facilitate patients' access to these therapies. Follow-on biologicals are potentially less expensive options that can deliver the same benefits of originator biotechnological therapeutics.

According to the US Food and Drug Administration (FDA) definition, a biosimilar is a biological product that is highly similar to an already-approved biological with no clinically meaningful differences from the originator [3]. The European Medicines Agency (EMA) was the first regulatory agency to lay down a biosimilar approval framework in 2005 [4]. Following this, in 2006, somatropin became the first biosimilar molecule that was granted European Union (EU) marketing authorization. Since then, several biosimilar products have been launched in Europe. In 2013, an infliximab biosimilar was the first biosimilar monoclonal antibody that received EMA approval. Due to the complex macromolecular structure of biologicals and their manufacturing procedures' sensitivity to small variations, approval frameworks outline the rigorous quality control and quality assurance measures required to ensure biosimilar and reference products' comparability. In addition, they define when clinical studies are required to demonstrate that a biosimilar product is highly similar to the originator in terms of efficacy and safety [5].

Following the development of EMA's biosimilar approval framework, the World Health Organization (WHO) and FDA established their own biosimilar authorization pathways [6, 7]. According to the guidelines published by EMA, FDA and WHO, several countries have established country-specific guidelines for biosimilar approval [8]. The Iranian pharmaceutical regulatory authority (Iran Food and Drug Administration, IFDA) developed its national biosimilar guidance based on WHO guidelines in 2010 [9].

The pharmaceutical industry in Iran began over 80 years ago [10]. In recent years, the commercial potential of producing follow-on biologicals and the favourable economic returns they offer, have encouraged several science-based companies to move towards producing biotechnological therapeutics. In 2000, Interferon alfa-2b was the first follow-on biological that was marketed in Iran. Since then, several other products have been developed and marketed in the country. This product,

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and other follow-on biologicals that were marketed before the issuance of IFDA biosimilar guidance in 2010, cannot be called biosimilars. This is because many of these follow-on products have not registered or published head-to-head clinical trials with the reference product and have not demonstrated that they are highly similar to their reference product, see Table 1.

The present study had several goals: (1) To identify the follow-on biologicals in the Iranian market and summarize the available information regarding their market entry and related clinical trials; (2) To assess the share of biotechnological therapeutics in Iran's pharmaceutical market and provide an overview of follow-on biologicals' share in terms of the number of units sold (sales volume), total sales (sales value), and domestic production/imports; (3) To estimate the potential and actualized cost-saving associated with the use of follow-on biologicals; (4) To summarize information regarding follow-on biological candidates that might enter the market in the future.

Methods

Information from the Iranian Registry of Clinical Trials (IRCT), clinicaltrials.gov, and the International Clinical Trials Registry Platform (ICTRP) was used to identify related phase I and III clinical trials between 2013 and 2018. A PubMed and Google

