Biopharma: How Can the "Death Valley" between R&D and Innovation Be Overcome?

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"Today Russian biopharma has two obvious main problems," believes Alexey Konov, investment director, and Andrey Leonov, investment manager, at Bioprocess Capital Partners Ltd.
Russian satirical poet Igor Guberman's line about a "crowd of researchers staring at life's enigma" was written more than 25 years ago. If we consider the sad end to that quatrain (about "life that sends all of those researchers far, far away") as an illustration of the process of putting new knowledge to practice, we must admit that the current situation is even worse.
In fact, until the collapse of the USSR (in the end of the 1980s), the pharmaceutical and biopharmaceutical industries provided most of the drugs the nation required. Biopharmacy in the USSR functioned the way modern corporations do. Each branch had specialized Research Institutes in which production-orientated R&D was conducted. There were also communal usage centers that worked on certain scientific tasks of the Soviet biopharmaceuticals industry. Centralized R&D and innovations made the Soviet Union one of the world's leaders in certain fields.

TWO KEY PROBLEMS

The two key problems today are (1) the lack of promising Russian R&D and (2) the absence of an internal market for that R&D

The first problem is the absence of innovations ready for registration and to go to market. The booming development of biopharmacy throughout the world in the 1980s–90s occurred as science and technology stagnated in Russia. The gap between us and the developed world in this field is very wide: we have no products that are ready for introduction nor do we even have the technology to produce them.

This is especially true for products produced by eukaryotic cells (recombinant proteins, blood coagulation factors, and therapeutic monoclonal antibodies). For this reason, the percentage of locally produced biotechnological products used in the Russian Federation (RF) for drug production is critically small (only 2%). For comparison, the share of locally produced hi-tech chemical substances used in our medical industry is significantly higher; 15 % quantity-wise and 5% money-wise. This gap is filled by imported substances. Our main partners are China and India, and large Western companies provide the most expensive biotechnological preparations. At the same time, development of new industrial strains and technologies happens very quickly abroad: the technologies there are much more developed than the domestic technologies that have been in use in Russia for 15 years. How can we design a portfolio of innovative projects? Obviously, there are two possibilities:

- we can attempt a transition from R&D to industry ourselves,
- we can try importing the good western innovations that have appeared on the market and are ready for registration and industrial production

The second problem is the absence of modern producers ready to accept the most advanced innovations. The standard scheme in the innovation process starts with research, followed by testing, and then introduction into the market. Even if we try to modify this process and adapt it to Russian realities, it is very unlikely we would succeed in the absence of an internal market of venture activity. Even if we create mechanisms for the incubation of these projects, we will face the problem of finding a buyer for them.

We lack any significant market in modern biotechnology in Russia; i.e., there are no big players ready to step in as the main consumers of the new technologies that might appear as the result of investments. The development of the biotechnological industry in Russia today lags behind that of most leading countries; Russia's share in the global production of biotechnological products is less than 0.3%, and we are almost absent in biopharmacy.

This means that we need to solve those two problems in combination: we need a portfolio of projects, and we need to build a system for accepting the products.

In this paper we will not address the important problem of importing innova-

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tions into Russia, we also will not touch on the extremely important problem of creating "acceptors" for those innovations.

We want to concentrate on the possibility of creating a domestic product that is ready to go to market. We will try to show below that none of the existing institutions of development and venture capital is fully adapted for work at the early (incubation) stages, when the product needs to be developed practically from the ground up.

DOMESTIC DEVELOPMENT: HOW TO OVERCOME TWO "DEATH VALLEYS"

As said in the strategy of the Pharma-2020 project, "In the current situation, the Russian pharmaceutical industry can not survive because it is squeezed between Western transnational corporations, which dictate the rules in the areas of technology and intellectual property, and producers from India and China, who put a constant downward pressure on price." Neither new budding Russian pharmaceutical companies nor the created venture funds are yet ready to finance the long-term and risky development of innovative pharmaceutical products.

