*Review Article*

# Iranian biopharmaceutical companies: products and services

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## ABSTRACT

Biopharmaceuticals are drugs or vaccines, developed via biotechnology process. Biopharming is production of pharmaceuticals in live organisms. Different platforms can be used for biopharmaceuticals production. Prokaryotes, yeast, fungi, insect cells, mammalian cells, transgenic plants, and transgenic animals can be used for production of recombinant proteins.

Genentech, the first biotech company, gained FDA approval for recombinant human insulin in 1982. Nowadays, more than 200 approved biopharmaceuticals have been brought to market. The world's top

pharmaceutical companies are producing biopharmaceuticals in their own factories. In Iran, there are twenty-three biopharmaceutical companies that produce about twenty-five biopharmaceutical products. Most of them formulate their products using active ingredients of other countries. Pooyesh darou, Cinnagen, Pasteur institute of Iran, Aryogen biopharma, and Aryatinagen produce active ingredients of drugs, and formulate biopharmaceuticals. Iranian biopharma companies will be able to produce more and better biopharmaceuticals in near future.

***Keywords:*** Biopharmaceuticals, biopharming, iranian biopharma companies, active ingredients, formulation

## INTRODUCTION

Recombinant human insulin, the first biopharmaceutical, was approved by FDA in 1982 [1, 2]. Another biopharmaceutical product was recombinant human growth hormone that was produced in Genentech for the first time and approved by FDA in 1985. One year later, Chiron, obtained FDA approval for recombinant hepatitis B vaccine. FDA approved interferon, as first anticancer biopharmaceutical and then Muromonab, anti CD3 antibody. FDA approved also Alglucerase, in 1991 and Rituximab in 1997. Other biopharmaceuticals, Avastin (a recombinant monoclonal antibody) and human papillomavirus vaccine were approved in 2004. Influenza vaccine, the first plant–based vaccine, was produced by genetically engineered tobacco leaves and an anti AIDS biopharmaceutical was produced in 2011. In 2012 Flucelvax, the first cell culture-derived vaccine was obtained [3, 4].

Etanercept, Infliximab, Bevacizumab, Rituximab, Adalimumab, Epoetin α, Trastuzumab, Insulin glargin, Peg-filgrastim and Darbopoetin α were best-selling biotech protein drugs [5].

In 2013, 907 biotech drugs and vaccines were in development process for more than 100 life-threatening diseases. Two hundred thirty-eight of them were for cancer. One hundred seventy six of them were for treatment of infectious diseases, and 71 of them were for treating autoimmune diseases, 58 of them were for treating cardiovascular diseases, and some of them were for treating AIDS [6-8].

Different live organisms can be used for producing biopharmaceuticals. There are some challenges for recombinant proteins production [9, 10]: (a) time for genetic engineering (convert gene to protein), (b) capital investment, (c) cost per each gram of raw material, (d) expression level, (e) cost to produce each gram protein, (f)

product localization, (g) protein folding, (h) N/O linked glycosylation, (i) safety concerns of products.

## The world's top pharmaceutical companies

The biggest pharmaceutical companies in drug market are Johnson and Johnson, Pfizer, Glaxo smith klein, Roche, Sanofi, Novartis, Astra Zeneca, Abbot, Merck, Wyeth, Bristol-myers squibb and Eli lilly. Most of these companies produce biopharmaceuticals [11, 12].

## Iranian biopharmaceutical companies

As table 1 show, 23 Iranian biopharma companies are producing 25 biopharmaceuticals. Pooyesh darou, and Exir are producing eight biopharmaceuticals and Cinnagen is producing seven biopharmaceuticals. Aryogen biopharma, Pasteur Institute of Iran and Daroupakhsh are producing six biopharmaceuticals and Osveh, Actoverco and Samen are producing three biopharmaceuticals. Ronak pharmaceuticals, Zistdaru danesh and Recombinant pharmaceuticals are producing two biopharmaceuticals and Kawsar biotech, Behin tamin roozamad, Saman daroo 8, Varian pharmed, Aryatinagen, Kharazmi, Loghman, Aburaihan, Tadbir kalay-e Jam and Shifa pharmed each one are producing one biopharmaceutical [13]. Most of these companies import active ingredients from Argentina, Australia, and other countries and formulate their biopharmaceuticals. However, Pooyesh darou, Cinnagen, Pasteur Institute of Iran, Aryogen biopharma and Aryatinagen produce active ingredients. Iranian biotech companies produce active ingredient from *E. coli* fermentation and mammalian cell culture for their products.