Table 1: Follow-on biologicals that are produced and marketed in Iran

Active substance	Follow-on biologicals		Comparator	Head-to-head studies	Publications
	Trade name	Company		Phase/clinical trial identifier	
Adalimumab	CinnoRA	CinnaGen	Humira	Phase I/NCT03273192 Phase III/NCT03172325	Jamshidi et al. [11, 12]
Bevacizumab	Stivant	AryoGen	Avastin	Phase III/NCT03288987	Rezvani et al. [13]
Epoetin alfa	PDpoetin	Pooyesh Darou	–	–	Javidan et al. [14]
Epoetin beta	CinnaPoietin	CinnaGen	Eprex	Phase III/NCT03408639	Azmandian et al. [15]
Etanercept	Altebrel	AryoGen	Enbrel	Phase I/NCT03273088 Phase III/IRCT201206266302N3	
Factor VIIa	AryoSeven	AryoGen	Novoseven	Phase III/IRCT201104266302N1 Phase III/IRCT201202106302N2	Faranoush et al. [16, 17]
Factor VIII	Safacto	Saman Daroo 8	Xyntha	Phase III/IRCT2014101218870N2	Abolghasemi et al. [18]
Filgrastim	PDgrastim	Pooyesh Darou	–	–	
	Tinagrast	AryaTina Gene	Neupogen	Phase III/IRCT2013062613776N1	
FSH recombinant	Cinnal-f	CinnaGen	Gonal-f	Phase III/IRCT201011155181N1	
Interferon alfa-2b	PDferon-B	Pooyesh Darou	–	–	
Interferon beta-1a (IM)	CinnoVex	CinnaGen	Avonex	Phase I/NCT03614715 Phase III/IRCT138711281696N1	Nafissi et al. [19]
Interferon beta-1a (SC)	ReciGen	CinnaGen	Rebif	Phase III/IRCT201112201859N3	
Liraglutide	Melitide	CinnaGen	Victoza	Phase III/NCT03421119	
Pegfilgrastim	PDlasta	Pooyesh Darou	PDgrastim	Phase III/IRCT20190504043465N1 Phase III/IRCT2015072623349N1	
	PegaGen	CinnaGen	–	Phase III/IRCT201205279875N1	
Rituximab	Zytux	AryoGen	MabThera	Phase III/IRCT201305296302N5	Toogeh et al. [20]
Somatropin	CinnaTropin	CinnaGen	Norditropin	Phase III/NCT03223025 Phase III/IRCT20150303021315N12	
	PDGrowth	Pooyesh Darou	–	–	
Teriparatide	CinnoPar	CinnaGen	Forteo	Phase III/IRCT138810121414N5	Tabatabaei-Malazy et al. [21]
Trastuzumab	AryoTrust	AryoGen	Herceptin	Phase I/CTRI/2019/03/018218 Phase III/NCT03425656	Farmahini Farahani et al. [22]

FSH: follicle-stimulating hormone, recombinant.

Scholar search was also conducted to find related scholarly articles. The descriptive search terms selected to retrieve data from online sources included the *brand name*, *company name*, *generic name*, *biosimilar*, *clinical trial registration identifier*, and *Iran*. The basic Boolean operator "AND" was used to combine the search terms in various ways in an effort to narrow down search results. Several articles were found using the snowball method by referring to article's bibliography to pinpoint other relevant articles. In addition, information regarding marketing approval date, brand name and pipeline products of the companies were gathered through referring to reliable pharmaceutical, organizational and governmental sites, as well as via Google search in both English and Persian.

The information regarding pharmaceutical products sales was obtained from IFDA database. This database, which is updated annually, compiles information from all the pharmaceutical wholesale and distribution companies in Iran. The information includes the generic and brand name, dosage form, administration route, producer company, sales volume, and value. The proportion of healthcare spending on biotechnological therapeutics was calculated by dividing total sales of biotechnological products by the total sales of pharmaceutical products in Iran. By identifying the originators and follow-on biologicals for each molecule in the database, the total number of units sold (sales volume) and the total sales (sales value) of biotechnological products were obtained for follow-on biologicals and originators. Also, by determining the finished product producer, the share of domestic production and imported products was calculated in terms of sales volume and sales value. The compound annual growth rate (CAGR) was calculated during the 2013–2018 period. Since most biotechnological therapeutics were available in different potencies, the number of units sold was converted into a specific potency for each molecule (unified sales volume). The unit price was obtained by dividing the sales value by sales volume for each product. All the sales values and unit prices were converted into United States Dollar (USD), based on the average annual exchange rates provided in the customs administration of Iran (IRICA) website.

The actualized and potential cost savings associated with using follow-on biologicals were calculated using two scenarios. The actualized cost saving was determined by subtracting the total sales value of the molecule (originator and biosimilar/follow-on biological) from the product of multiplication of total sales volume of the molecule (originator and biosimilar/follow-on biological) in originator's unit price. The potential cost saving that could be realized by using follow-on biologicals instead of originators was calculated by subtracting the product of the sales volume of originators in the unit price of the biosimilar/follow-on biological by year (if such an option was available that year) from the product of total sales volume (originator and biosimilar/follow-on biological) in the originator's unit price.

The quantitative data were analysed using Microsoft Excel 2016 (Microsoft Corporation, USA).