There are two "Death Valleys." The first is the transition from ideas and successful primary experiments to a working model. The second is the move from the stage of a brand-new business to that of a rapidly growing company. In standard practice around the world, venture capital takes care of the first valley and "cultivating funds" and "angels" (investors) cover the second valley. The angels in developed markets are usually what are called the 3 Fs: fools, family, and friends. It is not an easy task for Russia to find a way to cover both "valleys," but we need to find this solution!

Let's consider the standard western algorithms of commercialization of research in pharma/biopharma and try to spot the typical Russian "white spots" in this process (see the scheme in Fig. 1)

State laboratories perform research, which sometimes yields very promising results regarding the design of new drugs and technologies. However, there is a so-called "regulation process" between the drug prototype and drug on the market or industrial technology; this "regulation process" is very expensive, lengthy, and risky.

In Fig. 2, the scheme is shown: the risks of rejection and spending are extremely high in the early stages; however, spending is lower in the trial stage.

The imperfection in the law and the underdevelopment of institutions that specialize in providing seed money lead to a trough (the grey zone in Fig.1): most potentially promising projects go into a financial trough, and only a few go directly from the green zone to the yellow zone, where the mechanisms of venture capital financing start to work (because of this the grey zone is not very significant there). (See text for a more detailed description – *Ed.)*

The active substance (molecular) produced at the R&D stage should be tested on animals before trials on humans can begin. At the preclinical testing stage, the toxicity of the new molecular substance and its pharmacokinetic and pharmacodynamic parameters should be assessed and the effect should be modelled. Regulatory agencies analyze the information about a new drug from the preclinical tests and decide whether or not trials should proceed on humans.

Clinical trials of drugs before official permission for medical usage is received usually proceed in three stages traditionally called "phases of clinical trials."

At the first phase of clinical trials (phase I), clinico-pharmacological and biomedical trials are provided to a small group of (usually 36) healthy volunteers. At this stage, researchers investigate the side effects of a dose of the drug and its pharmacokinetic parameters and pharmacodynamic effects. This phase is important, because knowledge about the side effects and safety of the drug is necessary before deciding whether to continue investigations or end research.

The initial dose, regularity, and method of administering a certain drug are all usually established in preclinical tests on laboratory animals. However, because of the difference in human and animal pharmacokinetics and pharmacodinamics, correcting dosages could be required.

If the drug is safe and has no side effects, investigators start the second phase of clinical tests (phase II). This phase requires more volunteers, usually from 100–150 patients, but with diseases or conditions that the active ingredient in this drug is designed to cure, diagnose, or prevent.

The aim of phase II is to prove the clinical effectiveness of this drug for a certain group of patients (estimating the short-term safety and determining the therapeutic dose and scheme of dosage). Phase II trials are the most important step in deciding whether or not to continue the drug's development.

If the drug proves effective and safe in the second phase, the investigation continues into phase III. Clinical trials in the third phase are closely monitored investigations designed to assess the safety and effectiveness of the drugs in conditions that are very close to the real conditions of medical treatment.

The aim is to determine the long-term ratio of safety to effectiveness for the medical forms of the active component. Usually, these investigations are related to existing standard therapy (or placebo for a new class of drugs). Innovative products can be registered after this phase of clinical trials. The number of patients in this last phase of research could amount to a thousand people,

depending on the drug and condition. Therefore, each new step is more expensive than the previous one for the drug's developer.

It is obvious that state institutions are incapable of bringing a new medical drug to market. Promising products designed in Western countries, mostly in universities and laboratories, are proposed for sale. Pharmaceutical companies buy many products and technologies that are still simply ideas, through licences or direct purchases. More often, development at the early stages happens through a "partnership," with the possibility for the large company to own the product if it is successful.

