

Emerging Markets Outsourcing Report

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Phase II-IV Clinical Research

- CROs Struggle Under New Regulations on Local Trials in Russia... 1
- Phase II-IV Clinical Research in Brief...3

Business Conditions

- China Unveils New Whistleblower Program for Food and Drug Manufacturers3

Local Market Developments.....4

Commercial Dose Manufacturing5

API — Small Molecule5

Analytical Services.....5

Early Development.....5

Drug Discovery.....5

Commodity Suppliers6

Phase II-IV Clinical Research

CROs STRUGGLE UNDER NEW REGULATIONS ON LOCAL TRIALS IN RUSSIA

The Ministry of Health and Social Development of the Russian Federation (MoH) approved 132 new clinical trials in the third quarter of 2011, representing a 1.5% drop from Q3 2010 and a 13.7% drop from Q3 2009. According to the Association of Clinical Trials Organizations (ACTO), a Moscow-based group that represents the clinical research community in Russia, this decline in the overall number of approvals can be attributed to the restructuring of the regulatory system in the country that occurred in 2010.

However, the overall numbers have begun to improve since the end of last year. The ACTO affirmed in its Q3 2011 report on the clinical trials industry in Russia, "It is clear that productivity is on the rise." During Q4 2010, Q1 2011 and Q2 2011, the total number of approved trials were 36, 81 and 119, respectively.

Once again, as was illustrated by the previous approvals report from Q2 2011 (see [EMOR, October 2011](#)), the majority (64%) of approved trials during Q3 2011 were multinational, multi-center trials. In fact, 84 of these types of studies were approved during Q3 2011, a 40% increase from Q2 2010 levels.

"The increase [seen in Q3 2011] is relative," explained Igor Stefanov, the general manager of **Synergy Research Group**, a CRO based in Moscow. "As a matter of fact, we've just gotten closer to the normal pre-reform level, when 93 multinational, multi-center studies were approved in Q3 2010. So the system is still getting back on track in terms of the number of multinational, multi-center trials."

"The Russian clinical trials market is recovering after having dramatically dropped in the end of 2010 due to the regulatory system restructuring," continued Svetlana Zavidova, the executive director of ACTO. "Moreover, we believe that the number of multinational, multi-center clinical trials in Russia is growing as a result of new requirements. Now, pharmaceutical companies have to conduct local clinical trials for registration purposes or to provide the results of multinational, multi-center trials that include Russian centers. That's why many sponsors prefer to include Russia in new multinational projects for products in their pipeline in order to avoid further requests from the Russian regulatory authorities to conduct local trials for registration purposes."

In fact, the requirement for local trials has caused a ripple effect throughout the Russian bio/pharmaceutical industry for international and local companies, as well as for patients. In September 2010, the Russian authorities enacted the new Federal Law on Circulation of Medicines, which made local registration studies mandatory for approval and established a new two-stage registration process.

"According to the law, during the first stage, an applicant submits a registration file and conducts a clinical trial. During the second stage, the results of the trial are evaluated and a decision is made by the local regulatory authorities on

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USER TIP

The new version of the PharmSource **PharmSource ADVANTAGE** online contractor database features a revamped side-by-side contractor comparison feature. To produce a side-by-side comparison chart:

- ◇ Log in to the **PharmSource ADVANTAGE** home page.
- ◇ In the “Contract Service Providers” box, select one of the service provider categories by clicking on the plus sign at the left-hand side of each category.
- ◇ Select one of the sub-categories.
- ◇ Refine your search further by selecting additional criteria and then click the “Search” button.
- ◇ Select the “Side By Side Comparison” button at the top of the screen.
- ◇ Choose the names of two or more bio/pharmaceutical companies from the list by checking the left-hand box next to each name.
- ◇ Select the “View Side by Side Comparison” button at the top of the screen, and a chart illustrating the capabilities of each of the companies selected will be displayed

whether to register a medicine or not,” explained Zavidova. “The law divided trials by those that could be conducted irrespective of subsequent registration, such as multinational clinical trials and post-registration trials, and those that would be conducted within the framework of the registration process. The possibility of conducting local clinical trials of efficacy and safety outside of the framework of the registration process was simply ignored.” Thus, there has been a considerable reduction in local clinical trials due to the impossibility of conducting several types of studies outside the scope of registration. In fact, the number of local clinical trials decreased by 21% during Q3 2011 compared to Q3 2010.

