

Creation of a high-tech biopharmaceutical complex for the production of genetically engineered medicinal products in Pushchino of the Moscow region.

BIORAN Project — from import to export of insulin

Project concept	▪ BIORAN is a Project to create a high-tech biopharmaceutical complex for the production of genetically engineered antidiabetic medicinal products in the Pushchino science city of the Moscow region.
Project initiators	▪ The Project is implemented by Project company JSC «Research and Production Corporation BIORAN».
Project technologies	▪ The Project technology is based on the initial development of the academicians M.M. Shemyakin – Yu.A.Ovchinnikov Institute of Bioorganic Chemistry of the Russian Academy of Sciences (IBCh of the RAS). At the same time, the Project technology, the range and quality of products are radically improved in accordance with the latest world achievements in the field of production of insulin and its analogues. It should be noted that the improvements made by the Western specialists belong to the JSC RPC BIORAN on the basis of the right of ownership.
Project objectives and results to be achieved	▪ Creation of large innovative full-cycle production of insulin on the territory of the Russian Federation, from the active pharmaceutical substances (AFS) to finished dosage forms. ▪ Russia's entry into the world's leading manufacturers of insulin pharmaceutical products. The capacity of the project will allow to create production with a share of more than 5% in the world volume of production, and to bring JSC RPC BIORAN to the top 4 world producers. ▪ Foreign insulin products import substitution. The project will allow to fully meet the needs of the Russian market and the Customs Union countries (currently more than 90% of the Russian market is covered by 3 foreign companies: Danish Novo Nordick, Franco-German Sanofi and American Eli Lilly). ▪ Export of high-tech biotechnology products. The capacity of the Project will partially cover the growing needs of foreign markets. ▪ Ensuring drug safety of the state. ▪ Providing the Russian population with modern domestic insulin products, improving the demographic situation. ▪ Creation of new jobs in the perimeter of the complex and in related industries (production of raw materials, infrastructure, logistics, etc.) ▪ addressing demographic issues ▪ Provision of income for all project participants. The project is investment-attractive and cost-effective.

The insulin market in Russia is completely dependent on imports

Bioran

- ✓ Full-cycle manufacturers of the gene engineering insulin can produce up to 30 kg of GEHI substance, but are not certified by GMP and are not competitive both in power and in terms of technology. Experimental production of the IBCh of the RAS has been stopped 2 years ago.
- ✓ There are excessive capacities for production of the finished dosage forms from imported substance, both available and ready for launch in Russia.
- ✓ Major manufacturers of genetically engineered substance (Novo Nordisk, Sanofi-Aventis, Ely Lilly) are reluctant to distribute the substances, preferring to supply finished dosage forms, anticioating loss of technology (including producing strain).

Full-cycle manufacturers of the gene-engineering human insulin

OJSC GEROFARM-Bio (former OJSC National Biotechnology)

- commissioning of the site for the production of GEHI – 2012.
- capacity – 20 million bottles, 5 million cartridges per year (there are plans for expansion).
- the site is located in Obolensk, Moscow region.
- according to the results of 2014, the output is 0.45% of the market capacity = 2. 25 kg.

IBCh of the RAS

- pilot production
- produced and supplied preparations of human gene engineering insulin (trademark INSURAN®) by the order from the Moscow Healthcare Department.
- The production was freezed during the last 2 years

Manufacturers of FDF from imported substance

Novo Nordisk

- the establishment of packaging production was completed in 2014.
- site — industrial park Grabtsevo, Kaluga region.
- the volume of investments — up to 3 billion rubles.

Sanofi-Aventis

- in 2009 acquired 74% of shares of the CJSC Bioton Vostok, Orel.
- Sanofi-Aventis insulin filling was established at the facilities of the JSC Bioton Vostok
- production of the FDF from the imported substance is carried out
- Reaching the design capacity (up to 15 million units of dosage forms) — 2012

JSC "Pharmstandard"

- the company produces FDF from the raw material produced by Diosynth (France) only

LLC "Medsintez Factory"

- currently the company produces FDF from the raw material from Diosynth (France) only, and is experiencing issues with the supply of the substance.
- RUSNANO considered a joint project to organize the production of insulin substance, which was not supported due to the lack of a license

Science – State – Business: on the way to consolidation

- The Project was initiated by the Russian Academy of Sciences (Order of the Presidium of the Russian Academy of Sciences No.: 12300-647 dated September 6, 2006), with the support of the Industrial and Commercial Chamber of the Russian Federation and the Government of the Moscow Region (Order of the GMR No.: 723/29, dated July 31, 2006).