If a team of researchers from a state institution see that the product or technology created has serious commercial potential and believe they can start their own business, then they do so. The conditions in this situation are clear: all the rights to the product or technology belong to the company, and the state institution employing the team of researchers takes a stake in it. After that, there is a business plan, the aim of which is to attract external financing and continue research with the intention of bringing the product to market and the promise of a huge profit. After that, the founders of the company try to attract all potential venture capital funds. To secure investment, they need to persuade, convince, and lay out their dream. Most startups end at this stage, but some are lucky. If so, they receive some seed money in exchange for shares. They spend money on investigations, and if they have promising results, the startup can attract more investment. The results are usually not promising, investment dries up, and the startup dies. The reality is that very few survive. The companies that are lucky create a product that brings a big profit in comparison with the money invested, and shareholders benefit.

In Russia, we need direct licensing from state institutions to the pharmaceutical companies, and, even more importantly, we need to create a way for small startups with ideas to succeed. Let's consider the major problems which, in our opinion, could be stalling the effective development of small innovative pharmaceutical companies, particularly biopharmaceutical companies.

Organisational Problems: How Should the Company Be Founded and How Can Laboratory Investigations Be Done Legally and Effectively?

There is no tradition of small companies being founded by scientists in Russia. They simply do not understand what needs to be done, which papers are required, etc. We do not have specialised industrial parks or incubators which are ready to provide not only legal and organizational support, but also laboratories and logistical infrastructure. This is important, because in this case we are talking about a company involved in research. That means that, apart from the usual problems of a small company, this company will need permission to work with chemical reagents, biological objects, radioactivity, etc. Today this problem is usually solved by renting property at an institute where research has been done before. Very often, companies formally rent just a couple of square meters, but in practice they use all of the equipment there. This is possible, however, only when the director or dean allows it. Otherwise, the scientists work illegally or semi-legally.

How Should the Intellectual Rights to the Project Be Transferred to the New Company?

If a patent has not been registered yet, in the condition of "know how," the big question is who should be registered as the owner? If the owner is a state institution and the scientist is only the developer of the idea, the most he can ask for after commercialisation is to receive royalties. However, not a single state institution today is capable of bringing the product to market because of lack of funds, authority, and motivation. You're thinking maybe it is possible to register the idea to your name or to a company that has yet to be established? That's illegal, because all of the research was conducted during work hours, on equipment at work, and with the state's financial support. So, the key is to solve the question of intellectual property, with the rights to the results of the investigation going to the researchers and with the legal possibility of separating from the mother organization and founding a small enterprise (inside or outside the technology park).

Today, this is becoming possible because of very important amendments to the law.

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According to Federal Law 217, budget and education establishments, as well as scientific establishments, universities, and colleges that are founded by the state's science academies, "Have the right, without the agreement of the proprietor and with the notification of the federal body of the executive power which provides the functions of elaboration of state policies and normative legal regulation in the sphere of scientific and scientific-technical activity, to found (together with other persons) business companies whose activity practically apply (introduce) the results of intellectual activity."

Regarding the production of "custom" work in state establishments with the aim of introducing it into industry, we think that this scheme has proven to be inefficient. Nothing can be done without the direct material interest of developers, not only in the project report, but also upon bringing the product to market and growing the company.

HOW TO SECURE FINANCING?

Today, practically the only form of state support for a startup in Russia is the program of the Fund for Assisting Small Enterprises in the Scientific-Technical Area.

Over the last few years, the fund has created real working mechanisms for the commercialisation of scientific investigations. Financial support from the "Start," "Start-up," "Universities," and "Youth Business" programs

support projects at the early stages of R&D.

For several years, the fund provided up to 20% of the program's funds in the area of biotechnology and medicine. Remarkably, one of the fund's tasks for the nearest future is to collaborate with venture capital funds (as well as other structures) in order to provide financial support to projects throughout the whole innovation cycle.