**Table 1.** Iranian biopharma companies and their biopharmaceuticals

| Manufacturing Company | Drug (generic name) | Commercial name | Situation |
|---|---|---|---|
| **Pooyesh Daru** | Erythropoetin | Pdpoetin | Approved for distribution |
| | Filgrastim | PD-grastim | Approved for distribution |
| | Gonadorelin | | Approved principally |
| | Interferon α-2b | PD-feron | Approved for distribution |
| | PEG-Interferon α-2a | Pegaferon | Approved for distribution |
| | Peg-Filgrastim | | Clinical phase |
| | PTH | | Approved principally |
| **Exir** | Erythropoetin | Exipoetin | Approved for distribution |
| | Insulin aspart | | Approved for distribution |
| | Insulin | | Approved for distribution |

| | | | |
|---|---|---|---|
| | Insulin Pen | | Approved principally |
| | Interferon γ | Gamma-Immurex | Approved for distribution |
| **Exir** | Rituximab | | approved principally |
| | Somatropin | Norditropin | Approved for distribution |
| **Cinnagen** | Erythropoetin | Cinapoetin | In registration process |
| | Follitropin α | Cinnal-F | Clinical phase |
| | Interferon β 1a (44mg) | Recigen | Approved for distribution |
| | Interferon β 1b | Cinnaferon | Clinical phase |
| | Interferon β-1a (30mcg) | cinnovex | Approved for distribution |
| | Peg-Filgrastim | | Clinical phase |
| | PTH | | Finished clinical phase |
| **Aryogen biopharma** | Bevacizumab | | In registration process |
| | Etanercept | | Approved for distribution |
| | FactorVII | Aryoseven | Approved for distribution |
| | Interferon β 1b | Recferon | In registration process |
| | Rituximab | | Clinical phase |
| | Trastuzumab | | In registration process |
| **Pasteur Institute of Iran** | Erythropoetinα | Pasteopoetin | Approved for distribution |
| | Insulin | Insulin | approved principally |
| | Rituximab | | approved principally |
| | Streptokinase | Pasteokinase | In registration process |
| **Darou Pakhsh** | Erythropoetin | | approved principally |
| | Filgrastim | | approved principally |
| | Insulin | Insulin | |
| | Interferon α-2b | | approved principally |
| | PEG-Interferonα-2a | | approved principally |
| | Somatropin | | In registration process |
| **Osveh** | Erythropoetin | Osvehpoetin | Approved for distribution |
| | Follitropin α | | approved principally |
| | Reteplase | | In registration process |
| **Actoverco** | Interferon β 1a (44mg) | Actorif | Clinical phase |
| | Interferon β-1a (30mcg) | Actovex | Clinical phase |
| | Rituximab | | Approved principally |

| | | | |
|---|---|---|---|
| | Somatropin | Samtropin | Approved for distribution |
| **Ronak pharma** | Insulin | | Approved for distribution |
| | Rituximab | | Approved principally |
| **Zist daru danesh** | Interferon β 1a(44mg) | | Approved principally |
| | Interferon β 1b | Ziferon | Approved for distribution |
| **Recombinant pharmaceuticals** | Erythropoetin | Epolyrec | Approved for distribution |
| | PTH | | Approved principally |
| **KBC** | Anti-Timocyte glubolin | | Approved principally |
| **Behin tamin roozamad** | Filgrastim | | Clinical phase |
| **Saman daroo 8** | Factor VIII | | Clinical phase |
| **Varian pharmed** | Filgrastim | | Clinical phase |
| **Aryatinagen** | Filgrastim | | Clinical phase |
| **Kharazmi** | Insulin | | Approved for distribution |
| **Loghman** | Insulin | | In registration process |
| **Aburaihan** | Insulin | | Approved principally |
| **Tadbir Kalay-e Jam** | Rituximab | | Approved principally |

Pooyesh darou, as one of the most important Iranian biopharma companies, is a private company and it has been created in 1997. It is the first Iranian company that used genetic engineering modified bacteria and cells, by bacterial fermentation and cell culture facilities. This company is producing Reteplase, PTH, Gonadorelin, and two types of alfa-interferons. It is producing erythropoietin, filgrastim, and PEGylated formulations. It is performing protein sequencing, N-terminal sequencing of proteins and *in vitro* assays for analysis of its own products [14].