- Biotechnology is among the critical technologies approved by the President of the Russian Federation in 2006 and in the list of priorities of the Concept of long-term socio-economic development of the Russian Federation until 2020 along with nanotechnology and information technology. The technologies for production of insulin and its analogues are particularly complex and have been mastered by a limited number of countries (5-6).

- The strategy of development of the pharmaceutical industry in the Russian Federation "Pharma 2020" is designed to restore the domestic pharmaceutical industry. The government plans to create conditions on the Russian market by 2020 that the products of domestic pharmaceutical companies mainly consisted of innovative drugs.

- At the same time, today in monetary terms, the share of imported medicines is 76%, and only 24% is domestic production. In the physical volume, the situation is reverse: 65% — domestic drugs and 35% — in foreign drugs. This statistics confirms that the Russian pharmaceutical industry produces the single-type nomenclature of cheap medicines in large quantities using the outdated technologies.

- The Project meets the policy of import substitution, which has become critical in the conditions of sanctions imposed by Western countries in 2014.

Институт биоорганической химии

Торгово-промышленная палата Российской Федерации

Правительство Московской области

Concept of long-term socio-economic development of the Russian Federation

"Pharma 2020" events:

- ✓ Localization of high-tech pharmaceutical production in the Russian Federation.
- ✓ Organization of production of high-tech chemical and biotechnological substances in the Russian Federation.
- ✓ Transition of domestic pharmaceutical industrial enterprises to GMP standards
- ✓ Development and production of analogues of imported generic and innovative medicinal products.
- ✓ Ensuring medicine safety of the Russian Federation.
- ✓ Development of new and modification of existing educational and qualification programs to provide the pharmaceutical industry with personnel of a new type.

Key Features of the Project

Project concept	▪ The Project assumes construction of a full cycle biopharmaceutical complex for the production of genetically engineered medicinal products in Pushchino science city of Moscow region. The capacity of the project will allow to create production with a share of more than 5% in the world volume of production, and to bring OJSC RPC BIORAN to the top 4 world producers.
Products	▪ Gene-Engineering Human Insulin (GEHI) ▪ Insulin analogues (long and ultra-short acting insulin)
Design capacity of the complex	▪ 1000 kg/year. GEHI AFS on the production line; ▪ 51 kg/year. GEHI AFS on the pilot production line; ▪ 50 l/year. AFS of the cell cultures; ▪ 3 ml cartridges (GEHI), 84 million/year; ▪ Erythropoietin (epoetin alpha, beta, omega) (GEHI), 1 ml syringes, 300 K/year.
Terms of implementation of the Project	▪ 2021 – commissioning of the first stage into operation with a capacity of 270 kg of the finished dosage forms (FDF) of insulin (Insuran R, 100 IU/ml; Insuran NPH 100 IU/ml; Insuran MIxed 70/30) per year. ▪ 2023 – scale-up of production capacity to 650 kg of insulin (FDF) per year; ▪ 2024 – scale up of production capacity to 1000 kg of insulin FDF and its analogues (Insulin Glargin; Insulin Lispro; Insulin Aspartt) per year.
Project investment	▪ EUR 200 — 250 million (since 2019 to 2021)
Initial Project status	▪ JSC RPC BIORAN has a site with utility lines and legalized sanitary protection zone (SPZ) ▪ Design and construction will be carried out by Linde Engineering Dresden GmbH (Germany) under the EPC contract. ▪ The demand for the substance will be provided by Richter-Helm Biologics (RHB) under the off-take contract

[1] *Product quality will meet or exceed the requirements of the State Pharmacopoeia of the Russian Federation and the EU requirements for insulin and their analogues*

The unique Project technology meets the highest requirements and is protected by patents

- The production process at the Complex is based on the technology of IBCh of the RAS, which is already developed in the Russian bioindustry. The technology was provided by JSC RPC Bioran under the license agreement for the use for the purposes of the Project.
- The technology of IBCh of the RAS, the range and quality of the products planned for production were significantly optimized at the research center of the German biopharmaceutical company RHB by the order from JSC RPC Bioran to meet the requirements of EMA (European Medical Agency) and GMP (Good Manufacturing Practice) standards.
  - ✓ As a result of the complex of works conducted at Richter-Helm Biologics, an optimal production strain was obtained, a cell bank was created and the first part of the technological process (Upstream) was optimized with a significant increase in yield of the hybrid product protein.
  - ✓ Belgian company Shant Laboratories optimized the second part of the process (Downstream) by introducing additional process operations for deep purification of the target product on the basis of the state-of-art development (including the chromatographic stage of purification and enzymatic hydrolysis).
- After optimization, the process of JSC RPC Bioran represents a new high-performance bioprocess for production of recombinant human insulin.
- The rights for improvement belong to JSC RPC Bioran and are protected by 5 own patents.