If the company is established in Moscow, the Moscow government provides support. The government of Moscow founded a not-for-profit agency for developing innovative entrepreneurship, which has created a couple of interesting programmes, in particular:

- subsidies for small innovative enterprises for the production of prototypes or small batches (this is a very important step for demonstrating the "proof of principle," which is exactly what should be shown to venture capital investors when requesting financial support),
- subsidies for patenting the results of innovative activity both in the Russian Federation and abroad.

Similar local programs have begun in other regions as well.

Finally, we should mention the Rosnauka programs for development at the middle stages. The contribution of those programs in supporting some of the leading Russian laboratories of the Russian Academy of Sciences (RAS) is hard to overestimate; however, we should remember that these programs are mainly aimed at financing applied research. This may be why the effectiveness of these programs is far from what is desirable. Due to their status, mentality, and motivation, academic laboratories do not adapt very well to the design and introduction of their products into the market if they have to meet deadlines.

HOW AND WHEN TO CONDUCT TRIALS?

The company has been founded, R&D completed, and the trial (preclinical and clinical) stage begins. How and where can these trials be conducted according to Western standards with the possibility of selling this product in Western markets in the future? We are sure that today no small innovation company can support the whole cycle of trials by itself. A good plan for venture capital fi-

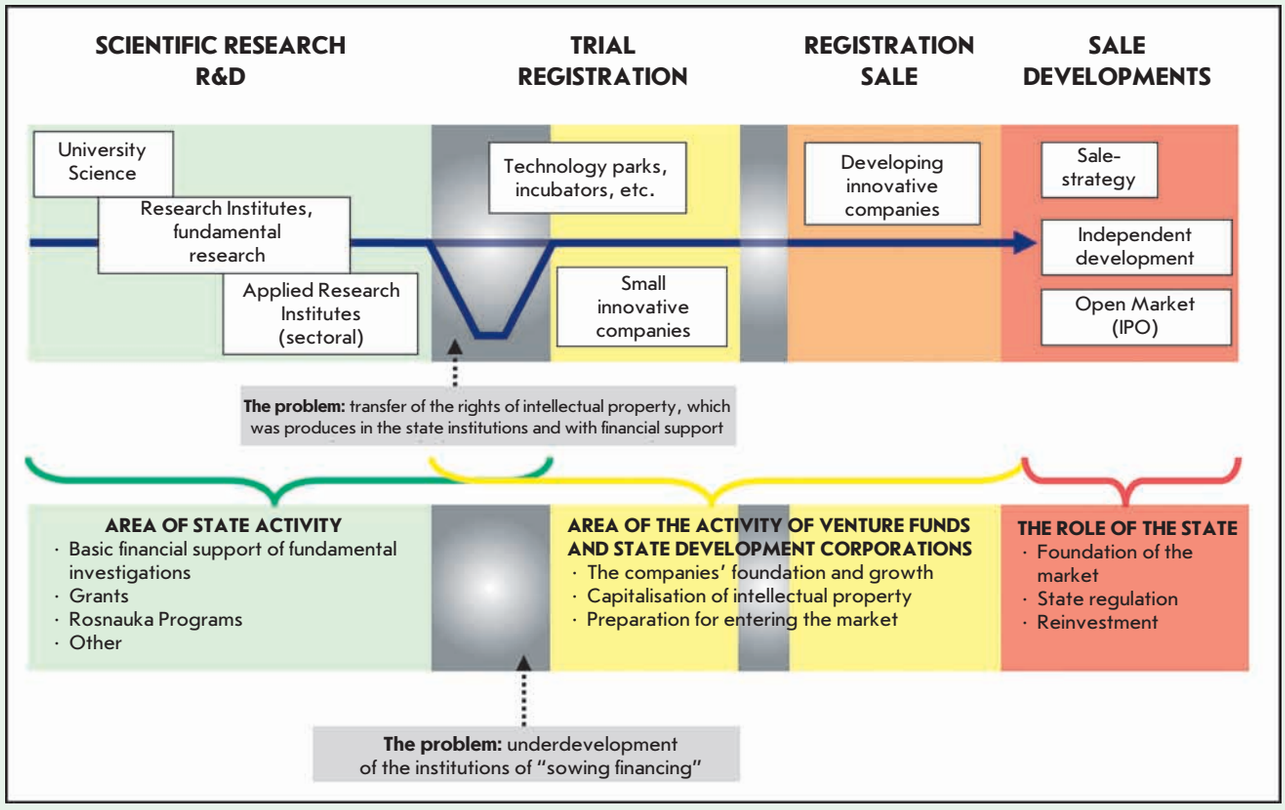

Fig.1. Standard scheme in the innovation process. The colors illustrate the maturation stages of projects from the initial (green) to the mature stage (red). In the area of pharmacy and, in particular, biopharmacy, development goes from the R&D stage through the trials and registration to appearance on the market (blue line in the figure). If the development appeared in a state institution (university or research institute), the first problem that appears on the way to future commercialization is how to transfer the rights to the intellectual property from the state institution to a private company. The long-awaited and recently passed amendments to the law (see "Federal Low N 17" FL dated August 3, 2009) should solve this problem; however, we need to wait and see how this new law works in practice. The second problem, in our view, is more serious: it is financing companies when they are in their early stages

