Kim Ribbink

PRIVYET! RUSSIA :

Growth *and* Opportunity

Efforts to bolster the domestic pharmaceutical sector's proven capabilities in clinical research make Russia an attractive proposition for global companies.

With its promise of expansion, its population of around 140 million potential customers, and a pool of highly qualified staff, Russia has long been recognized as an important market for pharmaceutical companies.

The pharma market in Russia has shown stable annual growth of 13% to 20% for several years, and growth forecasts for 2011 range from 8% to 15%.

Many pharmaceutical companies started their operations in Russia in the early 1990s, and today, most have offices in Russia with hundreds of full-time employees, says Pavel Tverdokhleb, senior director, clinical research, at PharmaNet.

Pharmaceutical companies have been expanding their presence in Russia in recent months, and more companies are expected to establish a local presence in response to efforts by the Russian government to bolster the domestic sector and cut dependence on imports through the 2020 Healthcare Development Program.

Outlook for Companies

In November 2010, Novartis announced plans to invest $500 million in Russia over the next five years, including plans to build a new full-scale pharmaceutical manufacturing plant. Nycomed, one of the pioneers in the Russian pharmaceutical industry, announced in 2009 that it would build a state-of-the art production plant in the region of Yaroslavl by 2014.

When up and running, Nycomed plans to produce products that are important for the local market, such as Cardiomagnyl, for the prevention of thrombosis diseases; Actovegin, for cerebral circulation, peripheral blood flow, skin graftings, burns, scalds, abrasions, wound-healing impairment, and radiation-induced skin and mucous membrane lesions; calcium; and warfarin, used to treat thrombosis and embolism of vessels.

"Nycomed's products had been registered in the USSR since the mid-1980s, and we officially opened a representative office in Russia in 1993," says Jostein Davidsen, senior VP and president of Nycomed Russia-CIS. "During these 18 years we managed to outpace the market growth by two-and-a-half times and be-

Upcoming Conferences

17th Annual International Russian Pharmaceutical Forum
May 17-19, 2011
Corinthia Saint-Petersburg Hotel,
St. Petersburg, Russia

come the biggest single region within the Nycomed Group."

In January, the company announced that it had entered into an agreement with specialty pharma company Eurand to market and distribute Zenpep, subject to regulatory review and approval, in Russia and the Commonwealth of Independent States (CIS). Zenpep is a pancreatic enzyme product indicated for the treatment of pancreatic insufficiency in patients with cystic fibrosis or other conditions, such as chronic pancreatitis, gastrointestinal surgery, and pancreatic cancer.

Other companies with a growing presence in Russia include Sanofi-Aventis and Novo Nordisk. Recently, AstraZeneca announced it would open a $150 million manufacturing plant by the spring of 2013 to produce cancer, cardiovascular, and other drugs.

Another major company looking to expand its presence in Russia is Boehringer Ingelheim.

"For decades we were dealing with Russia and the former Eastern Bloc from an office in Vienna," says Valentin Janz, who is responsible for coordinating Boehringer Ingelheim's initiatives in emerging markets (Russia and India). "We plan to establish a new legal entity in Russia in the first half of this year, which will give us more opportunities. At present we have 700 people working for us in Russia."

The potential of the market is a key attraction. According to Mr. Janz, sales are anticipated to double in the next five to six years.

Partnerships with local companies also are growing. GlaxoSmithKline partners with JSC Binnopharm, a unit of Sistema, for the secondary production of cervical cancer, rotavirus and pneumococcal vaccines, says Dominika Grzywinska, consulting analyst CEE healthcare at Frost & Sullivan. Roche and Viriom, a member of the Center for Innovative Technologies ChemRar, partnered in the development of innovative compounds for potential novel treatments for HIV/AIDS in Russia, including preclinical research and initiation of clinical studies. Johnson & Johnson entered a partnership with Russia's largest drug-maker Pharmstandard to localize secondary packaging of Velcade in one of its production plants.

Mr. Janz says Boehringer is drawing up a short list of potential Russian partnerships for one or two of its products, initially for packaging, but with a view to increasing domestic involvement. He says Russian companies that have demonstrated an ability to work with international firms and that are implementing GMPs will be considered.

"We are not ready to talk about this in board rooms, and there will be nothing before late this year," he says.

Mr. Davidsen says partnering has been at the core of Nycomed's global strategy.