Results

At the time of writing, 21 follow-on biologicals are produced and marketed in Iran, see Figure 1.

These products are related to 17 different reference products. Information regarding these follow-on biological products, including details of head-to-head studies with reference products, and their related publications, is summarized in Table 1.

The total biologicals market in Iran reached approximately US$745 million in 2018 (6-year CAGR = 21.51%). The proportion of healthcare spending on biologicals was 13.5% in 2018 (5-year CAGR = 1.38%).

In 2018, follow-on biologicals comprised approximately 47.2% of the total sales value of biotechnological therapeutics, up from 35.2% in 2013 (6-year CAGR = 28.6%). Despite demonstrating an upward trend (6-year CAGR = 16.64%), the proportional annual sales value of originators compared to the total sales value of biotechnological therapeutics decreased from 64.8% in 2013 to 52.8% in 2018, see Figure 2A. Conversely, in terms of the sales volume (number of units sold) the 6-year CAGR of follow-on biologicals (15.74%) was lower than the originators (43.49%). The proportional sales volume of follow-on biologicals in 2018 decreased to 34.6% from 60.7% in 2013. While originators proportional sales volume reached to 65.5% in 2018 up from 39.3% in 2013, see Figure 2B.

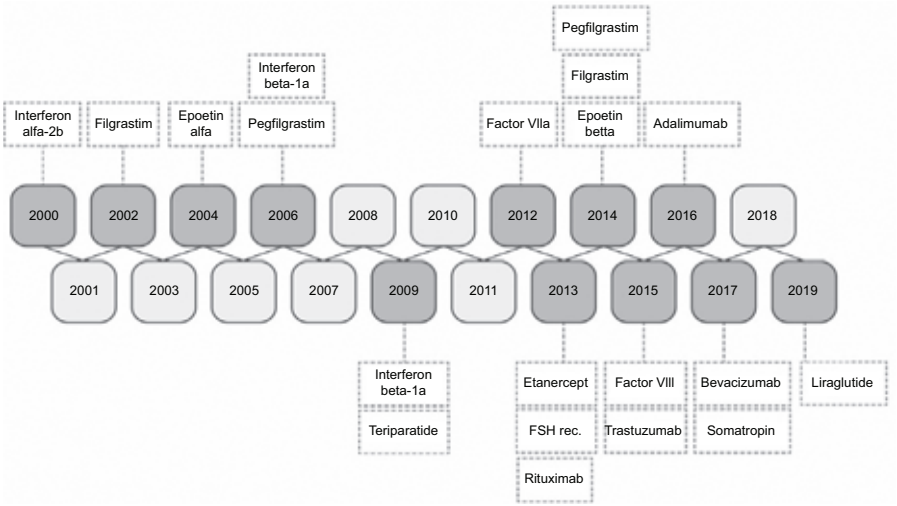
As is the case for originator products, some follow-on biologicals used in Iran are imported from other countries. Figure 3 represents the proportional share of the domestic production or import of the biotechnological therapeutics in Iran, in terms of sales value, see Figure 3A and sales volume, see Figure 3B. In 2018, 42.5% of the follow-on biologicals in the Iranian pharmaceutical market were produced domestically, up from 27.8% in 2013 (6-year CAGR = 28.86%). The proportional sales value of the imported products decreased from 72.2% in 2013 to 57.5% in 2018, despite having a positive 6-year CAGR of 16.64%, see Figure 3A. The 6-year CAGR of domestic products (15.29%) was lower than that for imported products (40.56%) with respect to sales volume. The proportional sales volume of domestic products declined from 53.2% in 2013 to 29.7% in 2018. While the proportional sales volume of the imported products reached 70.3% in 2018, up from 39.3% in 2013, see Figure 3B.

From 2013 to 2018, IFDA priced the follow-on biologicals on average at 54.3±17.8% (mean ± standard deviation) of the originators' price. during this time, the price of follow-on biologicals was 12%–78% lower than the originators.