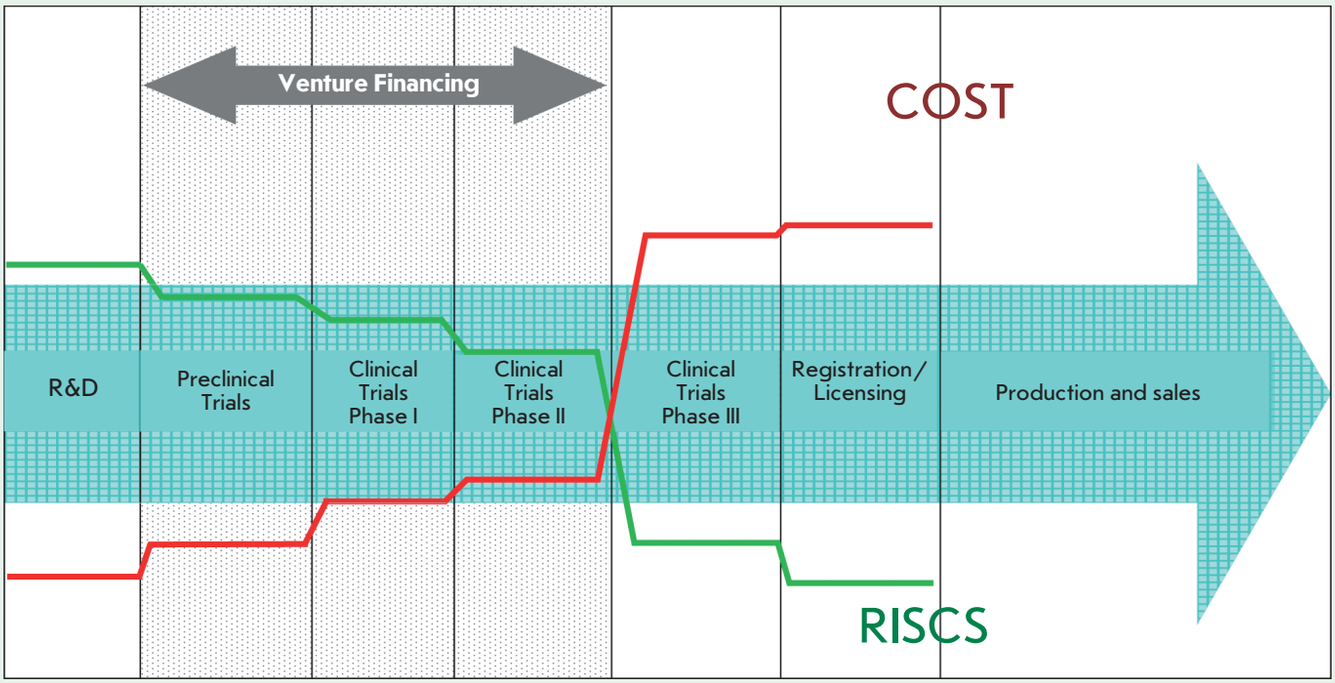

Fig. 2. Production of a new drug: from development to the market.
Venture financing is very commonly tapped after a successful completion of R&D. Funds usually dry up for the project before the clinical phase III, and often even earlier, after the second and even first clinical trials. (See description of stages in the text – *Ed.)*

nancing of the proposal, professionals in the preclinical and clinical trials, and secure partners (who are specialists in these types of research contract organisations) are required for this stage.

Project management and marketing are two parts of a successful pharmaceutical company; they should be fully covered by the company's own recourses.

Other activities are potential candidates for outsourcing. A broad variety of contract service organizations (CSOs) could work as subcontractors, i.e., Contract Research Organizations (CROs), which provide contracted services in preclinical and clinical trials, or Contract Manufacturing Organizations (CMOs), which optimize the process of production and production of active pharmaceutical substances and finished medicines for the trials, and, afterwards, for the market. Even today, small innovation companies around the world spend up to half of their entire R&D budget on CSO services.

HOW AND WHEN THE LIFE OF START-UP ENDS

The company has completed a whole set of trials, and the results of the first phase are good. What now? Attract a lot more money for phase II and phase III trials? Search for a partner? Sell the business?

It is hard to provide a simple answer. This depends on the type of drug and the situation in the company and on the market at the moment. Let's make a couple of general remarks.

If in the 1970s–1980s the largest companies in the world introduced 5–7 new molecules every year, today they introduce a maximum of 2–3 fully original molecules in the course of several years. To cover the expenses for both the leading development, as well as for the spinoff developments, the new molecular must bring in hundreds of millions of dollars every year. Over the last 20 years, the largest medical producers in the world had other options, mainly because of their biotech "hits," which were mainly developed by small companies. Today, the patents covering most of the bio-blockbusters that have been on the market for 15–20 years are running out; the industry is desperate for new "hits."