"Nycomed in Russia-CIS has a unique track record in partnering, with 12 new partnerships since 1999," he says. "The collaborations range from developing in-market brands and re-launches of products."

FACT

WHEN COMBINED WITH THE PUBLIC EXPENDITURE, PHARMACEUTICALS REPRESENT 40% OF TOTAL RUSSIAN HEALTHCARE SPENDING — A PERCENTAGE FAR HIGHER THAN MOST COUNTRIES.

Source: Cutting Edge Information

Local Growth

In terms of local products, Russia's biopharmaceutical market is still underdeveloped.

According to Ms. Grzywinska, the Russian biotech industry is estimated to account for 0.5% of the global market, two-thirds of which are pharmaceuticals.

The government is supporting R&D as a part of a national 10-year program promoting biotechnology, for example through emerging special economic zones and biotech clusters that aim to attract investors to commercialize in the technology.

"Without these options, hardly any domestic companies would have sufficient expertise to conduct R&D in a way to obtain market approvals in developed countries," she says. "Moreover, few Russian companies could afford the process of commercialization."

The Association of International Pharmaceutical Manufacturers also has pledged at least $1 billion in investments in Russian manufacturing, packaging, and R&D.

According to Ronny Schnel, executive director of business development and client services at Criterium, up-and-coming Russian pharma companies are looking for partners in the United States and Europe to introduce their products.

"Many marketing and promotional activities in Russia are oriented to direct to consumer."

NATALIA AKSENOVA / S&H/AG Loyalty

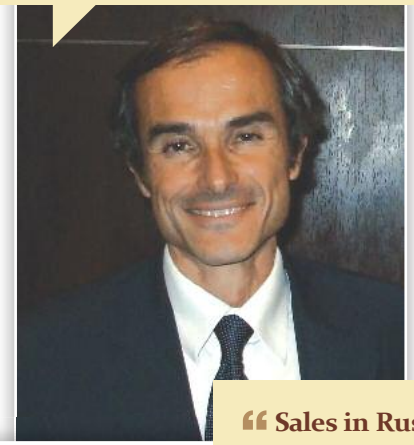
"Nycomed decided to invest in a state-of-the-art production plant in Russia based on the sales success of our products."

JOSTEIN DAVIDSEN
Nycomed

"Clinical trials for new products will continue to increase as the economy develops."

DR. TATJANA ZWEREVA / i3

> "In Russia, patients are highly motivated to take part in clinical trials in order to have access to the most advanced treatments."
>
> **DR. ANGELICO CARTA**
> Worldwide Clinical Trials



> "Sales in Russia are anticipated to double in the next five to six years."
>
> **VALENTIN JANZ**
> Boehringer Ingelheim

> "The Russian market is one of the largest in Europe for generic product sales, and during the last decade innovative product sales have also grown."
>
> **PAVEL TVERDOKHLEB** / PharmaNet

Angelico Carta, M.D., president of Worldwide Clinical Trials Global, says more opportunities are emerging from the local pharma sector, especially for periapproval and postmarketing activities.

"Another area of growth potential is biosimilars," says Tatjana Zwereva, M.D., Ph.D., country manager, i3 Russia. "A lack of restrictive regulations makes Russia attractive to biosimilar manufacturers."

Trial Capabilities

Today Russia is one of the top 15 countries worldwide for the number of its clinical studies, investigator sites, and study subjects, Mr. Tverdokhleb says.

Challenges do exist, such as complete understanding of the complex legal and regulatory environment in Russia and marginal local operational expertise, Dr. Carta says.

"Global pharma companies are finding that it is absolutely mandatory to partner with a reliable CRO that has extensive knowledge of global and local clinical research requirements and the operational infrastructure to support this complicated market," he says.

Ms. Schnel says site administration can be quite bureaucratic and diagnostic and office equipment is often old or missing at sites in more remote locations, though government programs are leading to improvements.

However, wide access to patient populations, a centralized healthcare system, highly qualified and motivated investigators, and proven quality of data provide opportunities for both local product launches and global research, Dr. Zwereva says.

"Many scientific-research institutes are dedicated to certain diseases or conditions, such as the Pulmonology Scientific-Research Institutes, the Kidney Institutes, and the Psychiatry Institutes," Ms. Schnel says.

She notes that international regulatory inspections, including those conducted by the FDA, show that clinical trials in Russia have good quality of data as well as speedy recruitment in the region.