ИБХ

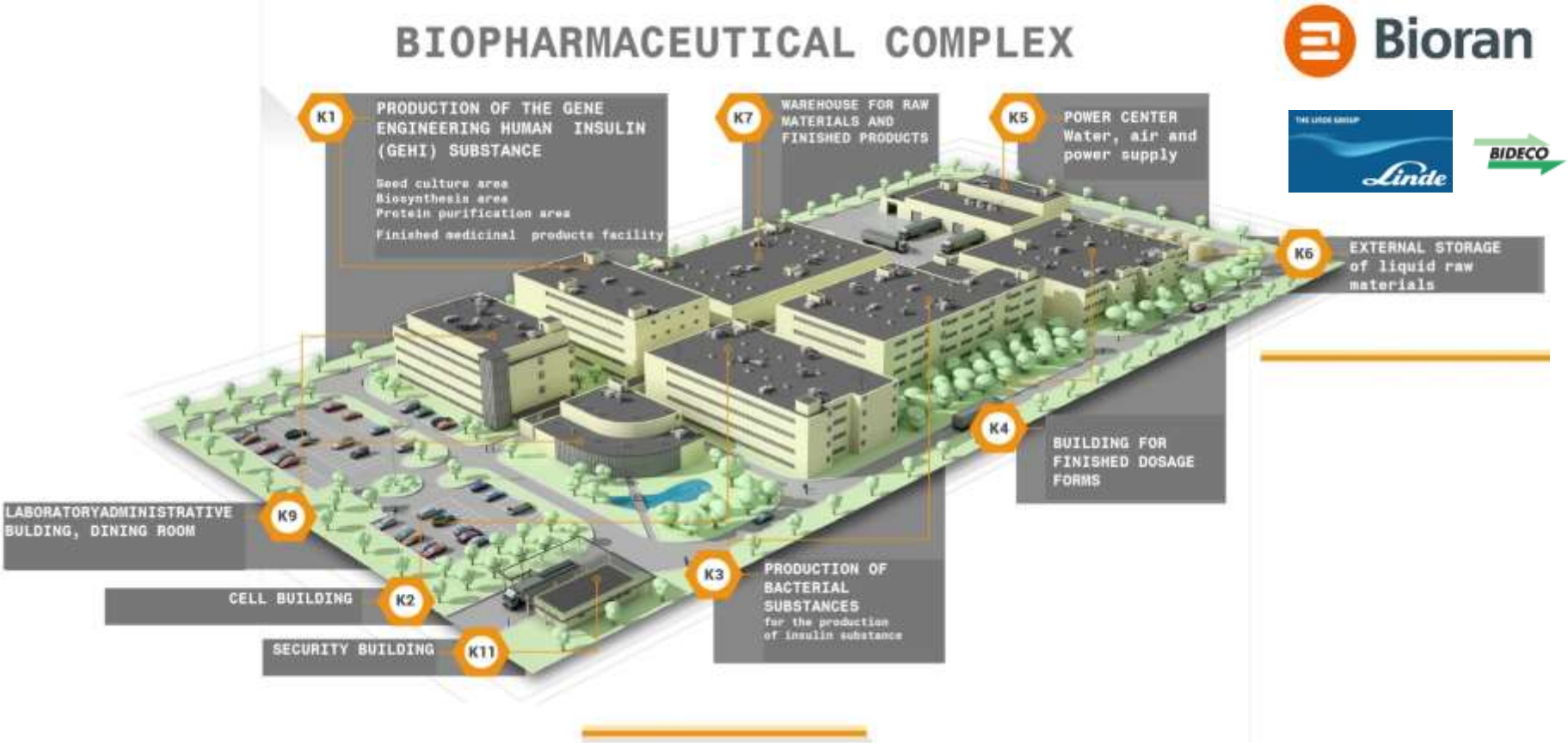
RICHTER-HELM BioLogics

SHANT LABORATORIES

Bioran

Designed biopharmaceutical complex BIORAN

- Linde Engineering Dresden GmbH (Germany), one of the leaders in the construction of biotechnological plants, will be engaged in the design and construction processes.
- For technological design it is planned to involve engineering company Bideco (Switzerland)