The difficulty with compounds reintroduced into the market, the appearance of new knowledge about how they act, and new statistics about their side effects have led to a shift in major expenses from R&D to trials. The EMEA and FDA, the leading international regulating agencies, demand more and more complicated trials of new drugs. As a result, today expenses for the introduction of a new molecular to the market have increased 3–5 times and can amount to 300–900 million dollars, which creates an insuperable barrier for small companies when they try to repeat the successes that venture legends Genentech and Amgen achieved 25 years ago.

However, small innovation companies can still attract venture capital at the early stages and develop new products up to the stage of the first trials (the end of preclinical trials or phase I of the clinical trial); after that, they can establish long-term cooperation with a "big player" as an investor in the next stage or simply sell the product to them.

The beginning of a recession in the global economy and the dearth of liquidity affecting the aforementioned big players and potential strategic

investors have brought forth the tendency to finance new developments in more advanced stages by attracting the next rounds of venture capital financing. For example, in September–October 2008, five companies secured the largest amount of late-stage venture capital financing; three of them were biotech companies. The company Proteolix, for instance, attracted 79 million dollars from venture capital investors to support the phase II clinical trial of a biopharmaceutical drug against autoimmune diseases and cancer; MacroGenics attracted 25 million dollars for the phases II/III of the clinical trial of an original monoclonal antibodies to fight diabetes; Link Medicine received 40 million in venture capital financing for the late stage of development of a cure for autoimmune diseases.