With more than 70% of Russians living in cities, there are more than 100 million potential trial subjects, says Alexandra Zaichenko, director of business development, Global Clinical Trials.

The Russian clinical trial market is far from saturated. In 2008, the country approved 615 new studies, its maximum to date, which is far below the level of other Eastern European countries, Dr. Zwereva says.

"At that rate, Russia's ratio is 4.33," she says. "According to clinicaltrials.gov, Poland's 592 trials/36.1 million population equals 16.4, and the Czech Republic's 383 trials/10.5 million population equals 36.5."

Russia: Healthcare System Fast Facts (2005 — 2009)

» Population	139.4 million
» No. 1 cause of death	Ischemic heart disease
» Total Healthcare Spending	$64 million
» Healthcare Spending per Capita	$460
» Out-of-Pocket Spending per Capita	$148
» Government Healthcare Budget	$39.7 billion
» Physician Density (per 10,000 people)	43

Source: Cutting Edge Information.
For more information, visit cuttingedgeinfo.com.

There is growth in clinical research from local companies, with about 60% of all clinical trials for Phase I-IV coming from multinational pharmaceutical companies, and 40% from local companies, Mr. Tverdokhleb says.

A factor helping to encourage more clinical research is the expected inclusion of Russia in the WTO in 2012, Ms. Schnel says, who explains this should improve protection of drug development and clinical trial data.

Patient Access and Marketing

Major therapeutic areas in terms of clinical research are oncology, diabetes, cardiovascular, and neuropsychiatry. There is also an increased interest in the development of chronic inflammatory and HIV treatments, Dr. Carta says.

Currently, accessibility to pharmaceuticals in Russia is below European averages, especially expensive and innovative pharmaceuticals, Ms. Grzywinska says. The situation is worse in rural regions.

"There is a big gap between what is needed and what is available, and even top-selling drugs rarely cover more than 10% of existing needs," she says. "For rheumatology or oncology, the gap is even larger."

Often participation in a clinical study is the only option for a patient to receive an adequate and timely treatment care. And over the last few years the demand for pharmaceuticals in oncology has only been increasing.

"Very high and persistent demand for treatments is due in part to poor state insurance in Russia and the very high cost of the treatments," Ms. Zaichenko says. "When given the choice of paying for expensive medicines or having them free as part of a research

> The Russian market for clinical trials is believed to be significantly underused although it is estimated to be fairly large. From 2001 until 2008 it almost doubled.

RONNY SCHNEL / Criterium

> In terms of accessibility to pharmaceuticals, the gap between what is needed and what is available is very large.

DOMINIKA GRZYWINSKA / Frost & Sullivan

> Russia is a major contributor in large multinational Phase III trials, often completing enrollment ahead of other countries.

ALEXANDRA ZAICHENKO
Global Clinical Trials

program, many patients will choose the research option."

Citizens rely heavily on generics, and even with these relatively low-cost substitutions many medical needs go unmet. The richest citizens can afford branded products, however, and the market continues to increase faster than most developed markets, Cutting Edge Information notes.

Natalia Aksenova, managing director, partner, at Sudler & Hennessey/AG Loyalty, says while there are strict limits on the amount of promotional activity companies can do in Russia, consumers can buy prescription drugs in pharmacies, which makes Russia a very dynamic market for diverse channels, such as DTC.

"This is why many marketing and promotional activities are oriented toward direct to consumer," she says. "We create brand substitutes — social, educational, or charity programs — in support of prescription drugs."

New regulations are placing restrictions on promotion to physicians, forcing companies to rethink their strategies to gain access.

"One recommendation we have is for companies to unite with patient advocacy groups," Ms. Aksenova says. "For example, we registered the social organization 'Life in Movement,' the goal of which is to help people with rheumatologic arthritis. All international producers supported our initiative, with projects oriented to patients and doctors." PV

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EXPERTS

NATALIA AKSENOVA. Managing Director, Partner, Sudler & Hennessey/AG Loyalty, The S&H Group is a global healthcare marketing and communications organization with offices around the world. (S&H entered a partnership with AG Loyalty Moscow in 2009 expanding its reach into the Russian Federation.) For more information, visit sudler.com.

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TATJANA ZWEREVA, M.D., PH.D. Country Manager, i3 Russia, i3 is a full-spectrum CRO with functional and therapeutic expertise to help biopharmaceutical companies across the globe gain insights that lead to better patient care. For more information, visit i3global.com.