Steep Learning Curve

It has also become increasingly clear that the new requirement for local trials has created a hurdle for international and local companies as they figure out how to operate under the new regulations. “There is a lack of understanding as to what is meant by a ‘local registration trial’ as there is no clear direction from officials,” explained David Passov, president and CEO of **ClinStar**, a CRO that manages clinical trials in Russia. “When a company makes a submission for marketing approval, they have to wait for feedback on what data needs to be generated in Russia. Uncertainty created by the new regulation is ultimately driving down the number of local clinical trials.”

“There’s a popular Russian saying – intention was to make things better, and the result is as usual,” continued Stefanov. “For international sponsors, the requirement for additional local trials is hardly understandable and can even contradict with the corporate SOPs. For local sponsors, the necessity of the whole registration dossier submission makes approval for trials longer and more complicated. Both need time to tailor to the new system.”

The requirement for local clinical trials is also being applied to generics. In fact, the decline in bioequivalence studies has been attributed to this fact. The number of bioequivalence studies dropped 53% in Q3 2011 compared to Q3 2010, and the share of these studies in relation to the total number of approvals

decreased from 24% in Q3 2010 to 11% in Q3 2011.

The ACTO asserts that the demand for local clinical trial services has led to an increased number of companies that specialize in these types of trials, but are “not encumbered with high moral standards and professionalism.” According to the ACTO, several of these CROs have offered promotions, including guaranteed trial approval from the MoH, and others have made up reports to facilitate the approval process.

Law Slated for Amendment

In the wake of fall-out over the new regulation, the Russian government has agreed to prepare a proposal to cancel the requirement for local registration studies. Officials have realized that the regulation is providing limited, if any, additional information about the drugs being considered for approval, while subjecting trial participants to potential unnecessary harm. In addition, the requirement is believed to have actually limited access to new medicines for patients in Russia.

“I don’t think the requirement has worked out for the best for both pharma companies and patients,” commented Passov. “Marketing approvals for many products are not being submitted because there is no Russian data, and ultimately patients that could be benefitting from these drugs are not.”

The regulation requiring local registration trials was slated to be overturned by September 1, 2011. However, no action has been taken to date. In the meantime, the ACTO continues to lobby for mutual recognition of clinical trial results in the hope that drugs approved by authorities from other nations would ultimately be fast-tracked for approval by the MoH. In fact, 50% of the drugs approved by the FDA during Q3 2011 and 61% of the drugs approved by the EMA during Q3 2011 were evaluated in clinical trials conducted in Russia.

Clinical Research in Brief

Indonesia

Quintiles (Durham, N.C., USA) expanded its partnership with **Prodia Clinical Laboratory** (Jakarta, Indonesia) to provide sample testing for clinical trials conducted in Indonesia. Under the terms of the agreement, Quintiles will offer services at Prodia's central laboratory for a two-year period.

Korea

inVentiv Health (Somerset, N.J., USA) established operations in Seoul, Korea to provide clinical development and commercial services. inVentiv Health Korea is initially providing clinical development services through PharmaNet/i3, the clinical segment of inVentiv Health. Jae-Hee Kim will serve as the president of inVentiv Health Korea.

Business Conditions

CHINA UNVEILS NEW WHISTLEBLOWER PROGRAM FOR FOOD AND DRUG MANUFACTURERS

The Shanghai district of the State Food and Drug Administration (SFDA) announced plans to reinstitute a program to reward informants with knowledge of illegal activity at manufacturing facilities for drugs, medical devices and food products. The new program is actually an updated version of the "Shanghai Food and Drug Administration Informant Rewards Measure," which was instituted five years ago. Under the new guidelines, the minimum reward for informants would be increased to CNY 500 (USD 79), and the maximum reward to CNY 200,000 (USD 31,440). Informants would be eligible to receive these awards after reporting cases of any confirmed illegal activity at manufacturing facilities. The maximum reward would be reserved for those who report illegal actions considered serious. In addition, the new program would allow rewards to be given retroactively after an incidence is already under judicial review.