The actualized cost saving associated with using follow-on biologicals has increased in recent years, with a 6-year CAGR of 8.91%, see Figure 4. The significant increase in cost saving in 2017 and 2018 has been mainly driven by an increase in the use of rituximab, adalimumab and trastuzumab follow-on biologicals. The potential cost-saving associated with using follow-on biologicals is also shown on Figure 4. The proportion of actualized cost saving to the potential cost saving was 82.68% on average. This means that it is possible to increase the uptake of follow-on biologicals and benefit from their associated cost savings.

As summarized in Table 2, several biosimilar candidates are under development in Iran. They may be granted marketing authorization in the future if they provide satisfactory comparative efficacy

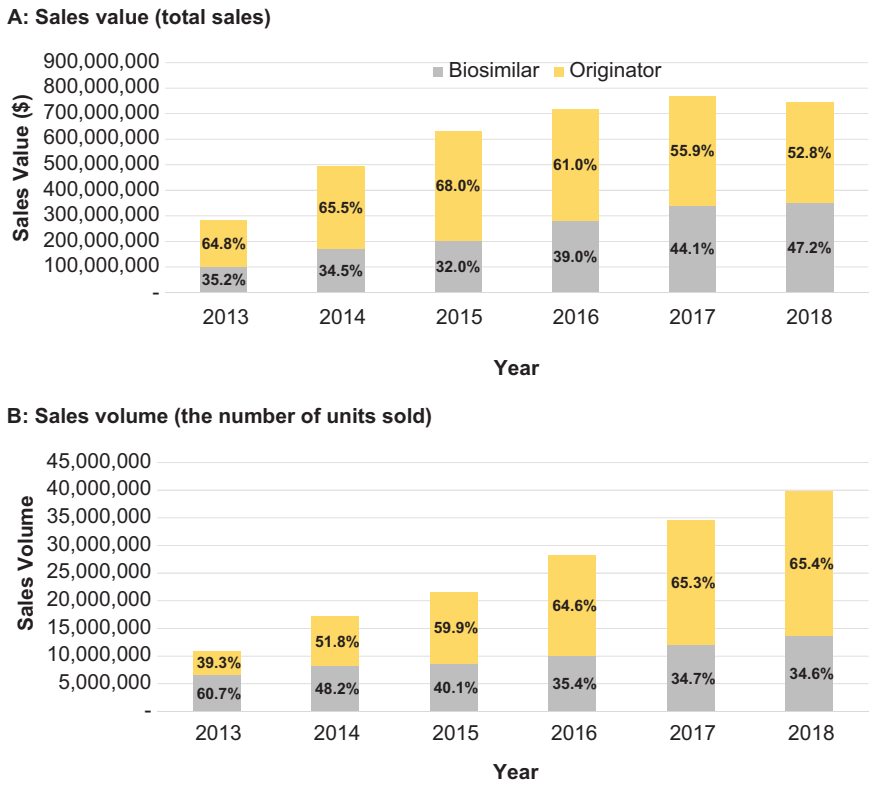
Figure 1: Marketing authorization of follow-on biologicals produced in Iran



The dark grey boxes denote the year in which marketing authorization was granted to a follow-on biological produced in Iran.

FSH rec: follicle-stimulating hormone, recombinant.

Figure 2: The share of follow-on biologicals versus originators from biotechnological therapeutics in Iran



The term biosimilar in Figures 2A and 2B represent both biosimilars and follow-on biologicals

CAGR: compound annual growth rate.