Kim Ribbink

Pharmaceuticals in Legislative Spotlight

The pharmaceutical market has been high on the Russian government's legislative agenda. A number of changes have been announced recently, though many questions remain unanswered.

The 2020 Pharmaceutical Development Program for the domestic pharmaceutical industry (Pharma 2020) was approved by the Russian Government in 2009 with a budget of more than $10 billion.

According to Natalia Aksenova, managing director, partner, at Sudler & Hennessey/AG Loyalty, one of its goals is to ensure at least 50% of the value of drugs circulated in the Russian market are of domestic origin; currently 80% of drugs on the market are foreign made.

"The cooperation of foreign and Russian pharma companies, which creates the products in Russia by local pharmaceutical factories promoted by worldwide pharma companies, is the way to realize this goal," Ms. Aksenova says.

According to Dominika Grzywinska, consulting analyst, CEE healthcare, Frost & Sullivan, it is still not certain whether the government will introduce state control over prices of pharmaceuticals in the domestic market.

"Currently, such a mechanism exists only with regard to drugs deemed to be of strategic importance for the well-being of society," she says.

Tatjana Zwereva, M.D, Ph.D., country manager, i3 Russia, says the goal of Pharma 2020 is to increase the competitive strength of the domestic market and reduce the dependence on drug importation.

"The government is encouraging international and domestic businesses to take the lead in modernizing the pharmaceutical industry," Dr. Zwereva says.

Valentin Janz, who is responsible for coordinating Boehringer Ingelheim's initiatives in emerging markets (Russia and India), says

> **"The government is encouraging international and domestic businesses to take the lead in modernizing the pharmaceutical industry."**
>
> **DR. TATJANA ZWEREVA** / i3 Russia

> **"Pharma companies and CROs conducting clinical trials in Russia need to get through the transition period with the new law on registering medicines."**
>
> **PAVEL TVERDOKHLEB** / PharmaNet

Russian authorities have not yet made clear how much would have to be done for its products to qualify as domestically produced and thus come under the umbrella of the 2020 agenda. However, plans by Boehringer to establish a new entity in Russia should fit well with the legislation.

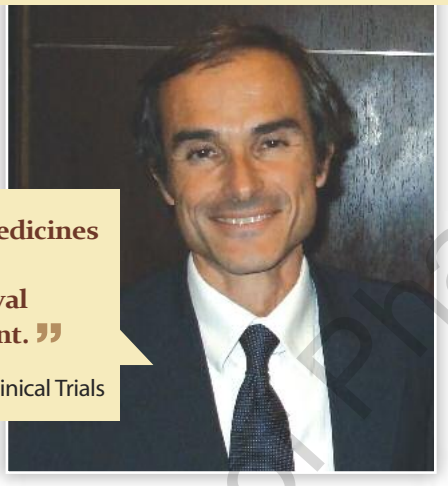
Registering Medicines

In September 2010, a new Federal law "On the Circulation of Medicines" came into effect in Russia.

The law seeks to create a more open process for registering medicines, aiming to make vital medicines more affordable and laying the ground work for further development of the industry, Dr. Zwereva says.

According to this law the right to issue a license for performing clinical research was transferred from The Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation (alias RosZ-

> **“The Russian government is trying to strictly regulate the pharmaceutical market due to the fact that 80% of drugs presented in Russia are foreign.”**
>
> **NATALIA AKSENOVA** / S&H/AG Loyalty



> **“The new law on registering medicines is expected to streamline review procedures and make the approval process shorter and more efficient.”**
>
> **DR. ANGELICO CARTA** / Worldwide Clinical Trials

dravNadzor, RZN) to the Ministry of Healthcare and Social Development.

Ms. Grzywinska says the changes include extending the list of state authorities' powers (previously, it was stipulated by secondary legislation) and shortens the duration of market authorization to 210 days (without clinical trials; before, the procedure this could take as long as two to two and a half years).

Ronny Schnel, executive director of business development and client services at Criterium, says data from the Association of Organization for Clinical Trials (Russia) show only 25% of the approvals for conducting clinical trials were provided in time.