The informant rewards program would also include mechanisms to protect those individuals who report illegal activity at facilities. For example, a special anonymous reporting system would be established, under which individuals could report illegal activity without disclosing their names. The system would also allow individuals to use a third party to represent them during the reporting process and collection of rewards. A dedicated hotline has already been reserved to receive reports of illegal activity, and the Shanghai authorities will be available to receive reports at local offices.

It appears as though the SFDA is setting up this program as a pilot for possible expansion throughout China. However, some believe that it will have little impact on the contract manufacturing industry, even in Shanghai, where it is currently being considered, since reputable local and international CMOs operating in China already follow GMPs, and this program will not change how they do business.

What it means 

Emerging Markets Outsourcing Report

“As of now, [this program] is just in Shanghai, and has yet to be formally adopted even there,” explained Lester Ross, a partner at WilmerHale who practices in the firm’s Beijing office. “This is still in draft form, so it is uncertain if and when it will be formally promulgated – but I would not expect it to have much impact. Regulated companies are already subject to supervision, and I am skeptical that the incentives will induce many employees to become whistleblowers, even when there is a basis for reporting a problem.”

This program, though, could serve as another tool for federal authorities to keep the heat on those local CMOs struggling to adopt GMPs.

Local Market Developments

- Brazil** **Bristol-Myers Squibb** (BMS - New York, N.Y., USA) signed a technology transfer agreement with the Brazilian Ministry of Health for local production of the HIV treatment REYATAZ (atazanavir sulfate). Under the terms of the agreement, Farmanguinhos, a unit of Fundação Oswaldo Cruz (Fiocruz) and one of the pharmaceutical laboratories associated with the Brazilian Ministry of Health, will manufacture and distribute 200 mg and 300 mg capsules of REYATAZ (atazanavir sulfate) in Brazil. In addition, the arrangement includes the transfer of the technology to an unnamed local API manufacturer.
- Chile** The **United States Pharmacopeial Convention** (USP) and the **Chilean Pharmacopoeia Foundation** (CPF) signed a memorandum of understanding to establish a partnership to improve quality and safety standards for medicines. Under the terms of the agreement, the two organizations will develop mutual reference materials for pharmacopeial standards testing, and establish a scientific exchange for staff and information through several joint programs.
- China** **China National Biotech Group**, a subsidiary of state-owned Sinopharm Group, announced plans to raise between USD 1.5 billion and USD 2 billion in an initial public offering on the Hong Kong stock exchange during Q1 2012. China National Biotech Group, which will be renamed China Biotech, produces a range of drugs, vaccines, blood products, and diagnostics. It also stores a quarter of China’s plasma.
- China** **Shanghai Modern Pharmaceutical** (Shanghai, China) announced plans to build a production plant to manufacture drugs considered essential for the Chinese market. The company will invest CNY 277 million (USD 44 million) in the project, which is expected to be completed in three years. The plant will contain seven manufacturing suites, as well as a finished-production storage and packaging warehouse.
- China** **WuXi PharmaTech** (Shanghai, China) formed a USD 50 million corporate venture fund to invest in technologies and life-sciences companies with capabilities to enhance WuXi’s services platform. In September 2011, this fund made its first investment in Hua Medicine, a drug developer based in Shanghai that plans to in-license drugs from western countries for development and commercialization in China.
- China, India** The **United States Pharmacopeial Convention** (USP) announced the publication of the first 10 standards to be included in its *USP Medicines Compendium*. The new standards, for medicines used as anti-HIV agents, antivirals, analgesics, oral contraceptives and antiparasitic treatments, were established by a USP Expert Committee in India. The next USP Expert Committee, which will develop a set of standards on excipients, will comprise Chinese scientists.
- India** **SOHM** (Buena Park, Calif., USA), a generics company with manufacturing facilities in India, acquired Pune-based **Novatrend Medicament**, adding 17 new products to its portfolio. Six of the acquired products are new to the Indian market; several have dermatological applications. This acquisition allows SOHM to not only include generics in its portfolio, but to add proprietary products, as well.