Exir is one of the largest Iranian pharmaceutical companies. This company has been founded in 1984. It is producing pharmaceuticals and biopharmaceuticals, medical devices for home usages and food complements. Three different types of insulin are being produced in this company [15].

Cinnagen is one of the largest biopharma companies in Iran and the Middle East. This private company has been founded in 1994. This company is exporting its products to 22 countries. Enzymes, molecular biology reagents and PCR kits, monoclonal antibodies for blood typing, biopharmaceuticals, recombinant

proteins, monoclonal antibodies and biosimilars are products of this company. Three types of beta-interferons, Cinnal-F (Follitropin α), Cinnarelin (GnRH-A), PTH, Pegagen (Peg-Filgrastim), Reditux (Ritoximab), Cinnapoetin (Erythropoetin), Cinnafact (Buserelin), Cinnarelin and Cinnotal (buserelin acetate) are being produced in this company [16].

Aryogen biopharma, a private biopharma company, was founded in 2009. This company is now producing three kinds of monoclonal antibodies (etanercept, rituximab, and trastuzumab), and three other recombinant proteins based biopharmaceuticals. Factor VIIa, Aryoseven, is being produced in this company. Totally, biopharmaceuticals used to treating blood and breast cancers, autoimmune and blood disorders are products of this company [17].

Daroupakhsh is one of the largest Iranian biopharmaceutical companies that have been founded in 1956. Investor of this company is tamin pharmaceutical investment company (TPICO) with 74.5% share contribution. This factory is working with Allen, Hanburys and Glaxo companies [18].

Pasteur institute of Iran has been founded in 1989. Recombinant products, antigens and antibodies, injection solutions, lab animals, vaccines, diagnostic kits, biotechnology unit and intravesical BCG are products of this company. Biological, microbial tests and electrophoresis, physicochemical, immunochemical, and animal tests, molecular assays, and environmental assays are being done in Pasteur institute of Iran [19].

Osveh, was founded in 1966 [20]. This company is now producing three biopharmaceuticals. Samen pharmaceutical factory was importing growth hormone active ingredient from Australia [21]. Actoverco was founded in 1969 as a pharmaceutical company and is producing two types of interferons. This company is providing its active ingredient from Argentina (Omega biotech) [22].

Ronak pharma, Zistdaru danesh and recombinant pharmaceuticals are producing recombinant drugs. Ronak pharma factory is importing blood products plus peptide and is producing lyophilized pharmaceuticals [23]. Zistdaru danesh is producing two interferons [24]. Recombinant pharmaceuticals and Ronak pharma were founded in 2000 and 2002, respectively. Ronak pharma is completing production of lyophilized products, rituximab, ronulin, insulin isophan (NPH) and anticancer drugs. Recombinant pharmaceutical is completing production of varigrastim, PTH, protein D, and recombinant biosimilar of human thrombin α. This company is producing erythropoetin. Production of recombinant products and importing are activities of this company [25].

Kawsar biotech was founded in 2006. Services of this company are sequencing, oligo synthesis, and fragment analysis. This company is producing cell culture media, PCR related products, DNA banking card, kits, lab instruments and biopharmaceuticals [26].

Aryatinagen is producing a biopharmaceutical (Tinagrast) and its services are gene cloning and vector construction. This company is located in Gorgan of Golestan [27].

Zahravi, Loghman, Sobhan [28] and Aburaihan [29] are public companies which are producing only one biopharmaceutical. Zahravi and Sobhan are located in Tabriz and Rasht respectively. Factory of two other companies are located in Tehran. Zahravi is producing soft gel capsules, biotech products and immunosupressor agents [30] and Loghman is producing antibiotic pharmaceuticals [31]. Behin tamin roozamad, Shifa pharmed [32], Varian pharmed, Kharazmi, Tadbir kalay-e Jam [33] and Saman daroo [34] are private companies with only one biopharmaceutical production. Varian pharmed was founded in 2009 and now is producing pharmaceuticals, medical devices and lab products [35]. Kharazmi, was founded in 1963 for production of anticancer pharmaceuticals [36].

## Iranian biopharmaceutical importer companies

Table 2 shows, some of Iranian biopharma companies which import these drugs. Kawsar biotech, Zistdaru danesh, Actoverco, Sobhan and Cinnagen produce biopharmaceuticals. Novo nordisk pars, akbarieh and rozhin daru, with 6, 5, and 3 importing biopharmaceuticals, respectively have the most share in importing biopharmaceuticals. Darmanara, jahan behbood, behestan darou, Cobel darou, omid darou salamat, shafayab, are importing two biopharmaceuticals. Actoverco, Zistdaru danesh, Cinnagen, Sobhan, Vitan pharma and Kawsar biotech are importing only one biopharmaceutical. The Iranian biopharma importer companies are listed in table 2.