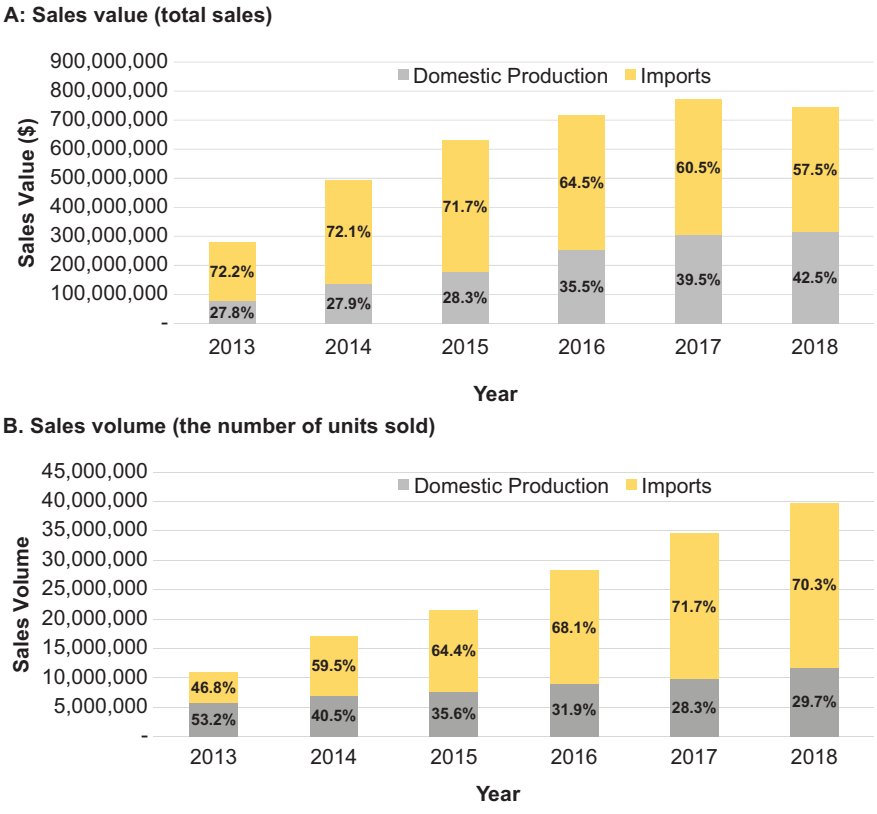
and safety results. These are biosimilar candidates for aflibercept, alteplase, cetuximab, denosumab, ocrelizumab, omalizumab, peginterferon beta-1a, pertuzumab, and tocilizumab. These biosimilar candidates are mostly monoclonal antibodies used to treat several life-threatening and debilitating conditions.

Discussion

In the present study, the current status of follow-on biologicals in the Iranian market has been investigated by evaluating their ongoing and completed clinical trials. The article has highlighted that, as some products were approved as follow-on biologicals prior to the issuance of IFDA biosimilar guidance, they have not registered or published head-to-head clinical trials against the reference product. As biosimilars offer exciting therapeutic opportunities for healthcare authorities and patients in Iran in the future, all efforts should be made to ensure that true biosimilars are approved that are highly similar to reference products in terms of quality, efficacy and safety.

The annual national wholesale data on pharmaceutical products suggests that the use of biologicals in Iran has increased considerably in recent years in terms of both sales value and sales volume. However, there was only a slight increase in the proportional share of biotechnological therapeutics with respect to the total medicines market (from 12.7% in 2013 to 13.5% in 2018). According to the IQVIA reports, in 2018, biologicals represented 29.9% of the total medicines market in Europe with a CAGR of 1.93%. In the US, 42% of healthcare costs for medicines were devoted to biotechnological therapeutics (5-year CAGR = 8.78%) [23, 24]. Despite an increasing trend in the use of biological therapeutics in Iran, the proportion of healthcare expenditure on biotechnological therapeutics here is considerably lower than in Europe and the US, see Figure 5. The unwillingness of the Iranian healthcare authorities to add new molecules, specifically biotechnological therapeutics, to Iran's national drug list may be a contributing fac-