Therefore, in the next 3–4 years, the situation on the market will be very favorable to small venture capital funds and developers of certain products: the large companies that weather the hard times will continue to actively buy new companies to boost their product portfolios. On the other hand, after raising funds in additional rounds of venture capital investment, there is now the unique opportunity to either grow the company to the stage when the product can be taken to market or sell the company to a strategic investor at a significantly advanced stage and for a much better price.

Regarding IPOs, we should note that, before the crisis, some biotechnological giants successfully went public. However, this is uncommon, because selling to a strategic investor in the form of a corporation involved in the same field remains the most attractive option for a venture biotech company. Today the IPO option is practically closed, and it is hard to predict the situation that will prevail in the next 3-4 years.

CONCLUSIONS AND RECOMMENDATIONS

To set up a process that will ensure mass production of innovations in the industry of biopharmaceuticals, we need, on the one hand, to solve the organizational, legal, and regulatory problems we have briefly mentioned in this paper. On the other hand, it is unlikely that that process would be efficient without the creation of an internal market for the results of the activities of small companies: we do not have companies of the size of Bayer or AstraZeneca, which are able to spend $100 million or more on development. In this context, small innovation companies must sell their developments to the West. The state should focus attention on creating a system in which Russia will have a chance to keep its rights at least on the Russian market. How should this be done? That's a separate question. Lets only say that one approach could be to consolidate several small innovation businesses into a large "virtual" big company; this would not involve a consolidation of buildings and equipment (i.e., immovable assets), but a consolidation of the rights to the intellectual property under development. Such a "disintegrated" company, which could outsource other steps in the process but conduct R&D and marketing itself, would, in effect, be a bureau that is flexible and can quickly react to the demands of the market. ●

THE DESIGN OF INNOVATIVE DRUGS INSIDE INDUSTRIAL COMPANIES

Figure 1 shows how a product designed by an industrial company is developed. Big transnational corporations have their own R&D departments with a wide range of research activities; however, efficiency here (the ratio between the amount spent and the quantity and quality of the newly developed drugs) is significantly lower than that of a small innovative company, which usually aims to create a certain drug or technology. Can we expect the development of an innovative product in Russian industry? That is unlikely! Existing companies, regardless of how they are run, are still, for the most part, not ready to invest in high-risk drug innovations. Usually Russian projects in the field of biopharmaceuticals follow the strategy "What's being done in the West? Let's replicate it quickly!" It is important to say that it is not a bad strategy. It works, and works well. One of the businesses we developed at "Bioprocess" (a producer of biogenerics such as interferon alpha, erythropoietin, and granulocyte-colonies stimulating factors) was built based on this model, and only after 5–6 years, when it began making a profit, was it possible to develop new products. China and India also built their industries based on this model, at least in the field of biopharmaceuticals. At the same time, industry in both countries had strong governmental support: direct funding, tax holidays, preferences in registration and purchases, etc. Now the Indians and the Chinese have begun beating developed countries at their own game, i.e., in the area of innovative products. It is important for us in Russia not to miss out! However, the sizes of even our own, most successful companies do not allow them to invest tens of millions of dollars into the development and registration of really innovative drugs without state support. Until recently, there were two main mechanisms for securing state co-funding for innovative pharmaceutical development: through the Federal Agency for Science and Innovation (Rosnauka) and through the program of the "Fund for the Support of Small Enterprises in the Sphere of Science and Technology." The fund's programs are meant for small companies; they are not suitable for large industrial ones. Rosnauka's programs, unfortunately, are not suitable for industry: the maximum funding period is three years, and the company must fulfill the requirements for "program indicators," which means production should generate a certain amount of money as a return on investment in that period of time. If development is at the stage of the first clinical trials, three years is not enough time not only for production and sale, but also for simply registering the product on the market.

The Ministry of Industry and Trade (Minpromtorg) has similar programs: the time limit for the return of investment has increased to four years, and the beginning of industrial production is the only indicator. This is a bit more realistic for businesses, but it is still far from what is desirable.