The main participants of the Project

Product & technology

JSC "RPC BIORAN"	Initiator of the Project. Holder of the license for the producing strain of human insulin IBCh of the RAS. It has a plot with supply lines and a sanitary area in Pushchino, Moscow Region. The company conducts research and development works for biopharmaceutical production establishment
IBCh of the RAS	The first producer of genetically engineered human insulin in Russia. Licensee and holder of patents, registration dossiers, technological regulations and other documentation related to the production and handling of medicines with the trade name «Insuran».
Linde Engineering Dresden GmbH *(Germany)*	One of the leaders in the construction of biotechnological industries. Involved as a general contractor under the EPC contract for turnkey construction, technology optimization and product registration in the EU.
BIDECO *(Switzerland)*	Engineering company is one of the world leaders in the field of industrial technology scaling. Involved for technological design

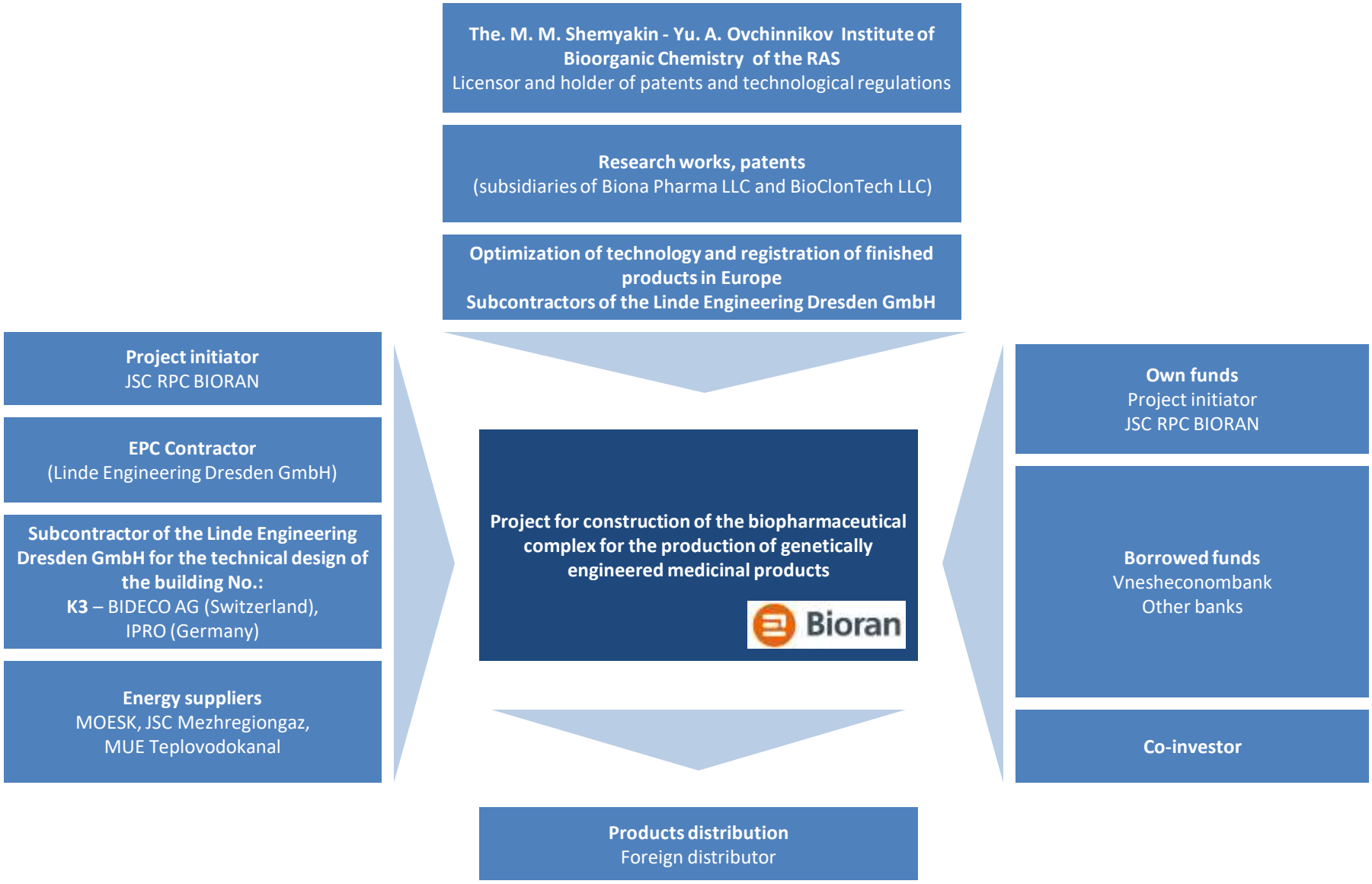
Marketing and distribution

Richter-Helm BioLogics and Richter-Helm BioTec *(Germany)*	The priority market is Russian Federation. Products distribution — according to the "single supplier" model. Excessive products are sold in the markets of the member countries of the Customs Union and at the world market. Distribution on the EU market — via HELM AG — company with total revenue of more than 9 billion Euro. HELM AG is a EU partner in technology optimization and registration of finished drug products. **It will ensure guaranteed demand** for **off-take contract** (Memorandum for the sale of up to 100% of manufactured products for a period of 10 years to EU and third countries was signed)