**Table 2.** Iranian biopharma importer companies

| Importer company | Manufacturer company | Drug (generic name) | Drug (brand name) | Situation |
|---|---|---|---|---|
| **Novo nordisk pars** | Novo nordisk | Factor VII | Novoseven | Approved for distribution |
| | | Glucagon | GlucaGen | |
| | | Insulin NPH | Insulatard | |
| | | Insulin aspart | Novorapid flexpen | |
| | | Insulin aspart | Novorapid vial | |
| | | Insulin aspart & protamine | Novomix | |

| | | Insulin Pen | Actrapid | |
|---|---|---|---|---|
| **Importer company** | **Manufacturer company** | **Drug (generic name)** | **Drug (brand name)** | **Situation** |
| **Novo nordisk pars** | Novo nordisk | Insulin Biphasic | Mixtard | |
| | | Somatropin | Nordilet (pen) | |
| **Akbarieh** | Roche | Bevacizumab | Avastin/100 mg | Approved for distribution |
| | | Filgrastim | Neupogen | |
| | | Interferon β 1b | Betaferon | |
| | | PEG-Interferon α-2a | PEGasys/50 | |
| | | Trastuzumab | Herceptin/150,440 | |
| **Ruzhindarou Ruzhindarou** | Merck serono | Follitropin alfa | Gonal-f | Approved for distribution |
| | Merck serono | Chorinic Gonadotropin | ovitrelle | |
| | Eli Lilly | Cetuximab | Erbitux | In registration process |
| **Darmanara** | CSL | Strepte kinase | Streptase | Approved for distribution |
| | Biofacter | Strepte kinase | | |
| **Jahanbehbood** | | Erythropoetin | Eprex | Approved for distribution |
| | wyeth | Etanercept | Enbrel | |
| **Behestandarou** | Sandoz | Filgrastim | Zarzio | Approved for distribution |
| | Janssen | Infliximab | Remicad | |
| **Cobeldarou** | Sonofiaventis | Insulin Glargine | lantus | Approved for distribution |
| | | Interferon β-1a (30mcg) | Avonex | |
| **Omiddarousalamat Omidsalamat** | Dawoong | Somatropin | Caretropin 22.5IU | Clinical phase |
| | LG | Follitropin alfa | Follitrop | Approved for distribution |
| **Shafayab** | | PTH | Forteo | Approved for distribution |
| | | Interferon β 1b | Extavia | |
| **Actoverco** | Roche | Reteplase | | In registration process |
| **Zistdarudanesh** | BSV | Strepte kinase | | Approved for distribution |
| **Cinnagen** | Dr.Reddy | Rituximab | Reditux | Clinical phase |
| **Sobhan** | Roche | Rituximab | Mabtera | Approved for distribution |
| **Vitan pharmed** | wockhardt | Insulin | Vitasulin | In registration process |
| **KBC** | | Interferon β 1a (44mg) | Rebif | Approved for distribution |

## DISCUSSION

Iranian factories recently were not able to produce active ingredients of small molecule pharmaceuticals, but now Iranian biopharma companies are producing more than 20 large and complex molecules of biopharmaceuticals which are the most popular and the best-selling of world biopharmaceuticals. These companies produce variety biopharmaceuticals, these

pharmaceuticals are often being produced in Ecoli. Iranian companies are able to carry out necessary controls such as N-terminal sequencing, protein sequencing and clinical and lab assessments.

The most complex world biopharmaceuticals are some of antibodies that essentially require to be produced in mammalian cells [37]. Iranian companies have managed to produce a number of these highly complex molecules. One of the most important steps of pharmaceutical production is the active ingredient production step [9, 10]. This step has been done on a number of Iranian biopharmaceuticals. One of the most time-consuming and the most expensive steps is the purification step [9, 10]. Quality, quantity and clinical controls are very important steps which have been performed in Iranian biopharma companies.

With all progresses in Iranian pharmaceutical biotechnology industry, Iranian companies are following top global pharmaceutical companies in biopharma production. World top companies are leading in this context because of their enormous investments. Biosimilar production will help Iranian Biopharma companies to improve their capabilities [38]. Iranian Biopharma companies will be able to produce more and better biopharmaceuticals with more government supports.

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