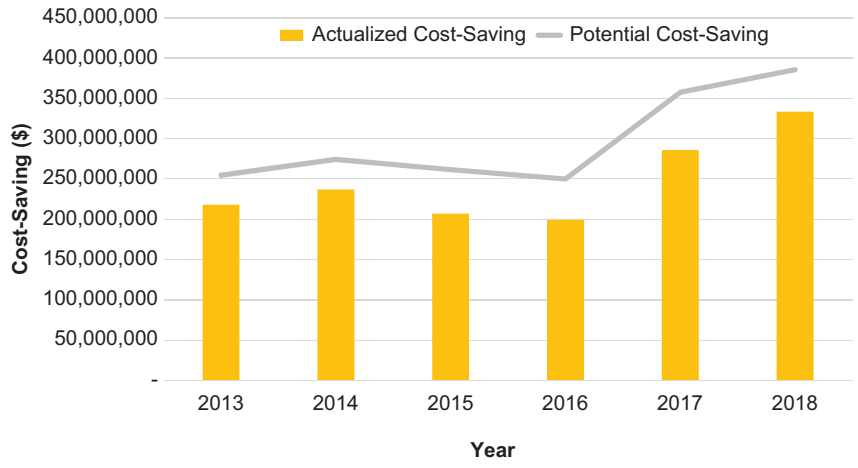
Figure 3: The share of domestic production/imports of the biotechnological therapeutics in Iran



Imported biosimilars and follow-on biologicals were included in the 'Imports' category on Figures 3A and 3B.

CAGR: compound annual growth rate.

Figure 4: The actualized and potential cost saving through using follow-on biologicals instead of originators in Iran



Actualized cost saving: [total sales volume of the molecule (originator and follow-on biological)*originator's unit price]-total sales value of the molecule (originator and follow-on biological)
Potential cost-saving: [total sales volume (originator and follow-on biological) in the originator's unit price]-[the sales volume of originators*the unit price of follow-on biological (if that option was available that year)]

tor to the comparatively low uptake of these products. This issue may stem from the greater cost associated with using biotechnological therapeutics and connected increase in healthcare burden. The importance of biotechnological therapeutics in the treatment of a wide range of severe and chronic diseases, together with escalating healthcare costs highlights the importance of using biosimilars as a lower-priced substitute for originator biologicals. The use of biosimilars can significantly reduce healthcare expenditure on biotechnological therapeutics. According to an evaluation by Mulchay et al. [25], it was projected that the emergence of biosimilars would reduce US healthcare spending by US$54 billion in 2026. The proportional difference in the use of biotechnological therapeutics in Iran compared to other regions might also be explained by various different pricing strategies adopted for biosimilars and follow-on biologicals. For example, in Europe, biosimilar developing companies have to price their products at least 30% lower than the originator [4]. According to a recent review of literature, the price difference between biosimilar developing companies and their originators ranges between 15%–30% [4]. While in Iran, from 2013 to 2018, follow-on biologicals' price has been approximately 54.3% of originators.

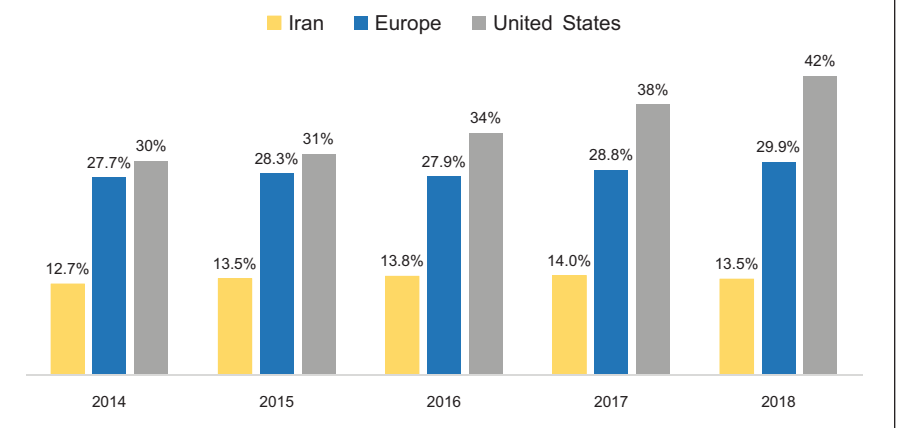
In recent years, the share of follow-on biologicals produced domestically has increased considerably in terms of sales value. At the same time, the trend of the increase in sales volume was moderate compared to sales value. This might suggest that pharmaceutical and biotechnology companies in Iran have been more willing to invest in high-value, low-volume production. This tendency is also apparent in the biosimilar candidates in the companies' pipelines. The majority of these products are monoclonal antibodies that usually have a high unit price.