Emerging Markets Outsourcing Report

India, Russia

The governments of India and Russia are expected to sign a memorandum of understanding to establish a fast-track program for the registration of drugs manufactured in India and intended for the Russian market, according to local press. In addition, the two countries are reportedly working together to encourage joint collaborations between Indian and Russian companies to set up testing facilities in Russia. Two such collaborations have already been established – **Dr. Reddy's Laboratories** (Hyderabad, India) signed a licensing, technology transfer, manufacturing and marketing agreement with **R-Pharm** (Moscow, Russia) in December 2010; in September 2011, **Aurobindo Pharma** (Hyderabad, India) formed a joint venture with **Diod** (Moscow, Russia) to produce and distribute generics in Russia, Belarus and Kazakhstan.

Russia

Binnopharm, a pharmaceutical company based in Moscow, Russia, entered an agreement with GlaxoSmithKline (GSK) and Pfizer to produce HIV drugs in Russia under the GSK/Pfizer HIV joint venture ViiV Healthcare. Binnopharm will be responsible for local secondary manufacture of the drugs and packaging. Production is scheduled to begin during the first quarter of 2012.

Commercial Dose Manufacturing

India

Biocon (Bangalore, India) signed an agreement with Haselmeier, a manufacturer of pen and auto-injection systems, to produce INSUPen in India. Under the terms of the agreement, Biocon will retain worldwide distribution rights for INSUPen, a reusable pen that will contain Biocon's insulin and insulin analogues.

API — Small Molecule

India

Aurobindo Pharma (Hyderabad, India), the parent company of **AuroSource**, announced that a fire occurred in the powder processing area of its API facility. Three employees were injured; however, production was not suspended due to the incident.

India, Mexico

Vivimed Labs (Hyderabad, India), a manufacturer of APIs and active ingredients for specialty chemicals, acquired **Uquifa**, another manufacturer of APIs and intermediates with operations in Spain and Mexico. Under the terms of the agreement, Vivimed Labs will pay USD 55 million for Uquifa, which will become a division of Vivimed Group.

Analytical Services

China

ShangPharma (Shanghai, China) announced plans to invest in a new facility for biology, chemistry and process development work that will be dedicated to the needs of one of its clients.

Early Development

China

Medicilon (Shanghai, China) signed an agreement to provide preclinical services to Seoul, Korea-based SK Biopharmaceuticals for the development of SKL-PSY, a drug being evaluated for treatment of depression and bipolar disorder. Under the terms of the agreement, Medicilon will provide data in preparation for SFDA and FDA IND submission.

Drug Discovery

China

BioBay (Suzhou, China), a life sciences company that maintains a biotechnology and nanotechnology incubator in China called the Suzhou Industrial Park Bio & Nano Technology Development Co., Ltd., entered an agreement with Roche and Harvard University to develop treatments for cancer and other diseases. Under the terms of the agreement, BioBay will provide medicinal chemistry and preclinical development services, while Roche will be responsible for drug discovery, development and commercialization.

Commodity Suppliers

- China** **Bosch Packaging Technology** (Waiblingen, Germany) announced plans to build a CNY 150 million (USD 23 million) production plant in Chengdu, China. Initial operations are expected to begin in Chengdu by 2012 in a leased, 66,000-square-meter production plant; construction on the new facility is scheduled for 2014. The new 13,500-square-meter facility will house a 7,200-square-meter production area and employ 300.
- China** **Schott** (Mainz, Germany) established a joint venture in China with Zhejiang Xinkang Pharmaceutical Glass. Schott will hold a majority stake in the company, which will provide pharmaceutical packaging products made of glass to the Chinese market. The products will be manufactured at Schott's current facilities in Suzhou and Jinyun.
- Mexico** **Stevanato** (Via Molinella, Italy), a company that specializes in primary packaging from glass tubing for pharmaceuticals, announced plans to double the size of its plant in Monterrey, Mexico. The company will invest EUR 30 million (USD 39 million) into the project, including an initial investment of EUR 4.5 million (USD 5.8 million). Stevanato opened the facility, which supplies glass containers, ampoules, vials and cartridges, three years ago. The expanded site is expected to be operational by 2012. It will measure 20,000 square meters and employ 250.

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PO Box 8163
Springfield, VA 22151-8163

Voice: 1-703-383-4903
Fax: 1-703-383-4905

E-mail: info@pharmsource.com
Website: www.pharmsource.com

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