Financing

Vnesheconombank	Borrowed funds are provided by Vnesheconombank.
	Own funds of the JSC RPC BIORAN Co-investor

Flow-chart of the interaction of Project participants



The stages of the Project implementation

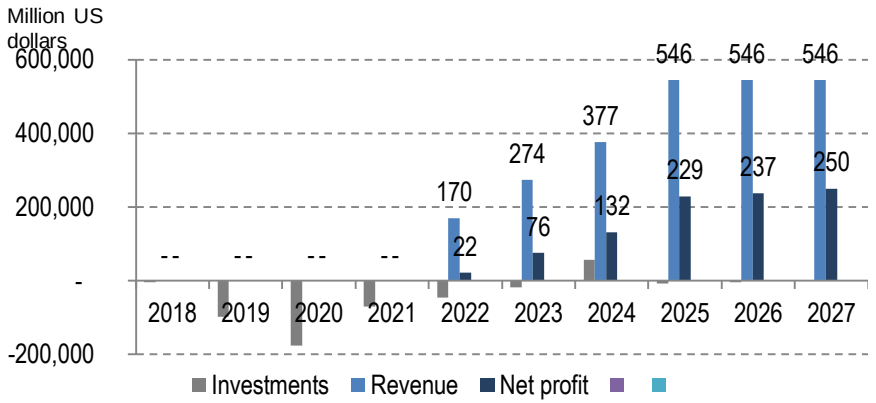
Bioran

Pre-investment phase 2013-2019	Investment phase 2019-2021	Operational phase Since 2022
▪ Receipt of IPD, entitling documents, TS for connection to the utility lines	▪ Design of stage “P” and “WD”	▪ Commissioning of fixed assets
▪ Clarification of the Project concept	▪ Expert examination of design documentations, obtaining a building permit	▪ Gradual increase of production capacity and reaching the production targets
▪ Development of the technological part of the Project	▪ Purchase and delivery of basic equipment	
▪ Conclusion of agreements with key Project participants	▪ Construction of nine buildings of the complex	
	▪ Construction of infrastructure	
	▪ Installation of equipment and preparation for the production start	
	▪ Registration of insulin preparations on the territory of the European Union	
	▪ Beginning of production of AFS and GEHI FDF in building K 3 (bacterial cultures)	

Financial and Investment Indicators of the Project

- ✓ In 2012 NEOCenter prepared a business plan and financial model of the Project for a capacity of 500 kg/y. AFS GEHI for submission to VEB.
- ✓ Specialists of the RPC Bioran with technical support of Project consultants optimized the technological process; previously it was proved that the ability to achieve the same amount of equipment productivity is 2 times higher (up to 1000 kg/y).
- ✓ Preliminary calculations demonstrate the high investment attractiveness of the Project at a capacity of 1000 kg/y.
- ✓ The assessment will require a full update of the business plan, and financial model with the participation of a specialized consultant, including the revision of the strategy from the export model to the internal market, as well as a reassessment of the investment needs of the Project and a detailed revision of the operating cost.

Dynamics of financial and investment indicators of the Project



Name	Units Changes	Parameter
Project investment		
The need for investment	**$ million**	**250**
Capital investments, incl.	$ million	200
Design work	$ million	10
Buildings and constructions	$ million	50
Machinery and equipment	$ million	140
Need for working capital	$ million	50
Terms of implementation of the Project		
Pre-investment phase		to 2019
Investment phase		2019-2021
Operation		**Since 2022**
Reaching the Project capacity		2022
Financial indicators of the Project (when reaching the design capacity)		
Revenue	$ million	546
Cash operating costs	$ million	218
EBITDA	$ million	327
EBITDA margin	***%***	***60%***
Net profit	$ million	229
Investment indicators of the Project		
NPV @ 21% up to 2030	$ million	227
Terminal value	$ million	88
Total current cost of the Project	**$ million**	**250**
IRR	**%**	**33.6%**
Payback period from the moment of the launch	years	2.5
Profit investment ratio		3.33

Contacts and location

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