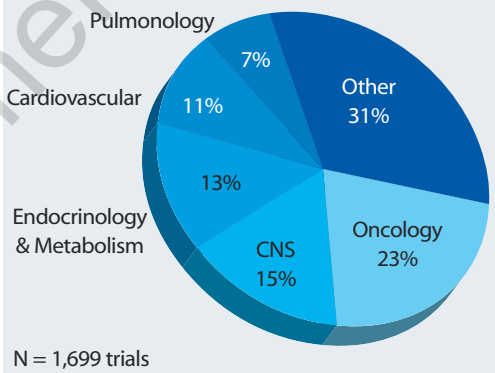
"The time for providing an import license for the CTS was 20 working days instead of five as defined in the law," she says. "The same for providing export licenses for the biosamples — 20 working days instead of 10 as per the law."

Pavel Tverdokhleb, senior director, clinical research, at PharmaNet, says the industry is still waiting for the new documents to be issued by the local authorities regarding insurance of study subjects, import of the study drug, how local clinical trials should be conducted to support a local registration dossier, as well as other areas of concern.

This law transferred the duty of approving the performance of clinical research from the Federal Service on Surveillance in Healthcare and Social Development to the Ministry of Healthcare and Social Development.

Dr. Zwereva says implementation of the law has been associated with increased bu-

International Clinical Trials in Russia 2005-2009



N = 1,699 trials

Source: Worldwide Clinical Trials.
For more information, visit wwctrials.com

Paying for Medicines

There are three segments within the pharmaceutical market in Russia: commercial retail, reimbursement, and hospital. Commercial retail is the largest one and constitutes more than 70% of the total market, whereas reimbursement, only makes up about 16%. This shows that the majority of pharmaceuticals are purchased on an out-of-pocket basis.

The reimbursement segment has existed since January 2005, when the Russian government launched its DLO Program (supplementary pharmaceutical provision). The program is a centralized public procurement of medicines for social security beneficiaries. It is the first comprehensive program for the provision of expensive pharmaceuticals. In 2007, the program was reformed and effectively split into two subprograms – "7-nosologies" and ONLS. "7-nosologies" is the centralized procurement of drugs (on a federal level) for the diseases that are most expensive to treat. Tenders by the Ministry of Health and Social Development are held twice a year. ONLS is the procurement of vitally important pharmaceuticals, with tenders held by respective regional healthcare authorities. The lists of diseases and drugs covered by the program are prepared annually, taking into consideration incidence of the diseases. Possible future scenarios for the segment's development include extension of 7-nosologies as well as dedicated reimbursement for socially significant diseases, such as oncology or TB.

Also on the horizon is a prospective pharmaceutical insurance initiative. It was originally expected to be announced in 2010, but that has been pushed forward to 2013. However, several contentious issues remain. For example, the patient has to cover a certain amount of the drug cost, which in cases such as oncology, might be impossible for the average Russian citizen. If implemented pharmaceutical insurance may replace the existing programs for provision of medicines and it could also release the burden on the hospital segment, since currently patients often demand in-patient treatment to receive free pharmaceuticals.

Source: Dominika Grzywinska, Consulting Analyst, CEE Healthcare, Frost & Sullivan.
For more information, visit frost.com

EXPERTS

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TATJANA ZWEREVA, M.D., PH.D. Country Manager, i3 Russia, i3 is a global pharmaceutical services company that includes i3 Research, a therapeutically specialized global CRO. For more information, visit i3global.com.

reaucracy and less transparency of procedures.

However, Angelico Carta, M.D., president of Worldwide Clinical Trials, says in the longer term the restructuring is expected to streamline review procedures and make the approval process shorter and more efficient.

The main regulatory challenge for pharma companies and CROs conducting clinical trials in Russia is to pass this transition period successfully, which is not an easy task both for the Ministry of Health of Russia and the industry, Mr. Tverdokhleb says.

"The good news is that Ministry of Health of Russia has already issued a number of clinical trial approvals for submissions completed after Sept. 1, 2010," he says.

According to a paper from Synergy Research Group, RZN approved 134 new clinical trials of all types including local and bioequivalence studies during the third quarter of 2010 demonstrating a 12% decrease compared with same time frame in 2009.

There are also new opportunities because of the new legislation, since the new drug law requires data from local clinical trials in Russian centers before submitting a marketing authorization request, Mr. Tverdokhleb says.

"Therefore, it is expected that there will be an increasing number of Phase II-III studies in Russia in the future," he says. "This year, we could see a number of small and medium U.S. and European companies entering the Russian clinical trials market for the first time. Many of them will look for local partners, so CROs already operating in Russia may benefit." PV

> **"Data show that only 25% of the approvals for conducting clinical trials are provided in time."**
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> **RONNY SCHNEL** / Criterium

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