The introduction of follow-on biologicals has offered significant cost saving for the Iranian healthcare system as actualized cost saving through follow-on biologicals use reached over US$300 million in 2018. These savings were influenced by the rate of follow-on biologicals use and the difference in unit price between follow-on biologicals and originators.

Table 2: Follow-on biological candidates that are under development in Iran

Active substance	Labelled Indication(s)	Company	Comparator	Head-to-head studies Phase/clinical trial identifier
Aflibercept	Age-related macular degeneration Diabetic macular oedema Diabetic retinopathy Macular edaema	CinnaGen	Eylea	IRCT20150303021315N14
Alteplase	Acute ischemic stroke Pulmonary embolism ST-elevation myocardial infarction	Arena Life Science	Actilyse	Phase III/IRCT20190729044366N1
Cetuximab	Colorectal cancer, metastatic Head and neck cancer, squamous cell	CinnaGen	Erbitux	Phase III/IRCT2017110821315N10 Phase III/NCT03391934
Denosumab	Androgen deprivation therapy-induced bone loss in males with prostate cancer Aromatase inhibitor-induced bone loss in females with breast cancer Osteoporosis	AryoGen	Prolia	Phase III/NCT03293108 Phase III/IRCT2017020521315N9
Ocrelizumab	Multiple sclerosis, relapsing or primary progressive	CinnaGen	Ocrevus	Phase III/IRCT20150303021315N13
Omalizumab	Asthma Chronic idiopathic urticaria	CinnaGen	Xolair	Phase III/ IRCT20150303021315N20
Peginterferon beta-1a	Multiple sclerosis, relapsing	CinnaGen	CinnoVex	Phase III/IRCT201612306135N8
Pertuzumab	Breast cancer, metastatic Breast cancer, early (adjuvant, neoadjuvant)	CinnaGen	Perjeta	Phase III/IRCT20150303021315N11
Tocilizumab	Cytokine release syndrome Giant cell arteritis Polyarticular juvenile idiopathic arthritis Rheumatoid arthritis Systemic juvenile idiopathic arthritis	AryoGen	Actemra	Phase III/IRCT20150303021315N9

Figure 5: The proportion of healthcare spending on biotechnological therapeutics from the total medicines market



Source: Europe and US data were obtained from IQVIA reports.

Rituximab, adalimumab and trastuzumab were the main drivers of the significant cost saving in 2017 and 2018. This figure is likely to increase in the upcoming years due to the market entry of other biosimilars/follow-on biologicals currently under development.

The pharmaceutical landscape of Iran has changed significantly in the past 20 years. In recent years, some biopharmaceutical companies in Iran (CinnaGen and AryoGen) have endeavoured to move towards regulated markets, such as Europe. As a preliminary step, they have acquired EU-good manufacturing practice (GMP), the certificate of GMP, that has been published on EMA's database [6, 7]. In 2017, CinnaGen initiated pharmacokinetics (PK) and pharmacodynamics (PD) studies of its interferon beta-1a biosimilar (CinnoVex®) in Finland [8]. As such, it seems that by the development of high-quality biosimilars bolstered by satisfactory non-clinical and clinical studies, Iranian pharmaceutical companies can expand their presence in regulated and semi-regulated markets.

Conclusion

Although biotechnological therapeutics have offered life-saving therapies to many critical diseases, their proportional uptake in Iran has remained constant in recent years. It seems that healthcare authorities can improve patients' access to these medicines through promoting the use of biosimilars/follow-on biologicals instead of costly originators once their quality, safety, and efficacy have been ensured. The significant cost saving associated with using biosimilars/follow-on biologicals can be allocated to helping new biotechnological medicines to be included in Iran's drug list.

Competing interests: Farhang Rezaei and Nassim Anjidani work in the medical department of Orchid Pharmed company which is in collaboration with AryoGen Pharmed and CinnaGen companies with respect to conducting clinical trials.

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